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FORM PTO-1390 (REV 10-95) U S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES PATENT AND TRADEMARK OFFICE DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
PC10030A

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)
Not yet assigned 09/402010

INTERNATIONAL APPLICATION NO.	**INTERNATIONAL FILING DATE**	**PRIORITY DATE CLAIMED**
PCT/IB98/01813	November 13, 1998 (11.13.1998)	December 31, 1997 (12.31.1997)

TITLE OF INVENTION
ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

APPLICANT(S) FOR DO/EO/US
Jotham Wadsworth COE and Paige Roanne Palmer BROOKS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is the **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern other documents(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
    ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

EXPRESS MAIL NO. EM484852791

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U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Not yet assigned 09/402010	PCT/IB98/01813	PC10030A

17. ☒ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5)):		
☒ Search Report has been prepared by the EPO or JPO $840.00		
☐ International preliminary examination fee paid to USPTO (37CFR 1.482) $670.00		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $760.00		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	- 20 =		X $ 18.00	$	
Independent Claims	- 3 =		X $ 78.00	$78	
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ $260.00	$	

TOTAL OF ABOVE CALCULATIONS =	$918	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note: 37 CFR 1.9, 1.27, 1.28)	$	
SUBTOTAL =	$918	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$	
TOTAL NATIONAL FEE =	$918	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$	
TOTAL FEES ENCLOSED =	$918	
Amount to be: Refunded	$	
Charged	$	

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 16-1445 in the amount of $ 918 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.16-1445. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Registration Number

EXPRESS MAIL NO. EM484852791

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Background of the Invention

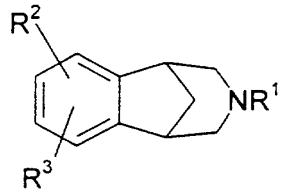
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory 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, 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), 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. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

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

R^2 and R^3 are selected, independently, from hydrogen, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1\text{-}C_6)$alkyl wherein q is zero, one or two, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, aryl-$(C_0\text{-}C_3)$alkyl- or aryl-$(C_0\text{-}C_3)$alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0\text{-}C_3)$alkyl- or heteroaryl-$(C_0\text{-}C_3)$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 $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1\text{-}C_6)$alkylamino- or $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- moiety of said $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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 $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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-$(C_0\text{-}C_3)$alkyl- and said heteroaryl-$(C_0\text{-}C_3)$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 $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro fluoro, bromo or iodo), $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1\text{-}$

C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$,

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, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$, and -$XC(=O)R^{13}$,

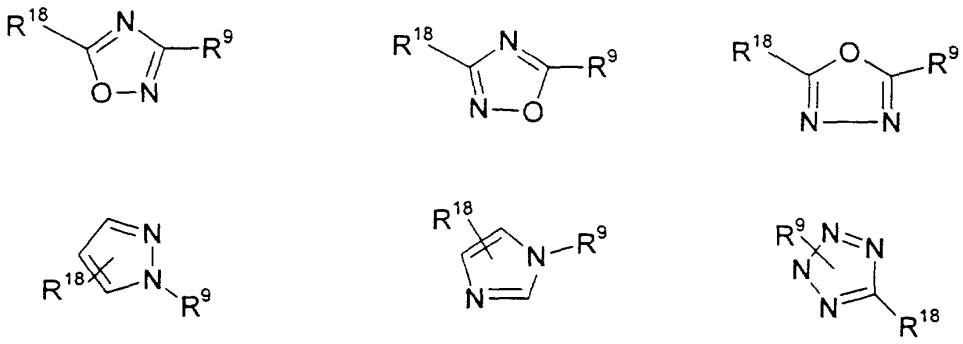
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine 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, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

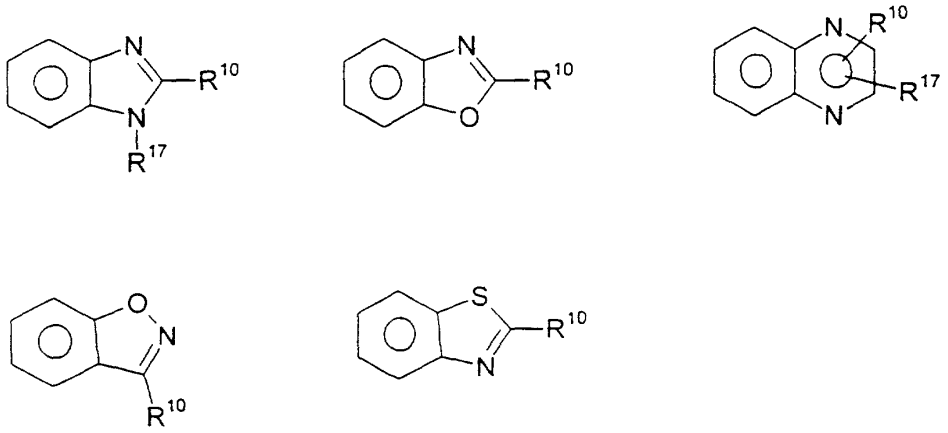
and the pharmaceutically acceptable salts of such compounds.

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



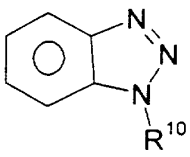
wherein one of R^9 and R^{18} is hydrogen or $(C_1\text{-}C_6)$alkyl, and the other is a bond to the benzo ring of formula I.

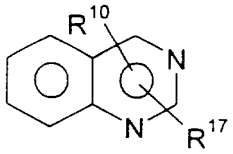
Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:

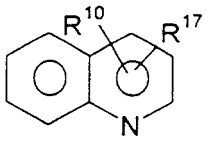


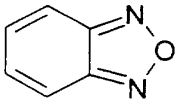
wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\ \text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

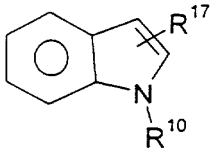
Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:

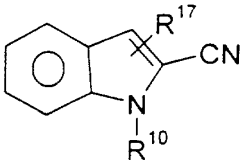


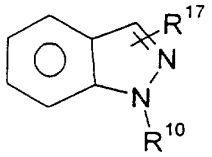


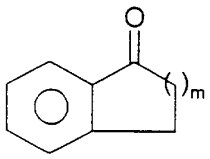


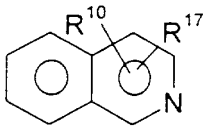


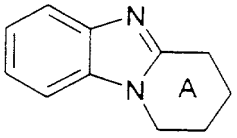


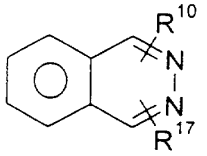












wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

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:

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-methyl-5-oxo-6,13-diazatetracyclo[9.3 1 $0^{2.10}$ $0^{4.8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9 3.1.$0^{2.10}$ $0^{4.8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene hydrochloride;

5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$ $0^{4.8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4\ 8}$]pentadeca-2(10),3,8-triene hydrochloride;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-triene hydrochloride;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

5-chloro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-triene hydrochloride;

5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1 $0^{2.10}$ $0^{4\ 8}$]pentadeca-2(10),3,8-triene hydrochloride;

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-triene hydrochloride;

4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride;

5-trifluoromethyl-10-aza-tricyclo[6 3 1 $0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6 3 1 $0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride,

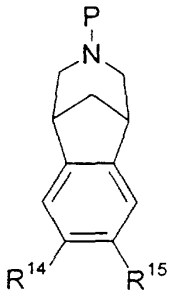
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3 1.$0^{2\ 10}$ $0^{4\ 8}$]pentadeca-2(10),3 8-triene hydrochloride;

7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2\ 10}$ $0^{4\ 8}$]pentadeca-2(10),3,8-triene hydrochloride;

6,7-dioxa-5,8,14-triazatetracyclo[10.3.1 $0^{2\ 11}$ $0^{4\ 9}$]hexadeca-2(11),3,9-triene hydrochloride; and

5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10 3 1 $0^{2\ 11}$ $0^{4\ 9}$]hexadeca-2(11),3,9-triene hydrochloride

This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, 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 or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $-C(=O)(C_1\text{-}C_6)$alkyl, cyano, hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$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.

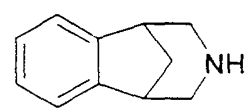
The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is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

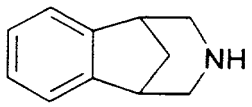
The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



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 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 administering to a mammal in need of such treatment an amount of a compound of the formula



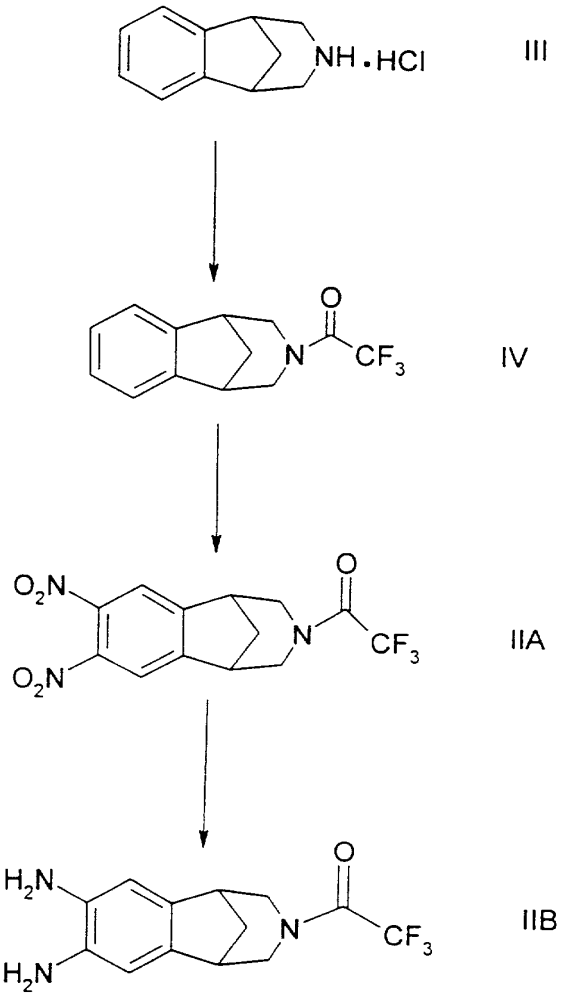
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

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.

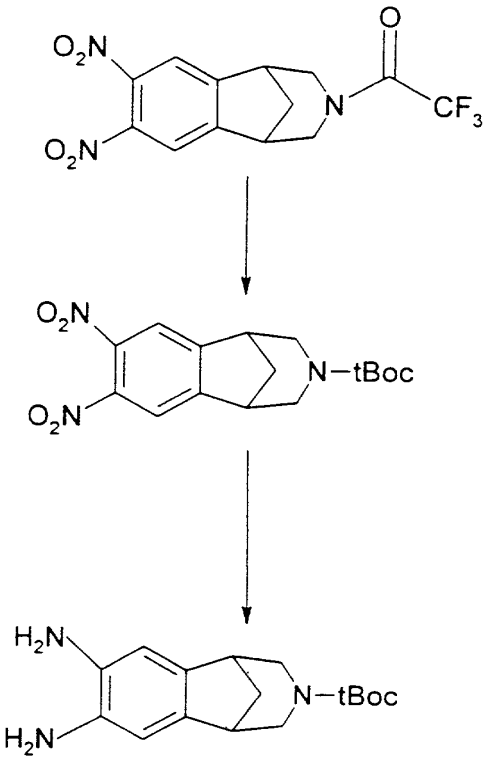
Detailed Description of the Invention

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.

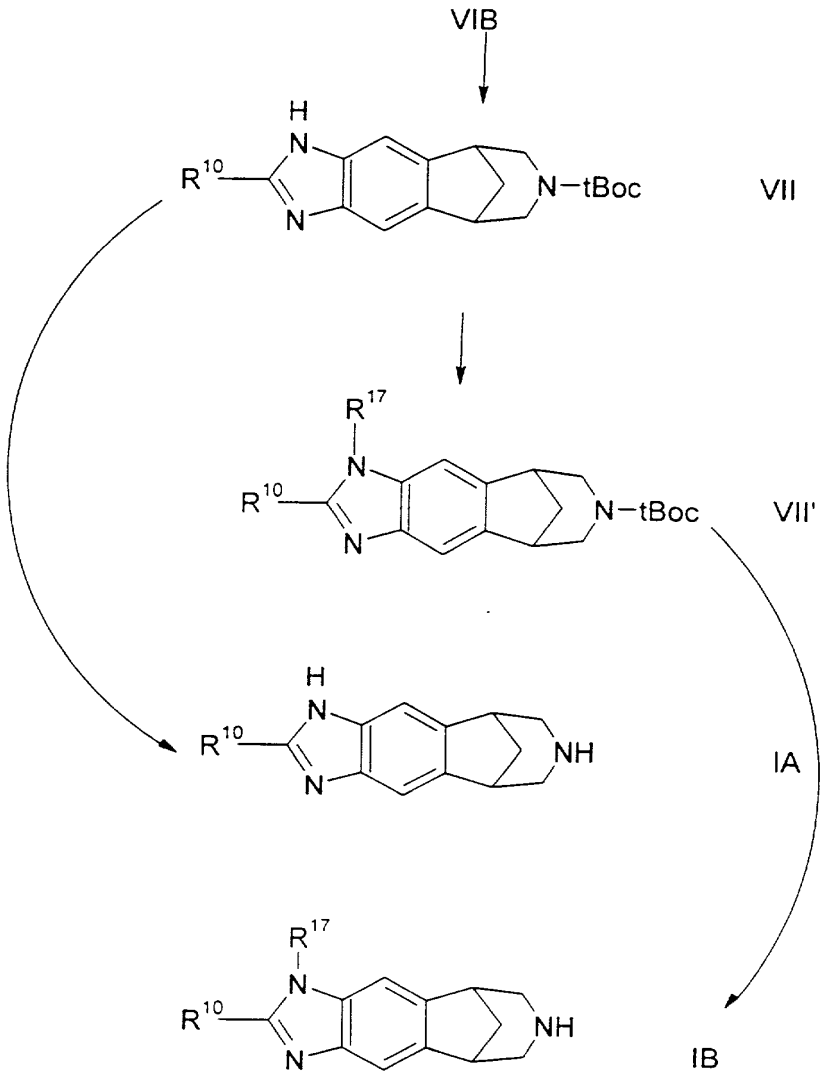
Scheme 1



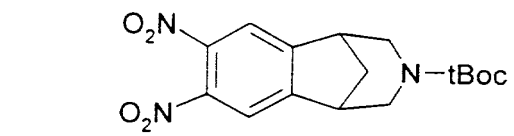
Scheme 2



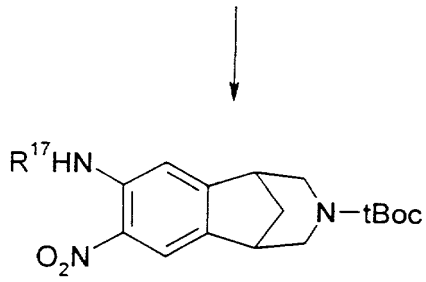
Scheme 2 continued



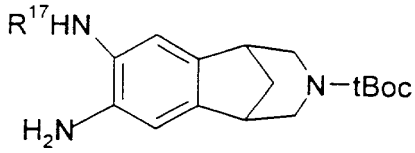
Scheme 3



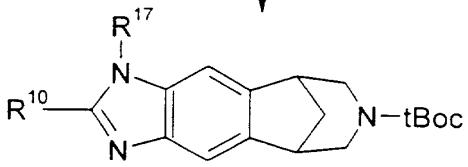
VIA



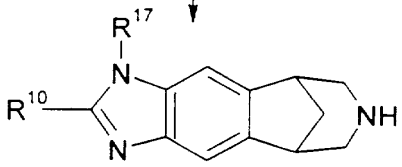
XXIII



XXIV

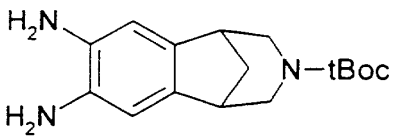


XXV

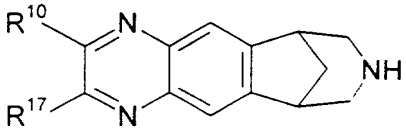


IB

Scheme 4

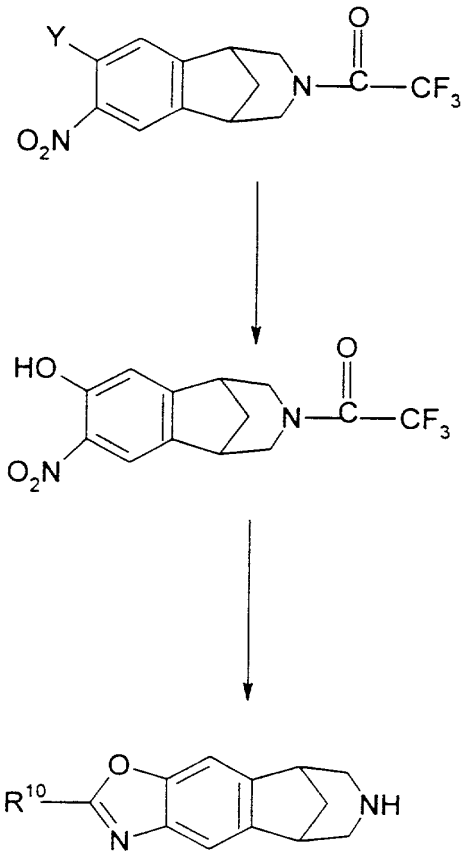


VIB

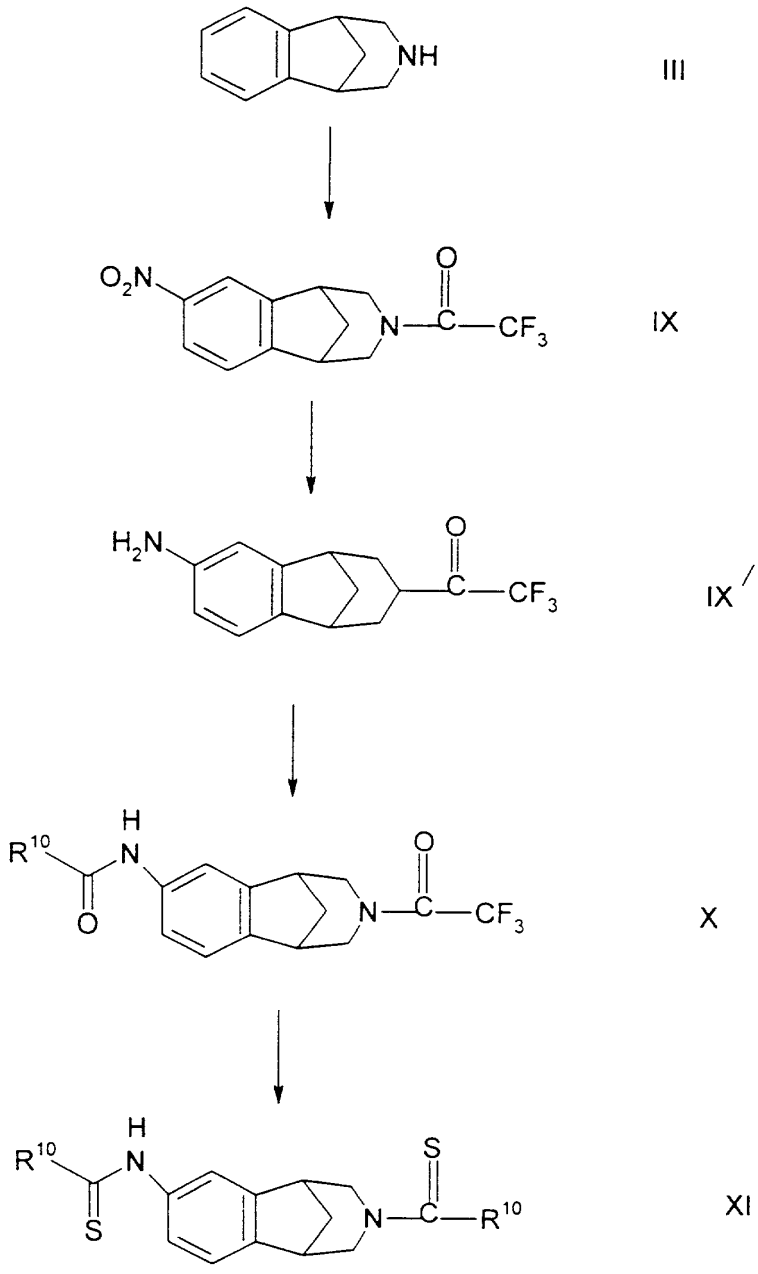


IC

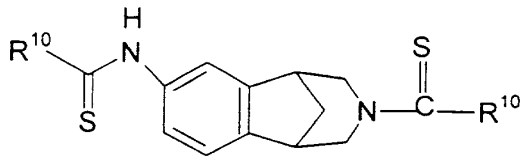
Scheme 5



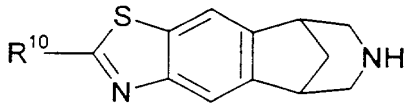
Scheme 6



Scheme 6 continued

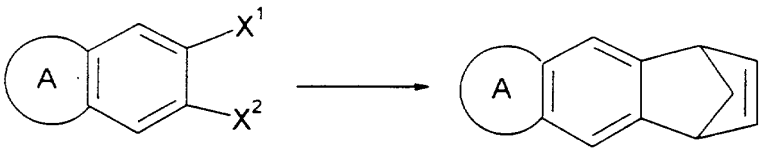


XI



IF

Scheme 7

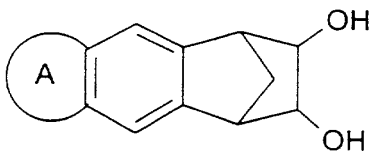


(ring A = present or absent)

XII

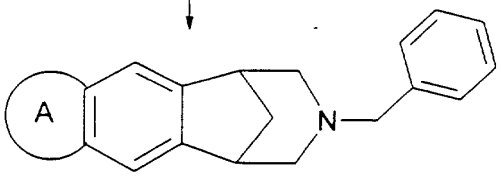
(ring A = present or absent)

XIII



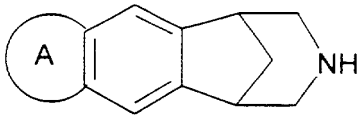
(ring A = present or absent)

XIIIA



(ring A = present or absent)

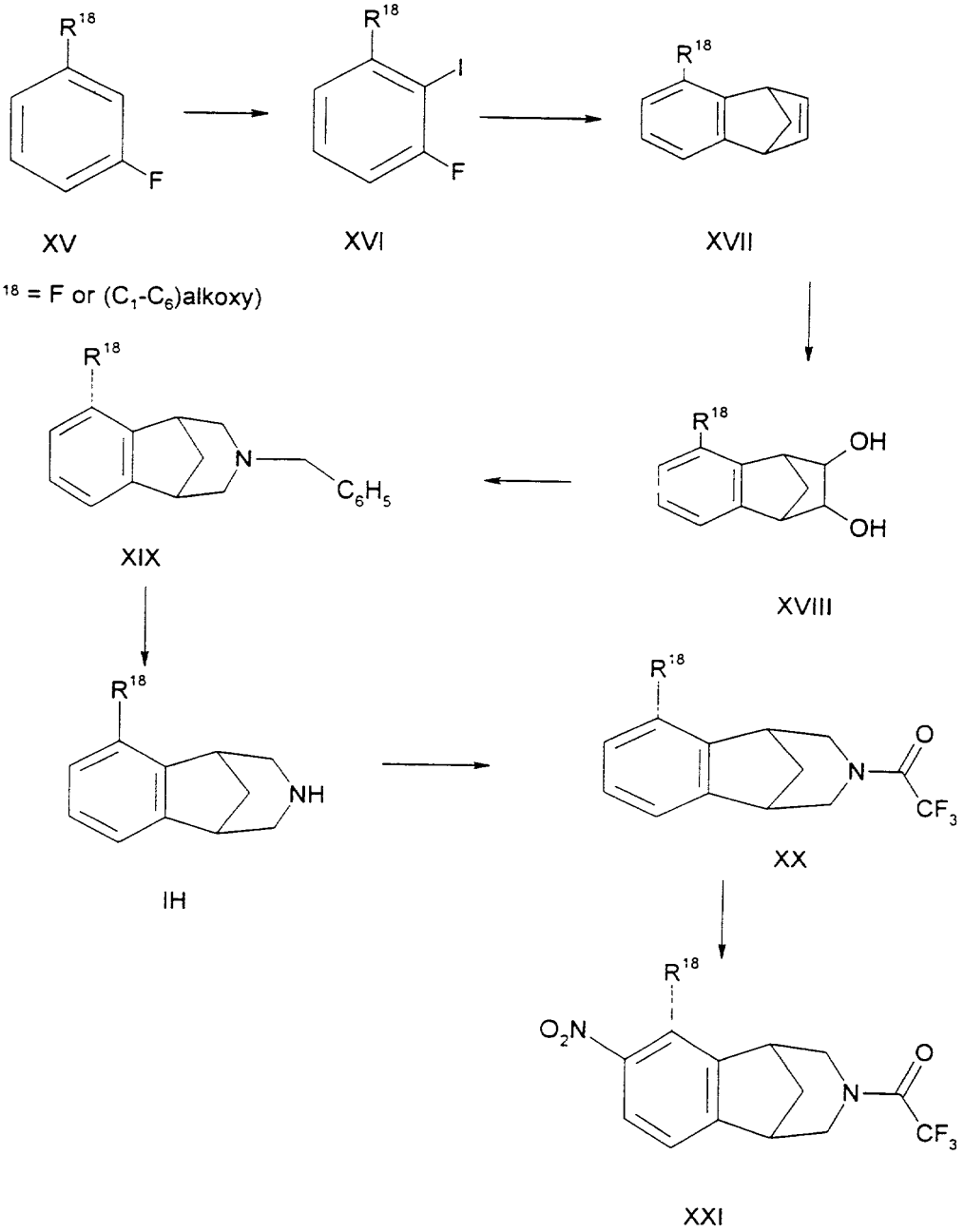
XIV



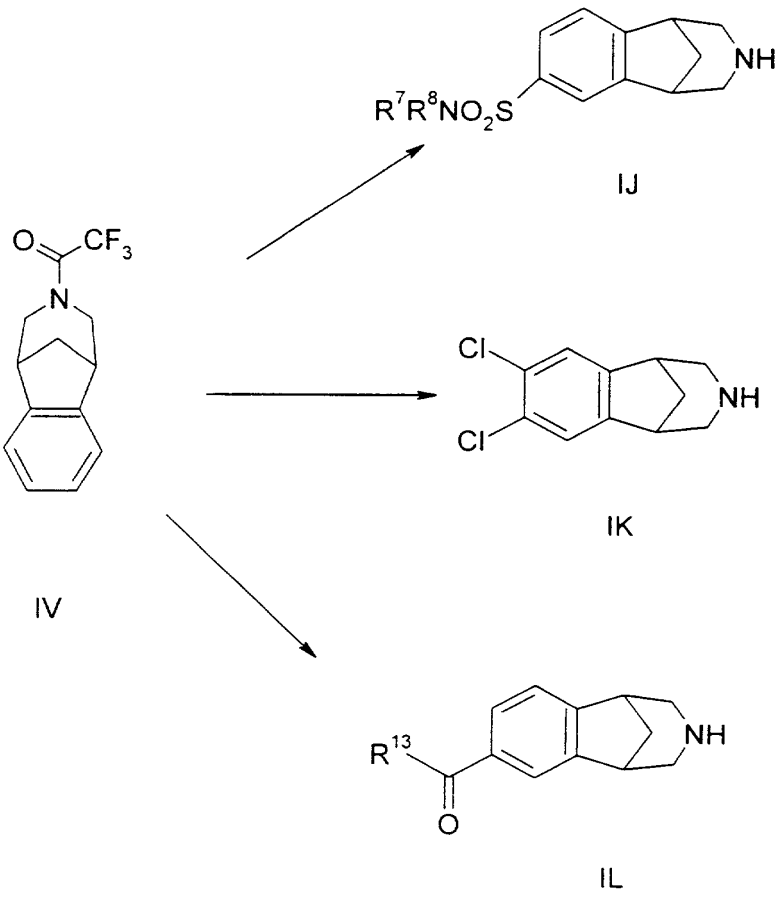
IG: (R^2 and R^3 form ring A)

III: (ring A = absent)

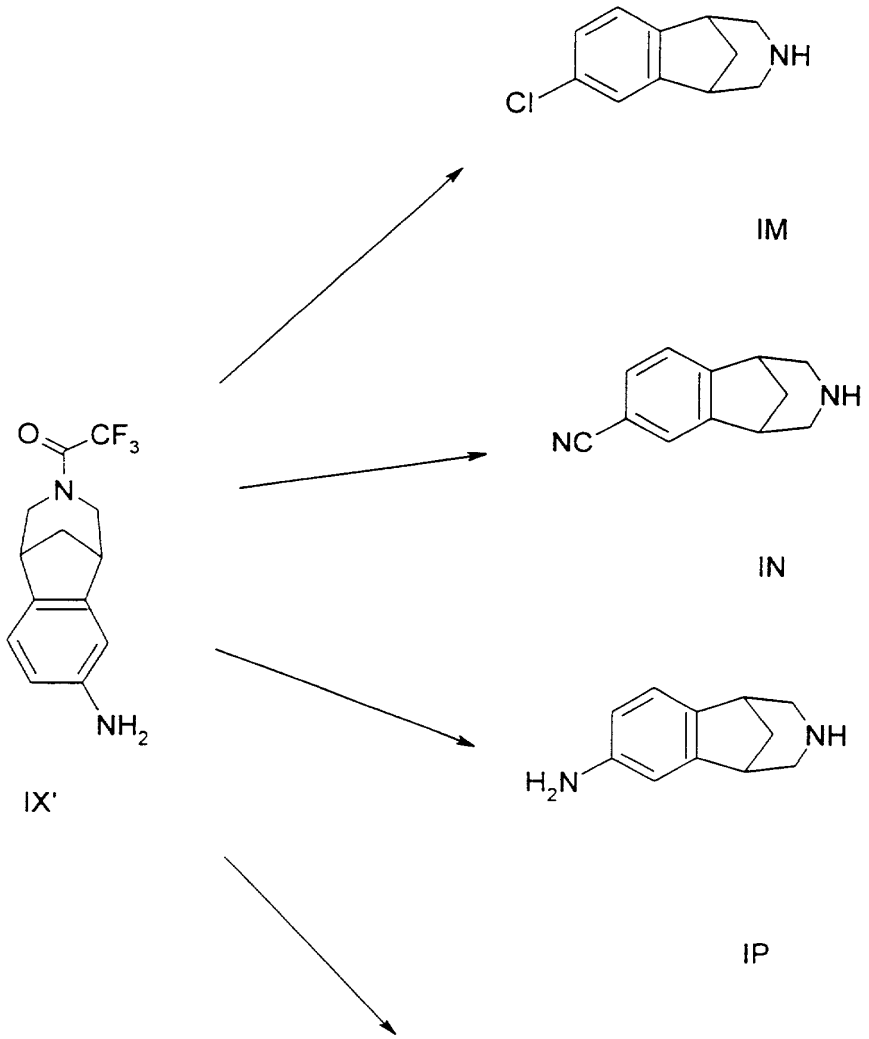
Scheme 8



Scheme 9



Scheme 10



Scheme 1-10 illustrate methods of synthesizing compounds of the formula I .

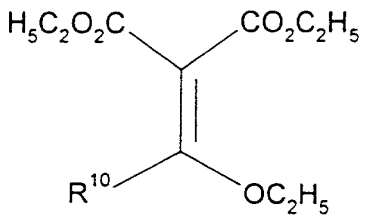
Referring to Scheme 1, the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 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.

Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) 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 VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula



XXIIA

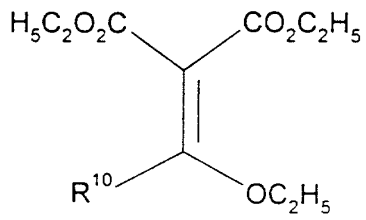
wherein R^{10} is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0$ -$C_3)$alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0$ -$C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings 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 VII the compound of formula VIB are described by Segelstein et al., Tetrahedron Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII 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 VII can be converted into the corresponding compound of formula IB 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, 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

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illlustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA 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. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV 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 IIA into a compound of the formula IIB in Scheme 1, and exemplied in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

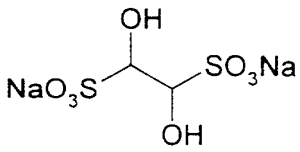


XXIIA

wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII

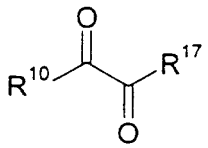
Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB 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 VIB 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.

The desired quinoxoline of formula IC 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 VII into one of the formula IA

Scheme 5 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 5 as chemical formula IE. Referring to Scheme 5, the compound of formula XXII, wherein Y is nitro, halo, trifluoromethanesulfonate or a diazonium salt, 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 VIII, which can then be converted into the desired compound having formula IE by the following procedure. First, the compound of formula VIII 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 $(C_1\text{-}C_6)$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

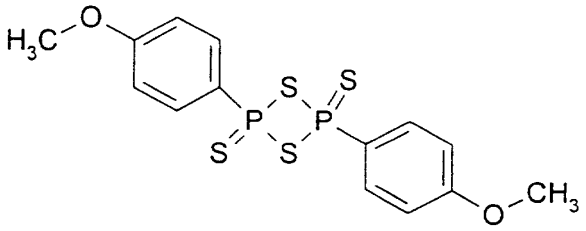
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IE. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) 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 6 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. Referring to Scheme 6, the compound of formula III 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 anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, 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 IX'.

The compound of formula IX' 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 R^{10} is hydrogen or $(C_1\text{-}C_6)$alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI 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 IF can be accomplished by reacting the compound of formula XI 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.

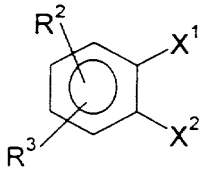
Scheme 7 illustrates a method of preparing the compound of formula III, which is used as the starting material for the process of Scheme 1, or a compound of the formula IG, wherein R^2 and R^3 form a ring (labeled "A" in the Scheme), as defined above in the definition of compounds of the formula I. Referring to Scheme 7, the compound of formula XII, wherein X^1 and X^2 are selected, independently, from chloro, fluoro, bromo and iodo, but where at least one of X^1 and X^2 is Br- or I-, reacted with cyclopentadiene, in the presence of magnesium metal, in a THF, dioxane or other ethereal solvent, at a temperature from about 40°C to about 100°C, preferably at about the reflux temperature, to form a compound of the formula XIII Reaction of the resulting compound of formula XIII with N-methylmorpholine-N-oxide (NMO) and osmium tetroxide in acetone at about room temperature yields the corresponding compound of the formula XIIIA.

The compound having formula XIIIA is then converted into the corresponding compound of formula XIV using the following procedure. First, the compound of formula XIIIA 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 and

sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0°C to about room temperature, preferably at about room temperature, to form the desired compound of formula XIV. Removal of the benzyl group from the compound of formula XIV yields the compound of formula III (when ring A is absent) or IG, (when ring A is present). This 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 of Scheme 7 can also be used to prepare compounds of the formula I wherein R^2 and R^3 do not form a ring and are not both hydrogen, by replacing the starting material of formula XII with the appropriate compound having the formula



XII'

Scheme 8, 9 and 10 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 8 illustrates a variation of the process shown in Scheme 7, which can be used to make a compound identical to that of formula III except that the benzo ring is substituted with a fluoro group or an alkoxy group (R^{18} in Scheme 8) This compound is depicted in Scheme 8 as chemical structure 1H Referring to Scheme 8, where, for example, R^{18} is F, 1,3-difluorobenzene is reacted with a strong base such as an alkali metal dialkylamine or an alkali metal alkyl (or aryl) in an ethereal solvent such as ethyl ether or THF, at a temperature below -50°C, followed by quenching with iodine or N-iodosuccinamide, to form 1,3-difluoro-2-iodobenzene The compound 1,3-difluoro-2-iodobenzene (structural formula XVI in Scheme 8) is then converted into the compound of formula IH by a series of reactions (represented in

Scheme 8 as ,XVI→XVII→XVIII→XIX→IH) that are analogous to the series of reactions described above and illustrated in Scheme 7 for converting compounds of the formula XIII into those of the formula IG or III. Conversion of the compound of formula XVI into the compound of formula XVII can also be accomplished by treating a mixture of the compound of formula XVI and cyclopentadiene with an alkyl lithium reagent, preferably n-butyl lithium, in an inert hydrocarbon solvent such as petroleum ether or methyl cyclohexane, at a temperature from about -20°C to about room temperature, preferably at about 0°C.

The compound of formula IH can then be converted into the corresponding nitrogen protected derivative of formula XX, using the methods described above for synthesizing the compound of formula IV in Scheme 1. Nitration of the compound of formula XX using the method described above for preparing the compound of formula IX in Scheme 6, yields the compound of formula XXI wherein the benzo ring is substituted with both a fluoro and nitro group or an alkoxy group and nitro group. The compound of formula XXI can be used to make a variety of compounds of the formula I wherein one of R^2 and R^3 is fluoro, using methods that are well known to those of skill in the art, for example, by first converting the nitro group to an amino group, converting the amino group to a variety of other substituents, as illustrated in Scheme 10, and then removing the nitrogen protecting group.

The compound of formula XXI acts as a regioisomeric functional equivalent of the compounds having formulas IIA, VIA and XXII, in that the fluorine atom of formula XXI reacts similarly to the nitro and Y groups of formula IIA, VIA, and XXII, and thus can be subjected to the same series of reactions as those described above for the latter three compounds, providing an alternate means for preparing the products of such reactions. Similarly, the alkoxy group of formula XXI (R^{18}=alkoxy) may be converted into a hydroxyl group before or after introduction of the nitro group, and then converted to isomeric products as described above. Also, the trifluoromethanesulfonate salt of such hydroxy derivative can act as a Y-group as described.

Preparation of compounds of formula I where R^2 = -O(C_1-C_6)alkyl, (C_1-C_6) alkyl or aryl wherein aryl is defined as above in the definition of formula I, and R^3 is H or one of the other substituents described above in the definition of formula I, can be prepared as described above and illustrated in Scheme 8 by replacing one of the fluorine atoms of the compound of formula XV with -O-(C_1-C_6)alkyl, (C_1-C_6)alkyl or aryl, respectively

Scheme 9 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 9, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV 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 IV 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 IV 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 IV 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 IV, as depicted in Scheme 9 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl, halo $(C_1\text{-}C_6)$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, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substited compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles

Scheme 10 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 10, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula IX' 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 by 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,N-dimethylpropylurea (DMPU) or DMSO, preferably DMF, at a temperature from about 50°C to about 180°C, preferably about 150°C. Nitrogen deprotection as described above provides the desired compound of formula IM.

The above described iodide 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 IX' provides the compound of the formula IP.

The compound of formula IX' 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.

In each of the reactions discussed above, or illustrated in Schemes 1-10, 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 Arneric, 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

10-AZA-TRICYCLO[6.3.1 $0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1,4-Dihydro-1,4-methano-naphthalene

(Based wholly or in part on a) Wittig, G.; Knauss, E. *Chem Ber.* **1958**, *91*, 895. b) Muir, D. J , Stothers, J. B. *Can. J. Chem.* **1993**, *71*, 1290.)

Magnesium turnings (36.5 g, 1.5 M) were stirred in anhydrous THF (250 mL) in a dried 2 L 3 neck round bottom flask equipped with a 250 mL non-equalizing addition funnel with a nitrogen (N_2) flow adapter, mechanical stirrer and efficient condenser equipped with a N_2 flow adapter The flask was stirred and warmed to reflux by a removable heating mantle. 2-Fluorobromobenzene (2g) was added followed by 1 mL of 3N ethylmagnesium bromide (EtMgBr in THF) The addition funnel was charged with a mixture of cyclopentadiene (94.4 g, 1 43 M Prepared by the method described in: *Org. Syn.* Col. Vol. V, 414-418) and bromofluorobenzene (250 g, 1 43 M) which was maintained at 0 °C in a separate flask by an ice bath, and transferred to the addition funnel via cannula. Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation), the heating mantle was removed and the contents of the addition funnel was added dropwise at such rate as to maintain reflux (1.5 hours) The heating mantle was re-applied and a reflux maintained for 1 5 hours. (TLC 100% hexanes R_f 0.67)

The reaction was cooled to room temperature and quenched with H_2O (500 mL) and carefully with 1N HCl (200 mL, produces H_2 evolution from unconsumed Mg) To this ~50 mL

concentrated HCl was added to dissolve solids. Total addition/quench time ~1 hour Saturated aqueous sodium chloride (NaCl) solution (300mL) was added and product hexanes extracted until no potassium permanganate ($KMnO_4$) active product is removed. (4 x ~250 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (250 mL), sodium bicarbonate Na_2SO_4 dried and concentrated to an oil (~200 g). The product was distilled at 78-83 °C @15mm (131 g, 64%). (An alternative workup is described on p.419 Fieser and Fieser, Vol. I, Reagents for Organic Synthesis, Wiley, NY., NY.; 1967).

B) 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol

(Except for the workup method and the quantity of OsO_4 used, based on VanRheenen, V ; Cha, D.Y.; Hartley, W M. *Org. Syn* **1988**, *6*, 342.)

In a 2 L 3 neck round bottom flask equipped with a N_2 flow adapter, mechanical stirrer was placed 1,4-dihydro-1,4-methano-naphthalene (79 5 g, 560 mmol) stirred in acetone (800 mL) and H_2O (100 mL) and N-methyl morpholine N-oxide (67 5 g, 576 mmol). To this was added osmium tetroxide (OsO_4) (15 mL of a 15mol% t-BuOH solution, 1.48 mmol. 0.26mol%) and the mixture was stirred vigorously. After 60 hours. the reaction was filtered, and the white product rinsed with acetone and air dried (60 9 g). The mother liquor was concentrated to an oily solid· acetone trituration, filtration and acetone rinse provided (27.4 g, total 88.3 g, 89%) (TLC 50% EtOAc/hexanes R_f ~0.5). mp 176-177.5 °C.

C) 10-Benzyl-10-aza-tricyclo[6.3 1.$0^{2,7}$]dodeca-2(7),3,5-triene

(Based on Abdel-Magid, A. F., Carson, K G , Harris, B. D.; Maryanoff, C. A.; Shah, R. D *J. Org. Chem.* **1996**, *61*, 3849, and Mazzocchi, P H ; Stahly, B C. *J. Med Chem* **1979**, *22*, 455.)

1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2.3-diol (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round bottom flask under nitrogen with cool water bath (~10 °C). To this sodium periodate ($NaIO_4$) (51 g. 239 mmol) and triethylbenzyl ammonium chloride (Et_3BnNCl) (50 mg) were added. The resulting mixture was stirred for 1 hour (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with DCE (200 mL) The organic layer was washed with H_2O (4 x 200 mL, or until no reaction to starch iodide is observed in the aqueous wash) then dried through a cotton plug. To this was added benzyl amine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 minutes then immediately transferred into the sodium triacetoxyborohydride $NaHB(OAc)_3$ /DCE (see below) over 10 minutes

In a separate 2 L round botton flask flask under nitrogen was magnetically stirred $NaHB(OAc)_3$ (154 g, 0.727 mmol) in DCE (800 mL) at 0 °C (ice bath). To this was added the above mixture over 10 minutes, without delay after the dialdehyde and amine were mixed. The resulting orange mixture was allowed to warm to room temperature and stirred for 30-60 minutes.

The reaction was quenched by addition of saturated sodium carbonate (Na_2CO_3) solution (~300 mL) carefully at first and the mixture was stirred for 1 hour (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, then evaporated to a red oil. This was dissolved in a minimum of Et_2O and filtered through a Silica pad (3 x 4 inch) eluting with 15% ethyl acetate (EtOAc)/hexanes +1% of 37% aqueous ammonium hydroxide (NH_4OH) solution to remove baseline red color. Concentration affords a light yellow oil (48.5 g, 194 8 mmol, 85.7%). (TLC 10% EtOAc/hexanes R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 7 16 (m, 7H), 6 89 (m, 2H), 3.48 (m, 2H), 3.08 (m, 2H), 2.80 (d, J=9.5 Hz, 2H), 2.42 (d, J=9.5 Hz, 2H), 2.27 (m, 1H), 1.67 (d, J=10.0 Hz, 1H). APCI MS *m/e* 250.3 [(M + 1)$^+$].

D) 10-Aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene (For an alternative synthesis, see; Mazzocchi, P. H.; Stahly, B. C. *J. Med Chem.* **1979**, *22*, 455.)

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3N HCl EtOAc (1 03 eq.) slowly with cooling (ice bath) The resulting precipitate was filtered and rinsed with EtOAc The solids were dissolved in MeOH (250 mL) in a parr bottle To this was added $Pd(OH)_2$ (7 g of 20%wt/C) and the mixture was shaken under 50-40 psi of H_2 for 24 hours or until done by TLC The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotroped with methanol (MeOH) (3x) then triturated with acetone, treated with ethyl ether (Et_2O) to precipitate product and filtered. Concentration of the mother liquors and a second treatment provided an off white solid (48 95 g, 251 mmol, 88%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 4H), 2.97 (m, 4H), 2.68 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 1.95 (d, J=11 0 Hz, 1H) APCI MS *m/e* 160.2 [(M + 1)$^+$].

EXAMPLE 2

4-FLUORO-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 6-Fluoro-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (0.66 g, 27.2 mmol) were stirred in anhydrous THF (10 mL) in a flame dried 75 mL 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,5-Difluorobromobenzene (0.1 g) was added followed by of 3N EtMgBr in THF (0.1 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (1.71 g, 25.9 mmol) and 2,5-difluorobromobenzene (5.0 g, 25.9 mmol). Small portions (~0.2 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for 1 hour

The reaction was cooled to room temperature and quenched with H_2O (20 mL) followed by aqueous 1N HCl solution (20 mL) to dissolve the solids. Saturated aqueous NaCl solution (30 mL) was added and product was extracted with hexanes (4 x 25mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil. Chromatography on Silica gel eluting with hexanes provided an oil (780 mg, 19%). (TLC hexanes R_f 0.38). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.80 (br s, 1H), 6.78 (br s, 1H), 6.59 (m, 1H), 3.87 (br s, 2H) 2.32 (d, J=7.0 Hz, 1H), 2.25 (d, J=7.0 Hz, 1H)

B) 6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

6-Fluoro-1,4-dihydro-1,4-methano-naphthalene (680 mg, 4.22 mmol) and N-methyl morpholine N-oxide (599 mg, 4.43 mmol) were stirred in acetone (50 mL) and H_2O (5 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt. solution in t-BuOH, 0.02 mmol). After 72 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1 hour. The florisil was filtered and the filtrate concentrated to produce a crystalline product which was triturated with acetone and filtered (524 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.10 (dd, J=8.0,5.0 Hz, 1H), 6.90 (dd, J=8 0,2.3 Hz, 1H), 6.75 (ddd, J=8.0,8.0,2.3 Hz, 1H), 3 79 (s, 2H), 3.18 (d, J=1.5 Hz, 2H), 2.22 (d, J=10.0 Hz, 1H), 1 92 (dd, J=10.0,1.5 Hz, 1H). GCMS *m/e* 194 (M^+)

C) 10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (524 mg, 2.68 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (15 mL) and H_2O (45 mL) then treated with sodium periodate (0.603 mg, 2.82 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 20 mL). The combined organic layer was washed with H_2O (4 x 20 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (0.308 mL, 2.82 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (1.82 g, 8.58 mmol) in DCE (50 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (520 mg, 80%). (TLC 2% acetone/CH_2Cl_2 R_f 0 40). ^1H NMR (400 MHz, $CDCl_3$) δ 7 18 (m, 1H), 6.88 (m, 2H), 3.48 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 2.27 (m, 1H), 1 69 (d, J=10.5 Hz, 1H).

D) 4-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene (390 mg, 1.461 mmol), ammonium formate (3.04 g, 48.2 mmol) and 10%$Pd(OH)_2$/C (30 mg) were combined in MeOH (50 mL) and brought to reflux under N_2 for 1 5 hours. Ammonium formate (1.0 g) was added and reflux continued for 0.5 hour The reaction mixture was filtered through a Celite pad which was rinsed with MeOH The filtrate was concentrated. The residues were treated with saturated aqueous Na_2CO_3 solution (30 mL) and product extracted with methylene chloride (CH_2Cl_2) (3 x 25 mL). The organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated The residue was treated with 2N HCl MeOH (5 mL) and concentrated then taken up in minimum of MeOH and saturated with Et_2O After stirring 18h, the white crystals were collected by filtration (86 mg, 28%) (TLC

5% MeOH/CH_2Cl_2 (NH_3) R_f 0.27) (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.83 (m, 2H), 2.89 (m, 4H), 2.61 (dd J=12.0 Hz, 2H), 2.37 (m, 1H), 1.87 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.2 [(M + 1)$^+$]. (HCl salt) mp 260-262 °C.

EXAMPLE 3

4-METHYL-10-AZA-TRICYCLO[6 3 1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-methylbromobenzene. (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J=7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 2.98-2 90 (m, 4H), 2.63 (m, 2H), 2.35 (m, 1H), 2.32 (s, 3H), 1.87 (d, J=11 5 Hz, 1H) APCI MS *m/e* 174.2 [(M + 1)$^+$]. (HCl salt) mp 254-255 °C. Anal. Calcd. for $C_{12}H_{12}F_3N$ HCl.1/3H_2O C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.82; N, 5.15.

EXAMPLE 4

4-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J., Seibel, W. L., Reitz, T J. *J Org. Chem.* **1983**, *48*, 2321-2327 Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*. 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-trifluoromethylbromobenzene ^1H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 7 64 (d, J=8.0 Hz, 1H), 7.57 (d, J=8 0 Hz, 1H) 3 46 (m, 4H), 3.21 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 2 16 (d, J=11.5 Hz, 1H) APCI MS *m/e* 228.2 [(M + 1)$^+$] (HCl salt) mp 244-246 °C. Anal Calcd. for $C_{12}H_{12}F_3N$ HCl.1/3H_2O C, 53 44, H, 5 11, N, 5.19. Found C, 53.77, H, 4 82; N, 5.18

EXAMPLE 5

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6 3 1 0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (Grunewald, G L.; Markovich, K M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene ^1H NMR (400 MHz, CD_3OD) δ 7.65 (s, 2H), 7.52 (m, 1H), 3.65 (br s, 1H), 3 49-3 43 (m, 3H). 3.20 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11 5 Hz, 1H) APCI MS *m/e* 228.2 [(M + 1)$^+$] (HCl salt) mp 275-277 °C.

EXAMPLE 6

3-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2,6-Difluoroiodobenzene (Roe, A. M.; Burton, R. A., Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968,** *11*, 814-819. Tamborski, C.; Soloski, E. *J. Org. Chem.* **1966**, *31*, 746-749. Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* **1986**, *29*, 1972-1982.) 1,3-Difluorobenzene (57.05 g, 0.5 M) in THF (75 mL) was added to a -78 °C stirred solution of n-butyllithium (n-BuLi) (200 mL, 2.5 M/hexanes, 0.5 M) and THF (500 mL) under N_2. By controlling the addition rate the internal temperature was maintained below -70 °C. The total addition time was ~1/2 hour. The resulting slurry was stirred an additional 1/2 hour, then the dispersion was treated with a solution of iodine (126.9 g, 0.5 M) in THF (300 mL) at a rate that maintained an internal temperature below -70 °C. After complete addition the mixture was allowed to warm to room temperature, and was treated with H_2O (100 mL) and 10% aqueous $Na_2S_2O_3$ solution (100 mL) and stirred. The layers were separated and the aqueous layer extracted with hexanes (2 x 250 mL). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4) filtered and concentrated to give a yellow oil (106.5 g). Distillation at ~1-5 mm at ~80 °C provided a light yellow oil (89.5 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H), 6.87 (m, 2H). GCMS *m/e* 240 (M^+).

B) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene

A solution of 2,6-difluoroiodobenzene (5.0 g, 20.8 mmol) and cyclopentadiene (2.07 g, 31.3 mmol) was stirred at 0 °C in P. ether (70 mL, 40-60 °C) under N_2 and treated with n-BuLi (8.74 mL, 2.5M in hexanes, 21.8 mmol) dropwise over 10 minutes. The reaction was quenched after 15 minutes by addition of aqueous 1N HCl solution and the product was extracted with hexanes (3 x 50 mL). The combined organic layer was washed with H_2O (50 mL), saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on Silica gel provided product as an oil (1.5 g, 45%) (TLC hexanes R_f 0.55). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (ddd, J=7.0,1.0,0.8 Hz, 1H), 6.96 (ddd, J=8.5,8.3,7.0 Hz, 1H), 6.86 (br s, 2H), 6.72 (ddd, J=8.5,8.3,0.8 Hz, 1H), 4.25 (br s, 1H), 3.98 (br s, 1H), 2.36 (ddd, J=7.2,1.7,1.7 Hz, 1H), 2.30 (ddd, J=7.2,1.7,1.5 Hz, 1H). GCMS *m/e* 160 (M^+).

C) 3-Fluoro-10-aza-tricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

The title compound was prepared by the methods described in Example 2B,C,D starting with 5-fluoro-1,4-dihydro-1,4-methano-naphthalene. ^{1}H NMR (400 MHz, CD_3OD) δ 7 36 (ddd J=8.3,7.3,5.0 Hz, 1H), 7.21 (d. J=7.3 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 3.62 (br s, 1H), 3.42-3.30 (m, 3H), 3.21 (m, 2H), 2.38 (m, 1H), 2.12 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.4 [(M + 1)$^+$]. mp 269-271 °C.

EXAMPLE 7

4-NITRO-10-AZATRICYCLO[6.3 1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(10-Aza-tricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (12.4 g, 63.9 mmol) was stirred in CH_2Cl_2 (200 mL). This was cooled (ice bath) and treated with pyridine (12.65 g 160 mmol) followed by trifluoroacetic anhydride (TFAA) (16.8 g, 11.3 mL, 80 mmol) from an addition funnel over 10 minutes. After ~3 hours, the solution was poured into 0.5N aqueous HCl (200 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with 0.5N aqueous HCl (50 mL), H_2O (2 x 50 mL) and saturated aqueous $NaHCO_3$ solution (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 which crystallized to give white needles (15.35 g, 60.2 mmol, 94%). (TLC 30% EtOAc/hexanes R_f 0.53). ^{1}H NMR (400 MHz $CDCl_3$) δ 7 18 (m, 4H), 4.29 (br d, J=12.6 Hz, 1H), 3 84 (br d, J=12.6 Hz, 1H), 3.51 (dd, J=12 6,1.5 Hz, 1H), 3.21 (br s, 1H), 3.10 (br s, 1H), 3.10 (br d, J=12.6 Hz, 1H), 2.37 (m, 1H), 1 92 (d, J=10.8 Hz, 1H). GCMS *m/e* 255 (M$^+$). mp 67-68 °C.

B) 1-(4-Nitro-10-aza-tricyclo[6 3 1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described by Coon, C. L., Blucher, W G , Hill, M. E. *J Org Chem.* **1973**, *25*, 4243)

To a solution of trifluoromethanesulfonic acid (2 4 ml, 13.7 mmol) in CH_2Cl_2 (10 ml) stirred at 0 °C was slowly added nitric acid (0.58 ml, 27 4 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to -78 °C and treated with 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.5 g, 13.7 mmol) in CH_2Cl_2 (15 ml) dropwise from an addition funnel over 5 minutes. The reaction was stirred at -78 °C for 30 minutes then warmed to 0 °C for 1 hour. The reaction mixture was poured into a vigorously stirred ice (100 g) The layers were separated and the aqueous layer

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 saturated aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to give an orange oil that solidified on standing (4.2 g). Chromatography yielded pure product as a crystalline solid (3.2 g, 78%). (TLC 30% EtOAc/hexanes R_f 0.23). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J=8.0 Hz, 1H), 8.08 (br s, 1H), 7.37 (br d, J=8.0 Hz, 1H), 4.38 (br d, J=12.6 Hz, 1H), 3.94 (br d, J=12.6 Hz, 1H), 3.59 (br d, J=12.6 Hz, 1H), 3.43-3.35 (m, 2H), 3.18 (br d, J=12.6 Hz, 1H), 2.48 (m, 1H), 2.07 (d, J=10.8 Hz, 1H). GCMS *m/e* 300 (M^+).

C) 4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (182 mg, 0.61 mmol) was stirred with Na_2CO_3 (160 mg, 1.21 mmol) in MeOH (3 mL) and H_2O (1 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with CH_2Cl_2. The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with CH_2Cl_2 (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3(s) and product was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug and concentrated to an oil. This was dissolved in MeOH and treated with 1N HCl MeOH, concentrated to solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (73 mg, 50%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.38). ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8 18 (dd, J=8.0,2.0 Hz, 1H), 7 59 (d, J=8.0 Hz, 1H), 3 43 (br s, 2H), 3.28 (m, 2H), 3.07 (dd, J= 13 0,13 0 Hz, 2H), 2.24 (m, 1H), 2.08 (d, J=11.5 Hz, 1H) APCI MS m/e 205.1 [(M + 1)$^+$] mp 265-270 °C

EXAMPLE 8

4-AMINO-10-AZATRICYCLO[6.3 1 0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (500 mg, 2.08 mmol) was stirred in 1,4-dioxane (40 mL) and treated with saturated aqueous Na_2CO_3 solution (15 mL) To this was added di-t-butyldicarbonate (1.8 g, 8 31 mmol) After stirring 18 hours the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried through a cotton plug and concentrated to provide an oil (500 mg, 91%)

This oil (500 mg, 1 64 mmol) was dissolved in MeOH (30 mL), treated with 10%Pd/C (~50 mg) and hydrogenated under a H_2 atmosphere (45 psi) for 1 hour The mixture was filtered through a Celite pad and concentrated to a clear oil (397 mg, 88%)

This oil (50 mg, 0.18 mmol) was stirred in 3N HCl EtOAc (3 mL) for 2 hours then concentrated to a white solid (25 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.10 (3H), 3.60 (br s, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.18 (m, 1H), 1.98 (d, J=11.5 Hz, 1H). APCI MS m/e 175.1 [(M + 1)$^+$] mp 189-192 °C.

EXAMPLE 9

N^1-[10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL]ACETAMIDE HYDROCHLORIDE

A) 1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Hydrogenation of 1-(4-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.0 g, 6.66 mmol) under a H_2 atmosphere (40 psi) and 10%Pd/C (200 mg) in MeOH over 1.5 hours, filtration through Celite and concentration affords a yellow oil (1.7 g). (TLC 50% EtOAc/hexanes R_f 0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 1H), 6.64 (br s, 1H), 6.57 (m, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.17-3.07 (m, 3H), 2.35 (m, 1H), 1.90 (d, J=10.8 Hz, 1H). GCMS *m/e* 270 (M$^+$).

B) N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-acetamide

1-(4-Amino-10-aza-tricyclo[6.3 1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (850 mg, 3.14 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with triethyl amine (0.53 mL, 3.76 mmol) and acetyl chloride (0.23 mL, 3.2 mmol) then stirred 18 hours. Standard $NaHCO_3$ workup yielded an oil which was chromatographed to provide a clear oil (850 mg, 87%). (50% EtOAc/hexanes R_f 0 28).

C) N^1-[10-Azatricyclo[6.3.1 0^{2,7}]dodeca-2(7),3,5-trien-4-yl]acetamide hydrochloride

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-acetamide (100 mg, 0.32 mmol) was stirred with Na_2CO_3 (70 mg, 0.64 mmol) in MeOH (10 mL) and H_2O (2 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with EtOAc The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with EtOAc (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3 (s) and product was extracted with EtOAc (3 x 20 mL). The organic layer was dried (sodium sulfate (Na_2SO_4)) and concentrated to an oil This material was dissolved in MeOH and treated with 3N HCl EtOAc (3 mL), concentrated and recrystallized

from MeOH/Et_2O to provide a solid (40 mg, 50%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.02 (br m, NH), 7.65 (s, 1H), 7.55 (br s, NH), 7.38 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 3.33 (m, 4H), 2.96 (m, 2H), 2.13 (m, 1H), 2.00 (s, 3H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 217.2 [(M + 1)$^+$]. mp 225-230 °C.

EXAMPLE 10

6-METHYL-5-THIA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) N-(10-Trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide (850 mg, 2.72 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.1 g, 2.72 mmol) were combined in toluene (10 mL) and brought to reflux for 1.5 hours. After cooling the reaction was worked up with EtOAc/saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to produce product (410 mg, 44%) (50% EtOAc/hexanes R_f 0.38)

B) 6-Methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

The above oil, 2,2,2-trifluoro-N-(10-trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide, (360 mg, 1.05 mmol) was dissolved in MeOH (10 mL) and 1N NaOH (5 mL) and added to potassium ferricyanide ($K_3Fe(CN)_6$)(1.72 g, 5.23 mmol) in H_2O (10 mL). This mixture was warmed to 60 °C for 1.5 hours, cooled, concentrated and worked up with EtOAc/H_2O This material was stirred in dioxane (20 mL) and treated with H_2O (50 mL) and Na_2CO_3 to achieve pH 10. To this was added di-t-butyldicarbonate (436 mg, 2.0 mmol) and the mixture was stirred for 18 hours. The reaction was concentrated, treated with H_2O and extracted with CH_2Cl_2. The product was chromatographed (Silica 30% EtOAc/hexanes R_f 0.41) to yield an oil (100 mg).

The above product was treated with 3N HCl/EtOAc (3 mL) and warmed to reflux for ~15 minutes then concentrated to a solid which was azeotroped with CH_2Cl_2 (2x). These solids were dissolved in a minimum amount of MeOH then saturated with Et_2O and stirred. The resulting white crystalline powder was collected by filtration (40 mg, 14%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, NH), 7.65 (s, 1H), 7 82 (s, 1H), 7.65 (br m, NH), 3.36 (m, 2H), 3.24 (m, 2H), 3.02 (m, 2H), 2.76 (s, 3H), 2.23 (m, 1H), 2.06 (d, J=10.8 Hz, 1H). APCI MS *m/e* 231.1 [(M + 1)$^+$] mp 183-184 °C.

EXAMPLE 11

4,5-DINITRO-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE

A) 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described in Coon, C. L.; Blucher, W G.; Hill, M. E. *J. Org. Chem.* **1973**, *25*, 4243. For an additional related example of dinitration see: Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512.)

To a solution of trifluoromethanesulfonic acid (79.8 ml, 902.1 mmol) in CH_2Cl_2 (550 ml) stirred at 0 °C was slowly added nitric acid (19.1 ml, 450.9 mmol) generating a white precipitate. After 10 minutes, 1-(10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (50 g, 196 mmol) in CH_2Cl_2 (300 ml) was added dropwise from an addition funnel over 30 minutes. The reaction was stirred at 0 °C for 2.5 hours and then stirred at room temperature for 24 hours. The reaction mixture was poured into a vigorously stirred mixture of H_2O (500 ml) and ice (400 g). The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3 x 300 ml). The organic layer was combined and washed with H_2O (3 x 300 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution (200 mL) and H_2O (200 mL) then dried through a cotton plug and concentrated to solids Trituration with EtOAc/hexanes produced off white solids which were filtered and dried (52 g, 151 mmol, 77% The mother liquor was chromatographed to give an additional 4.0 g for a total of 56.0 g (82.8%). (TLC 50% EtOAc/hexanes R_f 0.29) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 77 (s, 1H), 7.75 (s, 1H), 4 39 (br d, J=13.0 Hz, 1H), 3.98 (br d, J=13.0 Hz, 1H), 3.65 (d, J=13.0 Hz, 1H), 3.49 (br s, 1H), 3 44 (br s, 1H), 3 24 (br d, J=12.6 Hz, 1H), 2.53 (m, 1H), 2.14 (d, J=11 5 Hz, 1H). GCMS *m/e* 345 (M$^+$)

B) 4,5-Dinitro-10-aza-tricyclo[6.3.1 0^{2,7}]dodeca-2(7),3,5-triene

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.7 g, 10 7 mmol) and Na_2CO_3 (2.3 g, 21.4 mmol) were combined in MeOH (50 mL) and H_2O (20 mL) then warmed to reflux for 18 hours. The reaction was cooled, concentrated, treated with H_2O and extracted with CH_2Cl_2 (3 x 50 mL) then dried through a cotton plug After concentration, the residue was chromatographed to provide brown solids. (1.9 g, 71%)

(TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.36). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 3.17 (br s, 2H), 3.11 (d, J=12.6 Hz, 2H), 2.53 (m, 1H), 2.07 (d, J=11 0 Hz, 1H) GCMS *m/e* 249 (M^+).

EXAMPLE 12

6-METHYL-7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3 1 $0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene, (1.9 g, 7.6 mmol) was stirred in 1,4-dioxane (75 mL) and treated with saturated aqueous Na_2CO_3 solution (10 mL). To this was added di-t-butyldicarbonate (3.31 g, 15.2 mmol). After stirring 6 hours the reaction was treated with H_2O (50 mL) and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide product (1.9 g, 71%). (TLC 30% EtOAc/hexanes (NH_3) R_f 0 58). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.72 (br s, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.39 (br s, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.46 (m, 1H), 2.02 (d, J=11.0 Hz, 1H).

B) 4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7) 3,5-triene-10-carboxylic acid tert-butyl ester (1.9 g, 5 44 mmol) was hydrogenated in MeOH under a H_2 atmosphere (45 psi) over 10%Pd/C (100 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (1.57 g, 100%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0 14)

C) 6-Methyl-5,7,13-triazatetracyclo[9.3 1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E., Chenard, B. L.; Macor, J. E., Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897)

4,5-Diamino-10-aza-tricyclo[6 3 1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (700 mg, 2 42 mmol) was dissolved in EtOH (10 mL) and acetic acid (HOAc) (1 mL) and treated with 1-ethoxyethylenemalononitrile (329 mg, 2 42 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried (Na_2SO_4) After filtration and concentration, the residue was

chromatographed to provide brown solids (247 mg, 36%) (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28).

D) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Pilarski, B. *Liebigs Ann. Chem.* **1983**, 1078.)

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (80 mg, 0.267 mmol) was stirred in 50% aqueous NaOH solution (3 mL) and DMSO (1 mL) then treated with 1-iodopropane (0.03 mL, 0.321 mmol). This mixture was warmed to 40 °C for 2 hours then cooled, treated with H_2O and extracted with EtOAc. The organic layer was washed with H_2O (3x) then dried (Na_2SO_4), filtered and concentrated to an oil (90 mg, 0.253 mmol). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.15).

E) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (90 mg, 0.253 mmol) was dissolved in 3N HCl EtOAc (5 mL) and warmed to 100 °C for 1/2 hour. The mixture was cooled, concentrated, slurried in EtOAc, and filtered to provide a white solid (25 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, NH), 7.91 (s, 1H), 7.83 (br m, NH), 7.74 (s, 1H), 4.38 (m, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.10 (m, 2H), 2.87 (s, 3H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H) 1.85 (m, 2H), 0.97 (m, 3H). mp 147-150 °C.

EXAMPLE 13

5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E., Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.0 g, 3.45 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and treated with ethoxymethylenemalononitrile (421 mg, 3.45 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried

(Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (580 mg, 56%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28)

B) 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.95 (s, 1H), 7.67 (s, 2H), 3.45 (br s, 2H), 3.31 (d, J=12.5 Hz, 2H), 3.13 (d, J=12.5 Hz, 2H), 2.30 (m, 1H), 1.99 (d, J=11.5 Hz, 1H). APCI MS m/e 200.1 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 14

7-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.97 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 3.94 (s, 3H), 3.48 (m, 2H), 3.33 (d, J=12.2 Hz, 2H), 3.14 (d, J=12.2 Hz, 2H), 2.34 (m, 1H), 2.03 (d, J=11.5 Hz, 1H). APCI MS m/e 214.2 [(M + 1)$^+$].

EXAMPLE 15

6-METHYL-5,7,13-TRIAZATETRACYCLO[9 3.1 $0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

6-Methyl-5,7,13-triazatetracyclo[9.3.1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9 40 (br m, NH), 7.77 (br m, NH), 7.70 (s, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.05 (br d, J=11 0 Hz, 2H), 2.79 (s, 3H), 2.23 (m, 1H), 2.10 (d, J=10.8 Hz, 1H). GCMS m/e 213.5 (M$^+$).

EXAMPLE 16

6,7-DIMETHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl

ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, NH), 7 84 (s, 1H), 7.82 (br m, NH), 7.72 (s, 1H), 3.90 (s, 3H), 3 45 (m, 2H), 3.28 (m, 2H), 3.04 (m, 2H), 2.82 (s, 3H), 2.23 (m, 1H), 2.12 (d, J=11 0 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$] mp 225-230 °C.

EXAMPLE 17

7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodopropane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 9.45 (br s, NH), 7.97 (s, 1H), 7.85 (s, 1H), 7 83 (br m, NH), 4.43 (m, 2H), 3 49 (m, 2H), 3.33 (m, 2H), 3.08 (m, 2H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.92 (m, 2H), 0.93 (m, 3H). APCI MS *m/e* 242.2 [(M + 1)$^+$]. mp 170-171 °C (subl.).

EXAMPLE 18

7-BUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1 0^{2,10} 0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4-Butylamino-5-nitro-10-aza-tricyclo[6.3 1 0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (For conditions, see; Senskey, M D.; Bradshaw, J. D., Tessier, C A., Youngs, W. J. *Tetrahedron Lett.* **1995**, *36*, 6217.)

4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (500 mg, 1 43 mmol) and 1-butylamine (1 42 mL, 14 3 mmol) were combined in THF (5 mL) and stirred 4 hours. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (3 x 30 mL) then dried (Na_2SO_4), filtered and concentrated to an oil. This oil was passed through a Silica gel filter column to remove baseline impurities eluting with 30% EtOAc/hexanes (510 mg, 1.41 mmol, 99%).

B) 4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (460 mg, 1.27 mmol) was treated with ammonium formate (850 mg, 12.7

mmol) and 10%$Pd(OH)_2$/C (50 mg) in MeOH (20 mL) and brought to reflux for 1 hour then filtered through a Celite pad and concentrated. The solids were treated with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 (3 x 30 mL) and dried by filtration through a cotton plug to give an oil (440 mg, 100%)

C) 7-Butyl-5,7,13-triazatetracyclo[9 3 1 $0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (440 mg, 1.27 mmol) was dissolved in EtOH (20 mL) and HOAc (2 mL) and treated with ethoxymethylenemalononitrile (186 mg, 1.52 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated, treated with H_2O and saturated aqueous Na_2CO_3 solution then extracted with EtOAc (3 x 50 mL) and dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide a yellow oil (400 mg, 89%) (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0 70)

D) 7-Butyl-5,7,13-triazatetracyclo[9.3 1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (brs, NH), 9.68 (s, 1H), 7.99 (s, 1H), 7 92 (br m, NH), 7.87 (s, 1H), 4.50 (m, 2H), 3 49 (m, 2H), 3.30 (m. 2H), 3 08 (m, 2H), 2.26 (m, 1H), 2 15 (d, J=11 0 Hz, 1H), 1 88 (m, 2H), 1.32 (m, 2H), 0.82 (t, J=7 0 Hz, 3H) APCI MS *m/e* 256 2 [(M + 1)$^+$] mp 204-208 °C

EXAMPLE 19

7-Isobutyl-5,7,13-triazatetracyclo[9.3.1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

4,5-Dinitro-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and isobutylamine were converted to the title compound utilizing the methods described in Example 18A-D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 74 (s, 1H), 7 52 (s, 1H), 7.14 (s, 1H), 3 90 (dd, J=7.5,2.0 Hz, 2H), 3.04-2 97 (m, 4H), 2.70 (dd, J=12.8,2.3 Hz, 2H), 2.42 (m, 1H), 2 19 (m, 1H), 1.98 (d, J=10.5 Hz, 1H), 0.93 (m, 6H) APCI MS *m/e* 256.2 [(M + 1)$^+$]. mp 147-150 °C (subl.).

EXAMPLE 20

6-METHYL-7-ISOBUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Amino-5-isobutylamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (250 mg, 0.74 mmol) from Example 19B was dissolved in EtOH (10 mL) and HOAc (2 mL) and treated with 1-ethoxyethylenemalononitrile (118 mg, 0.87 mmol). The reaction proceeded as in Example 18C (18h) and was worked up similarly to provide product (TLC 3% MeOH/CH_2Cl_2 (NH_3) R_f 0.57).

B) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. APCI MS *m/e* 270 3 [(M + 1)$^+$] mp 129-130 °C (subl.)

EXAMPLE 21

7-PHENYL-5,7,13-TRIAZATETRACYCLO[9 3 1 $0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to 4-phenylamino-5-nitro-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl at 75 °C for 4 hours in the coupling step. This was then converted to the title compound utilizing the methods described in Example 18B,C,D ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (1H), 7 78-7.57 (m, 7H), 3 47-3.00 (m, 6H), 2.23 (m, 1H), 2.09 (d, J=11 5 Hz, 1H). APCI MS *m/e* 276.2 [(M + 1)$^+$]. mp 210-213 °C.

EXAMPLE 22

6-METHYL-7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and Example 20, 4,5-dinitro-10-aza-tricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were

converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.73-7.56 (m, 5H), 7.32 (s, 1H), 3.46-2.99 (m, 6H), 2.66 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). APCI MS *m/e* 290.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 23

7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10} 0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A-D, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. t-Boc precursor GCMS *m/e* 369 (M$^+$). (HCl salt) mp >250 °C.

EXAMPLE 24

6-METHYL-7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10} 0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s ,1H), 7 27 (s ,1H), 7.02 (br s, , NH), 4 41 (t, J=13.0 Hz, 2H), 3.90 (s, 3H), 3.47-3.26 (m, 6H), 2.20 (m, 1H), 2.00 (d, J=11 5 Hz, 1H), 0.90 (s, 9H). t-Boc precursor APCI MS *m/e* 384.2 [(M + 1)$^+$] mp >250 °C.

EXAMPLE 25

6,7-DIMETHYL-5,8,14-TRIAZATETRACYCLO[10 3 1.0^{2,11} 0^{4,9}]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE (Based on the following procedure: Jones, R G.; McLaughlin, K. C. *Org. Syn.* **1963**, *4*, 824. b) Ehrlich, J., Bobert, M. T. *J. Org. Chem.* **1947**, 522.)

4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (100 mg, 0.35 mmol) was warmed to 80 °C in H_2O (5 mL). To this butane 2,3-dione (0.034 mL, 0.38 mmol) was added under N_2 for 2 hours. The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml) The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an oil (120 mg, 100%) The oil was dissolved in 2N HCl MeOH (5 mL) and warmed to reflux for 30 minutes, then concentrated. Recrystallization from MeOH/Et_2O provided a white powder (50 mg, 43%) (TLC EtOAc R_f 0 14) ^{1}H NMR (400 MHz, DMSO-d_6)

δ 7.85 (s, 2H), 3.50 (br s, 2H), 3.32 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.64 (s, 6H), 2.24 (m, 1H), 2.13 (d, J=11.0 Hz, 1H). t-Boc precursor APCI MS *m/e* 340.3 [(M + 1)$^+$].

EXAMPLE 26

5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$ $0^{4,9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

A) 1-(4,5-Diamino-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.0 g, 8.70 mmol) was hydrogenated in MeOH (30 ml) under H_2 (45 psi) over $Pd(OH)_2$ (300 mg of 20 wt%/C, 10%wt). After 2.5 hours the reaction was filtered through a Celite pad and rinsed with MeOH (30 ml). The solution was concentrated to a light brown oil which crystallized (2.42 g, 96%). (TLC 10% MeOH/CH_2Cl_2 R_f 0.56). APCI MS *m/e* 286.2 [(M + 1)$^+$] mp 129-131 °C.

B) 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$ $0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.75 mmol) was stirred in THF (2 ml). This mixture was treated with H_2O (2 mL) and glyoxal sodium bisulfite addition compound hydrate (931 mg, 3.50 mmol) then stirred at 55 °C for 2.5 hours The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml) The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an off white powder (329 mg, 60%) (TLC 25% EtOAc/hexanes R_f 0 40). mp 164-166 °C.

C) 5,8,14-Triazatetracyclo[10 3 1.$0^{2,11}$ $0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene hydrochloride

1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (320 mg, 1.04 mmol) was slurried in MeOH (2.0 ml) and treated with Na_2CO_3 (221 mg, 2.08 mmol) in H_2O (2.0 ml) The mixture was warmed to 70 °C for 2 hours, then concentrated, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 ml) The organic layer was dried through a cotton plug and concentrated to give a light yellow oil (183 mg, 83%) which solidified upon standing (mp 138-140 °C). This material was dissolved in MeOH (10 mL), treated with 3M HCl/EtOAc (3 ml), concentrated and azeotroped with MeOH

(2 x 20 mL) to give solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (208 mg, 97%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (400 MHz, CD_3OD) δ 8.94 (s, 2H), 8.12 (s, 2H), 3.70 (m, 2H), 3.54 (d, J=12.5 Hz, 2H), 3.35 (d, J=12.5 Hz, 2H), 2.49 (m, 1H), 2.08 (d, J=11.0 Hz, 1H) GCMS *m/e* 211 (M^+). mp 225-230 °C.

EXAMPLE 27

14-METHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2.11}$.$0^{4.9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

5,8,14-Triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene (207 mg, 0.98 mmol) was treated with 37% aqueous formaline solution (1 mL) and formic acid (1 mL) then warmed to 80 °C for 1 hour. The reaction was poured into water, made basic (NaOH, pH ~11) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on Silica gel to provide a yellow solid. This was stirred in MeOH (2 mL) and treated with 3N HCl EtOAc (2 mL). After concentration the solids were recrystallized from MeOH/Et_2O to afford product as a white solid (70 mg, 27%). (2% MeOH/CH_2Cl_2 (NH_3) R_f 0.47). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 7.80 (s, 2H), 3 37 (br s, 2H), 3.03 (m, 2H), 2.47 (m, 2H), 2.32 (m, 1H), 2.18 (br s, 3H), 1.84 (d, J=11.0 Hz, 1H). APCI MS *m/e* 226.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 28

5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2.10}$.$0^{4.8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (900 mg, 2.61 mmol) and potassium acetate (KOAc) (2.6 g, 26.1 mmol) were dissolved in DMSO (10 mL) and warmed with stirring to 100 °C for 16 hours. The mixture was cooled and diluted with H_2O (50 mL) then extracted with 80% EtOAc/hexanes (6 x 25 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and purified by chromatography to give an oil (575 mg, 70%) (TLC 50% EtOAc/hexanes (NH_3) R_f 0.56)

B) 2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6 3 1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (575 mg, 1.82 mmol) was hydrogenated in MeOH under a H_2 atmosphere at (45 psi) over 10%Pd/C (80 mg) for 1 5 hours then filtered through a Celite pad and concentrated to white solids (450 mg, 86%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.6). ^{1}H NMR (400 MHz, CD_3OD) δ 6.67-6.59 (m, 2H), 4.12 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.24 (m, 1H), 1.94 (d, J=10.5 Hz, 1H). GCMS *m/e* 286 (M^+).

C) 2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* **1990**, *27*, 335)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), trimethyl orthoformate (0.19 mL, 1.73 mmol) pyridinium-p-toluenesulfonic acid (PPTS, 18 mg, 0 07 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. The mixture was cooled, treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered, concentrated and purified by chromatography to give an oil (110 mg, 71%). (TLC 20% EtOAc/hexanes R_f 0.40)

D) 5-Oxa-7,13-diazatetracyclo[9.3 1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3 1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (110 mg, 0 37 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (78 mg, 0.74 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into aqueous 1N HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. The product was extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4), concentrated and chromatographed on Silica gel to produce an oil. (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0 19).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes After 18 hours, the product was collected by filtration (55 mg, 63%). ^{1}H NMR (400 MHz, CD_3OD) δ 8 47 (s, 1H), 7.70 (s 1H), 7 65 (s, 1H), 3.41 (m, 2H), 3.30 (m, 2H), 3 10 (d, J=12.5 Hz, 2H), 2.47 (m, 1H), 2.15 (d, J=11 0 Hz, 1H) APCI MS *m/e* 201.03 [$(M + 1)^+$]

EXAMPLE 29

6-METHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3 1 $0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), triethyl orthoacetate (0.34 mL, 1.83 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. Workup, isolation and purification as in Example 28C provided the title compound (90 mg, 55%).

B) 6-Methyl-5-oxa-7,13-diazatetracyclo[9.3.1 $0^{2,10}$ $0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (90 mg, 0.30 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (61 mg, 0.58 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The solution was dried (Na_2SO_4), concentrated, and chromatographed on Silica gel to produce an oil. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.18). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ 7 40 (s, 1H), 7.26 (s, 1H), 3.05-2.98 (m, 4H), 2.72 (d, J=12.8 Hz, 2H), 2.59 (s, 3H), 2 46 (m, 1H), 1.98 (d, J=10.5 Hz, 1H)

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes After 18 hours, the product was collected by filtration (10 mg, 13%) APCI MS *m/e* 215.2 [(M + 1)$^+$] mp >250 °C.

EXAMPLE 30

2-FLUORO-N-(5-HYDROXY-10-AZA-TRICYCLO[6.3.1 $0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-BENZAMIDE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), 2-fluorobenzoyl chloride (0.07 mL, 0.576 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol), pyridine (0.046 mL, 0.576 mmol) and xylenes (5 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. After 24 hours, additional PPTS (50 mg) was added and the material stirred at 135 °C for an additional 24 hours Workup as above provided crude product (145 mg, 0.375 mmol) which was

combined with Na_2CO_3(s) (80 mg, 0.75 mmol) in MeOH (5 mL) and H_2O (2 mL) and heated to reflux After 3 hours, the reaction was cooled and diluted with water then extracted with CH_2Cl_2 (4 x 40 mL), dried through a cotton plug then chromatographed to remove baseline impurity (5% MeOH/CH_2Cl_2 (NH_3)). The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of MeOH and the solution was saturated with Et_2O and stirred. After stirring 4 hours the product was collected by filtration (85 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (m, 2H), 7.59 (m, 1H), 7.36-7.23 (m, 2H), 6.82 (s, 1H), 2.99 (m, 4H), 2.78 (m, 2H), 2.35 (m, 1H), 1 96 (d, J=10.5 Hz, 1H). APCI MS *m/e* 313 1 [(M + 1)$^+$]. mp 125-130 °C (subl.).

EXAMPLE 31

4-CHLORO-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4-Chloro-10-aza-tricyclo[6.3 1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Copper(I)chloride (CuCl) was prepared as follows: $CuSO_4$ (4 3 g) and NaCl (1.2 g) were dissolved in hot H_2O (14 mL) sodium bisulfite ($NaHSO_3$) (1 g) and sodium hydroxide (NaOH) (690 mg) were dissolved in H_2O (7 mL) and added to the hot acidic solution over 5 minutes. The precipitated white solids were filtered and washed with water.

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (460 mg, 1.7 mmol) was dissolved in H_2O (2 mL) and concentrated HCl solution(1 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (275 mg) in H_2O (1 mL) dropwise. To the resulting solution was added a CuCl (202 mg, prepared as described above, 2.04 mmol) in concentrated HCl solution (2 mL) over 10 minutes (gas evolution observed) The resulting solution was warmed to 60 °C for 15 minutes, then was cooled to room temperature and extracted with EtOAc (4 x 30 mL) After drying over Na_2SO_4, the solution was filtered and concentrated to an oil which was filtered through a Silica pad to remove baseline material eluting with 50% EtOAc/hexanes to give an oil (470 mg, 95%).

B) 4-Chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (470 mg, 1 62 mmol) and Na_2CO_3 (344 mg, 3.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were heated to reflux After 2 hours, the reaction was cooled and diluted with water then extracted with EtOAc (4 x 40 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude material was treated with excess 3N HCl EtOAc and concentrated, then

dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred. After stirring 4 hours the product was collected by filtration (155 mg, 42%). ^1H NMR (free base) (400 MHz, $CDCl_3$) δ 7 15 (m, 2H), 7.09 (d, J=8.0 Hz, 1H), 3.00-2.94 (m, 4H), 2.68, (m, 2H), 2.38 (m, 1H), 1.92 (d, J=10.5 Hz, 1H). ^1H NMR (HCl salt) (400 MHz, DMSO-d_6) δ 7.30-7.20 (m, 3H), 3.30-3.15 (m, 6H), 2.37 (m, 1H), 1.89 (d, J=11.0 Hz, 1H). APCI MS *m/e* 194.1 [(M + 1)$^+$].

EXAMPLE 32

10-AZATRICYCLO[6 3.1.0~2,7~]DODECA-2(7),3,5-TRIEN-4-YL CYANIDE HYDROCHLORIDE

A) 1-(4-Iodo-10-aza-tricyclo[6 3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.85 mmol) was dissolved in H_2O (5 mL) and concentrated H_2SO_4 solution (0.5 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (140 mg, 2.04 mmol) in H_2O (2 mL) dropwise. Potassium iodide (460 mg, 2.78 mmol) in 1N H_2SO_4 solution (0.5 mL) was added over 10 minutes (reaction becomes dark red). The resulting solution was warmed to room temperature and stirred 18 hours. The reaction was quenched with $NaHSO_3$ and water (pH 2.5) then extracted with EtOAc (4 x 30 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to a yellow oil which was chromatographed on Silica gel to provide a yellow oil. (260 mg, 37%). (TLC 30% EtOAc/hexanes R_f 0.70). (A 5 4 g scale performed as above yielded 5 g, 67%).

B) 4-Iodo-10-aza-tricyclo[6.3 1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (5 g, 13.1 mmol) and 37% saturated aqueous NH_4OH solution (50 mL) were stirred in MeOH (250 ml) for 2 hours then concentrated and azeotroped with MeOH (2 x 50 mL). The resulting product was stirred in 1,4-dioxane (75 mL) and treated with saturated Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (5.71 g, 26.2 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel (TLC 20% EtOAc/hexanes) to provide product as an oil (4.9 g, 98%).

C) 4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (Utilizing the methods described in House, H. O.; Fischer, W. F. *J. Org. Chem* **1969**, 3626.)

CuCN (108 mg, 1.21 mmol) and NaCN (59 mg, 1.21 mmol) were combined in dry DMF (6 mL) and warmed to 150 °C under N_2 Solution occurs in 20 minutes. To this was added 4-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (232 mg, 0.6 mmol) in DMF (3.5 mL) and the mixture was stirred for 18 hours at 150 °C. The reaction was cooled and diluted with 50% saturated aqueous NaCl solution and extracted with 50% EtOAc/hexanes (3 x 30 mL). After drying (Na_2SO_4), filtration and concentration the product was isolated by chromatography (86 mg, 50%). (TLC 20% EtOAc/hexanes R_f 0.28).

D) 10-Azatricyclo[6.3.1.0~2,7~]dodeca-2(7),3,5-trien-4-yl cyanide hydrochloride

4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester was treated with 3N HCl EtOAc (6 mL) and warmed to reflux for 2 hours, then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred 18 hours The product was collected by filtration (49 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (br s. NH), 7 86 (br s, NH), 7.74-7.70 (m, 2H), 7.49 (d, J=7 5 Hz, 1H), 3.33-2.97 (m, 6H), 2.17 (m, 1H), 2.01 (d, J=11.0 Hz, 1H). GCMS *m/e* 184 (M^+) mp 268-273 °C.

EXAMPLE 33

3-(10-AZATRICYCLO[6 3 1 $0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-5-METHYL-1,2,4-OXADIAZOLE HYDROCHLORIDE

4-Cyano-10-aza-tricyclo[6 3.1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (300 mg, 1 1 mmol) was stirred in EtOH (10 mL) To this hydroxyl amine hydrochloride (382 mg, 5.5 mmol) and NaOH (242 mg, 6 05 mmol) were added and the mixture was warmed to reflux. After 45 minutes, the reaction was cooled, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid (110 mg, 0.35 mmol). This solid was dissolved in pyridine (1 mL) and treated with acetyl chloride (0.03 mL, 0 415 mmol) and warmed to 100°C for 18 hours. The reaction was cooled, treated with H_2O and extracted with EtOAc. The organic extracts were washed with water and saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel afforded product (50 mg, 0.15 mmol). (25% EtOAc/hexanes R_f 0.18) This product was treated with 2N HCl MeOH (10 mL), heated to 70 °C for 1 hour, cooled, concentrated and recrystallized from MeOH/Et_2O to provide product (15 mg). APCI MS *m/e* 242.2 [(M + 1)$^+$].

EXAMPLE 34

1-(10-AZATRICYCLO[6 3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-1-ETHANONE HYDROCHLORIDE

A) 1-(4-Acetyl-10-aza-tricyclo[6 3.1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(10-Aza-tricyclo[6.3 1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (253 mg, 1 0 mmol) and AcCl (0.68 mL, 10 mmol) were dissolved in DCE (3 mL) and treated with aluminum chloride ($AlCl_3$) (667 mg, 5.0 mmol). The resulting yellow mixture was stirred for 30 minutes then poured over ice and saturated aqueous $NaHCO_3$ solution. After stirring 20 minutes the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug then concentrated to a orange-yellow oil (255 mg, 86%).

B) 4-Acetyl-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-tnen-10-yl)-2,2,2-trifluoro-ethanone (1 3 g, 4.37 mmol) and 37% aqueous NH_4OH solution (10 mL) were stirred in MeOH (30 ml) for 3 hours, then concentrated and azeotroped with MeOH (2 x 50 mL). (This product could be converted to an HCl salt directly: see the next example.) The resulting product was stirred in 1,4-dioxane (20 mL) and treated with saturated aqueous Na_2CO_3 solution (5 mL). To this was added di-t-butyldicarbonate (1.91 g, 8.74 mmol). After stirring 2 hours, the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide an oil (1.3 g, 100%). (TLC 40% EtOAc/hexanes R_f 0.56)

C) 1-(10-Azatricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone hydrochloride

4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (190 mg, 0.63 mmol) was treated with excess 3N HCl EtOAc and warmed to 70°C for 1 hour then concentrated and dissolved in a minimum of MeOH The resulting solution was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (81 mg, 54%). ^1H NMR (400 MHz, DMSO-d_6) δ 9 75 (br s, NH), 7 89 (s, 1H), 7.88 (d, J=8 0 Hz, 1H), 7.74 (br s, NH), 7 44 (d, J=8 0 Hz, 1H), 3.33 (br s, 2H), 3.22 (br s, 2H), 3.00 (br m, 2H), 2 54 (s, 3H). 2.17 (m, 1H), 2.02 (d, J=11.0 Hz, 1H) GCMS *m/e* 201 (M^+). mp 198-202 °C.

EXAMPLE 35

10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-OL HYDROCHLORIDE

A) Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.5 g, 8.41 mmol) and 3-chloroperoxybenzoic acid (m-CPBA) (7.5 g, 42 mmol) were stirred in CH_2Cl_2 (20 mL) and warmed to 40°C for 18 hours. The mixture was cooled to room temperature, then treated with dimethylsulfide (Me_2S) (3 mL, 40.8 mmol) and stirred 24 hours. The resulting mixture was poured into ice and saturated aqueous Na_2CO_3 solution (100 mL) then extracted with Et_2O (4 x 40 mL). The organic layer was washed saturated aqueous Na_2CO_3 solution (3 x 40 mL) then dried (Na_2SO_4), filtered and concentrated to afford an oil (1.83 g, 69%). (TLC EtOAc R_f 0.80).

B) 2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (900 mg, 2.87 mmol) was stirred in MeOH (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) for 48 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Chromatography on Silica gel provided pure product (420 mg, 54%). (TLC 5% MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 1H), 6.70 (m, 1H), 6.62 (m, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.48 (m, 1H), 3.21 (br s, 1H), 3.16 (br s, 1H), 3.09 (m, 1H), 2.38 (m, 1H), 1.97 (d, J=11.0 Hz, 1H)

C) 10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol hydrochloride

2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (50 mg, 0.184 mmol) was dissolved in MeOH/H_2O (3/1, 5 mL), treated with Na_2CO_3(s) (40 mg, 0.369 mmol) and warmed to 65°C for 2 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Filtration through a Silica gel plug provided an oil (10% MeOH/CH_2Cl_2) which was treated with 3N HCl EtOAc (3 mL) then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (10 mg, 26%). ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.16 (d, J=8.0 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.72 (dd, J=8.0,2.0 Hz, 1H), 3.32-3.28 (4H), 3.09 (dd, J=14.5,12.0 Hz, 2H), 2.32 (m, 1H), 2.03 (d, J=11.0 Hz, 1H) APCI MS *m/e* 176.2 [(M + 1)$^+$] mp 308 (dec.) °C.

EXAMPLE 36

7-METHYL-5-OXA-6,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$ $0^{4,8}$]PENTADECA-2,4(8),6,9-TETRAENE HYDROCHLORIDE

A) 1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (800 mg, 2.55 mmol) was combined with $AlCl_3$ (1.0 g, 7.65 mmol) and warmed to 170°C for 2 hours. The mixture was cooled and treated with 1N aqueous HCl solution (20 mL), extracted with EtOAc and dried (Na_2SO_4). Chromatography affords an oil (190 mg, 24%). (TLC EtOAc R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 0.5H), 12.52 (s, 0.5H), 7.53 (s, 1H), 6.86 (s, 1H), 4 33 (m, 1H), 3.91 (m, 1H), 3.56 (m, 1H), 3.28 (br s, 1H), 3.24 (br s, 1H), 3.14 (m, 1H), 2.35 (m, 1H), 1.97 (br d, J=11.2 Hz, 1H).

B) 2,2,2-Trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6 3 1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone

1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3 1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (190 mg, 0.605 mmol), hydroxylamine HCl (99 mg, 1.21 mmol) and NaOAc (118 mg, 1.21 mmol) were combined in MeOH (4 mL) and H_2O (1 mL) and warmed to 65°C for 18 hours The mixture was cooled, diluted with H_2O and extracted with EtOAc which was dried (Na_2SO_4), filtered and concentrated to provide a yellow oil (177 mg, 93%).

C) 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3 1 $0^{2,10}$ $0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone

The above oil, 2,2,2-trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone (177 mg, 0 54 mmol) was stirred in DCE (3 mL), treated with triethylamine (0 4 mL, 2.8 mmol) and acetic anhydride (Ac_2O) (0.3 mL, 2.8 mmol) then stirred 18 hours. The reaction was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated to a yellow oil which was dissolved in anhydrous DMF (3 mL) and treated with 60% NaH in oil (32 mg, 1 08 mmol). After stirring 18 hours, additional 60% NaH in oil was introduced (33 mg) and the mixture was stirred 2 hours. The reaction was quenched with H_2O (5 mL) and extracted with 80% EtOAc/hexanes (3 x 30 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and chromatographed to provide an oil (40% EtOAc/hexanes R_f 0 56).

D) 7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1 $0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene hydrochloride

Utilizing the methods described in Example 9C, 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2\ 10}$.$0^{4\ 8}$]pentadeca-2.4(8),6,9-tetraene-ethanone was converted to the title compound. This was treated with 3N HCl EtOAc (3 mL), concentrated and dissolved in a minimum of CH_2Cl_2 which was saturated with hexanes and stirred. After 18 hours the white crystalline product was collected by filtration (18 mg, 13% overall). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.63 (s, 1H), 3 42-2.98 (m, 6H), 2.50 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=10.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 37

4-(2-Methyl-2H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride and 4-(1-Methyl-1H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1. $0^{2,7}$dodeca-2(7),3,5-triene hydrochloride

1-(4-Acetyl-10-aza-tricyclo[6.3.1 $0^{2\ 7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.0 g, 3.3 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (4.0 g, 33.6 mmol) were warmed to 140°C for 18 hours. After cooling, a crystalline precipitate was filtered and rinsed with EtOAc (690 mg, 58%).

The above solid, 3-dimethylamino-1-(10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-propenone, (200 mg, 0 56 mmol) was dissolved in EtOH (2 mL) and treated with 5N HCl EtOH (0.1 mL) followed by methyl hydrazine (0.6 mmol). The resulting mixture was warmed to 70°C for 4 hours. The mixture was cooled, diluted with water and extracted with EtOAc, dried (Na_2SO_4) and concentrated Chromatography on Silica gel provided a 3/1 mixture of regioisomeric products (130 mg, 68%) (TLC 50% EtOAc/hexanes R_f 0.40)

The above oil (130 mg, 0.388 mmol) and Na_2CO_3(s) (82 mg, 0 775 mmol) were stirred in MeOH (10 mL) and H_2O (5 mL) for 18 hours. After cooling the reaction was diluted with water, extracted with CH_2Cl_2 dried through a cotton plug and concentrated. The product was purified by chromatography on Silica gel and concentrated to an oil. The salt was generated with 2N HCl MeOH, concentrated and recrystallized from MeOH/EtOAc to provide a 3/1 mixture of regioisomeric pyrrazoles (85 mg, 58%). (5% MeOH/CH_2Cl_2 (NH_3) R_f 0.25) TFA-precursor APCI MS *m/e* 336.2 [(M + 1)$^+$]

EXAMPLE 38

4,5-DICHLORO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on Campaigne, E.; Thompson, W. *J. Org. Chem.* **1950**, *72*, 629.)

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (539 mg, 2.1 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with ICl_3 (s) (982 mg, 4.21 mmol). The resulting orange solution was stirred 0.5 hours, poured into saturated aqueous $NaHSO_3$ solution (25 mL), extracted with CH_2Cl_2 (3 x 25 mL), dried through a cotton plug and concentrated to an oil (570 mg, 84%) (TLC 50% EtOAc/hexanes R_f 0.62).

B) 4,5-dichloro-10-azatricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4,5-Dichloro-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (570 mg, 1 75 mmol) was stirred in MeOH (25mL) and treated with Na_2CO_3(s) (5 g, 47 mmol) in H_2O (5 mL) The stirred mixture was warmed to 70°C for 4 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into 1N aqueous HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. Product was extracted with CH_2Cl_2 (3 x 40 mL), filtered through a cotton plug and concentrated to an oil (400 mg, 100%)

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours The product was collected by filtration (210 mg, 45%) (TLC 50% EtOAc/hexanes (NH_3) R_f 0 08) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 2H), 3 33-2.97 (m, 6H), 2 18 (m, 1H), 1 99 (d, J=10 5 Hz, 1H) ^{13}C NMR (100 MHz,DMSO-d_6) δ 141 02, 130 60, 126.58, 45.54 40.55, 38.30 GCMS *m/e* 227, 229 (M^+) mp 283-291 °C.

EXAMPLE 39

N^4,N^4-DIMETHYL-10-AZATRICYCLO[6.3.1 $0^{2,7}$]DODECA-2(7),3,5-TRIENE-4-SULFONAMIDE HYDROCHLORIDE

A) 10-Trifluoroacetyl-10-aza-tricyclo[6.3 1 $0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride

1-(10-Aza-tricyclo[6 3 1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (530 mg, 2 1 mmol) was added to chlorosulfonic acid (2 mL, 30 mmol) and stirred for 5 minutes

The mixture was quenched with ice, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to provide an oil (640 mg, 87%). (TLC 30% EtOAc/hexanes R_f 0.15).

B) N^4,N^4-Dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide hydrochloride

10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) was stirred in THF (10 mL) and treated with 40% Me_2NH/H_2O (1.5 mL). After 10 minutes the mixture was concentrated and chromatographed on Silica gel (TLC 30% EtOAc/hexanes R_f 0.31) to provide an oil (256 mg, 78%). This material was dissolved in MeOH (6 mL) and NH_4OH (2 mL) and stirred 18 hours. The mixture was concentrated and azeotroped from MeOH (3x) The resulting oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL), concentrated, dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration as a white powder (163 mg, 59%). (TLC 10% MeOH/ CH_2Cl_2 (NH_3) R_f 0.54) ^{1}H NMR (data, free base) (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7 41 (d, J=8 0 Hz, 1H), 3 30 (m, 2H), 3.20 (d, J=12.5 Hz, 2H), 3.07 (dd, J=12.5,2.2 Hz, 2H), 2.69 (s, 6H) 2 45, (m, 1H), 2.00 (d, J=11 0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128,43, 124.16, 122,75, 46.67, 46.55, 42 11, 39,44, 37,81 GCMS *m/e* 266 (M^+) (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68-7.52 (3H), 3.38 (m, 2H), 3.24 (m, 2H), 3.04 (m, 2H), 2.58 (s, 6H), 2.22 (m, 1H), 2.04 (d, J=11 0 Hz, 1H) GCMS *m/e* 266 (M^+). Anal Calcd for $C_{13}H_{18}N_2O_2HCl$: C, 51 56, H, 6.32, N, 9 25 Found C, 51.36; H,6.09; N,9.09.

EXAMPLE 40

4-(1-PYRROLIDINYLSULFONYL)-10-AZATRICYCLO[6 3 1 $0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The pyrrolidine analogue was prepared from 10-trifluoroacetyl-10-aza-tricyclo[6 3.1.$0^{2\ 7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) as by substituting pyrroline in the coupling step described in Example 39B. The TFA product was isolated as an oil (314 mg, 89%) Deprotection and conversion to the salt as in Example 39B affords a white powder (189 mg. 63%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.60). (TLC 50% EtOAc/hexanes R_f 0.65). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 66 (d, J=8.0 Hz, 1H), 7.64 (s, 1H), 7 37 (d, J=8.0 Hz, 1H), 3 30-3.15 (m, 8H), 3.00 (m 2H), 2.39 (m, 1H), 1 98 (d, J=11.5 Hz, 1H), 1 72 (m, 4H) ^{13}C NMR (100 MHz $CDCl_3$) δ 146.91, 144 08, 136.65, 127. 90, 124.18, 122 36, 50 43, 47 87, 46 80, 46 63, 42.11, 39.63, 25 10. APCI MS *m/e* 293 [(M + 1) $^+$]. (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ 9 78 (br s, NH), 8 1 (br s, NH), 7 73 (d, J =1 5 Hz,1H), 7 66

(dd, J=8.0,1 5 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 3.39-3.01 (10H), 2.21 (m, 1H), 2.04 (d, J=11.0 Hz, 1H), 1.66 (m, 4H). GCMS *m/e* 292 (M^+). Anal. Calcd. For $C_{13}H_{18}N_2O_2HCl.1/2MeOH$: C, 54.07, H, 6 47; N, 8.51. Found C, 53.98, H,6.72, N, 8.12

EXAMPLE 41

5,13-DIAZATETRACYCLO[9.3 1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2,4(8),9-TRIEN-6-ONE HYDROCHLORIDE (The title compound was prepared following the procedures described in Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53, treating 4,5-dinitro-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester as an equivalent to an ortho fluoro phenyl moiety.) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, NH), 9.88 (br s, NH), 7.52 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 3.41 (d, J=5.0 Hz, 2H), 3.35-3.13 (m, 4H), 2.93 (m, 2H), 2.12 (m, 1H), 1.95 (d, J=11.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 42

6-OXO-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE (For references, see: Nachman, R J. *J. Het. Chem.* **1982**, 1545)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (317 mg, 1 11 mmol) was stirred in THF (10 mL), treated with carbonyldiimidazole (269 mg, 1.66 mmol) and warmed to 60°C for 18 hours. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL) and washed with 1N aqueous HCl solution (3 x 10 mL) The organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel (50% EtOAc/Hexanes) to provide an oil (130 mg). This material converted to the title compound by the methods described in Example 9C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11 78 (s, NH), 9.56 (br s, NH), 7 63 (br s, NH), 7 24 (s, 1H), 7 07 (s,1H), 3 26 (br s, 2H), 3.16 (br t, J=9.5 Hz, 1H), 2.93 (br s, 1H), 2 18 (m, 1H), 1 97 (d, J=11 0 Hz, 1H). APCI MS *m/e* 217.2 [(M + 1)$^+$].

EXAMPLE 43

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3 1 $0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G L., Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M A , Sall, D. J , Seibel, W L.; Reitz, T. J. *J. Org. Chem.* **1983**, *48*, 2321-2327 Grunewald, G. L ; Markovich, K. M.; Sall. D. J. *J. Med Chem* **1987**, *30*, 2191-2208)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.67-7.50

(3H), 3 65 (br s, 1H), 3.49-3.42 (m, 2H), 3 29 (s, 1H), 3.28-3.16 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11 5 Hz, 1H) APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 275-277 °C. Anal. Calcd. for $C_{12}H_{12}F_3N$ HCl.1/3H_2O: C, 53.44; H, 5.11: N, 5.19 Found C, 53.73, H, 4.83; N, 5.16.

EXAMPLE 44

3-PHENYL-10-AZA-TRICYCLO[6.3.1 $0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene and 5-iodo-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (9.37 g, 385 mmol) were stirred in anhydrous THF (1000 mL) in a flame dried 2L 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter The flask was stirred and warmed to reflux by a removable heating mantle. 2,6-Difluoro-iodobenzene (0.3 g) was added followed by of 3N EtMgBr in THF (0.3 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (24.24 g, 367 mmol) and 2,6-difluoro-iodobenzene (88 0 g, 367 mmol). Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for ~1 hour (no SM by GCMS).

The reaction was cooled to room temperature and quenched with H_2O (200 mL) followed by aqueous 1N HCl solution (200 mL) to dissolve the solids. Product was extracted with hexanes (4 x 150 mL) The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil (70 g). Chromatography on Silica gel eluting with hexanes provided two lots (9.0 and 21.0 g), which contained primarily 5-iodo-1,4-dihydro-1,4-methano-naphthalene. (TLC hexanes R_f 0 63)

B) 5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

5-Iodo-1,4-dihydro-1,4-methano-naphthalene (20 g) and N-methyl morpholine N-oxide (17 61 g, 130 mmol) were stirred in acetone (90 mL) and H_2O (13 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt solution in t-BuOH, 0 02 mmol) After 144 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1/2 hour. The

mixture was filtered through a Celite pad and the filtrate concentrated to produce an oil which was purified by chromatography on Silica gel eluting with a gradient of hexanes to 100% EtOAc to provide a yellow solid (13.73 g). APCI MS *m/e* 301.1 [(M - 1)$^+$].

C) 10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (8.33 g, 27.6 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (25 mL) and H_2O (75 mL) then treated with sodium periodate (6.17 g, 29.0 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 40 mL). The combined organic layer was washed with H_2O (4 x 30 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (30 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (3.16 mL, 29.0 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (18.72 g, 88.0 mmol) in DCE (150 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (6.3 g, 61%) (TLC 5% EtOAc/hexanes R_f 0.10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J= 8.0 Hz, 1H), 7.28-7.22 (m, 3H), 7.13 (d, J=8.0 Hz,1H), 6.98-6.94 (m, 3H), 3.58 (AB dd, J=14.2 Hz, 2H), 3.26 (br s, 1H), 3.21 (br s, 1H), 3.04 (br d, J=10.2 Hz, 1H), 2.83 (br d, J=10.2 Hz, 1H), 2.47 (d, J=10.0 Hz, 1H), 2.39 (d, J=10.0 Hz, 1H), 2.34 (m, 1H), 1.72 (d, J=10.5 Hz, 1H) APCI MS *m/e* 376.0 [(M + 1)$^+$]

D) 10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

(For a discussion, see: Miyaura, N ; Suzuki, A *Chem Rev* **1995**, *95*, 2457-2483.)

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (375.3 mg, 1.0 mmol), potassium acetate (785 mg, 8.0 mmol) and phenyl boronic acid (183 mg, 1.5 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) (57.5 mg, 0.05 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 (180 mg, 55%) (TLC 4%EtOAc/hexanes R_f 0.18) GCMS *m/e* 325 (M)$^+$.

E) 3-Phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene was converted into the title compound utilizing the conditions described in Example 2D (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.30). (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.15 (8H), 3.17 (br s, 1H), 3.01 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.72 (dd, J=10.5,2.5 Hz, 1H), 2.63 (dd, J=10.5,2.5 Hz, 1H), 2.41 (m, 1H), 1.91 (d, J=10.5 Hz, 1H). APCI MS *m/e* 236.2 [(M + 1)$^+$] (HCl salt) mp 262-265 °C. Anal. Calcd. for $C_{17}H_{17}N.HCl.1/3H_2O$: C, 73.26; H, 6.86; N, 5.19 Found C, 73.50; H, 6.77; N, 5.04.

EXAMPLE 45

3-HYDROXY-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (3.0 g, 7.99 mmol) was stirred in anhydrous THF (40 mL) at -78 °C under nitrogen and treated dropwise with n-BuLi (3.84 mL of 2.5M soln. in hexanes, 9.59 mmol) After 10 minutes, tri-isopropylborate (4.61 mL, 20.0 mmol) was added dropwise. After ~1/2 hour, the reaction was poured into saturated aqueous $NaHCO_3$ solution, stirred 5 minutes and extracted with EtOAc (3 x 50 mL) and concentrated The residue was dissolved in 30% Et_2O/hexanes and extracted with 1N NaOH aqueous solution (4 x 50 mL). The combined aqueous basic layer was treated with concentrated HCl to achieve pH 8 and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4) and stripped. Chromatography on Silica gel eluting first with 3% EtOAc/hexanes to remove non-polar components, then with 5% MeOH/CH_2Cl_2 provides the title compound. (TLC 25% EtOAc/hexanes R_f 0.60)

B) 10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (140 mg 0.48 mmol) dissolved in THF (5 mL) was treated with N-methylmorpholine-N-oxide (64.5 mg, 0.48 mmol) and brought to reflux for 1 hour. The reaction was concentrated and chromatographed on Silica gel to provide product. (TLC 25% EtOAc/hexanes R_f 0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.15 (3H), 7.04 (dd, J= 8.0,7.0 Hz, 1H), 6.95 (m, 2H), 6.75 (d, J=7.0 Hz, 1H), 6.59 (dd, J=8.0,1.0 Hz, 1H), 3.53 (br s, OH), 3.51 (AB d, J=14.0 Hz, 2H), 3.28 (br s, 1H), 3.06 (br s, 1H), 2.91 (dd, J=8.5,1.5 Hz, 1H), 2.79 (ddd, J=8.5,1.5,1.5 Hz, 1H), 2.42 (d, J=11.0 Hz, 1H), 2.39 (d, J=11.0 Hz, 1H), 2.23 (m, 1H), 1.65 (d, J=10.5 Hz, 1H). APCI MS *m/e* 266.5 [(M + 1)$^+$]

C) 3-Hydroxy-10-aza-tricyclo[6 3 1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (160 mg, 0.60 mmol) was converted into the title compound by the methods described in Example 1D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 15 (dd, J=8.0,7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 3.51 (br s, 1H), 3.33-3.25 (3H), 3 16 (d, J=12.0 Hz, 1H), 3.09 (d, J=12.0 Hz, 1H), 2.29 (m, 1H), 2.02 (d, J=11 0 Hz, 1H). APCI MS *m/e* 175.8 [(M + 1)$^+$]. (HCl salt) mp 253-255 °C.

EXAMPLE 46

4,5-DIFLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2,4,5-trifluorobromobenzene ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J=8.5 Hz, 2H), 3 48-3.13 (6H), 2.38 (m, 1H), 2.11 (d, J=11.5 Hz, 1H). APCI MS *m/e* 196.2 [(M + 1) $^+$]. (HCl salt) mp 301-303 °C. Anal. Calcd. for $C_{11}H_{11}F_2N.HCl.1/6H_2O$: C, 56.30; H, 5.30; N, 5.97 Found C, 56.66, H, 5 41; N, 5.96

EXAMPLE 47

6-ETHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1 $0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1 $0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and propionyl chloride were converted to the title compound following the procedures described in Example 30 and Goldstein, S. W; Dambek, P. J *J. Het. Chem.* **1990**, *27*, 335. ^{1}H NMR (400 MHz, CD_3OD) δ 7 64 (s, 1H), 7.62 (s, 1H), 3 48 (d, J=2.5 Hz, 2H), 3 41 (d, J=12.0 Hz, 2H), 3.20 (2H), 3 01 (q, J=7.5 Hz, 2H), 2.45 (m, 1H), 2.17 (d, J=11.5 Hz, 1H), 1 42 (t, J=7 5 Hz, 3H) APCI MS *m/e* 229.2 [(M + 1)$^+$]

EXAMPLE 48

6-ISOPROPYL-5-OXA-7 13-DIAZATETRACYCLO[9 3 1 $0^{2,10}$ $0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and isobutyryl chloride were converted to the title compound following the procedures described in EXAMPLE 47 (TLC 25% EtOAc/hexanes R_f 0.14) ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (2H), 3.49 (br s, 2H), 3 41 (d, J=12.0 Hz, 2H), 3 33-3 19 (3H), 2.45 (m, 1H), 2.18 (d, J=11 5 Hz, 1H), 1 45 (d, J=7 0 Hz, 6H). APCI MS *m/e* 243.2 [(M + 1)$^+$] (HCl salt) mp 249-251 °C.

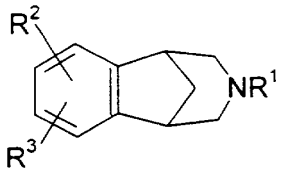
EXAMPLE 49

6-BENZYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and phenyl-acetyl chloride were converted to the title compound following the procedures described in EXAMPLE 47. ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.58 (s, 1H), 7.36-7.24 (5H), 4.29 (s, 2H), 3.46 (d, J=2.5 Hz, 2H), 3.39 (d, J=12.0 Hz, 2H), 3.18 (2H), 2.42 (m, 1H), 2.15 (d, J=11.5 Hz, 1H). APCI MS *m/e* 291.2 [(M + 1)$^+$].

CLAIMS

1. A compound of the formula



(I)

R^1 is hydrogen, (C_1-C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$ 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), (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)alkylamino-, $[(C_1-C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and $-XC(=O)R^{13}$,

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic or 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_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, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

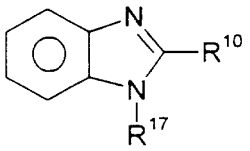
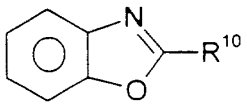
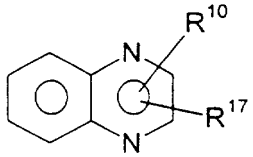
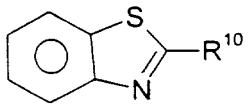
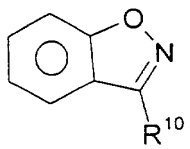
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, N-(C_1-C_6)alkylpiperizine or thiomorpholine 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, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;

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 (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, cyano, halo,

amino, $(C_1$-$C_6)$alkylamino-, $[(C_1$-$C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur,

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.

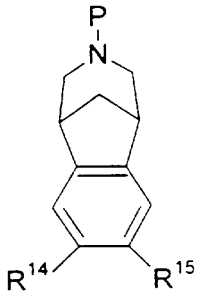
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (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 according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

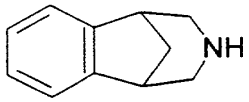
A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 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.

A compound of the formula



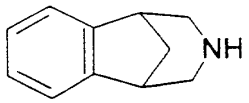
wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, allyl or 2,2,2-trichloroethyl, $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo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

12. 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 comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

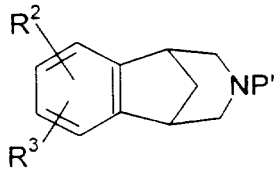
13. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 administering to a mammal in need of such treatment an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof;

that is effective in treating such disorder or condition

14. A compound of the formula



(I′)

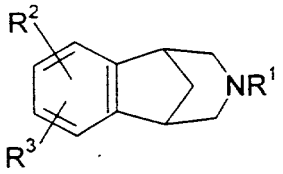
wherein R^2 and R^3 are defined as in claim 1, and P′ is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl, $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in claim 2,

-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).

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Abstract

Compounds of the formula



(I)

and their pharmaceutically acceptable salts, wherein R^1, R^2, R^3 and n 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.

PTO/SB/01(12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration submitted with Initial Filing

☐ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e)) required)

Attorney Docket Number	PC 10030A
First Named Inventor	Jotham Wadsworth COE
COMPLETE IF KNOWN	
Application Number	Not yet assigned
Filing Date	Filed herewith
Group Art Unit	Not yet assigned
Examiner Name	Not yet assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 11/13/1998 as United States Application Number or PCT International Application Number PCT/IB98/01813 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)
60/070,245	12/31/1997

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B sheet attached hereto.

EXPRESS MAIL NO. EM484852791

PTO/SB/01 (12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION ---- Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 U.S.C. 1.56, which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application Number or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number or ☒ Registered practioner(s) name/registation number listed below

Place Customer Number Bar Code Label here

Name	Registration Number	Name	Registration Number
Peter C. Richardson	~~27,526~~	Mark Dryer	28,775
Allen J. Spiegel	~~25,749~~	Lawrence C. Akers	~~28,587~~
Paul H. Ginsburg	~~28,718~~	A. Dean Olson	~~31,185~~
J. Trevor Lumb	28,567	Mervin E. Brokke	32,723
James T. Jones	30,561	Valerie M. Fedowich	33,688
Gregg C. Benson	30,977	Bryan C. Zielinski	34,462
Robert F. Sheyka	31,304	Robert T. Ronau	36,257
Grover F. Fuller Jr.	~~31,760~~	B. Timothy Creagan	39,156
Karen DeBenedictis	32,977	Alan L. Koller	37,371
Lorraine B. Ling	35,251	Jolene W. Appleman	35,428
Garth Butterfield	36,997	Kristina L. Konstas	37,864
Carl J. Goddard	39,203	Seth H. Jacobs	32,140
Raymond M. Speer	26,810	Martha A. Gammill	31,820
Jennifer A. Kispert	40,049	Gregory P. Raymer	36,647
Jacob M. Levine	32,509	E. Victor Donahue	35,492
Israel Nissenbaum	~~27,582~~	Roy F. Waldron	42,208
Steven W. Collier	42,429	Todd M. Chrissey	37,807

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label | OR ☒ Correspondence address below

Name	~~Paul H. Ginsburg~~				
Address	~~Pfizer Inc~~				
Address	~~235 East 42nd Street, 20th Floor~~				
City	New York	State	New York	Zip Code	10017-5755
Country	United States Of America	Telephone	(212)573-2369	Fax	(212)573-1939

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Jotham Wadsworth ~~Wadsworth~~	COE

Inventor's Signature	Jotham W. Coe							Date	9/22/99
Residence: City	Niantic		State	CT ~~CT~~	Country	US		Citizenship	US
Post Office Address	8 Bush Hill Drive								
Post Office Address									
City	Niantic	State	CT	Zip	06357	Country	US		

☒ Additional inventors are being named on the supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

EXPRESS MAIL NO. EM484852791

Please type a plus sign (+) inside this box → [+]

PTO/SB/02A(3/97)
Approved for use through 09/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION	**ADDITIONAL INVENTOR(S)** Supplemental Sheet

200

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Paige Roanne Palmer				BROOKS			
Inventor's Signature	Paige Roanne Palmer Brooks					**Date**	9/23/99
Residence: City	North Stonington	**State**	CT	**Country**	US	**Citizenship**	US
Post Office Address	9 Wyassup Road						
Post Office Address							
City	North Stonington	**State**	CT	**Zip**	06359	**Country**	US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**Zip**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**Zip**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
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City		**State**		**Zip**		**Country**	

EXPRESS MAIL NO. EM484852791

ISSUE CLASSIFICATION	Class	Subclass
	514	289

FILED UNDER 35 U.S.C. 371

PATENT NUMBER

6410550

6410550

U.S. UTILITY PATENT APPLICATION

O.I.P.E.	PATENT DATE
SCANNED ITW Q.A.	JUN 25 2002

SECTOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
	514	289	1624	

FILED WITH: ☐ DISK (CRF) ☐ FICHE
(Attached in pocket on right inside flap)

PREPARED AND APPROVED FOR ISSUE

ISSUING CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
514	289	514	210.21	228.2	232.8	253.02	253.03	256
INTERNATIONAL CLASSIFICATION			281	295				
A61K	31/44	546	43	74	97			
A61K	31/505	544	58.2	60	125	126	242	361
C07D	221/22							
C07D	413/00							
A61P	1/00			☐ Continued on Issue Slip Inside File Jacket				

☐ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
	0	0	0	15	1

☐ a) The term of this patent subsequent to _____ (date) has been disclaimed.

☐ b) The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____

☐ c) The terminal ____months of this patent have been disclaimed.

_____ (Assistant Examiner) _____ (Date)

BRENDA COLEMAN
PRIMARY EXAMINER

Brenda Coleman (Primary Examiner) 2-7-02 (Date)

C. Stupp (Legal Instruments Examiner) 2/15/02 (Date)

NOTICE OF ALLOWANCE MAILED: 2-11-02

ISSUE FEE (W)

Amount Due	Date Paid
1280-00	5-20-02

ISSUE BATCH NUMBER

WARNING:
The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A
(Rev. 6/98)

ISSUE FEE IN FILE

(LABEL AREA)

(FACE)

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[redacted]

Briefed 9-26-00

SEARCHED

Class	Sub.	Date	Exmr.
546	43, 74, 97	9/26/00	BC
544	58.2, 60, 125, 126, 242, 361		
514	210.21, 228.2, 232.8, 253.02, 253.03, 256, 281, 289, 295		
Updated		2/7/02	BC

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
CAS Online	9/18/00	BC
updated	2/7/02	BC

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
546	43. 74, 97	2/7/02	BC
544	58.2, 60 125, 126, 242, 361		
514	210.21, 228.2, 232.8, 253.02, 253.03, 256, 281, 289, 295		

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ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION			
O.I.P.E. CLASSIFIER		[illegible]	1-11-00
FORMALITY REVIEW			

INDEX OF CLAIMS

✔	Rejected	N	Non-elected
=	Allowed	I	Interference
—	(Through numeral)... Canceled	A	Appeal
÷	Restricted	O	Objected

Claim Final	Claim Original	Date 9-26-00	Date 3-24-01	Date 2-7-02
1	1	✔	✔	=
2	2	✔	✔	=
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	4	✔		
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If more than 150 claims or 10 actions staple additional sheet here

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524 Rec'd PCT/PTO 28 SEP 1999

FORM PTO-1390 (REV 10-95) U. S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES PATENT AND TRADEMARK OFFICE DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
PC10030A	
U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) Not yet assigned	09/402010

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB98/01813	November 13, 1998 (11.13.1998)	December 31, 1997 (12.31.1997)

TITLE OF INVENTION
ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

APPLICANT(S) FOR DO/EO/US
Jotham Wadsworth COE and Paige Roanne Palmer BROOKS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is the **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern other documents(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
    ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

EXPRESS MAIL NO. EM484852791

514 Rec'd PCT/PTO 28 SEP 1999

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Not yet assigned 09/402010	PCT/IB98/01813	PC10030A

17. ☒ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5)):		
☒ Search Report has been prepared by the EPO or JPO $840.00		
☐ International preliminary examination fee paid to USPTO (37CFR 1.482) $670.00		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $760.00		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	- 20 =		X $ 18.00	$	
Independent Claims	- 3 =		X $ 78.00	$78	
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ $260.00	$	

TOTAL OF ABOVE CALCULATIONS =	$918	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note: 37 CFR 1.9, 1.27, 1.28)	$	
SUBTOTAL =	$918	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$	
TOTAL NATIONAL FEE =	$918	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$	
TOTAL FEES ENCLOSED =	$918	
Amount to be: Refunded		$
Charged		$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 16-1445 in the amount of $ 918 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.16-1445. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Background of the Invention

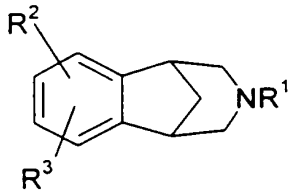
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory 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, ~~amyotropic~~ amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive ~~supramuscular~~ supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, ~~barbituates.~~ barbiturates 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. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

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

R^2 and R^3 are selected, independently, from hydrogen, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1\text{-}C_6)$alkyl wherein q is zero, one or two, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, aryl-$(C_0\text{-}C_3)$alkyl- or aryl-$(C_0\text{-}C_3)$alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0\text{-}C_3)$alkyl- or heteroaryl-$(C_0\text{-}C_3)$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 $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1\text{-}C_6)$alkylamino- or $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- moiety of said $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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 $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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-$(C_0\text{-}C_3)$alkyl- and said heteroaryl-$(C_0\text{-}C_3)$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 $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1\text{-}$

C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

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, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$, and -$XC(=O)R^{13}$;

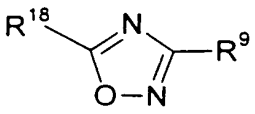
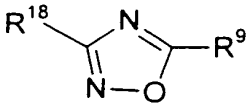
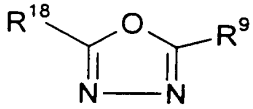
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine 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, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

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:

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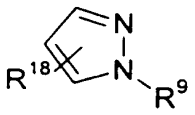
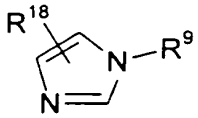
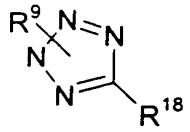
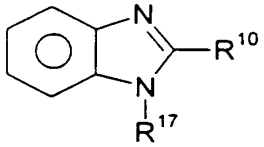
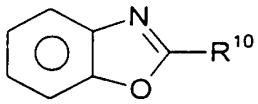
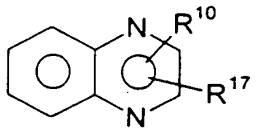




wherein one of R^9 and R^{18} is hydrogen or $(C_1\text{-}C_6)$alkyl, and the other is a bond to the benzo ring of formula I.

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:

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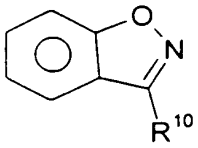
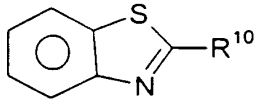
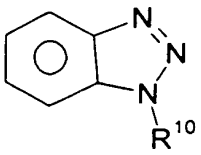
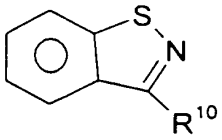
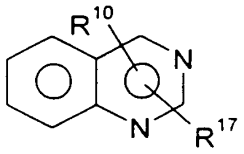



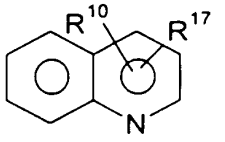
wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

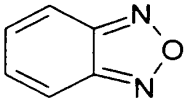
Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:

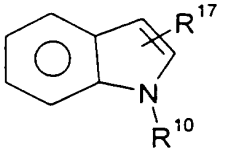


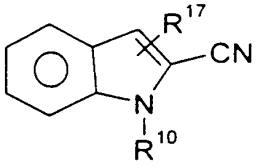


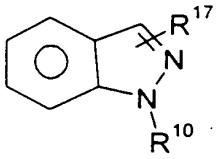


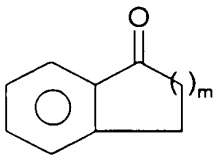


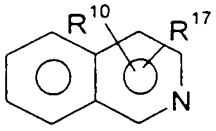


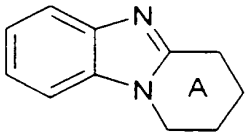


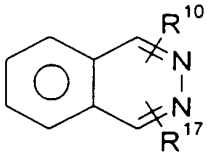












wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

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:

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

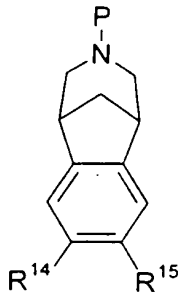
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride; and

5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride.

This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, 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 or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $-C(=O)(C_1\text{-}C_6)$alkyl, cyano, hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$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.

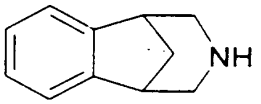
The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is 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, amyotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear 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, ~~amyliotropic~~ amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive ~~supramuscular~~ supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, ~~barbituates~~ barbiturates, 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 acceptable salt thereof, 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, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



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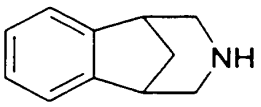
or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method 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, ~~amyliotropic~~ amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive ~~supramuscular~~ supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, ~~barbituates~~ barbiturates, 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



or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

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.

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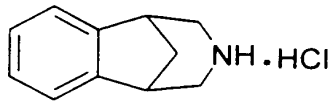
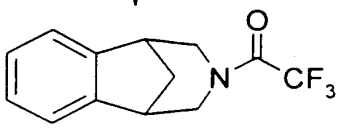
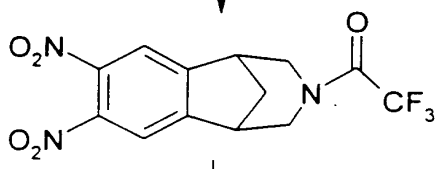
Scheme 1



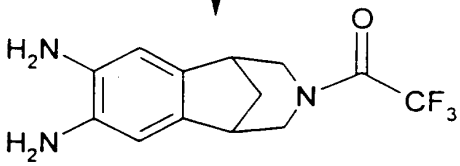
III



IV

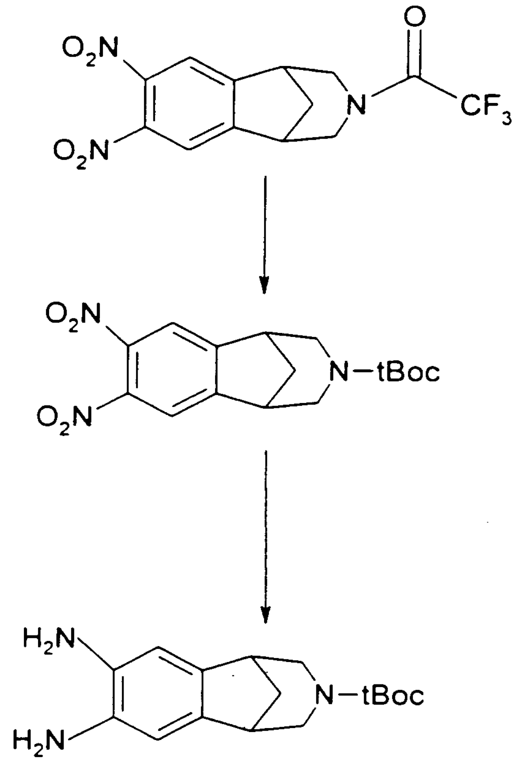


IIA



IIB

Scheme 2

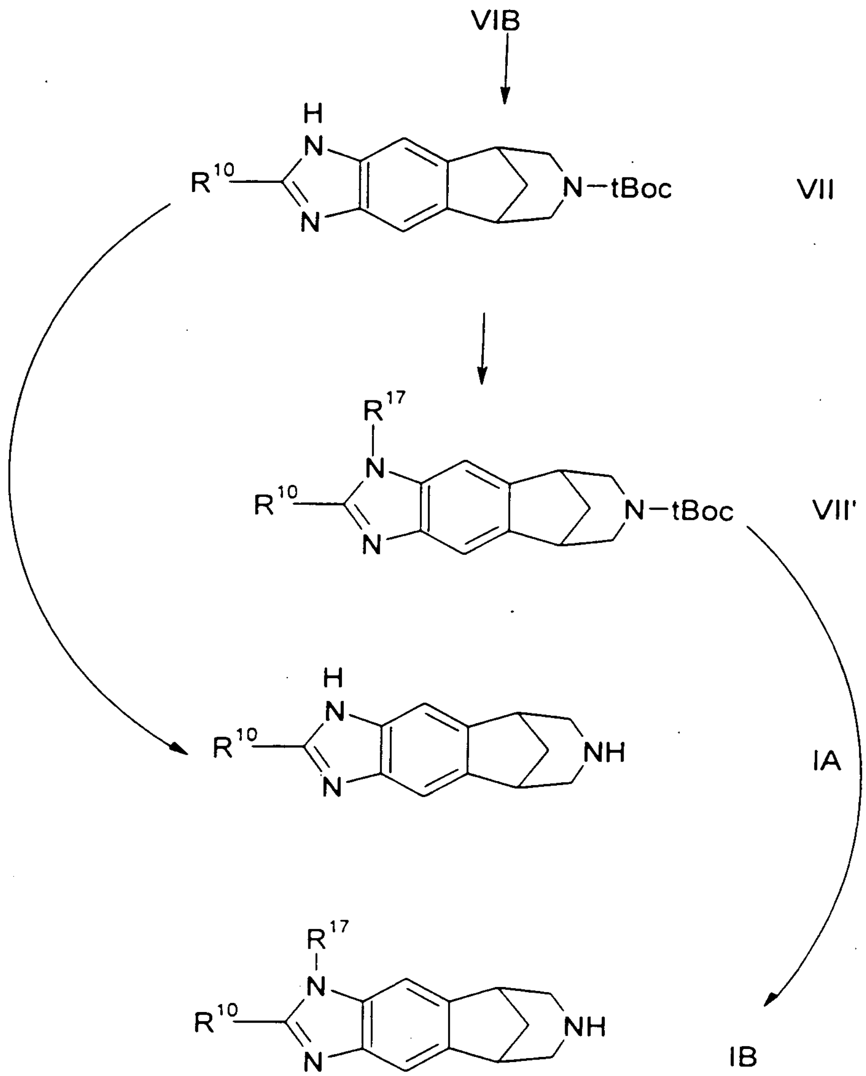


IIA

VIA

VIB

Scheme 2 continued



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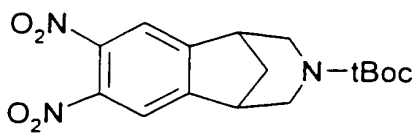
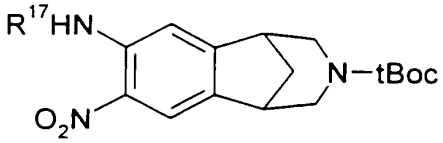
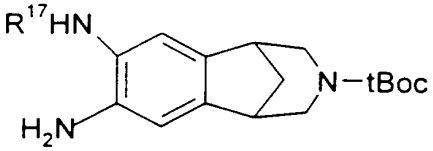
Scheme 3



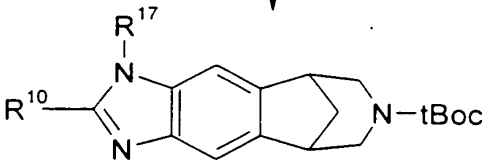
VIA



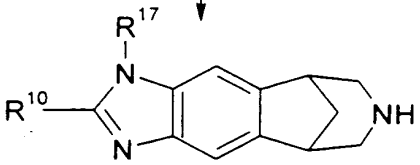
XXIII



XXIV



XXV



IB

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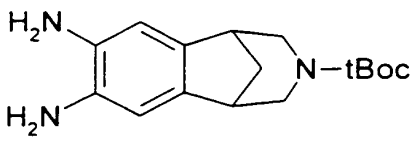
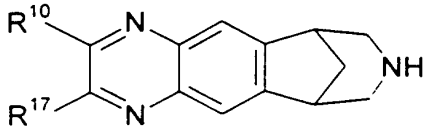
Scheme 4



VIB



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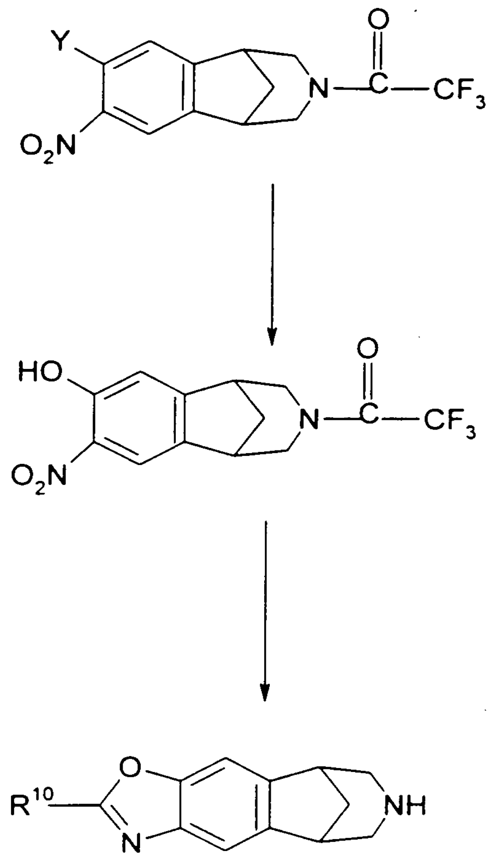
Scheme 5

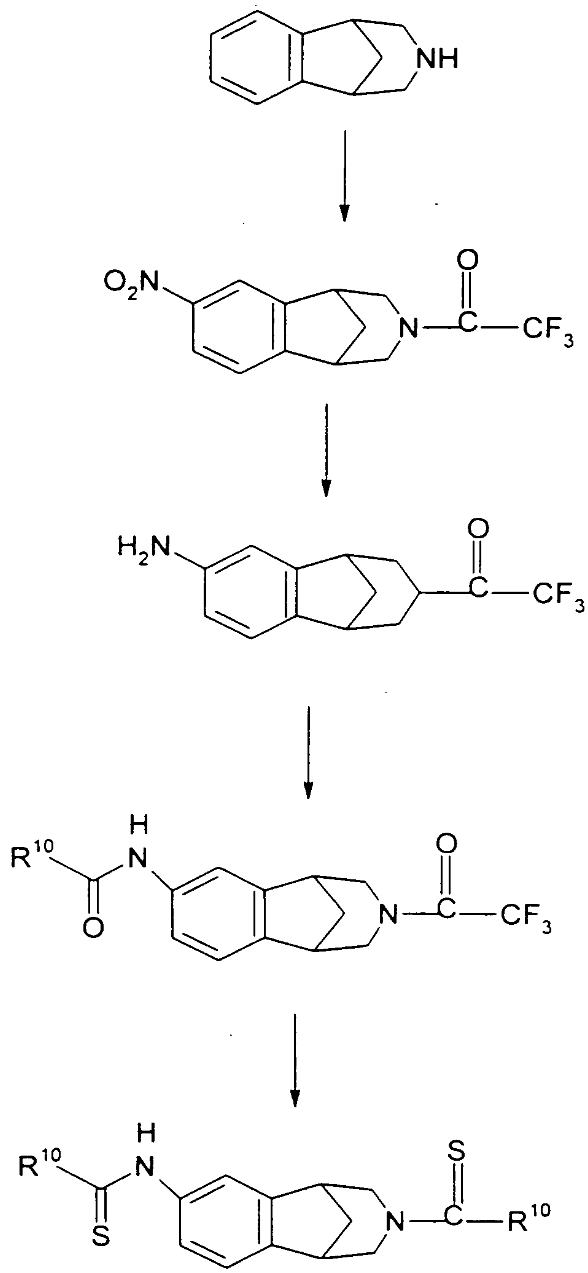


XXII

VIII

IE

Scheme 6



III

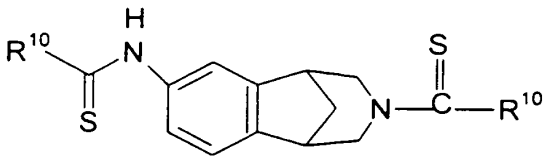
IX

IX'

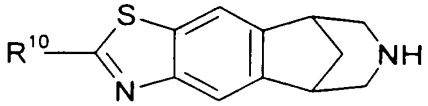
X

XI

Scheme 6 continued

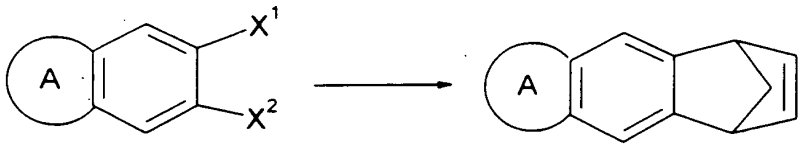


XI



IF

Scheme 7

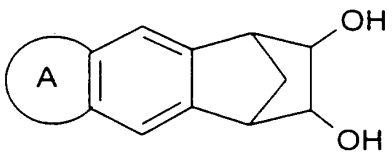


(ring A = present or absent)

XII

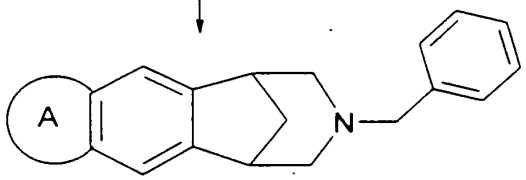
(ring A = present or absent)

XIII



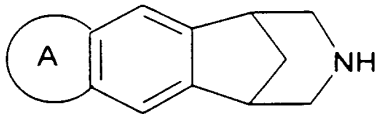
(ring A = present or absent)

XIIIA



(ring A = present or absent)

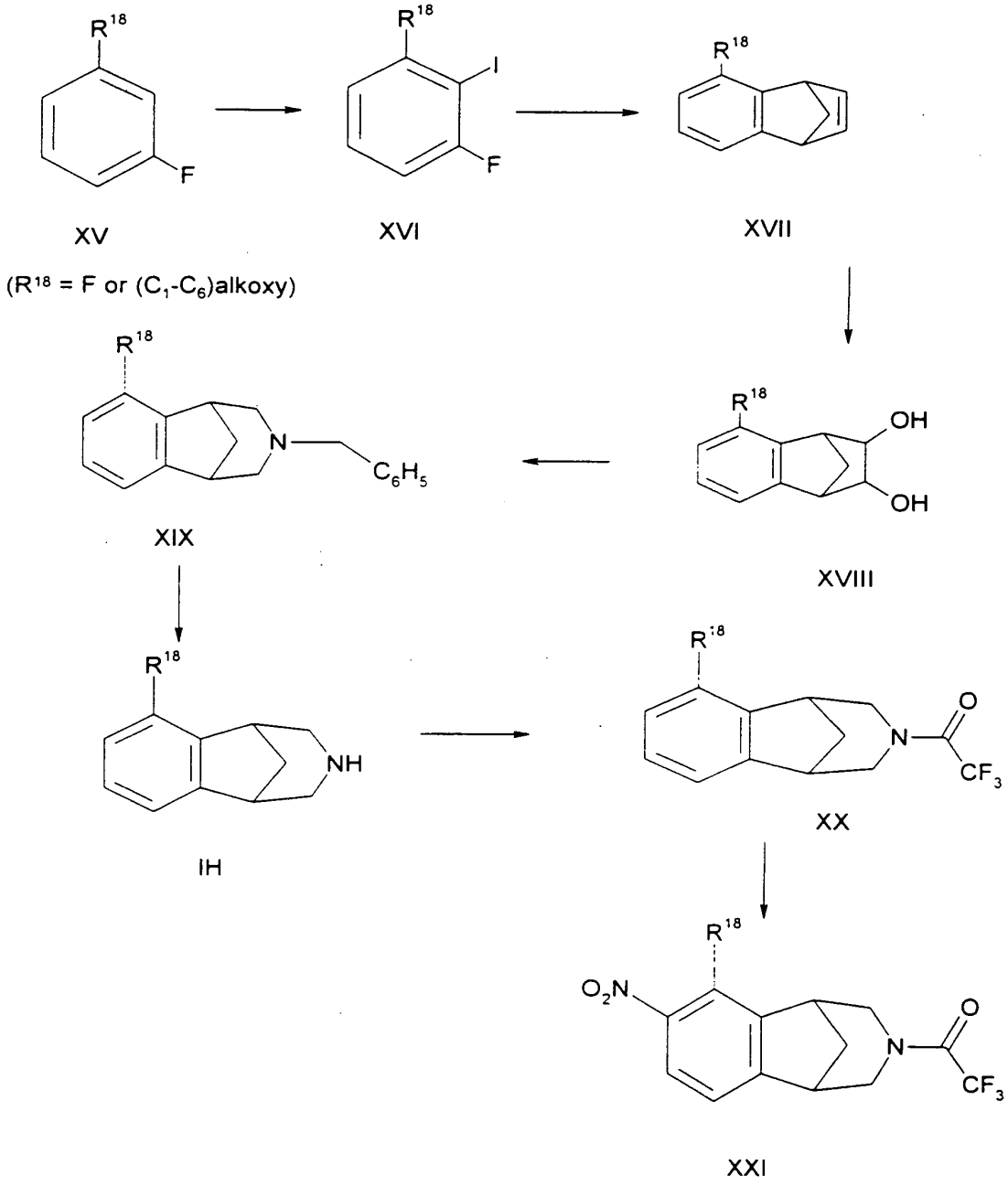
XIV



IG: (R^2 and R^3 form ring A)

III: (ring A = absent)

Scheme 8



XV

(R^{18} = F or (C_1-C_6)alkoxy)

XVI

XVII

XVIII

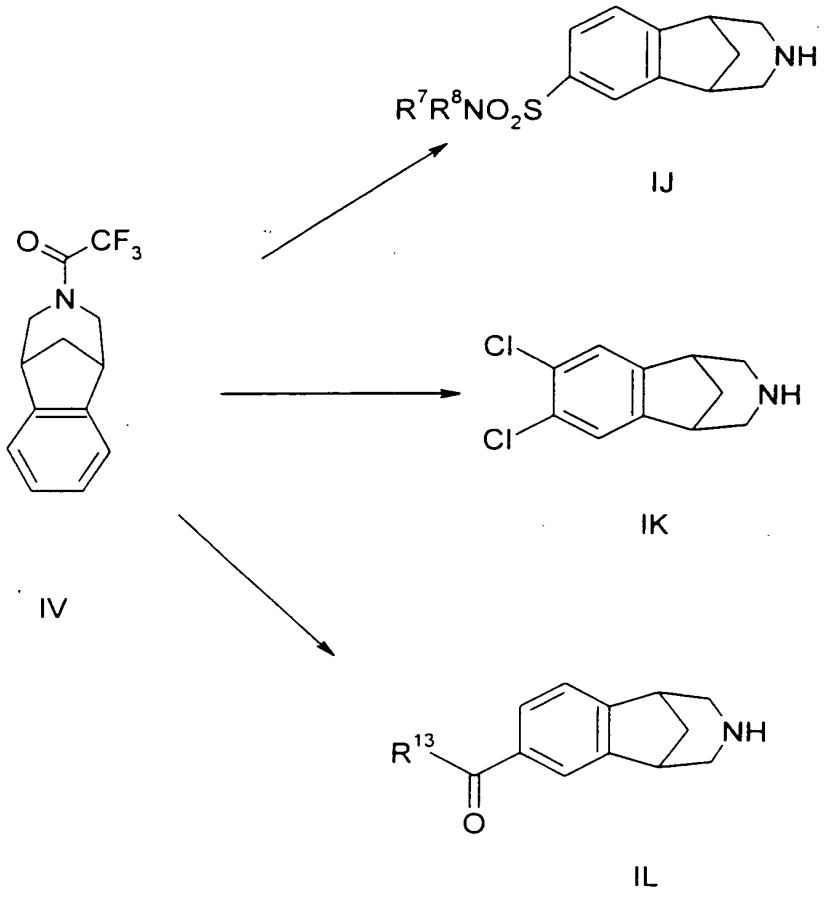
XIX

IH

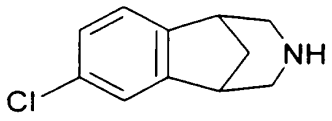
XX

XXI

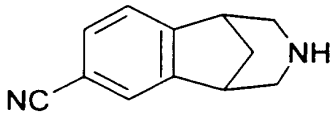
Scheme 9



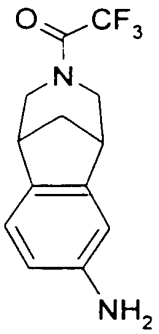
Scheme 10



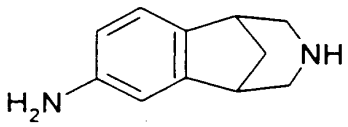
IM



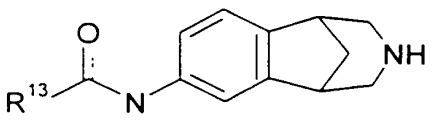
IN



IX'



IP



IQ

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Scheme 1-10 illustrate methods of synthesizing compounds of the formula I .

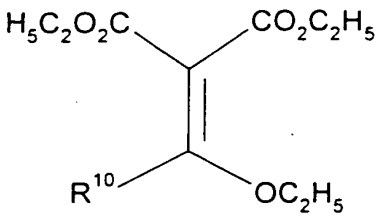
Referring to Scheme 1, the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV. This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, ~~dichoroethane~~ dichloroethane (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.

Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) 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 VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula



XXIIA

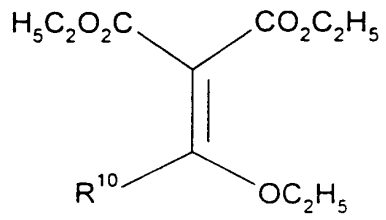
wherein R^{10} is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0$ -$C_3)$alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0$ -$C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, 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 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 VII the compound of formula VIB are described by Segelstein et al., Tetrahedrón Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII 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 VII can be converted into the corresponding compound of formula IB 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, 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.

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA 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. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV 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 IIA into a compound of the formula IIB in Scheme 1, and exemplified in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

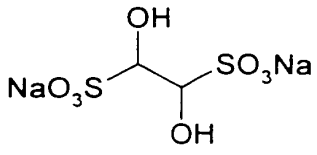


XXIIA

wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII.

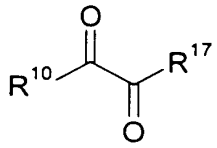
Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII.

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB 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 VIB 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.

The desired quinoxoline of formula IC 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 VII into one of the formula IA.

Scheme 5 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 5 as chemical formula IE. Referring to Scheme 5, the compound of formula XXII, wherein Y is nitro, halo, trifluoromethanesulfonate or a diazonium salt, 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 VIII, which can then be converted into the desired compound having formula IE by the following procedure. First, the compound of formula VIII 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 $(C_1\text{-}C_6)$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~~ Stoichiometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or ~~pyridinum~~ pyridinium 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.

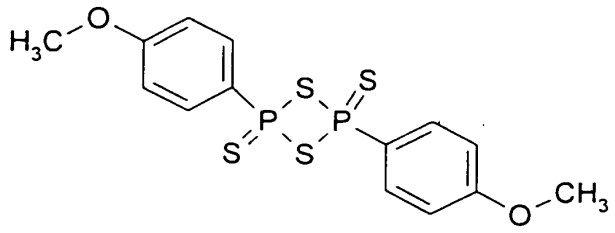
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IE. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) 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 6 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. Referring to Scheme 6, the compound of formula III 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 anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, 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 IX'.

The compound of formula IX' 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 R^{10} is hydrogen or $(C_1\text{-}C_6)$alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI by reacting it with Lawesson's reagent, which is depicted below.



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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 IF can be accomplished by reacting the compound of formula XI 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.

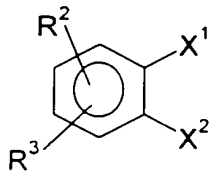
Scheme 7 illustrates a method of preparing the compound of formula III, which is used as the starting material for the process of Scheme 1, or a compound of the formula IG, wherein R^2 and R^3 form a ring (labeled "A" in the Scheme), as defined above in the definition of compounds of the formula I. Referring to Scheme 7, the compound of formula XII, wherein X^1 and X^2 are selected, independently, from chloro, fluoro, bromo and iodo, but where at least one of X^1 and X^2 is Br- or I-, reacted with cyclopentadiene, in the presence of magnesium metal, in a THF, dioxane or other ethereal solvent, at a temperature from about 40°C to about 100°C, preferably at about the reflux temperature, to form a compound of the formula XIII. Reaction of the resulting compound of formula XIII with N-methylmorpholine-N-oxide (NMO) and osmium tetroxide in acetone at about room temperature yields the corresponding compound of the formula XIIIA.

The compound having formula XIIIA is then converted into the corresponding compound of formula XIV using the following procedure. First, the compound of formula XIIIA 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 and

sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0°C to about room temperature, preferably at about room temperature, to form the desired compound of formula XIV. Removal of the benzyl group from the compound of formula XIV yields the compound of formula III (when ring A is absent) or IG, (when ring A is present). This 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 of Scheme 7 can also be used to prepare compounds of the formula I wherein R^2 and R^3 do not form a ring and are not both hydrogen, by replacing the starting material of formula XII with the appropriate compound having the formula



XII'

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Scheme 8, 9 and 10 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 8 illustrates a variation of the process shown in Scheme 7, which can be used to make a compound identical to that of formula III except that the benzo ring is substituted with a fluoro group or an alkoxy group (R^{18} in Scheme 8). This compound is depicted in Scheme 8 as chemical structure 1H. Referring to Scheme 8, where, for example, R^{18} is F, 1,3-difluorobenzene is reacted with a strong base such as an alkali metal dialkylamine or an alkali metal alkyl (or aryl) in an ethereal solvent such as ethyl ether or THF, at a temperature below -50°C, followed by quenching with iodine or N-iodosuccinamide, to form 1,3-difluoro-2-iodobenzene. The compound 1,3-difluoro-2-iodobenzene (structural formula XVI in Scheme 8) is then converted into the compound of formula IH by a series of reactions (represented in

Scheme 8 as XVI→XVII→XVIII→XIX→IH) that are analogous to the series of reactions described above and illustrated in Scheme 7 for converting compounds of the formula XIII into those of the formula IG or III. Conversion of the compound of formula XVI into the compound of formula XVII can also be accomplished by treating a mixture of the compound of formula XVI and cyclopentadiene with an alkyl lithium reagent, preferably n-butyl lithium, in an inert hydrocarbon solvent such as petroleum ether or methyl cyclohexane, at a temperature from about -20°C to about room temperature, preferably at about 0°C.

The compound of formula IH can then be converted into the corresponding nitrogen protected derivative of formula XX, using the methods described above for synthesizing the compound of formula IV in Scheme 1. Nitration of the compound of formula XX using the method described above for preparing the compound of formula IX in Scheme 6, yields the compound of formula XXI wherein the benzo ring is substituted with both a fluoro and nitro group or an alkoxy group and nitro group. The compound of formula XXI can be used to make a variety of compounds of the formula I wherein one of R^2 and R^3 is fluoro, using methods that are well known to those of skill in the art, for example, by first converting the nitro group to an amino group, converting the amino group to a variety of other substituents, as illustrated in Scheme 10, and then removing the nitrogen protecting group.

The compound of formula XXI acts as a regioisomeric functional equivalent of the compounds having formulas IIA, VIA and XXII, in that the fluorine atom of formula XXI reacts similarly to the nitro and Y groups of formula IIA, VIA, and XXII, and thus can be subjected to the same series of reactions as those described above for the latter three compounds, providing an alternate means for preparing the products of such reactions. Similarly, the alkoxy group of formula XXI (R^{18}=alkoxy) may be converted into a hydroxyl group before or after introduction of the nitro group, and then converted to isomeric products as described above. Also, the trifluoromethanesulfonate salt of such hydroxy derivative can act as a Y-group as described.

Preparation of compounds of formula I where R^2 = -O(C_1-C_6)alkyl, (C_1-C_6) alkyl or aryl wherein aryl is defined as above in the definition of formula I, and R^3 is H or one of the other substituents described above in the definition of formula I, can be prepared as described above and illustrated in Scheme 8 by replacing one of the fluorine atoms of the compound of formula XV with -O-(C_1-C_6)alkyl, (C_1-C_6)alkyl or aryl, respectively.

Scheme 9 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 9, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV 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 IV 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 IV with N-iodosuccinimide or N-bromosuccinimide in a ~~trifluoromethanesulfonic~~ trifluoromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

Reaction of the compound of IV 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~~ acylation 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 IV, as depicted in Scheme 9 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$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, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy ~~substited~~ substituted compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles.

Scheme 10 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 10, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula IX' 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 by 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,N-dimethylpropylurea (DMPU) or DMSO, preferably DMF, at a temperature from about 50°C to about 180°C, preferably about 150°C. Nitrogen deprotection as described above provides the desired compound of formula IM.

The above described iodide 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 IX' provides the compound of the formula IP.

The compound of formula IX' 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 $-COCF_3$, $-COCCl_3$, $-COOCH_2CCl_3$, $-COO(C_1\text{-}C_6)$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.

In each of the reactions discussed above, or illustrated in Schemes 1-10, 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 Arneric, 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

10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1,4-Dihydro-1,4-methano-naphthalene

(Based wholly or in part on a) Wittig, G.; Knauss, E. *Chem. Ber.* **1958**, *91*, 895. b) Muir, D. J.; Stothers, J. B. *Can. J. Chem.* **1993**, *71*, 1290.)

Magnesium turnings (36.5 g, 1.5 M) were stirred in anhydrous THF (250 mL) in a dried 2 L 3 neck round bottom flask equipped with a 250 mL non-equalizing addition funnel with a nitrogen (N_2) flow adapter, mechanical stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2-Fluorobromobenzene (2g) was added followed by 1 mL of 3N ethylmagnesium bromide (EtMgBr in THF). The addition funnel was charged with a mixture of cyclopentadiene (94.4 g, 1.43 M. Prepared by the method described in: *Org. Syn.* Col. Vol. V, 414-418) and bromofluorobenzene (250 g, 1.43 M) which was maintained at 0 °C in a separate flask by an ice bath, and transferred to the addition funnel via cannula. Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation), the heating mantle was removed and the contents of the addition funnel was added dropwise at such rate as to maintain reflux (1.5 hours). The heating mantle was re-applied and a reflux maintained for 1.5 hours. (TLC 100% hexanes R_f 0.67).

The reaction was cooled to room temperature and quenched with H_2O (500 mL) and carefully with 1N HCl (200 mL, produces H_2 evolution from unconsumed Mg). To this ~50 mL

concentrated HCl was added to dissolve solids. Total addition/quench time ~1 hour. Saturated aqueous sodium chloride (NaCl) solution (300mL) was added and product hexanes extracted until no potassium permanganate ($KMnO_4$) active product is removed. (4 x ~250 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (250 mL), sodium bicarbonate Na_2SO_4 dried and concentrated to an oil (~200 g). The product was distilled at 78-83 °C @15mm (131 g, 64%). (An alternative workup is described on p.419 Fieser and Fieser, Vol. I, Reagents for Organic Synthesis, Wiley, NY., NY.; 1967).

B) 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol

(Except for the workup method and the quantity of OsO_4 used, based on VanRheenen, V.; Cha, D.Y.; Hartley, W. M. *Org. Syn.* **1988**, *6*, 342.)

In a 2 L 3 neck round bottom flask equipped with a N_2 flow adapter, mechanical stirrer was placed 1,4-dihydro-1,4-methano-naphthalene (79.5 g, 560 mmol) stirred in acetone (800 mL) and H_2O (100 mL) and N-methyl morpholine N-oxide (67.5 g, 576 mmol). To this was added osmium tetroxide (OsO_4) (15 mL of a 15mol% t-BuOH solution, 1.48 mmol, 0.26mol%) and the mixture was stirred vigorously. After 60 hours, the reaction was filtered, and the white product rinsed with acetone and air dried (60.9 g). The mother liquor was concentrated to an oily solid: acetone trituration, filtration and acetone rinse provided (27.4 g, total 88.3 g, 89%). (TLC 50% EtOAc/hexanes R_f ~0.5). mp 176-177.5 °C.

C) 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(Based on Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849; and Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455.)

1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round bottom flask under nitrogen with cool water bath (~10 °C). To this sodium periodate ($NaIO_4$) (51 g, 239 mmol) and triethylbenzyl ammonium chloride (Et_3BnNCl) (50 mg) were added. The resulting mixture was stirred for 1 hour (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with DCE (200 mL). The organic layer was washed with H_2O (4 x 200 mL, or until no reaction to starch iodide is observed in the aqueous wash) then dried through a cotton plug. To this was added benzyl amine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 minutes then immediately transferred into the sodium triacetoxyborohydride $NaHB(OAc)_3$ /DCE (see below) over 10 minutes.

In a separate 2 L round botton flask flask under nitrogen was magnetically stirred $NaHB(OAc)_3$ (154 g, 0.727 mmol) in DCE (800 mL) at 0 °C (ice bath). To this was added the above mixture over 10 minutes, without delay after the dialdehyde and amine were mixed. The resulting orange mixture was allowed to warm to room temperature and stirred for 30-60 minutes.

The reaction was quenched by addition of saturated sodium carbonate (Na_2CO_3) solution (~300 mL) carefully at first and the mixture was stirred for 1 hour (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, then evaporated to a red oil. This was dissolved in a minimum of Et_2O and filtered through a Silica pad (3 x 4 inch) eluting with 15% ethyl acetate (EtOAc)/hexanes +1% of 37% aqueous ammonium hydroxide (NH_4OH) solution to remove baseline red color. Concentration affords a light yellow oil (48.5 g, 194.8 mmol, 85.7%). (TLC 10% EtOAc/hexanes R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 7H), 6.89 (m, 2H), 3.48 (m, 2H), 3.08 (m, 2H), 2.80 (d, J=9.5 Hz, 2H), 2.42 (d, J=9.5 Hz, 2H), 2.27 (m, 1H), 1.67 (d, J=10.0 Hz, 1H). APCI MS *m/e* 250.3 [(M + 1)$^+$].

D) 10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (For an alternative synthesis, see; Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455.)

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3N HCl EtOAc (1.03 eq.) slowly with cooling (ice bath). The resulting precipitate was filtered and rinsed with EtOAc. The solids were dissolved in MeOH (250 mL) in a parr bottle. To this was added $Pd(OH)_2$ (7 g of 20%wt/C) and the mixture was shaken under 50-40 psi of H_2 for 24 hours or until done by TLC. The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotroped with methanol (MeOH) (3x) then triturated with acetone, treated with ethyl ether (Et_2O) to precipitate product and filtered. Concentration of the mother liquors and a second treatment provided an off white solid (48.95 g, 251 mmol, 88%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 4H), 2.97 (m, 4H), 2.68 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 1.95 (d, J=11.0 Hz, 1H). APCI MS *m/e* 160.2 [(M + 1)$^+$].

EXAMPLE 2

4-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 6-Fluoro-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (0.66 g, 27.2 mmol) were stirred in anhydrous THF (10 mL) in a flame dried 75 mL 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,5-Difluorobromobenzene (0.1 g) was added followed by of 3N EtMgBr in THF (0.1 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (1.71 g, 25.9 mmol) and 2,5-difluorobromobenzene (5.0 g, 25.9 mmol). Small portions (~0.2 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for 1 hour.

The reaction was cooled to room temperature and quenched with H_2O (20 mL) followed by aqueous 1N HCl solution (20 mL) to dissolve the solids. Saturated aqueous NaCl solution (30 mL) was added and product was extracted with hexanes (4 x 25mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil. Chromatography on Silica gel eluting with hexanes provided an oil (780 mg, 19%). (TLC hexanes R_f 0.38). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.80 (br s, 1H), 6.78 (br s, 1H), 6.59 (m, 1H), 3.87 (br s, 2H), 2.32 (d, J=7.0 Hz, 1H), 2.25 (d, J=7.0 Hz, 1H).

B) 6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

6-Fluoro-1,4-dihydro-1,4-methano-naphthalene (680 mg, 4.22 mmol) and N-methyl morpholine N-oxide (599 mg, 4.43 mmol) were stirred in acetone (50 mL) and H_2O (5 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt. solution in t-BuOH, 0.02 mmol). After 72 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1 hour. The florisil was filtered and the filtrate concentrated to produce a crystalline product which was triturated with acetone and filtered (524 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.10 (dd, J=8.0,5.0 Hz, 1H), 6.90 (dd, J=8.0,2.3 Hz, 1H), 6.75 (ddd, J=8.0,8.0,2.3 Hz, 1H), 3.79 (s, 2H), 3.18 (d, J=1.5 Hz, 2H), 2.22 (d, J=10.0 Hz, 1H), 1.92 (dd, J=10.0,1.5 Hz, 1H). GCMS *m/e* 194 (M^+).

C) 10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (524 mg, 2.68 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (15 mL) and H_2O (45 mL) then treated with sodium periodate (0.603 mg, 2.82 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 20 mL). The combined organic layer was washed with H_2O (4 x 20 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (0.308 mL, 2.82 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (1.82 g, 8.58 mmol) in DCE (50 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (520 mg, 80%). (TLC 2% acetone/CH_2Cl_2 R_f 0.40). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 6.88 (m, 2H), 3.48 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 2.27 (m, 1H), 1.69 (d, J=10.5 Hz, 1H).

D) 4-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (390 mg, 1.461 mmol), ammonium formate (3.04 g, 48.2 mmol) and 10%$Pd(OH)_2$/C (30 mg) were combined in MeOH (50 mL) and brought to reflux under N_2 for 1.5 hours. Ammonium formate (1.0 g) was added and reflux continued for 0.5 hour. The reaction mixture was filtered through a Celite pad which was rinsed with MeOH. The filtrate was concentrated. The residues were treated with saturated aqueous Na_2CO_3 solution (30 mL) and product extracted with methylene chloride (CH_2Cl_2) (3 x 25 mL). The organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. The residue was treated with 2N HCl MeOH (5 mL) and concentrated then taken up in minimum of MeOH and saturated with Et_2O. After stirring 18h, the white crystals were collected by filtration (86 mg, 28%). (TLC

5% MeOH/CH_2Cl_2 (NH_3) R_f 0.27). (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.83 (m, 2H), 2.89 (m, 4H), 2.61 (dd, J=12.0 Hz, 2H), 2.37 (m, 1H), 1.87 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.2 [(M + 1)$^+$]. (HCl salt) mp 260-262 °C.

EXAMPLE 3

4-METHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-methylbromobenzene. (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J=7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 2.98-2.90 (m, 4H), 2.63 (m, 2H), 2.35 (m, 1H), 2.32 (s, 3H), 1.87 (d, J=11.5 Hz, 1H). APCI MS *m/e* 174.2 [(M + 1)$^+$]. (HCl salt) mp 254-255 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.82; N, 5.15.

EXAMPLE 4

4-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* **1983**, *48*, 2321-2327. Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**. *30*. 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-trifluoromethylbromobenzene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H). 3.46 (m, 4H), 3.21 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 2.16 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 244-246 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.77; H, 4.82; N, 5.18.

EXAMPLE 5

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (s, 2H), 7.52 (m, 1H), 3.65 (br s, 1H), 3.49-3.43 (m, 3H). 3.20 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 275-277 °C.

EXAMPLE 6

3-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2,6-Difluoroiodobenzene (Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968,** *11*, 814-819. Tamborski, C.; Soloski, E. *J. Org. Chem.* **1966**, *31*, 746-749. Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* **1986**, *29*, 1972-1982.) 1,3-Difluorobenzene (57.05 g, 0.5 M) in THF (75 mL) was added to a -78 °C stirred solution of n-butyllithium (n-BuLi) (200 mL, 2.5 M/hexanes, 0.5 M) and THF (500 mL) under N_2. By controlling the addition rate the internal temperature was maintained below -70 °C. The total addition time was ~1/2 hour. The resulting slurry was stirred an additional 1/2 hour, then the dispersion was treated with a solution of iodine (126.9 g, 0.5 M) in THF (300 mL) at a rate that maintained an internal temperature below -70 °C. After complete addition the mixture was allowed to warm to room temperature, and was treated with H_2O (100 mL) and 10% aqueous $Na_2S_2O_3$ solution (100 mL) and stirred. The layers were separated and the aqueous layer extracted with hexanes (2 x 250 mL). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4) filtered and concentrated to give a yellow oil (106.5 g). Distillation at ~1-5 mm at ~80 °C provided a light yellow oil (89.5 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H), 6.87 (m, 2H). GCMS *m/e* 240 (M^+).

B) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene

A solution of 2,6-difluoroiodobenzene (5.0 g, 20.8 mmol) and cyclopentadiene (2.07 g, 31.3 mmol) was stirred at 0 °C in P. ether (70 mL, 40-60 °C) under N_2 and treated with n-BuLi (8.74 mL, 2.5M in hexanes, 21.8 mmol) dropwise over 10 minutes. The reaction was quenched after 15 minutes by addition of aqueous 1N HCl solution and the product was extracted with hexanes (3 x 50 mL). The combined organic layer was washed with H_2O (50 mL), saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on Silica gel provided product as an oil (1.5 g, 45%). (TLC hexanes R_f 0.55). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (ddd, J=7.0,1.0,0.8 Hz, 1H), 6.96 (ddd, J=8.5,8.3,7.0 Hz, 1H), 6.86 (br s, 2H), 6.72 (ddd, J=8.5,8.3,0.8 Hz, 1H), 4.25 (br s, 1H), 3.98 (br s, 1H), 2.36 (ddd, J=7.2,1.7,1.7 Hz, 1H), 2.30 (ddd, J=7.2,1.7,1.5 Hz, 1H). GCMS *m/e* 160 (M^+).

C) 3-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

The title compound was prepared by the methods described in Example 2B,C,D starting with 5-fluoro-1,4-dihydro-1,4-methano-naphthalene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (ddd, J=8.3,7.3,5.0 Hz, 1H), 7.21 (d, J=7.3 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 3.62 (br s, 1H), 3.42-3.30 (m, 3H), 3.21 (m, 2H), 2.38 (m, 1H), 2.12 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.4 [(M + 1)$^+$]. mp 269-271 °C.

EXAMPLE 7

4-NITRO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (12.4 g, 63.9 mmol) was stirred in CH_2Cl_2 (200 mL). This was cooled (ice bath) and treated with pyridine (12.65 g 160 mmol) followed by trifluoroacetic anhydride (TFAA) (16.8 g, 11.3 mL, 80 mmol) from an addition funnel over 10 minutes. After ~3 hours, the solution was poured into 0.5N aqueous HCl (200 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with 0.5N aqueous HCl (50 mL), H_2O (2 x 50 mL) and saturated aqueous $NaHCO_3$ solution (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 which crystallized to give white needles (15.35 g, 60.2 mmol, 94%). (TLC 30% EtOAc/hexanes R_f 0.53). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 4H), 4.29 (br d, J=12.6 Hz, 1H), 3.84 (br d, J=12.6 Hz, 1H), 3.51 (dd, J=12.6,1.5 Hz, 1H), 3.21 (br s, 1H), 3.10 (br s, 1H), 3.10 (br d, J=12.6 Hz, 1H), 2.37 (m, 1H), 1.92 (d, J=10.8 Hz, 1H). GCMS *m/e* 255 (M$^+$). mp 67-68 °C.

B) 1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described by Coon, C. L.; Blucher, W.G.; Hill, M. E. *J. Org. Chem.* **1973**, *25*, 4243.)

To a solution of trifluoromethanesulfonic acid (2.4 ml, 13.7 mmol) in CH_2Cl_2 (10 ml) stirred at 0 °C was slowly added nitric acid (0.58 ml, 27.4 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to -78 °C and treated with 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.5 g, 13.7 mmol) in CH_2Cl_2 (15 ml) dropwise from an addition funnel over 5 minutes. The reaction was stirred at -78 °C for 30 minutes then warmed to 0 °C for 1 hour. The reaction mixture was poured into a vigorously stirred ice (100 g). The layers were separated and the aqueous layer

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 saturated aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to give an orange oil that solidified on standing (4.2 g). Chromatography yielded pure product as a crystalline solid (3.2 g, 78%). (TLC 30% EtOAc/hexanes R_f 0.23). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J=8.0 Hz, 1H), 8.08 (br s, 1H), 7.37 (br d, J=8.0 Hz, 1H), 4.38 (br d, J=12.6 Hz, 1H), 3.94 (br d, J=12.6 Hz, 1H), 3.59 (br d, J=12.6 Hz, 1H), 3.43-3.35 (m, 2H), 3.18 (br d, J=12.6 Hz, 1H), 2.48 (m, 1H), 2.07 (d, J=10.8 Hz, 1H). GCMS *m/e* 300 (M^+).

C) 4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (182 mg, 0.61 mmol) was stirred with Na_2CO_3 (160 mg, 1.21 mmol) in MeOH (3 mL) and H_2O (1 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with CH_2Cl_2. The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with CH_2Cl_2 (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3(s) and product was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug and concentrated to an oil. This was dissolved in MeOH and treated with 1N HCl MeOH, concentrated to solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (73 mg, 50%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.38). ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.18 (dd, J=8.0,2.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 3.43 (br s, 2H), 3.28 (m, 2H), 3.07 (dd, J= 13.0,13.0 Hz, 2H), 2.24 (m, 1H), 2.08 (d, J=11.5 Hz, 1H). APCI MS m/e 205.1 [(M + 1)$^+$] mp 265-270 °C.

EXAMPLE 8

4-AMINO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (500 mg, 2.08 mmol) was stirred in 1,4-dioxane (40 mL) and treated with saturated aqueous Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (1.8 g, 8.31 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried through a cotton plug and concentrated to provide an oil (500 mg, 91%).

This oil (500 mg, 1.64 mmol) was dissolved in MeOH (30 mL), treated with 10%Pd/C (~50 mg) and hydrogenated under a H_2 atmosphere (45 psi) for 1 hour. The mixture was filtered through a Celite pad and concentrated to a clear oil (397 mg, 88%).

This oil (50 mg, 0.18 mmol) was stirred in 3N HCl EtOAc (3 mL) for 2 hours then concentrated to a white solid (25 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.10 (3H), 3.60 (br s, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.18 (m, 1H), 1.98 (d, J=11.5 Hz, 1H). APCI MS m/e 175.1 [(M + 1)$^+$] mp 189-192 °C.

EXAMPLE 9

N^1-[10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL]ACETAMIDE HYDROCHLORIDE

A) 1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Hydrogenation of 1-(4-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.0 g, 6.66 mmol) under a H_2 atmosphere (40 psi) and 10%Pd/C (200 mg) in MeOH over 1.5 hours, filtration through Celite and concentration affords a yellow oil (1.7 g). (TLC 50% EtOAc/hexanes R_f 0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 1H), 6.64 (br s, 1H), 6.57 (m, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.17-3.07 (m, 3H), 2.35 (m, 1H), 1.90 (d, J=10.8 Hz, 1H). GCMS *m/e* 270 (M$^+$).

B) N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-acetamide

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (850 mg, 3.14 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with triethyl amine (0.53 mL, 3.76 mmol) and acetyl chloride (0.23 mL, 3.2 mmol) then stirred 18 hours. Standard $NaHCO_3$ workup yielded an oil which was chromatographed to provide a clear oil (850 mg, 87%). (50% EtOAc/hexanes R_f 0.28).

C) N^1-[10-Azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl]acetamide hydrochloride

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-acetamide (100 mg, 0.32 mmol) was stirred with Na_2CO_3 (70 mg, 0.64 mmol) in MeOH (10 mL) and H_2O (2 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with EtOAc. The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with EtOAc (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3 (s) and product was extracted with EtOAc (3 x 20 mL). The organic layer was dried (sodium sulfate (Na_2SO_4)) and concentrated to an oil. This material was dissolved in MeOH and treated with 3N HCl EtOAc (3 mL), concentrated and recrystallized

from MeOH/Et_2O to provide a solid (40 mg, 50%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.02 (br m, NH), 7.65 (s, 1H), 7.55 (br s, NH), 7.38 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 3.33 (m, 4H), 2.96 (m, 2H), 2.13 (m, 1H), 2.00 (s, 3H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 217.2 [(M + 1)$^+$]. mp 225-230 °C.

EXAMPLE 10

6-METHYL-5-THIA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) N-(10-Trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5 -trien-4-yl)-thioacetamide

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide (850 mg, 2.72 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.1 g, 2.72 mmol) were combined in toluene (10 mL) and brought to reflux for 1.5 hours. After cooling the reaction was worked up with EtOAc/saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to produce product (410 mg, 44%). (50% EtOAc/hexanes R_f 0.38)

B) 6-Methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

The above oil, 2,2,2-trifluoro-N-(10-trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide, (360 mg, 1.05 mmol) was dissolved in MeOH (10 mL) and 1N NaOH (5 mL) and added to potassium ferricyanide ($K_3Fe(CN)_6$)(1.72 g, 5.23 mmol) in H_2O (10 mL). This mixture was warmed to 60 °C for 1.5 hours, cooled, concentrated and worked up with EtOAc/H_2O. This material was stirred in dioxane (20 mL) and treated with H_2O (50 mL) and Na_2CO_3 to achieve pH 10. To this was added di-t-butyldicarbonate (436 mg, 2.0 mmol) and the mixture was stirred for 18 hours. The reaction was concentrated, treated with H_2O and extracted with CH_2Cl_2. The product was chromatographed (Silica 30% EtOAc/hexanes R_f 0.41) to yield an oil (100 mg).

The above product was treated with 3N HCl/EtOAc (3 mL) and warmed to reflux for ~15 minutes then concentrated to a solid which was azeotroped with CH_2Cl_2 (2x). These solids were dissolved in a minimum amount of MeOH then saturated with Et_2O and stirred. The resulting white crystalline powder was collected by filtration (40 mg, 14%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, NH), 7.65 (s, 1H), 7.82 (s, 1H), 7.65 (br m, NH), 3.36 (m, 2H), 3.24 (m, 2H), 3.02 (m, 2H), 2.76 (s, 3H), 2.23 (m, 1H), 2.06 (d, J=10.8 Hz, 1H). APCI MS *m/e* 231.1 [(M + 1)$^+$]. mp 183-184 °C.

EXAMPLE 11

4,5-DINITRO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described in Coon, C. L.; Blucher, W. G.; Hill, M. E. *J. Org. Chem.* **1973**, *25*, 4243. For an additional related example of dinitration see: Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512.)

To a solution of trifluoromethanesulfonic acid (79.8 ml, 902.1 mmol) in CH_2Cl_2 (550 ml) stirred at 0 °C was slowly added nitric acid (19.1 ml, 450.9 mmol) generating a white precipitate. After 10 minutes, 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (50 g, 196 mmol) in CH_2Cl_2 (300 ml) was added dropwise from an addition funnel over 30 minutes. The reaction was stirred at 0 °C for 2.5 hours and then stirred at room temperature for 24 hours. The reaction mixture was poured into a vigorously stirred mixture of H_2O (500 ml) and ice (400 g). The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3 x 300 ml). The organic layer was combined and washed with H_2O (3 x 300 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution (200 mL) and H_2O (200 mL) then dried through a cotton plug and concentrated to solids. Trituration with EtOAc/hexanes produced off white solids which were filtered and dried (52 g, 151 mmol, 77%. The mother liquor was chromatographed to give an additional 4.0 g for a total of 56.0 g (82.8%). (TLC 50% EtOAc/hexanes R_f 0.29) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (s, 1H), 4.39 (br d, J=13.0 Hz, 1H), 3.98 (br d, J=13.0 Hz, 1H), 3.65 (d, J=13.0 Hz, 1H), 3.49 (br s, 1H), 3.44 (br s, 1H), 3.24 (br d, J=12.6 Hz, 1H), 2.53 (m, 1H), 2.14 (d, J=11.5 Hz, 1H). GCMS *m/e* 345 (M$^+$).

B) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.7 g, 10.7 mmol) and Na_2CO_3 (2.3 g, 21.4 mmol) were combined in MeOH (50 mL) and H_2O (20 mL) then warmed to reflux for 18 hours. The reaction was cooled, concentrated, treated with H_2O and extracted with CH_2Cl_2 (3 x 50 mL) then dried through a cotton plug. After concentration, the residue was chromatographed to provide brown solids. (1.9 g, 71%).

(TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.36). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 3.17 (br s, 2H), 3.11 (d, J=12.6 Hz, 2H), 2.53 (m, 1H), 2.07 (d, J=11.0 Hz, 1H). GCMS *m/e* 249 (M^+).

EXAMPLE 12

6-METHYL-7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene, (1.9 g, 7.6 mmol) was stirred in 1,4-dioxane (75 mL) and treated with saturated aqueous Na_2CO_3 solution (10 mL). To this was added di-t-butyldicarbonate (3.31 g, 15.2 mmol). After stirring 6 hours the reaction was treated with H_2O (50 mL) and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide product (1.9 g, 71%). (TLC 30% EtOAc/hexanes (NH_3) R_f 0.58). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.72 (br s, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.39 (br s, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.46 (m, 1H), 2.02 (d, J=11.0 Hz, 1H).

B) 4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.9 g, 5.44 mmol) was hydrogenated in MeOH under a H_2 atmosphere (45 psi) over 10%Pd/C (100 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (1.57 g, 100%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.14).

C) 6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (700 mg, 2.42 mmol) was dissolved in EtOH (10 mL) and acetic acid (HOAc) (1 mL) and treated with 1-ethoxyethylenemalononitrile (329 mg, 2.42 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was

chromatographed to provide brown solids (247 mg, 36%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28).

D) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Pilarski, B. *Liebigs Ann. Chem.* **1983**, 1078.)

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (80 mg, 0.267 mmol) was stirred in 50% aqueous NaOH solution (3 mL) and DMSO (1 mL) then treated with 1-iodopropane (0.03 mL, 0.321 mmol). This mixture was warmed to 40 °C for 2 hours then cooled, treated with H_2O and extracted with EtOAc. The organic layer was washed with H_2O (3x) then dried (Na_2SO_4), filtered and concentrated to an oil (90 mg, 0.253 mmol). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.15).

E) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (90 mg, 0.253 mmol) was dissolved in 3N HCl EtOAc (5 mL) and warmed to 100 °C for 1/2 hour. The mixture was cooled, concentrated, slurried in EtOAc, and filtered to provide a white solid (25 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, NH), 7.91 (s, 1H), 7.83 (br m, NH), 7.74 (s, 1H), 4.38 (m, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.10 (m, 2H), 2.87 (s, 3H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H) 1.85 (m, 2H), 0.97 (m, 3H). mp 147-150 °C.

EXAMPLE 13

5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.0 g, 3.45 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and treated with ethoxymethylenemalononitrile (421 mg, 3.45 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried

(Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (580 mg, 56%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28)

B) 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.95 (s, 1H), 7.67 (s, 2H), 3.45 (br s, 2H), 3.31 (d, J=12.5 Hz, 2H), 3.13 (d, J=12.5 Hz, 2H), 2.30 (m, 1H), 1.99 (d, J=11.5 Hz, 1H). APCI MS m/e 200.1 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 14

7-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.97 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 3.94 (s, 3H), 3.48 (m, 2H), 3.33 (d, J=12.2 Hz, 2H), 3.14 (d, J=12.2 Hz, 2H), 2.34 (m, 1H), 2.03 (d, J=11.5 Hz, 1H). APCI MS m/e 214.2 [(M + 1)$^+$].

EXAMPLE 15

6-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (br m, NH), 7.77 (br m, NH), 7.70 (s, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.05 (br d, J=11.0 Hz, 2H), 2.79 (s, 3H), 2.23 (m, 1H), 2.10 (d, J=10.8 Hz, 1H). GCMS m/e 213.5 (M$^+$).

EXAMPLE 16

6,7-DIMETHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl

ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, NH), 7.84 (s, 1H), 7.82 (br m, NH), 7.72 (s, 1H), 3.90 (s, 3H), 3.45 (m, 2H), 3.28 (m, 2H), 3.04 (m, 2H), 2.82 (s, 3H), 2.23 (m, 1H), 2.12 (d, J=11.0 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. mp 225-230 °C.

EXAMPLE 17

7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodopropane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 9.45 (br s, NH), 7.97 (s, 1H), 7.85 (s, 1H), 7.83 (br m, NH), 4.43 (m, 2H), 3.49 (m, 2H), 3.33 (m, 2H), 3.08 (m, 2H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.92 (m, 2H), 0.93 (m, 3H). APCI MS *m/e* 242.2 [(M + 1)$^+$]. mp 170-171 °C (subl.).

EXAMPLE 18

7-BUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (For conditions, see; Senskey, M. D.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *Tetrahedron Lett.* **1995**, *36*, 6217.)

4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (500 mg, 1.43 mmol) and 1-butylamine (1.42 mL, 14.3 mmol) were combined in THF (5 mL) and stirred 4 hours. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (3 x 30 mL) then dried (Na_2SO_4), filtered and concentrated to an oil. This oil was passed through a Silica gel filter column to remove baseline impurities eluting with 30% EtOAc/hexanes (510 mg, 1.41 mmol, 99%).

B) 4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (460 mg, 1.27 mmol) was treated with ammonium formate (850 mg, 12.7

mmol) and 10%$Pd(OH)_2/C$ (50 mg) in MeOH (20 mL) and brought to reflux for 1 hour then filtered through a Celite pad and concentrated. The solids were treated with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 (3 x 30 mL) and dried by filtration through a cotton plug to give an oil (440 mg, 100%).

C) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (440 mg, 1.27 mmol) was dissolved in EtOH (20 mL) and HOAc (2 mL) and treated with ethoxymethylenemalononitrile (186 mg, 1.52 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated, treated with H_2O and saturated aqueous Na_2CO_3 solution then extracted with EtOAc (3 x 50 mL) and dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide a yellow oil. (400 mg, 89%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.70).

D) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (brs, NH), 9.68 (s, 1H), 7.99 (s, 1H), 7.92 (br m, NH), 7.87 (s, 1H), 4.50 (m, 2H), 3.49 (m, 2H), 3.30 (m, 2H), 3.08 (m, 2H), 2.26 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.88 (m, 2H), 1.32 (m, 2H), 0.82 (t, J=7.0 Hz, 3H). APCI MS *m/e* 256.2 [(M + 1)$^+$]. mp 204-208 °C.

EXAMPLE 19

7-Isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and isobutylamine were converted to the title compound utilizing the methods described in Example 18A-D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.52 (s, 1H), 7.14 (s, 1H), 3.90 (dd, J=7.5,2.0 Hz, 2H), 3.04-2.97 (m, 4H), 2.70 (dd, J=12.8,2.3 Hz, 2H), 2.42 (m, 1H), 2.19 (m, 1H), 1.98 (d, J=10.5 Hz, 1H), 0.93 (m, 6H). APCI MS *m/e* 256.2 [(M + 1)$^+$]. mp 147-150 °C (subl.).

EXAMPLE 20

6-METHYL-7-ISOBUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Amino-5-isobutylamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (250 mg, 0.74 mmol) from Example 19B was dissolved in EtOH (10 mL) and HOAc (2 mL) and treated with 1-ethoxyethylenemalononitrile (118 mg, 0.87 mmol). The reaction proceeded as in Example 18C (18h) and was worked up similarly to provide product (TLC 3% MeOH/CH_2Cl_2 (NH_3) R_f 0.57).

B) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. APCI MS *m/e* 270.3 [(M + 1)$^+$]. mp 129-130 °C (subl.).

EXAMPLE 21

7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to 4-phenylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl at 75 °C for 4 hours in the coupling step. This was then converted to the title compound utilizing the methods described in Example 18B,C,D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (1H), 7.78-7.57 (m, 7H), 3.47-3.00 (m, 6H), 2.23 (m, 1H), 2.09 (d, J=11.5 Hz, 1H). APCI MS *m/e* 276.2 [(M + 1)$^+$]. mp 210-213 °C.

EXAMPLE 22

6-METHYL-7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and Example 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were

converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.73-7.56 (m, 5H), 7.32 (s, 1H), 3.46-2.99 (m, 6H), 2.66 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). APCI MS *m/e* 290.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 23

7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A-D, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. t-Boc precursor GCMS *m/e* 369 (M$^+$). (HCl salt) mp >250 °C.

EXAMPLE 24

6-METHYL-7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s ,1H), 7.27 (s ,1H), 7.02 (br s, , NH), 4.41 (t, J=13.0 Hz, 2H), 3.90 (s, 3H), 3.47-3.26 (m, 6H), 2.20 (m, 1H), 2.00 (d, J=11.5 Hz, 1H), 0.90 (s, 9H). t-Boc precursor APCI MS *m/e* 384.2 [(M + 1) $^+$]. mp >250 °C.

EXAMPLE 25

6,7-DIMETHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE (Based on the following procedure: Jones, R. G.; McLaughlin, K. C. *Org. Syn.* **1963**, *4*, 824. b) Ehrlich, J., Bobert, M. T. *J. Org. Chem.* **1947**, 522.)

4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (100 mg, 0.35 mmol) was warmed to 80 °C in H_2O (5 mL). To this butane 2,3-dione (0.034 mL, 0.38 mmol) was added under N_2 for 2 hours. The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml). The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an oil (120 mg, 100%). The oil was dissolved in 2N HCl MeOH (5 mL) and warmed to reflux for 30 minutes, then concentrated. Recrystallization from MeOH/Et_2O provided a white powder (50 mg, 43%). (TLC EtOAc R_f 0.14). ^{1}H NMR (400 MHz, DMSO-d_6)

δ 7.85 (s, 2H), 3.50 (br s, 2H), 3.32 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.64 (s, 6H), 2.24 (m, 1H), 2.13 (d, J=11.0 Hz, 1H). t-Boc precursor APCI MS *m/e* 340.3 [(M + 1)$^+$].

EXAMPLE 26

5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

A) 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.0 g, 8.70 mmol) was hydrogenated in MeOH (30 ml) under H_2 (45 psi) over $Pd(OH)_2$ (300 mg of 20 wt%/C, 10%wt). After 2.5 hours the reaction was filtered through a Celite pad and rinsed with MeOH (30 ml). The solution was concentrated to a light brown oil which crystallized (2.42 g, 96%). (TLC 10% MeOH/CH_2Cl_2 R_f 0.56). APCI MS *m/e* 286.2 [(M + 1)$^+$]. mp 129-131 °C.

B) 1-(5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.75 mmol) was stirred in THF (2 ml). This mixture was treated with H_2O (2 mL) and glyoxal sodium bisulfite addition compound hydrate (931 mg, 3.50 mmol) then stirred at 55 °C for 2.5 hours. The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml). The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an off white powder (329 mg, 60%). (TLC 25% EtOAc/hexanes R_f 0.40). mp 164-166 °C.

C) 5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene hydrochloride

1-(5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (320 mg, 1.04 mmol) was slurried in MeOH (2.0 ml) and treated with Na_2CO_3 (221 mg, 2.08 mmol) in H_2O (2.0 ml). The mixture was warmed to 70 °C for 2 hours, then concentrated, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was dried through a cotton plug and concentrated to give a light yellow oil (183 mg, 83%) which solidified upon standing (mp 138-140 °C). This material was dissolved in MeOH (10 mL), treated with 3M HCl/EtOAc (3 ml), concentrated and azeotroped with MeOH

(2 x 20 mL) to give solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (208 mg, 97%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (400 MHz, CD_3OD) δ 8.94 (s, 2H), 8.12 (s, 2H), 3.70 (m, 2H), 3.54 (d, J=12.5 Hz, 2H), 3.35 (d, J=12.5 Hz, 2H), 2.49 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). GCMS *m/e* 211 (M^+). mp 225-230 °C.

EXAMPLE 27

14-METHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene (207 mg, 0.98 mmol) was treated with 37% aqueous formaline solution (1 mL) and formic acid (1 mL) then warmed to 80 °C for 1 hour. The reaction was poured into water, made basic (NaOH, pH ~11) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on Silica gel to provide a yellow solid. This was stirred in MeOH (2 mL) and treated with 3N HCl EtOAc (2 mL). After concentration the solids were recrystallized from MeOH/Et_2O to afford product as a white solid (70 mg, 27%). (2% MeOH/CH_2Cl_2 (NH_3) R_f 0.47). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 7.80 (s, 2H), 3.37 (br s, 2H), 3.03 (m, 2H), 2.47 (m, 2H), 2.32 (m, 1H), 2.18 (br s, 3H), 1.84 (d, J=11.0 Hz, 1H). APCI MS *m/e* 226.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 28

5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (900 mg, 2.61 mmol) and potassium acetate (KOAc) (2.6 g, 26.1 mmol) were dissolved in DMSO (10 mL) and warmed with stirring to 100 °C for 16 hours. The mixture was cooled and diluted with H_2O (50 mL) then extracted with 80% EtOAc/hexanes (6 x 25 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and purified by chromatography to give an oil (575 mg, 70%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.56)

B) 2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (575 mg, 1.82 mmol) was hydrogenated in MeOH under a H_2 atmosphere at (45 psi) over 10%Pd/C (80 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (450 mg, 86%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.6). ^{1}H NMR (400 MHz, CD_3OD) δ 6.67-6.59 (m, 2H), 4.12 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.24 (m, 1H), 1.94 (d, J=10.5 Hz, 1H). GCMS *m/e* 286 (M^+).

C) 2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* **1990**, *27*, 335.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), trimethyl orthoformate (0.19 mL, 1.73 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 18 mg, 0.07 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. The mixture was cooled, treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered, concentrated and purified by chromatography to give an oil (110 mg, 71%). (TLC 20% EtOAc/hexanes R_f 0.40)

D) 5-Oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (110 mg, 0.37 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (78 mg, 0.74 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into aqueous 1N HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. The product was extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4), concentrated and chromatographed on Silica gel to produce an oil. (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.19).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (55 mg, 63%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 3.41 (m, 2H), 3.30 (m, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.47 (m, 1H), 2.15 (d, J=11.0 Hz, 1H). APCI MS *m/e* 201.03 [$(M + 1)^+$].

EXAMPLE 29

6-METHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), triethyl orthoacetate (0.34 mL, 1.83 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. Workup, isolation and purification as in Example 28C provided the title compound (90 mg, 55%).

B) 6-Methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (90 mg, 0.30 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (61 mg, 0.58 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The solution was dried (Na_2SO_4), concentrated, and chromatographed on Silica gel to produce an oil. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.18). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.26 (s, 1H), 3.05-2.98 (m, 4H), 2.72 (d, J=12.8 Hz, 2H), 2.59 (s, 3H), 2.46 (m, 1H), 1.98 (d, J=10.5 Hz, 1H).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (10 mg, 13%). APCI MS *m/e* 215.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 30

2-FLUORO-N-(5-HYDROXY-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-BENZAMIDE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), 2-fluorobenzoyl chloride (0.07 mL, 0.576 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol), pyridine (0.046 mL, 0.576 mmol) and xylenes (5 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. After 24 hours, additional PPTS (50 mg) was added and the material stirred at 135 °C for an additional 24 hours. Workup as above provided crude product (145 mg, 0.375 mmol) which was

combined with Na_2CO_3(s) (80 mg, 0.75 mmol) in MeOH (5 mL) and H_2O (2 mL) and heated to reflux. After 3 hours, the reaction was cooled and diluted with water then extracted with CH_2Cl_2 (4 x 40 mL), dried through a cotton plug then chromatographed to remove baseline impurity (5% MeOH/CH_2Cl_2 (NH_3)). The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of MeOH and the solution was saturated with Et_2O and stirred. After stirring 4 hours the product was collected by filtration (85 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (m, 2H), 7.59 (m, 1H), 7.36-7.23 (m, 2H), 6.82 (s, 1H), 2.99 (m, 4H), 2.78 (m, 2H), 2.35 (m, 1H), 1.96 (d, J=10.5 Hz, 1H). APCI MS *m/e* 313.1 [(M + 1)$^+$]. mp 125-130 °C (subl.).

EXAMPLE 31

4-CHLORO-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Copper(I)chloride (CuCl) was prepared as follows: $CuSO_4$ (4.3 g) and NaCl (1.2 g) were dissolved in hot H_2O (14 mL). sodium bisulfite ($NaHSO_3$) (1 g) and sodium hydroxide (NaOH) (690 mg) were dissolved in H_2O (7 mL) and added to the hot acidic solution over 5 minutes. The precipitated white solids were filtered and washed with water.

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (460 mg, 1.7 mmol) was dissolved in H_2O (2 mL) and concentrated HCl solution(1 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (275 mg) in H_2O (1 mL) dropwise. To the resulting solution was added a CuCl (202 mg, prepared as described above, 2.04 mmol) in concentrated HCl solution (2 mL) over 10 minutes (gas evolution observed). The resulting solution was warmed to 60 °C for 15 minutes, then was cooled to room temperature and extracted with EtOAc (4 x 30 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to an oil which was filtered through a Silica pad to remove baseline material eluting with 50% EtOAc/hexanes to give an oil (470 mg, 95%).

B) 4-Chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (470 mg, 1.62 mmol) and Na_2CO_3 (344 mg, 3.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were heated to reflux. After 2 hours, the reaction was cooled and diluted with water then extracted with EtOAc (4 x 40 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude material was treated with excess 3N HCl EtOAc and concentrated, then

dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred. After stirring 4 hours the product was collected by filtration (155 mg, 42%). ^1H NMR (free base) (400 MHz, $CDCl_3$) δ 7.15 (m, 2H), 7.09 (d, J=8.0 Hz, 1H), 3.00-2.94 (m, 4H), 2.68, (m, 2H), 2.38 (m, 1H), 1.92 (d, J=10.5 Hz, 1H). ^1H NMR (HCl salt) (400 MHz, DMSO-d_6) δ 7.30-7.20 (m, 3H), 3.30-3.15 (m, 6H), 2.37 (m, 1H), 1.89 (d, J=11.0 Hz, 1H). APCI MS *m/e* 194.1 [(M + 1)$^+$].

EXAMPLE 32

10-AZATRICYCLO[6.3.1.0~2,7~]DODECA-2(7),3,5-TRIEN-4-YL CYANIDE HYDROCHLORIDE

A) 1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.85 mmol) was dissolved in H_2O (5 mL) and concentrated H_2SO_4 solution (0.5 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (140 mg, 2.04 mmol) in H_2O (2 mL) dropwise. Potassium iodide (460 mg, 2.78 mmol) in 1N H_2SO_4 solution (0.5 mL) was added over 10 minutes (reaction becomes dark red). The resulting solution was warmed to room temperature and stirred 18 hours. The reaction was quenched with $NaHSO_3$ and water (pH 2.5) then extracted with EtOAc (4 x 30 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to a yellow oil which was chromatographed on Silica gel to provide a yellow oil. (260 mg, 37%). (TLC 30% EtOAc/hexanes R_f 0.70). (A 5.4 g scale performed as above yielded 5 g, 67%).

B) 4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (5 g, 13.1 mmol) and 37% saturated aqueous NH_4OH solution (50 mL) were stirred in MeOH (250 ml) for 2 hours then concentrated and azeotroped with MeOH (2 x 50 mL). The resulting product was stirred in 1,4-dioxane (75 mL) and treated with saturated Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (5.71 g, 26.2 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel (TLC 20% EtOAc/hexanes) to provide product as an oil (4.9 g, 98%).

C) 4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (Utilizing the methods described in: House, H. O.; Fischer, W. F. *J. Org. Chem.* **1969**, 3626.)

CuCN (108 mg, 1.21 mmol) and NaCN (59 mg, 1.21 mmol) were combined in dry DMF (6 mL) and warmed to 150 °C under N_2. Solution occurs in 20 minutes. To this was added 4-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (232 mg, 0.6 mmol) in DMF (3.5 mL) and the mixture was stirred for 18 hours at 150 °C. The reaction was cooled and diluted with 50% saturated aqueous NaCl solution and extracted with 50% EtOAc/hexanes (3 x 30 mL). After drying (Na_2SO_4), filtration and concentration the product was isolated by chromatography (86 mg, 50%). (TLC 20% EtOAc/hexanes R_f 0.28).

D) 10-Azatricyclo[6.3.1.0~2,7~]dodeca-2(7),3,5-trien-4-yl cyanide hydrochloride

4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester was treated with 3N HCl EtOAc (6 mL) and warmed to reflux for 2 hours, then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (49 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (br s, NH), 7.86 (br s, NH), 7.74-7.70 (m, 2H), 7.49 (d, J=7.5 Hz, 1H), 3.33-2.97 (m, 6H), 2.17 (m, 1H), 2.01 (d, J=11.0 Hz, 1H). GCMS *m/e* 184 (M^+). mp 268-273 °C.

EXAMPLE 33

3-(10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-5-METHYL-1,2,4-OXADIAZOLE HYDROCHLORIDE

4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (300 mg, 1.1 mmol) was stirred in EtOH (10 mL). To this hydroxyl amine hydrochloride (382 mg, 5.5 mmol) and NaOH (242 mg, 6.05 mmol) were added and the mixture was warmed to reflux. After 45 minutes, the reaction was cooled, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid (110 mg, 0.35 mmol). This solid was dissolved in pyridine (1 mL) and treated with acetyl chloride (0.03 mL, 0.415 mmol) and warmed to 100°C for 18 hours. The reaction was cooled, treated with H_2O and extracted with EtOAc. The organic extracts were washed with water and saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel afforded product (50 mg, 0.15 mmol). (25% EtOAc/hexanes R_f 0.18). This product was treated with 2N HCl MeOH (10 mL), heated to 70 °C for 1 hour, cooled, concentrated and recrystallized from MeOH/Et_2O to provide product (15 mg). APCI MS *m/e* 242.2 [(M + 1)$^+$].

EXAMPLE 34

1-(10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-1-ETHANONE HYDROCHLORIDE

A) 1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (253 mg, 1.0 mmol) and AcCl (0.68 mL, 10 mmol) were dissolved in DCE (3 mL) and treated with aluminum chloride ($AlCl_3$) (667 mg, 5.0 mmol). The resulting yellow mixture was stirred for 30 minutes then poured over ice and saturated aqueous $NaHCO_3$ solution. After stirring 20 minutes the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug then concentrated to a orange-yellow oil (255 mg, 86%).

B) 4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.3 g, 4.37 mmol) and 37% aqueous NH_4OH solution (10 mL) were stirred in MeOH (30 ml) for 3 hours, then concentrated and azeotroped with MeOH (2 x 50 mL). (This product could be converted to an HCl salt directly: see the next example.) The resulting product was stirred in 1,4-dioxane (20 mL) and treated with saturated aqueous Na_2CO_3 solution (5 mL). To this was added di-t-butyldicarbonate (1.91 g, 8.74 mmol). After stirring 2 hours, the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide an oil (1.3 g, 100%). (TLC 40% EtOAc/hexanes R_f 0.56).

C) 1-(10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone hydrochloride

4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (190 mg, 0.63 mmol) was treated with excess 3N HCl EtOAc and warmed to 70°C for 1 hour then concentrated and dissolved in a minimum of MeOH. The resulting solution was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (81 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (br s, NH), 7.89 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.74 (br s, NH), 7.44 (d, J=8.0 Hz, 1H), 3.33 (br s, 2H), 3.22 (br s, 2H), 3.00 (br m, 2H), 2.54 (s, 3H), 2.17 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). GCMS *m/e* 201 (M^+). mp 198-202 °C.

EXAMPLE 35

10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-OL HYDROCHLORIDE

A) Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.5 g, 8.41 mmol) and 3-chloroperoxybenzoic acid (m-CPBA) (7.5 g, 42 mmol) were stirred in CH_2Cl_2 (20 mL) and warmed to 40°C for 18 hours. The mixture was cooled to room temperature, then treated with dimethylsulfide (Me_2S) (3 mL, 40.8 mmol) and stirred 24 hours. The resulting mixture was poured into ice and saturated aqueous Na_2CO_3 solution (100 mL) then extracted with Et_2O (4 x 40 mL). The organic layer was washed saturated aqueous Na_2CO_3 solution (3 x 40 mL) then dried (Na_2SO_4), filtered and concentrated to afford an oil (1.83 g, 69%). (TLC EtOAc R_f 0.80).

B) 2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (900 mg, 2.87 mmol) was stirred in MeOH (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) for 48 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Chromatography on Silica gel provided pure product (420 mg, 54%). (TLC 5% MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 1H), 6.70 (m, 1H), 6.62 (m, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.48 (m, 1H), 3.21 (br s, 1H), 3.16 (br s, 1H), 3.09 (m, 1H), 2.38 (m, 1H), 1.97 (d, J=11.0 Hz, 1H).

C) 10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol hydrochloride

2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (50 mg, 0.184 mmol) was dissolved in MeOH/H_2O (3/1, 5 mL), treated with Na_2CO_3(s) (40 mg, 0.369 mmol) and warmed to 65°C for 2 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Filtration through a Silica gel plug provided an oil (10% MeOH/CH_2Cl_2) which was treated with 3N HCl EtOAc (3 mL) then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (10 mg, 26%). ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.16 (d, J=8.0 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.72 (dd, J=8.0,2.0 Hz, 1H), 3.32-3.28 (4H), 3.09 (dd, J=14.5,12.0 Hz, 2H), 2.32 (m, 1H), 2.03 (d, J=11.0 Hz, 1H). APCI MS *m/e* 176.2 [(M + 1)$^+$]. mp 308 (dec.) °C.

EXAMPLE 36

7-METHYL-5-OXA-6,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2.4(8),6,9-TETRAENE HYDROCHLORIDE

A) 1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (800 mg, 2.55 mmol) was combined with $AlCl_3$ (1.0 g, 7.65 mmol) and warmed to 170°C for 2 hours. The mixture was cooled and treated with 1N aqueous HCl solution (20 mL), extracted with EtOAc and dried (Na_2SO_4). Chromatography affords an oil (190 mg, 24%). (TLC EtOAc R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 0.5H), 12.52 (s, 0.5H), 7.53 (s, 1H), 6.86 (s, 1H), 4.33 (m, 1H), 3.91 (m, 1H), 3.56 (m, 1H), 3.28 (br s, 1H), 3.24 (br s, 1H), 3.14 (m, 1H), 2.35 (m, 1H), 1.97 (br d, J=11.2 Hz, 1H).

B) 2,2,2-Trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone

1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (190 mg, 0.605 mmol), hydroxylamine HCl (99 mg, 1.21 mmol) and NaOAc (118 mg, 1.21 mmol) were combined in MeOH (4 mL) and H_2O (1 mL) and warmed to 65°C for 18 hours. The mixture was cooled, diluted with H_2O and extracted with EtOAc which was dried (Na_2SO_4), filtered and concentrated to provide a yellow oil (177 mg, 93%).

C) 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone

The above oil, 2,2,2-trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone (177 mg, 0.54 mmol) was stirred in DCE (3 mL), treated with triethylamine (0.4 mL, 2.8 mmol) and acetic anhydride (Ac_2O) (0.3 mL, 2.8 mmol) then stirred 18 hours. The reaction was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated to a yellow oil which was dissolved in anhydrous DMF (3 mL) and treated with 60% NaH in oil (32 mg, 1.08 mmol). After stirring 18 hours, additional 60% NaH in oil was introduced (33 mg) and the mixture was stirred 2 hours. The reaction was quenched with H_2O (5 mL) and extracted with 80% EtOAc/hexanes (3 x 30 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and chromatographed to provide an oil (40% EtOAc/hexanes R_f 0.56).

D) 7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2,4(8),6,9-tetraene hydrochloride

Utilizing the methods described in Example 9C, 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2.4(8),6,9-tetraene-ethanone was converted to the title compound. This was treated with 3N HCl EtOAc (3 mL), concentrated and dissolved in a minimum of CH_2Cl_2 which was saturated with hexanes and stirred. After 18 hours the white crystalline product was collected by filtration (18 mg, 13% overall). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.63 (s, 1H), 3.42-2.98 (m, 6H), 2.50 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=10.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 37

4-(2-Methyl-2H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride and 4-(1-Methyl-1H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1. $0^{2.7}$dodeca-2(7),3,5-triene hydrochloride

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.0 g, 3.3 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (4.0 g, 33.6 mmol) were warmed to 140°C for 18 hours. After cooling, a crystalline precipitate was filtered and rinsed with EtOAc (690 mg, 58%).

The above solid, 3-dimethylamino-1-(10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl)-propenone, (200 mg, 0.56 mmol) was dissolved in EtOH (2 mL) and treated with 5N HCl EtOH (0.1 mL) followed by methyl hydrazine (0.6 mmol). The resulting mixture was warmed to 70°C for 4 hours. The mixture was cooled, diluted with water and extracted with EtOAc, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel provided a 3/1 mixture of regioisomeric products (130 mg, 68%). (TLC 50% EtOAc/hexanes R_f 0.40).

The above oil (130 mg, 0.388 mmol) and Na_2CO_3(s) (82 mg, 0.775 mmol) were stirred in MeOH (10 mL) and H_2O (5 mL) for 18 hours. After cooling the reaction was diluted with water, extracted with CH_2Cl_2 dried through a cotton plug and concentrated. The product was purified by chromatography on Silica gel and concentrated to an oil. The salt was generated with 2N HCl MeOH, concentrated and recrystallized from MeOH/EtOAc to provide a 3/1 mixture of regioisomeric pyrrazoles (85 mg, 58%). (5% MeOH/CH_2Cl_2 (NH_3) R_f 0.25). TFA-precursor APCI MS *m/e* 336.2 [(M + 1)$^+$].

EXAMPLE 38

4,5-DICHLORO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on Campaigne, E.; Thompson, W. *J. Org. Chem.* **1950**, *72*, 629.)

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (539 mg, 2.1 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with ICl_3 (s) (982 mg, 4.21 mmol). The resulting orange solution was stirred 0.5 hours, poured into saturated aqueous $NaHSO_3$ solution (25 mL), extracted with CH_2Cl_2 (3 x 25 mL), dried through a cotton plug and concentrated to an oil (570 mg, 84%) (TLC 50% EtOAc/hexanes R_f 0.62).

B) 4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (570 mg, 1.75 mmol) was stirred in MeOH (25mL) and treated with Na_2CO_3(s) (5 g, 47 mmol) in H_2O (5 mL). The stirred mixture was warmed to 70°C for 4 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into 1N aqueous HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. Product was extracted with CH_2Cl_2 (3 x 40 mL), filtered through a cotton plug and concentrated to an oil (400 mg, 100%).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (210 mg, 45%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.08). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 2H), 3.33-2.97 (m, 6H), 2.18 (m, 1H), 1.99 (d, J=10.5 Hz, 1H). ^{13}C NMR (100 MHz,DMSO-d_6) δ 141.02, 130.60, 126.58, 45.54, 40.55, 38.30. GCMS *m/e* 227, 229 (M^+). mp 283-291 °C.

EXAMPLE 39

N^4,N^4-DIMETHYL-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE-4-SULFONAMIDE HYDROCHLORIDE

A) 10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (530 mg, 2.1 mmol) was added to chlorosulfonic acid (2 mL, 30 mmol) and stirred for 5 minutes.

The mixture was quenched with ice, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to provide an oil (640 mg, 87%). (TLC 30% EtOAc/hexanes R_f 0.15).

B) N^4,N^4-Dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide hydrochloride

10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) was stirred in THF (10 mL) and treated with 40% Me_2NH/H_2O (1.5 mL). After 10 minutes the mixture was concentrated and chromatographed on Silica gel (TLC 30% EtOAc/hexanes R_f 0.31) to provide an oil (256 mg, 78%). This material was dissolved in MeOH (6 mL) and NH_4OH (2 mL) and stirred 18 hours. The mixture was concentrated and azeotroped from MeOH (3x) The resulting oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL), concentrated, dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration as a white powder (163 mg, 59%). (TLC 10% MeOH/ CH_2Cl_2 (NH_3) R_f 0.54). ^{1}H NMR (data, free base) (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.41 (d, J=8.0 Hz, 1H), 3.30 (m, 2H), 3.20 (d, J=12.5 Hz, 2H), 3.07 (dd, J=12.5,2.2 Hz, 2H), 2.69 (s, 6H). 2.45, (m, 1H), 2.00 (d, J=11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128,43, 124.16, 122,75, 46.67, 46.55, 42.11, 39,44, 37,81. GCMS *m/e* 266 (M^+). (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68-7.52 (3H), 3.38 (m, 2H), 3.24 (m, 2H), 3.04 (m, 2H), 2.58 (s, 6H), 2.22 (m, 1H), 2.04 (d, J=11.0 Hz, 1H). GCMS *m/e* 266 (M^+). Anal. Calcd. for $C_{13}H_{18}N_2O_2HCl$: C, 51.56; H, 6.32; N, 9.25. Found C, 51.36; H,6.09; N,9.09.

EXAMPLE 40

4-(1-PYRROLIDINYLSULFONYL)-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The pyrrolidine analogue was prepared from 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) as by substituting pyrroline in the coupling step described in Example 39B. The TFA product was isolated as an oil (314 mg, 89%). Deprotection and conversion to the salt as in Example 39B affords a white powder (189 mg. 63%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.60). (TLC 50% EtOAc/hexanes R_f 0.65). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=8.0 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J=8.0 Hz, 1H), 3.30-3.15 (m, 8H), 3.00 (m 2H), 2.39 (m, 1H), 1.98 (d, J=11.5 Hz, 1H), 1.72 (m, 4H). ^{13}C NMR (100 MHz. $CDCl_3$) δ 146.91, 144.08, 136.65, 127. 90, 124.18, 122.36, 50.43, 47.87, 46.80, 46.63, 42.11, 39.63, 25.10. APCI MS *m/e* 293 [(M + 1) $^+$]. (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (br s, NH), 8.1 (br s, NH), 7.73 (d, J =1.5 Hz,1H), 7.66

(dd, J=8.0,1.5 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 3.39-3.01 (10H), 2.21 (m, 1H), 2.04 (d, J=11.0 Hz, 1H), 1.66 (m, 4H). GCMS *m/e* 292 (M^+). Anal. Calcd. For $C_{13}H_{18}N_2O_2HCl.1/2MeOH$: C, 54.07; H, 6.47; N, 8.51. Found C, 53.98; H,6.72; N, 8.12

EXAMPLE 41

5,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2,4(8),9-TRIEN-6-ONE HYDROCHLORIDE (The title compound was prepared following the procedures described in Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53, treating 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester as an equivalent to an ortho fluoro phenyl moiety.) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, NH), 9.88 (br s, NH), 7.52 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 3.41 (d, J=5.0 Hz, 2H), 3.35-3.13 (m, 4H), 2.93 (m, 2H), 2.12 (m, 1H), 1.95 (d, J=11.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 42

6-OXO-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE (For references, see: Nachman, R. J. *J. Het. Chem.* **1982**, 1545.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (317 mg, 1.11 mmol) was stirred in THF (10 mL), treated with carbonyldiimidazole (269 mg, 1.66 mmol) and warmed to 60°C for 18 hours. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL) and washed with 1N aqueous HCl solution (3 x 10 mL). The organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel (50% EtOAc/Hexanes) to provide an oil (130 mg). This material converted to the title compound by the methods described in Example 9C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, NH), 9.56 (br s, NH), 7.63 (br s, NH), 7.24 (s, 1H), 7.07 (s,1H), 3.26 (br s, 2H), 3.16 (br t, J=9.5 Hz, 1H), 2.93 (br s, 1H), 2.18 (m, 1H), 1.97 (d, J=11.0 Hz, 1H). APCI MS *m/e* 217.2 [(M + 1)$^+$].

EXAMPLE 43

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* **1983**, *48*, 2321-2327. Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.67-7.50

(3H), 3.65 (br s, 1H), 3.49-3.42 (m, 2H), 3.29 (s, 1H), 3.28-3.16 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 275-277 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.83; N, 5.16.

EXAMPLE 44

3-PHENYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene and 5-iodo-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (9.37 g, 385 mmol) were stirred in anhydrous THF (1000 mL) in a flame dried 2L 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,6-Difluoro-iodobenzene (0.3 g) was added followed by of 3N EtMgBr in THF (0.3 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (24.24 g, 367 mmol) and 2,6-difluoro-iodobenzene (88.0 g, 367 mmol). Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for ~1 hour (no SM by GCMS).

The reaction was cooled to room temperature and quenched with H_2O (200 mL) followed by aqueous 1N HCl solution (200 mL) to dissolve the solids. Product was extracted with hexanes (4 x 150 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil (70 g). Chromatography on Silica gel eluting with hexanes provided two lots (9.0 and 21.0 g), which contained primarily 5-iodo-1,4-dihydro-1,4-methano-naphthalene. (TLC hexanes R_f 0.63).

B) 5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

5-Iodo-1,4-dihydro-1,4-methano-naphthalene (20 g) and N-methyl morpholine N-oxide (17.61 g, 130 mmol) were stirred in acetone (90 mL) and H_2O (13 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt. solution in t-BuOH, 0.02 mmol). After 144 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1/2 hour. The

mixture was filtered through a Celite pad and the filtrate concentrated to produce an oil which was purified by chromatography on Silica gel eluting with a gradient of hexanes to 100% EtOAc to provide a yellow solid (13.73 g). APCI MS *m/e* 301.1 [(M - 1)$^+$].

C) 10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (8.33 g, 27.6 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (25 mL) and H_2O (75 mL) then treated with sodium periodate (6.17 g, 29.0 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 40 mL). The combined organic layer was washed with H_2O (4 x 30 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (30 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (3.16 mL, 29.0 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (18.72 g, 88.0 mmol) in DCE (150 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (6.3 g, 61%). (TLC 5% EtOAc/hexanes R_f 0.10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J= 8.0 Hz, 1H), 7.28-7.22 (m, 3H), 7.13 (d, J=8.0 Hz,1H), 6.98-6.94 (m, 3H), 3.58 (AB dd, J=14.2 Hz, 2H), 3.26 (br s, 1H), 3.21 (br s, 1H), 3.04 (br d, J=10.2 Hz, 1H), 2.83 (br d, J=10.2 Hz, 1H), 2.47 (d, J=10.0 Hz, 1H), 2.39 (d, J=10.0 Hz, 1H), 2.34 (m, 1H), 1.72 (d, J=10.5 Hz, 1H). APCI MS *m/e* 376.0 [(M + 1)$^+$].

D) 10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

(For a discussion, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.)

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (375.3 mg, 1.0 mmol), potassium acetate (785 mg, 8.0 mmol) and phenyl boronic acid (183 mg, 1.5 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) (57.5 mg, 0.05 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 (180 mg, 55%). (TLC 4%EtOAc/hexanes R_f 0.18). GCMS *m/e* 325 (M)$^+$.

E) 3-Phenyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene was converted into the title compound utilizing the conditions described in Example 2D. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.30). (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.15 (8H), 3.17 (br s, 1H), 3.01 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.72 (dd, J=10.5,2.5 Hz, 1H), 2.63 (dd, J=10.5,2.5 Hz, 1H), 2.41 (m, 1H), 1.91 (d, J=10.5 Hz, 1H). APCI MS *m/e* 236.2 [(M + 1)$^+$]. (HCl salt) mp 262-265 °C. Anal. Calcd. for $C_{17}H_{17}N.HCl.1/3H_2O$: C, 73.26; H, 6.86; N, 5.19. Found C, 73.50; H, 6.77; N, 5.04.

EXAMPLE 45

3-HYDROXY-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (3.0 g, 7.99 mmol) was stirred in anhydrous THF (40 mL) at -78 °C under nitrogen and treated dropwise with n-BuLi (3.84 mL of 2.5M soln. in hexanes, 9.59 mmol). After 10 minutes, tri-isopropylborate (4.61 mL, 20.0 mmol) was added dropwise. After ~1/2 hour, the reaction was poured into saturated aqueous $NaHCO_3$ solution, stirred 5 minutes and extracted with EtOAc (3 x 50 mL) and concentrated. The residue was dissolved in 30% Et_2O/hexanes and extracted with 1N NaOH aqueous solution (4 x 50 mL). The combined aqueous basic layer was treated with concentrated HCl to achieve pH 8 and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4) and stripped. Chromatography on Silica gel eluting first with 3% EtOAc/hexanes to remove non-polar components, then with 5% MeOH/CH_2Cl_2 provides the title compound. (TLC 25% EtOAc/hexanes R_f 0.60).

B) 10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (140 mg, 0.48 mmol) dissolved in THF (5 mL) was treated with N-methylmorpholine-N-oxide (64.5 mg, 0.48 mmol) and brought to reflux for 1 hour. The reaction was concentrated and chromatographed on Silica gel to provide product. (TLC 25% EtOAc/hexanes R_f 0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.15 (3H), 7.04 (dd, J= 8.0,7.0 Hz, 1H), 6.95 (m, 2H), 6.75 (d, J=7.0 Hz, 1H), 6.59 (dd, J=8.0,1.0 Hz, 1H), 3.53 (br s, OH), 3.51 (AB d, J=14.0 Hz, 2H), 3.28 (br s, 1H), 3.06 (br s, 1H), 2.91 (dd, J=8.5,1.5 Hz, 1H), 2.79 (ddd, J=8.5,1.5,1.5 Hz, 1H), 2.42 (d, J=11.0 Hz, 1H), 2.39 (d, J=11.0 Hz, 1H), 2.23 (m, 1H), 1.65 (d, J=10.5 Hz, 1H). APCI MS *m/e* 266.5 [(M + 1)$^+$].

C) 3-Hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (160 mg, 0.60 mmol) was converted into the title compound by the methods described in Example 1D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J=8.0,7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 3.51 (br s, 1H), 3.33-3.25 (3H), 3.16 (d, J=12.0 Hz, 1H), 3.09 (d, J=12.0 Hz, 1H), 2.29 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). APCI MS *m/e* 175.8 [(M + 1)$^+$]. (HCl salt) mp 253-255 °C.

EXAMPLE 46

4,5-DIFLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2,4,5-trifluorobromobenzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J=8.5 Hz, 2H), 3.48-3.13 (6H), 2.38 (m, 1H), 2.11 (d, J=11.5 Hz, 1H). APCI MS *m/e* 196.2 [(M + 1)$^+$]. (HCl salt) mp 301-303 °C. Anal. Calcd. for $C_{11}H_{11}F_2N.HCl.1/6H_2O$: C, 56.30; H, 5.30; N, 5.97. Found C, 56.66; H, 5.41; N, 5.96.

EXAMPLE 47

6-ETHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and propionyl chloride were converted to the title compound following the procedures described in Example 30 and Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* **1990**, *27*, 335. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.62 (s, 1H), 3.48 (d, J=2.5 Hz, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.20 (2H), 3.01 (q, J=7.5 Hz, 2H), 2.45 (m, 1H), 2.17 (d, J=11.5 Hz, 1H), 1.42 (t, J=7.5 Hz, 3H). APCI MS *m/e* 229.2 [(M + 1)$^+$].

EXAMPLE 48

6-ISOPROPYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and isobutyryl chloride were converted to the title compound following the procedures described in EXAMPLE 47. (TLC 25% EtOAc/hexanes R_f 0.14). ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (2H), 3.49 (br s, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.33-3.19 (3H), 2.45 (m, 1H), 2.18 (d, J=11.5 Hz, 1H), 1.45 (d, J=7.0 Hz, 6H). APCI MS *m/e* 243.2 [(M + 1)$^+$]. (HCl salt) mp 249-251 °C.

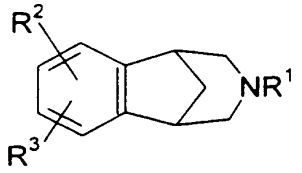
EXAMPLE 49

6-BENZYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and phenyl-acetyl chloride were converted to the title compound following the procedures described in EXAMPLE 47. ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.58 (s, 1H), 7.36-7.24 (5H), 4.29 (s, 2H), 3.46 (d, J=2.5 Hz, 2H), 3.39 (d, J=12.0 Hz, 2H), 3.18 (2H), 2.42 (m, 1H), 2.15 (d, J=11.5 Hz, 1H). APCI MS *m/e* 291.2 [$(M + 1)^+$].

CLAIMS

1. A compound of the formula



(I)

R^1 is hydrogen, $(C_1$ -$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, $XC(=O)R^{13}$ 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), $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$alkylamino-, $[(C_1$-$C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and -$XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or 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_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, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

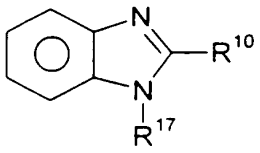
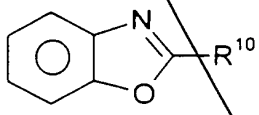
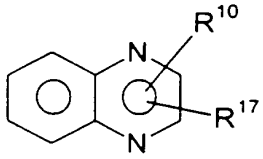
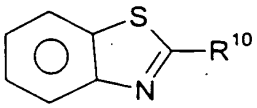
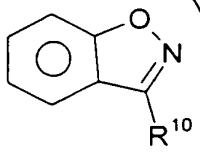
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, N-(C_1-C_6)alkylpiperizine or thiomorpholine 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, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;

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 (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, cyano, halo,

amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur,

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 $(C_1\text{-}C_6)$alkyl.

5. A compound according to claim 1, wherein one of R^2 and R^3 is $-COR^{13}$ wherein R^{13} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$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.

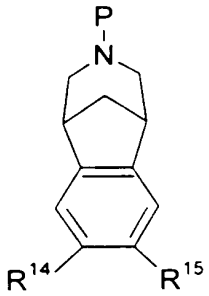
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (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 according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

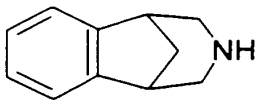
10. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 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



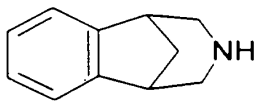
wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo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

12. 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 comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

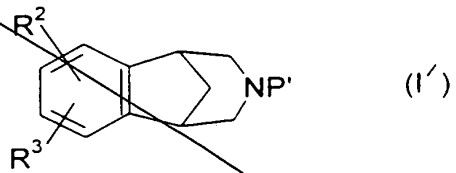
13. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 administering to a mammal in need of such treatment an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof;

that is effective in treating such disorder or condition.

14. A compound of the formula



(I′)

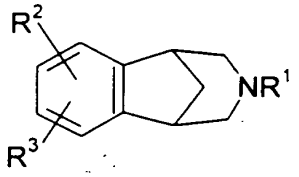
wherein R^2 and R^3 are defined as in claim 1; and P′ is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1\text{-}C_6)$alkyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in claim 2;

-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).

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Abstract

Compounds of the formula



(I)

and their pharmaceutically acceptable salts, wherein R^1, R^2, R^3 and ~~R~~ 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~~.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration submitted with Initial Filing

☐ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e)) required)

Attorney Docket Number	PC 10030A
First Named Inventor	Jotham Wadsworth COE
COMPLETE IF KNOWN	
Application Number	Not yet assigned
Filing Date	Filed herewith
Group Art Unit	Not yet assigned
Examiner Name	Not yet assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 11/13/1998 as United States Application Number or PCT International Application Number PCT/IB98/01813 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/070,245	12/31/1997	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B sheet attached hereto.

EXPRESS MAIL NO. EM484852791

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12/97)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION ---- Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 U.S.C. 1.56, which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application Number or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number or ☒ Registered practioner(s) name/registation number listed below

Place Customer Number Bar Code Label here

Name	Registration Number	Name	Registration Number
Peter C. Richardson	~~27,626~~	Mark Dryer	28,775
Allen J. Spiegel	~~25,740~~	Lawrence C. Akers	~~28,687~~
Paul H. Ginsburg	~~28,718~~	A. Dean Olson	~~31,185~~
J. Trevor Lumb	28,567	Mervin E. Brokke	32,723
James T. Jones	30,561	Valerie M. Fedowich	33,688
Gregg C. Benson	30,977	Bryan C. Zielinski	34,462
Robert F. Sheyka	31,304	Robert T. Ronau	36,257
Grover F. Fuller Jr.	~~31,760~~	B. Timothy Creagan	39,156
Karen DeBenedictis	32,977	Alan L. Koller	37,371
Lorraine B. Ling	35,251	Jolene W. Appleman	35,428
Garth Butterfield	36,997	Kristina L. Konstas	37,864
Carl J. Goddard	39,203	Seth H. Jacobs	32,140
Raymond M. Speer	26,810	Martha A. Gammill	31,820
Jennifer A. Kispert	40,049	Gregory P. Raymer	36,647
Jacob M. Levine	32,509	E. Victor Donahue	35,492
Israel Nissenbaum	~~27,582~~	Roy F. Waldron	42,208
Steven W. Collier	42,429	Todd M. Chrissey	37,807

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label | OR ☒ Correspondence address below

Name	~~Paul H. Ginsburg~~				
Address	~~Pfizer Inc~~				
Address	~~235 East 42nd Street, 20th Floor~~				
City	New York	State	New York	Zip Code	10017-5755
Country	United States Of America	Telephone	(212)573-2369	Fax	(212)573-1939

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Jotham Wadsworth ~~Wadsworth Jr~~	COE

Inventor's Signature	Jotham W. Coe						Date	9/22/99	
Residence: City	Niantic		State	CT~~CT~~	Country	US	Citizenship	US	
Post Office Address	8 Bush Hill Drive								
Post Office Address									
City	Niantic	State	CT	Zip	06357	Country	US		

☒ Additional inventors are being named on the supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

EXPRESS MAIL NO. EM484852797

PTO/SB/02A(3/97)
A[illegible]ed for use through 09/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet

200

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Paige Roanne Palmer				BROOKS			
Inventor's Signature	Paige Roanne Palmer Brooks					Date	9/23/99
Residence: City	North Stonington	State	CT	Country	US	Citizenship	US
Post Office Address	9 Wyassup Road						
Post Office Address							
City	North Stonington	State	CT	Zip	06359	Country	US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

EXPRESS MAIL NO. EM484852791

DO/EO BIBLIOGRAPHIC DATA ENTRY

SERIAL NUMBER:	09 / 402010	RECEIPT DATE:	09 / 28 / 99
IA NUMBER: PCT/	IB98 / 01813	IA FILING DATE:	11 / 13 / 98
FAMILY NAME:	COE	DELAY WAIVED (Y/N):	Y
GIVEN NAME:	JOTHAM WADSWORTH	DEMAND RECEIVED (Y/N):	Y
PRIORITY CLAIMED (Y/N):	Y	PRIORITY DATE:	12 / 31 / 97
NO BASIC FEE (Y/N):	N	US DESIGNATED ONLY (Y/N):	N
ATTORNEY DOCKET NUMBER:	PC10030A	COUNTRY:	IBX

CORRESPONDENCE NAME/ADDRESS: CUSTOMER NUMBER: TELEPHONE FAX

NAME: PAUL H GINSBURG
PFIZER INC
STREET: 235 EAST 42ND STREET

CITY: NEW YORK
STATE/COUNTRY: NY ZIP: 100175755
EMAIL:
APPLICATION TITLES:
ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

TAB TO LAST POSITION, PUSH SEND

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/402,010	09/28/99	514	1614	PC10030A

APPLICANT

JOTHAM WADSWORTH COE, NIANTIC, CT; PAIGE ROANNE PALMER BROOKS, NORTH STONINGTON, CT.

CONTINUING DOMESTIC DATA********
WHICH CLAIMS BENEFIT OF 60/070,245 12/31/1997

BC

371 (NAT'L STAGE) DATA********
VERIFIED THIS APPLN IS A 371 OF PCT/IB98/01813 11/13/98

BC

FOREIGN APPLICATIONS********
VERIFIED

NONE BC

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 01/13/00

Foreign Priority claimed / 35 USC 119 (a-d) conditions met / Verified and Acknowledged	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐yes ☑no / ☐yes ☑no ☐Met after Allowance / BC Examiner's Initials ____ Initials	CT	0	14	4

ADDRESS

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TITLE

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	
$918		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

PATENT APPLICATION SERIAL NO. 09/402010

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

10/01/1999 WCLAYBRO 00000152 161445 09402010

01 FC:970 840.00 CH
02 FC:964 78.00 CH

PATENT APPLICATION FEE DETERMINATION RECORD
Effective November 10, 1998

Application or Docket Number
09/402010

CLAIMS AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
BASIC FEE		
TOTAL CLAIMS	14 minus 20=	* —
INDEPENDENT CLAIMS	4 minus 3 =	* 1
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ RATE	FEE	OR	OTHER THAN SMALL ENTITY RATE	FEE
	380.00	OR		840
X$ 9=		OR	X$18=	
X39=		OR	X78=	78
+130=		OR	+260=	
TOTAL		OR	TOTAL	918

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

CLAIMS

SERIAL NO. 09/402010 | FILING DATE 28 SEP 1999

APPLICANT(S) Cal

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		1				
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8		1				
9		1				
10		1				
11	1					
12	1					
13	1					
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TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

FORM PTO-2022 (1-98)

U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. Government Printing Office: 1998 - 433-214/70303

EO/US
PCT/IB98/01813

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing: 15 July 1999 (15.07.99)	
International application No.: PCT/IB98/01813	Applicant's or agent's file reference: PC10030AKXD
International filing date: 13 November 1998 (13.11.98)	Priority date: 31 December 1997 (31.12.97)
Applicant: COE, Jotham, Wadsworth et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

06 April 1999 (06.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38

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Form PCT/IB/331 (July 1992)

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PATENT COOPERATION TREATY

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REC'D 16 MAR 2000

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PC10030AKXD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB98/01813	13/11/1998	31/12/1997
International Patent Classification (IPC) or national classification and IPC		
C07D221/22		
Applicant		
PFIZER PRODUCTS INC. et al.		

RECEIVED

APR 24 2000

TECH CENTER 1600/2900

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 19 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/04/1999	14.03.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Von Daacke, A Telephone No. +49 89 2399 8286

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/01813

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,6,10-22,26,28-30, 32-73	as originally filed			
2-5,5A,7,7A,8,9, 23-25,27,31	as received on	26/01/2000	with letter of	24/01/2000

Claims, No.:

14 (part)	as originally filed			
1-13,14 (part)	as received on	26/01/2000	with letter of	24/01/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7-10,12,13(Industrial Applicability).

because:

☒ the said international application, or the said claims Nos. 7-10,12,13 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4-14
	No:	Claims	1,3
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,11,14
	No:	Claims	

2. Citations and explanations

see separate sheet

I BASIS

Description pages 2-4 and claim pages 74 and 75 as amended cannot be considered as the replacement '$X^2(C_0$-$C_6)$alkyl- and $X^2(C_1$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl' goes beyond the content of the application as originally filed (Art. 34(2)b) PCT). It should be noted that such an amendment was also not necessary. Due to the wording (e.g. page 74, line 19: 'contains at least one carbon atom' the original definition covers alkyl, alkoxy and alkoxyalkyl, each optionally substituted by X^2 etc.. Thus, the International Preliminary Examination Report is based on the original pages 2-4 and 74,75.

III NON-ESTABLISHMENT

Claims 7-10,12 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: PAUL H. MAZZOCHI ET AL: 'Synthesis and pharmacological activity of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzaz epines' JOURNAL OF MEDICINAL CHEMISTRY., vol. 22, no. 4, 1979, pages 455-457, XP002090422 WASHINGTON US
D2: US-A-3 471 503 (CARSON JOHN R) 7 October 1969

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 1 and 3 is anticipated by D1 (Article 33(2) PCT). D1 discloses N alkyl derivatives of formula I which are covered from the definitions as set out in Claims 1 and 3. The remaining claims are considered as novel.

3. INVENTIVE STEP

The novel subject-matter of Claims 1-14 appears to fulfil the requirements of Article 33(3) PCT because the pharmaceutical profile of the compounds of D1 and D2, i.e. antinociceptive and hypotensive properties, respectively differs from that of the present application. The pharmacological activity of the present compounds, i.e. the ability to bind to neuronal nicotinic acetylcholine specific receptor sites, is not obvious in view of D1 and/or D2.

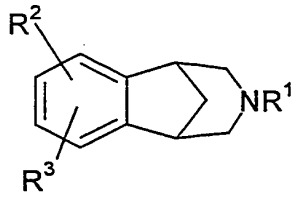
4. INDUSTRIAL APPLICABILITY

No objection for Claims 1-6, 11 and 14. For the assessment of the present Claims 7-10, 12 and 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

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

R^2 and R^3 are selected, independently, from hydrogen, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1\text{-}C_6)$alkyl wherein q is zero, one or two, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, aryl-$(C_0\text{-}C_3)$alkyl- or aryl-$(C_0\text{-}C_3)$alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0\text{-}C_3)$alkyl- or heteroaryl-$(C_0\text{-}C_3)$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 $X^2(C_0\text{-}C_6)$alkyl- and $X^2(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1\text{-}C_6)$alkylamino- or $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0\text{-}C_6)$alkyl- or $(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- moieties of said $X^2(C_0\text{-}C_6)$alkyl- and $X^2(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0\text{-}C_6)$alkyl- or $(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- moieties 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 $(C_0\text{-}C_6)$alkyl- or $(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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-$(C_0\text{-}C_3)$alkyl- and said heteroaryl-$(C_0\text{-}C_3)$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 $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1\text{-}$

C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

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 non-fused 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)alkyl- or (C_1 -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, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$, and -$XC(=O)R^{13}$;

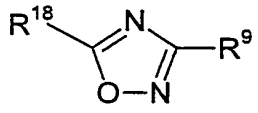
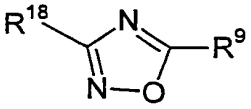
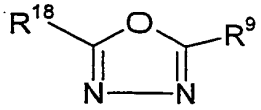
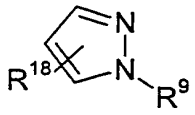
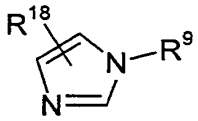
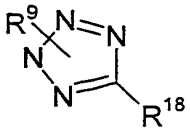
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine 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, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be hydrogen, (C_1-C_6)alkyl, or unconjugated (C_3-C_6)alkenyl;

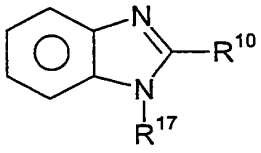
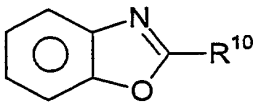
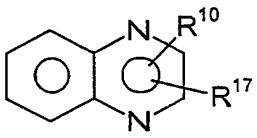
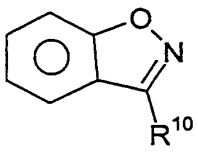
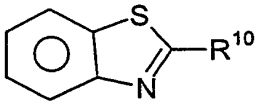
and the pharmaceutically acceptable salts of such compounds.

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 $(C_1\text{-}C_6)$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:

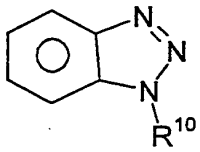






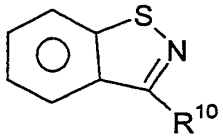
wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkyl- and $(C_1\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\ \text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I 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:

SUBSTITUTE PAGE

AMENDED SHEET





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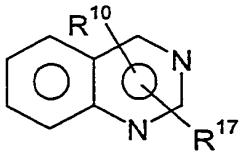

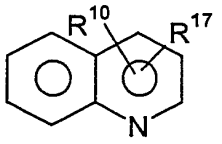

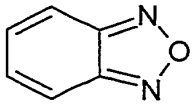

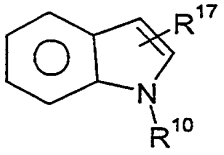

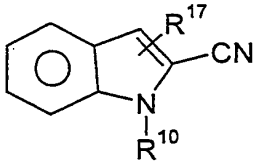

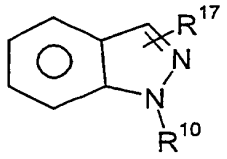

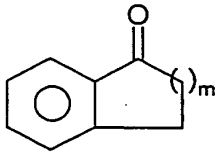

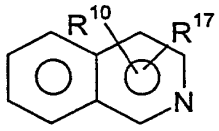

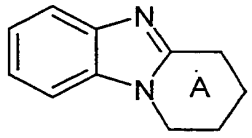

wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

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, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

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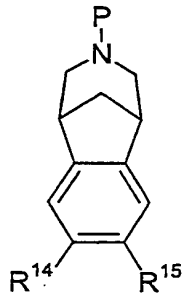
Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5. –;

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

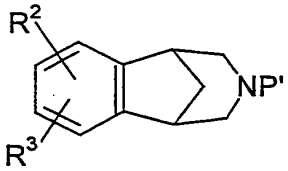
Examples of specific compounds of the formula I are the following:

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, 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 or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $-C(=O)(C_1\text{-}C_6)$alkyl, cyano, hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$alkyl or halo; with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen, $(C_1\text{-}C_6)$alkyl, or unconjugated $(C_3\text{-}C_6)$alkenyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

The invention also relates to a compound of the formula



(I′)

wherein R^2 and R^3 are defined above; and P′ 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 claim 2; -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).

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.

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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 radiolabeled forms of the compounds of the formula I. Preferred radiolabeled 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 radiolabeled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

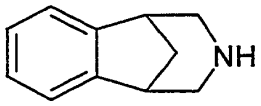
The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is 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, 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), obsessive-compulsive disorder (OCD), 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), obsessive-compulsive disorder (OCD), 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 acceptable salt thereof, 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, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



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 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), obsessive-compulsive disorder (OCD), psychosis, Huntington's

Scheme 1-10 illustrate methods of synthesizing compounds of the formula I .

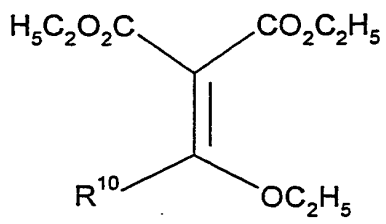
Referring to Scheme 1, the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV. This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, dichloroethane (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.

Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) 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 VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula



XXIIA

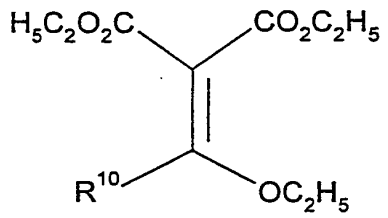
wherein R^{10} is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0$-$C_3)$alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0$-$C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, 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 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 VII the compound of formula VIB are described by Segelstein et al., Tetrahedron Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII 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 VII can be converted into the corresponding compound of formula IB 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, 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.

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA 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. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV 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 IIA into a compound of the formula IIB in Scheme 1, and exemplified in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

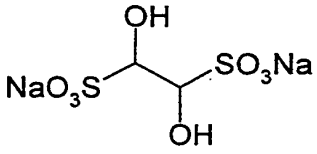


XXIIA

wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII.

Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII.

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB is reacted with a compound of the formula



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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 stoichiometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or pyridinium 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 IE. 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 6 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. Referring to Scheme 6, the compound of formula III 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 anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, 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 IX'.

The compound of formula IX' 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 R^{10} is hydrogen or (C_1-C_6)alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI by reacting it with Lawesson's reagent, which is depicted below.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV 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 IV 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 IV with N-iodosuccinimide or N-bromosuccinimide in a trifluoromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

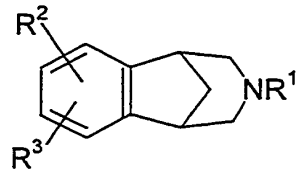
Reaction of the compound of IV with an acid halide of the formula $R^{13}COCl$ or an acid anhydride of the formula $(R^{13}CO)_2O$, with or without a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, in the presence of Lewis acid such as aluminum chloride, 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 acylation 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 IV, as depicted in Scheme 9 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, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substituted compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles.

CLAIMS

1. A compound of the formula



(I)

R^1 is hydrogen, (C_1 -C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$, benzyl 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, X^2(C_0-C_6)alkyl- and X^2(C_1-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)alkyl- or (C_1-C_6)alkoxy-(C_0-C_6)alkyl- moieties of said X^2(C_0-C_6)alkyl- or X^2(C_1-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 X^2(C_0-C_6)alkyl- or (C_1-C_6)alkoxy-(C_0-C_6)alkyl- moieties 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)alkyl- or (C_1-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, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

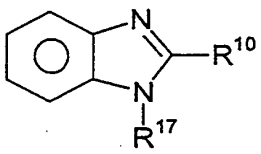
or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part

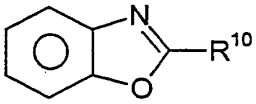
of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C_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, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

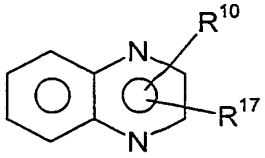
wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, N-(C_1-C_6)alkylpiperazine or thiomorpholine 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;

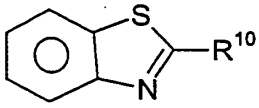
with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen, (C_1-C_6)alkyl, or unconjugated (C_3-C_6)alkenyl; or a pharmaceutically acceptable salt thereof;

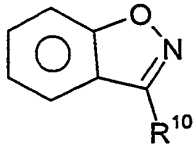
2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:











wherein R^{10} and R^{17} are selected, independently, from (C_0-C_6)alkyl- and (C_1-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, cyano, halo,

amino, (C_1-C_6)alkylamino-, $[(C_1-C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, 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 wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in claim 1.

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.

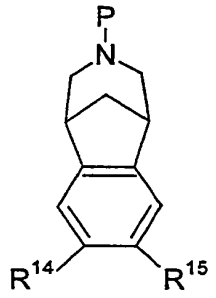
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, 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; 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 (OCD), 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, ulcerative colitis, pyoderma gangrenosum, 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; 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 (OCD), 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



wherein 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 claim 1 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, and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $-C(=O)(C_1\text{-}C_6)$alkyl, cyano, hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$alkyl and halo; with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen, $(C_1\text{-}C_6)$alkyl, or unconjugated $(C_3\text{-}C_6)$alkenyl.

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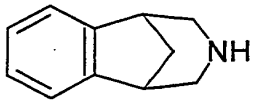
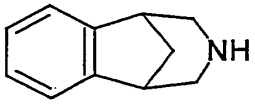
12. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



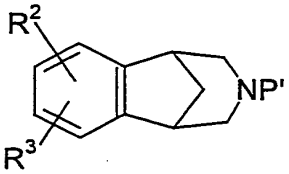
or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

13. A method for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, 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; 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 (OCD), 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



or a pharmaceutically acceptable salt thereof;
that is effective in treating such disorder or condition.

14. A compound of the formula



(I′)

wherein R^2 and R^3 are defined as in claim 1; and P′ 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 claim 1;

SUBSTITUTE PAGE

AMENDED SHEET

PC 10030

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
SPIEGEL, Allen J.
Pfizer Inc.
235 East 42nd Street
New York, NY 10017
UNITED STATES OF AMERICA

Applicant's or agent's file reference PC10030AKXD	Date of mailing *(day/month/year)* 03/02/1999 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB 98/01813	International filing date *(day/month/year)* 13/11/1998
Applicant PFIZER PRODUCTS INC. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

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

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PC10030AKXD		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 98/01813	13/11/1998	31/12/1997

Applicant

PFIZER PRODUCTS INC. et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application.

   [ ] furnished by the applicant separately from the international application.

   [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/01813

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 8,10,12,13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8,10,12,13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/01813

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/22 A61K31/435 C07D471/08 C07D498/08 C07D513/08

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 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL H. MAZZOCHI ET AL: "Synthesis and pharmacological activity of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 22, no. 4, 1979, pages 455-457, XP002090422 WASHINGTON US see the whole document ---	1,9,11
A	US 3 471 503 A (CARSON JOHN R) 7 October 1969 see the whole document -----	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 1999	03/02/1999

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	Henry, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

rnational Application No
PCT/IB 98/01813

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3471503 A	07-10-1969	NONE	

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(72) Inventors; and
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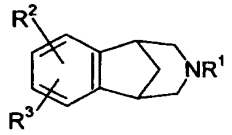
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(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 n 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.

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ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Background of the Invention

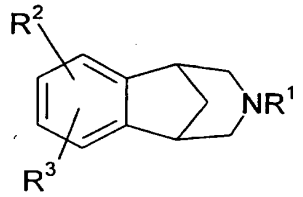
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory 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, 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), 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. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

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

R^2 and R^3 are selected, independently, from hydrogen, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1\text{-}C_6)$alkyl wherein q is zero, one or two, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, aryl-$(C_0\text{-}C_3)$alkyl- or aryl-$(C_0\text{-}C_3)$alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0\text{-}C_3)$alkyl- or heteroaryl-$(C_0\text{-}C_3)$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 $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1\text{-}C_6)$alkylamino- or $[(C_1\text{-}C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- moiety of said $X^2(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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 $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$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-$(C_0\text{-}C_3)$alkyl- and said heteroaryl-$(C_0\text{-}C_3)$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 $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1\text{-}C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1\text{-}$

C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

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, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, [(C_1-C_6)alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$, and -$XC(=O)R^{13}$;

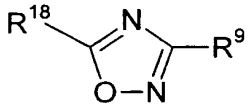
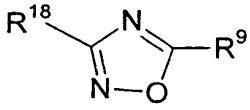
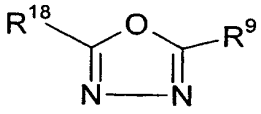
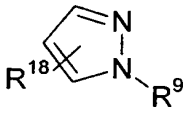
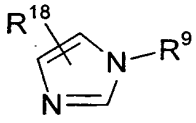
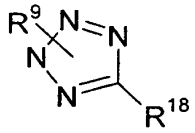
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine 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, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

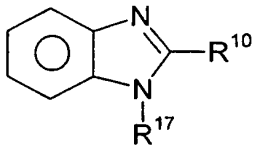
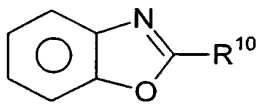
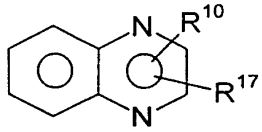
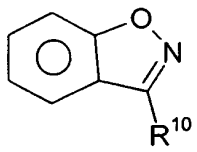
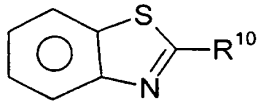
and the pharmaceutically acceptable salts of such compounds.

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:

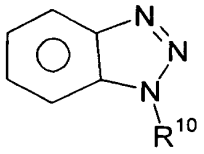
wherein one of R^9 and R^{18} is hydrogen or $(C_1\text{-}C_6)$alkyl, and the other is a bond to the benzo ring of formula I.

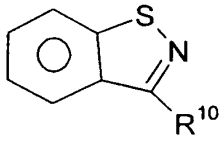
Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:

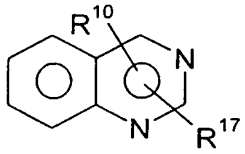






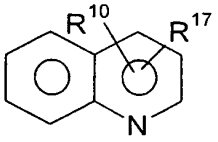
wherein R^{10} and R^{17} are selected, independently, from $(C_0\text{-}C_6)$alkoxy-$(C_0\text{-}C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1\text{-}C_6)$alkylamino-, $[(C_1\text{-}C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

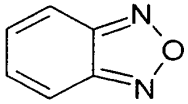
Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:

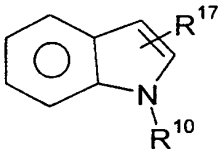


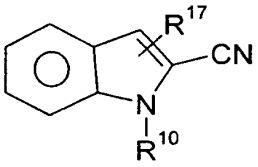


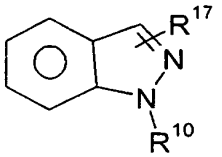


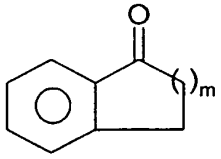


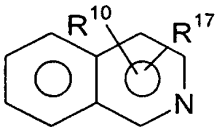


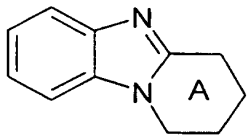












wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

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:

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;

4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;

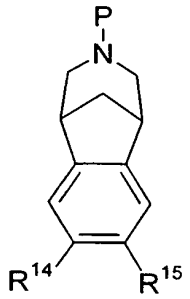
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;

6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride; and

5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride.

This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, 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 or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $-C(=O)(C_1\text{-}C_6)$alkyl, cyano, hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$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.

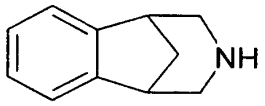
The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is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

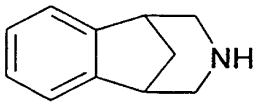
The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



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 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 administering to a mammal in need of such treatment an amount of a compound of the formula



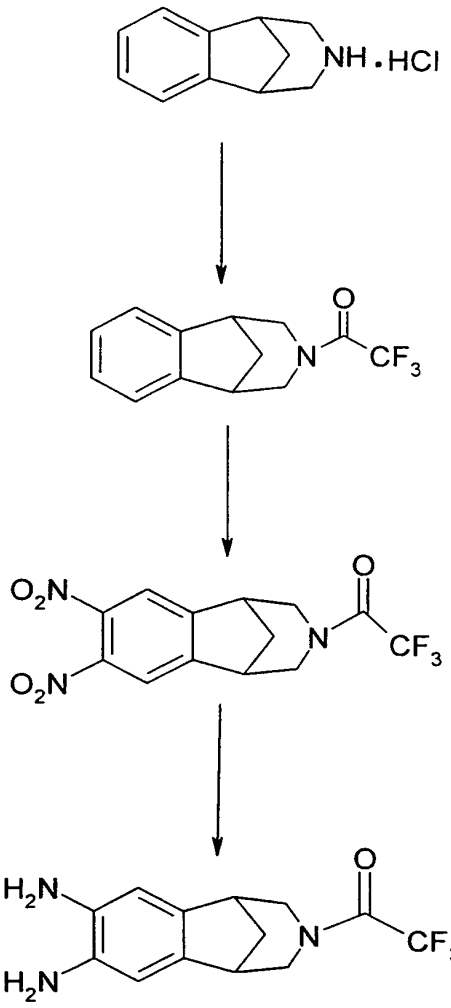
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

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



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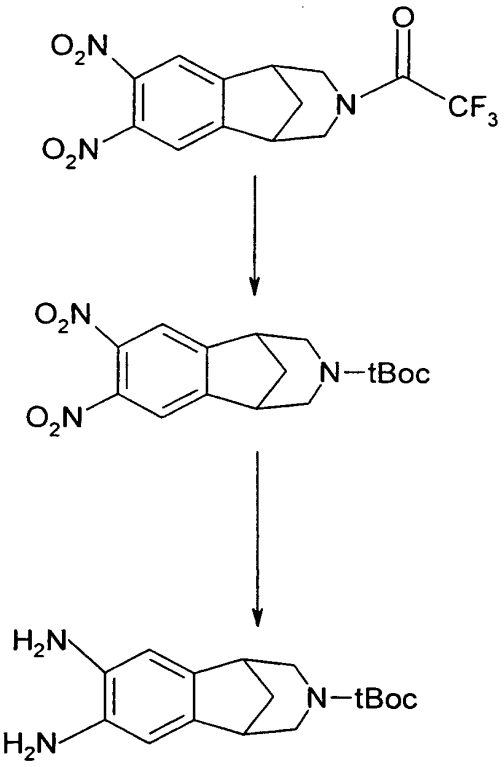
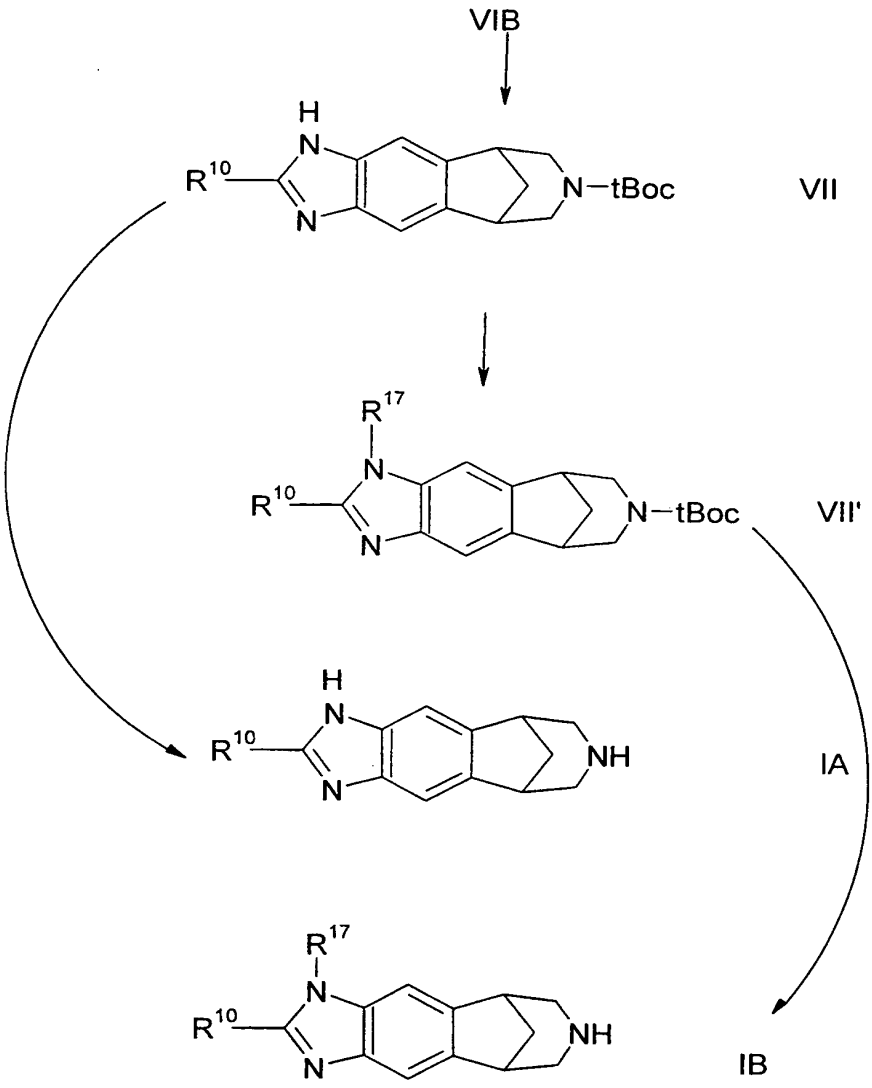
Scheme 2



Scheme 2 continued



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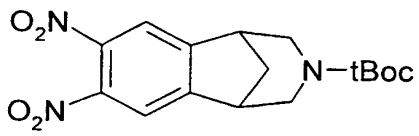
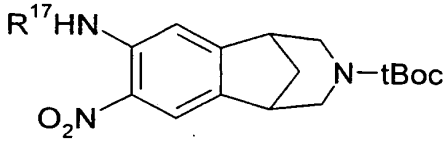
Scheme 3



VIA



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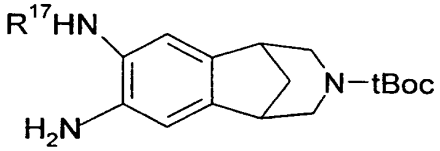

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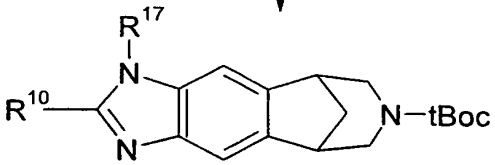

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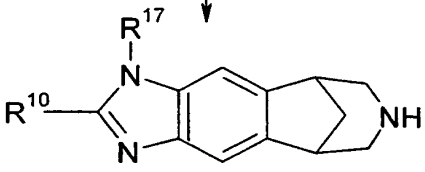

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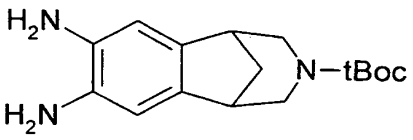
Scheme 4



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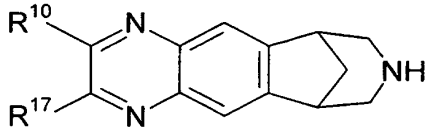

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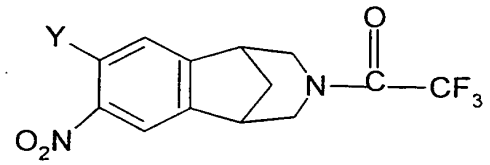
Scheme 5



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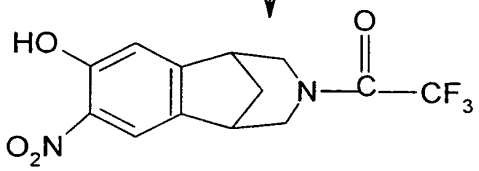
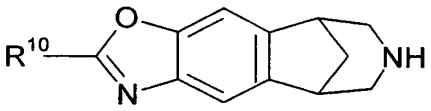


VIII



IE

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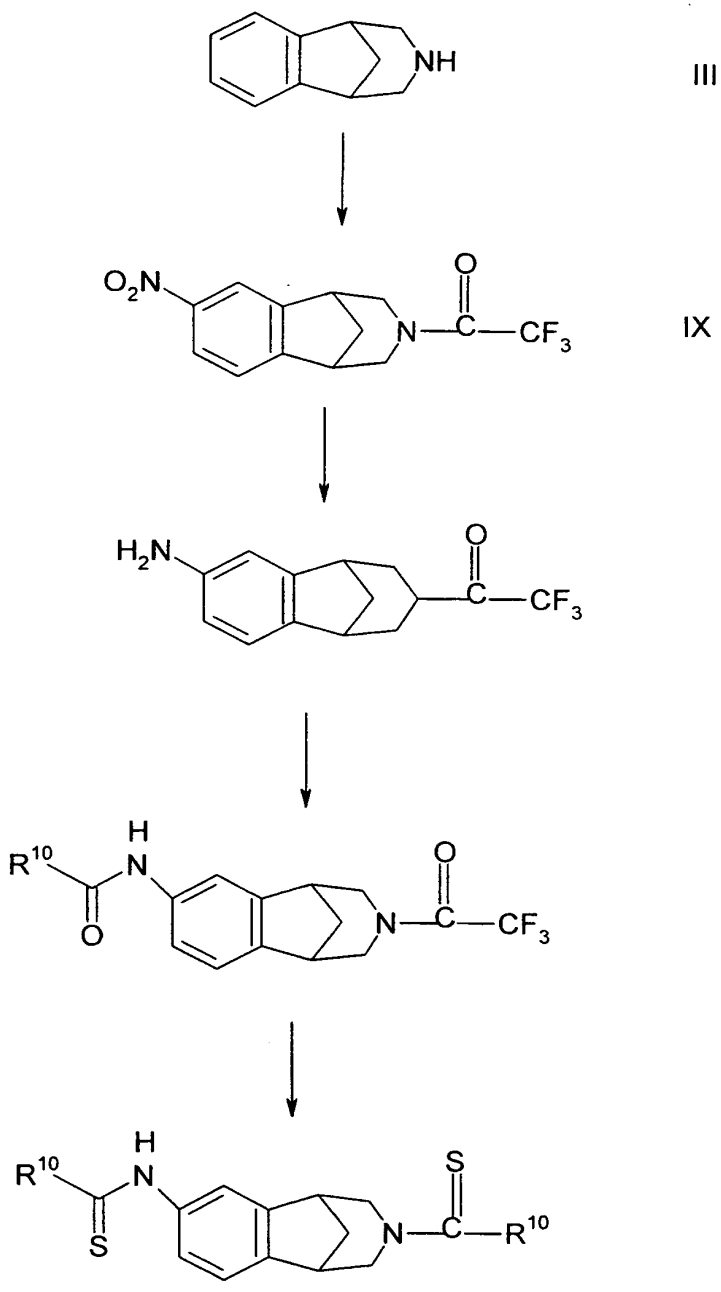
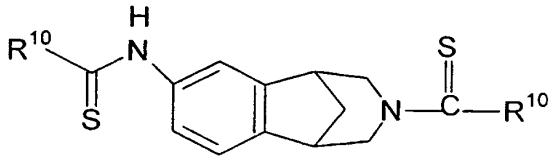
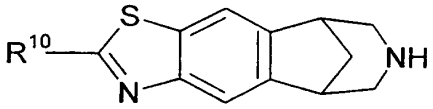
Scheme 6



Scheme 6 continued



XI



IF

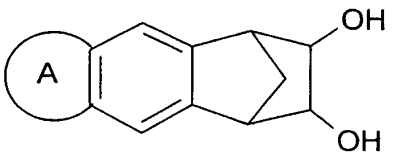
Scheme 7

(ring A = present or absent)

XII

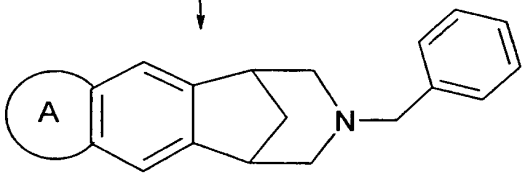
(ring A = present or absent)

XIII



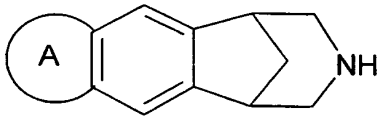
(ring A = present or absent)

XIIIA



(ring A = present or absent)

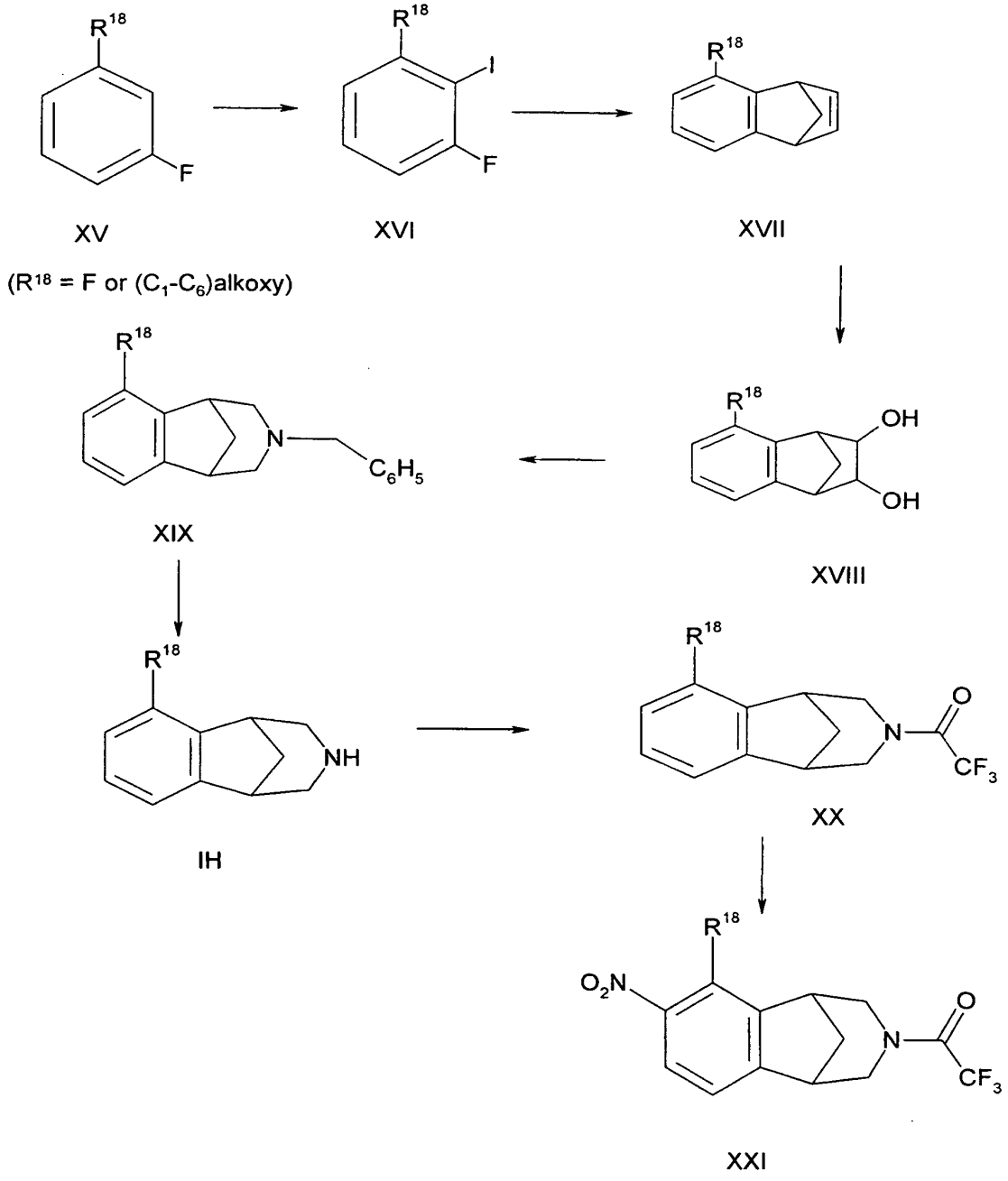
XIV



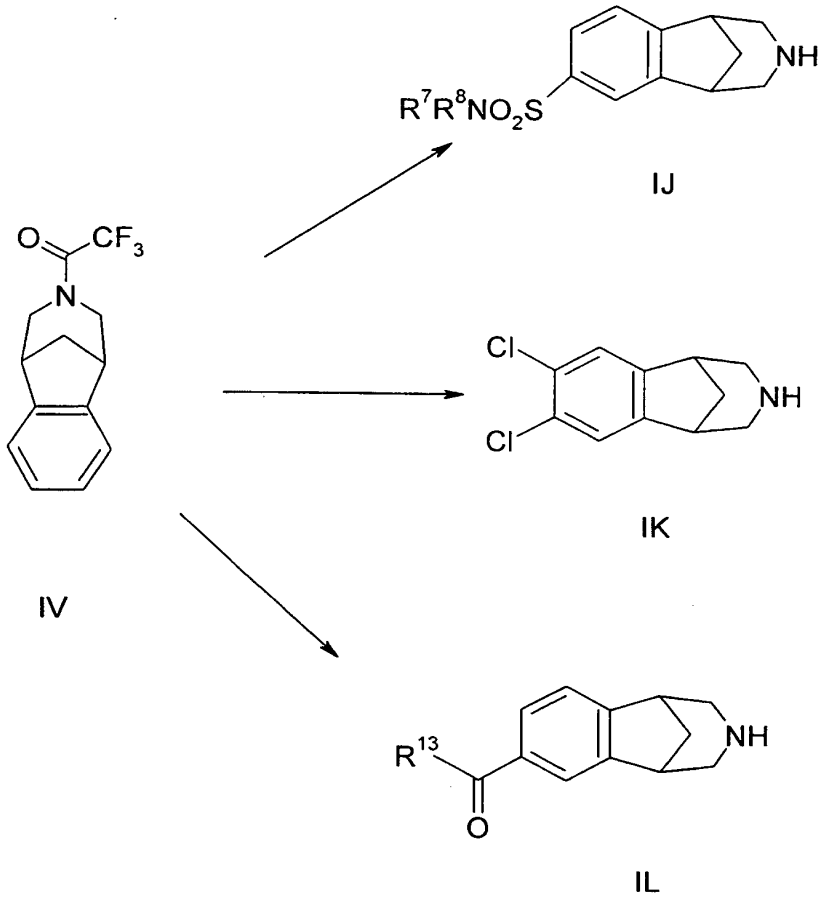
IG: (R^2 and R^3 form ring A)

III: (ring A = absent)

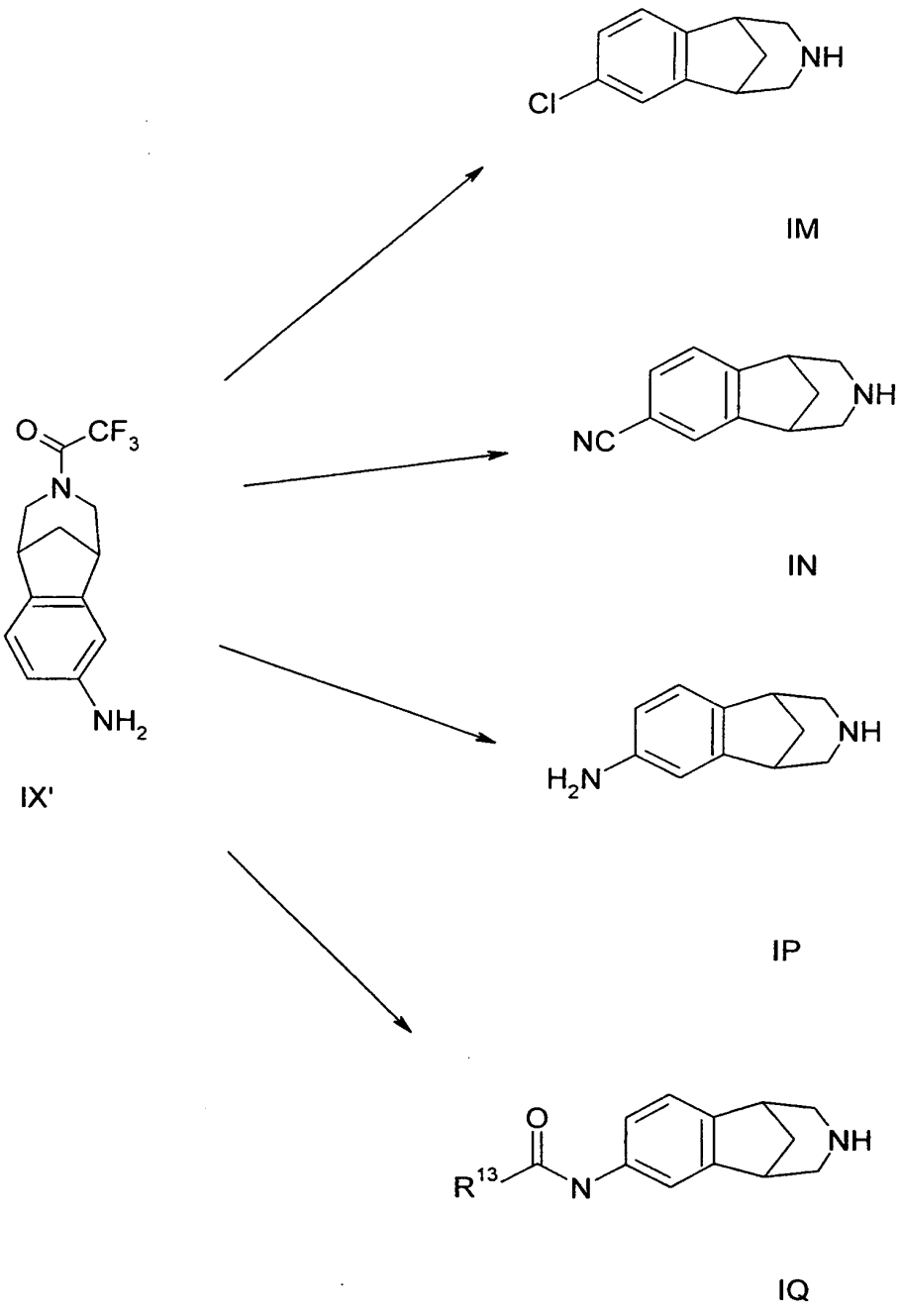
Scheme 8



Scheme 9



Scheme 10



Scheme 1-10 illustrate methods of synthesizing compounds of the formula I .

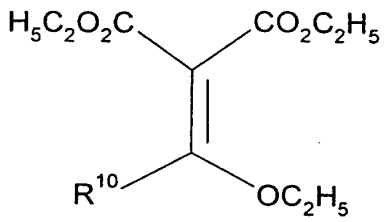
Referring to Scheme 1, the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV. This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 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.

Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) 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 VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula



XXIIA

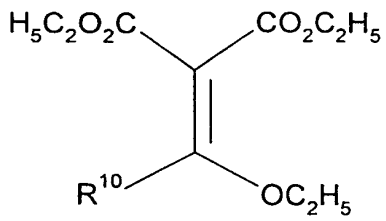
wherein R^{10} is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0$ -$C_3)$alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0$ -$C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings 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 VII the compound of formula VIB are described by Segelstein et al., Tetrahedron Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII 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 VII can be converted into the corresponding compound of formula IB 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, 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.

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illlustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA 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. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV 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 IIA into a compound of the formula IIB in Scheme 1, and exemplied in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

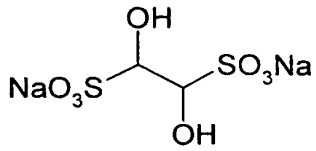


XXIIA

wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII.

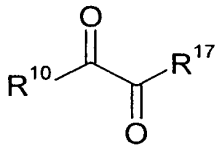
Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII.

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB 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 VIB 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.

The desired quinoxoline of formula IC 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 VII into one of the formula IA.

Scheme 5 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 5 as chemical formula IE. Referring to Scheme 5, the compound of formula XXII, wherein Y is nitro, halo, trifluoromethanesulfonate or a diazonium salt, 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 VIII, which can then be converted into the desired compound having formula IE by the following procedure. First, the compound of formula VIII 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 $(C_1\text{-}C_6)$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.

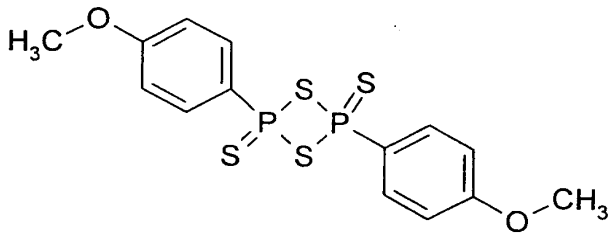
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IE. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) 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 6 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. Referring to Scheme 6, the compound of formula III 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 anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, 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 IX′.

The compound of formula IX′ 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 R^{10} is hydrogen or $(C_1\text{-}C_6)$alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI 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 IF can be accomplished by reacting the compound of formula XI 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.

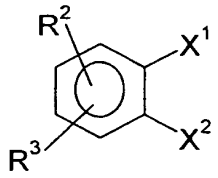
Scheme 7 illustrates a method of preparing the compound of formula III, which is used as the starting material for the process of Scheme 1, or a compound of the formula IG, wherein R^2 and R^3 form a ring (labeled "A" in the Scheme), as defined above in the definition of compounds of the formula I. Referring to Scheme 7, the compound of formula XII, wherein X^1 and X^2 are selected, independently, from chloro, fluoro, bromo and iodo, but where at least one of X^1 and X^2 is Br- or I-, reacted with cyclopentadiene, in the presence of magnesium metal, in a THF, dioxane or other ethereal solvent, at a temperature from about 40°C to about 100°C, preferably at about the reflux temperature, to form a compound of the formula XIII. Reaction of the resulting compound of formula XIII with N-methylmorpholine-N-oxide (NMO) and osmium tetroxide in acetone at about room temperature yields the corresponding compound of the formula XIIIA.

The compound having formula XIIIA is then converted into the corresponding compound of formula XIV using the following procedure. First, the compound of formula XIIIA 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 and

sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0°C to about room temperature, preferably at about room temperature, to form the desired compound of formula XIV. Removal of the benzyl group from the compound of formula XIV yields the compound of formula III (when ring A is absent) or IG, (when ring A is present). This 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 of Scheme 7 can also be used to prepare compounds of the formula I wherein R^2 and R^3 do not form a ring and are not both hydrogen, by replacing the starting material of formula XII with the appropriate compound having the formula



XII'

Scheme 8, 9 and 10 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 8 illustrates a variation of the process shown in Scheme 7, which can be used to make a compound identical to that of formula III except that the benzo ring is substituted with a fluoro group or an alkoxy group (R^{18} in Scheme 8). This compound is depicted in Scheme 8 as chemical structure 1H. Referring to Scheme 8, where, for example, R^{18} is F, 1,3-difluorobenzene is reacted with a strong base such as an alkali metal dialkylamine or an alkali metal alkyl (or aryl) in an ethereal solvent such as ethyl ether or THF, at a temperature below -50°C, followed by quenching with iodine or N-iodosuccinamide, to form 1,3-difluoro-2-iodobenzene. The compound 1,3-difluoro-2-iodobenzene (structural formula XVI in Scheme 8) is then converted into the compound of formula IH by a series of reactions (represented in

Scheme 8 as XVI→XVII→XVIII→XIX→IH) that are analogous to the series of reactions described above and illustrated in Scheme 7 for converting compounds of the formula XIII into those of the formula IG or III. Conversion of the compound of formula XVI into the compound of formula XVII can also be accomplished by treating a mixture of the compound of formula XVI and cyclopentadiene with an alkyl lithium reagent, preferably n-butyl lithium, in an inert hydrocarbon solvent such as petroleum ether or methyl cyclohexane, at a temperature from about -20°C to about room temperature, preferably at about 0°C.

The compound of formula IH can then be converted into the corresponding nitrogen protected derivative of formula XX, using the methods described above for synthesizing the compound of formula IV in Scheme 1. Nitration of the compound of formula XX using the method described above for preparing the compound of formula IX in Scheme 6, yields the compound of formula XXI wherein the benzo ring is substituted with both a fluoro and nitro group or an alkoxy group and nitro group. The compound of formula XXI can be used to make a variety of compounds of the formula I wherein one of R^2 and R^3 is fluoro, using methods that are well known to those of skill in the art, for example, by first converting the nitro group to an amino group, converting the amino group to a variety of other substituents, as illustrated in Scheme 10, and then removing the nitrogen protecting group.

The compound of formula XXI acts as a regioisomeric functional equivalent of the compounds having formulas IIA, VIA and XXII, in that the fluorine atom of formula XXI reacts similarly to the nitro and Y groups of formula IIA, VIA, and XXII, and thus can be subjected to the same series of reactions as those described above for the latter three compounds, providing an alternate means for preparing the products of such reactions. Similarly, the alkoxy group of formula XXI (R^{18}=alkoxy) may be converted into a hydroxyl group before or after introduction of the nitro group, and then converted to isomeric products as described above. Also, the trifluoromethanesulfonate salt of such hydroxy derivative can act as a Y-group as described.

Preparation of compounds of formula I where R^2 = -O(C_1-C_6)alkyl, (C_1-C_6) alkyl or aryl wherein aryl is defined as above in the definition of formula I, and R^3 is H or one of the other substituents described above in the definition of formula I, can be prepared as described above and illustrated in Scheme 8 by replacing one of the fluorine atoms of the compound of formula XV with -O-(C_1-C_6)alkyl, (C_1-C_6)alkyl or aryl, respectively.

Scheme 9 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 9, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV 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 IV 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 IV 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 IV 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 IV, as depicted in Scheme 9 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$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, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substited compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles.

Scheme 10 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 10, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula IX' 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 by 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,N-dimethylpropylurea (DMPU) or DMSO, preferably DMF, at a temperature from about 50°C to about 180°C, preferably about 150°C. Nitrogen deprotection as described above provides the desired compound of formula IM.

The above described iodide 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 IX' provides the compound of the formula IP.

The compound of formula IX' 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.

In each of the reactions discussed above, or illustrated in Schemes 1-10, 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 Arneric, 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

10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1,4-Dihydro-1,4-methano-naphthalene

(Based wholly or in part on a) Wittig, G.; Knauss, E. *Chem. Ber.* **1958**, *91*, 895. b) Muir, D. J.; Stothers, J. B. *Can. J. Chem.* **1993**, *71*, 1290.)

Magnesium turnings (36.5 g, 1.5 M) were stirred in anhydrous THF (250 mL) in a dried 2 L 3 neck round bottom flask equipped with a 250 mL non-equalizing addition funnel with a nitrogen (N_2) flow adapter, mechanical stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2-Fluorobromobenzene (2g) was added followed by 1 mL of 3N ethylmagnesium bromide (EtMgBr in THF). The addition funnel was charged with a mixture of cyclopentadiene (94.4 g, 1.43 M, Prepared by the method described in: *Org. Syn.* Col. Vol. V, 414-418) and bromofluorobenzene (250 g, 1.43 M) which was maintained at 0 °C in a separate flask by an ice bath, and transferred to the addition funnel via cannula. Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation), the heating mantle was removed and the contents of the addition funnel was added dropwise at such rate as to maintain reflux (1.5 hours). The heating mantle was re-applied and a reflux maintained for 1.5 hours. (TLC 100% hexanes R_f 0.67).

The reaction was cooled to room temperature and quenched with H_2O (500 mL) and carefully with 1N HCl (200 mL, produces H_2 evolution from unconsumed Mg). To this ~50 mL

concentrated HCl was added to dissolve solids. Total addition/quench time ~1 hour. Saturated aqueous sodium chloride (NaCl) solution (300mL) was added and product hexanes extracted until no potassium permanganate ($KMnO_4$) active product is removed. (4 x ~250 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (250 mL), sodium bicarbonate Na_2SO_4 dried and concentrated to an oil (~200 g). The product was distilled at 78-83 °C @15mm (131 g, 64%). (An alternative workup is described on p.419 Fieser and Fieser, Vol. I, Reagents for Organic Synthesis, Wiley, NY., NY.; 1967).

B) 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol

(Except for the workup method and the quantity of OsO_4 used, based on VanRheenen, V.; Cha, D.Y.; Hartley, W. M. *Org. Syn.* **1988**, *6*, 342.)

In a 2 L 3 neck round bottom flask equipped with a N_2 flow adapter, mechanical stirrer was placed 1,4-dihydro-1,4-methano-naphthalene (79.5 g, 560 mmol) stirred in acetone (800 mL) and H_2O (100 mL) and N-methyl morpholine N-oxide (67.5 g, 576 mmol). To this was added osmium tetroxide (OsO_4) (15 mL of a 15mol% t-BuOH solution, 1.48 mmol, 0.26mol%) and the mixture was stirred vigorously. After 60 hours, the reaction was filtered, and the white product rinsed with acetone and air dried (60.9 g). The mother liquor was concentrated to an oily solid: acetone trituration, filtration and acetone rinse provided (27.4 g, total 88.3 g, 89%). (TLC 50% EtOAc/hexanes R_f ~0.5). mp 176-177.5 °C.

C) 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(Based on Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849; and Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455.)

1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round bottom flask under nitrogen with cool water bath (~10 °C). To this sodium periodate ($NaIO_4$) (51 g, 239 mmol) and triethylbenzyl ammonium chloride (Et_3BnNCl) (50 mg) were added. The resulting mixture was stirred for 1 hour (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with DCE (200 mL). The organic layer was washed with H_2O (4 x 200 mL, or until no reaction to starch iodide is observed in the aqueous wash) then dried through a cotton plug. To this was added benzyl amine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 minutes then immediately transferred into the sodium triacetoxyborohydride $NaHB(OAc)_3$ /DCE (see below) over 10 minutes.

In a separate 2 L round botton flask flask under nitrogen was magnetically stirred $NaHB(OAc)_3$ (154 g, 0.727 mmol) in DCE (800 mL) at 0 °C (ice bath). To this was added the above mixture over 10 minutes, without delay after the dialdehyde and amine were mixed. The resulting orange mixture was allowed to warm to room temperature and stirred for 30-60 minutes.

The reaction was quenched by addition of saturated sodium carbonate (Na_2CO_3) solution (~300 mL) carefully at first and the mixture was stirred for 1 hour (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, then evaporated to a red oil. This was dissolved in a minimum of Et_2O and filtered through a Silica pad (3 x 4 inch) eluting with 15% ethyl acetate (EtOAc)/hexanes +1% of 37% aqueous ammonium hydroxide (NH_4OH) solution to remove baseline red color. Concentration affords a light yellow oil (48.5 g, 194.8 mmol, 85.7%). (TLC 10% EtOAc/hexanes R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 7H), 6.89 (m, 2H), 3.48 (m, 2H), 3.08 (m, 2H), 2.80 (d, J=9.5 Hz, 2H), 2.42 (d, J=9.5 Hz, 2H), 2.27 (m, 1H), 1.67 (d, J=10.0 Hz, 1H). APCI MS *m/e* 250.3 [(M + 1)$^+$].

D) 10-Aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (For an alternative synthesis, see; Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* **1979**, *22*, 455.)

10-Benzyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3N HCl EtOAc (1.03 eq.) slowly with cooling (ice bath). The resulting precipitate was filtered and rinsed with EtOAc. The solids were dissolved in MeOH (250 mL) in a parr bottle. To this was added $Pd(OH)_2$ (7 g of 20%wt/C) and the mixture was shaken under 50-40 psi of H_2 for 24 hours or until done by TLC. The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotroped with methanol (MeOH) (3x) then triturated with acetone, treated with ethyl ether (Et_2O) to precipitate product and filtered. Concentration of the mother liquors and a second treatment provided an off white solid (48.95 g, 251 mmol, 88%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 4H), 2.97 (m, 4H), 2.68 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 1.95 (d, J=11.0 Hz, 1H). APCI MS *m/e* 160.2 [(M + 1)$^+$].

EXAMPLE 2

4-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 6-Fluoro-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (0.66 g, 27.2 mmol) were stirred in anhydrous THF (10 mL) in a flame dried 75 mL 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,5-Difluorobromobenzene (0.1 g) was added followed by of 3N EtMgBr in THF (0.1 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (1.71 g, 25.9 mmol) and 2,5-difluorobromobenzene (5.0 g, 25.9 mmol). Small portions (~0.2 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for 1 hour.

The reaction was cooled to room temperature and quenched with H_2O (20 mL) followed by aqueous 1N HCl solution (20 mL) to dissolve the solids. Saturated aqueous NaCl solution (30 mL) was added and product was extracted with hexanes (4 x 25mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil. Chromatography on Silica gel eluting with hexanes provided an oil (780 mg, 19%). (TLC hexanes R_f 0.38). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.80 (br s, 1H), 6.78 (br s, 1H), 6.59 (m, 1H), 3.87 (br s, 2H), 2.32 (d, J=7.0 Hz, 1H), 2.25 (d, J=7.0 Hz, 1H).

B) 6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

6-Fluoro-1,4-dihydro-1,4-methano-naphthalene (680 mg, 4.22 mmol) and N-methyl morpholine N-oxide (599 mg, 4.43 mmol) were stirred in acetone (50 mL) and H_2O (5 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt. solution in t-BuOH, 0.02 mmol). After 72 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1 hour. The florisil was filtered and the filtrate concentrated to produce a crystalline product which was triturated with acetone and filtered (524 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.10 (dd, J=8.0,5.0 Hz, 1H), 6.90 (dd, J=8.0,2.3 Hz, 1H), 6.75 (ddd, J=8.0,8.0,2.3 Hz, 1H), 3.79 (s, 2H), 3.18 (d, J=1.5 Hz, 2H), 2.22 (d, J=10.0 Hz, 1H), 1.92 (dd, J=10.0,1.5 Hz, 1H). GCMS *m/e* 194 (M^+).

C) 10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (524 mg, 2.68 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (15 mL) and H_2O (45 mL) then treated with sodium periodate (0.603 mg, 2.82 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 20 mL). The combined organic layer was washed with H_2O (4 x 20 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (0.308 mL, 2.82 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (1.82 g, 8.58 mmol) in DCE (50 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (520 mg, 80%). (TLC 2% acetone/CH_2Cl_2 R_f 0.40). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 6.88 (m, 2H), 3.48 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 2.27 (m, 1H), 1.69 (d, J=10.5 Hz, 1H).

D) 4-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (390 mg, 1.461 mmol), ammonium formate (3.04 g, 48.2 mmol) and 10%$Pd(OH)_2$/C (30 mg) were combined in MeOH (50 mL) and brought to reflux under N_2 for 1.5 hours. Ammonium formate (1.0 g) was added and reflux continued for 0.5 hour. The reaction mixture was filtered through a Celite pad which was rinsed with MeOH. The filtrate was concentrated. The residues were treated with saturated aqueous Na_2CO_3 solution (30 mL) and product extracted with methylene chloride (CH_2Cl_2) (3 x 25 mL). The organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. The residue was treated with 2N HCl MeOH (5 mL) and concentrated then taken up in minimum of MeOH and saturated with Et_2O. After stirring 18h, the white crystals were collected by filtration (86 mg, 28%). (TLC

5% MeOH/CH_2Cl_2 (NH_3) R_f 0.27). (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.83 (m, 2H), 2.89 (m, 4H), 2.61 (dd, J=12.0 Hz, 2H), 2.37 (m, 1H), 1.87 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.2 [(M + 1)$^+$]. (HCl salt) mp 260-262 °C.

EXAMPLE 3

4-METHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-methylbromobenzene. (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J=7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 2.98-2.90 (m, 4H), 2.63 (m, 2H), 2.35 (m, 1H), 2.32 (s, 3H), 1.87 (d, J=11.5 Hz, 1H). APCI MS *m/e* 174.2 [(M + 1)$^+$]. (HCl salt) mp 254-255 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.82; N, 5.15.

EXAMPLE 4

4-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* **1983**, *48*, 2321-2327. Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 3.46 (m, 4H), 3.21 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 2.16 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 244-246 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.77; H, 4.82; N, 5.18.

EXAMPLE 5

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ 7.65 (s, 2H), 7.52 (m, 1H), 3.65 (br s, 1H), 3.49-3.43 (m, 3H), 3.20 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 275-277 °C.

EXAMPLE 6

3-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2,6-Difluoroiodobenzene (Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968,** *11*, 814-819. Tamborski, C.; Soloski, E. *J. Org. Chem.* **1966**, *31*, 746-749. Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* **1986**, *29*, 1972-1982.) 1,3-Difluorobenzene (57.05 g, 0.5 M) in THF (75 mL) was added to a -78 °C stirred solution of n-butyllithium (n-BuLi) (200 mL, 2.5 M/hexanes, 0.5 M) and THF (500 mL) under N_2. By controlling the addition rate the internal temperature was maintained below -70 °C. The total addition time was ~1/2 hour. The resulting slurry was stirred an additional 1/2 hour, then the dispersion was treated with a solution of iodine (126.9 g, 0.5 M) in THF (300 mL) at a rate that maintained an internal temperature below -70 °C. After complete addition the mixture was allowed to warm to room temperature, and was treated with H_2O (100 mL) and 10% aqueous $Na_2S_2O_3$ solution (100 mL) and stirred. The layers were separated and the aqueous layer extracted with hexanes (2 x 250 mL). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4) filtered and concentrated to give a yellow oil (106.5 g). Distillation at ~1-5 mm at ~80 °C provided a light yellow oil (89.5 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H), 6.87 (m, 2H). GCMS *m/e* 240 (M^+).

B) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene

A solution of 2,6-difluoroiodobenzene (5.0 g, 20.8 mmol) and cyclopentadiene (2.07 g, 31.3 mmol) was stirred at 0 °C in P. ether (70 mL, 40-60 °C) under N_2 and treated with n-BuLi (8.74 mL, 2.5M in hexanes, 21.8 mmol) dropwise over 10 minutes. The reaction was quenched after 15 minutes by addition of aqueous 1N HCl solution and the product was extracted with hexanes (3 x 50 mL). The combined organic layer was washed with H_2O (50 mL), saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on Silica gel provided product as an oil (1.5 g, 45%). (TLC hexanes R_f 0.55). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (ddd, J=7.0,1.0,0.8 Hz, 1H), 6.96 (ddd, J=8.5,8.3,7.0 Hz, 1H), 6.86 (br s, 2H), 6.72 (ddd, J=8.5,8.3,0.8 Hz, 1H), 4.25 (br s, 1H), 3.98 (br s, 1H), 2.36 (ddd, J=7.2,1.7,1.7 Hz, 1H), 2.30 (ddd, J=7.2,1.7,1.5 Hz, 1H). GCMS *m/e* 160 (M^+).

C) 3-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

The title compound was prepared by the methods described in Example 2B,C,D starting with 5-fluoro-1,4-dihydro-1,4-methano-naphthalene. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (ddd, J=8.3,7.3,5.0 Hz, 1H), 7.21 (d, J=7.3 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 3.62 (br s, 1H), 3.42-3.30 (m, 3H), 3.21 (m, 2H), 2.38 (m, 1H), 2.12 (d, J=11.5 Hz, 1H). APCI MS *m/e* 178.4 [(M + 1)$^+$]. mp 269-271 °C.

EXAMPLE 7

4-NITRO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (12.4 g, 63.9 mmol) was stirred in CH_2Cl_2 (200 mL). This was cooled (ice bath) and treated with pyridine (12.65 g, 160 mmol) followed by trifluoroacetic anhydride (TFAA) (16.8 g, 11.3 mL, 80 mmol) from an addition funnel over 10 minutes. After ~3 hours, the solution was poured into 0.5N aqueous HCl (200 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with 0.5N aqueous HCl (50 mL), H_2O (2 x 50 mL) and saturated aqueous $NaHCO_3$ solution (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 which crystallized to give white needles (15.35 g, 60.2 mmol, 94%). (TLC 30% EtOAc/hexanes R_f 0.53). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 4H), 4.29 (br d, J=12.6 Hz, 1H), 3.84 (br d, J=12.6 Hz, 1H), 3.51 (dd, J=12.6,1.5 Hz, 1H), 3.21 (br s, 1H), 3.10 (br s, 1H), 3.10 (br d, J=12.6 Hz, 1H), 2.37 (m, 1H), 1.92 (d, J=10.8 Hz, 1H). GCMS *m/e* 255 (M$^+$). mp 67-68 °C.

B) 1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described by Coon, C. L.; Blucher, W.G.; Hill, M. E. *J. Org. Chem.* **1973**, *25*, 4243.)

To a solution of trifluoromethanesulfonic acid (2.4 ml, 13.7 mmol) in CH_2Cl_2 (10 ml) stirred at 0 °C was slowly added nitric acid (0.58 ml, 27.4 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to -78 °C and treated with 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.5 g, 13.7 mmol) in CH_2Cl_2 (15 ml) dropwise from an addition funnel over 5 minutes. The reaction was stirred at -78 °C for 30 minutes then warmed to 0 °C for 1 hour. The reaction mixture was poured into a vigorously stirred ice (100 g). The layers were separated and the aqueous layer

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 saturated aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to give an orange oil that solidified on standing (4.2 g). Chromatography yielded pure product as a crystalline solid (3.2 g, 78%). (TLC 30% EtOAc/hexanes R_f 0.23). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J=8.0 Hz, 1H), 8.08 (br s, 1H), 7.37 (br d, J=8.0 Hz, 1H), 4.38 (br d, J=12.6 Hz, 1H), 3.94 (br d, J=12.6 Hz, 1H), 3.59 (br d, J=12.6 Hz, 1H), 3.43-3.35 (m, 2H), 3.18 (br d, J=12.6 Hz, 1H), 2.48 (m, 1H), 2.07 (d, J=10.8 Hz, 1H). GCMS *m/e* 300 (M^+).

C) 4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (182 mg, 0.61 mmol) was stirred with Na_2CO_3 (160 mg, 1.21 mmol) in MeOH (3 mL) and H_2O (1 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with CH_2Cl_2. The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with CH_2Cl_2 (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3(s) and product was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug and concentrated to an oil. This was dissolved in MeOH and treated with 1N HCl MeOH, concentrated to solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (73 mg, 50%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.38). ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.18 (dd, J=8.0,2.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 3.43 (br s, 2H), 3.28 (m, 2H), 3.07 (dd, J= 13.0,13.0 Hz, 2H), 2.24 (m, 1H), 2.08 (d, J=11.5 Hz, 1H). APCI MS m/e 205.1 [$(M + 1)^+$] mp 265-270 °C.

EXAMPLE 8

4-AMINO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (500 mg, 2.08 mmol) was stirred in 1,4-dioxane (40 mL) and treated with saturated aqueous Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (1.8 g, 8.31 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried through a cotton plug and concentrated to provide an oil (500 mg, 91%).

This oil (500 mg, 1.64 mmol) was dissolved in MeOH (30 mL), treated with 10%Pd/C (~50 mg) and hydrogenated under a H_2 atmosphere (45 psi) for 1 hour. The mixture was filtered through a Celite pad and concentrated to a clear oil (397 mg, 88%).

This oil (50 mg, 0.18 mmol) was stirred in 3N HCl EtOAc (3 mL) for 2 hours then concentrated to a white solid (25 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.10 (3H), 3.60 (br s, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.18 (m, 1H), 1.98 (d, J=11.5 Hz, 1H). APCI MS m/e 175.1 [(M + 1)$^+$] mp 189-192 °C.

EXAMPLE 9

N^1-[10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL]ACETAMIDE HYDROCHLORIDE

A) 1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Hydrogenation of 1-(4-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.0 g, 6.66 mmol) under a H_2 atmosphere (40 psi) and 10%Pd/C (200 mg) in MeOH over 1.5 hours, filtration through Celite and concentration affords a yellow oil (1.7 g). (TLC 50% EtOAc/hexanes R_f 0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 1H), 6.64 (br s, 1H), 6.57 (m, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.17-3.07 (m, 3H), 2.35 (m, 1H), 1.90 (d, J=10.8 Hz, 1H). GCMS *m/e* 270 (M^+).

B) N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide

1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (850 mg, 3.14 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with triethyl amine (0.53 mL, 3.76 mmol) and acetyl chloride (0.23 mL, 3.2 mmol) then stirred 18 hours. Standard $NaHCO_3$ workup yielded an oil which was chromatographed to provide a clear oil (850 mg, 87%). (50% EtOAc/hexanes R_f 0.28).

C) N^1-[10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl]acetamide hydrochloride

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide (100 mg, 0.32 mmol) was stirred with Na_2CO_3 (70 mg, 0.64 mmol) in MeOH (10 mL) and H_2O (2 mL) at 70 °C for 18 hours. The mixture was concentrated, water was added and the product was extracted with EtOAc. The organic layer was extracted with 1N aqueous HCl (3 x 20 mL) and the acidic layer washed with EtOAc (2 x 20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3 (s) and product was extracted with EtOAc (3 x 20 mL). The organic layer was dried (sodium sulfate (Na_2SO_4)) and concentrated to an oil. This material was dissolved in MeOH and treated with 3N HCl EtOAc (3 mL), concentrated and recrystallized

from MeOH/Et_2O to provide a solid (40 mg, 50%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.02 (br m, NH), 7.65 (s, 1H), 7.55 (br s, NH), 7.38 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 3.33 (m, 4H), 2.96 (m, 2H), 2.13 (m, 1H), 2.00 (s, 3H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 217.2 [$(M + 1)^+$]. mp 225-230 °C.

EXAMPLE 10

6-METHYL-5-THIA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) N-(10-Trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5 -trien-4-yl)-thioacetamide

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide (850 mg, 2.72 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.1 g, 2.72 mmol) were combined in toluene (10 mL) and brought to reflux for 1.5 hours. After cooling the reaction was worked up with EtOAc/saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to produce product (410 mg, 44%). (50% EtOAc/hexanes R_f 0.38)

B) 6-Methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

The above oil, 2,2,2-trifluoro-N-(10-trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide, (360 mg, 1.05 mmol) was dissolved in MeOH (10 mL) and 1N NaOH (5 mL) and added to potassium ferricyanide ($K_3Fe(CN)_6$)(1.72 g, 5.23 mmol) in H_2O (10 mL). This mixture was warmed to 60 °C for 1.5 hours, cooled, concentrated and worked up with EtOAc/H_2O. This material was stirred in dioxane (20 mL) and treated with H_2O (50 mL) and Na_2CO_3 to achieve pH 10. To this was added di-t-butyldicarbonate (436 mg, 2.0 mmol) and the mixture was stirred for 18 hours. The reaction was concentrated, treated with H_2O and extracted with CH_2Cl_2. The product was chromatographed (Silica 30% EtOAc/hexanes R_f 0.41) to yield an oil (100 mg).

The above product was treated with 3N HCl/EtOAc (3 mL) and warmed to reflux for ~15 minutes then concentrated to a solid which was azeotroped with CH_2Cl_2 (2x). These solids were dissolved in a minimum amount of MeOH then saturated with Et_2O and stirred. The resulting white crystalline powder was collected by filtration (40 mg, 14%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, NH), 7.65 (s, 1H), 7.82 (s, 1H), 7.65 (br m, NH), 3.36 (m, 2H), 3.24 (m, 2H), 3.02 (m, 2H), 2.76 (s, 3H), 2.23 (m, 1H), 2.06 (d, J=10.8 Hz, 1H). APCI MS *m/e* 231.1 [(M + 1)$^+$]. mp 183-184 °C.

EXAMPLE 11

4,5-DINITRO-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE

A) 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on the method described in Coon, C. L.; Blucher, W. G.; Hill, M. E. *J. Org. Chem.* **1973**, *25*, 4243. For an additional related example of dinitration see: Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512.)

To a solution of trifluoromethanesulfonic acid (79.8 ml, 902.1 mmol) in CH_2Cl_2 (550 ml) stirred at 0 °C was slowly added nitric acid (19.1 ml, 450.9 mmol) generating a white precipitate. After 10 minutes, 1-(10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (50 g, 196 mmol) in CH_2Cl_2 (300 ml) was added dropwise from an addition funnel over 30 minutes. The reaction was stirred at 0 °C for 2.5 hours and then stirred at room temperature for 24 hours. The reaction mixture was poured into a vigorously stirred mixture of H_2O (500 ml) and ice (400 g). The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3 x 300 ml). The organic layer was combined and washed with H_2O (3 x 300 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution (200 mL) and H_2O (200 mL) then dried through a cotton plug and concentrated to solids. Trituration with EtOAc/hexanes produced off white solids which were filtered and dried (52 g, 151 mmol, 77%. The mother liquor was chromatographed to give an additional 4.0 g for a total of 56.0 g (82.8%). (TLC 50% EtOAc/hexanes R_f 0.29) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (s, 1H), 4.39 (br d, J=13.0 Hz, 1H), 3.98 (br d, J=13.0 Hz, 1H), 3.65 (d, J=13.0 Hz, 1H), 3.49 (br s, 1H), 3.44 (br s, 1H), 3.24 (br d, J=12.6 Hz, 1H), 2.53 (m, 1H), 2.14 (d, J=11.5 Hz, 1H). GCMS *m/e* 345 (M$^+$).

B) 4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.7 g, 10.7 mmol) and Na_2CO_3 (2.3 g, 21.4 mmol) were combined in MeOH (50 mL) and H_2O (20 mL) then warmed to reflux for 18 hours. The reaction was cooled, concentrated, treated with H_2O and extracted with CH_2Cl_2 (3 x 50 mL) then dried through a cotton plug. After concentration, the residue was chromatographed to provide brown solids. (1.9 g, 71%).

(TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.36). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 3.17 (br s, 2H), 3.11 (d, J=12.6 Hz, 2H), 2.53 (m, 1H), 2.07 (d, J=11.0 Hz, 1H). GCMS *m/e* 249 (M^+).

EXAMPLE 12

6-METHYL-7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene, (1.9 g, 7.6 mmol) was stirred in 1,4-dioxane (75 mL) and treated with saturated aqueous Na_2CO_3 solution (10 mL). To this was added di-t-butyldicarbonate (3.31 g, 15.2 mmol). After stirring 6 hours the reaction was treated with H_2O (50 mL) and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide product (1.9 g, 71%). (TLC 30% EtOAc/hexanes (NH_3) R_f 0.58). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.72 (br s, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.39 (br s, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.46 (m, 1H), 2.02 (d, J=11.0 Hz, 1H).

B) 4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.9 g, 5.44 mmol) was hydrogenated in MeOH under a H_2 atmosphere (45 psi) over 10%Pd/C (100 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (1.57 g, 100%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.14).

C) 6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (700 mg, 2.42 mmol) was dissolved in EtOH (10 mL) and acetic acid (HOAc) (1 mL) and treated with 1-ethoxyethylenemalononitrile (329 mg, 2.42 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was

chromatographed to provide brown solids (247 mg, 36%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28).

D) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Pilarski, B. *Liebigs Ann. Chem.* **1983**, 1078.)

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (80 mg, 0.267 mmol) was stirred in 50% aqueous NaOH solution (3 mL) and DMSO (1 mL) then treated with 1-iodopropane (0.03 mL, 0.321 mmol). This mixture was warmed to 40 °C for 2 hours then cooled, treated with H_2O and extracted with EtOAc. The organic layer was washed with H_2O (3x) then dried (Na_2SO_4), filtered and concentrated to an oil (90 mg, 0.253 mmol). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.15).

E) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (90 mg, 0.253 mmol) was dissolved in 3N HCl EtOAc (5 mL) and warmed to 100 °C for 1/2 hour. The mixture was cooled, concentrated, slurried in EtOAc, and filtered to provide a white solid (25 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, NH), 7.91 (s, 1H), 7.83 (br m, NH), 7.74 (s, 1H), 4.38 (m, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.10 (m, 2H), 2.87 (s, 3H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H) 1.85 (m, 2H), 0.97 (m, 3H). mp 147-150 °C.

EXAMPLE 13

5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* **1993**, *34*, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.0 g, 3.45 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and treated with ethoxymethylenemalononitrile (421 mg, 3.45 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 50 mL), then dried

(Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (580 mg, 56%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.28)

B) 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.95 (s, 1H), 7.67 (s, 2H), 3.45 (br s, 2H), 3.31 (d, J=12.5 Hz, 2H), 3.13 (d, J=12.5 Hz, 2H), 2.30 (m, 1H), 1.99 (d, J=11.5 Hz, 1H). APCI MS m/e 200.1 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 14

7-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ 8.97 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 3.94 (s, 3H), 3.48 (m, 2H), 3.33 (d, J=12.2 Hz, 2H), 3.14 (d, J=12.2 Hz, 2H), 2.34 (m, 1H), 2.03 (d, J=11.5 Hz, 1H). APCI MS m/e 214.2 [(M + 1)$^+$].

EXAMPLE 15

6-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz; DMSO-d_6) δ 9.40 (br m, NH), 7.77 (br m, NH), 7.70 (s, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.05 (br d, J=11.0 Hz, 2H), 2.79 (s, 3H), 2.23 (m, 1H), 2.10 (d, J=10.8 Hz, 1H). GCMS m/e 213.5 (M$^+$).

EXAMPLE 16

6,7-DIMETHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl

ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, NH), 7.84 (s, 1H), 7.82 (br m, NH), 7.72 (s, 1H), 3.90 (s, 3H), 3.45 (m, 2H), 3.28 (m, 2H), 3.04 (m, 2H), 2.82 (s, 3H), 2.23 (m, 1H), 2.12 (d, J=11.0 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. mp 225-230 °C.

EXAMPLE 17

7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodopropane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 9.45 (br s, NH), 7.97 (s, 1H), 7.85 (s, 1H), 7.83 (br m, NH), 4.43 (m, 2H), 3.49 (m, 2H), 3.33 (m, 2H), 3.08 (m, 2H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.92 (m, 2H), 0.93 (m, 3H). APCI MS *m/e* 242.2 [(M + 1)$^+$]. mp 170-171 °C (subl.).

EXAMPLE 18

7-BUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (For conditions, see; Senskey, M. D.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *Tetrahedron Lett.* **1995**, *36*, 6217.)

4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (500 mg, 1.43 mmol) and 1-butylamine (1.42 mL, 14.3 mmol) were combined in THF (5 mL) and stirred 4 hours. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (3 x 30 mL) then dried (Na_2SO_4), filtered and concentrated to an oil. This oil was passed through a Silica gel filter column to remove baseline impurities eluting with 30% EtOAc/hexanes (510 mg, 1.41 mmol, 99%).

B) 4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (460 mg, 1.27 mmol) was treated with ammonium formate (850 mg, 12.7

mmol) and 10%$Pd(OH)_2$/C (50 mg) in MeOH (20 mL) and brought to reflux for 1 hour then filtered through a Celite pad and concentrated. The solids were treated with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 (3 x 30 mL) and dried by filtration through a cotton plug to give an oil (440 mg, 100%).

C) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (440 mg, 1.27 mmol) was dissolved in EtOH (20 mL) and HOAc (2 mL) and treated with ethoxymethylenemalononitrile (186 mg, 1.52 mmol). The resulting mixture was warmed to 60 °C and stirred 18 hours. The reaction was cooled, concentrated, treated with H_2O and saturated aqueous Na_2CO_3 solution then extracted with EtOAc (3 x 50 mL) and dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide a yellow oil. (400 mg, 89%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.70).

D) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

7-Butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (brs, NH), 9.68 (s, 1H), 7.99 (s, 1H), 7.92 (br m, NH), 7.87 (s, 1H), 4.50 (m, 2H), 3.49 (m, 2H), 3.30 (m, 2H), 3.08 (m, 2H), 2.26 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.88 (m, 2H), 1.32 (m, 2H), 0.82 (t, J=7.0 Hz, 3H). APCI MS *m/e* 256.2 [(M + 1)$^+$]. mp 204-208 °C.

EXAMPLE 19

7-Isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and isobutylamine were converted to the title compound utilizing the methods described in Example 18A-D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.52 (s, 1H), 7.14 (s, 1H), 3.90 (dd, J=7.5,2.0 Hz, 2H), 3.04-2.97 (m, 4H), 2.70 (dd, J=12.8,2.3 Hz, 2H), 2.42 (m, 1H), 2.19 (m, 1H), 1.98 (d, J=10.5 Hz, 1H), 0.93 (m, 6H). APCI MS *m/e* 256.2 [(M + 1)$^+$]. mp 147-150 °C (subl.).

EXAMPLE 20

6-METHYL-7-ISOBUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Amino-5-isobutylamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (250 mg, 0.74 mmol) from Example 19B was dissolved in EtOH (10 mL) and HOAc (2 mL) and treated with 1-ethoxyethylenemalononitrile (118 mg, 0.87 mmol). The reaction proceeded as in Example 18C (18h) and was worked up similarly to provide product (TLC 3% MeOH/CH_2Cl_2 (NH_3) R_f 0.57).

B) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. APCI MS *m/e* 270.3 [(M + 1)$^+$]. mp 129-130 °C (subl.).

EXAMPLE 21

7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to 4-phenylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl at 75 °C for 4 hours in the coupling step. This was then converted to the title compound utilizing the methods described in Example 18B,C,D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (1H), 7.78-7.57 (m, 7H), 3.47-3.00 (m, 6H), 2.23 (m, 1H), 2.09 (d, J=11.5 Hz, 1H). APCI MS *m/e* 276.2 [(M + 1)$^+$]. mp 210-213 °C.

EXAMPLE 22

6-METHYL-7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and Example 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were

converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.73-7.56 (m, 5H), 7.32 (s, 1H), 3.46-2.99 (m, 6H), 2.66 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). APCI MS *m/e* 290.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 23

7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A-D, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. t-Boc precursor GCMS *m/e* 369 (M$^+$). (HCl salt) mp >250 °C.

EXAMPLE 24

6-METHYL-7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s ,1H), 7.27 (s ,1H), 7.02 (br s, , NH), 4.41 (t, J=13.0 Hz, 2H), 3.90 (s, 3H), 3.47-3.26 (m, 6H), 2.20 (m, 1H), 2.00 (d, J=11.5 Hz, 1H), 0.90 (s, 9H). t-Boc precursor APCI MS *m/e* 384.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 25

6,7-DIMETHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE (Based on the following procedure: Jones, R. G.; McLaughlin, K. C. *Org. Syn.* **1963**, *4*, 824. b) Ehrlich, J., Bobert, M. T. *J. Org. Chem.* **1947**, 522.)

4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (100 mg, 0.35 mmol) was warmed to 80 °C in H_2O (5 mL). To this butane 2,3-dione (0.034 mL, 0.38 mmol) was added under N_2 for 2 hours. The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml). The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an oil (120 mg, 100%). The oil was dissolved in 2N HCl MeOH (5 mL) and warmed to reflux for 30 minutes, then concentrated. Recrystallization from MeOH/Et_2O provided a white powder (50 mg, 43%). (TLC EtOAc R_f 0.14). ^{1}H NMR (400 MHz, DMSO-d_6)

δ 7.85 (s, 2H), 3.50 (br s, 2H), 3.32 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.64 (s, 6H), 2.24 (m, 1H), 2.13 (d, J=11.0 Hz, 1H). t-Boc precursor APCI MS *m/e* 340.3 [(M + 1)$^+$].

EXAMPLE 26

5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

A) 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (3.0 g, 8.70 mmol) was hydrogenated in MeOH (30 ml) under H_2 (45 psi) over $Pd(OH)_2$ (300 mg of 20 wt%/C, 10%wt). After 2.5 hours the reaction was filtered through a Celite pad and rinsed with MeOH (30 ml). The solution was concentrated to a light brown oil which crystallized (2.42 g, 96%). (TLC 10% MeOH/CH_2Cl_2 R_f 0.56). APCI MS *m/e* 286.2 [(M + 1)$^+$]. mp 129-131 °C.

B) 1-(5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.75 mmol) was stirred in THF (2 ml). This mixture was treated with H_2O (2 mL) and glyoxal sodium bisulfite addition compound hydrate (931 mg, 3.50 mmol) then stirred at 55 °C for 2.5 hours. The reaction was cooled to room temperature and extracted with EtOAc (3 x 40 ml). The combined organic layer was washed with H_2O (2 x 30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an off white powder (329 mg, 60%). (TLC 25% EtOAc/hexanes R_f 0.40). mp 164-166 °C.

C) 5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene hydrochloride

1-(5,8,14-Triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (320 mg, 1.04 mmol) was slurried in MeOH (2.0 ml) and treated with Na_2CO_3 (221 mg, 2.08 mmol) in H_2O (2.0 ml). The mixture was warmed to 70 °C for 2 hours, then concentrated, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was dried through a cotton plug and concentrated to give a light yellow oil (183 mg, 83%) which solidified upon standing (mp 138-140 °C). This material was dissolved in MeOH (10 mL), treated with 3M HCl/EtOAc (3 ml), concentrated and azeotroped with MeOH

(2 x 20 mL) to give solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (208 mg, 97%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (400 MHz, CD_3OD) δ 8.94 (s, 2H), 8.12 (s, 2H), 3.70 (m, 2H), 3.54 (d, J=12.5 Hz, 2H), 3.35 (d, J=12.5 Hz, 2H), 2.49 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). GCMS *m/e* 211 (M^+). mp 225-230 °C.

EXAMPLE 27

14-METHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene (207 mg, 0.98 mmol) was treated with 37% aqueous formaline solution (1 mL) and formic acid (1 mL) then warmed to 80 °C for 1 hour. The reaction was poured into water, made basic (NaOH, pH ~11) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on Silica gel to provide a yellow solid. This was stirred in MeOH (2 mL) and treated with 3N HCl EtOAc (2 mL). After concentration the solids were recrystallized from MeOH/Et_2O to afford product as a white solid (70 mg, 27%). (2% MeOH/CH_2Cl_2 (NH_3) R_f 0.47). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 7.80 (s, 2H), 3.37 (br s, 2H), 3.03 (m, 2H), 2.47 (m, 2H), 2.32 (m, 1H), 2.18 (br s, 3H), 1.84 (d, J=11.0 Hz, 1H). APCI MS *m/e* 226.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 28

5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (900 mg, 2.61 mmol) and potassium acetate (KOAc) (2.6 g, 26.1 mmol) were dissolved in DMSO (10 mL) and warmed with stirring to 100 °C for 16 hours. The mixture was cooled and diluted with H_2O (50 mL) then extracted with 80% EtOAc/hexanes (6 x 25 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and purified by chromatography to give an oil (575 mg, 70%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.56)

B) 2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (575 mg, 1.82 mmol) was hydrogenated in MeOH under a H_2 atmosphere at (45 psi) over 10%Pd/C (80 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (450 mg, 86%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.6). ^{1}H NMR (400 MHz, CD_3OD) δ 6.67-6.59 (m, 2H), 4.12 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.24 (m, 1H), 1.94 (d, J=10.5 Hz, 1H). GCMS *m/e* 286 (M^+).

C) 2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* **1990**, *27*, 335.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), trimethyl orthoformate (0.19 mL, 1.73 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 18 mg, 0.07 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. The mixture was cooled, treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered, concentrated and purified by chromatography to give an oil (110 mg, 71%). (TLC 20% EtOAc/hexanes R_f 0.40)

D) 5-Oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (110 mg, 0.37 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (78 mg, 0.74 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into aqueous 1N HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. The product was extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4), concentrated and chromatographed on Silica gel to produce an oil. (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.19).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (55 mg, 63%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 3.41 (m, 2H), 3.30 (m, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.47 (m, 1H), 2.15 (d, J=11.0 Hz, 1H). APCI MS *m/e* 201.03 [$(M + 1)^+$].

EXAMPLE 29

6-METHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), triethyl orthoacetate (0.34 mL, 1.83 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. Workup, isolation and purification as in Example 28C provided the title compound (90 mg, 55%).

B) 6-Methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (90 mg, 0.30 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (61 mg, 0.58 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80 °C for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The solution was dried (Na_2SO_4), concentrated, and chromatographed on Silica gel to produce an oil. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.18). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.26 (s, 1H), 3.05-2.98 (m, 4H), 2.72 (d, J=12.8 Hz, 2H), 2.59 (s, 3H), 2.46 (m, 1H), 1.98 (d, J=10.5 Hz, 1H).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (10 mg, 13%). APCI MS *m/e* 215.2 [(M + 1)$^+$]. mp >250 °C.

EXAMPLE 30

2-FLUORO-N-(5-HYDROXY-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-BENZAMIDE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), 2-fluorobenzoyl chloride (0.07 mL, 0.576 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol), pyridine (0.046 mL, 0.576 mmol) and xylenes (5 mL) were combined under nitrogen and stirred at 135 °C for 18 hours. After 24 hours, additional PPTS (50 mg) was added and the material stirred at 135 °C for an additional 24 hours. Workup as above provided crude product (145 mg, 0.375 mmol) which was

combined with Na_2CO_3(s) (80 mg, 0.75 mmol) in MeOH (5 mL) and H_2O (2 mL) and heated to reflux. After 3 hours, the reaction was cooled and diluted with water then extracted with CH_2Cl_2 (4 x 40 mL), dried through a cotton plug then chromatographed to remove baseline impurity (5% MeOH/CH_2Cl_2 (NH_3)). The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of MeOH and the solution was saturated with Et_2O and stirred. After stirring 4 hours the product was collected by filtration (85 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (m, 2H), 7.59 (m, 1H), 7.36-7.23 (m, 2H), 6.82 (s, 1H), 2.99 (m, 4H), 2.78 (m, 2H), 2.35 (m, 1H), 1.96 (d, J=10.5 Hz, 1H). APCI MS *m/e* 313.1 [(M + 1)$^+$]. mp 125-130 °C (subl.).

EXAMPLE 31

4-CHLORO-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Copper(I)chloride (CuCl) was prepared as follows: $CuSO_4$ (4.3 g) and NaCl (1.2 g) were dissolved in hot H_2O (14 mL). sodium bisulfite ($NaHSO_3$) (1 g) and sodium hydroxide (NaOH) (690 mg) were dissolved in H_2O (7 mL) and added to the hot acidic solution over 5 minutes. The precipitated white solids were filtered and washed with water.

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (460 mg, 1.7 mmol) was dissolved in H_2O (2 mL) and concentrated HCl solution(1 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (275 mg) in H_2O (1 mL) dropwise. To the resulting solution was added a CuCl (202 mg, prepared as described above, 2.04 mmol) in concentrated HCl solution (2 mL) over 10 minutes (gas evolution observed). The resulting solution was warmed to 60 °C for 15 minutes, then was cooled to room temperature and extracted with EtOAc (4 x 30 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to an oil which was filtered through a Silica pad to remove baseline material eluting with 50% EtOAc/hexanes to give an oil (470 mg, 95%).

B) 4-Chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (470 mg, 1.62 mmol) and Na_2CO_3 (344 mg, 3.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were heated to reflux. After 2 hours, the reaction was cooled and diluted with water then extracted with EtOAc (4 x 40 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude material was treated with excess 3N HCl EtOAc and concentrated, then

dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred. After stirring 4 hours the product was collected by filtration (155 mg, 42%). ^1H NMR (free base) (400 MHz, $CDCl_3$) δ 7.15 (m, 2H), 7.09 (d, J=8.0 Hz, 1H), 3.00-2.94 (m, 4H), 2.68, (m, 2H), 2.38 (m, 1H), 1.92 (d, J=10.5 Hz, 1H). ^1H NMR (HCl salt) (400 MHz, DMSO-d_6) δ 7.30-7.20 (m, 3H), 3.30-3.15 (m, 6H), 2.37 (m, 1H), 1.89 (d, J=11.0 Hz, 1H). APCI MS *m/e* 194.1 [(M + 1)$^+$].

EXAMPLE 32

10-AZATRICYCLO[6.3.1.0~2,7~]DODECA-2(7),3,5-TRIEN-4-YL CYANIDE HYDROCHLORIDE

A) 1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.85 mmol) was dissolved in H_2O (5 mL) and concentrated H_2SO_4 solution (0.5 mL) then cooled to 0 °C and treated with a solution of sodium nitrite ($NaNO_2$) (140 mg, 2.04 mmol) in H_2O (2 mL) dropwise. Potassium iodide (460 mg, 2.78 mmol) in 1N H_2SO_4 solution (0.5 mL) was added over 10 minutes (reaction becomes dark red). The resulting solution was warmed to room temperature and stirred 18 hours. The reaction was quenched with $NaHSO_3$ and water (pH 2.5) then extracted with EtOAc (4 x 30 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to a yellow oil which was chromatographed on Silica gel to provide a yellow oil. (260 mg, 37%). (TLC 30% EtOAc/hexanes R_f 0.70). (A 5.4 g scale performed as above yielded 5 g, 67%).

B) 4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (5 g, 13.1 mmol) and 37% saturated aqueous NH_4OH solution (50 mL) were stirred in MeOH (250 ml) for 2 hours then concentrated and azeotroped with MeOH (2 x 50 mL). The resulting product was stirred in 1,4-dioxane (75 mL) and treated with saturated Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (5.71 g, 26.2 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel (TLC 20% EtOAc/hexanes) to provide product as an oil (4.9 g, 98%).

C) 4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (Utilizing the methods described in: House, H. O.; Fischer, W. F. *J. Org. Chem.* **1969**, 3626.)

CuCN (108 mg, 1.21 mmol) and NaCN (59 mg, 1.21 mmol) were combined in dry DMF (6 mL) and warmed to 150 °C under N_2. Solution occurs in 20 minutes. To this was added 4-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (232 mg, 0.6 mmol) in DMF (3.5 mL) and the mixture was stirred for 18 hours at 150 °C. The reaction was cooled and diluted with 50% saturated aqueous NaCl solution and extracted with 50% EtOAc/hexanes (3 x 30 mL). After drying (Na_2SO_4), filtration and concentration the product was isolated by chromatography (86 mg, 50%). (TLC 20% EtOAc/hexanes R_f 0.28).

D) 10-Azatricyclo[6.3.1.0~2,7~]dodeca-2(7),3,5-trien-4-yl cyanide hydrochloride

4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester was treated with 3N HCl EtOAc (6 mL) and warmed to reflux for 2 hours, then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (49 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (br s, NH), 7.86 (br s, NH), 7.74-7.70 (m, 2H), 7.49 (d, J=7.5 Hz, 1H), 3.33-2.97 (m, 6H), 2.17 (m, 1H), 2.01 (d, J=11.0 Hz, 1H). GCMS *m/e* 184 (M^+). mp 268-273 °C.

EXAMPLE 33

3-(10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-5-METHYL-1,2,4-OXADIAZOLE HYDROCHLORIDE

4-Cyano-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (300 mg, 1.1 mmol) was stirred in EtOH (10 mL). To this hydroxyl amine hydrochloride (382 mg, 5.5 mmol) and NaOH (242 mg, 6.05 mmol) were added and the mixture was warmed to reflux. After 45 minutes, the reaction was cooled, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid (110 mg, 0.35 mmol). This solid was dissolved in pyridine (1 mL) and treated with acetyl chloride (0.03 mL, 0.415 mmol) and warmed to 100°C for 18 hours. The reaction was cooled, treated with H_2O and extracted with EtOAc. The organic extracts were washed with water and saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel afforded product (50 mg, 0.15 mmol). (25% EtOAc/hexanes R_f 0.18). This product was treated with 2N HCl MeOH (10 mL), heated to 70 °C for 1 hour, cooled, concentrated and recrystallized from MeOH/Et_2O to provide product (15 mg). APCI MS *m/e* 242.2 [(M + 1)$^+$].

EXAMPLE 34

1-(10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-1-ETHANONE HYDROCHLORIDE

A) 1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (253 mg, 1.0 mmol) and AcCl (0.68 mL, 10 mmol) were dissolved in DCE (3 mL) and treated with aluminum chloride ($AlCl_3$) (667 mg, 5.0 mmol). The resulting yellow mixture was stirred for 30 minutes then poured over ice and saturated aqueous $NaHCO_3$ solution. After stirring 20 minutes the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried through a cotton plug then concentrated to a orange-yellow oil (255 mg, 86%).

B) 4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.3 g, 4.37 mmol) and 37% aqueous NH_4OH solution (10 mL) were stirred in MeOH (30 ml) for 3 hours, then concentrated and azeotroped with MeOH (2 x 50 mL). (This product could be converted to an HCl salt directly: see the next example.) The resulting product was stirred in 1,4-dioxane (20 mL) and treated with saturated aqueous Na_2CO_3 solution (5 mL). To this was added di-t-butyldicarbonate (1.91 g, 8.74 mmol). After stirring 2 hours, the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4 x 30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide an oil (1.3 g, 100%). (TLC 40% EtOAc/hexanes R_f 0.56).

C) 1-(10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone hydrochloride

4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (190 mg, 0.63 mmol) was treated with excess 3N HCl EtOAc and warmed to 70°C for 1 hour then concentrated and dissolved in a minimum of MeOH. The resulting solution was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (81 mg, 54%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.75 (br s, NH), 7.89 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.74 (br s, NH), 7.44 (d, J=8.0 Hz, 1H), 3.33 (br s, 2H), 3.22 (br s, 2H), 3.00 (br m, 2H), 2.54 (s, 3H), 2.17 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). GCMS *m/e* 201 (M^+). mp 198-202 °C.

EXAMPLE 35

10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-OL HYDROCHLORIDE

A) Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.5 g, 8.41 mmol) and 3-chloroperoxybenzoic acid (m-CPBA) (7.5 g, 42 mmol) were stirred in CH_2Cl_2 (20 mL) and warmed to 40°C for 18 hours. The mixture was cooled to room temperature, then treated with dimethylsulfide (Me_2S) (3 mL, 40.8 mmol) and stirred 24 hours. The resulting mixture was poured into ice and saturated aqueous Na_2CO_3 solution (100 mL) then extracted with Et_2O (4 x 40 mL). The organic layer was washed saturated aqueous Na_2CO_3 solution (3 x 40 mL) then dried (Na_2SO_4), filtered and concentrated to afford an oil (1.83 g, 69%). (TLC EtOAc R_f 0.80).

B) 2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (900 mg, 2.87 mmol) was stirred in MeOH (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) for 48 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Chromatography on Silica gel provided pure product (420 mg, 54%). (TLC 5% MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 1H), 6.70 (m, 1H), 6.62 (m, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.48 (m, 1H), 3.21 (br s, 1H), 3.16 (br s, 1H), 3.09 (m, 1H), 2.38 (m, 1H), 1.97 (d, J=11.0 Hz, 1H).

C) 10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol hydrochloride

2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (50 mg, 0.184 mmol) was dissolved in MeOH/H_2O (3/1, 5 mL), treated with Na_2CO_3(s) (40 mg, 0.369 mmol) and warmed to 65°C for 2 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL) then dried through a cotton plug. Filtration through a Silica gel plug provided an oil (10% MeOH/CH_2Cl_2) which was treated with 3N HCl EtOAc (3 mL) then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (10 mg, 26%). ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.16 (d, J=8.0 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.72 (dd, J=8.0,2.0 Hz, 1H), 3.32-3.28 (4H), 3.09 (dd, J=14.5,12.0 Hz, 2H), 2.32 (m, 1H), 2.03 (d, J=11.0 Hz, 1H). APCI MS *m/e* 176.2 [(M + 1)$^+$]. mp 308 (dec.) °C.

EXAMPLE 36

7-METHYL-5-OXA-6,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2,4(8),6,9-TETRAENE HYDROCHLORIDE

A) 1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl ester (800 mg, 2.55 mmol) was combined with $AlCl_3$ (1.0 g, 7.65 mmol) and warmed to 170°C for 2 hours. The mixture was cooled and treated with 1N aqueous HCl solution (20 mL), extracted with EtOAc and dried (Na_2SO_4). Chromatography affords an oil (190 mg, 24%). (TLC EtOAc R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 0.5H), 12.52 (s, 0.5H), 7.53 (s, 1H), 6.86 (s, 1H), 4.33 (m, 1H), 3.91 (m, 1H), 3.56 (m, 1H), 3.28 (br s, 1H), 3.24 (br s, 1H), 3.14 (m, 1H), 2.35 (m, 1H), 1.97 (br d, J=11.2 Hz, 1H).

B) 2,2,2-Trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone

1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (190 mg, 0.605 mmol), hydroxylamine HCl (99 mg, 1.21 mmol) and NaOAc (118 mg, 1.21 mmol) were combined in MeOH (4 mL) and H_2O (1 mL) and warmed to 65°C for 18 hours. The mixture was cooled, diluted with H_2O and extracted with EtOAc which was dried (Na_2SO_4), filtered and concentrated to provide a yellow oil (177 mg, 93%).

C) 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone

The above oil, 2,2,2-trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone (177 mg, 0.54 mmol) was stirred in DCE (3 mL), treated with triethylamine (0.4 mL, 2.8 mmol) and acetic anhydride (Ac_2O) (0.3 mL, 2.8 mmol) then stirred 18 hours. The reaction was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated to a yellow oil which was dissolved in anhydrous DMF (3 mL) and treated with 60% NaH in oil (32 mg, 1.08 mmol). After stirring 18 hours, additional 60% NaH in oil was introduced (33 mg) and the mixture was stirred 2 hours. The reaction was quenched with H_2O (5 mL) and extracted with 80% EtOAc/hexanes (3 x 30 mL). The organic layer was washed with H_2O (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated and chromatographed to provide an oil (40% EtOAc/hexanes R_f 0.56).

D) 7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene hydrochloride

Utilizing the methods described in Example 9C, 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone was converted to the title compound. This was treated with 3N HCl EtOAc (3 mL), concentrated and dissolved in a minimum of CH_2Cl_2 which was saturated with hexanes and stirred. After 18 hours the white crystalline product was collected by filtration (18 mg, 13% overall). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.63 (s, 1H), 3.42-2.98 (m, 6H), 2.50 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=10.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 37

4-(2-Methyl-2H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride and 4-(1-Methyl-1H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1. $0^{2,7}$dodeca-2(7),3,5-triene hydrochloride

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.0 g, 3.3 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (4.0 g, 33.6 mmol) were warmed to 140°C for 18 hours. After cooling, a crystalline precipitate was filtered and rinsed with EtOAc (690 mg, 58%).

The above solid, 3-dimethylamino-1-(10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-propenone, (200 mg, 0.56 mmol) was dissolved in EtOH (2 mL) and treated with 5N HCl EtOH (0.1 mL) followed by methyl hydrazine (0.6 mmol). The resulting mixture was warmed to 70°C for 4 hours. The mixture was cooled, diluted with water and extracted with EtOAc, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel provided a 3/1 mixture of regioisomeric products (130 mg, 68%). (TLC 50% EtOAc/hexanes R_f 0.40).

The above oil (130 mg, 0.388 mmol) and Na_2CO_3(s) (82 mg, 0.775 mmol) were stirred in MeOH (10 mL) and H_2O (5 mL) for 18 hours. After cooling the reaction was diluted with water, extracted with CH_2Cl_2 dried through a cotton plug and concentrated. The product was purified by chromatography on Silica gel and concentrated to an oil. The salt was generated with 2N HCl MeOH, concentrated and recrystallized from MeOH/EtOAc to provide a 3/1 mixture of regioisomeric pyrrazoles (85 mg, 58%). (5% MeOH/CH_2Cl_2 (NH_3) R_f 0.25). TFA-precursor APCI MS *m/e* 336.2 [(M + 1)$^+$].

EXAMPLE 38

4,5-DICHLORO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on Campaigne, E.; Thompson, W. *J. Org. Chem.* **1950**, *72*, 629.)

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (539 mg, 2.1 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with ICl_3 (s) (982 mg, 4.21 mmol). The resulting orange solution was stirred 0.5 hours, poured into saturated aqueous $NaHSO_3$ solution (25 mL), extracted with CH_2Cl_2 (3 x 25 mL), dried through a cotton plug and concentrated to an oil (570 mg, 84%) (TLC 50% EtOAc/hexanes R_f 0.62).

B) 4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (570 mg, 1.75 mmol) was stirred in MeOH (25mL) and treated with Na_2CO_3(s) (5 g, 47 mmol) in H_2O (5 mL). The stirred mixture was warmed to 70°C for 4 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3 x 40 mL). The product was extracted into 1N aqueous HCl solution (2 x 40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. Product was extracted with CH_2Cl_2 (3 x 40 mL), filtered through a cotton plug and concentrated to an oil (400 mg, 100%).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (210 mg, 45%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.08). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 2H), 3.33-2.97 (m, 6H), 2.18 (m, 1H), 1.99 (d, J=10.5 Hz, 1H). ^{13}C NMR (100 MHz,DMSO-d_6) δ 141.02, 130.60, 126.58, 45.54, 40.55, 38.30. GCMS *m/e* 227, 229 (M^+). mp 283-291 °C.

EXAMPLE 39

N^4,N^4-DIMETHYL-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE-4-SULFONAMIDE HYDROCHLORIDE

A) 10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (530 mg, 2.1 mmol) was added to chlorosulfonic acid (2 mL, 30 mmol) and stirred for 5 minutes.

The mixture was quenched with ice, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to provide an oil (640 mg, 87%). (TLC 30% EtOAc/hexanes R_f 0.15).

B) N^4,N^4-Dimethyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonamide hydrochloride

10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) was stirred in THF (10 mL) and treated with 40% Me_2NH/H_2O (1.5 mL). After 10 minutes the mixture was concentrated and chromatographed on Silica gel (TLC 30% EtOAc/hexanes R_f 0.31) to provide an oil (256 mg, 78%). This material was dissolved in MeOH (6 mL) and NH_4OH (2 mL) and stirred 18 hours. The mixture was concentrated and azeotroped from MeOH (3x) The resulting oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL), concentrated, dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration as a white powder (163 mg, 59%). (TLC 10% MeOH/ CH_2Cl_2 (NH_3) R_f 0.54). ^1H NMR (data, free base) (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.41 (d, J=8.0 Hz, 1H), 3.30 (m, 2H), 3.20 (d, J=12.5 Hz, 2H), 3.07 (dd, J=12.5,2.2 Hz, 2H), 2.69 (s, 6H), 2.45, (m, 1H), 2.00 (d, J=11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128,43, 124.16, 122,75, 46.67, 46.55, 42.11, 39,44, 37,81. GCMS *m/e* 266 (M^+). (data HCl salt) ^1H NMR (400 MHz, DMSO-d_6) δ 7.68-7.52 (3H), 3.38 (m, 2H), 3.24 (m, 2H), 3.04 (m, 2H), 2.58 (s, 6H), 2.22 (m, 1H), 2.04 (d, J=11.0 Hz, 1H). GCMS *m/e* 266 (M^+). Anal. Calcd. for $C_{13}H_{18}N_2O_2HCl$: C, 51.56; H, 6.32; N, 9.25. Found C, 51.36; H,6.09; N,9.09.

EXAMPLE 40

4-(1-PYRROLIDINYLSULFONYL)-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The pyrrolidine analogue was prepared from 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) as by substituting pyrroline in the coupling step described in Example 39B. The TFA product was isolated as an oil (314 mg, 89%). Deprotection and conversion to the salt as in Example 39B affords a white powder (189 mg, 63%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.60). (TLC 50% EtOAc/hexanes R_f 0.65). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=8.0 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J=8.0 Hz, 1H), 3.30-3.15 (m, 8H), 3.00 (m 2H), 2.39 (m, 1H), 1.98 (d, J=11.5 Hz, 1H), 1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.91, 144.08, 136.65, 127. 90, 124.18, 122.36, 50.43, 47.87, 46.80, 46.63, 42.11, 39.63, 25.10. APCI MS *m/e* 293 [(M + 1) $^+$]. (data HCl salt) ^1H NMR (400 MHz, DMSO-d_6) δ 9.78 (br s, NH), 8.1 (br s, NH), 7.73 (d, J =1.5 Hz,1H), 7.66

(dd, J=8.0,1.5 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 3.39-3.01 (10H), 2.21 (m, 1H), 2.04 (d, J=11.0 Hz, 1H), 1.66 (m, 4H). GCMS *m/e* 292 (M^+). Anal. Calcd. For $C_{13}H_{18}N_2O_2HCl.1/2MeOH$: C, 54.07; H, 6.47; N, 8.51. Found C, 53.98; H,6.72; N, 8.12

EXAMPLE 41

5,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2,4(8),9-TRIEN-6-ONE HYDROCHLORIDE (The title compound was prepared following the procedures described in Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53, treating 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester as an equivalent to an ortho fluoro phenyl moiety.) ^1H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, NH), 9.88 (br s, NH), 7.52 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 3.41 (d, J=5.0 Hz, 2H), 3.35-3.13 (m, 4H), 2.93 (m, 2H), 2.12 (m, 1H), 1.95 (d, J=11.5 Hz, 1H). APCI MS *m/e* 215.2 [(M + 1)$^+$].

EXAMPLE 42

6-OXO-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE (For references, see: Nachman, R. J. *J. Het. Chem.* **1982**, 1545.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (317 mg, 1.11 mmol) was stirred in THF (10 mL), treated with carbonyldiimidazole (269 mg, 1.66 mmol) and warmed to 60°C for 18 hours. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL) and washed with 1N aqueous HCl solution (3 x 10 mL). The organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel (50% EtOAc/Hexanes) to provide an oil (130 mg). This material converted to the title compound by the methods described in Example 9C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, NH), 9.56 (br s, NH), 7.63 (br s, NH), 7.24 (s, 1H), 7.07 (s,1H), 3.26 (br s, 2H), 3.16 (br t, J=9.5 Hz, 1H), 2.93 (br s, 1H), 2.18 (m, 1H), 1.97 (d, J=11.0 Hz, 1H). APCI MS *m/e* 217.2 [(M + 1)$^+$].

EXAMPLE 43

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* **1983**, *48*, 2321-2327. Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* **1987**, *30*, 2191-2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ 7.67-7.50

(3H), 3.65 (br s, 1H), 3.49-3.42 (m, 2H), 3.29 (s, 1H), 3.28-3.16 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS *m/e* 228.2 [(M + 1)$^+$]. (HCl salt) mp 275-277 °C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.83; N, 5.16.

EXAMPLE 44

3-PHENYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene and 5-iodo-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* **1976**, *98*, 753-761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* **1977**, *99*, 3723-3733.)

Magnesium turnings (9.37 g, 385 mmol) were stirred in anhydrous THF (1000 mL) in a flame dried 2L 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,6-Difluoro-iodobenzene (0.3 g) was added followed by of 3N EtMgBr in THF (0.3 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (24.24 g, 367 mmol) and 2,6-difluoro-iodobenzene (88.0 g, 367 mmol). Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4x). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for ~1 hour (no SM by GCMS).

The reaction was cooled to room temperature and quenched with H_2O (200 mL) followed by aqueous 1N HCl solution (200 mL) to dissolve the solids. Product was extracted with hexanes (4 x 150 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil (70 g). Chromatography on Silica gel eluting with hexanes provided two lots (9.0 and 21.0 g), which contained primarily 5-iodo-1,4-dihydro-1,4-methano-naphthalene. (TLC hexanes R_f 0.63).

B) 5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

5-Iodo-1,4-dihydro-1,4-methano-naphthalene (20 g) and N-methyl morpholine N-oxide (17.61 g, 130 mmol) were stirred in acetone (90 mL) and H_2O (13 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5%wt. solution in t-BuOH, 0.02 mmol). After 144 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1/2 hour. The

mixture was filtered through a Celite pad and the filtrate concentrated to produce an oil which was purified by chromatography on Silica gel eluting with a gradient of hexanes to 100% EtOAc to provide a yellow solid (13.73 g). APCI MS *m/e* 301.1 $[(M - 1)^+]$.

C) 10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (8.33 g, 27.6 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (25 mL) and H_2O (75 mL) then treated with sodium periodate (6.17 g, 29.0 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2 x 40 mL). The combined organic layer was washed with H_2O (4 x 30 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (30 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (3.16 mL, 29.0 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0 °C) mixture of $NaHB(OAc)_3$ (18.72 g, 88.0 mmol) in DCE (150 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (6.3 g, 61%). (TLC 5% EtOAc/hexanes R_f 0.10). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J= 8.0 Hz, 1H), 7.28-7.22 (m, 3H), 7.13 (d, J=8.0 Hz,1H), 6.98-6.94 (m, 3H), 3.58 (AB dd, J=14.2 Hz, 2H), 3.26 (br s, 1H), 3.21 (br s, 1H), 3.04 (br d, J=10.2 Hz, 1H), 2.83 (br d, J=10.2 Hz, 1H), 2.47 (d, J=10.0 Hz, 1H), 2.39 (d, J=10.0 Hz, 1H), 2.34 (m, 1H), 1.72 (d, J=10.5 Hz, 1H). APCI MS *m/e* 376.0 $[(M + 1)^+]$.

D) 10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(For a discussion, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.)

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (375.3 mg, 1.0 mmol), potassium acetate (785 mg, 8.0 mmol) and phenyl boronic acid (183 mg, 1.5 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) (57.5 mg, 0.05 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 (180 mg, 55%). (TLC 4%EtOAc/hexanes R_f 0.18). GCMS *m/e* 325 $(M)^+$.

E) 3-Phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene was converted into the title compound utilizing the conditions described in Example 2D. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.30). (data for free base) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.15 (8H), 3.17 (br s, 1H), 3.01 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.72 (dd, J=10.5,2.5 Hz, 1H), 2.63 (dd, J=10.5,2.5 Hz, 1H), 2.41 (m, 1H), 1.91 (d, J=10.5 Hz, 1H). APCI MS *m/e* 236.2 [(M + 1)$^+$]. (HCl salt) mp 262-265 °C. Anal. Calcd. for $C_{17}H_{17}N.HCl.1/3H_2O$: C, 73.26; H, 6.86; N, 5.19. Found C, 73.50; H, 6.77; N, 5.04.

EXAMPLE 45

3-HYDROXY-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (3.0 g, 7.99 mmol) was stirred in anhydrous THF (40 mL) at -78 °C under nitrogen and treated dropwise with n-BuLi (3.84 mL of 2.5M soln. in hexanes, 9.59 mmol). After 10 minutes, tri-isopropylborate (4.61 mL, 20.0 mmol) was added dropwise. After ~1/2 hour, the reaction was poured into saturated aqueous $NaHCO_3$ solution, stirred 5 minutes and extracted with EtOAc (3 x 50 mL) and concentrated. The residue was dissolved in 30% Et_2O/hexanes and extracted with 1N NaOH aqueous solution (4 x 50 mL). The combined aqueous basic layer was treated with concentrated HCl to achieve pH 8 and extracted with EtOAc (4 x 25 mL), dried (Na_2SO_4) and stripped. Chromatography on Silica gel eluting first with 3% EtOAc/hexanes to remove non-polar components, then with 5% MeOH/CH_2Cl_2 provides the title compound. (TLC 25% EtOAc/hexanes R_f 0.60).

B) 10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (140 mg, 0.48 mmol) dissolved in THF (5 mL) was treated with N-methylmorpholine-N-oxide (64.5 mg, 0.48 mmol) and brought to reflux for 1 hour. The reaction was concentrated and chromatographed on Silica gel to provide product. (TLC 25% EtOAc/hexanes R_f 0.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.15 (3H), 7.04 (dd, J= 8.0,7.0 Hz, 1H), 6.95 (m, 2H), 6.75 (d, J=7.0 Hz, 1H), 6.59 (dd, J=8.0,1.0 Hz, 1H), 3.53 (br s, OH), 3.51 (AB d, J=14.0 Hz, 2H), 3.28 (br s, 1H), 3.06 (br s, 1H), 2.91 (dd, J=8.5,1.5 Hz, 1H), 2.79 (ddd, J=8.5,1.5,1.5 Hz, 1H), 2.42 (d, J=11.0 Hz, 1H), 2.39 (d, J=11.0 Hz, 1H), 2.23 (m, 1H), 1.65 (d, J=10.5 Hz, 1H). APCI MS *m/e* 266.5 [(M + 1)$^+$].

C) 3-Hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (160 mg, 0.60 mmol) was converted into the title compound by the methods described in Example 1D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J=8.0,7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 3.51 (br s, 1H), 3.33-3.25 (3H), 3.16 (d, J=12.0 Hz, 1H), 3.09 (d, J=12.0 Hz, 1H), 2.29 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). APCI MS *m/e* 175.8 [(M + 1)$^+$]. (HCl salt) mp 253-255 °C.

EXAMPLE 46

4,5-DIFLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2,4,5-trifluorobromobenzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J=8.5 Hz, 2H), 3.48-3.13 (6H), 2.38 (m, 1H), 2.11 (d, J=11.5 Hz, 1H). APCI MS *m/e* 196.2 [(M + 1) $^+$]. (HCl salt) mp 301-303 °C. Anal. Calcd. for $C_{11}H_{11}F_2N.HCl.1/6H_2O$: C, 56.30; H, 5.30; N, 5.97. Found C, 56.66; H, 5.41; N, 5.96.

EXAMPLE 47

6-ETHYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and propionyl chloride were converted to the title compound following the procedures described in Example 30 and Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* **1990**, *27*, 335. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.62 (s, 1H), 3.48 (d, J=2.5 Hz, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.20 (2H), 3.01 (q, J=7.5 Hz, 2H), 2.45 (m, 1H), 2.17 (d, J=11.5 Hz, 1H), 1.42 (t, J=7.5 Hz, 3H). APCI MS *m/e* 229.2 [(M + 1)$^+$].

EXAMPLE 48

6-ISOPROPYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and isobutyryl chloride were converted to the title compound following the procedures described in EXAMPLE 47. (TLC 25% EtOAc/hexanes R_f 0.14). ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (2H), 3.49 (br s, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.33-3.19 (3H), 2.45 (m, 1H), 2.18 (d, J=11.5 Hz, 1H), 1.45 (d, J=7.0 Hz, 6H). APCI MS *m/e* 243.2 [(M + 1)$^+$]. (HCl salt) mp 249-251 °C.

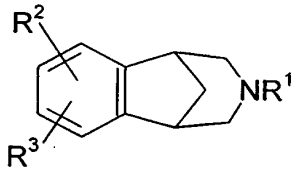
EXAMPLE 49

6-BENZYL-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and phenyl-acetyl chloride were converted to the title compound following the procedures described in EXAMPLE 47. ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.58 (s, 1H), 7.36-7.24 (5H), 4.29 (s, 2H), 3.46 (d, J=2.5 Hz, 2H), 3.39 (d, J=12.0 Hz, 2H), 3.18 (2H), 2.42 (m, 1H), 2.15 (d, J=11.5 Hz, 1H). APCI MS *m/e* 291.2 [(M + 1)$^+$].

CLAIMS

1. A compound of the formula



(I)

R^1 is hydrogen, (C_1 -C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$ 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), (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or 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_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, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

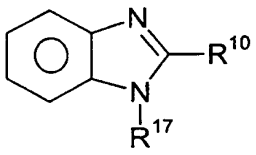
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, N-(C_1-C_6)alkylpiperizine or thiomorpholine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

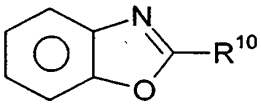
each X is, independently, (C_1-C_6)alkylene;

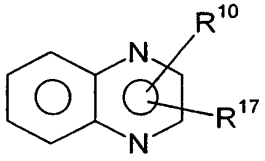
with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;

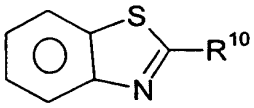
or a pharmaceutically acceptable salt thereof;

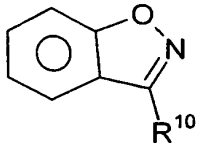
2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:











wherein R^{10} and R^{17} are selected, independently, from (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, cyano, halo,

amino, (C_1-C_6)alkylamino-, $[(C_1-C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur,

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.

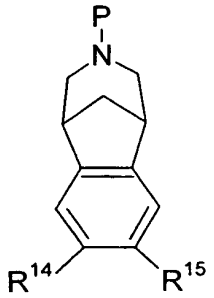
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (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 according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

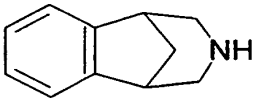
10. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 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



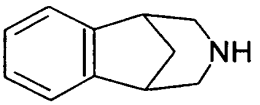
wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo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

12. 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 comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

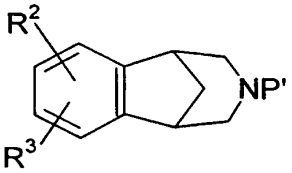
13. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 administering to a mammal in need of such treatment an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof;

that is effective in treating such disorder or condition.

14. A compound of the formula



(I′)

wherein R^2 and R^3 are defined as in claim 1; and P′ is $COOR^{16}$ 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 claim 2;

-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).

INTERNATIONAL SEARCH REPORT

Inte[illegible] Application No
PCT/IB 98/01813

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/22 A61K31/435 C07D471/08 C07D498/08 C07D513/08

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 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL H. MAZZOCHI ET AL: "Synthesis and pharmacological activity of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 22, no. 4, 1979, pages 455-457, XP002090422 WASHINGTON US see the whole document ---	1,9,11
A	US 3 471 503 A (CARSON JOHN R) 7 October 1969 see the whole document -----	1-14

☐ 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
20 January 1999	03/02/1999

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	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte: ...nal Application No
PCT/IB 98/01813

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3471503 A	07-10-1969	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PC10030AKXD		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 98/01813	13/11/1998	31/12/1997
Applicant		
PFIZER PRODUCTS INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application.
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. -
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/IB 98/01813

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 8,10,12,13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8,10,12,13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter[redacted]al Application No
PC[redacted]B 98/01813

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/22 A61K31/435 C07D471/08 C07D498/08 C07D513/08

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 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL H. MAZZOCHI ET AL: "Synthesis and pharmacological activity of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 22, no. 4, 1979, pages 455-457, XP002090422 WASHINGTON US see the whole document	1,9,11
A	US 3 471 503 A (CARSON JOHN R) 7 October 1969 see the whole document	1-14

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"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

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"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
20 January 1999	03/02/1999

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	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/01813

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3471503 A	07-10-1969	NONE	

DO/ EO WORKSHEET

U.S. Appl. No. 09/402010 International Appl. No. IB98/01813

Application filed by : ☐ 20 months ☐ 30 months

WIPO PUBLICATION INFORMATION :

Publication No.: WO 99/35573 Publication Language : English

Publication Date : 15 July 99 Not Published : ☐ U.S. only designated ☐ EP request

Francine Young
National Stage Processing
Paralegal Specialist
(703) 305-3662

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE :

- ☑ International Application *(RECORD COPY)*
- ☐ Article 19 Amendments
- ☑ PCT/IB/331
- ☐ PCT/IPEA/409 IPER (PCT/IPEA/416 on front)
- ☐ Annexes to 409
- ☐ Priority Document (s) No. _____
- ☐ International Appl. on Double Sided Paper *(COPIES MADE)*
- ☑ Request form PCT/RO/101
- ☑ PCT/ISA/210 - Search Report
- ☑ Search Report References
- ☐ Other : _____

RECEIPTS FROM THE APPLICANT *(other than checked above) :*

- ☑ Baisc National Fee *(paid or authorized to charge)*
  - ☐ Description
  - ☐ Claims
  - ☐ Words in the Drawing Figure(s)
  - ☐ Article 19 Amendments
  - ☐ Annexes to 409 ☐ entered ☐ not entered
- ☑ Oath/ Declaration (executed) 28 Sep 99
- ☐ DNA Diskette
- ☐ Preliminary Amendment(s) Filed on : _____ _____
- ☐ Information Disclosure Statement(s) Filed on : _____ _____
- ☐ Assignment Document
- ☐ Power of Attorney/ Change of Address
- ☐ Substitute Specification Filed on : _____ _____
- ☐ Verified Small Status Claim *(If submitted after Receipt Date - Is it timely ? Y/N)*
- ☐ Other : _____

NOTES :

35 U.S.C. 371 - Receipt of Request (PTO-1390)
Date Acceptable Oath/ Declaration Received
Date Complete 35 U.S.C. 371
102(e) Date
Date of Completion of DO/ EO 906 - Notification of Missing 102(e) Requirements
Date of Completion of DO/ EO 907 - Notification of Acceptance for 102(e) Date
Date of Completion of DO/ EO 911 - Application Accepted Under 35 U.S.C. 111
Date of Completion of DO/ EO 905 - Notification of Missing Requirements
Date of Completion of DO/ EO 916 - Notification of Defective Response
Date of Completion of DO/ EO 903 - Notification of Acceptance
Date of Completion of DO/ EO 909 - Notification of Abandonment

09/402,010

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

U.S. APPLICATION NO.	COE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/402,010		J	PC10030A

09/402,010

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
NEW YORK NY 10017-5755

5071

INTERNATIONAL APPLICATION NO. PCT/IB98/01813

PCT/IB98/01813

I.A. FILING DATE 11/13/98 PRIORITY DATE 12/31/97

DATE MAILED: 11/13/98 12/15/99

NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☑ a Designated Office (37 CFR 1.494), ☐ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

28 SEP 1999
35 U.S.C. 102(e) DATE

28 SEP 1999
DATE OF RECEIPT OF
35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371(C) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

3. ☑ A request for immediate examination under 35 U.S.C. 371(f) was received on 28 SEP 1999 and the application will be examined in turn.

4. The following items have been received:
- ☑ U.S. Basic National Fee.
- ☑ Copy of the international application in:
  - ☐ a non-English language.
  - ☑ English.
- ☐ Translation of the international application into English.
- ☐ Oath or Declaration of inventors(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
  The Article 19 amendments ☐ have ☐ have not been entered.
- ☐ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Copy of the Annexes to the International Preliminary Examination Report (IPER).
  - ☐ Translation of Annexes to the IPER into English.
  The Annexes ☐ have ☐ have not been entered.
- ☐ Preliminary amendment(s) filed _____ and _____.
- ☐ Information Disclosure Statement(s) filed _____ and _____.
- ☐ Assignment document.
- ☐ Power of Attorney and/or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Statement Claiming Small Entity Status.
- ☑ Priority Document.
- ☑ Copy of the International Search Report ☑ and copies of the references cited therein.
- ☐ Other:

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

Francine Young
National Stage Processing
Paralegal Specialist
(703) 305-3662

Telephone: (703)

FORM PCT/DO/EO/903 (December 1997)

4P11

John Please

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

25309

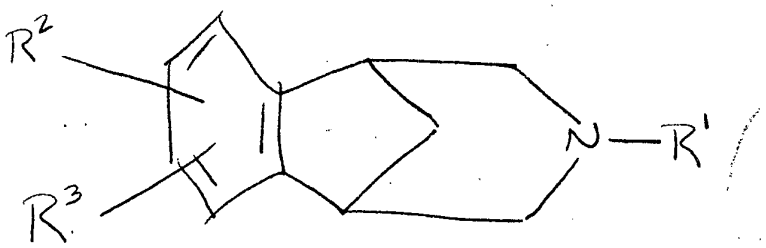
Requestor's Name: Brenda Coleman

Serial Number: 09/402,010

Date: Sept. 18, 2000 Phone: 305-1880 Art Unit: 1624

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).



see claims 1, 11 and 14

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SEP 19 2000
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Point of Contact:
John Dantzman
Technical Info. Specialist
CM1 1E05 Tel: 308-4488

STAFF USE ONLY

PU 9-20-00

Date completed: 9-20-00

Searcher: JOHN DANTZMAN

Terminal time: 35

Elapsed time:

CPU time:

Total time: 55

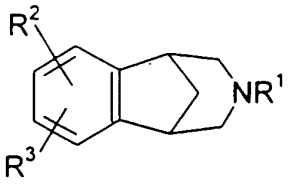
Number of Searches:

Number of Databases:

Search Site		Vendors	
✓	STIC		IG Suite
	CM-1	✓	STN
	Pre-S		Dialog
Type of Search			APS
	N.A. Sequence		Geninfo
	A.A. Sequence		SDC
	Structure		DARC/Questel
	Bibliographic		Other

CLAIMS

1. A compound of the formula



(I)

R^1 is hydrogen, $(C_1$ -$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, $XC(=O)R^{13}$ 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), $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$alkylamino-, $[(C_1$-$C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and -$XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or 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_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, nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

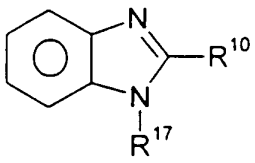
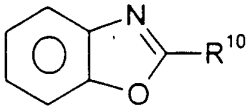
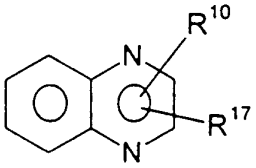
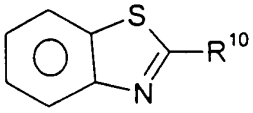
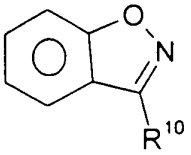
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, N-(C_1-C_6)alkylpiperizine or thiomorpholine 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, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;

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 (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, cyano, halo,

amino, $(C_1$-$C_6)$alkylamino-, $[(C_1$-$C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur,

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.

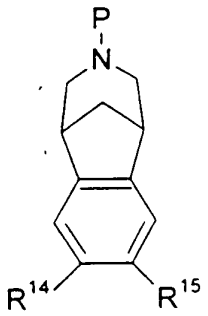
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (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 according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

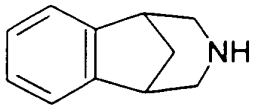
10. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 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



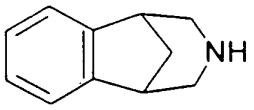
wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; $-C(=O)H$, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3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

12. 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 comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

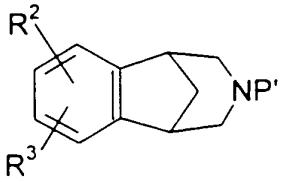
13. A method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, 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 administering to a mammal in need of such treatment an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof;

that is effective in treating such disorder or condition.

14. A compound of the formula



(I′)

wherein R^2 and R^3 are defined as in claim 1; and P′ is $COOR^{16}$ 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 claim 2;

-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).

Brenda

I based structure search on a dictionary search in the registry file.

I searched for the set that has

C6/es = Benzene No fusion

C6/ess = benzene with fusion allowed

C5/es = cyclopentane No fusion

C5/ess = cyclo pentane with fusion allowed

NC5/es = pyperidine No fusion

NC5/ess = pyperidine with fusion allowed

S = Same ring system

benzene ↓ cyclopentane ↓ pyperidine ↓

L18 => C6/ess (S) C5/ess (S) NC5/ess

↑ allows fusion ↑ Same ring system

I used this for a substructure search

John D.

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=> d his

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L2              0 S L1
L3                SCR 1840
L4              0 S L1 AND L3
L5          18336 S C6/ESS(S)C5/ESS(S)NC4/ESS
L6              2 S L1 AND L3 SSS SAM SUB=L5
L7             37 S L1 AND L3 SSS FUL SUB=L5

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L8              8 S L7

     FILE 'CAOLD' ENTERED AT 07:08:33 ON 20 SEP 2000
L9              0 S L7

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L13           387 S BROOKS P?/AU
L14             3 S L12 AND L13
                  SELECT RN L14 1-3

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L17             1 S L14 NOT L16

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L19             7 S L1 AND L3 SSS SAM SUB=L18
L20           134 S L1 AND L3 SSS FUL SUB=L18

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L23             0 S L10 FUL

     FILE 'REGISTRY' ENTERED AT 07:20:39 ON 20 SEP 2000
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Inventor Search

Searched by John Dantzman 703-308-4488

=> d all

L17 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:332706 HCAPLUS
TI Boron trichloride/tetra-n-butylammonium iodide: A mild, selective combination reagent for the cleavage of 1.degree.-alkyl aryl ethers.
AU **Coe, Jotham**; Wirtz, Michael C.; **Brooks, Paige R.**; Rescek, Diane M.; Woodworth, Graeme F.; Morgan, Bradley P.
CS Neuroscience, Pfizer, Inc, Groton, CT, 06340, USA
SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), ORGN-579 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CLAC
DT Conference; Meeting Abstract
LA English
AB The combination of BCl3 and anhyd. n-Bu4NI in CH2Cl2 has been found to be a valuable reagent for the cleavage of 1 o-alkyl aryl ethers to the corresponding phenols. Methyl-, ethyl-, allyl- and benzyl-aryl ethers readily cleave at low to ambient temp. when exposed to 1.1 equiv of anhyd.
n-Bu4NI and 1.5 equiv of BCl3 in CH2Cl2. The method is mild, generally applicable, and operationally simple. In some cases the combination reagent is more reactive than BBr3, yet it is less prone to the handling difficulties assocd. with BBr3. Selective cleavage of electron rich ethers is achieved in the presence of conjugated ethers.

Searched by John Dantzman 703-308-4488

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'BUB' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'
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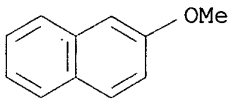
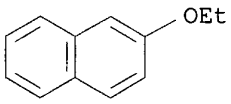
=> d bib abs hitstr l16

L16 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:757856 HCAPLUS
DN 132:137145
TI Boron trichloride/tetra-n-butylammonium iodide: a mild, selective combination reagent for the cleavage of primary alkyl aryl ethers
AU **Brooks, Paige R.**; Wirtz, Michael C.; Vetelino, Michael G.; Rescek, Diane M.; Woodworth, Graeme F.; Morgan, Bradley P.; **Coe, Jotham W.**
CS Central Research Division, Pfizer Inc., Groton, CT, 06340, USA
SO J. Org. Chem. (1999), 64(26), 9719-9721
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
OS CASREACT 132:137145
AB The title reagents were used to cleave a variety of alkyl aryl ethers, e.g., 2-methoxynaphthalene, 3-methoxybenzonitrile, and 7-(ethoxymethoxy)chromen-2-one, to give the phenols in 64 to 98% yields. No reaction was obsd. for sterically hindered compds. such as 2-isopropoxynaphthalene and 2,6-di-tert-butylmethoxybenzene. Compds. with resonance stabilization of the alkoxy group, such as 4-methoxybenzonitrile, undergo the dealkylation more slowly, or in the case of 6-methoxy-1-tetralone, not at all. The reaction requires 1.5 equiv. BCl3 and an addnl. 1.0 equiv. for each added Lewis base substituent.
IT **93-04-9**, 2-Methoxynaphthalene **93-18-5**, 2-Ethoxynaphthalene **94-59-7**, Safrole **311-28-4**, Tetra-n-butylammonium iodide **607-58-9**, 1-(Benzyloxy)naphthalene **874-90-8**, 4-Methoxybenzonitrile **1004-66-6**, 2-Methoxy-1,3-dimethylbenzene **1078-19-9**, 6-Methoxy-1-tetralone **1527-89-5**, 3-Methoxybenzonitrile **2472-22-2**, 6-Methoxy-2-tetralone **3188-13-4**, Chloromethylethyl ether **5312-97-0**, 2,5-Dimethoxybenzonitrile **5328-01-8**, 1-Ethoxynaphthalene **10294-34-5**, Boron trichloride **15799-79-8**, 3-Methoxy-N,N-dimethylaniline **21144-16-1** **23786-14-3**, Methyl 4-methoxyphenylacetate **31005-03-5** **52189-63-6**
RL: RCT (Reactant)
(cleavage of alkyl aryl ethers to substituted phenols with boron trichloride and tetra-n-butylammonium iodide)
RN 93-04-9 HCAPLUS
CN Naphthalene, 2-methoxy- (8CI, 9CI) (CA INDEX NAME)

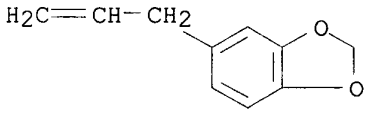
Searched by John Dantzman 703-308-4488



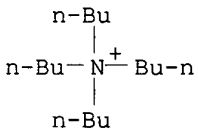
RN 93-18-5 HCAPLUS
CN Naphthalene, 2-ethoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 94-59-7 HCAPLUS
CN 1,3-Benzodioxole, 5-(2-propenyl)- (9CI) (CA INDEX NAME)

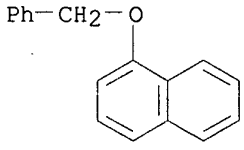


RN 311-28-4 HCAPLUS
CN 1-Butanaminium, N,N,N-tributyl-, iodide (9CI) (CA INDEX NAME)



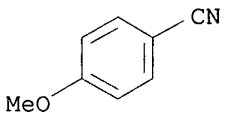
● I^-

RN 607-58-9 HCAPLUS
CN Naphthalene, 1-(phenylmethoxy)- (9CI) (CA INDEX NAME)

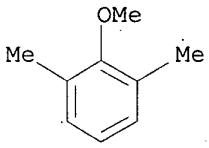


RN 874-90-8 HCAPLUS
CN Benzonitrile, 4-methoxy- (9CI) (CA INDEX NAME)

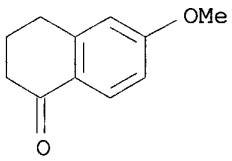
Searched by John Dantzman 703-308-4488



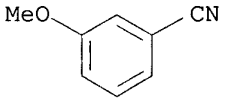
RN 1004-66-6 HCAPLUS
CN Benzene, 2-methoxy-1,3-dimethyl- (9CI) (CA INDEX NAME)



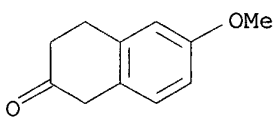
RN 1078-19-9 HCAPLUS
CN 1(2H)-Naphthalenone, 3,4-dihydro-6-methoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 1527-89-5 HCAPLUS
CN Benzonitrile, 3-methoxy- (9CI) (CA INDEX NAME)

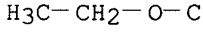


RN 2472-22-2 HCAPLUS
CN 2(1H)-Naphthalenone, 3,4-dihydro-6-methoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

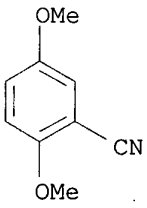


RN 3188-13-4 HCAPLUS
CN Ethane, (chloromethoxy)- (9CI) (CA INDEX NAME)

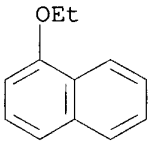
Searched by John Dantzman 703-308-4488



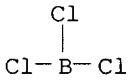
RN 5312-97-0 HCAPLUS
CN Benzonitrile, 2,5-dimethoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)



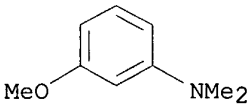
RN 5328-01-8 HCAPLUS
CN Naphthalene, 1-ethoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



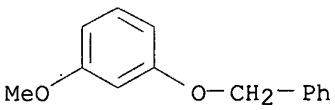
RN 10294-34-5 HCAPLUS
CN Borane, trichloro- (9CI) (CA INDEX NAME)



RN 15799-79-8 HCAPLUS
CN Benzenamine, 3-methoxy-N,N-dimethyl- (9CI) (CA INDEX NAME)

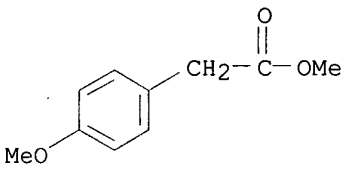


RN 21144-16-1 HCAPLUS
CN Benzene, 1-methoxy-3-(phenylmethoxy)- (9CI) (CA INDEX NAME)

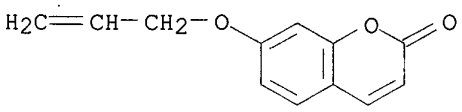


Searched by John Dantzman 703-308-4488

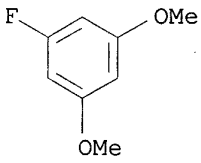
RN 23786-14-3 HCAPLUS
CN Benzeneacetic acid, 4-methoxy-, methyl ester (9CI) (CA INDEX NAME)



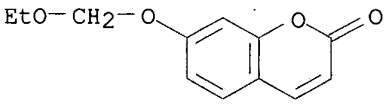
RN 31005-03-5 HCAPLUS
CN 2H-1-Benzopyran-2-one, 7-(2-propenyloxy)- (9CI) (CA INDEX NAME)



RN 52189-63-6 HCAPLUS
CN Benzene, 1-fluoro-3,5-dimethoxy- (9CI) (CA INDEX NAME)



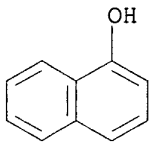
IT **257291-96-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(cleavage of alkyl aryl ethers to substituted phenols with boron trichloride and tetra-n-butylammonium iodide)
RN 257291-96-6 HCAPLUS
CN 2H-1-Benzopyran-2-one, 7-(ethoxymethoxy)- (9CI) (CA INDEX NAME)



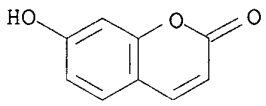
IT **90-15-3P**, .alpha.-Naphthol **93-35-6P** **99-07-0P**, 3-(Dimethylamino)phenol **135-19-3P**, .beta.-Naphthol, preparation **150-19-6P**, 3-Methoxyphenol **576-26-1P**, 2,6-Dimethylphenol **767-00-0P**, 4-Hydroxybenzonitrile **873-62-1P**, 3-Hydroxybenzonitrile **1126-61-0P**, 4-Allylcatechol **14199-15-6P**, Methyl 4-hydroxyphenylacetate **52727-28-3P** **75996-29-1P** **180526-90-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
Searched by John Dantzman 703-308-4488

(cleavage of alkyl aryl ethers to substituted phenols with boron trichloride and tetra-n-butylammonium iodide)

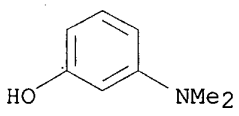
RN 90-15-3 HCAPLUS
CN 1-Naphthalenol (9CI) (CA INDEX NAME)



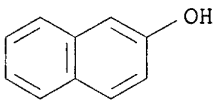
RN 93-35-6 HCAPLUS
CN 2H-1-Benzopyran-2-one, 7-hydroxy- (9CI) (CA INDEX NAME)



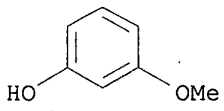
RN 99-07-0 HCAPLUS
CN Phenol, 3-(dimethylamino)- (9CI) (CA INDEX NAME)



RN 135-19-3 HCAPLUS
CN 2-Naphthalenol (9CI) (CA INDEX NAME)

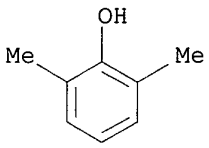


RN 150-19-6 HCAPLUS
CN Phenol, 3-methoxy- (9CI) (CA INDEX NAME)

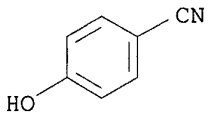


RN 576-26-1 HCAPLUS
CN Phenol, 2,6-dimethyl- (9CI) (CA INDEX NAME)

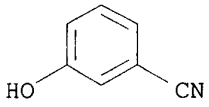
Searched by John Dantzman 703-308-4488



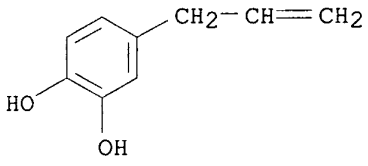
RN 767-00-0 HCAPLUS
CN Benzonitrile, 4-hydroxy- (9CI) (CA INDEX NAME)



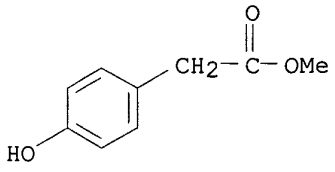
RN 873-62-1 HCAPLUS
CN Benzonitrile, 3-hydroxy- (9CI) (CA INDEX NAME)



RN 1126-61-0 HCAPLUS
CN 1,2-Benzenediol, 4-(2-propenyl)- (9CI) (CA INDEX NAME)

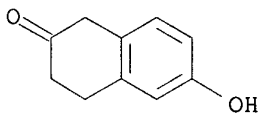


RN 14199-15-6 HCAPLUS
CN Benzeneacetic acid, 4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

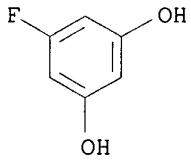


RN 52727-28-3 HCAPLUS
CN 2(1H)-Naphthalenone, 3,4-dihydro-6-hydroxy- (9CI) (CA INDEX NAME)

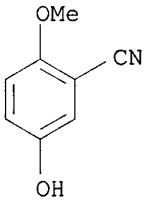
Searched by John Dantzman 703-308-4488



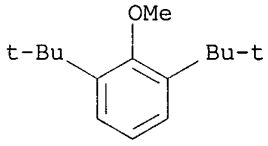
RN 75996-29-1 HCAPLUS
CN 1,3-Benzenediol, 5-fluoro- (9CI) (CA INDEX NAME)



RN 180526-90-3 HCAPLUS
CN Benzonitrile, 5-hydroxy-2-methoxy- (9CI) (CA INDEX NAME)

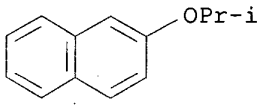


IT **1516-95-6**
RL: RCT (Reactant)
(failed cleavage of 2,6-di(tert-butyl) substituted phenolic ether with boron trichloride and tetra-n-butylammonium iodide)
RN 1516-95-6 HCAPLUS
CN Benzene, 1,3-bis(1,1-dimethylethyl)-2-methoxy- (9CI) (CA INDEX NAME)



IT **15052-09-2**, 2-Isopropoxynaphthalene
RL: RCT (Reactant)
(failed cleavage of 2-isopropoxynaphthalene to .beta.-naphthol with boron trichloride and tetra-n-butylammonium iodide)
RN 15052-09-2 HCAPLUS
CN Naphthalene, 2-(1-methylethoxy)- (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



RE.CNT 44
RE
(1) Anton, K; Chem Ber 1984, V117, P2479 HCAPLUS
(2) Banwell, M; J Org Chem 1998, V63, P9139 HCAPLUS
(3) Bayer, H; J Med Chem 1991, V34, P2685 HCAPLUS
(5) Bhatt, M; J Organomet Chem 1978, V156, P221 HCAPLUS
(6) Bhatt, M; Synthesis 1983, P249 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

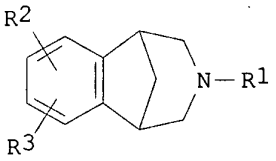
Searched by John Dantzman 703-308-4488

=> d bib abs hitstr l16 2

L16 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:451282 HCAPLUS
DN 131:102204
TI Preparation of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands
IN **Coe, Jotham Wadsworth; Brooks, Paige Roanne Palmer**
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9935131	A1	19990715	WO 1998-IB1813	19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9896416	A1	19990726	AU 1998-96416	19981113

PRAI US 1997-70245 19971231
WO 1998-IB1813 19981113
OS MARPAT 131:102204
GI



I

AB Title compds. [I; R1 = H, alk(en)yl, alkoxyethyl, oxoalkyl, etc.; R2,R3 = H, halo, (di)(alkyl)amino, alkyl, etc.; R2R3 = atoms to complete a ring] were prepd. Thus, 2-FC6H4Br was cyclocondensed with cyclopentadiene and the product osmylated to give 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol which was treated with NaIO4 and the product cyclocondensed with PhCH2NH2 to give, after deprotection, I (R1-R3 = H). Data for biol. activity of I were given.

IT **69718-72-5P 230614-99-0P 230615-00-6P 230615-01-7P 230615-02-8P 230615-03-9P 230615-04-0P 230615-05-1P 230615-06-2P 230615-07-3P 230615-08-4P 230615-09-5P 230615-10-8P 230615-11-9P 230615-12-0P 230615-13-1P 230615-14-2P 230615-15-3P 230615-16-4P 230615-17-5P 230615-18-6P**

Searched by John Dantzman 703-308-4488

230615-19-7P 230615-20-0P 230615-21-1P
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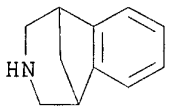
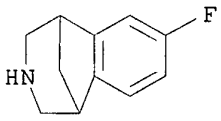
230615-43-7P 230615-44-8P 230615-45-9P
230615-46-0P 230615-52-8P 230615-75-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands)

RN 69718-72-5 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro- (9CI) (CA INDEX NAME)

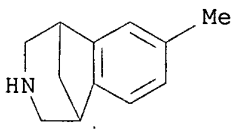


RN 230614-99-0 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-fluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

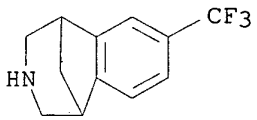
RN 230615-00-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-methyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

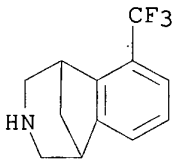
Searched by John Dantzman 703-308-4488

RN 230615-01-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(trifluoromethyl)-, hydrochloride (9CI) (CA INDEX NAME)



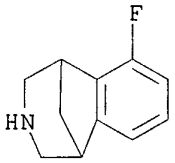
● HCl

RN 230615-02-8 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-6-(trifluoromethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

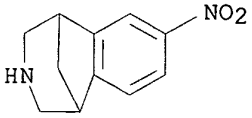
RN 230615-03-9 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 6-fluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

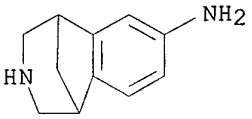
RN 230615-04-0 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-nitro-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



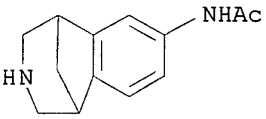
● HCl

RN 230615-05-1 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-amine, 2,3,4,5-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

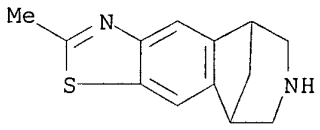
RN 230615-06-2 HCAPLUS
CN Acetamide, N-(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

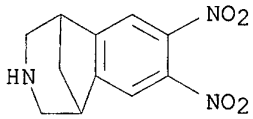
RN 230615-07-3 HCAPLUS
CN 5,9-Methano-5H-thiazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-
, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488

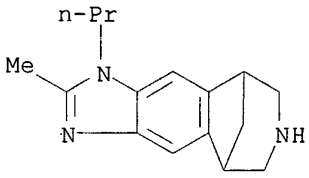


● HCl

RN 230615-08-4 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7,8-dinitro- (9CI) (CA INDEX NAME)

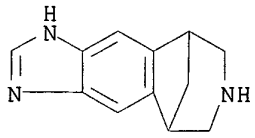


RN 230615-09-5 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



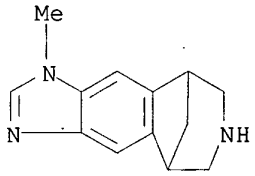
● HCl

RN 230615-10-8 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



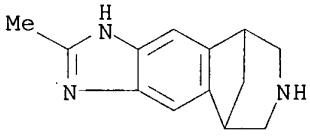
● HCl

RN 230615-11-9 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

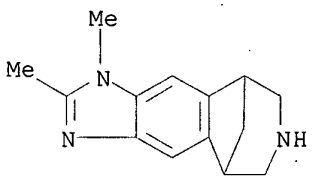
RN 230615-12-0 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

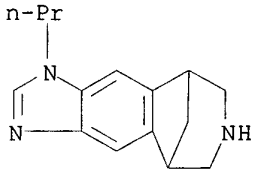
RN 230615-13-1 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



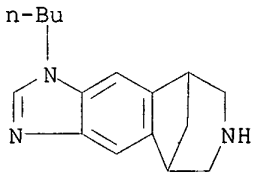
● HCl

RN 230615-14-2 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

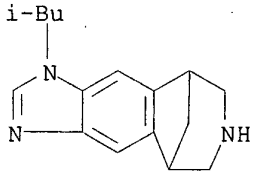
RN 230615-15-3 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

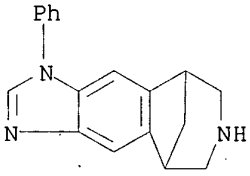
RN 230615-16-4 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



● HCl

RN 230615-17-5 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



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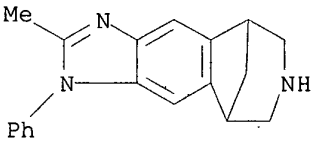
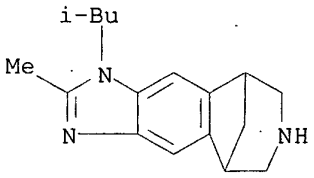
RN 230615-18-6 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

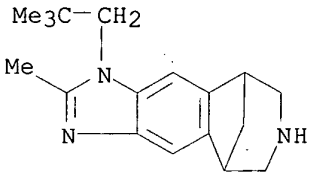
RN 230615-19-7 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



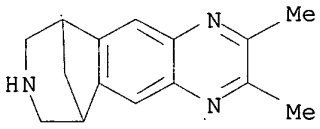
● HCl

RN 230615-20-0 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

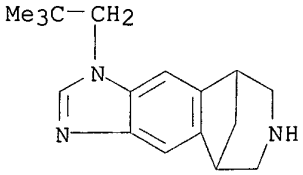
RN 230615-21-1 HCAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-22-2 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



● HCl

RN 230615-23-3 HCAPLUS
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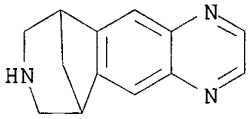
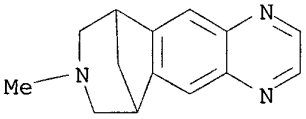


● HCl

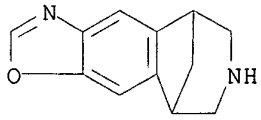
RN 230615-24-4 HCAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

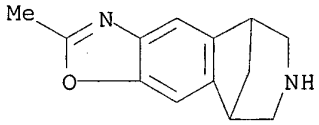
RN 230615-25-5 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



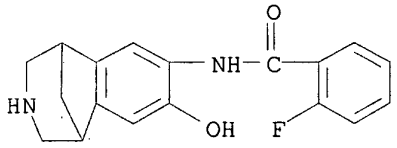
● HCl

RN 230615-26-6 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

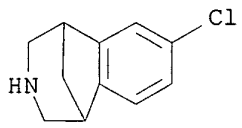
RN 230615-27-7 HCAPLUS
CN Benzamide, 2-fluoro-N-(2,3,4,5-tetrahydro-8-hydroxy-1,5-methano-1H-3-benzazepin-7-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

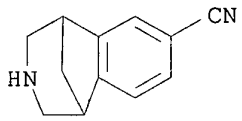
RN 230615-28-8 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-chloro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



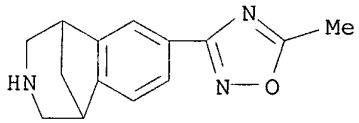
● HCl

RN 230615-29-9 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-carbonitrile, 2,3,4,5-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



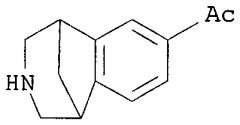
● HCl

RN 230615-30-2 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(5-methyl-1,2,4-oxadiazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



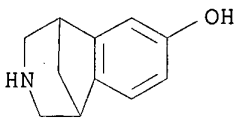
● HCl

RN 230615-31-3 HCAPLUS
CN Ethanone, 1-(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)-, hydrochloride (9CI) (CA INDEX NAME)



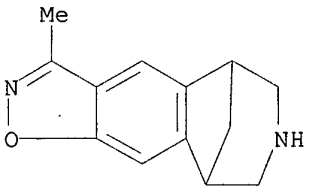
● HCl

RN 230615-32-4 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-, hydrochloride (9CI)
(CA INDEX NAME)



● HCl

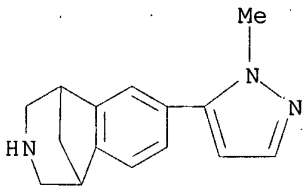
RN 230615-33-5 HCAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-
, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

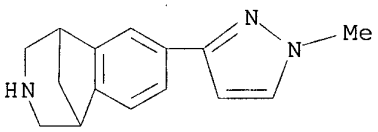
RN 230615-34-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-methyl-1H-pyrazol-5-yl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



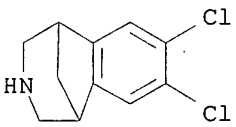
● HCl

RN 230615-35-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-methyl-1H-pyrazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

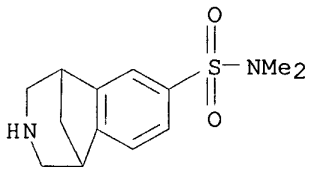
RN 230615-36-8 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-dichloro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

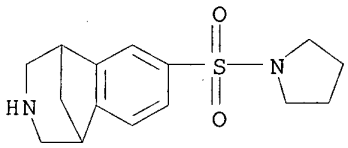
RN 230615-37-9 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-sulfonamide, 2,3,4,5-tetrahydro-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



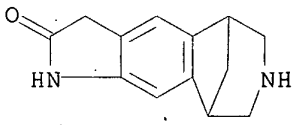
● HCl

RN 230615-38-0 HCAPLUS
CN Pyrrolidine, 1-[(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

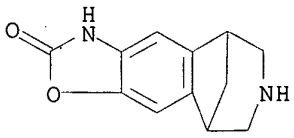
RN 230615-39-1 HCAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

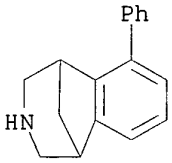
RN 230615-40-4 HCAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



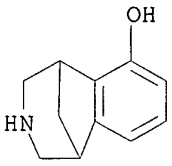
● HCl

RN 230615-41-5 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-6-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

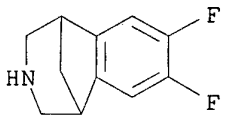
RN 230615-42-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-6-ol, 2,3,4,5-tetrahydro-, hydrochloride (9CI)
(CA INDEX NAME)



● HCl

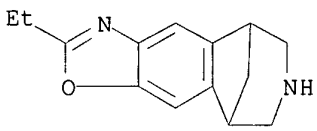
RN 230615-43-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-difluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



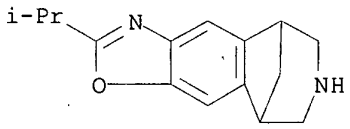
● HCl

RN 230615-44-8 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 2-ethyl-6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

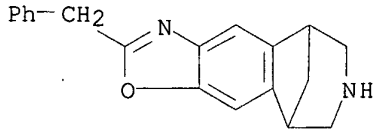
RN 230615-45-9 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(1-methylethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

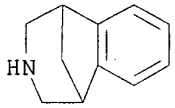
RN 230615-46-0 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



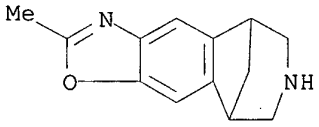
● HCl

RN 230615-52-8 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-75-5 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-(9CI) (CA INDEX NAME)



IT **62-53-3**, Benzenamine, reactions **78-81-9**, Isobutylamine **79-03-8**, Propionyl chloride **79-30-1**, Isobutyryl chloride **100-46-9**, Benzylamine, reactions **103-80-0**, Phenylacetyl chloride **107-08-4**, 1-Iodopropane **109-73-9**, 1-Butylamine, reactions **123-75-1**, Pyrrolidine, reactions **327-52-6**, 2,4,5-Trifluorobromobenzene **372-18-9**, 1,3-Difluorobenzene **393-52-2**, 2-Fluorobenzoyl chloride **399-94-0**, 2,5-Difluoro-1-bromobenzene **431-03-8**, 2,3-Butanedione **452-62-0**, 2-Fluoro-5-methyl-1-bromobenzene **542-92-7**, Cyclopentadiene, reactions **1072-85-1**, 2-Fluorobromobenzene **5813-64-9**, Neopentylamine **68322-84-9**, 2-Fluoro-5-trifluoromethyl-1-bromobenzene **104540-42-3**, 2-Fluoro-6-trifluoromethylbromobenzene
RL: RCT (Reactant)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor

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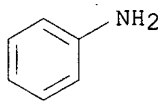
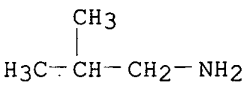
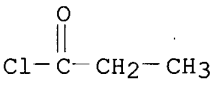
ligands)
RN 62-53-3 HCAPLUS
CN Benzenamine (9CI) (CA INDEX NAME)



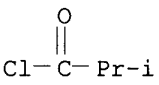
RN 78-81-9 HCAPLUS
CN 1-Propanamine, 2-methyl- (9CI) (CA INDEX NAME)



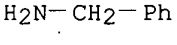
RN 79-03-8 HCAPLUS
CN Propanoyl chloride (9CI) (CA INDEX NAME)



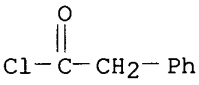
RN 79-30-1 HCAPLUS
CN Propanoyl chloride, 2-methyl- (9CI) (CA INDEX NAME)



RN 100-46-9 HCAPLUS
CN Benzenemethanamine (9CI) (CA INDEX NAME)



RN 103-80-0 HCAPLUS
CN Benzeneacetyl chloride (9CI) (CA INDEX NAME)



RN 107-08-4 HCAPLUS
CN Propane, 1-iodo- (8CI, 9CI) (CA INDEX NAME)

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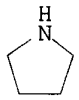
$H_3C-CH_2-CH_2-I$

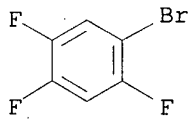
RN 109-73-9 HCAPLUS
CN 1-Butanamine (9CI) (CA INDEX NAME)

$H_3C-CH_2-CH_2-CH_2-NH_2$

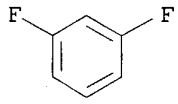
RN 123-75-1 HCAPLUS
CN Pyrrolidine (8CI, 9CI) (CA INDEX NAME)



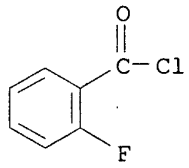
RN 327-52-6 HCAPLUS
CN Benzene, 1-bromo-2,4,5-trifluoro- (8CI, 9CI) (CA INDEX NAME)



RN 372-18-9 HCAPLUS
CN Benzene, 1,3-difluoro- (9CI) (CA INDEX NAME)

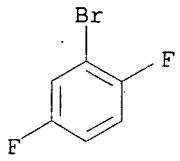


RN 393-52-2 HCAPLUS
CN Benzoyl chloride, 2-fluoro- (9CI) (CA INDEX NAME)

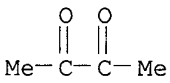


RN 399-94-0 HCAPLUS
CN Benzene, 2-bromo-1,4-difluoro- (6CI, 8CI, 9CI) (CA INDEX NAME)

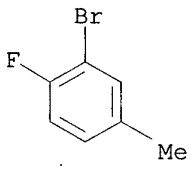
Searched by John Dantzman 703-308-4488



RN 431-03-8 HCAPLUS
CN 2,3-Butanedione (8CI, 9CI) (CA INDEX NAME)

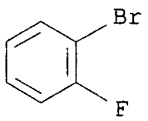


RN 452-62-0 HCAPLUS
CN Benzene, 2-bromo-1-fluoro-4-methyl- (9CI) (CA INDEX NAME)

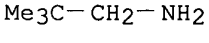


RN 542-92-7 HCAPLUS
CN 1,3-Cyclopentadiene (8CI, 9CI) (CA INDEX NAME)

RN 1072-85-1 HCAPLUS
CN Benzene, 1-bromo-2-fluoro- (7CI, 8CI, 9CI) (CA INDEX NAME)

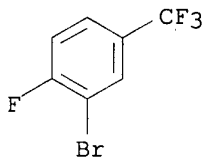


RN 5813-64-9 HCAPLUS
CN 1-Propanamine, 2,2-dimethyl- (9CI) (CA INDEX NAME)

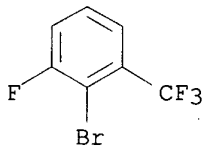


Searched by John Dantzman 703-308-4488

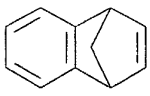
RN 68322-84-9 HCAPLUS
CN Benzene, 2-bromo-1-fluoro-4-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 104540-42-3 HCAPLUS
CN Benzene, 2-bromo-1-fluoro-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

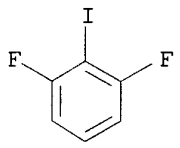


IT **4453-90-1P**, 1,4-Dihydro-1,4-methanonaphthalene **13697-89-7P**
, 2,6-Difluoroiodobenzene **58653-71-7P 61346-81-4P**
63608-69-5P 230615-47-1P 230615-48-2P
230615-49-3P 230615-50-6P 230615-51-7P
230615-53-9P 230615-54-0P 230615-55-1P
230615-56-2P 230615-57-3P 230615-58-4P
230615-59-5P 230615-60-8P 230615-61-9P
230615-62-0P 230615-63-1P 230615-64-2P
230615-65-3P 230615-66-4P 230615-67-5P
230615-68-6P 230615-69-7P 230615-70-0P
230615-71-1P 230615-72-2P 230615-73-3P
230615-74-4P 230615-76-6P 230615-77-7P
230615-78-8P 230615-79-9P 230615-80-2P
230615-81-3P 230615-82-4P 230615-83-5P
230615-84-6P 230615-85-7P 230615-86-8P
230615-87-9P 230615-88-0P 230615-89-1P
230615-90-4P 230615-91-5P 230615-92-6P
230615-93-7P 230615-94-8P 230615-95-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor
ligands)
RN 4453-90-1 HCAPLUS
CN 1,4-Methanonaphthalene, 1,4-dihydro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

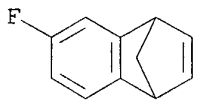


Searched by John Dantzman 703-308-4488

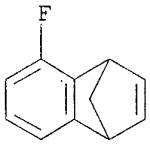
RN 13697-89-7 HCAPLUS
CN Benzene, 1,3-difluoro-2-iodo- (8CI, 9CI) (CA INDEX NAME)



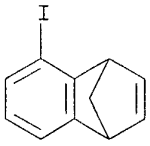
RN 58653-71-7 HCAPLUS
CN 1,4-Methanonaphthalene, 6-fluoro-1,4-dihydro- (9CI) (CA INDEX NAME)



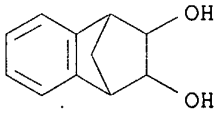
RN 61346-81-4 HCAPLUS
CN 1,4-Methanonaphthalene, 5-fluoro-1,4-dihydro- (9CI) (CA INDEX NAME)



RN 63608-69-5 HCAPLUS
CN 1,4-Methanonaphthalene, 1,4-dihydro-5-iodo- (9CI) (CA INDEX NAME)

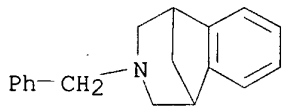


RN 230615-47-1 HCAPLUS
CN 1,4-Methanonaphthalene-2,3-diol, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

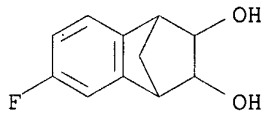


Searched by John Dantzman 703-308-4488

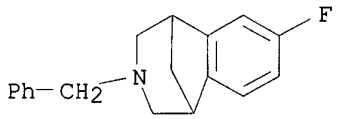
RN 230615-48-2 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(phenylmethyl)- (9CI) (CA INDEX NAME)



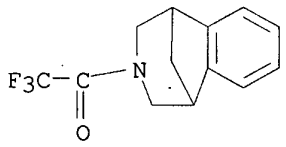
RN 230615-49-3 HCAPLUS
CN 1,4-Methanonaphthalene-2,3-diol, 6-fluoro-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



RN 230615-50-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-fluoro-2,3,4,5-tetrahydro-3-(phenylmethyl)- (9CI) (CA INDEX NAME)

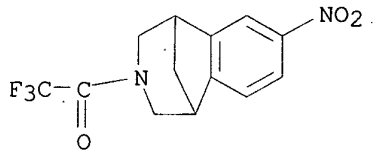


RN 230615-51-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

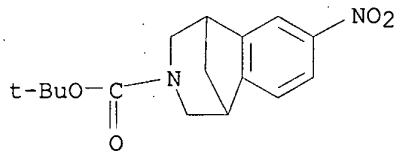


RN 230615-53-9 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-nitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

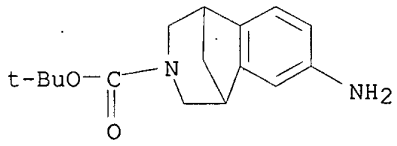
Searched by John Dantzman 703-308-4488



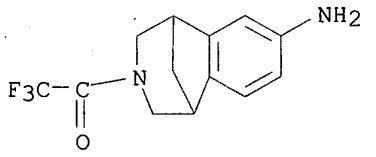
RN 230615-54-0 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7-nitro-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-55-1 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-amino-1,2,4,5-tetrahydro-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

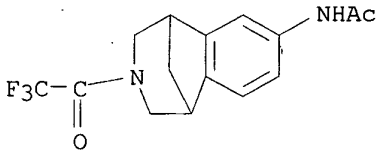


RN 230615-56-2 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-amine, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

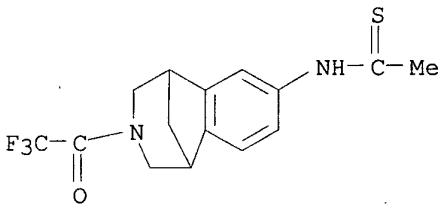


RN 230615-57-3 HCAPLUS
CN Acetamide, N-[2,3,4,5-tetrahydro-3-(trifluoroacetyl)-1,5-methano-1H-3-benzazepin-7-yl]- (9CI) (CA INDEX NAME)

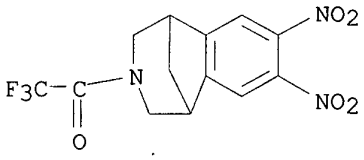
Searched by John Dantzman 703-308-4488



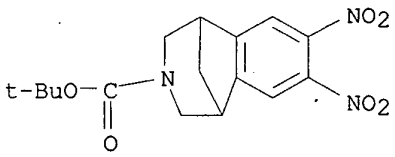
RN 230615-58-4 HCAPLUS
CN Ethanethioamide, N-[2,3,4,5-tetrahydro-3-(trifluoroacetyl)-1,5-methano-1H-3-benzazepin-7-yl]- (9CI) (CA INDEX NAME)



RN 230615-59-5 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7,8-dinitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

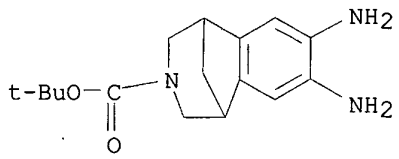


RN 230615-60-8 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7,8-dinitro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

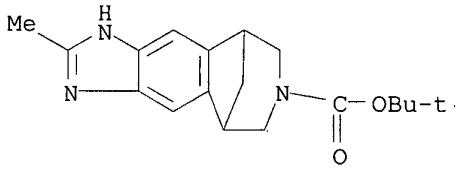


RN 230615-61-9 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7,8-diamino-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

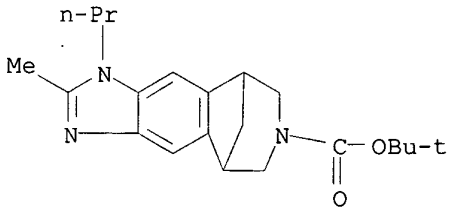
Searched by John Dantzman 703-308-4488



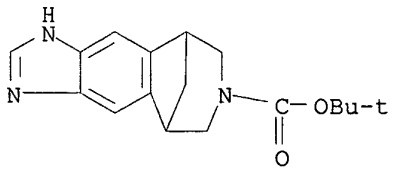
RN 230615-62-0 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-63-1 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-propyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

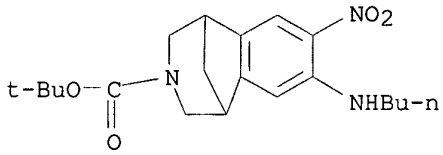


RN 230615-64-2 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

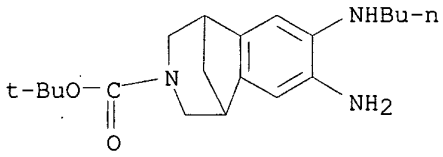


RN 230615-65-3 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-(butylamino)-1,2,4,5-tetrahydro-8-nitro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

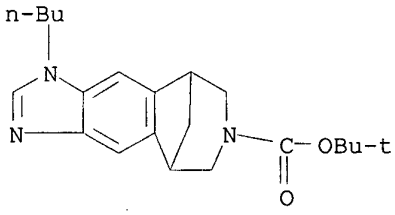
Searched by John Dantzman 703-308-4488



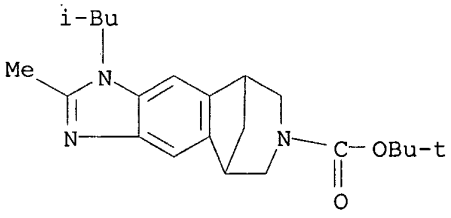
RN 230615-66-4 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-amino-8-(butylamino)-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-67-5 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-butyl-5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

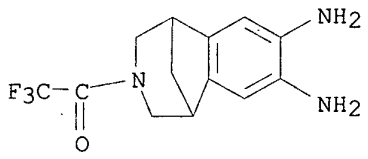


RN 230615-68-6 HCAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-(2-methylpropyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

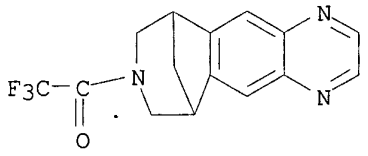


RN 230615-69-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine-7,8-diamine, 2,3,4,5-tetrahydro-3-

(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-70-0 HCAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



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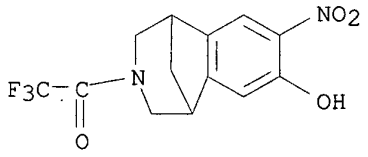
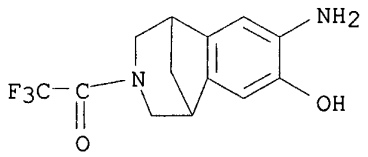
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-8-nitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

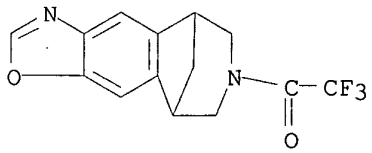


RN 230615-72-2 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 8-amino-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

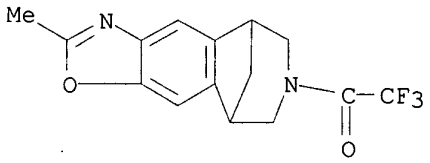


RN 230615-73-3 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

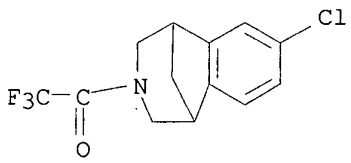
Searched by John Dantzman 703-308-4488



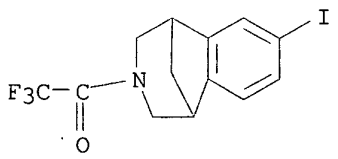
RN 230615-74-4 HCAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-76-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-chloro-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

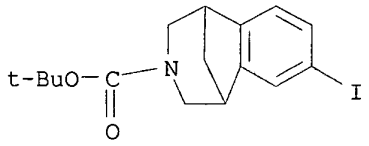


RN 230615-77-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-iodo-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

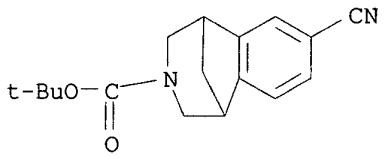


RN 230615-78-8 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7-iodo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

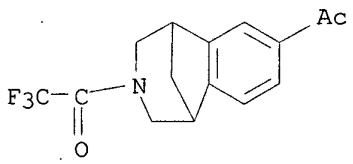
Searched by John Dantzman 703-308-4488



RN 230615-79-9 HCAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-cyano-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-80-2 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-acetyl-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-81-3 HCAPLUS
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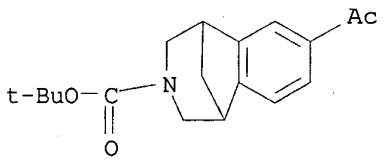
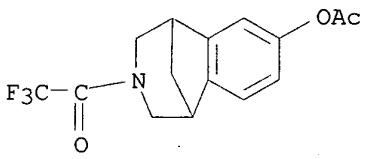


RN 230615-82-4 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)-, acetate (ester) (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



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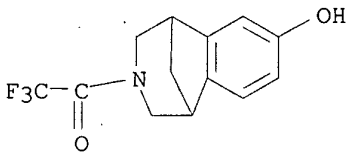
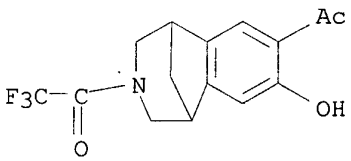
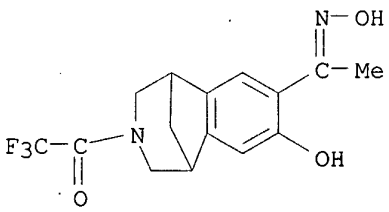


RN 230615-84-6 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 8-acetyl-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

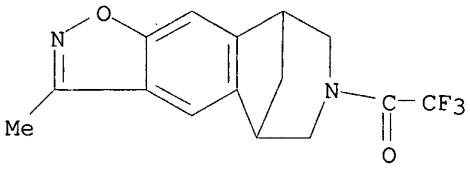


RN 230615-85-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-8-[1-(hydroxyimino)ethyl]-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-86-8 HCAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



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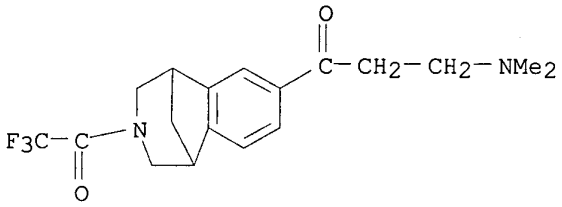

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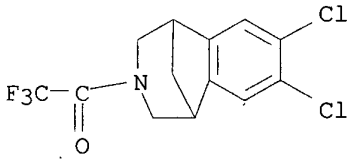
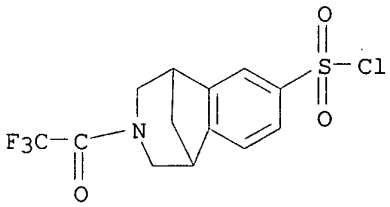
CN 1,5-Methano-1H-3-benzazepine, 7,8-dichloro-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-89-1 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-sulfonyl chloride, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



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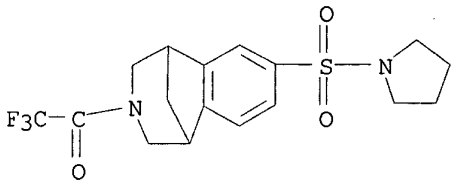
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-pyrrolidinylsulfonyl)-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



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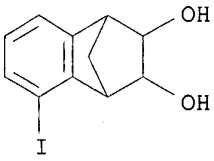

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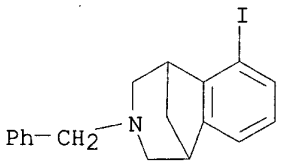
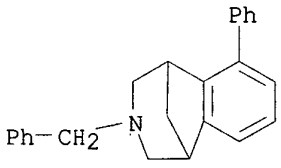


RN 230615-93-7 HCAPLUS
CN 1,5-Methano-1H-3-benzazepine,
2,3,4,5-tetrahydro-6-phenyl-3-(phenylmethyl)-
(9CI) (CA INDEX NAME)



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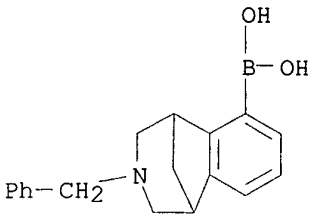
Searched by John Dantzman 703-308-4488



RN 230615-95-9 HCAPLUS
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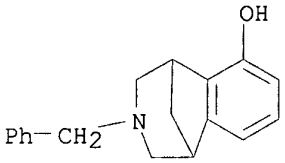
(9CI) (CA INDEX NAME)



RE.CNT 2
RE
(1) Carson, J; US 3471503 A 1969 HCAPLUS
(2) Mazzochi, P; Journal of Medicinal Chemistry 1979, V22(4), P455

Searched by John Dantzman 703-308-4488

Summary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L3             SCR 1840
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L5       18336 S C6/ESS(S)C5/ESS(S)NC4/ESS
L6           2 S L1 AND L3 SSS SAM SUB=L5
L7          37 S L1 AND L3 SSS FUL SUB=L5

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L8           8 S L7

     FILE 'CAOLD' ENTERED AT 07:08:33 ON 20 SEP 2000
L9           0 S L7

     FILE 'BEILSTEIN' ENTERED AT 07:08:38 ON 20 SEP 2000
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L13        387 S BROOKS P?/AU
L14          3 S L12 AND L13
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     FILE 'HCAPLUS' ENTERED AT 07:14:55 ON 20 SEP 2000
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L17          1 S L14 NOT L16

     FILE 'REGISTRY' ENTERED AT 07:16:50 ON 20 SEP 2000
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L19          7 S L1 AND L3 SSS SAM SUB=L18
L20        134 S L1 AND L3 SSS FUL SUB=L18

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     FILE 'CAOLD' ENTERED AT 07:19:59 ON 20 SEP 2000
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L23          0 S L10 FUL

     FILE 'REGISTRY' ENTERED AT 07:20:39 ON 20 SEP 2000
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134 compounds

5 cites caplus

Ø cites caold

Ø Compounds Beilstein

Searched by John Dantzman 703-308-4488

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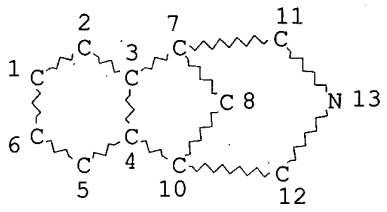


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  12

STEREO ATTRIBUTES: NONE
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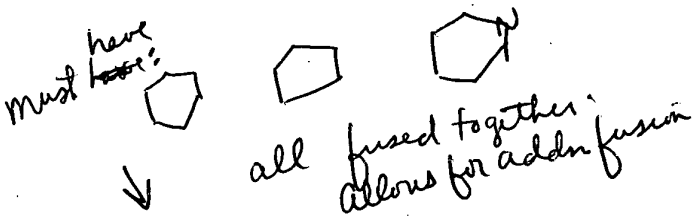

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L21 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 2000:553442 CAPLUS
DN 133:168383
TI Pharmaceutical compositions containing nicotine or a ligand of nicotine receptors and a monamine oxidase inhibitor and their use for treating tobacco withdrawal symptoms
IN Caille, Dominique; George, Pascal; Jegham, Samir; Robineau, Pascale; Scatton, Bernard; Zivkovic, Branimir
PA Sanofi-Synthelabo, Fr.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA French

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000045846	A1	20000810	WO 2000-FR193	20000128
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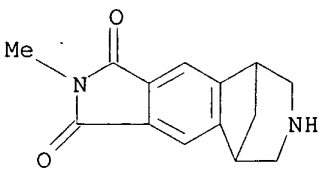
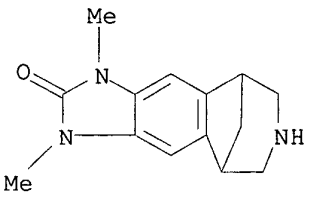
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2788982	A1	20000804	FR 1999-1144	19990202

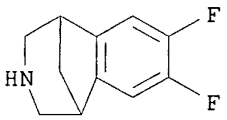
PRAI FR 1999-1144 19990202
OS MARPAT 133:168383
AB The invention concerns novel pharmaceutical compns. contg. nicotine or a ligand of nicotine receptors and a monamine oxidase inhibitor designed for treating tobacco withdrawal symptoms. A bilayer tablet contained befloxatone 5, lactose 66, microcryst. cellulose 20, povidone 4, crospovidone 4, and magnesium stearate 1% in the first layer, and nicotine polacrylix 5, microcryst. cellulose 20 povidone 4, hydroxypropyl Me cellulose 25, magnesium stearate 1, and lactose q.s. 100% in the second layer.
IT **287973-24-4 287973-25-5 287973-26-6 287973-27-7 287973-28-8 287973-29-9 287973-32-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. nicotine or ligand of nicotine receptors and monamine oxidase inhibitor and their use for treating tobacco withdrawal symptoms)
RN 287973-24-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



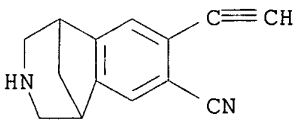
RN 287973-25-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



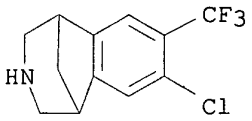
RN 287973-26-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-difluoro-2,3,4,5-tetrahydro- (9CI) (CA INDEX NAME)



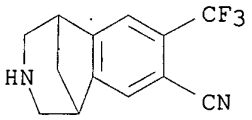
RN 287973-27-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-carbonitrile, 8-ethynyl-2,3,4,5-tetrahydro- (9CI) (CA INDEX NAME)



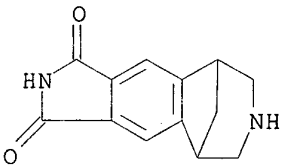
RN 287973-28-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-chloro-2,3,4,5-tetrahydro-8-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 287973-29-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-carbonitrile, 2,3,4,5-tetrahydro-8-(trifluoromethyl)- (9CI) (CA INDEX NAME)



RN 287973-32-4 CAPLUS
CN 5,9-Methanopyrrolo[3,4-h][3]benzazepine-1,3(2H,5H)-dione, 5,6,7,8-tetrahydro- (9CI) (CA INDEX NAME)



RE.CNT 3
RE
(1) Cinciripini, P; ONCOLOGY 1998
(2) La Roche, H; WO 9528934 A 1995
(3) Williams, J; US 5803081 A 1998

Searched by John Dantzman 703-308-4488

Applicants

=> d bib abs hitstr 2

L21 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1999:451282 CAPLUS
DN 131:102204
TI Preparation of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands
IN Coe, Jotham Wadsworth; Brooks, Paige Roanne Palmer
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9935131	A1	19990715	WO 1998-IB1813	19981113
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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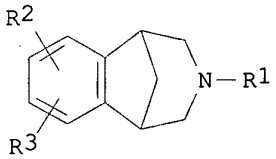
	AU 9896416	A1	19990726	AU 1998-96416	19981113
PRAI	US 1997-70245		19971231		
	WO 1998-IB1813		19981113		

OS MARPAT 131:102204
GI



I

AB Title compds. [I; R1 = H, alk(en)yl, alkoxyethyl, oxoalkyl, etc.; R2,R3 = H, halo, (di)(alkyl)amino, alkyl, etc.; R2R3 = atoms to complete a ring] were prepd. Thus, 2-FC6H4Br was cyclocondensed with cyclopentadiene and the product osmylated to give 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol which was treated with NaIO4 and the product cyclocondensed with PhCH2NH2 to give, after deprotection, I (R1-R3 = H). Data for biol. activity of I were given.

IT **69718-72-5P 230614-99-0P 230615-00-6P 230615-01-7P 230615-02-8P 230615-03-9P 230615-04-0P 230615-05-1P 230615-06-2P 230615-07-3P 230615-08-4P 230615-09-5P 230615-10-8P 230615-11-9P 230615-12-0P 230615-13-1P 230615-14-2P 230615-15-3P 230615-16-4P 230615-17-5P 230615-18-6P**

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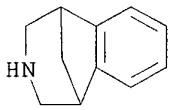
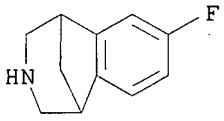
230615-46-0P 230615-52-8P 230615-75-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands)

RN 69718-72-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro- (9CI) (CA INDEX NAME)

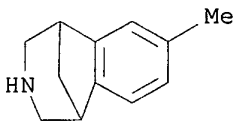


RN 230614-99-0 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-fluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

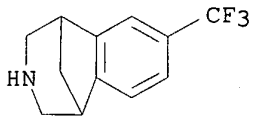
RN 230615-00-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-methyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

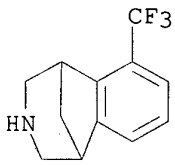
Searched by John Dantzman 703-308-4488

RN 230615-01-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(trifluoromethyl)-, hydrochloride (9CI) (CA INDEX NAME)



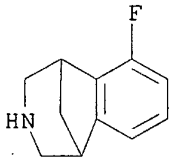
• HCl

RN 230615-02-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-6-(trifluoromethyl)-, hydrochloride (9CI) (CA INDEX NAME)



• HCl

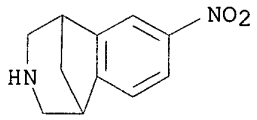
RN 230615-03-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 6-fluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



• HCl

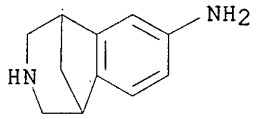
RN 230615-04-0 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-nitro-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



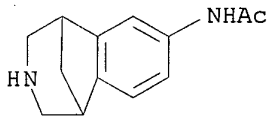
● HCl

RN 230615-05-1 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-amine, 2,3,4,5-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

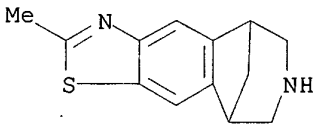
RN 230615-06-2 CAPLUS
CN Acetamide, N-(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-07-3 CAPLUS
CN 5,9-Methano-5H-thiazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-
, monohydrochloride (9CI) (CA INDEX NAME)

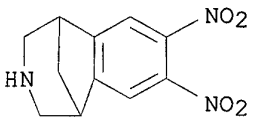
Searched by John Dantzman 703-308-4488



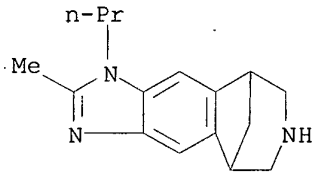
cl.17

● HCl

RN 230615-08-4 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7,8-dinitro- (9CI) (CA INDEX NAME)



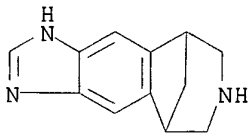
RN 230615-09-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



cl.18

● HCl

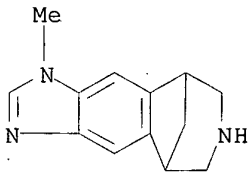
RN 230615-10-8 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



Cl.15

● HCl

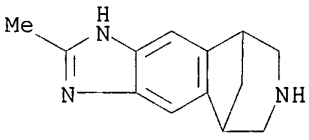
RN 230615-11-9 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



Cl.15

● HCl

RN 230615-12-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

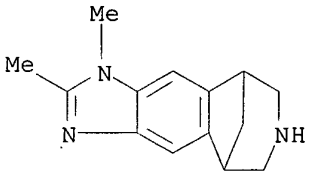


Cl.15

● HCl

RN 230615-13-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1,2-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

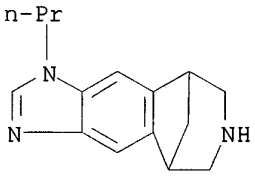
Searched by John Dantzman 703-308-4488



cl.19

● HCl

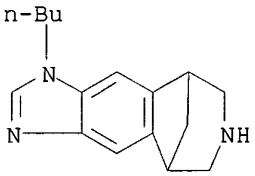
RN 230615-14-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-propyl-, monohydrochloride (9CI) (CA INDEX NAME)



cl.15

● HCl

RN 230615-15-3 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-butyl-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)

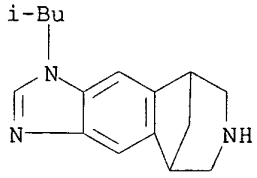


cl.15

● HCl

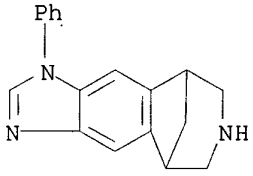
RN 230615-16-4 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



● HCl

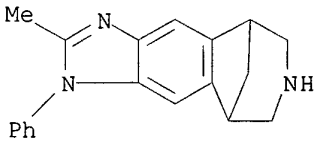
RN 230615-17-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



Cl.15

● HCl

RN 230615-18-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

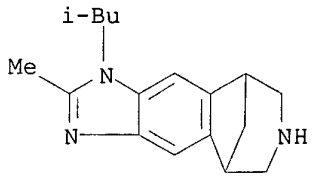


Cl.15

● HCl

RN 230615-19-7 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1,5,6,7,8,9-hexahydro-2-methyl-1-(2-methylpropyl)-, monohydrochloride (9CI) (CA INDEX NAME)

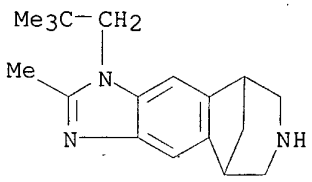
Searched by John Dantzman 703-308-4488



Cl.15

● HCl

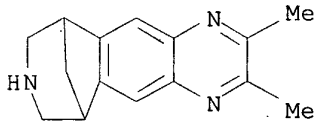
RN 230615-20-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



Cl.15

● HCl

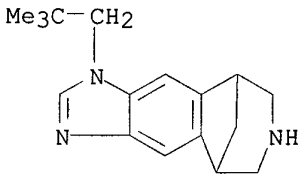
RN 230615-21-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



Cl.20

● HCl

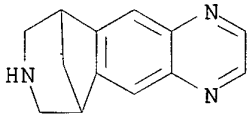
RN 230615-22-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine, 1-(2,2-dimethylpropyl)-1,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



C1.15

● HCl

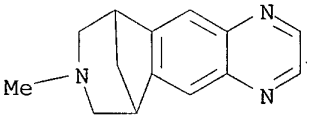
RN 230615-23-3 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



C1.21

● HCl

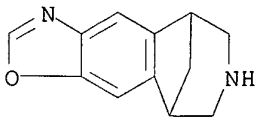
RN 230615-24-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



C1.22

● HCl

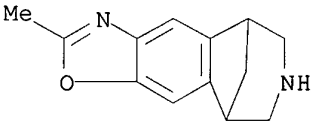
RN 230615-25-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



cl.23

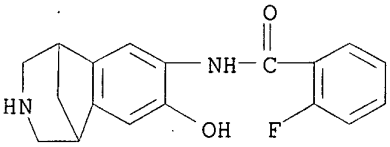
● HCl

RN 230615-26-6 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

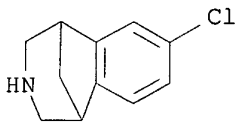
RN 230615-27-7 CAPLUS
CN Benzamide, 2-fluoro-N-(2,3,4,5-tetrahydro-8-hydroxy-1,5-methano-1H-3-benzazepin-7-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

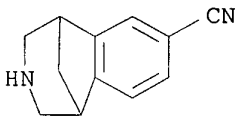
RN 230615-28-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-chloro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



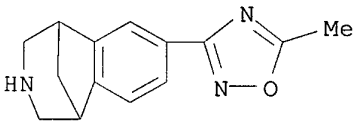
● HCl

RN 230615-29-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-carbonitrile, 2,3,4,5-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



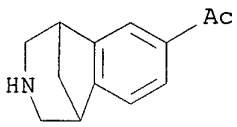
● HCl

RN 230615-30-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(5-methyl-1,2,4-oxadiazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



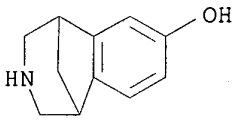
● HCl

RN 230615-31-3 CAPLUS
CN Ethanone, 1-(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)-, hydrochloride (9CI) (CA INDEX NAME)



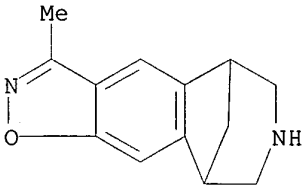
● HCl

RN 230615-32-4 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-, hydrochloride (9CI)
(CA INDEX NAME)



● HCl

RN 230615-33-5 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-
, monohydrochloride (9CI) (CA INDEX NAME)

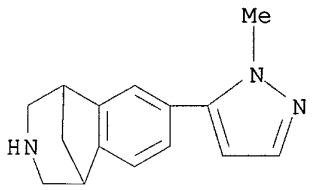


cl.24

● HCl

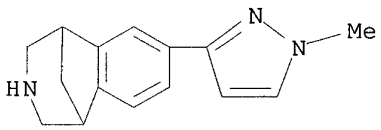
RN 230615-34-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-methyl-1H-pyrazol-5-yl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



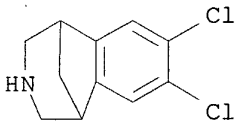
● HCl

RN 230615-35-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-methyl-1H-pyrazol-3-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

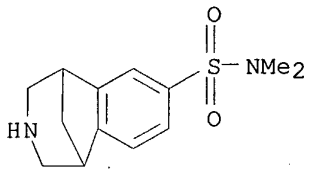
RN 230615-36-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-dichloro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

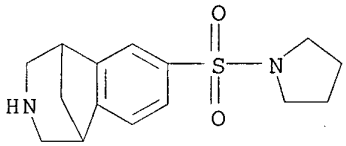
RN 230615-37-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-sulfonamide, 2,3,4,5-tetrahydro-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



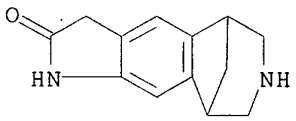
• HCl

RN 230615-38-0 CAPLUS
CN Pyrrolidine, 1-[(2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepin-7-yl)sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



• HCl

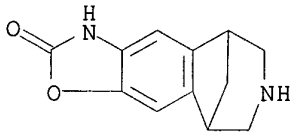
RN 230615-39-1 CAPLUS
CN 5,9-Methanopyrrolo[2,3-h][3]benzazepin-2(1H)-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



C1.25

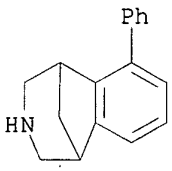
• HCl

RN 230615-40-4 CAPLUS
CN 5,9-Methano-2H-oxazolo[4,5-h][3]benzazepin-2-one, 3,5,6,7,8,9-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



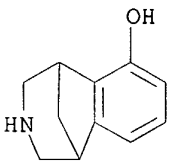
● HCl

RN 230615-41-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-6-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

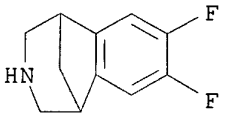
RN 230615-42-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-6-ol, 2,3,4,5-tetrahydro-, hydrochloride (9CI)
(CA INDEX NAME)



● HCl

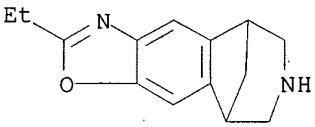
RN 230615-43-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-difluoro-2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



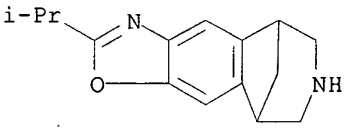
● HCl

RN 230615-44-8 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 2-ethyl-6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

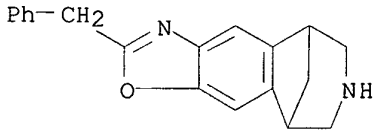
RN 230615-45-9 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(1-methylethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

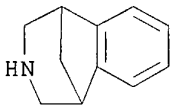
RN 230615-46-0 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488



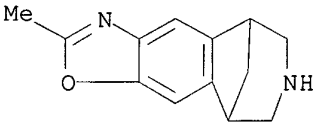
● HCl

RN 230615-52-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-75-5 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-(9CI) (CA INDEX NAME)



cl.15

IT **230615-48-2P 230615-50-6P 230615-51-7P**
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230615-56-2P 230615-57-3P 230615-58-4P
230615-59-5P 230615-60-8P 230615-61-9P
230615-62-0P 230615-63-1P 230615-64-2P
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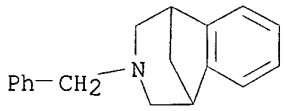
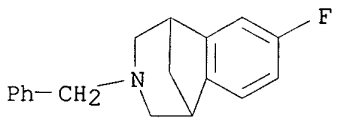
230615-87-9P 230615-88-0P 230615-89-1P
230615-90-4P 230615-92-6P 230615-93-7P
230615-94-8P 230615-95-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
Searched by John Dantzman 703-308-4488

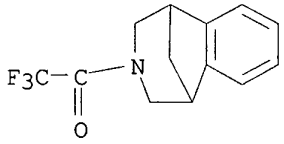
(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor
ligands)
RN 230615-48-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(phenylmethyl)- (9CI) (CA INDEX NAME)



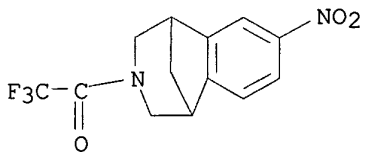
RN 230615-50-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-fluoro-2,3,4,5-tetrahydro-3-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 230615-51-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

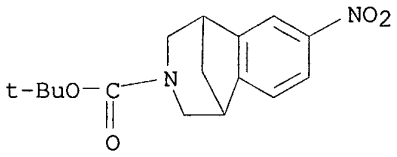


RN 230615-53-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-nitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

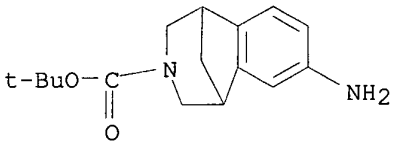


RN 230615-54-0 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7-nitro-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

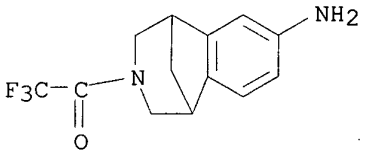
Searched by John Dantzman 703-308-4488



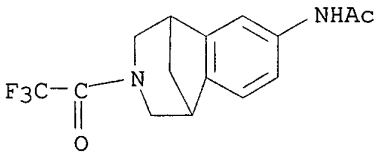
RN 230615-55-1 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-amino-1,2,4,5-tetrahydro-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-56-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-amine, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

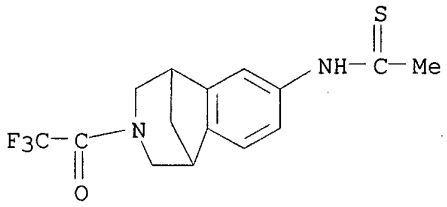


RN 230615-57-3 CAPLUS
CN Acetamide, N-[2,3,4,5-tetrahydro-3-(trifluoroacetyl)-1,5-methano-1H-3-benzazepin-7-yl]- (9CI) (CA INDEX NAME)

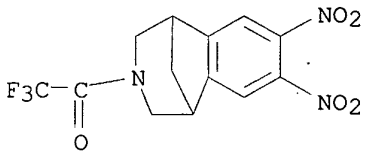


RN 230615-58-4 CAPLUS
CN Ethanethioamide, N-[2,3,4,5-tetrahydro-3-(trifluoroacetyl)-1,5-methano-1H-3-benzazepin-7-yl]- (9CI) (CA INDEX NAME)

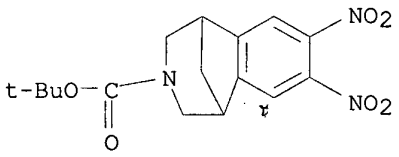
Searched by John Dantzman 703-308-4488



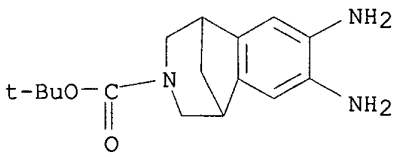
RN 230615-59-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7,8-dinitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-60-8 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7,8-dinitro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

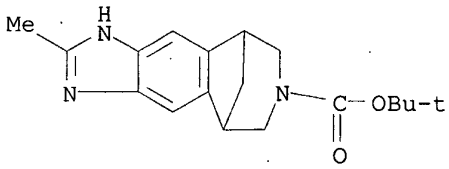


RN 230615-61-9 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7,8-diamino-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

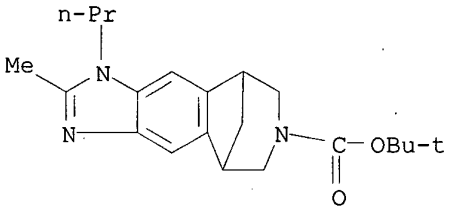


RN 230615-62-0 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

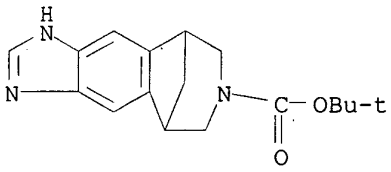
Searched by John Dantzman 703-308-4488



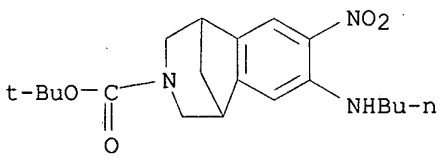
RN 230615-63-1 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-propyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-64-2 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

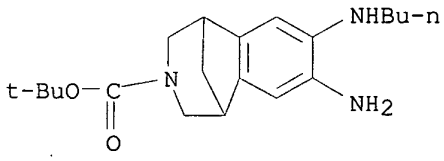


RN 230615-65-3 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-(butylamino)-1,2,4,5-tetrahydro-8-nitro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

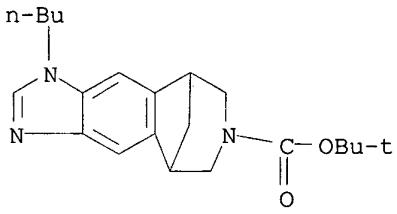


RN 230615-66-4 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-amino-8-(butylamino)-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

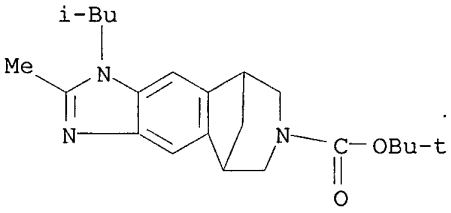
Searched by John Dantzman 703-308-4488



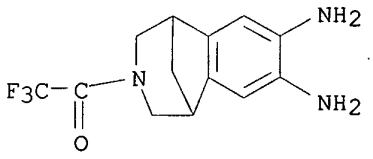
RN 230615-67-5 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 1-butyl-5,6,8,9-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 230615-68-6 CAPLUS
CN 5,9-Methanoimidazo[4,5-h][3]benzazepine-7(1H)-carboxylic acid, 5,6,8,9-tetrahydro-2-methyl-1-(2-methylpropyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

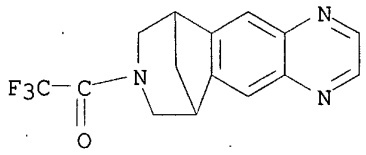


RN 230615-69-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7,8-diamine, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

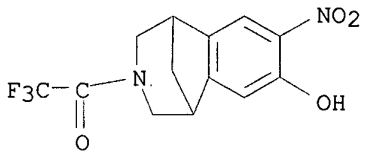


RN 230615-70-0 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-8-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

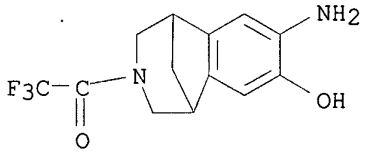
Searched by John Dantzman 703-308-4488



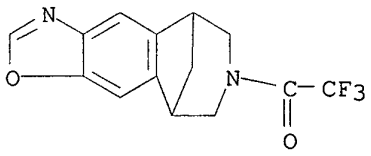
RN 230615-71-1 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-8-nitro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-72-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 8-amino-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

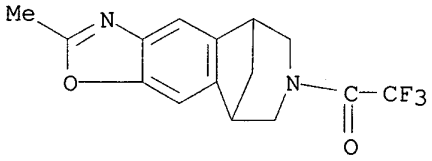


RN 230615-73-3 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

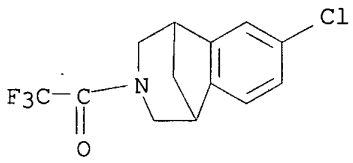


RN 230615-74-4 CAPLUS
CN 5,9-Methano-5H-oxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-2-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

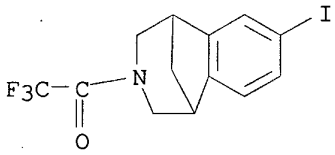
Searched by John Dantzman 703-308-4488



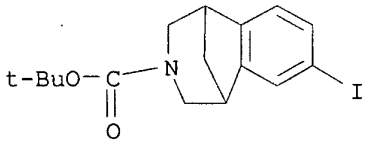
RN 230615-76-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-chloro-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-77-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-iodo-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

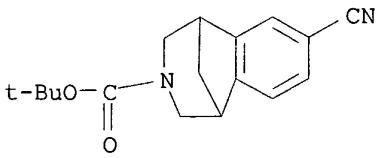


RN 230615-78-8 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 1,2,4,5-tetrahydro-7-iodo-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

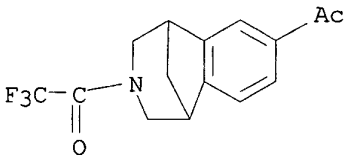


RN 230615-79-9 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-cyano-1,2,4,5-tetrahydro-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

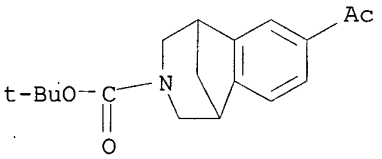
Searched by John Dantzman 703-308-4488



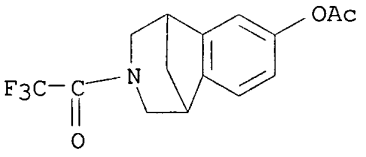
RN 230615-80-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7-acetyl-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-81-3 CAPLUS
CN 1,5-Methano-3H-3-benzazepine-3-carboxylic acid, 7-acetyl-1,2,4,5-tetrahydro-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

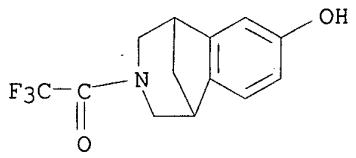


RN 230615-82-4 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)-, acetate (ester) (9CI) (CA INDEX NAME)

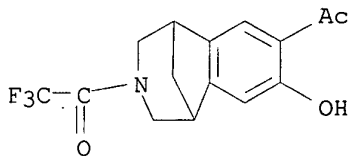


RN 230615-83-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

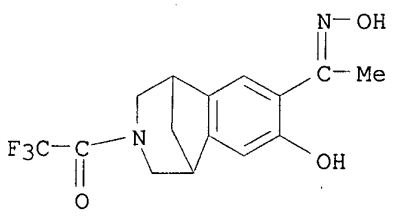
Searched by John Dantzman 703-308-4488



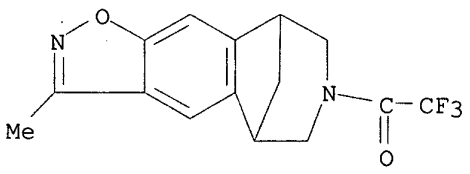
RN 230615-84-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 8-acetyl-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-85-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-7-ol, 2,3,4,5-tetrahydro-8-[1-(hydroxyimino)ethyl]-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

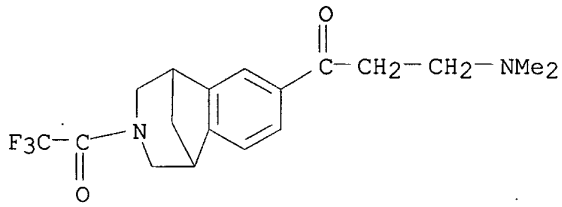


RN 230615-86-8 CAPLUS
CN 5,9-Methano-5H-isoxazolo[4,5-h][3]benzazepine, 6,7,8,9-tetrahydro-3-methyl-7-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

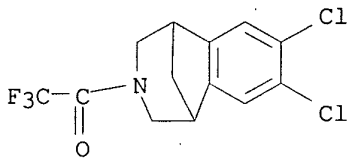


RN 230615-87-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-propanamine, 2,3,4,5-tetrahydro-N,N-dimethyl-.gamma.-oxo-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

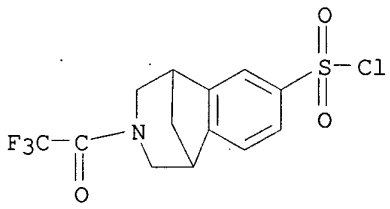
Searched by John Dantzman 703-308-4488



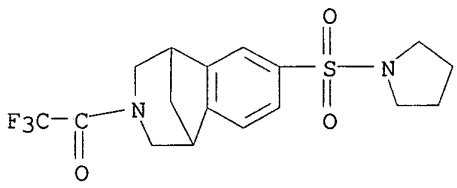
RN 230615-88-0 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 7,8-dichloro-2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)



RN 230615-89-1 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-7-sulfonyl chloride, 2,3,4,5-tetrahydro-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

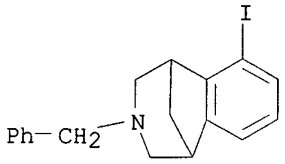


RN 230615-90-4 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-7-(1-pyrrolidinylsulfonyl)-3-(trifluoroacetyl)- (9CI) (CA INDEX NAME)

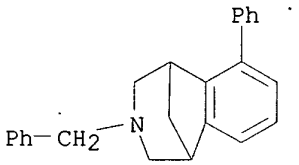


RN 230615-92-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-6-iodo-3-(phenylmethyl)-(9CI) (CA INDEX NAME)

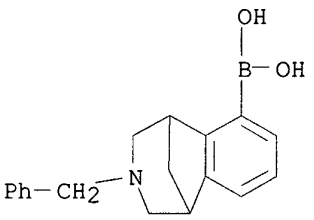
Searched by John Dantzman 703-308-4488



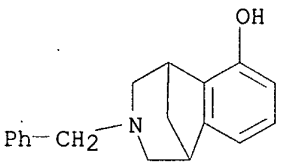
RN 230615-93-7 CAPLUS
CN 1,5-Methano-1H-3-benzazepine,
2,3,4,5-tetrahydro-6-phenyl-3-(phenylmethyl)-
(9CI) (CA INDEX NAME)



RN 230615-94-8 CAPLUS
CN Boronic acid, [2,3,4,5-tetrahydro-3-(phenylmethyl)-1,5-methano-1H-3-benzazepin-6-yl]- (9CI) (CA INDEX NAME)



RN 230615-95-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepin-6-ol, 2,3,4,5-tetrahydro-3-(phenylmethyl)-
(9CI) (CA INDEX NAME)

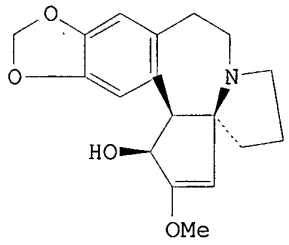


RE.CNT 2
RE
(1) Carson, J; US 3471503 A 1969 CAPLUS
(2) Mazzochi, P; Journal of Medicinal Chemistry 1979, V22(4), P455

Searched by John Dantzman 703-308-4488

=> d bib abs hitstr 3

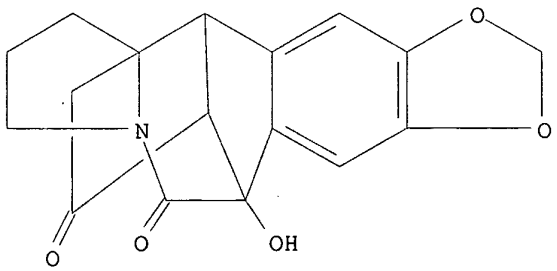
L21 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1993:495893 CAPLUS
DN 119:95893
TI Synthetic approaches to 11-hydroxycephalotaxine
AU Ikeda, Masazumi; Kosaka, Keigo; Sakakibara, Minoru; Okano, Masahiko
CS Kyoto Pharm. Univ., Kyoto, 607, Japan
SO Heterocycles (1993), 35(1), 81-4
CODEN: HTCYAM; ISSN: 0385-5414
DT Journal
LA English
GI



I

AB Several approaches to functionalize the cephalotaxine (I) skeleton based on the Pummerer reaction and Moriarty oxidn. are described.

IT **148679-83-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 148679-83-8 CAPLUS
CN 8H-10a,5,11-[1]Propanyl[3]ylidene-6H-1,3-dioxolo[4,5-h]pyrrolo[2,1-b][3]benzazepine-6,14-dione, 5,9,10,11-tetrahydro-, [5S-(5.alpha.,10a.beta.,11.beta.,13R*)]- (9CI) (CA INDEX NAME)



Searched by John Dantzman 703-308-4488

=> d bib abs hitstr 4

L21 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1989:423537 CAPLUS
DN 111:23537
TI Preparation of psychotropic N-(piperazinylalkyl) polycyclic imides
IN Stack, Gary Paul; Golobish, Thomas David; Abou-Gharbia, Magid Abdel Megid
PA American Home Products Corp., USA
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 286263	A1	19881012	EP 1988-302499	19880322
	EP 286263	B1	19910515		
	R: AT, BE, CH, DE, ES, FR, GR, IT, LI, LU, NL, SE				
	US 4797488	A	19890110	US 1987-34820	19870403
	CA 1306251	A1	19920811	CA 1988-561882	19880318
	GB 2203428	A1	19881019	GB 1988-6778	19880322
	GB 2203428	B2	19901031		
	AT 63551	E	19910615	AT 1988-302499	19880322
	ES 2039617	T3	19931001	ES 1988-302499	19880322
	AU 8813512	A1	19881006	AU 1988-13512	19880323
	AU 597480	B2	19900531		
	WO 8807529	A1	19881006	WO 1988-US973	19880331
	W: DK, JP, KR				
	JP 01502756	T2	19890921	JP 1988-503414	19880331
	US 4824999	A	19890425	US 1988-248769	19880923
	DK 8806738	A	19881202	DK 1988-6738	19881202
	AU 9051158	A1	19900628	AU 1990-51158	19900308
	AU 617930	B2	19911205		
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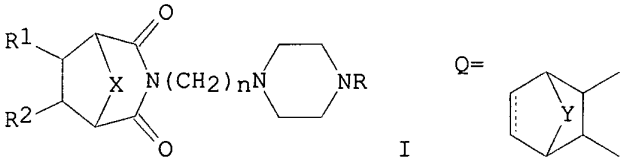
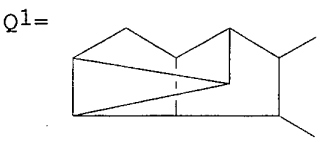
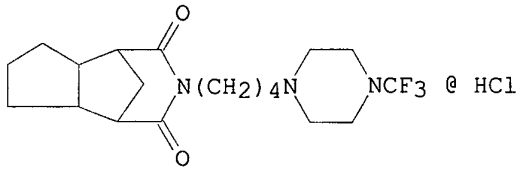
	EP 1988-302499	19880322			
	WO 1988-US973	19880331			

OS MARPAT 111:23537
GI



I





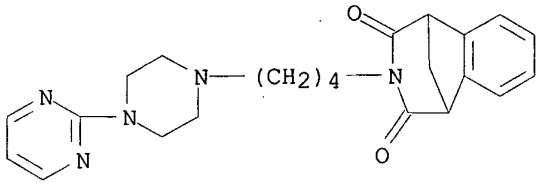
II

AB The title compds. [I; R = (halo)-2-pyrimidinyl, (halo)pyrazinyl, (halo)quinolinyl, (un)substituted Ph, pyridinyl; R1R2 = C3-5 alkylene, C3-5 alkenylene, polycyclic alkanediyl moiety Q, Q1, atoms to complete a fused benzo ring; X = R3R4C, S, SO, SO2; R3, R4 = H, C1-4 alkyl; R3R4 = C2-4 alkylene; Y = CH2, CH2CH2, O, S; n = 2-5; dotted line represents optional double bond] and their pharmaceutically acceptable salts were prepd. as psychotropic agents, useful as antipsychotics and anxiolytics. Bicyclo[3.3.0]octane-2,4-dicaboxylic acid was refluxed 3 h in Ac2O to give its anhydride which was refluxed 48 h with 1-(4-aminobutyl)-4-(trifluoromethyl)piperazine in xylene to give, after acidification, methanocyclopentazepinedione II. In rats, II inhibited the conditioned avoidance response with an ED50 of 46.17 mg/kg orally and inhibited apomorphine-induced stereotypy and climbing behavior with ED50 of 42.37 and 18.89 mg/kg orally, resp.

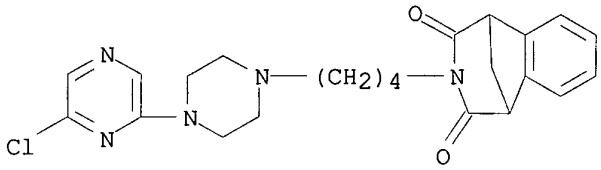
IT **121305-54-2P 121305-55-3P 121305-69-9P 121305-70-2P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antipsychotic)

RN 121305-54-2 CAPLUS

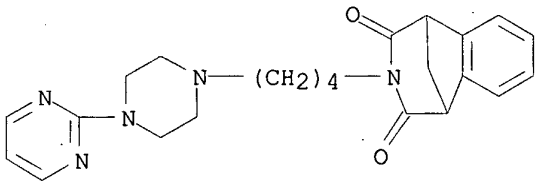
CN 1,5-Methano-1H-3-benzazepine-2,4(3H,5H)-dione, 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]- (9CI) (CA INDEX NAME)



RN 121305-55-3 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-2,4(3H,5H)-dione, 3-[4-[4-(6-chloropyrazinyl)-1-piperazinyl]butyl]- (9CI) (CA INDEX NAME)



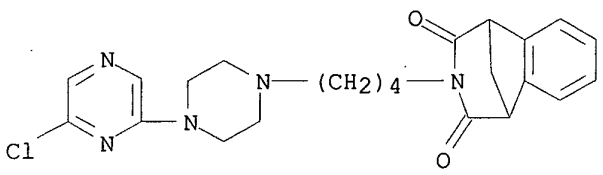
RN 121305-69-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-2,4(3H,5H)-dione, 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

RN 121305-70-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepine-2,4(3H,5H)-dione, 3-[4-[4-(6-chloropyrazinyl)-1-piperazinyl]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

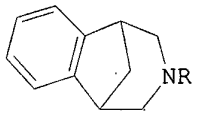
Searched by John Dantzman 703-308-4488



● HCl

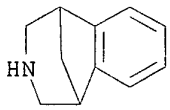
=> d bib abs hitstr 5

L21 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1979:432639 CAPLUS
DN 91:32639
TI Synthesis and pharmacological activity of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepines
AU Mazzocchi, Paul H.; Stahly, Barbara C.
CS Dep. Chem., Univ. Maryland, College Park, MD, USA
SO J. Med. Chem. (1979), 22(4), 455-7
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI



I

AB The title compds. I (R = H, alkyl, allyl, etc.) were prepd. from 2,3-dioxobenzonorbornene. 3-Allyl-2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepine oxalate (1:1) showed a slight antinociceptive activity in the mouse hot-plate assay and little antagonistic activity in the tail-flick assay. None of other I showed significant analgesic activity and all except 2,3,4,5-tetrahydro-3-(2-phenylethyl)-1,5-methano-1H-3-benzazepine oxalate (1:1) were toxic. Structure-activity relations are discussed.
IT **69718-72-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and alkylation of)
RN 69718-72-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro- (9CI) (CA INDEX NAME)



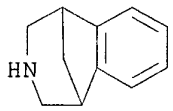
IT **69718-73-6P 69718-78-1P 69718-80-5P**
69718-83-8P 69718-85-0P 69718-87-2P
69718-89-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and analgesic and narcotic antagonist activities of)
RN 69718-73-6 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 69718-72-5

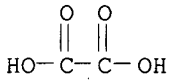
Searched by John Dantzman 703-308-4488

CMF C11 H13 N



CM 2

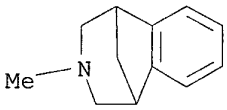
CRN 144-62-7
CMF C2 H2 O4



RN 69718-78-1 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-methyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

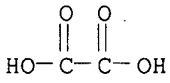
CM 1

CRN 69718-77-0
CMF C12 H15 N



CM 2

CRN 144-62-7
CMF C2 H2 O4

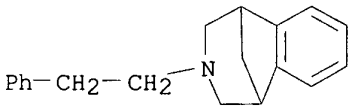


RN 69718-80-5 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(2-phenylethyl)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

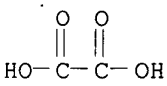
CRN 69718-79-2
CMF C19 H21 N

Searched by John Dantzman 703-308-4488



CM 2

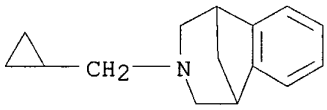
CRN 144-62-7
CMF C2 H2 O4



RN 69718-83-8 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 3-(cyclopropylmethyl)-2,3,4,5-tetrahydro-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

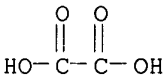
CM 1

CRN 69718-82-7
CMF C15 H19 N



CM 2

CRN 144-62-7
CMF C2 H2 O4

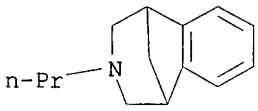


RN 69718-85-0 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-propyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

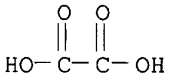
CRN 69718-84-9
CMF C14 H19 N

Searched by John Dantzman 703-308-4488



CM 2

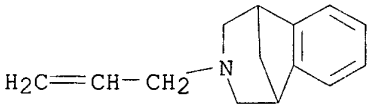
CRN 144-62-7
CMF C2 H2 O4



RN 69718-87-2 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(2-propenyl)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 69718-86-1
CMF C14 H17 N



CM 2

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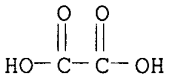
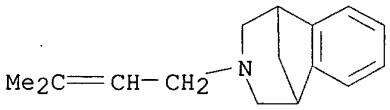


RN 69718-89-4 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-(3-methyl-2-butenyl)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 69718-88-3
CMF C16 H21 N

Searched by John Dantzman 703-308-4488



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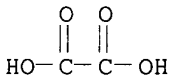

IT **69718-76-9P 69718-81-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and redn. of)
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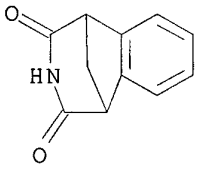

RN 69718-81-6 CAPLUS
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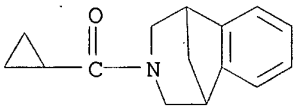
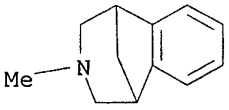
(9CI) (CA INDEX NAME)

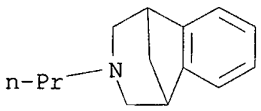


IT **69718-77-0P 69718-84-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 69718-77-0 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-methyl- (9CI) (CA
INDEX NAME)



Searched by John Dantzman 703-308-4488

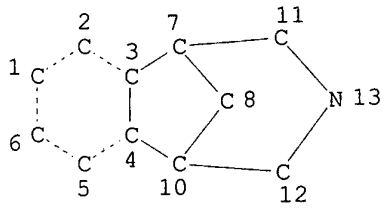
RN 69718-84-9 CAPLUS
CN 1,5-Methano-1H-3-benzazepine, 2,3,4,5-tetrahydro-3-propyl- (9CI) (CA INDEX NAME)



Searched by John Dantzman 703-308-4488

=> d que l23

L10 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L23 0 SEA FILE=BEILSTEIN SSS FUL L10

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/402,010	09/28/99	COE J	PC10030A

HM12/0929

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
20TH FLOOR
NEW YORK NY 10017-5755

EXAMINER	
COLEMAN, B	
ART UNIT	**PAPER NUMBER**
1624	3

DATE MAILED: 09/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/402,010	COE et al.
Examiner	**Group Art Unit**
Brenda Coleman	1624

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *12* is/are allowed.

☒ Claim(s) *1-11, 13, and 14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 1-14 are pending in the application.

Priority

1. Any non-provisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross - references to other related applications may be made when appropriate.

"This application is a national stage entry under 35 U.S.C. § 371 of PCT/IB98/01813, filed November 13, 1998 which claims the benefit of U.S. Provisional Application No. 60/070,245, filed December 31, 1997." is suggested.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1 (and claims dependent thereon) recite the broad recitation "aryl and heteroaryl groups may optionally be substituted with one or more substituents", and the claims also recite "preferably from zero to two substituents" which is the narrower statement of the range/limitation.

b) Regarding claims 1 (and claims dependent thereon), the phrase "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

c) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1 (and claims dependent thereon) recite the broad recitation "monocyclic and bicyclic rings may optionally be substituted with one or more substituents", and the claims also recite "preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings" which is the narrower statement of the range/limitation.

d) Claim 1 is vague and indefinite in that it is not known what is missing from the claim since the claim does not end with a period.

e) Claim 2 recites the limitation "(C_0-C_6)alkoxy-(C_0-C_6)alkyl-" in definition of R^{10} and R^{17}. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 2 recites the limitation "phenyl and monocyclic heteroaryl" in definition of R^{10} and R^{17}. There is insufficient antecedent basis for this limitation in the claim.

g) Claim 9 is a substantial duplicate of claim 7, as the only difference is a statement of intended use which is not given material weight. Note In re Tuominen 213 USPQ 89.

h) Regarding claims 9, 10 and 13, the phrase "including but not limited to" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "including but not limited to"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

i) Regarding claims 9, 10 and 13, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

j) Regarding claims 9, 10 and 13, the phrase "including" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "including"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

k) Claim 11 is vague and indefinite in that the definitions of R^5 and R^6 are "defined as in formula I above", however, they are not defined within the claim.

l) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation "from 1 to 3 halo atoms", and the claim also recites "from 1 to 3 fluoro or chloro atoms" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Mazzocchi et al., Journal of Medicinal Chemistry. Mazzocchi teaches the compounds of the instant invention where R^1 is $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_3$, $-CH_2-CH=CH_2$ or $-CH_2CH=CMe_2$. See examples 4c, 4d, 4e or 4f on page 456.

Claim Objections

4. Claim 14 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Allowable Subject Matter

5. Claim 12 is allowed. None of the prior art of record nor a search in the pertinent art area teaches the method of use of 2,3,4,5-tetrahydro-1,5-methano-1H-3-benzazepine as claimed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Monday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
September 26, 2000

Notice of References Cited

Application No.	Applicant(s)		
09/402,010	COE et al.		
Examiner	Group Art Unit	Page 1 of 1	
Brenda Coleman	1624		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
x	A	3,471,503	10/1969	CARSON	260	294.7
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
x	U	Mazzocchi et al., Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-methano-1H-3-benzazepines, Journal of Medicinal Chemistry, Vol. 22, No. 4, pages 455-457.	1979
	V		
	W		
	X		

Brenda Coleman

* A copy of this reference is not being furnished with this Office action. (See Manual of Patent Examining Procedure, Section 707.05(a).)

Sept. 26, 2000

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this 29th day of December, 2000.

By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

#4/A
4/5/01
C. Stiles

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al. :

Examiner: B. Coleman

SER. NO.: 09/402,010 :

Group Art Unit: 1624

FILING DATE: September 28, 1999 :

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS :

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE AND AMENDMENT UNDER 37 C.F.R. § 1.111

This is responsive to the Office Action mailed September 29, 2000, a Response to which was due on December 29, 2000. Accordingly, this response is timely.

Applicants request the following amendments to the application be entered.

IN THE ABSTRACT

at page 80, line 9, "R^3 and n" are deleted and -- and R^3 -- is substituted therefor;

at page 80, line 12, "are claimed" is deleted.

IN THE SPECIFICATION

at page 1, line 5, add the following text:

-- This application is a national stage entry under 35 U.S.C. § 371 of PCT/IB98/01813, filed November 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed December 31, 1997. --

at page 1, line 13, delete "amylotropic" and substitute therefor -- amyotrophic --;

at page 1, line 15, delete "supramuscular" and substitute therefor -- supranuclear --;

at page 1, line 17, delete "barbituates" and substitute therefor -- barbiturates --;

at page 3, line 22, "piperizine, -N-(C_1-C_6)alkylpiperizine" is deleted and -- piperazine, -N-(C_1-C_6)alkylpiperazine -- is substituted therefor;

77

A

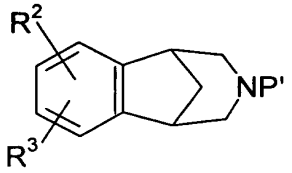
at page 5, after line 11, the following paragraphs are inserted:

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is $(C_1\text{-}C_6)$alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_3)$alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

at page 7, after line 14 insert the following text:

-- The invention also relates to a compound of the formula



(I′)

wherein R^2 and R^3 are defined above; and P′ 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 claim 2; $-C(=O)H$, $-C(=O)(C_1\text{-}C_6)$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). --

at page 8, line 7, "radiolabelled" is deleted and -- radiolabeled -- is substituted therefor;

at page 8, line 8, "formulae" is deleted, and -- formula -- is substituted therefor;

at page 8, line 9, "radiolabelled" is deleted and -- radiolabeled -- is substituted therefor;

at page 8, line 26, delete "amylotropic" and substitute therefor -- amyotrophic --;

at page 8, line 28, delete "supramuscular" and substitute therefor -- supranuclear --;

at page 8, line 30, delete "barbituates" and substitute therefor -- barbiturates --;

at page 8, line 31, after "(TBI)", the words -- obsessive-compulsive disorder (OCD) -- are inserted;

at page 9, line 9, delete "amylotropic" and substitute therefor -- amyotrophic --;

at page 9, line 11, delete "supramuscular" and substitute therefor -- supranuclear --;

at page 9, line 13, delete "barbituates" and substitute therefor -- barbiturates --;

at page 9, line 14, after "(TBI)", the words -- obsessive-compulsive disorder (OCD) -- are inserted;

at page 9, line 19, "accepable" is deleted and -- acceptable -- is substituted therefor;

at page 9, line 30, delete "amylotropic" and substitute therefor -- amyotrophic --;

at page 9, line 32, delete "supramuscular" and substitute therefor -- supranuclear --;

at page 9, line 34, delete "barbituates" and substitute therefor -- barbiturates --;

at page 9, line 35, after "(TBI)", the words -- obsessive-compulsive disorder (OCD) -- are inserted;

at page 23, line 13, "dichoroethane" is deleted and -- dichloroethane -- is substituted therefor;

at page 24, line 9, "heteratoms" is deleted and -- heteroatoms -- is substituted therefor;

at page 24, line 10, "heteroryl" is deleted and -- heteroaryl -- is substituted therefor;

at page 25, line 8, "illlustrated" is deleted and -- illustrated -- is substituted therefor;

at page 25, line 16, "exemplied" is deleted and -- exemplified -- is substituted therefor;

at page 27, line 7, "stoicheometric" is deleted and -- stoichiometric -- is substituted therefor;

at page 27, line 8, "pyridinum" is deleted and -- pyridinium -- is substituted therefor;

at page 31, line 17, "trifluromethansulfonic" is deleted and -- trifluoromethanesulfonic -- is substituted therefor;

at page 31, line 24, "acylations" is deleted and -- acylation -- is substituted therefor;

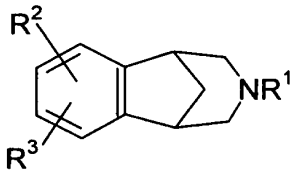
at page 31, line 36, "substited" is deleted and -- substituted -- is substituted therefor;

IN THE CLAIMS

Cancel claims 3, 4, 5, 6, 7, 11, 12 and 13.

Replace claims 1, 2, 9, 10 and 14 with the amended versions immediately following:

1. (Once Amended) A compound of the formula



(I)

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

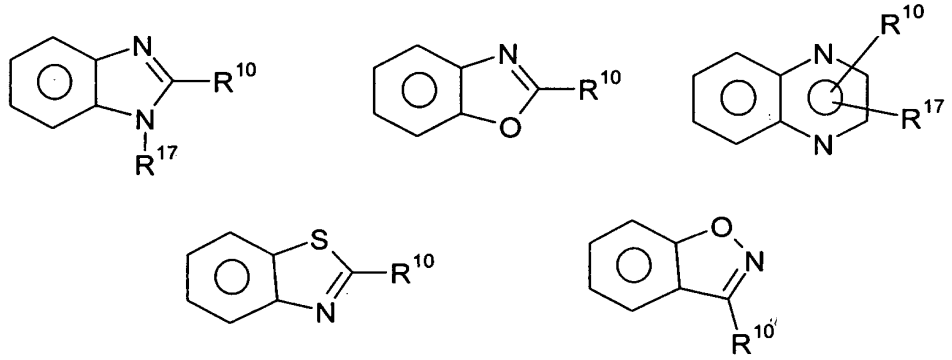
R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five 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 that are selected, independently, 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; nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and ((C_1 -C_6)alkyl)$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

wherein 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, piperazine, -N-(C_1-C_6)alkylpiperazine 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;

or a pharmaceutically acceptable salt thereof.

2. (Once Amended) 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 (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; (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and ((C_1 -C_6) alkyl)$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$ and wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in claim 1.

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9. (Once Amended) A pharmaceutical composition comprising an amount of a compound according to claim 1 and a pharmaceutical acceptable carrier.

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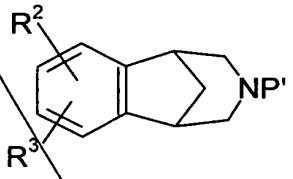
10. (Once Amended) A method for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, 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.

14. (Once Amended) A compound of the formula



(I′)

wherein R^2 and R^3 are defined as in claim 1; and P′ is $COOR^{16}$ 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 selected, independently, from hydrogen and $(C_1$ -$C_6)$ alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-$(C_1$-$C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; -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; benzyl, or t-butoxycarbonyl (t-Boc).

Add new claims 15 through 26.

-- 15. A compound according to claim 1 selected from the group consisting of: 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

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7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
and pharmaceutically acceptable salts thereof. --

-- 16. A compound according to claim 1 selected from the group consisting of:
6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
6-methyl-5-thia-5-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
7-dimethylamino-5-thia-5-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
6,7-dioxo-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene;
5,8-dimethyl-6,7-dioxo-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,9-triene;
5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
and pharmaceutically acceptable salts thereof. --

-- 17. A compound according to claim 1 which is:
6-methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof. --

-- 18. A compound according to claim 1 which is:
6-methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof. --

-- 19. A compound according to claim 1 which is:
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
or a pharmaceutically acceptable salt thereof. --

-- 20. A compound according to claim 1 which is:
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof. --

-- 21. A compound according to claim 1 which is:
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof. --

-- 22. A compound according to claim 1 which is:
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
or a pharmaceutically acceptable salt thereof. --

-- 23. A compound according to claim 1 which is:
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof. --

-- 24. A compound according to claim 1 which is:
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
or a pharmaceutically acceptable salt thereof. --

-- 25. A compound according to claim 1 which is:
5,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),9-trien-6-one;
or a pharmaceutically acceptable salt thereof. --

-- 26. A compound according to claim 1 which is:
6-oxo-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
or a pharmaceutically acceptable salt thereof. --

REMARKS

Applicants have amended the Abstract to correct the description of the variables as presented in the structure. Applicants have inserted a statement on page 1 of the application to indicate the priority required by 37 C.F.R. § 1.78. Applicants have corrected a number of typographical and spelling errors on pages 1, 3, 8, 9, 23-25, 27 and 31, as specifically set forth above.

Applicants have inserted text on page 5 relating to other embodiments of the invention that are fully supported by claims 3-6 as originally filed. The insertion of the text at page 7 of the structure of formula (I') and accompanying description has full literal support in claim 14 in the application as originally filed. The insertion of "obsessive-compulsive disorder" at pages 8 and 9 and claim 10 into the lists of diseases, disorders or conditions for which pharmaceutical compositions comprising the compounds of the invention, and methods employing those compounds/compositions is supported by the description at page 1, line 18.

Applicants have amended claim 1 such that it relates only to compounds where R^2 and R^3 join to form a ring and thus deletes the substituent list for R^2 and R^3 do not form a ring . This amendment has support in the specification at page 3, lines 7-19; and from page 4, line 8 to page 5, line 8. Consistent with this amendment to claim 1, Applicants have canceled dependent claims 3, 4, 5 and 6 which all relate to compounds where the groups R^2 and R^3 do not together form a ring and now fall without the scope of amended claim 1. Further, Applicants have canceled claims 11, 12 and 13. Applicants have made these amendments and cancellations of claims without prejudice to file divisional application(s) drawn to the canceled subject matter.

Claim 2 now recites definitions of R^{10} and R^{17} that are consistent with the appropriate definitions in claim 1 from which it depends. Applicants have amended claim 9 to recite a pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier with the deletion of other descriptors in the claim. Applicants have canceled claim 7 to avoid overlap with claim 9. Applicants have amended claim 10 to correct several typographical, spelling and format errors. Applicants have amended claim 14 to insert a definition of R^5 and R^6 directly from claim 1.

New claims 15 through 26 set forth species corresponding to the invention. New claim 15 is supported by Examples 13-15, 17-18, 20-24, and 29. New claim 16 is supported by the specification at page 5, line 14 to page 6, line 36. New claims 17 through 26 are supported by Examples 10, 12, 16, 25, 26, 27, 28, 36, 41 and 42, respectively.

All of the foregoing amendments have support in the application as filed. These amendments add no new matter to the application.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-11, 13 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has set forth the following particular objections:

a. Claim 1 - "Preferably from zero to two substituents"

The Examiner has objected to the statements of "range/limitation" for "aryl and heteroaryl group" wherein both descriptors "optionally be substituted with one or more substituents" and "preferably from zero to two substituents" are present.

Applicants have deleted the particular passage from claim 1 in which "aryl and heteroaryl groups" are accompanied by these descriptors. Accordingly, this objection is now moot.

b. Claim 1 - "e.g."

The Examiner has objected to the phrase "e.g." in claim 1.

Applicants have deleted the passage wherein that expression occurs from claim 1. Accordingly, this objection is now moot.

c. Claim 1 - "Preferably from zero to two substituents" - Mono/Bicyclic Rings

The Examiner has objected to the statements of "range/limitation" for "monocyclic and bicyclic rings" wherein both descriptors "optionally be substituted with one or more substituents" and "preferably from zero to two substituents for the monocyclic rings and zero to three substituents for the bicyclic rings" are present.

Applicants have amended claim 1 to delete the phrase "preferably from zero to two substituents for the monocyclic rings and zero to three substituents for the bicyclic rings" and overcome this objection. Accordingly, Applicants request the Examiner withdraw this particular objection.

d. Claim 1 - Missing Period

The Examiner has asserted that claim 1 is "vague and indefinite in that . . . the claim does not end with a period."

Applicants have amended claim 1 to insert a period at the end of the claim.

e. Claim 2 - "(C_0-C_6)alkoxy-(C_0-C_6)alkyl-"

The Examiner urges "that the limitation '(C_0-C_6)alkoxy-(C_0-C_6)alkyl-' in the definition of R^{10} and R^{17}" in claim 2 has insufficient antecedent basis in claim 1.

Applicants have amended claim 2 to replace the definitions of R^{10} and R^{17} to reflect the substituent pattern as set forth in claim 1. Accordingly, Applicants request withdrawal of this objection.

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f. Claim 2 - Phenyl and Monocyclic Heteroaryl

The Examiner urges "that the limitation 'phenyl and monocyclic heteroaryl' in the definition of R^{10} and R^{17}" in claim 2 has insufficient antecedent basis in claim 1.

Applicants have amended claim 2 to replace the definitions of R^{10} and R^{17} to reflect the substituent pattern as set forth in claim 1. Accordingly, Applicants request withdrawal of this objection.

g. Claim 9 - "Intended Use"

The Examiner has objected to claim 9 as a substantial duplicate of claim 7 "as the only difference is a statement of intended use which is not given material weight."

Applicants have canceled claim 7 and amended claim 9 to recite a pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier. Accordingly, Applicants have overcome this objection.

h. Claims 9, 10 and 13 - "Including but not limited to"

The Examiner has objected to claims 9, 10 and 13 because the phrase "including by not limited to" renders the claims indefinite.

Applicants have canceled claims 9 and 13 in this application and have amended claim 10 to avoid the use of the phrase to which the Examiner has objected. Accordingly, the Examiner should withdraw this objection.

i. Claims 9, 10 and 13 - "e.g"

The Examiner has objected to claims 9, 10 and 13 because the phrase "e.g." renders the claims indefinite.

Applicants have canceled claims 9 and 13 in this application and have amended claim 10 to avoid the use of the phrase to which the Examiner has objected. Accordingly, the Examiner should withdraw this objection.

j. Claims 9, 10 and 13 - "Including"

The Examiner has objected to claims 9, 10 and 13 because the phrase "including" renders the claims indefinite.

Applicants have canceled claims 9 and 13 in this application and have amended claim 10 to avoid the use of the term to which the Examiner has objected. Accordingly, the Examiner should withdraw this objection.

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k. Claim 11 - "Defined as in formula I above"

The Examiner has objected to the use of the phrase "defined as in formula I above" to define the substituents R^5 and R^6 in that claim.

Applicants have canceled claim 11 thereby rendering this objection moot.

l. Claim 14 - "From 1 to 3 halo atoms"

The Examiner has objected to the statements of "range/limitation" for a particular alkyl moiety wherein both descriptors of substitution pattern, "from 1 to 3 halo atoms" and "preferably from 1 to 3 fluoro or chloro atoms", are present.

Applicants have amended claim 1 to delete the phrase "preferably from 1 to 3 fluoro or chloro atoms" and overcome this objection. Accordingly, Applicants request the Examiner withdraw this particular objection.

Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 1 and 3 under 35 U.S.C. § 102(b) as being anticipated by Mazzocchi et al., *J. Med. Chem.*, **22(4)**: 455-457 (1979) ("Mazzocchi"). The Examiner asserts that Mazzocchi "teaches the compounds of the instant invention where R^1 is $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_3$, $-CH_2-CH=CH_2$ or $-CH_2-CH=CMe_2$."

Applicants have amended claim 1 to exclude certain classes of compounds without prejudice to file divisional applications thereto. The claims presently cover compounds of formula I wherein R^2 and R^3 together form an additional ring. The amendments to claim 1 render this objection moot because the compounds as claimed do not encompass the compounds of Mazzocchi and hence cannot be anticipated by that reference under 35 U.S.C. § 102.

Accordingly, Applicants request that the Examiner withdraw this rejection.

Claim Objections - Claim 14

The Examiner has objected to claim 14 as being in improper form because a multiple dependent claim should refer to other claims in the alternative only.

Applicants have amended claim 14 to insert definition of the substituent groups R^5 and R^6 into the claim itself and thereby canceled the dependence upon claim 2. Accordingly, Applicants have overcome this particular claim objection.

Applicants believe the present amendments render the set of pending claims in condition for allowance and request the issuance of a Notice of Allowance. If a telephone interview would

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assist the furtherance of the prosecution of this application, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Date: 12/29/2000

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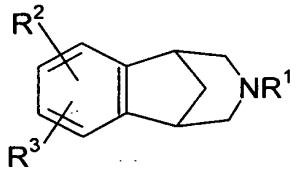
ATTACHMENT TO RESPONSE AND AMENDMENT

MARKED-UP VERSIONS OF AMENDED CLAIMS

1. (Once Amended) A compound of the formula



(I)

R^1 is hydrogen, (C_1 -C_6)alkyl, unconjugated (C_3-C_6)alkenyl, $XC(=O)R^{13}$, benzyl 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), (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, nitro, cyano, amino, (C_1-C_6)alkylamino-, [(C_1-C_6) alkyl]$_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and $-XC(=O)R^{13}$;]

[or] R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be

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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_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 [,] ; nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and [(C_1 -C_6) alkyl]$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

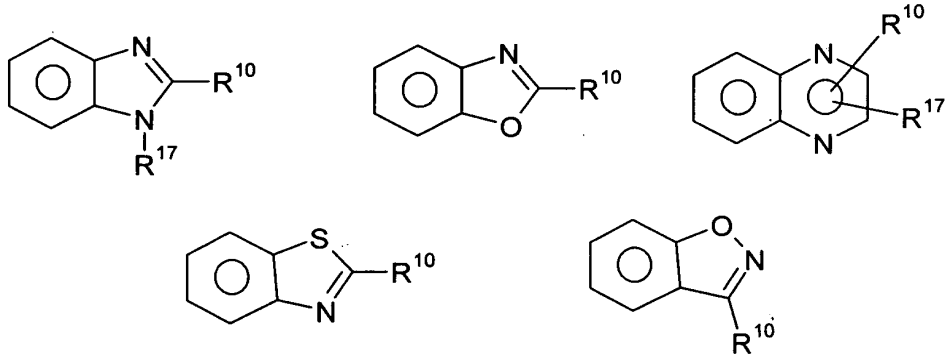
wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine [piperizine, 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, and (b) when R^2 and R^3 are both hydrogen, R^1 cannot be hydrogen or methyl;]

or a pharmaceutically acceptable salt thereof [;] .

2. (Once Amended) 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 (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; (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino and ((C_1 -C_6)alkyl)$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -

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XC(=O)R^{13} [(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, cyano, halo, amino, (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}, phenyl and monocyclic heteroaryl, 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 wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in claim 1.

9. (Once Amended) 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 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 , [(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, amyotrophic [amylotropic] lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear [supramuscular] palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), [chemical dependencies and

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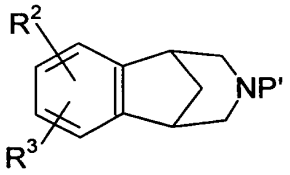
addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI),] psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct 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 according to claim 1 that is effective in treating such disorder or condition.

14. (Once Amended) A compound of the formula



(I′)

wherein R^2 and R^3 are defined as in claim 1; and P′ is $COOR^{16}$ 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 claim 2] selected, independently, from hydrogen and $(C_1$ -$C_6)$ alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-$(C_1$-$C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone ; -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).

A

Patent Application
Attorney Docket No. PC10030A

#5
4/6/01
C.Styles

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this 29th day of December, 2000.

By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al.

SER. NO.: 09/402,010

FILING DATE: September 28, 1999

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Examiner: B. Coleman

Group Art Unit: 1624

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL LETTER

Applicants submit herewith an Information Disclosure Statement pursuant to 37 C.F.R. §§ 1.97(c) and 1.98 with accompanying Form PTO-A820. This Statement is being filed after the mailing of a first Office Action on the merits but before the mailing date of either a final action or a notice of allowance. The submission of this Statement is accompanied by the fee of $180.00 as required under 37 C.F.R. § 1.17(p).

The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. §§1.16 and 1.17, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,

Date: 12/29/2000

Roy F. Waldron
Attorney for Applicant(s)
Reg. No. 42,208

Pfizer Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755
(212) 733-5086

01/08/2001 VVAN11 00000116 161445 09402010

01 FC:126 180.00 CH

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this 29th day of December, 2000.

By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al. :

Examiner: B. Coleman

SER. NO.: 09/402,010 :

Group Art Unit: 1624

FILING DATE: September 28, 1999 :

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS :

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97 ET SEQ.

Applicants herewith make available to the U.S. Patent and Trademark Office this Information Disclosure Statement pursuant to 37 C.F.R. §§ 1.97 and 1.98, a Form PTO-FB-A820 (2x). This Information Disclosure Statement contains a listing of references which were cited in a Search Report issued by the International Searching Authority on February 3, 1999. A copy of the Search Report and the references are enclosed herewith.

The Examiner is requested to consider carefully the complete text of these references in connection with the examination of the above-identified application in accordance with 37 C.F.R. § 1.104(a). It is believed the Examiner will concur with Applicants' belief that the subject matter presently claimed is neither anticipated nor rendered obvious by the foregoing references.

It is requested that the references listed on the attached form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing from this application (M.P.E.P. § 1302.12).

The references listed on the PTO-FB-A820 are as follows:

U.S. Patents

3,471,503, issued October 7, 1969

Other Documents

P. Mazzocchi et al., "Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-methano-1H-3-benzazepines," J. Med. Chem., 22(4), 455-457 (1979).

Applicants also bring to the attention of the Examiner U.S. co-pending application Ser. No. 09/514,002, filed February 25, 2000, which is a continuation in part application of the present application.

A favorable response is earnestly solicited.

Respectfully submitted,

Date: 12/29/2000

Roy F. Waldron
Attorney for Applicant(s)
Reg. No. 42,208

Pfizer Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755
(212) 733-5086

Patent Application
Attorney Docket No. PC10030A

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By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al.

SER. NO.: 09/402,010

FILING DATE: September 28, 1999

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Examiner: B. Coleman

Group Art Unit: 1624

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

TRANSMITTAL LETTER

Transmitted herewith is [X] a Response and Amendment; in the above-identified application.

The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims Remaining After Amendment		(3)	(4) Highest Number Previously Paid For		(5) Present Extra	(6) Rate	Additional Fee
Total Claims	18	*	minus	20	**	= 0	X $18.00	0
Independent Claims	1	*	minus	3	***	= 0	X $78.00	0
☐ Multiple Dependent Claim(s) fee							$260.00	0
							TOTAL=	0

* If the entry in column 2 is less than the entry in column 4, write "0" in column 5.
** If the "Highest No. Previously Paid for" is less than 20, write "20" in this space.
*** If the "Highest No. Previously Paid for" is less than 3, write "3" in this space.

☒ No additional fee is required.

☐ A Petition for Extension of Time for responding within ____ months of the response date is also enclosed. The Commissioner is authorized to charge the fee pursuant to 37 C.F.R. § 1.17(a)(2) in the amount of $ _____. Two copies of this paper are enclosed.

☐ Please charge Deposit Account No. 16-1445 in the amount of $ _____. Two copies of this paper are enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. §§1.16 and 1.17, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,

Date: 12/29/2000

Roy F. Waldron
Attorney for Applicants
Reg. No. 42,208

Pfizer, Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755
(212) 733-5086

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/402,010	09/28/99	COE J	PC10030A

HM12/0725

PAUL H GINSBURG
PFIZER INC
235 EAST 42ND STREET
20TH FLOOR
NEW YORK NY 10017-5755

EXAMINER	
COLEMAN, B	
ART UNIT	**PAPER NUMBER**
1624	6

DATE MAILED: 07/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/402,010	COE et al.
Examiner	**Art Unit**
Brenda Coleman	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 3, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 8-10, and 14-26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 8-10, and 14-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1, 2, 8-10 and 14-26 are pending in the application.

This action is in response to applicants' amendment dated January 3, 2001. Claim 17, 76, 78, 91 and 97 were amended and claim 96 was canceled.

Response to Arguments

Applicant's arguments filed January 3, 2001 have been fully considered with the following effect:

1. The applicant's amendments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejections of the last office action which are hereby **withdrawn**.

2. The applicant's amendments are sufficient to overcome the 35 U.S.C. § 102 anticipation rejection of the last office action which is hereby **withdrawn**.

In view of the amendment dated January 3, 2001, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment filed January 3, 2001, included the addition of claim 16 which contains eleven species that are not described in the specification.

Applicant is required to cancel the new matter in the reply to this Office action.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 16, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claim 15 recites the limitation "7-phenyl" in the seventh and eighth species. There is insufficient antecedent basis for this limitation in the claim.

b) Claim 16 recites the limitation "5,7-dioxo" in the first and fourth species. There is insufficient antecedent basis for this limitation in the claim.

c) Claim 16 recites the limitation "5-oxo" in the second and fifth species. There is insufficient antecedent basis for this limitation in the claim.

d) Claim 16 recites the limitation "6-oxo" in the third, sixth and eleventh species. There is insufficient antecedent basis for this limitation in the claim.

e) Claim 16 recites the limitation "5-dioxo" in the seventh and eighth species. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 16 recites the limitation "6,7-dioxo" in the ninth and tenth species. There is insufficient antecedent basis for this limitation in the claim.

g) Claim 25 recites the limitation "6-one" in the species. There is insufficient antecedent basis for this limitation in the claim.

h) Claim 26 recites the limitation "6-oxo" in the species. There is insufficient antecedent basis for this limitation in the claim.

i) Claim 26 is vague and indefinite in that it is not known what is meant by 2(10),3,6,8-tetraene where the double bond to the 6 position creates a pentavalent carbon atom.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 2, 8-10 and 14-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7-11, 15, 17, 18, 21-24, 27-29 and 32 of copending Application No. 09/514,002. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of the instant invention embrace the compounds of 09/514,002.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Monday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
July 24, 2001

#5

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	ATTY. DOCKET NO. PC10030A	SERIAL NO. 09/402,010
	APPLICANT J. W. COE et al.	
	FILING DATE 09/28/1999	GROUP 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	US 3 7 1 5 0 3	10/7/69	CARSON	260	294.7	5/5/67

FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (*Including Author, Title, Date, Pertinent Pages, Etc.*)

P. Mazzocchi et al., "Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-methano-1H-3-benzazepines," J. Med. Chem., 22(4), 455-457 (1979).

EXAMINER B. COLEMAN Brenda Coleman DATE CONSIDERED July 24, 2001

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Conforms with FORM PTO-FB-A820 INFORMATION DISCLOSURE

COPY

Patent Application
Attorney Docket No. PC10030A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this 16th day of November, 2001.

9/amdt B
CR
12/8/01

By _____
(Signature of person mailing)
ROY F. WALDNER
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al.

SER. NO.: 09/402,010

FILING DATE: September 28, 1999

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Examiner: B. Coleman

Group Art Unit: 1624

Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE AND AMENDMENT UNDER 37 C.F.R. § 1.111

This is responsive to the Office Action mailed July 25, 2001, a Response to which is due on October 25, 2001. Applicants have submitted herewith a Petition for Extension of Time to extend the period of response up to and including November 25, 2001 and paid the requisite fee. Accordingly, this response is timely.

Applicants request the following amendments to the application be entered.

IN THE CLAIMS

Cancel claims 16, 25 and 26.

Replace claims 14 and 15 with the amended version immediately following (marked-up versions are set forth in the Appendix hereto)

CLEAN COPY- ENTER

15

~~14~~. (Twice Amended) A compound of the formula (I')

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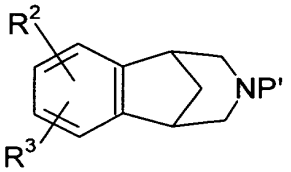

(I')

wherein R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be

84

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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 that are selected, independently, 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; nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and ((C_1 -C_6)alkyl)$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

wherein 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, piperazine, -N-(C_1-C_6)alkylpiperazine 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;

and P′ is $COOR^{16}$ 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 selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; -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; benzyl, or t-butoxycarbonyl (t-Boc).

15. (Amended) A compound according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

and pharmaceutically acceptable salts thereof.

REMARKS

Applicants have amended claim 14 to replace the term "defined as in claim 1" as applied to the variables R^2 and R^3 with the actual definitions of those variable as set forth in claim 1. Also, Applicants have amended claim 15 to delete the seventh and eighth listed species. Applicants have canceled claims 16, 25 and 26. Applicants make these cancellations without prejudice to their right to prosecute the subject matter of canceled claims in related continuation applications. None of these amendments adds new matter to the application.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 16 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Applicants have canceled claim 16 thereby rendering this rejection moot. Applicants make this cancellation without prejudice to their right to prosecute the subject matter of canceled claim 16 in related continuation applications.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 15, 16, 25 and 26 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has set forth the following particular objections:

a) Claim 15: "7-phenyl"

The Examiner has objected to the recitation of the "limitation '7-phenyl' in the seventh and eighth species" of claim 15 as having "insufficient antecedent basis" in claim 1.

Applicants have deleted the seventh and eighth compounds from claim 15. Accordingly, this objection is now moot.

b)-f) Claim 16: "5,7-dioxo", "5-oxo", "6-oxo", "5-dioxo" and "6,7-dioxo"

The Examiner has objected to claim 16 as having "insufficient antecedent basis" to support the presence of the terms: "5,7-dioxo" in the first and fourth species, "5-oxo" in the second and fifth species, "6-oxo" in the third, sixth and eleventh species, "5-dioxo" in the seventh and eighth species and "6,7-dioxo"in the ninth and tenth species.

Applicants have canceled claim 16, as noted above, thereby rendering this series of objections moot.

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g) Claim 25: "6-one"

The Examiner has objected to the "limitation '6-one' in the species" in claim 25 as "having insufficient antecedent basis."

Applicants have deleted claim 25, thereby rendering this objection moot. Applicants make this cancellation without prejudice to their right to prosecute the subject matter of canceled claim 25 in related continuation applications.

h) -i) Claim 26: "6-oxo" and double bond at 6-position

The Examiner has objected to the "limitation '6-oxo' in the species" in claim 26 as "having insufficient antecedent basis." In addition, the Examiner has asserted that claim 26 is "vague and indefinite in that it is not known what is means by 2(10),3,6,8,-tetraene where the double bond to the 6 position creates a pentavalent carbon atom.

Applicants have deleted claim 26, thereby rendering this objection moot. Applicants make this cancellation without prejudice to their right to prosecute the subject matter of canceled claim 26 in related continuation applications.

Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1, 2, 8-10 and 14-26 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7-11, 15, 17, 18, 21-24, 27-29 and 32 of co-pending application Ser. No. 09/514,002. The Examiner states that although "the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of the instant invention embrace the compounds of" Ser. No. 09/514,002.

Applicants traverse. The currently pending claims as amended herein do not present any conflict with the claims in co-pending parent application No. 09/514,002. The claims of the present application relate to compounds of formula (I) wherein the R^2 and R^3 groups together with carbon atoms to which they are attached form a ring structure. The claims of co-pending parent application No. 09/514,002 relate solely to those compounds of formula (I) wherein the R^2 and R^3 groups do not together with carbon atoms to which they are attached form a ring structure. Accordingly, in the absence of any conflicting claims, the Examiner is requested to withdraw this obviousness-type double pending rejection.

Applicants believe the present amendments render the set of pending claims in condition for allowance and request the prompt issuance of a Notice of Allowance. If a telephone interview would assist the furtherance of the prosecution of this application, the Examiner is kindly invited to contact the undersigned.

Respectfully submitted,

Date: 11/14/2001

Roy F. Waldron
Registration No. 42,208
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(212) 733-5086

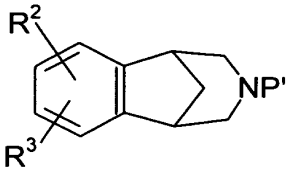
B

APPENDIX TO RESPONSE AND AMENDMENT
USSN 09/402,010

MARKED-UP VERSIONS OF AMENDED CLAIMS - DO NOT ENTER

Please enter claims 14 and 15 amended as set forth below:

14. (Twice Amended) A compound of the formula (I')



(I')

wherein R^2 and R^3 [~~are defined as in claim 1;~~] , together with the carbons to which they are attached, form a four to seven membered monocyclic, or 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 that are selected, independently, 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; nitro, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1 -C_6)alkylamino and ((C_1 -C_6)alkyl)$_2$amino, -CO_2R^4, -$CONR^5R^6$, -$SO_2NR^7R^8$, -$C(=O)R^{13}$ and -$XC(=O)R^{13}$;

wherein 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, piperazine, -N-(C_1-C_6)alkylpiperazine 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;

and P' is $COOR^{16}$ 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 selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; -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; benzyl, or t-butoxycarbonyl (t-Boc).

15. (Amended) A compound according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

~~[7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;~~

~~6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;~~]

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

and pharmaceutically acceptable salts thereof.

B.

8/Suppl. IDS CA 12-8-01

Patent Application
Attorney Docket No. PC10030A

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By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. COE et al.

Examiner: B. Coleman

APPLICATION NO.: 09/402,010

Group Art Unit: 1624

FILING DATE: September 28, 1999

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Commissioner for Patents
Washington, D.C. 20231

Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97 ET SEQ.

Applicant herewith makes available to the U.S. Patent and Trademark Office this Supplemental Information Disclosure Statement pursuant to 37 C.F.R. § 1.98, and a Form PTO-FB-A820 (2x). This Supplemental Information Disclosure Statement contains a listing of references cited in the PCT Search Report (copy enclosed) for International Application No. PCT/IB01/00153 (published as WO 01/62736 A1) (a counterpart of a CIP application of the present application, U.S. Serial No. 09/514,002). References cited on the enclosed Search Report that were previously cited an earlier Information Disclosure Statement (filed December 29, 2000) are not listed in this Statement.

The Examiner is requested to consider carefully the complete text of these references in connection with the examination of the above-identified application in accordance with 37 C.F.R. § 1.104(a). It is believed the Examiner will concur with Applicant's belief that the subject matter presently claimed is neither anticipated nor rendered obvious by the foregoing references.

12/04/2001 MGEBREM1 00000088 161445 09402010
01 FC:126 180.00 CH

Patent Application
Attorney Docket No. PC10030A

It is requested that the references listed on the attached form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing from this application (M.P.E.P. § 1302.12).

The references listed on the PTO-FB-A820 are as follows:

Foreign Patents

EP 1 078 637, published February 28, 2001
EP 0 955 301, published November 10, 1999
WO 00/45846, published August 10, 2000
WO 00/44755, published August 3, 2000
WO 99/55680, published November 4, 1999

A favorable response is earnestly solicited.

Respectfully submitted,

Date: 11/16/2001

Roy F. Waldron
Attorney for Applicant(s)
Reg. No. 42,208

Pfizer Inc
Patent Department
150 East 42nd Street (150/05/49)
New York, NY 10017-5755
(212) 733-5086

INFORMATION DISCLOSURE CITATION *(Use several sheets if necessary)*	ATTY. DOCKET NO. PC10030A	SERIAL NO. 09/402,010
	APPLICANT J. W. COE et al.	
	FILING DATE 09/28/1999	GROUP 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER								DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	EP	1	0	7	8	6	3	7	02/28/01	EPO	A61K	45/06		
	EP	0	9	5	5	3	0	1	11/10/99	EPO	C07D	487/08		
	WO	0	0	4	5	8	4	6	08/10/00	PCT	A61K	45/06		X
	WO	0	0	4	4	7	5	5	08/03/00	PCT	C07D	487/08		
	WO	9	9	5	5	6	8	0	11/04/99	PCT	C07D	221/22		

OTHER DOCUMENTS (*Including Author, Title, Date, Pertinent Pages, Etc.*)

EXAMINER B. COLEMAN

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Conforms with FORM PTO-FB-A820

INFORMATION DISCLOSURE

COPY

Patent Application
Attorney Docket No. PC10030A

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1 EXT of Time (1)
12/8/01

By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe *et al.*

SER. NO.: 09/402,010

FILING DATE: September 28, 1999

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Examiner: B. Coleman

Group Art Unit: 1624

Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. §1.136(a)

Pursuant to the provisions of 37 C.F.R. §§1.7 and 1.136, it is requested that the term for response to the Examiner's Action in this application, mailed on July 25, 2001, and having an original period for response of three months, which expired on October 25, 2001, be extended by one month(s), such that it expires on November 25, 2001.

Authorization is hereby provided to charge the amount of $ 110.00 as stated under 37 C.F.R. §1.17(a)(1), as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,

Date: 11/16/2001

Roy F. Waldron
Attorney for Applicant(s)
Reg. No. 42,208

Pfizer, Inc
Patent Department
150 East 42nd Street (150/05/49)
New York, NY 10017-5755
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12/04/2001 MGEBREM1 00000088 161445 09402010
02 FC:115 110.00 CH

1624/9

Patent Application
Attorney Docket No. PC10030A

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(Signature of person mailing)
ROY F. WALDRON

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: J. W. Coe et al. :

Examiner: B. Coleman

SER. NO.: 09/402,010 :

Group Art Unit: 1624

FILING DATE: September 28, 1999 :

TITLE: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS :

Commissioner for Patents
Washington, D.C. 20231

Sir:

TRANSMITTAL LETTER

Transmitted herewith is [X] a Response and Amendment; [X] a Petition for Extension of Time; [X] a Supplemental Information Disclosure Statement; and [X] a Form PTO-FB-A820 (2x); in the above-identified application.

The fee has been calculated as shown below.

CLAIMS AS AMENDED

(1)	(2) Claims Remaining After Amendment		(3)	(4) Highest Number Previously Paid For		(5) Present Extra	(6) Rate	Additional Fee
Total Claims	15	*	minus	20	**	= 0	X $18.00	0
Independent Claims	2	*	minus	3	***	= 0	X $84.00	0
☐ Multiple Dependent Claim(s) fee							$280.00	0
							TOTAL=	0

* If the entry in column 2 is less than the entry in column 4, write "0" in column 5.
** If the "Highest No. Previously Paid for" is less than 20, write "20" in this space.
*** If the "Highest No. Previously Paid for" is less than 3, write "3" in this space.

☒ No additional fee is required.

B

☒ A **Petition for Extension of Time** for responding within one month(s) of the response date is also enclosed. The Commissioner is authorized to charge the fee pursuant to 37 C.F.R. § 1.17(a)(2) in the amount of **$ 110.00** to Pfizer Deposit Account No. 16-1445. Two copies of this paper are enclosed.

☒ Applicants submit herewith an **Information Disclosure Statement** pursuant to 37 C.F.R. §§ 1.97(c) and 1.98 with accompanying Form PTO-A820 (2x). This Statement is being filed more than three months after the filing date of the application and after the receipt of a First Office Action on the merits, but before the mailing date of either a final action under § 1.113 or a notice of allowance under § 1.311. The Commissioner is hereby authorized to charge the requisite fee under 1.17(p) of **$ 180.00** to Deposit Account No. 16-1445, as well as any other additional fees which may be required under 37 C.F.R. §§ 1.16 and 1.17, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

☐ Please charge Deposit Account No. 16-1445 in the amount of $ _____. Two copies of this paper are enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. §§1.16 and 1.17, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,

Date: 11/16/2001

Roy F. Waldron
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(54) Composition for the treatment and prevention of nicotine addiction containing a nicotine receptor agonist and an anti-depressant or anti-anxiety drug

(57) Pharmaceutical compositions are disclosed for the treatment of nicotine dependence or addiction, tobacco dependence or addiction, reduction of nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The pharmaceutical compositions are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent and a pharmaceutically acceptable carrier. The method of using these compounds is also disclosed.

EP 1 078 637 A2

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Description

Background of the Invention

[0001] The present invention relates to pharmaceutical compositions for the treatment of nicotine dependence or addiction in a mammal (e.g. human) comprising a nicotine receptor partial agonist (NRPA) and an antidepressant or anxiolytic agent. The term NRPA refers to all chemical compounds which bind at neuronal nicotinic acetylcholine specific receptor sites in mammalian tissue and elicit a partial agonist response. A partial agonist response is defined here to mean a partial, or incomplete functional effect in a given functional assay. Additionally, a partial agonist will also exhibit some degree of antagonist activity by its ability to block the action of a full agonist (Feldman, R.S., Meyer, J.S. & Quenzer, L.F. Principles of Neuropsychopharmacology, 1997; Sinauer Assoc. Inc.). The present invention may be used to treat mammals (e.g. humans) for tobacco dependence or addiction and nicotine dependence or addiction; to palliate the effects of nicotine withdrawal and to enhance the outcomes of other smoking cessation therapies.

[0002] The invention also relates to aryl fused azapolycylic compounds that bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function and are referred to in WO 9818798-A1, WO 9935131-A1 and WO 9955680-A1. The foregoing applications are owned in common with the present application and are incorporated herein by reference in their entireties.

[0003] The NRPA compounds that bind to neuronal nicotinic receptor sites can be used in combination with an anti-depressant such as for example, a tricyclic antidepressant (e.g. amitryptyline, imipramine), a serotonin reuptake inhibitor anti-depressant (SRI) (e.g. sertraline, paroxetine, or fluoxetine), an atypical anti-depressant (bupropion, nefazodone), or a monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine) in order to treat the depression associated with addiction such as to nicotine or tobacco, alcohol dependence, cocaine addiction or tobacco or nicotine dependence independently of other psychiatric illness. The compounds that bind to neuronal nicotinic receptor sites can be used in combination with anxiolytic agents, such as for example, a benzodiazepine (e.g. diazepam, alprazolam, chlordiazepoxide) or non-benzodiazepine anxiolytics (e.g. buspirone, hydroxyzine, doxepin) in order to treat the anxiety associated with addiction such as to nicotine or tobacco, alcohol dependence, cocaine addiction or tobacco or nicotine dependence independently of other psychiatric illness.

[0004] Tobacco dependence represents the most important preventable cause of illness and death in our society, responsible for more than 400,000 deaths each year. Half of all smokers will die of diseases directly related to tobacco use, and many smokers will suffer significant morbidity.

[0005] People smoke because of the reinforcing effects of nicotine. Nicotine is a powerful psychoactive agent that activates the same brain pathways as cocaine and other psychostimulants, producing agent-associated tolerance and withdrawal effects.

[0006] Nicotine replacement therapies (NRTs) have been used for smoking cessation. These are available in the form of gum, the transdermal patch, and nasal inhaler. The gum Nicorette® (nicotine polacrilex) delivers nicotine through buccal absorption following chewing. There are also non-nicotine pharmacologic therapies for treating nicotine addiction.

Summary of Invention

[0007] The invention provides a pharmaceutical composition for treating nicotine dependence or addiction, tobacco dependence or addiction, reducing nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The therapeutically effective pharmaceutical combination is comprised of a nicotine receptor partial agonist and an antidepressant or anxiolytic agent and a pharmaceutically acceptable carrier.

[0008] In a more specific embodiment of the invention, the anti-depressant is selected from a tricyclic antidepressant, a serotonin reuptake inhibitor anti-depressant (SRI), an atypical anti-depressant or a monoamine oxidase inhibitor, their pharmaceutically active salts and their optical isomers. In another more specific embodiment of the invention, the anti-depressant is selected from amitryptyline, imipramine, sertraline, paroxetine, fluoxetine, bupropion, nefazodone, phenelzine, tranylcypromine, moclobemide, venlafaxine or a pharmaceutically acceptable salt or their optical isomers thereof. A preferred antidepressant is buproprion hydrochloride or one of its optical isomers.

[0009] In another more specific embodiment of this invention, the nicotine receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4.5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricydo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracydo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2,4(8),6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-5-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;
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;
5,6-dimethyl-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;
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.$0^{2.11}$.$0^{4.9}$]heptade-

ca-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;
5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,6,8-tetraene;
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-triene;
4-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;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-trien-5-ol;
4-nitro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
5-nitro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene; and
6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene and

their pharmaceutically acceptable salts and their optical isomers.

[0010] Preferably, the nicotine receptor partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1.2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydrol 1,5-methano-pyrido [1,2a][1,5]diazocin-8-one;
9-cyano-1,2.3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo [9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,8-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2.10}$.$0^{4.8}$]pentadeca-2(10),3,6,8-tetraene;
10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
11-azatricyclo[7.3.1.$0^{2.7}$]trideca-2(7),3,5-triene-5-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;
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;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2.10}$.$0^{4.8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2.10}$.

$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol and

their pharmaceutically acceptable salts and their optical isomers.

[0011] The invention also provides a method of treating a mammal having a condition which presents with tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction. The mammal is administered a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof, and an antidepressant or anxiolytic agent or a pharmaceutically acceptable salt thereof. The nicotine receptor partial agonist and the anti-depressant or anxiolytic agent are present in amounts that render the composition effective in the treatment of tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction. In a more specific embodiment of the invention, the anti-depressant is selected from a tricyclic anti-depressant, a serotonin reuptake inhibitor anti-depressant, (SRI), an atypical anti-depressant, and a monoamine oxidase inhibitor. In another more specific embodiment of this invention anxiolytic agent is selected from a benzodiazepine or a non-benzodiazepine anxiolytic. In another more specific embodiment of this invention, the anxiolytic agent is a benzodiazepine or a non-benzodiazepine anxiolytic. In a more specific embodiment of the invention, the anxiolytic agent is selected from diazepam, alprazolam, chlordiazepoxide, buspirone, hydroxyzine and doxepin or a pharmaceutically acceptable salt thereof. A preferable anxiolytic is doxepin or a pharmaceutically acceptable salt or optical isomers thereof.

[0012] In another more specific embodiment of this invention the nicotine receptor partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3,1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-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;
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;
5,6-dimethyl-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;
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;
5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
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-triene;
4-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;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3,1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;
4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene and

their pharmaceutically acceptable salts and their optical isomers.

[0013] Preferably, the nicotine receptor partial agonist is selected from