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(54) Title: HETEROCYCLIC COMPOUNDS (57) Abstract The present invention provides heterocyclic 2-aza-bicyclo[2.2.1]heptane compounds which are useful for modulating a muscarinic receptor.		

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HETEROCYCLIC COMPOUNDS

The present invention relates to
5 therapeutically active 2-azabicyclo-2.2.1 compounds
having surprising potency and favorable side effect
profile. The novel compounds are useful as stimulants of
the cognitive function of the forebrain and hippocampus
of mammals.

10

Due to the generally improved health situation
in the western world, elderly-related diseases are much
more common now than in the past and are likely to be
even more common in the future.

15

One of the elderly-related symptoms is a reduction
of the cognitive functions. This symptom is especially
pronounced in the pathophysiological disease known as
Alzheimer's disease. This disease is combined with, and
also most likely caused by, an up to 90% degeneration of the
20 muscarinic cholinergic neurons in nucleus basalis, which is
part of substantia innominata. These neurons project to the
prefrontal cortex and hippocampus and have a general
stimulatory effect on the cognitive functions of the
forebrain as well as of hippocampus, namely learning,
25 association, consolidation, and recognition.

25

It is a characteristic of Alzheimer's disease
that although the cholinergic neurons degenerate, the
postsynaptic muscarinic receptors in the forebrain and
hippocampus still exist. Therefore, muscarinic
30 cholinergic agonists are useful in the treatment of
Alzheimer's disease, in halting its progression, and in
improving the cognitive functions of elderly people.

30

Compounds active at a muscarinic cholinergic
receptor are also useful analgesic agents and therefore
35 are useful in the treatment of severely painful
conditions.

35

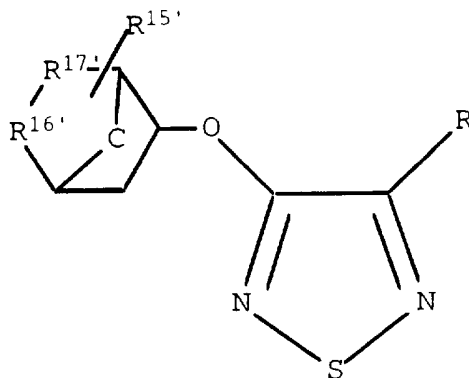
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Furthermore, muscarinic cholinergic receptor active compounds are useful in the treatment of glaucoma, psychosis, anxiety, mania, bipolar disorder, schizophrenia or schizophreniform conditions, depression, sleeping disorders, epilepsy, cerebral ischemia, and gastrointestinal motility disorders.

Therefore, new compounds having muscarinic cholinergic activity are desired. Some muscarinic cholinergic receptor active compounds are associated with side effects attributed to undesired modulation of the muscarinic cholinergic receptors, for example, such undesired modulation may cause excessive salivation and gastrointestinal upset. Thus, the most desired muscarinic cholinergic compounds shall have high potency and at the same time a favorable side effect profile, including a low incidence of excessive salivation.

The presently claimed compounds are surprisingly potent and also provide a favorable side effect profile. The observed characteristics of these compounds suggest that they will be especially desirable muscarinic receptor active compounds which can be useful pharmaceutically active agents.

This invention provides compounds of the formula



R is selected from the group consisting of -OR⁴, -SR⁴, and SO₂R⁴;

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R⁴ is selected from the group consisting of C₁-15-alkyl, C₂-15-alkenyl, C₂-15-alkynyl, fused aromatic, and 5-membered heterocycle; each of which is optionally substituted with one or more independently selected from the group consisting of C₃-C₈ cycloalkyl, halogen(s), -CF₃, -CN, C₁-4 alkoxy, fused aromatic, 5-membered heterocycle, phenyl and phenoxy wherein phenyl, fused aromatic, and phenoxy is optionally substituted with one or more independently selected from the group consisting of halogen, -CN, C₁-4-alkyl, C₁-4-alkoxy, -OCF₃, -CF₃, -CONH₂ and -CSNH₂;

R^{16'} is carbon or nitrogen;

R^{17'} is carbon or nitrogen;

provided that one, and only one, of R^{16'} and R^{17'} must be nitrogen and when R^{16'} is nitrogen then R^{17'} is carbon and when R^{17'} is nitrogen then R^{16'} is carbon;

R^{15'} is selected from the group consisting of hydrogen, C₁-4 alkyl, C₁-4 alkenyl, C₁-4 alkynyl, -C(O)OR^{20'} and C₃-C₈ cycloalkyl;

R^{20'} is C₁-C₆ alkyl; or

a pharmaceutically acceptable salt or solvate thereof.

It is an object of the invention to provide new muscarinic cholinergic compounds having surprising potency and a favorable side effect profile.

It is to be understood that the invention extends to each of the stereoisomeric forms of the compounds of the present invention as well as the pure diastereomeric, pure enantiomeric, and racemic forms of the compounds of this invention.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or

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alleviation of the characteristic symptoms of such condition.

As used herein the phrase "interacting with a muscarinic cholinergic receptor" shall include compounds which block muscarinic cholinergic receptors or modulate such receptors. The phrase shall include the effect observed when compounds act as agonists, partial agonists and/or antagonists at a muscarinic cholinergic receptor.

As used herein, the R^{15'} substituent may be at any position in the azacyclic ring system, including, but not limited to at the bridgehead position and on the nitrogen atom of the ring system.

As used herein, the term "halogen" means Cl, Br, F, and I. Especially preferred halogens include Cl, Br, and I.

As used herein the phrase "one or more selected from" shall more preferredly refer to from 1-3 substituents. The term shall further preferredly refer to from 1-2 substituents.

The terms "C₁-C_{n'} alkyl" wherein n' can be from 2 through 15, as used herein, represent a branched or linear alkyl group having from one to the specified number of carbon atoms. Typical C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

The terms "C₂-C_{n'} alkenyl" wherein n' can be from 3 through 10, as used herein, represents an olefinically unsaturated branched or linear group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, 1-propenyl, 2-propenyl (-CH₂-CH=CH₂), 1,3-butadienyl, (-CH=CHCH=CH₂), 1-butenyl (-CH=CHCH₂CH₃), hexenyl, pentenyl, and the like.

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The term " $C_2-C_{n'}$ alkynyl" wherein n' can be from 3 to 15, refers to an unsaturated branched or linear group having from 2 to n' carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 1-pentynyl, and the like.

The term " C_3-C_n cycloalkyl" wherein $n=4-8$, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term " C_5-C_8 cycloalkenyl" represents an olefinically unsaturated ring having five to eight carbon atoms. Such groups include, but are not limited to, cyclohexyl-1,3-dienyl, cyclohexenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexyl-1,4-dienyl, cycloheptyl-1,4-dienyl, cyclooctyl-1,3,5-trienyl and the like.

As used herein the term "carboxy" refers to a substituent having the common meaning understood by the skilled artisan, wherein the point of attachment may be through the carbon or oxygen atom of the group.

As used herein, the term "optionally substituted" refers to from zero to four substituents, wherein the substituents are each independently selected. More preferably, the term refers to from zero to three independently selected substituents. Each of the independently selected substituents may be the same or different than other substituents.

As used herein the term "aryl" means an organic radical derived from an aromatic hydrocarbon by the removal of one atom; e.g., phenyl or naphthyl. Most preferably, aryl refers to C_6-C_{10} aryl, wherein the aryl ring system, including any alkyl substitutions, comprises from 6 to 10 carbon atoms; e.g., phenyl, 3,3-dimethylphenyl, naphthyl, and the like. The aryl radical may be substituted by one or two C_1-C_6 straight or branched alkyl. The term "aryl(C_1-C_3)alkyl" refers to

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any aryl group which is attached to the parent moiety via the alkyl group.

The phrase "5-membered heterocycle" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles).

10 The term "heterocyclic group" refers to a C₃-C₈ cycloalkyl group containing from one to three heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, and nitrogen.

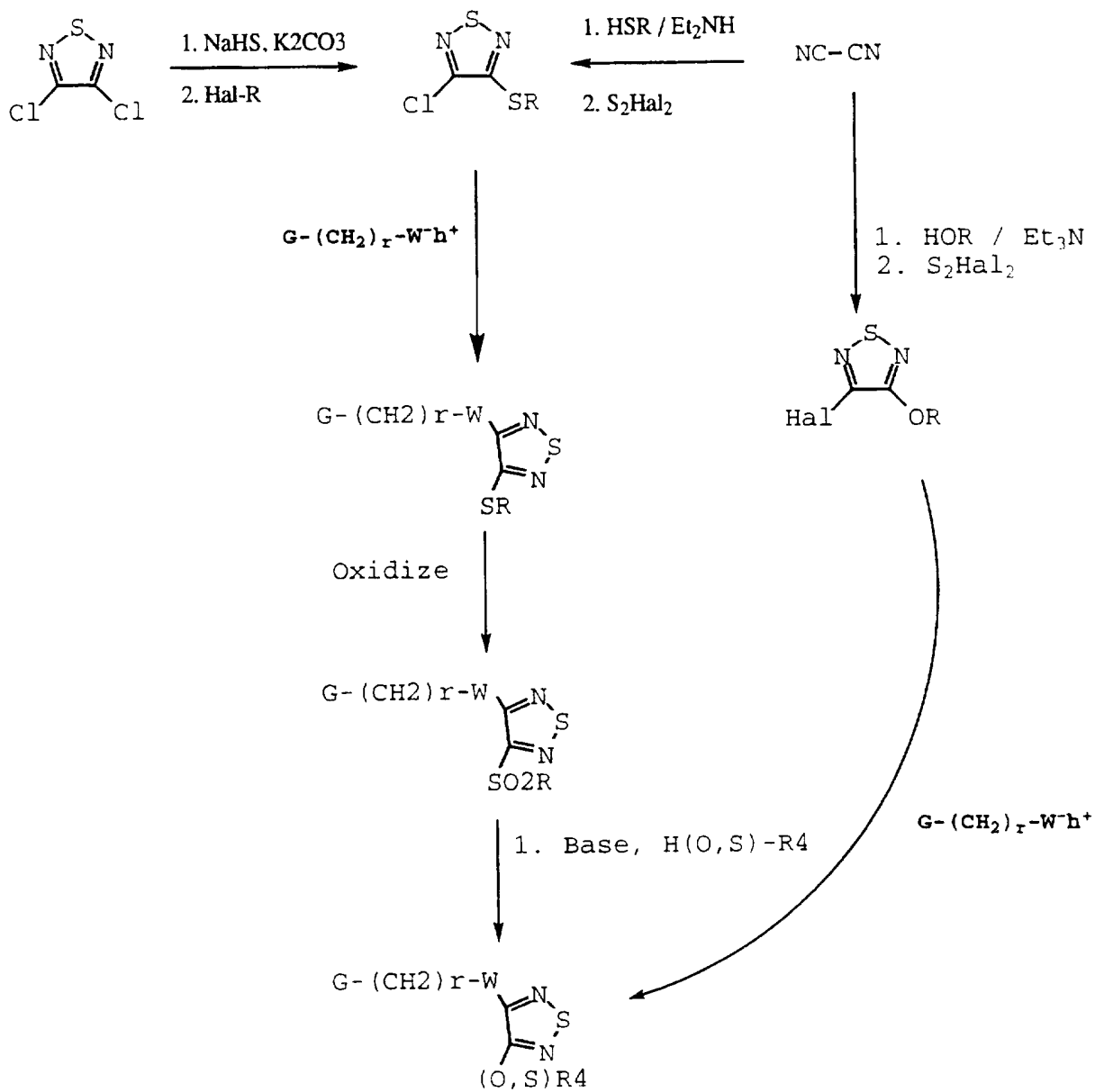
15 The term "fused aromatic" refers to a C₃-C₈ cycloalkyl group or C₃-C₈ heterocyclic group fused to an aryl group, as defined supra. An especially preferred aryl is a phenyl group fused to the heterocyclic group. The fused aromatic may be substituted at any position on the substituent including on the heterocyclic group and
20 on the aromatic group.

 Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate,
25 oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, **66**, 2 (1977) which are known to the skilled artisan. The compounds of this invention may
30 form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

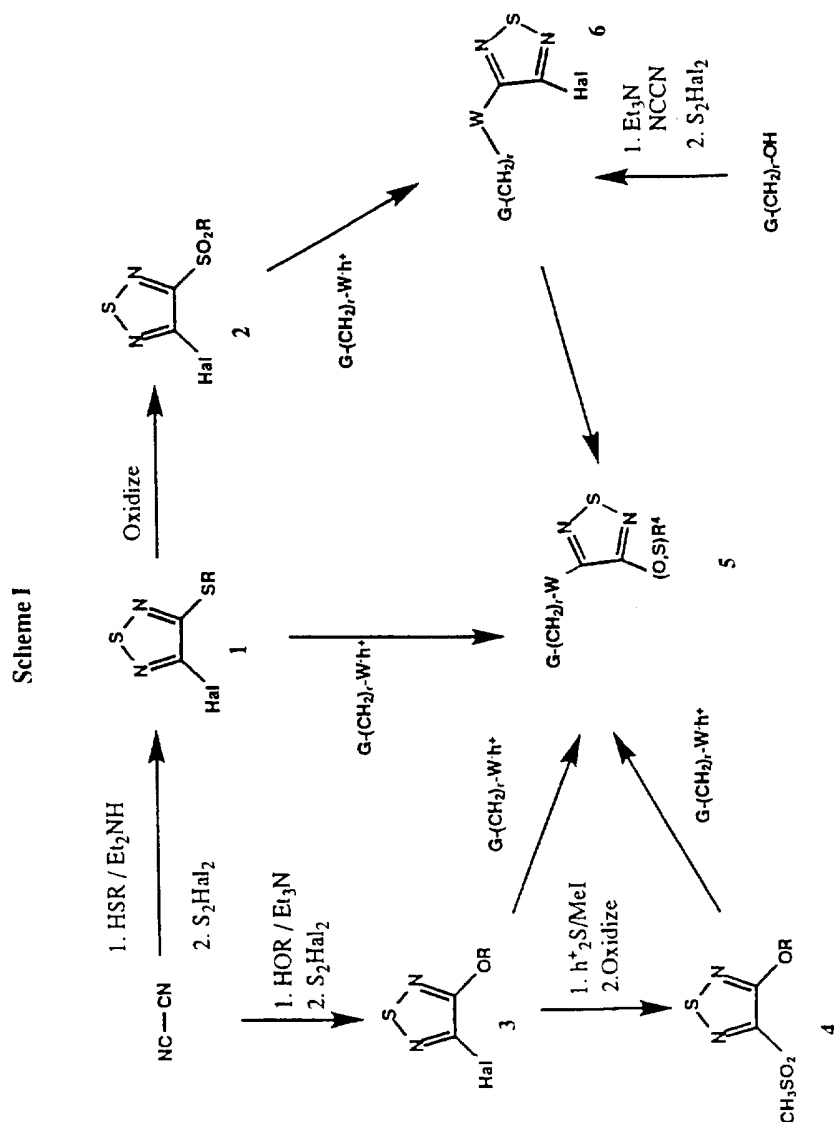
 The compounds of this invention can be prepared using the chemical processes illustrated in Scheme I' and Scheme I. The starting materials for the illustrated
35 process are commercially available or may be prepared using methods known to the skilled artisan.

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SCHEME I
Synthesis Scheme for 2-Aza compounds



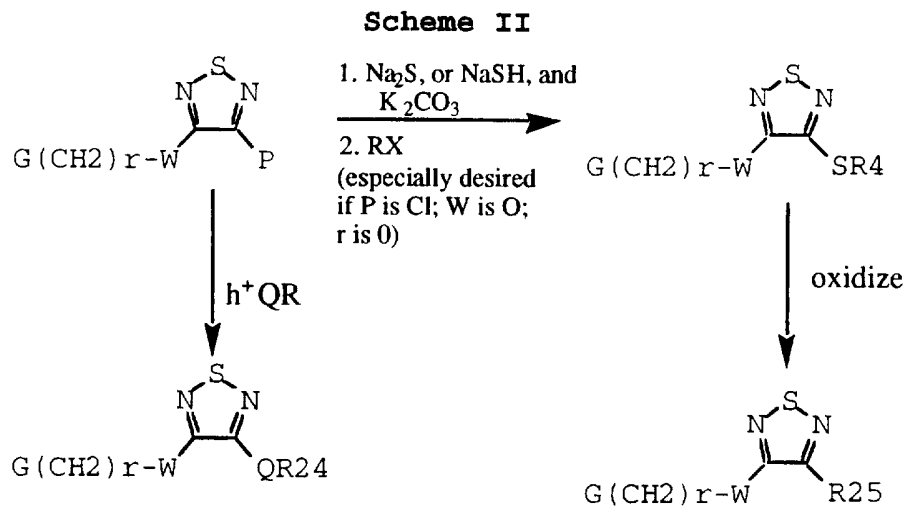
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As used in Scheme I, R, h⁺, and G are as defined *supra*. As used in Scheme I, the term "Hal" refers to Cl, Br, and R⁹SO₂. Preferred oxidizing agents for the process of Scheme I include oxone and sodium periodate. Oxone is an especially preferred oxidizing agent for the process of Scheme I. Compounds of Formula 3, as illustrated in Scheme I wherein the OR group is replaced by an R⁴ group, can be prepared using methods well known in the art. See for example, U.S. Patent Number 5,043,345.

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Further, compounds of Formula I may be prepared using the process illustrated in the following Scheme II

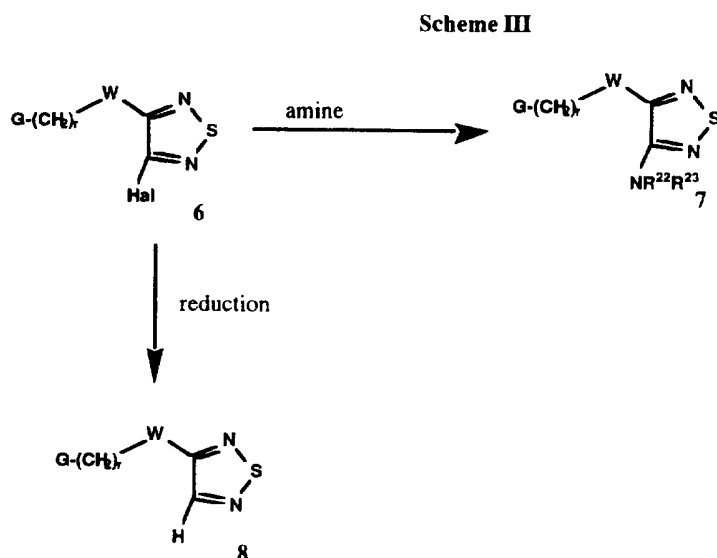


5

As used in Scheme II, Q may be N, O or S; R²⁴ is selected from the group consisting of hydrogen, R⁴, R⁵, R⁶, and R⁷; R²⁵ is selected from the group consisting of SR⁴ and SO₂R⁴; all other meanings are as defined

10 *supra*.

Additional compounds of Formula I may be prepared using the process illustrated by Scheme III.



15

As used in Scheme III, Hal, W, r, and G are as defined *supra*. As used in Scheme III, R²² and R²³ are

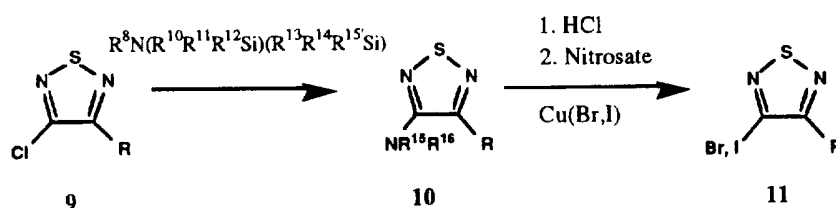
-10-

independently selected from the group consisting of hydrogen, R^6 and R^7 .

Certain intermediates of the present invention may be prepared using the process illustrated in Scheme

5 IV.

Scheme IV



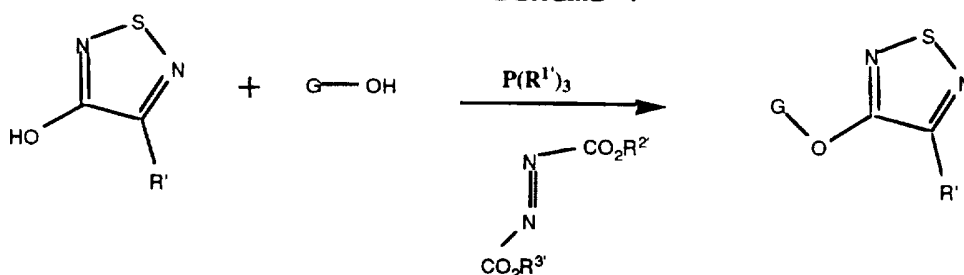
As used in Scheme IV, R⁸, Si, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R^{15'}, R¹⁵ and R¹⁶ are as defined *supra*. For example, R⁸N[(R¹⁰R¹¹R¹²Si)(R¹³R¹⁴R^{15'}Si)] may be, but is not limited to lithium bis(tri-2-propylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium bis(tri-2-propylsilyl)amide, sodium bis(ethyl dimethylsilyl)amide, potassium bis(1-propylethyl methylsilyl)amide, lithium bis(tri-phenylsilyl)amide, sodium bis(tri-phenyl methylsilyl)amide, potassium bis(2-butyl-2-propyl methylsilyl)amide, lithium (tri-2-propylsilyl)(2-butyldiethylsilyl)amide, sodium (trimethylsilyl)(triphenylsilyl)amide, potassium (dimethyl phenylsilyl)(ethyl dimethylsilyl)amide, and the like. Most preferably, R¹⁵ and R¹⁶ are each hydrogen when the process of Scheme III is used for preparing a compound of 11 from a compound of 10. The intermediate 10 may be nitrosated using standard nitrosating procedures. A preferred nitrosating agent is isoamyl nitrite; however, other known nitrosating agents are appropriate. As used in Scheme III, the term "Cu(Br,I)" refers to copper (I) bromide, copper (II) bromide, or copper (I) iodide. The artisan will recognize that the copper (I) bromide, copper (II) bromide, or copper (I)

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iodide reagent shall determine the substitution on the product of the process illustrated in Scheme III.

Certain compounds of this invention may more preferably be prepared by a process using a
 5 hydroxyalkylamine (G-OH) wherein G has the meaning defined *supra*. in the presence of a phosphorus(III) compound and a diester of azodicarboxylate to give the 1,2,5-thiadiazoyloxyalkylamine as illustrated by Scheme V.

Scheme V



10

The G group is 2-aza-bicyclo[2.2.1]heptane.
 The R' is selected from the group consisting of -OR⁴ and -SR⁴
 R⁴ is selected from the group consisting of C₁-15-alkyl,
 15 C₂-15-alkenyl, C₂-15-alkynyl and 5-membered heterocycle,
 each of which is optionally substituted with one or more
 independently selected from the group consisting of
 halogen(s), -CF₃, -CN, Y, phenyl and phenoxy wherein
 phenyl or phenoxy is optionally substituted with one or
 20 more independently selected from the group consisting of
 halogen, -CN, C₁-4-alkyl, C₁-4-alkoxy, -OCF₃, or -CF₃; or
 R' is phenyl or benzyloxycarbonyl, each of which is
 optionally substituted with one or more independently
 selected from the group consisting of halogen, -CN, C₁-4-
 25 alkyl, C₁-4-alkoxy, -OCF₃, and -CF₃; or
 R' selected from the group consisting of -OR⁵Y, -SR⁵Y,
 OR⁵-Z-Y, -SR⁵ZY, -O-R⁵-Z-R⁴ and -S-R⁵-Z-R⁴;
 Z is oxygen or sulphur;
 R⁵ is selected from the group consisting of C₁-15-alkyl,
 30 C₂-15-alkenyl, and C₂-15-alkynyl;
 Y is a 5-membered heterocyclic group;

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R^{1'} is selected from the group consisting of phenyl, C₁-15-alkyl, C₂-5-alkenyl, C₂-5-alkynyl and (NR^{2'})₃;

R^{2'} and R^{3'} are independently selected from the group consisting of hydrogen, C₁-15-alkyl, C₂-5-alkenyl, C₂-5-alkynyl, and C₁-5-alkyl substituted with one or more selected from the group consisting of halogen and phenyl;

W is oxygen or sulphur;

R⁶, and R⁷ independently are C₁-6-alkyl; or

R⁶ and R⁷ together with the nitrogen atom optionally form a 4- to 6-member ring;

R¹ and R² are independently selected from hydrogen, C₁-15-alkyl, C₂-5-alkenyl, C₂-5-alkynyl, C₁-10-alkoxy, and C₁-5-alkyl substituted with one or more independently selected from the group consisting of -COR^{6'}, halogen, and phenyl;

R^{6'} is hydrogen or C₁-C₃ alkyl;

R³ is selected from the group consisting of C₁-5-alkyl, C₂-5-alkenyl and C₂-5-alkynyl;

n is 0, 1 or 2;

m is 0, 1 or 2;

p is 0, 1 or 2;

q is 1 or 2;

r is 0, 1 or 2;

..... is a single or double bond.

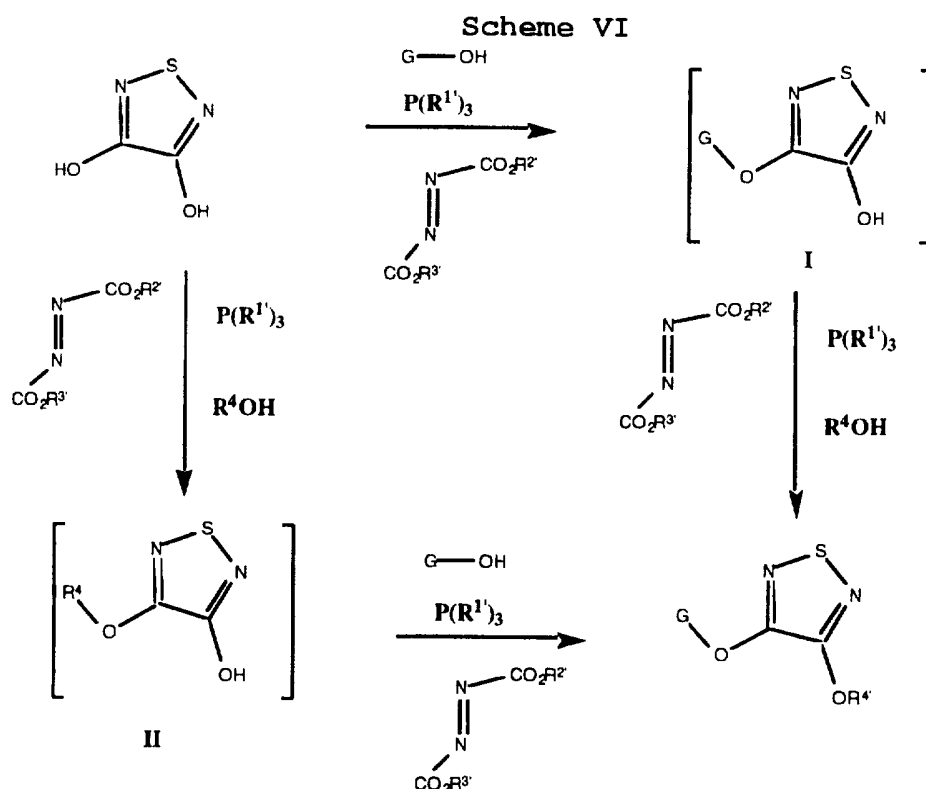
Preferred R^{1'} groups include phenyl, C₁-15-alkyl, and (NR^{2'})₃. The process of Scheme IV is particularly advantageous because the process provides a method for inverting the stereochemistry at the carbon bearing the hydroxyl group in G.

Another new process illustrated by Scheme VI, involves the sequential reaction of 3,4-dihydroxy-1,2,5-thiadiazole with G-OH wherein G is defined as defined *supra*. in the presence of a phosphorous(III) compounds and a diester of azodicarboxylate to give an unisolated hydroxy-1,2,5-thiadiazole ether I'' followed by reaction of I'' with R⁴OH where R⁴ is defined as *supra*. with phosphorous(III)

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compounds and a diester of azodicarboxylate to give the diethers of 3,4-dihydroxy-1,2,5-thiadiazole which are useful as muscarinic agonists and antagonists. (See, *Org. Prep. & Procedures* **1969**, 1, 255-258) The substituents illustrated

5 in Scheme VI are as defined *supra*.



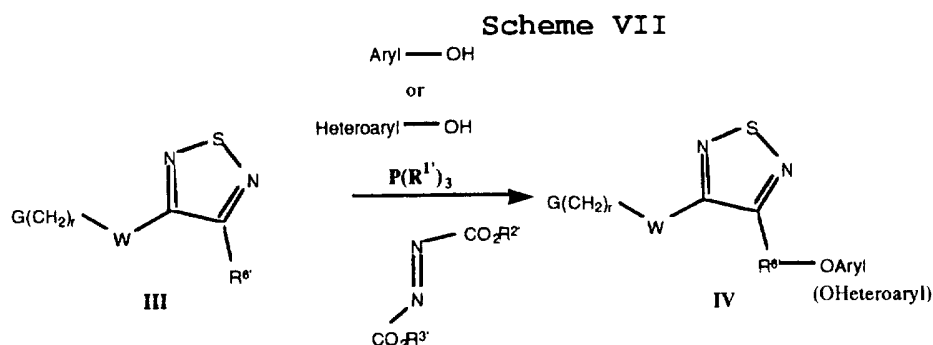
Alternatively, the order of addition of the alcohols may be reversed as shown above to give unisolated

10 hydroxy-1,2,5-thiadiazole ether **II** which is subsequently converted to the same final muscarinic active compound.

The process illustrated by Scheme VII encompasses the reaction of a phenol or hydroxyheteroaryl compound with compound **III** in the presence of a phosphorus(III) compound

15 and a diester of azodicarboxylate to give compound **IV**.

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In compound III, $G(\text{CH}_2)_r\text{W}$ is 2-Aza-

bicyclo[2.2.1]heptane and $\text{R}^{6'}$ is selected from the group

5 consisting of R^7 , $-\text{OR}^7$, $-\text{SR}^7$, $-\text{SOR}^7$, $-\text{SO}_2\text{R}^7$, $\text{C}_3\text{-10-}$
 cycloalkyl, $\text{C}_4\text{-12-}(\text{cycloalkylalkyl})$, $-\text{Z-C}_3\text{-10-cycloalkyl}$ and
 $-\text{Z-C}_4\text{-12-}(\text{cycloalkylalkyl})$;

R^7 is $\text{C}_1\text{-15-alkyl}$, $\text{C}_2\text{-15-alkenyl}$, $\text{C}_2\text{-15-alkynyl}$, each of

10 which is optionally substituted with one or more
 independently selected from the group consisting of
 halogen(s), $-\text{CF}_3$, $-\text{CN}$, Y, phenyl and phenoxy; wherein phenyl
 or phenoxy is optionally substituted with one or more
 selected from the group consisting of halogen, $-\text{CN}$, $\text{C}_1\text{-4-}$
 alkyl, $\text{C}_1\text{-4-alkoxy}$, $-\text{OCF}_3$, and $-\text{CF}_3$;

15 provided that at least one alkyl atom of $\text{R}^{6'}$ is substituted
 with a hydroxyl group or $\text{R}^{6'}$ is a substituent selected from
 the group consisting of $-\text{OR}^8\text{Y}$, $-\text{SR}^8\text{Y}$, $\text{OR}^8\text{-Z-Y}$, $-\text{SR}^8\text{ZY}$, $-\text{O-}$
 $\text{R}^8\text{-Z-R}^7$ and $-\text{S-R}^8\text{-Z-R}^7$ wherein each $-\text{OR}^8\text{Y}$, $-\text{SR}^8\text{Y}$, $\text{OR}^8\text{-Z-Y}$, $-\text{S-}$
 R^8ZY , $-\text{O-R}^8\text{-Z-R}^7$ and $-\text{S-R}^8\text{-Z-R}^7$ is substituted with a

20 alkylhydroxyl;

Y is a 5 or 6 membered heterocyclic group;

Z is oxygen or sulphur;

R^8 is $\text{C}_1\text{-15-alkyl}$, $\text{C}_2\text{-15-alkenyl}$, $\text{C}_2\text{-15-alkynyl}$;

aryl and heteroaryl is optionally substituted with one or

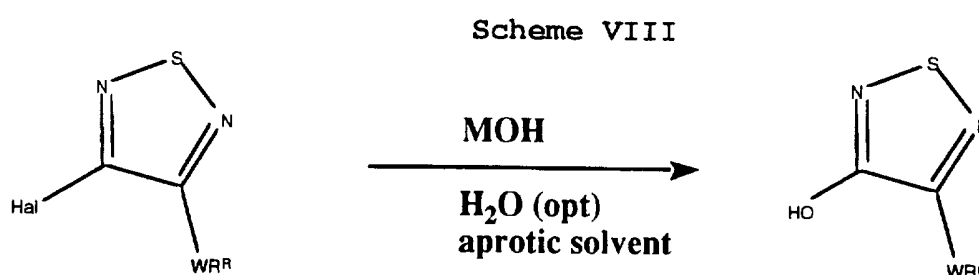
25 more independently selected from the group consisting of
 halogen, $-\text{CN}$, $\text{C}_1\text{-4-alkyl}$, $\text{C}_1\text{-4-alkoxy}$, $\text{C}_1\text{-4-alkylthio}$, $\text{C}_1\text{-4-}$
 alkylsulfone, $\text{C}_1\text{-4-alkylsulfoxide}$, $-\text{OCF}_3$, NO_2 , $\text{N(R}^7)_2$, and $-\text{CF}_3$;
 heteroaryl group is a 5 or 6 membered heterocycle
 containing one to four N, O, or S atoms or a combination

30 thereof.

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Another process of this invention, illustrated by Scheme VIII, is the synthesis of 3-hydroxy-4-alkylthio-1,2,5-thiadiazoles by treating 3-halo-4-alkylthio-1,2,5-thiadiazoles with aqueous alkaline metal hydroxides in the presence or absence of a dipolar aprotic solvent. In this scheme, Hal has the meanings defined *supra*. and M is an alkali metal, W is O or S.

10



R^R is hydrogen, R^4 , C_{3-10} -cycloalkyl, C_{4-12} -(cycloalkylalkyl), R^4 -Z- C_{3-10} -cycloalkyl and R^4 -Z- C_{4-12} -(cycloalkylalkyl); W is oxygen or sulfur;

R^4 is selected from the group consisting of C_{1-15} -alkyl, C_{2-15} -alkenyl, and C_{2-15} -alkynyl, each of which is optionally substituted with one or more independently selected from the group consisting of halogen(s), $-\text{CF}_3$, Y, phenyl and phenoxy; wherein phenyl or phenoxy is optionally substituted with one or more selected from the group consisting of halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, and $-\text{CF}_3$; or

R^R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with one or more selected from the group consisting of halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, and $-\text{CF}_3$; or

R^R is R^4 - OR^5 Y, R^4 - SR^5 Y, R^4 - OR^5 -Z-Y, R^4 - SR^5 ZY, R^4 -O- R^5 -Z- R^4 or R^4 -S- R^5 -Z-;

Z is oxygen or sulphur;

R^5 is selected from the group consisting of C_{1-15} -alkyl, C_{2-15} -alkenyl, and C_{2-15} -alkynyl;

Y is a 5 or 6 membered heterocyclic group; and

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R⁶, and R⁷ independently are hydrogen, C₁₋₆-alkyl, or R⁶ and R⁷ together with the nitrogen atom optionally form a 4- to 6-member ring;

R¹ and R² independently are hydrogen, C₁₋₁₅-alkyl, C₂₋₅-alkenyl, C₂₋₅-alkynyl, C₁₋₁₀-alkoxy, C₁₋₅-alkyl substituted with -OH, -COR^{6'}, CH₂-OH, halogen, -NH₂, carboxy, or phenyl;

R^{6'} is hydrogen or C₁₋₃ alkyl;

W is O or S;

10 Hal is selected from Cl, Br, F, I, and if W is O then Hal may be SO₂R^{4'};

R^{4'} is C₁₋₃ alkyl or phenyl.

The compounds (11) are useful intermediates for the preparation of 1,2,5-thiadiazole compounds. The artisan will recognize that the intermediates 11 are useful for preparing 1,2,5-thiadiazole compounds as illustrated by the processes of Schemes I, II, and III.

When the G substituent contains a secondary nitrogen protected by a protecting group, the protecting group may be removed using standard methods known to the skilled artisan. An especially preferred protecting group is carbamate. One particularly useful reference concerning protecting groups is Greene, Protecting Groups in Organic Synthesis, (John Wiley & Sons, New York, 1981).

The concentration of the reactants is not critical. The art worker can alter the concentration of the reactants to achieve the desired rate of reaction and product yield.

The length of time for carrying out the processes described are not critical. As is always the case in chemistry, the rate of the reaction depends on a variety of factors, such as the temperature and the exact compound which is to be prepared. The course of the reaction may be followed using methods such as thin layer chromatography

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(TLC), high performance liquid chromatography (HPLC), gas chromatography (GC) and nuclear magnetic resonance spectroscopy (NMR) to detect the degree of completion of the reaction. The operator may obtain maximum yields using the process by extending the reaction time. Alternatively, the operator may wish to obtain maximum throughput by cutting off the reaction at the point at which it reaches an economical degree of completion.

When the product of a step in the following process is an oil, it may be isolated by standard methods. Such methods include distillation, flash chromatography, HPLC and the like.

As used herein the term "malfunctioning of the muscarinic cholinergic system" shall have the meaning accepted by the skilled artisan. For example the term shall refer to, but is not in any way limited to, conditions such as glaucoma, psychosis, schizophrenia or schizophreniform conditions, depression, sleeping disorders, epilepsy, and gastrointestinal motility disorders. Other such conditions include Alzheimer's Disease and incontinence.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^3H -Oxotremorine-M (^3H -Oxo). Birdsall N.J.M., Hulme E.C., and Burgen A.S.V. (1980). "The Character of Muscarinic Receptors in Different Regions of the Rat Brain". Proc. Roy. Soc. London (Series B) 207,1.

^3H -Oxo labels muscarinic receptor in the CNS (with a preference for agonist domains of the receptors). Three different sites are labeled by ^3H -Oxo. These sites have affinity of 1.8, 20 and 3000 nM, respectively. Using the present experimental conditions only the high and medium affinity sites are determined.

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The inhibitory effects of compounds on ^3H -oxo binding reflects the affinity for muscarinic acetylcholine receptors.

5 All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-250 g) is homogenized for 5-10 seconds in 10 mL 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 10 mL of
10 buffer and the combined suspension centrifuged for 15 min. at 40,000 x g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 2 x 10 mL of buffer and centrifuged for 10 min. at 40,000 x g.

15 The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 mL per g of original tissue) and used for binding assay. Aliquots of 0.5 mL is added 25 μL of test solution and 25 μL of ^3H -Oxotremorine (1.0 nM, final
20 concentration) mixed and incubated for 30 min. at 25°C. Non-specific binding is determined in triplicate using arecoline (1 $\mu\text{g/mL}$, final concentration) as the test substance. After incubation samples are added 5 mL of ice-cold buffer and poured directly onto Whatman GF/C
25 glass fiber filters under suction and immediately washed 2 times with 5 mL of ice-cold buffer. The amount of radioactivity on the filters are determined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding.

30 Test substances are dissolved in 10 mL water (if necessary heated on a steam-bath for less than 5 min.) at a concentration of 2.2 mg/mL. 25-75% inhibition of specific binding must be obtained before calculation
35 of IC_{50} . The test value will be given as IC_{50} (the

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concentration (nM) of the test substance which inhibits the specific binding of ^3H -oxo by 50%).

$\text{IC}_{50} = (\text{applied test substance concentration}) \times (C_x/C_o - C_x)\text{nM}$ where C_o is specific binding in control assays and
5 C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Furthermore the pharmacological properties of the compounds of the invention can also be illustrated by
10 determining their capability to inhibit $^3\text{HPRZ}$ (pirenzepine, [N-methyl- ^3H]) binding to rat cerebral cortex membranes.

Pirenzepine binds selectively to subtype of
15 muscarinic receptors. Historically the type is named the M_1 -site, whereas pirenzepine sensitive site would be more appropriate. Although selective for M_1 -sites pirenzepine also interact with M_2 -sites.

20 All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-200 g) is homogenized for 5-10 s in 10 mL 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 2 x 10 mL of buffer and
25 the combined suspension centrifuged for 15 min. at 40,000 x g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 3 x 10 mL of buffer and centrifuged for 10 min. at 40,000 x g.

30 The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 mL per g of original tissue) and used for binding assay. Aliquots of 0.5 mL is added 20 μL of test solution and 25 μL of $^3\text{HPRZ}$ (1.0 nM, final conc.), mixed and incubated for 60 min. at 20°C. Non-specific binding
35 is determined in triplicate using atropine (1 $\mu\text{g/mL}$, final conc.) as the test substance. After incubation samples are added 5 mL of ice-cold buffer and poured

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directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 mL of ice-cold buffer. The amount of radioactivity on the filters are

- 5 determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

10 Test substances are dissolved in 10 mL water, at a concentration of 0.22 mg/mL. 25-75% inhibition of specific binding must be obtained before calculation of IC₅₀.

The test value will be given as IC₅₀ (the
15 concentration (nM) of the test substance which inhibits the specific binding of ³HPRZ by 50%).
IC₅₀ = (applied test substance concentration) x (C_x/C₀ - C_x) nM where C₀ is specific binding in control assays and C_x is the specific binding in the test assay. (The
20 calculations assume normal mass-action kinetics).

Additionally, the pharmacological activity and tendency to produce salivation can be determined using the following methods:

25

Stimulation of phosphoinositol hydrolysis in A9 L-m1 cells:

A9-L-m1 cells were cultured to confluence in 75 mL flasks containing Dubecco's modified essential media. Cells were
30 prelabeled with 1 µCi/mL of myo[2-3H]inositol (Amersham Inc, 16.3 Ci/mmol) for 48 h prior to assay. On the day of assay, cells were detached using a 30 s exposure to 0.25% trypsin in 1 mM EDTA. The cells were collected by centrifugation (300xg for 5 min) and resuspended in oxygenated HEPES buffer
35 containing 10 mM LiCl, 142 mM NaCl, 5.6 mM KCl, 2.2 mM CaCl₂, 1 mM MgCl₂, 3.6 mM NaHCO₃, 5.6 mM D-glucose, and 30 mM sodium HEPES at pH 7.4. Cells were incubated at 37 C for

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45 min in the presence of varying concentrations of drug. The reaction was terminated by the addition of 3 mL of ice cold 10 mM LiCl, sonicated, and centrifugated at 20,000xg. The supernatant was decanted over a Accell QMA anion

5 exchange SEP-PAK cartridge in the formate form (Waters Associates, Milford, MA). The cartridges were washed with 10 mL of H₂O followed by 10 mL of 5 mM sodium borate.

[3H]PI was eluted directly into scintillation vials for counting with 4 mL of 0.1 ammonium formate/0.01 mM formic
10 acid/5 mM sodium borate. Data is expressed as the percent of total [3H]PI stimulated in the presence of 1 mM carbachol. Half-maximal values (EC₅₀) were determined from the mean of seven point curves using a four parameter logistic model.

15

Salivation in mice:

Mice weighing 20 to 30 g were used for salivation testing. Mice, in groups of five, were injected i.p. with 10 mg/kg
20 doses of compound dissolved in distilled water. After, 30 min, salivation and tremor were scored on a scale of 0, 1, or 2, where 0 = no effect, 1 = moderate salivation or tremor, and 2 = marked salivation or tremor. Those compounds producing an average score of 1 were tested at
25 half log lower doses until a score lower than 1 was achieved. The lowest dose of compound producing a score of 1 was expressed at the minimum effective dose (MED).

Table I illustrates several additional formula
30 I compounds as claimed herein.

35

Table I

R	R ⁴	R	R ⁴
OR ⁴	phenyl	SR ⁴	phenyl
OR ⁴	methoxyphenyl	SR ⁴	methoxyphenyl
OR ⁴	fluorophenyl	SR ⁴	fluorophenyl
OR ⁴	chlorophenyl	SR ⁴	chlorophenyl
OR ⁴	trifluoromethylphenyl	SR ⁴	trifluoromethylphenyl
OR ⁴	N-alkylthiazolidinones	SR ⁴	N-alkylthiazolidinones
OR ⁴	N-alkyloxazolidinones	SR ⁴	N-alkyloxazolidinones
OR ⁴	S-alkylmercaptothiophenes	SR ⁴	S-alkylmercaptothiophenes
OR ⁴	benzothiophenemethyl	SR ⁴	benzothiophenemethyl
OR ⁴	1,4-benzodioxanmethyl	SR ⁴	1,4-benzodioxanmethyl
OR ⁴	decahydronaphthyl	SR ⁴	decahydronaphthyl
OR ⁴	tetrahydronaphthyl	SR ⁴	tetrahydronaphthyl
OR ⁴	chromanyl	SR ⁴	chromanyl
OR ⁴	allyl	SR ⁴	allyl
OR ⁴	(alkyl)allyl	SR ⁴	(alkyl)allyl
OR ⁴	cinnamyl	SR ⁴	cinnamyl
OR ⁴	phenylpropargyl	SR ⁴	phenylpropargyl
OR ⁴	methoxyphenylpropargyl	SR ⁴	methoxyphenylpropargyl
OR ⁴	fluorophenylpropargyl	SR ⁴	fluorophenylpropargyl
OR ⁴	chlorophenylpropargyl	SR ⁴	chlorophenylpropargyl
OR ⁴	trifluoromethoxyphenylpropargyl	SR ⁴	trifluoromethoxyphenylpropargyl
OR ⁴	trifluoromethylphenylpropargyl	SR ⁴	trifluoromethylphenylpropargyl
OR ⁴	indanyl	SR ⁴	indanyl
OR ⁴	methoxyindanyl	SR ⁴	methoxyindanyl
OR ⁴	fluoroindanyl	SR ⁴	fluoroindanyl
OR ⁴	chloroindanyl	SR ⁴	chloroindanyl
OR ⁴	trifluoromethoxyindanyl	SR ⁴	trifluoromethoxyindanyl
OR ⁴	trifluoroindanyl	SR ⁴	trifluoroindanyl
OR ⁴	cyclopropylvinyl	SR ⁴	cyclopropylvinyl
OR ⁴	cyclobutylvinyl	SR ⁴	cyclobutylvinyl
OR ⁴	cyclopentylvinyl	SR ⁴	cyclopentylvinyl
OR ⁴	cyclohexylvinyl	SR ⁴	cyclohexylvinyl
OR ⁴	phenoxyalkyl	SR ⁴	phenoxyalkyl
OR ⁴	fluorophenoxyalkyl	SR ⁴	fluorophenoxyalkyl
OR ⁴	chlorophenoxyalkyl	SR ⁴	chlorophenoxyalkyl
OR ⁴	trifluoromethylphenoxyalkyl	SR ⁴	trifluoromethylphenoxyalkyl
OR ⁴	trifluoromethoxyphenoxyalkyl	SR ⁴	trifluoromethoxyphenoxyalkyl
OR ⁴	methoxyphenoxyalkyl	SR ⁴	methoxyphenoxyalkyl

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The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients suffering from diseases in the central nervous system caused by malfunctioning of the muscarinic cholinergic system it may frequently be necessary to begin with a dosage of from about 20 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or prescribing caregiver in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, depot, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper,

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or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

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Generally, the compounds are dispensed in unit form comprising from about 0.1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

5

The compounds of this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferred, the animal is a vertebrate. Most preferred, a compound of this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. The most preferred mammal is a human. For such purposes, a compound of this invention may be administered as a feed additive.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention in any way.

Formulation 1

A typical tablet, appropriate for use in this method, may be prepared using conventional techniques and may contain:

	Amount per Tablet	Concentration by Weight (%)
30 (1S,4R,6S)-(2-aza-((4-cyclobutylethoxy- 1,2,5-thiadiazol-3-yl)oxy) bicyclo[2.2.1]- heptane	5.0 mg	4.7
Lactosum	67.8 mg Ph. Eur.	64.2
35 Avicel®	31.4 mg	29.8
Amberlite®	1.0 mg	1.0
magnesium stearate	<u>0.25 mg</u>	<u>0.3</u>

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105.45 mg

100

Formulation 2

Hard gelatin capsules are prepared using the
 5 following ingredients:

	Amount per Tablet	Concentration by Weight (%)
(1S,4R,6S)-(2-aza-((4-cyclopropylmethoxy- 10 1,2,5-thiadiazol-3-yl)oxy) bicyclo[2.2.1]- heptane	0.1 mg	0.05
starch dried	200 mg	95.2
magnesium stearate	<u>10 mg</u>	<u>4.8</u>
15	210.1 mg	100

The above ingredients are mixed and filled into
 hard gelatin capsules in 210.1 mg quantities.

20

Formulation 3

Suspensions each containing 1 mg of medicament
 per 5 mL dose are as follows:

	Amount per 5mL of <u>suspension</u>
25 (1S,4R,6S)-2-aza-((4-(3-chlorophenylmethylthio) 1,2,5-thiadiazol-3-yl)oxy) bicyclo[2.2.1]- heptane	1 mg
sodium carboxymethyl cellulose	50 mg
30 syrup	1.25 mL
benzoic acid solution	0.10 mL
flavor	q.v
color	q.v.
water	q.s. to 5 mL
35	

The medicament is passed through a No. 45 mesh
 U.S. sieve and mixed with the sodium carboxymethyl

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cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring.

5 Sufficient water is then added to produce the required volume.

The intermediates and processes of the present invention are useful for preparing compounds having beneficial muscarinic receptor activity. The compounds of the present invention have such useful muscarinic receptor
10 activity. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The
15 following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

Some preferred characteristics of compounds of formula I are:

- 20 A) R is OR⁴;
B) R is SR⁴;
C) R⁴ is methyl substituted with cyclobutyl;
D) R⁴ is C₃-C₆ alkyl;
E) R⁴ is 5-membered heterocycle having one
25 heterocycle selected from S and N;
F) R⁴ is C₃-C₆ alkenyl;
G)

The invention will now be described in further
30 detail with reference to the following examples. The examples are provided for illustrative purposes, and are not to be construed as limiting the scope of the invention in any way.

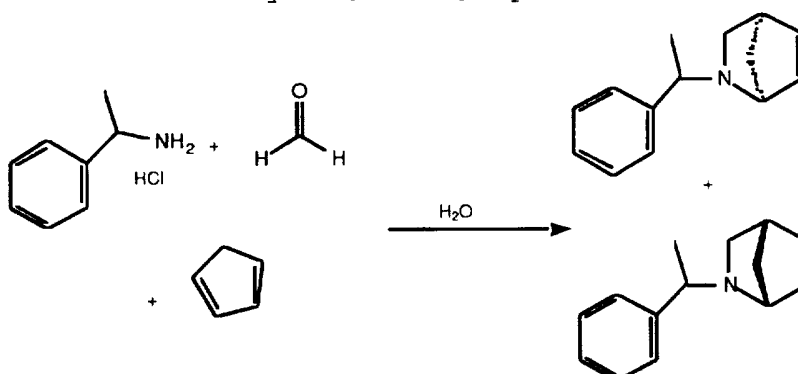
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Preparation 1

(1S,4R,1'R)-2-(1'-Phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene
and (1R,4S,1'R)-2-(1'-Phenylethyl)-2-

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azabicyclo[2.2.1]hept-5-ene



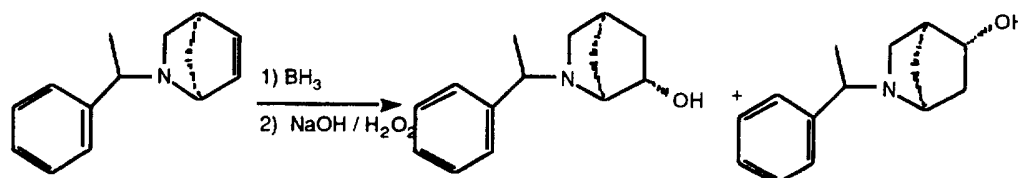
37% Aqueous formaldehyde (773.4mmol) was added to a solution
 5 of cyclopentadiene (1.105mol) and (R)-1-phenylethylamine
 hydrochloride (552.4mmol) at 0_C. The solution was stirred
 at 0_C for 24 hours. Water (350mL) was added to the
 reaction which was then washed with diethyl ether (2x250mL).
 The aqueous layer was basified with solid potassium
 10 hydroxide then extracted with ethyl acetate (3x400mL). The
 combined extracts were dried over magnesium sulfate,
 evaporated, then purified by preparative HPLC using silica
 gel eluting with 2 to 20% (10% triethylamine in ethanol) in
 ethyl acetate to yield (1S,4R,1'R)-2-(1'-phenylethyl)-2-
 15 azabicyclo[2.2.1]hept-5-ene(64.9g/326.1mmol) and
 (1R,4S,1'R)-2-(1'-phenylethyl)-2-azabicyclo[2.2.1]hept-5-
 ene(22g/110.6mmol).

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Preparation 2

(1S,4R, 6S, 1'R)-2-(1'-Phenylethyl)-2-azabicyclo[2.2.1]heptan-6-ol and (1S,4R, 6S, 1'R)-2-(1'-Phenylethyl)-2-azabicyclo[2.2.1]heptan-5-ol

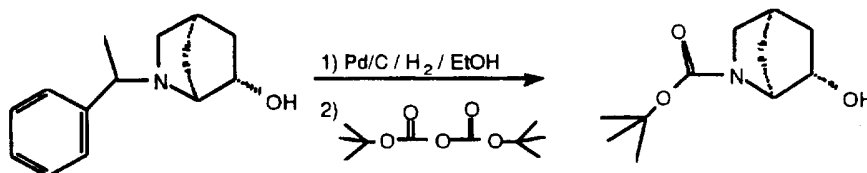
5



A 1.0M Borane:THF in tetrahydrofuran (628mmol) was added to a solution of (1S,4R,1'R)-2-(1'-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene (316.6mmol) in tetrahydrofuran (750mL) at 0_C. Stirred at 0_C for 2 hours whereupon water in tetrahydrofuran was added to the reaction to destroy excess borane. While keeping the reaction temperature below 10_C, 3N Aqueous sodium hydroxide (88mL) was added to the reaction immediately followed by 30% aqueous hydrogen peroxide (147mL). The reaction temperature was allowed to rise to 40_C then stirred for 1.5 hours. Potassium carbonate (30g) was added to the reaction then evaporated to remove the tetrahydrofuran. The aqueous residue was extracted with dichloromethane (3x200mL). The organic extracts were washed with water then dried over sodium chloride/sodium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 1 to 15% (10% triethylamine in ethanol) in ethyl acetate to yield (1S,4R, 6S, 1'R)-2-(1'-phenylethyl)-2-azabicyclo[2.2.1]heptan-6-ol (32.5g/149.8mmol) and (1S,4R, 6S, 1'R)-2-(1'-phenylethyl)-2-azabicyclo[2.2.1]heptan-5-ol (9.9g/45.6mmol).

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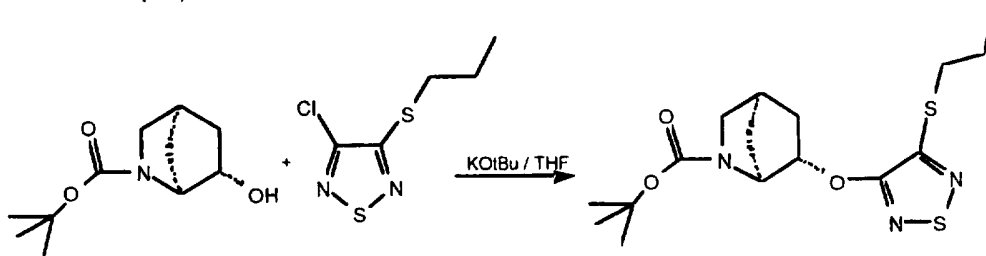
Preparation 3
(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-
bicyclo[2.2.1]heptan-6-ol



- 5 A solution of (1S,4R, 6S, 1'R)-2-(1'-phenylethyl)-2-azabicyclo[2.2.1]heptan-6-ol (30mmol) in ethanol (150mL) was hydrogenated with 10% Pd/C (3.3g) at 60 PSIG of hydrogen at room temperature for 16 hours. The catalyst was filtered off and the filtrate was evaporated. A solution of the
 10 filtrate in tetrahydrofuran (100mL) and H₂O (50mL) was cooled to 0°C. The pH was adjusted to 10 with 5N aqueous sodium hydroxide. Di-*t*-butylcarbonate (45mmol) was added to the reaction solution while the pH was maintained >10 with 5N aqueous sodium hydroxide. The reaction was stirred at
 15 0°C for four hours, poured into brine, extracted with ethyl acetate (3x150mL), dried over sodium chloride/sodium sulfate, then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 25 to 100% ethyl acetate in hexanes to yield (1S,4R, 6S)-2-Aza-2-(*t*-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (30mmol).
 20

Example 1

(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



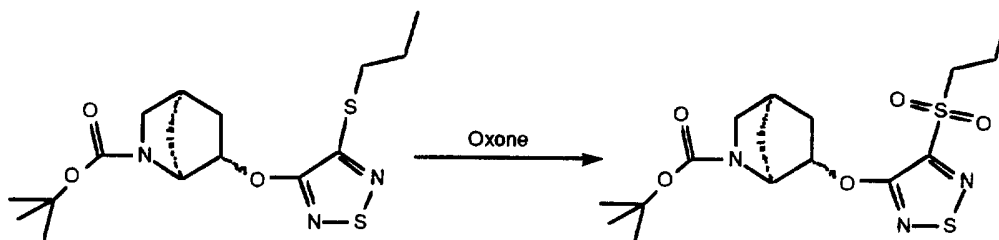
- 25 Potassium *t*-butoxide (39mmol) was added to a solution of (1S,4R, 6S)-2-Aza-2-(*t*-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (30mmol) in tetrahydrofuran (500mL). Stirred at -5°C for 45 minutes whereupon 3-chloro-4-(propylthio)-1,2,5-

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thiadiazole(36mmol) in tetrahydrofuran (100mL) was added to the reaction. Stirred for four hours at -5_C. The reaction mixture was poured into brine and extracted with ethyl acetate (3x250mL). The organic extracts were dried and evaporated. The residue was purified by preparative HPLC using silica gel eluting with 10 to 50% ethyl acetate in hexanes to yield (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane(4.7g/12.7mmol).

Example 2

(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

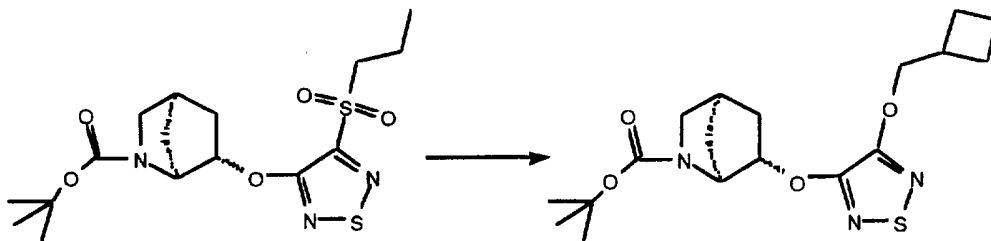


A solution of Oxone®(24.2g/39.3mmol) in water(75mL) was added to a solution of (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (4.7g/12.7mmol), water (25mL), and tetrahydrofuran (75mL). Stirred at room temperature for 16 hours. The reaction was poured into water then extracted with ethyl acetate (3x150mL). The organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then evaporated to yield **LY354006**, (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (4.7g/11.7mmol).

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Example 3

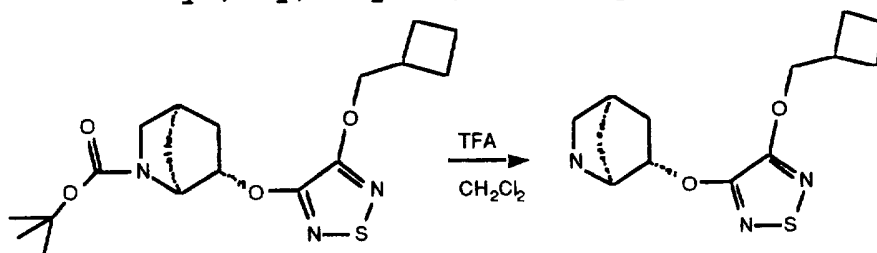
(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium butoxide (7.8mmol) was added to a solution of cyclobutylmethanol (10.2mmol) and tetrahydrofuran (75mL) at 0°C. The reaction was stirred for 1 hour at 0°C. (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5mmol) in tetrahydrofuran (25mL) was added to the reaction. The reaction was stirred for 2 hours at 0°C. The reaction was poured into brine then extracted with ethyl acetate (3x100mL). The extracts were dried over magnesium sulfate then evaporated to yield (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5mmol).

Example 4

(1S,4R, 6S)-2-Aza-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Trifluoroacetic acid (2.5mL) was added to a solution of (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5mmol) in methylene chloride (40mL) at 0°C. The reaction was stirred at 0°C for about

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one hour then warmed to room temperature and stirred for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield (1S,4R, 6S)-2-Aza-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 540mg of the desired compound (mp = 154-156_C).

Example 5

The following compounds were made by following substantially the same procedure described above in Example 4, except that the corresponding starting materials were selected to provide the desired compounds.

(1S,4R, 6S)-2-Aza-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY354893**, mp 122-123_C.

(1S,4R, 6S)-2-Aza-((4-(diphenylmethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368585**, mp 168-171_C.

(1S,4R, 6S)-2-Aza-((4-propoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY354166**, mp 181-182_C.

(1S,4R, 6S)-E-2-Aza-((4-(3-phenylprop-2-eneoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY354735**, mp 191-192_C.

(1S,4R, 6S)-2-Aza-((4-(3,3,3-trifluoropropoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY355169**, mp 144-145_C.

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- (1S,4R, 6S)-2-Aza-((4-cyclopentoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357209**, mp 200-202_C.
- 5 (1S,4R, 6S)-2-Aza-((4-cyclohexoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357633**, mp 193-195_C.
- (1S,4R, 6S)-2-Aza-((4-(1-methylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357817**, mp 179-180_C.
- 10
- (1S,4R, 6S)-2-Aza-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357834**, mp 171-173_C.
- 15
- (1S,4R, 6S)-2-Aza-((4-(2-methylpropoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357878**, mp 146-148_C.
- 20
- (1S,4R, 6S)-2-Aza-((4-cyclobutoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357879**, mp 204-206_C.
- 25
- (1S,4R, 6S)-2-Aza-((4-heptoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY357880**, mp 186-187_C.
- (1S,4R, 6S)-2-Aza-((4-(3-methylbutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359056**, mp 167-168_C.
- 30
- (1S,4R, 6S)-2-Aza-((4-cyclohexylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359166**, mp 168-169_C.
- 35

-35-

(1S,4R, 6S)-2-Aza-((4-cyclopentylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359167**, mp 169-170_C.

5 (1S,4R, 6S)-2-Aza-((4-(2-cyclohexylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359491**, mp 169-171_C.

10 (1S,4R, 6S)-2-Aza-((4-(2-oxetane-2-methylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359684**, mp 115-118_C.

15 (1S,4R, 6S)-2-Aza-((4-cycloheptylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359686**, mp 183-185_C.

Example 6

Substantially the same procedure described above in Example 4 was used to make the following compounds, except (S)-1-phenylethylamine hydrochloride was used as the starting material.

25 (1R,4S,6R)-2-Aza-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY353547**, mp 142-44_C.

30 (1R,4S,6R)-2-Aza-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY353548**, mp 112-115_C.

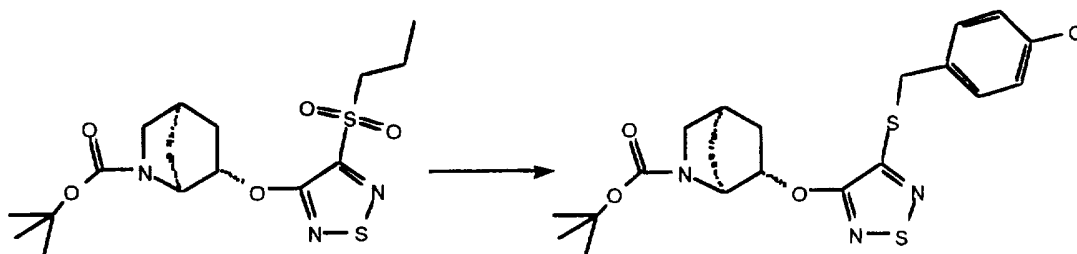
(1R,4S,6R)-2-Aza-((4-propoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY354398**, mp 177-179_C.

35 (1R,4S,6R,1'R,4'S,6'R)-3,4-Di-((2-azabicyclo[2.2.1]heptan-6-yl)oxy)-1,2,5-thiadiazole, **LY359681**, mp 186_C.

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Example 7

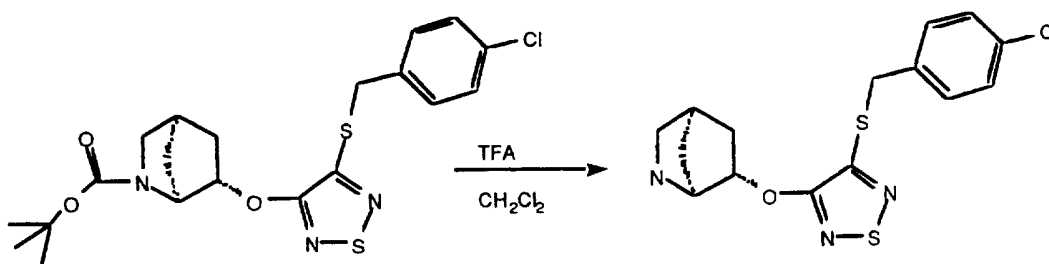
(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-(4-chlorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



5 Sodium sulfide nonahydrate (3.9mmol) was added to a solution of (1S,4R, 6S)-2-aza-2-(t-butoxycarbonyl)--6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5mmol) in dimethylformamide
 10 (20mL). The reaction was heated at 100_C for one hour whereupon 4-chlorobenzyl chloride (3.9mmol) in dimethylformamide (5mL) was added to the reaction then heated at 100_C for an additional three hours. The reaction was poured into brine then extracted with ethyl acetate
 15 (3x75mL). The organic extracts were dried over magnesium sulfate then evaporated. The residue was purified by radial chromatography using silica gel eluting with 20% ethyl acetate in hexanes to yield (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)--6-((4-(4-chlorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.9g/2.0mmol).
 20

Example 8

(1S,4R, 6S)-2-Aza-((4-(4-chlorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



25

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Trifluoroacetic acid (2.0mL) was added to a solution of (1S,4R, 6S)-2-Aza-((4-(4-chlorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.0mmol) in methylene chloride (40mL) at 0_C. The reaction was stirred at 0_C for one hour then warmed to room temperature and stirred for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield (1S,4R, 6S)-2-aza-((4-(4-chlorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 620mg of **LY359057** (mp = 211-212_C).

Example 9

The following compounds were prepared using substantially the same procedure as described above in Example 8.

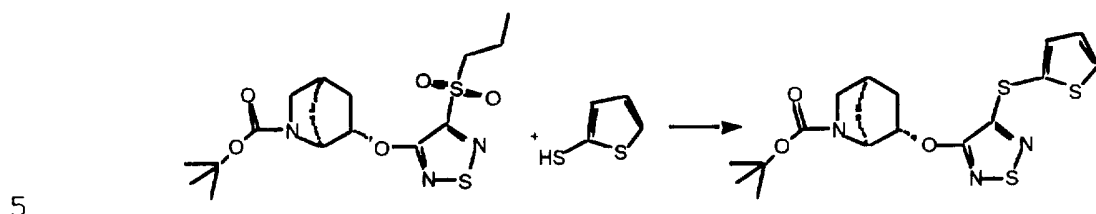
(1S,4R, 6S)-2-Aza-((4-cyclobutylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359058**, mp 144-146_C.

(1S,4R, 6S)-2-Aza-((4-(4-fluorophenylmethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359683**, mp 165-169_C.

(1S,4R, 6S)-2-Aza-((4-(2-cyclopropylethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359685**, mp 121-123_C.

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(1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

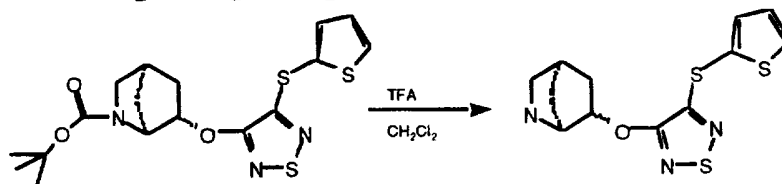


Potassium carbonate (2.1mmol) was added to a solution 2-mercaptothiophene (4.0mmol) in dimethylformamide (25mL) heated at 75_C. Stirred for one hour whereupon (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.0mmol) in dimethylformamide (5mL) was added to the reaction and stirred for sixteen hours at 75_C. The reaction was poured into brine then extracted with ethyl acetate (3x75mL). The organic extracts were dried over magnesium sulfate then evaporated. The residue was purified by radial chromatography using silica gel eluting with 25% ethyl acetate in hexanes to yield (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.26g/0.6mmol).

20

Example 11

(1S,4R, 6S)-2-Aza-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



25 Trifluoroacetic acid (0.6mL) was added to a solution of (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.6mmol) in methylene chloride (50mL). The reaction was stirred at room temperature for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was

30

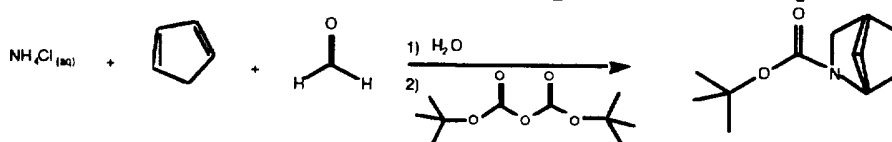
-39-

basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield (1S,4R, 6S)-2-Aza-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 140mg of **LY359682** (mp = 174-180_C).

10 **[exo] 2-Aza-2-(t-butoxycarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane**

Preparation of:

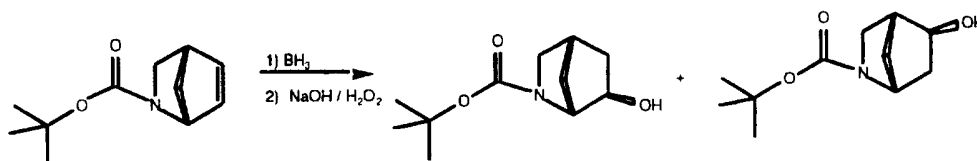
2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene



15 Cyclopentadiene (1.20mol) was added to a solution of saturated aqueous ammonium chloride (257mL) and 37% aqueous formaldehyde (0.84mol). The solution was stirred at room temperature for 16 hours. Water (130mL) was added to the reaction then washed with diethyl ether (2x150mL). The aqueous layer was basified with solid potassium hydroxide. Di-t-butyl dicarbonate (1.00mol) was added to the aqueous layer while maintaining the pH between 9.5 and 10. Stirred overnight at room temperature. The reaction was extracted with ethyl acetate (3x500mL). The combined extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated. The residue was purified by preparative HPLC over silica gel eluting with 25 to 75% ethyl acetate in hexanes to yield 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene (62g/318mmol).

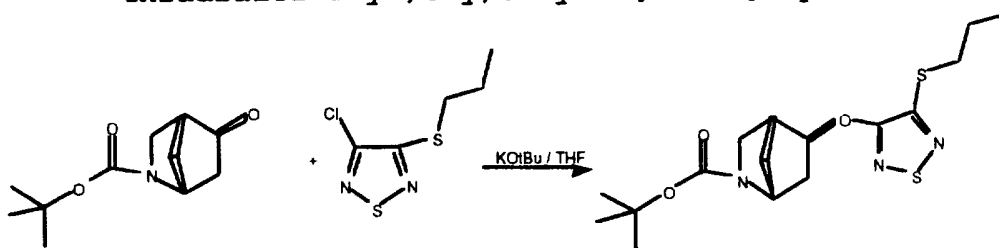
20 **[exo] 2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol**
and [exo] 2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol

-40-



1.0M Borane:THF in tetrahydrofuran (626mmol) was added to a solution of 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene (315mmol) in tetrahydrofuran (700mL) at 0_C. Stirred at 0_C for 2 hours whereupon water in tetrahydrofuran was added to the reaction to destroy excess borane. While keeping the reaction temperature below 10_C, 3N Aqueous sodium hydroxide (88mL) was added to the reaction immediately followed by 30% aqueous hydrogen peroxide (148mL). The reaction temperature was allowed to rise to 40_C then stirred for 1.5 hours. Potassium carbonate (30g) was added to the reaction then evaporated to remove the tetrahydrofuran. The aqueous residue was extracted with dichloromethane. The organic extracts were washed with a saturated sodium chloride solution then dried over sodium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 10 to 75% ethyl acetate in hexanes to yield [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol (14.0g/65.7mmol) and [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (14.5g/68.1mmol).

[exo] 2-Aza-2-(t-butoxycarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium t-butoxide (56.3mmol) was added to a solution of [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol (56.3mmol) in tetrahydrofuran (550mL) at room temperature. Stirred for one hour whereupon the reaction was cooled to -10_C and 3-chloro-4-propylthio-1,2,5-thiadiazole (13.1/67.6mmol) in tetrahydrofuran (50mL). The reaction was

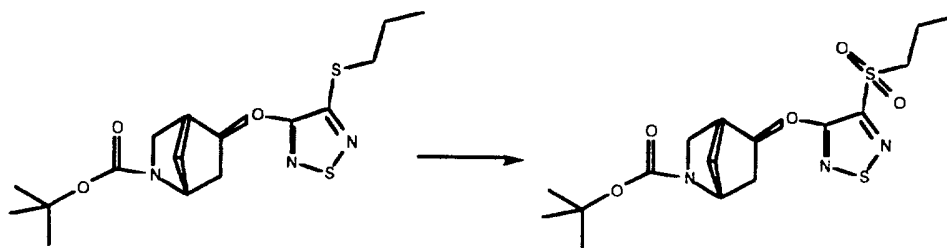
-41-

stirred at -10_C for four hours then the reaction was poured into brine then extracted with ethyl acetate (3x500mL). The combined organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then
 5 evaporated. The residue was purified by preparative HPLC using silica gel eluting with 15 to 60% ethyl acetate in hexanes to yield [exo] 2-aza-2-(t-butylcarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (5.3g/14.3mmol).

10

Example 13

[exo] 2-Aza-2-(t-butoxycarbonyl)-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



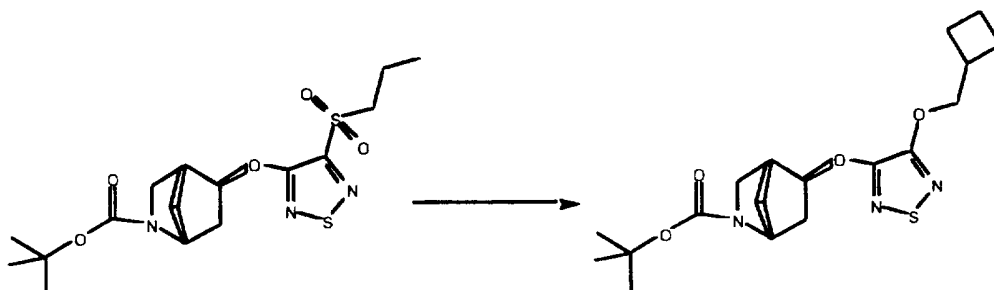
15 A solution of Oxone® (26.4g/14.3mmol) in water (120mL) was added to a solution of [exo] 2-aza-2-(t-butylcarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (4.7g/12.7mmol) and tetrahydrofuran (80mL). Stirred at room temperature for 16
 20 hours. The reaction was poured into water then extracted with ethyl acetate (3x150mL). The organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then evaporated to yield [exo] 2-aza-2-(t-butoxycarbonyl)-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (5.5g/14.3mmol).
 25

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Example 14

[*exo*]2-Aza-2-(*t*-butoxycarbonyl)-5-((4-cyclobutylmethylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

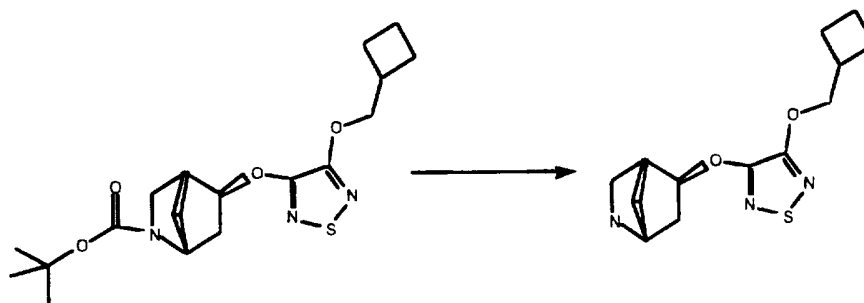


5 Potassium butoxide (6.0mmol) was added to a solution of cyclobutylmethanol (7.0mmol) and tetrahydrofuran (75mL) at 0°C. The reaction was stirred for 1 hour at 0°C. [*exo*] 2-Aza-2-(*t*-butoxycarbonyl)-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.0mmol) in
 10 tetrahydrofuran (25mL) was added to the reaction. The reaction was stirred for 2 hours at 0°C. The reaction was poured into brine then extracted with ethyl acetate (3x100mL). The extracts were dried over magnesium sulfate then evaporated to yield [*exo*] 2-aza-2-(*t*-butoxycarbonyl)-5-
 15 ((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5mmol).

Example 15

[*exo*]2-Aza-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

20



Trifluoroacetic acid (2.0mL) was added to a solution of [*exo*]-2-aza-2-(*t*-butoxycarbonyl)-5-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.0mmol) in
 25 methylene chloride (50mL) at 0°C. The reaction was stirred

-43-

at 0_C for one hour then warmed to room temperature and stirred for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield [exo]-2-aza-5-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 540mg of **LY354889** (mp = 146-149_C).

Example 16

The following compounds were prepared using substantially the same procedure as described above in Example 15.

[exo]-2-aza-5-((4-hexoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY355776**, mp 130-135_C.

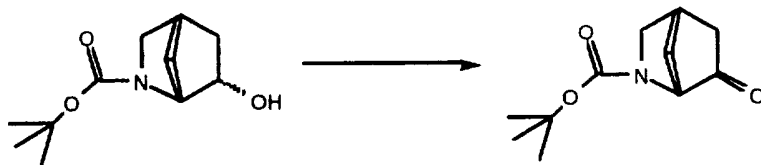
[exo]-2-aza-5-((4-(2-methylpropoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY359977**, mp 142-144_C.

[exo]-2-aza-5-((4-(4-fluorophenylmethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362269**, mp 165-167_C.

ENDO-2-Aza-2-(t-butoxycarbonyl)-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

Preparation of 2-Aza-2-(t-butoxycarbonyl)bicyclo[2.2.1]heptan-6-one

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Dimethylsulfoxide (169.3mmol) was added to a solution of oxalyl chloride (77.9mmol) in dichloromethane (275mL) at -78_C. Stirred for 20 minutes whereupon [endo]2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (15.0g/70.4mmol) in dichloromethane (25mL). Stirred at -78_C for 3 hours then triethylamine (352mmol) was added to the reaction then warmed to room temperature for one hour. Brine (150mL) was added then the reaction was extracted with dichloromethane (3x200mL). The organic extracts were dried over magnesium sulfate then evaporated. The residue was purified by flash chromatography over silica gel eluting with 25% ethyl acetate in hexanes to yield 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-one (12.6g/59.7mmol).

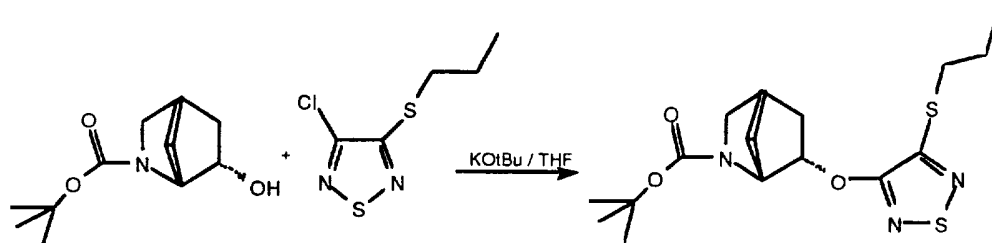
[endo]-2-Aza-2-(t-butoxycarbonyl)bicyclo[2.2.1]heptan-6-ol



L-Selectride (151mmol) was added to a solution of 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-one (59.7mmol) in tetrahydrofuran (300mL) at -78_C. Stirred for three hours at -78_C then warmed to 0_C whereupon 3N aqueous sodium hydroxide (67mL) followed by 30% aqueous hydrogen peroxide (33mL). Stirred at room temperature for two hours then evaporated the tetrahydrofuran. The residue was extracted with dichloromethane (3x150mL). Dried the organic extracts over magnesium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 10% to 50% ethyl acetate in hexanes to yield [endo] 2-aza-2-benzylbicyclo[2.2.1]heptan-6-ol (12g/56.3mmol).

-45-

ENDO-2-Aza-2-(t-butoxycarbonyl)-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

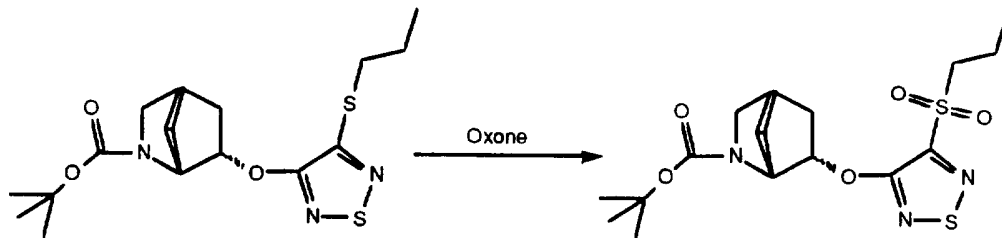


Postassium t-butoxide (56.3mmol) was added to a solution of
 5 [endo]-2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-
 ol(56.3mmol) in tetrahydrofuran (500mL). Stirred at -5_C
 for 45 minutes whereupon 3-chloro-4-(propylthio)-1,2,5-
 thiadiazole(67.6mmol) in tetrahydrofuran (100mL) was added
 to the reaction. Stirred for four hours at -5_C. Poured
 10 the reaction into brine and extracted with ethyl acetate
 (3x250mL). The organic extracts were washed with a
 saturated sodium chloride solution and dried over sodium
 sulfate then evaporated. The residue was purified by
 preparative HPLC using silica gel eluting with 10 to 75%
 15 ethyl acetate in hexanes to yield [endo]-2-aza-2-(t-
 butoxycarbonyl)-6-((4-(propylthio)-1,2,5-thiadiazol-3-
 yl)oxy)bicyclo[2.2.1]heptane(2.6g/7.0mmol).

20

Example 18

[endo]-2-Aza-2-(t-butoxycarbonyl)--6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



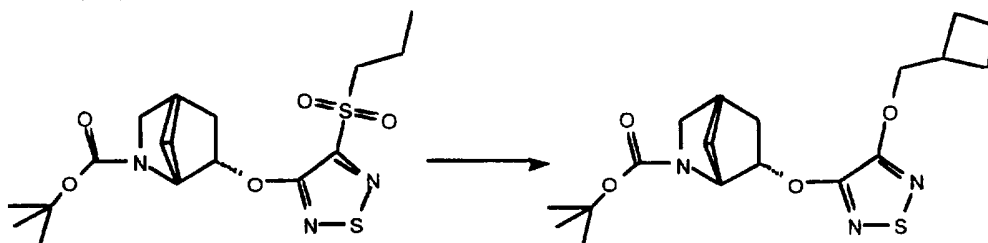
A solution of Oxone®(12.9g/21.0mmol) in water(40mL) was
 25 added to a solution of [endo]-2-aza-2-(t-butoxycarbonyl)-6-
 ((4-(propylthio)-1,2,5-thiadiazol-3-
 yl)oxy)bicyclo[2.2.1]heptane (7.0mmol), water (20mL), and
 tetrahydrofuran (40mL). Stirred at room temperature for 16

-46-

hours. The reaction was poured into water then extracted with ethyl acetate (3x150mL). The organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then evaporated to yield [endo]-2-aza-2-(t-butoxycarbonyl)-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.5g/6.2mmol).

Example 19

10 [endo]-2-Aza-2-(t-butoxycarbonyl)-6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

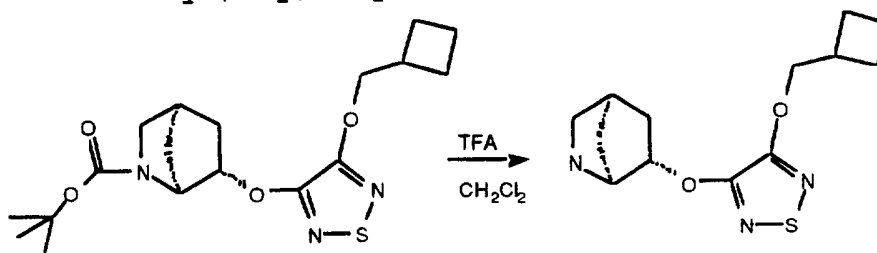


Potassium butoxide (3.1mmol) was added to a solution of cyclobutylmethanol (4.8mmol) and tetrahydrofuran (75mL) at 0°C. The reaction was stirred for 1 hour at 0°C. [endo]-2-aza-2-(t-butoxycarbonyl)-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (1.2mmol) in tetrahydrofuran (25mL) was added to the reaction. The reaction was stirred for 2 hours at 0°C. The reaction was poured into brine then extracted with ethyl acetate (3x100mL). The extracts were dried over magnesium sulfate then evaporated to yield [endo]-2-aza-2-(t-butoxycarbonyl)-6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.45g/1.2mmol).

25

Example 20

[endo]-2-Aza-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



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Trifluoroacetic acid (1.2mL) was added to a solution of [endo]-2-aza-2-(t-butoxycarbonyl)-6-((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (1.2mmol) in methylene chloride (35mL) and stirred at room temperature
5 for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield [endo]-2-aza-6-
10 ((4-cyclobutylmethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 200mg of **LY362567** (mp = 158-160_C).

15

Example 21

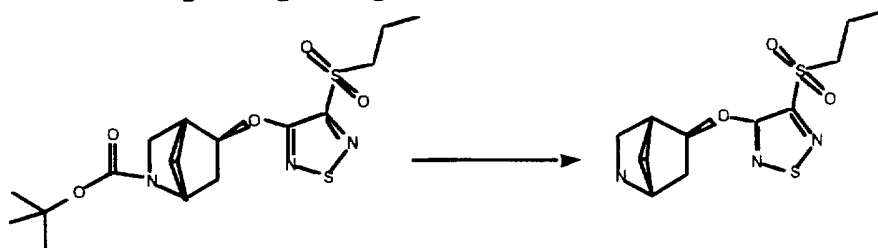
The following compounds were prepared using substantially the same procedure as described above in Example 20.

20 [endo]-2-aza-6-((4-(4-fluorophenylmethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362519**, mp 176-178_C.

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Example 22

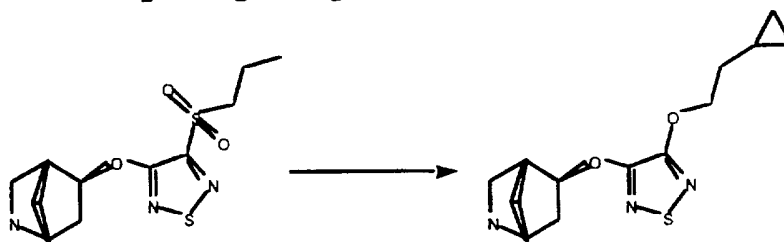
[*exo*]-2-Aza-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



5 Trifluoroacetic acid (3.0mL) was added to a solution of [*exo*]-2-aza-2-(t-butoxycarbonyl)-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (3.0mmol) in methylene chloride (10mL) at 0°C. The reaction was stirred at 0°C for four hours then warmed to room temperature and
 10 stirred for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was taken up in 1N HCl(aq), washed with diethyl ether, basified with aqueous potassium carbonate then extracted with ethyl acetate (3x100mL). The combined organic extracts were dried over
 15 magnesium sulfate then evaporated to yield [*exo*]-2-aza-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.3mmol).

Example 23

20 [*exo*]-2-Aza-5-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



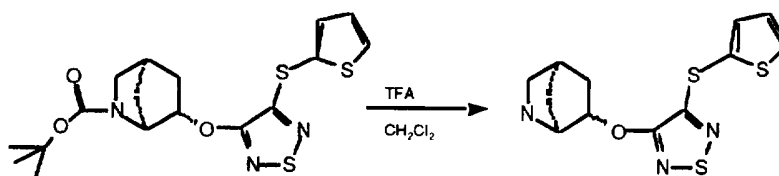
Potassium butoxide (6.9mmol) was added to a solution of 2-cyclopropylethanol (6.9mmol) and tetrahydrofuran (30mL) room
 25 temperature. The reaction was stirred for one hour then [*exo*]-2-aza-5-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.3mmol) in tetrahydrofuran (5mL) was added to the reaction. The reaction was stirred

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for sixteen hours at room temperature. The reaction was concentrated on a rotary evaporator and the residue was taken up in 1N HCl(aq), washed with diethyl ether, basified with aqueous potassium carbonate then extracted with ethyl acetate (3x75mL). The extracts were dried over magnesium sulfate then evaporated and the residue was purified by radial chromatography eluting with 1% aqueous ammonium hydroxide / 10% ethanol in chloroform to yield [exo] 2-aza-5-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 450mg of **LY349456** (mp = 143-144_C).

Example 24

(1S,4R, 6S)-2-Aza-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Trifluoroacetic acid (0.6mL) was added to a solution of (1S,4R, 6S)-2-Aza-2-(t-butoxycarbonyl)-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.6mmol) in methylene chloride (50mL). The reaction was stirred at room temperature for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield (1S,4R, 6S)-2-Aza-((4-(2-thienylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 140mg of **LY359682** (mp = 174-180_C).

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Example 25

Substantially the same procedure described above in Example 24 was used to make the following compounds, except (S)-1-phenylethylamine hydrochloride was used as the starting material.

(1R,4S,6R)-2-Aza-((4-(4-fluorophenylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY366961**, mp 149-151_C.

Example 26

ENDO-2-Aza-2-(t-butoxycarbonyl)-5-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

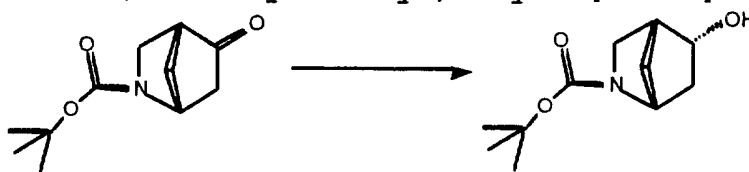
Preparation of 2-Aza-2-(t-butoxycarbonyl)bicyclo[2.2.1]heptan-5-one



Dimethylsulfoxide (85.9mmol) was added to a solution of oxalyl chloride (39.5mmol) in dichloromethane (100mL) at -78_C. Stirred for 20 minutes whereupon [exo]2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol (35.7mmol) in dichloromethane (50mL). Stirred at -78_C for 3 hours then triethylamine (179mmol) was added to the reaction then warmed to room temperature for one hour. Brine was added then the reaction was extracted with dichloromethane (3x200mL). The organic extracts were dried over magnesium sulfate then evaporated. The residue was purified by preparative HPLC over silica gel eluting with 10% to 75% ethyl acetate in hexanes to yield 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-one (31.3mmol).

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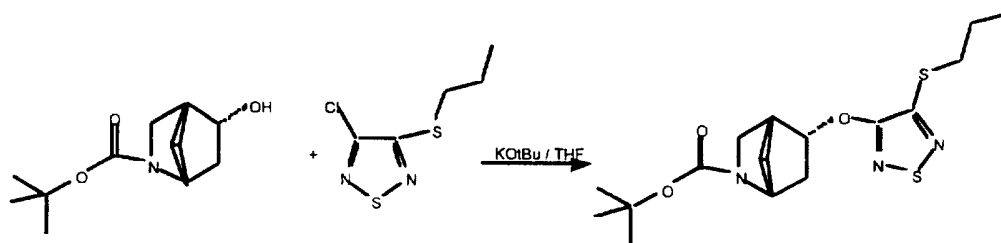
[endo]-2-Aza-2-(t-butoxycarbonyl)bicyclo[2.2.1]heptan-5-ol



L-Selectride (79mmol) was added to a solution of 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-one (31.3mmol) in tetrahydrofuran (160mL) at -78_C. Stirred for three hours at -78_C then warmed to 0_C whereupon 3N aqueous sodium hydroxide (35mL) followed by 30% aqueous hydrogen peroxide (17.3mL). Stirred at room temperature for two hours then evaporated the tetrahydrofuran. The residue was extracted with dichloromethane (3x75mL). Dried the organic extracts over magnesium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 10% to 50% ethyl acetate in hexanes to yield [endo] 2-aza-2-benzylbicyclo[2.2.1]heptan-5-ol (23.5mmol).

15

[endo] 2-Aza-2-(t-butoxycarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium t-butoxide (23.5mmol) was added to a solution of [endo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol (23.5mmol) in tetrahydrofuran (250mL) at room temperature. Stirred for one hour whereupon the reaction was cooled to -10_C and 3-chloro-4-propylthio-1,2,5-thiadiazole (28.2mmol) in tetrahydrofuran (50mL). The reaction was stirred at -10_C for four hours then the reaction was poured into brine then extracted with ethyl acetate (3x200mL). The combined organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then evaporated. The residue was purified by preparative HPLC

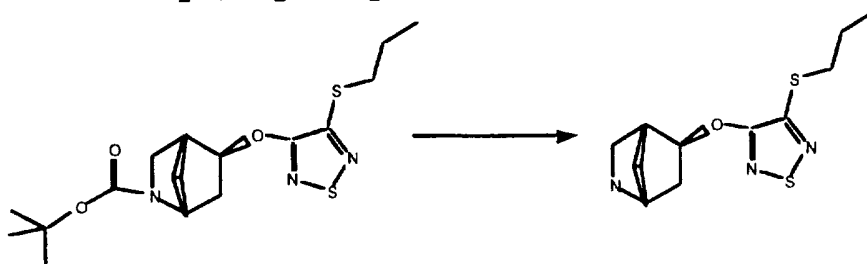
-52-

using silica gel eluting with 15 to 60% ethyl acetate in hexanes to yield [endo] 2-aza-2-(t-butylcarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (11.3mmol).

5

Example 27

[endo]2-Aza-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

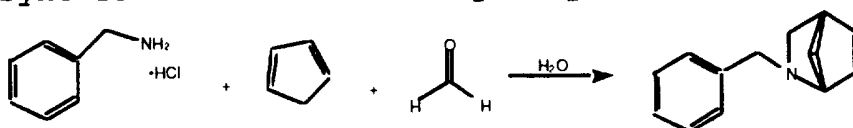


10 Trifluoroacetic acid (1.3mL) was added to a solution of [endo]-2-aza-2-(t-butoxycarbonyl)-5-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (1.3mmol) in methylene chloride (35mL) at 0°C. The reaction was stirred at 0°C for one hour then warmed to room temperature and
15 stirred for sixteen hours. The reaction was concentrated on a rotary evaporator and the residue was basified with aqueous sodium bicarbonate then extracted with ethyl acetate (3x75mL). The combined organic extracts were dried over magnesium sulfate then evaporated to yield [endo]-2-aza-5-
20 ((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 201mg of **LY368586** (mp = 82-86°C).

25

Example 28

Synthesis of 2-Aza-2-benzylbicyclo[2.2.1]hept-5-ene

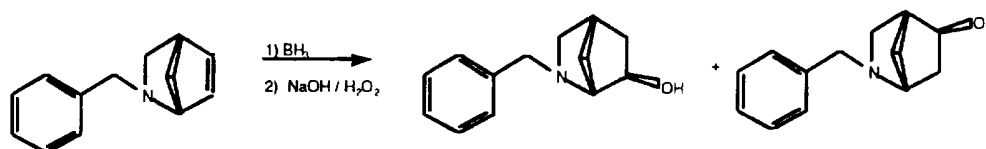


30 Cyclopentadiene (61.7g/935mmol) was added to a solution of benzylamine hydrochloride (67.1g/467mmol), 37% aqueous

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formaldehyde (65.4mL/807mmol), and water (190mL). The solution was stirred at room temperature for three hours. Water (190mL) was added to the reaction then washed with diethyl ether (2x250mL). The aqueous layer was basified with solid KOH then extracted with diethyl ether (3x250mL). The combined extracts were dried over magnesium sulfate then evaporated to yield 2-aza-2-benzylbicyclo[2.2.1]hept-5-ene (79.6g/430mmol).

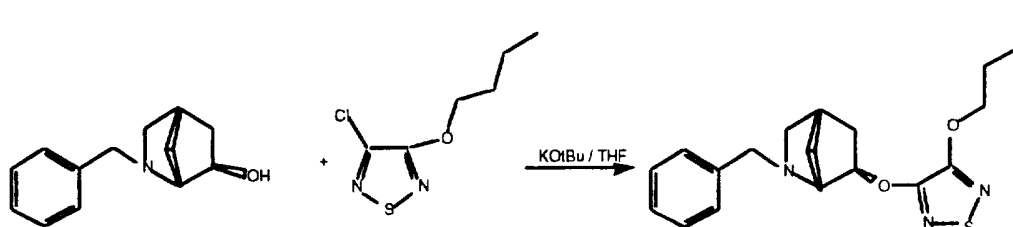
10 **Synthesis of [exo] 2-Aza-2-benzylbicyclo[2.2.1]heptan-5-ol and [exo] 2-Aza-2-benzylbicyclo[2.2.1]heptan-6-ol**



1.0M Borane:THF in tetrahydrofuran (500mL/500mmol) was added to a solution of 2-aza-2-benzylbicyclo[2.2.1]hept-5-ene (46.7g/252.2mmol) in tetrahydrofuran (570mL) at 0°C. Stirred at 0°C for 2 hours whereupon water in tetrahydrofuran was added to the reaction to destroy excess borane. While keeping the reaction temperature below 10°C, 3N Aqueous sodium hydroxide (30mL) was added to the reaction immediately followed by 30% aqueous hydrogen peroxide (50mL). The reaction temperature was allowed to rise to 40°C then stirred for 1.5 hours. Potassium carbonate (10g) was added to the reaction then evaporated to remove the tetrahydrofuran. The aqueous residue was extracted with dichloromethane (3x100mL). The organic extracts were washed with water then dried over sodium chloride/sodium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 1 to 20% (10% ammonium hydroxide in methanol) in dichloromethane to yield [exo] 2-aza-2-benzylbicyclo[2.2.1]heptan-5-ol (7.2g/36mmol) and [exo] 2-aza-2-benzylbicyclo[2.2.1]heptan-6-ol (31.2g/154mmol).

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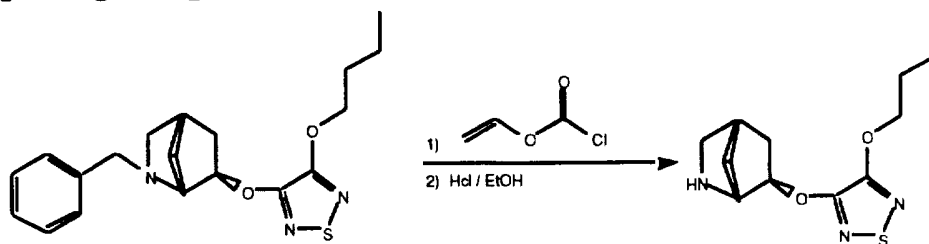
Synthesis of [exo] 2-Aza-2-benzyl-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium t-butoxide (0.66g/5.9mmol) was added to a solution of [exo] 2-aza-2-benzylbicyclo[2.2.1]heptan-6-ol (1.2g/5.9mmol) in tetrahydrofuran (50mL) at -78_C. Stirred for 30 minutes where upon 3-chloro-4-butoxy-1,2,5-thiadiazole (1.1g/5.9mmol) in tetrahydrofuran (20mL). The reaction was stirred at -78_C for 16 hours then 1 hour at room temperature. The reaction was poured into brine then extracted with ethyl acetate (3x75mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, then evaporated. The residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes to yield [exo] 2-aza-2-benzyl-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.4g/1.1mmol).

Example 29

Synthesis of [exo] 2-Aza-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Vinyl chloroformate (2.2mL/25.8mmol) was added to a solution of [exo] 2-aza-2-benzyl-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.7g/1.9mmol), proton sponge (0.8g/3.8mmol), and dichloromethane (50mL). The reaction was refluxed for 16 hours. The reaction was diluted with diethyl ether (110mL) then washed with 1N aqueous

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hydrochloric acid (3x20mL), saturated aqueous sodium bicarbonate (20mL), and brine (20mL). The organic layer was dried over magnesium sulfate then evaporated. The residue was taken up in ethanol (15mL) and ethanol saturated with hydrochloric acid (15mL) then refluxed for 6 hours. The solution was evaporated, basified with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate (3x50mL). The organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated. The residue was purified by radial chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield [exo] - 2-aza-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the oxalate salt to yield 250mg of **LY335838** (mp = 165-167_C).

The following compounds were made using substantially the same procedure.

[exo] 2-Aza-2-benzyl-6-((4-propyl thio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane oxalate, **LY338901**, mp 151-154_C.

[exo] 2-Aza-6-((4-propyl thio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY338902**, mp 167-70_C.

[exo] 2-Aza-5-((4-propyl thio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane oxalate, **LY341211**, mp 159-162_C.

[exo] 2-Aza-5-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane oxlate, **LY343125**, mp 161-162_C.

[exo] 2-Aza-5-((4-propoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344087**, mp 144-146_C.

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Example 30

Synthesis of 2-Aza-2-benzylbicyclo[2.2.1]heptan-6-one



Dimethylsulfoxide (5.9mL/82.9mmol) was added to a solution
5 of oxalyl chloride (3.3mL/38.0mmol) in dichloromethane
(125mL) at -78_C. Stirred for 20 minutes whereupon [exo]2-
aza-2-benzylbicyclo[2.2.1]heptan-6-ol (7.0g/34.5mmol) in
dichloromethane (15mL). Stirred at -78_C for 3 hours then
triethylamine (24mL/172.5mmol) was added to the reaction
10 then warmed to room temperature for 1 hour. Brine (75mL)
was added then the reaction was extracted with
dichloromethane (3x100mL). The organic extracts were dried
over magnesium sulfate then evaporated. The residue was
purified by flash chromatography over silica gel eluting
15 with ethyl acetate in hexanes to yield 2-aza-2-
benzylbicyclo[2.2.1]heptan-6-one (3.5g/17.4mmol).

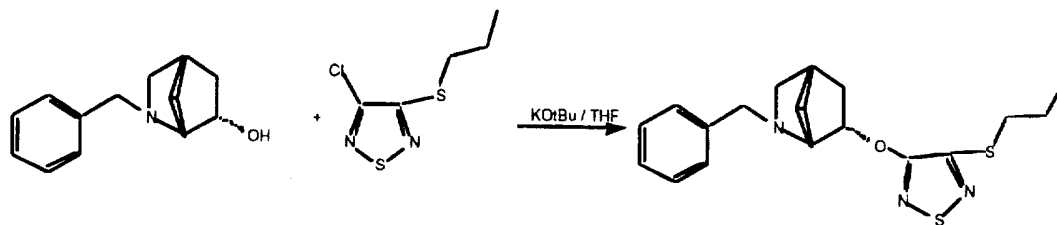
Synthesis of [endo] 2-Aza-2-benzylbicyclo[2.2.1]heptan-6-ol



20 L-Selectride (44.1mL/44.1mmol) was added to a solution of 2-
aza-2-benzylbicyclo[2.2.1]heptan-6-one (3.5g/17.4mmol) in
tetrahydrofuran (90mL) at -78_C. Stirred for 3 hours at -
78_C then warmed to 0_C whereupon 3N aqueous sodium hydroxide
(19mL) followed by 30% aqueous hydrogen peroxide (9.5mL).
25 Stirred at room temperature for 2 hours then evaporated the
tetrahydrofuran. The residue was extracted with
dichloromethane (3x75mL). Dried the organic extracts over
magnesium sulfate then evaporated. The residue was purified
by 1% ammonium hydroxide / 9% methanol / 40% chloroform /
30 50% dichloromethane to yield [endo] 2-aza-2-
benzylbicyclo[2.2.1]heptan-6-ol (3g/14.8mmol)

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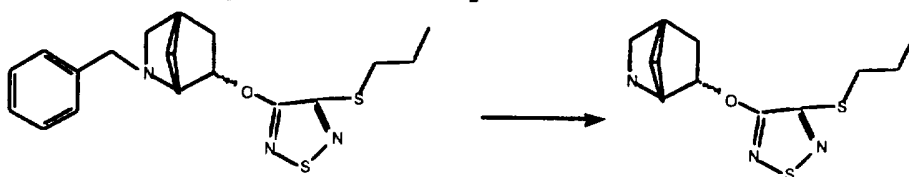
Synthesis of [endo] 2-Aza-2-benzyl-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium t-butoxide (1.7g/14.8mmol) was added to a solution of [endo] 2-aza-2-benzylbicyclo[2.2.1]heptan-6-ol (3.0g/14.8mmol) in tetrahydrofuran (150mL) at room temperature. Stirred for 45 minutes where upon 3-chloro-4-propylthio-1,2,5-thiadiazole (2.8g/14.5mmol) in tetrahydrofuran (25mL). The reaction was stirred at room temperature for 16 hours then 1 hour at room temperature. The reaction was poured into brine then extracted with ethyl acetate (3x75mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, then evaporated. The residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes to yield [endo] 2-aza-2-benzyl-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.9g/2.5mmol).

Example 31

Synthesis of [endo] 2-Aza-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



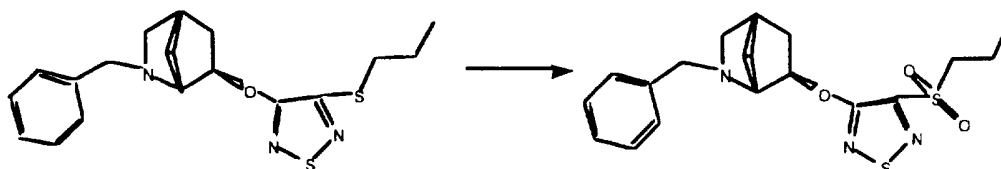
Vinyl chloroformate (0.6mL/6.6mmol) was added to a solution of [endo] 2-aza-2-benzyl-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.8g/2.2mmol), proton sponge (0.9g/4.4mmol), and dichloromethane (40mL). The reaction was refluxed for 16 hours. The reaction was diluted with diethyl ether (100mL) then washed with 1N aqueous hydrochloric acid (3x20mL), saturated aqueous sodium bicarbonate (20mL), and brine (20mL). The organic layer was

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dried over magnesium sulfate then evaporated. The residue was taken up in ethanol (15mL) and ethanol saturated with hydrochloric acid (15mL) then refluxed for 6 hours. The solution was evaporated, basified with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate (3x50mL). The organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated. The residue was purified by radial chromatography on silica gel eluting with 0.5% conc. ammonium hydroxide / 5% ethanol in chloroform to yield [endo] - 2-aza-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 130mg of **LY338903** (mp = 163-164_C).

Example 32

Synthesis of [exo] 2-Aza-2-benzyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

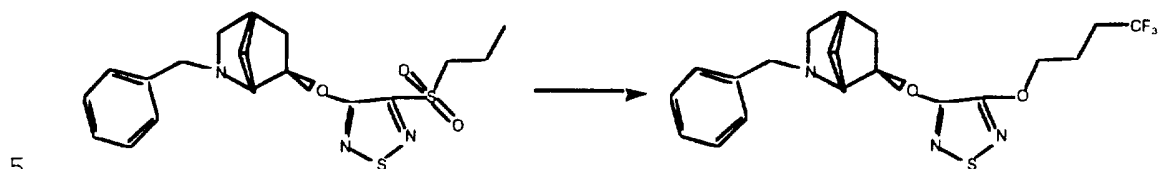


A solution of Oxone® (36.9g/60.1mmol) in water (75mL) was added to a solution of [exo] 2-Aza-2-benzyl-6-((4-propylthio-1,2,5-thiadiazol-3-yloxy)bicyclo[2.2.1]heptane (10.7g/29.6mmol), 1N aqueous hydrochloric acid (30mL), water (75mL), and tetrahydrofuran (75mL). Stirred at room temperature for 16 hours. Saturated aqueous sodium bisulfite was added to the reaction which was extracted with diethyl ether (3x200mL). The organic extracts were washed with water, saturated aqueous sodium bicarbonate, water, dried over magnesium sulfate, then evaporated to yield [exo] 2-Aza-2-benzyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (12g).

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Example 33

Synthesis of [exo] 2-Aza-2-benzyl-6-((4-(4,4,4-trifluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

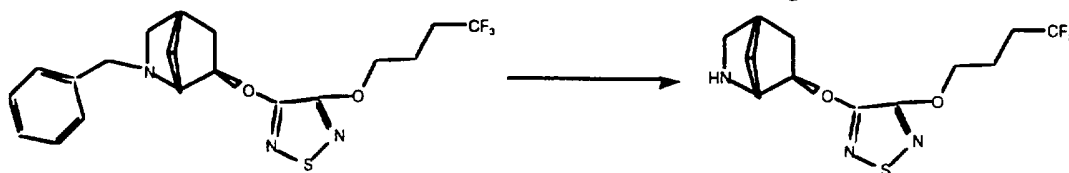


4,4,4-Trifluorobutanol (2.0g/15.3mmol) was added to a mixture of sodium hydride (14.0mmol) and tetrahydrofuran (40mL). The reaction was stirred for 1 hour at room temperature. [exo] 2-Aza-2-benzyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.0g/5.1mmol) in tetrahydrofuran (10mL) was added to the reaction. The reaction was stirred for 16 hours then evaporated. The residue was taken up in water and extracted with ethyl acetate (3x100mL). The extracts were dried over sodium chloride / sodium sulfate then evaporated. The residue was purified by flash chromatography over silica gel eluting with 25% ethyl acetate in hexanes to yield [exo] 2-Aza-2-benzyl-6-((4-(4,4,4-trifluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (1.1g/2.7mmol).

20

Example 34

Synthesis of [exo] 2-Aza-6-((4-(4,4,4-trifluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



25 Vinyl chloroformate (0.8mL/9.3mmol) was added to a solution of [exo] 2-Aza-2-benzyl-6-((4-(4,4,4-trifluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (1.5g/3.1mmol), proton sponge (1.3g/6.2mmol), and dichloromethane (100mL). The reaction was refluxed for 16 hours. The reaction was diluted with diethyl ether (500mL) then washed with 1N aqueous hydrochloric acid (3x80mL), saturated aqueous sodium

30

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bicarbonate (80mL), and brine (80mL). The organic layer was dried over magnesium sulfate then evaporated. The residue was taken up in ethanol (60mL) and ethanol saturated with hydrochloric acid (60mL) then refluxed for 6 hours. The solution was evaporated, basified with saturated aqueous sodium bicarbonate, then extracted with ethyl acetate (3x50mL). The organic extracts washed with a saturated sodium chloride solution and were dried over sodium sulfate then evaporated. The residue was purified by radial chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield [exo] 2-Aza-6-((4-(4,4,4-trifluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane which was isolated as the hydrochloride salt to yield 130mg of **LY343953** (mp = 128-130_C).

The following compounds were made using substantially the same procedure.

[exo] 2-Aza-6-((4-(4-(trifluoromethoxy)benzyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY343954**, mp 147-149_C.

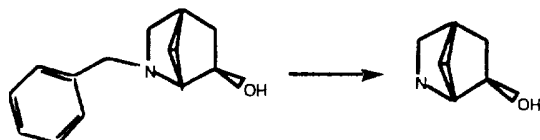
[exo] 2-Aza-6-((4-propoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY343955**, mp 173-174_C.

[exo] 2-Aza-6-((4-ethyloxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344032**, mp 177-179_C.

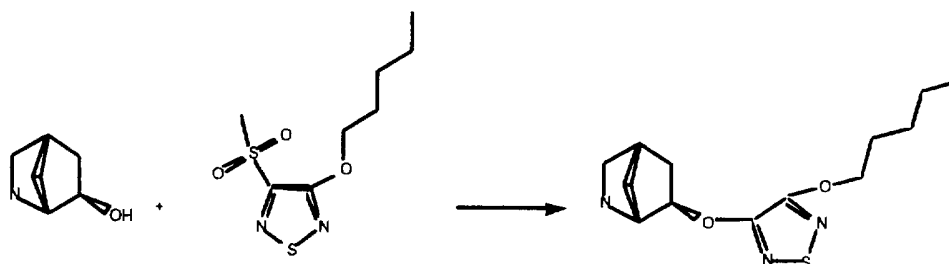
-61-

Example 35

Synthesis of [exo] 2-Aza-bicyclo[2.2.1]heptan-6-ol



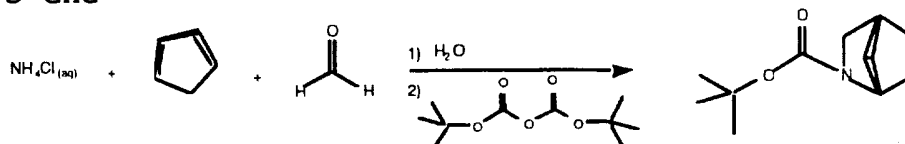
A solution of [exo] 2-aza-2-benzylbicyclo[2.2.1]heptan-6-ol
 5 (23.1g/113.8mmol) in ethanol (470mL) was hydrogenated with
 5% Pd/C (7g) at 60 PSIG of hydrogen at room temperature for
 16 hours. Filtered off the catalyst the evaporated the
 filtrate. Isolated as the hydrochloride salt to yield
 [exo] 2-azabicyclo[2.2.1]heptan-6-ol hydrochloride (13g).
 10 **Synthesis of [exo] 2-Aza-6-(4-hexoxy-1,2,5-thiadiazol-3-
 yloxy)bicyclo[2.2.1]heptane**



1.6M n-Butyllithium in hexanes (8.4mL/13.4mmol) was added to
 a solution of [exo] 2-azabicyclo[2.2.1]heptan-6-ol
 15 hydrochloride (1.0g/6.7mmol) in tetrahydrofuran (80mL) at
 room temperature. Stirred for 1 hour then added 3-
 (methanesulfonyl)-4-hexyloxy-1,2,5-thiadiazole
 (2.0g/8.0mmol) in tetrahydrofuran (20mL). Stirred at room
 temperature for 16 hours. Quenched the reaction with water
 20 then extracted with ethyl acetate (3x100mL). The organic
 extracts were evaporated then taken up in 1N aqueous
 hydrochloric acid. The aqueous layer was washed with
 diethyl ether (2x50mL) the basified with potassium carbonate
 then extracted the ethyl acetate (3x75mL). The organic
 25 extracts were dried over magnesium sulfate then evaporated. The
 residue was treated with hydrochloric acid in diethyl ether to
 yield [exo] 2-Aza-6-(4-hexoxy-1,2,5-thiadiazol-3-
 yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY341711** (mp=131-
 134_c).

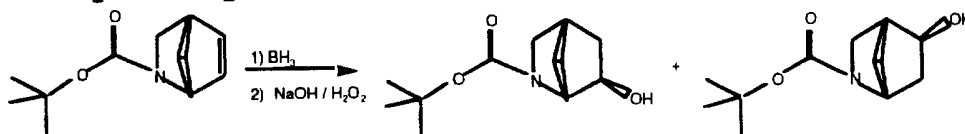
Example 36

Synthesis of 2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene



5 Cyclopentadiene (79g/1.20mol) was added to a solution of saturated aqueous ammonium chloride (257mL) and 37% aqueous formaldehyde (68.1mL/0.84mol). The solution was stirred at room temperature for 16 hours. Water (130mL) was added to
 10 the reaction then washed with diethyl ether (2x150mL). The aqueous layer was basified with solid KOH. Di-tert-butyl dicarbonate (218g/1.00mol) was added to the aqueous layer while maintaining the pH between 9.5 and 10. Stirred overnight at room temperature. The reaction was extracted
 15 with ethyl acetate (3x500mL). The combined extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated. The residue was purified by preparative HPLC over silica gel eluting with 25 to 75% ethyl acetate in hexanes to yield 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene (62g/318mmol).
 20

Synthesis of [exo] 2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol and [exo] 2-Aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol

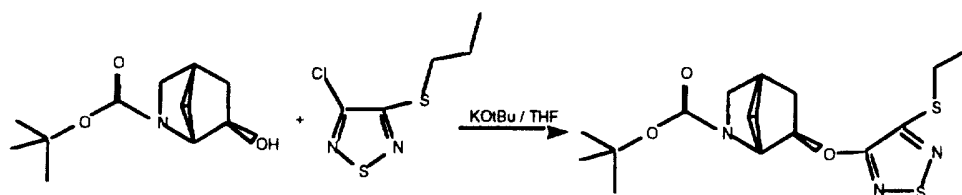


25 1.0M Borane:THF in tetrahydrofuran (626mL/626mmol) was added to a solution of 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]hept-5-ene (61.5g/315mmol) in tetrahydrofuran (700mL) at 0°C. Stirred at 0°C for 2 hours whereupon water
 30 in tetrahydrofuran was added to the reaction to destroy excess borane. While keeping the reaction temperature below 10°C, 3N Aqueous sodium hydroxide (88mL) was added to the

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reaction immediately followed by 30% aqueous hydrogen peroxide (148mL). The reaction temperature was allowed to rise to 40_C then stirred for 1.5 hours. Potassium carbonate (30g) was added to the reaction then evaporated to remove the tetrahydrofuran. The aqueous residue was extracted with dichloromethane. The organic extracts were washed with a saturated sodium chloride and then dried over sodium sulfate then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 10 to 75% ethyl acetate in hexanes to yield [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-5-ol (14.0g/65.7mmol) and [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (14.5g/68.1mmol).

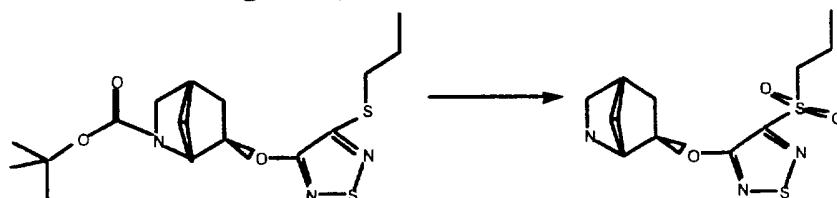
Synthesis of [exo] 2-Aza-2-t-butoxycarbonyl)-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



Potassium t-butoxide (2.6g/23.5mmol) was added to a solution of [exo] 2-aza-2-(t-butoxycarbonyl)-bicyclo[2.2.1]heptan-6-ol (5.0g/23.5mmol) in tetrahydrofuran (250mL) at room temperature. Stirred for 2 hours whereupon the reaction was cooled to -10_C and 3-chloro-4-propylthio-1,2,5-thiadiazole (4.6g/23.5mmol) in tetrahydrofuran (50mL). The reaction was stirred at -10_C for 1 hour then the reaction was poured into brine then extracted with ethyl acetate (3x250mL). The combined organic extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate, then evaporated. The residue was purified by preparative HPLC using silica gel eluting with 5 to 50% ethyl acetate in hexanes to yield [exo] 2-aza-2-(t-butoxycarbonyl)-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (3.5g/9.4mmol).

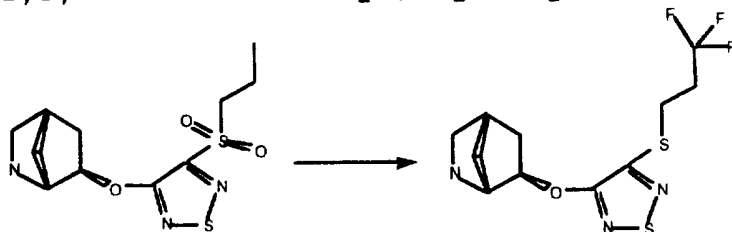
Example 37

Synthesis of [exo] 2-Aza-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



- 5 A solution of Oxone® (11.7g/9.4mmol) in water (40mL) was added to a solution of [exo] 2-aza-2-(t-butoxycarbonyl)-6-((4-propylthio-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (3.5g/9.4mmol), 1N aqueous hydrochloric acid (10mL), water (10mL), and tetrahydrofuran (50mL). Stirred at room
- 10 temperature for 16 hours. Saturated aqueous sodium bisulfite was added to the reaction which was extracted with ethyl acetate (3x100mL). The organic extracts were dried over sodium chloride / sodium sulfate, then evaporated. The residue was taken up in dichloromethane (10mL) then was
- 15 treated with trifluoroacetic acid (5mL) at room temperature. Stirred for 2 hours the evaporated. The residue was taken up in saturated aqueous sodium bicarbonate then extracted with ethyl acetate (3x50mL). The organic extracts were
- 20 washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated to yield [exo] 2-Aza-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.2g).

- 25 **Synthesis of [exo] 2-Aza-6-((4-(3,3,3-trifluoropropoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane**



3,3,3-Trifluoropropanol (570mg/1.7mmol) was added to a mixture of potassium t-butoxide (560mg/5.0mmol) and tetrahydrofuran (15mL). The reaction was stirred for 30

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minutes at room temperature then cooled to -10_C. [exo] 2-Aza-6-((4-propylsulfonyl-1,2,5-thiadiazyl-3-oxy)bicyclo[2.2.1]heptane(500mg/1.7mmol) in tetrahydrofuran (5mL) was added to the reaction. The reaction was stirred
5 for 1.5 hours. The reaction was quenched with brine and extracted with ethyl acetate (3x75mL). The extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate then evaporated. The residue was purified by radial chromatography over silica gel eluting
10 with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield [exo] 2-Aza-6-((4-(3,3,3-trifluoropropoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (158mg/0.51mmol) which was isolated as the hydrochloride salt, **LY344390** (mp = 150-153_C).

15

The following compounds were made using substantially the same procedure.

[exo] 2-Aza-6-((4-methoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344790**, mp
20 180-182_C.

-66-

Example 402-Methoxycarbonyl-2-aza-[2.2.1]-bicycloheptan-6-ol.

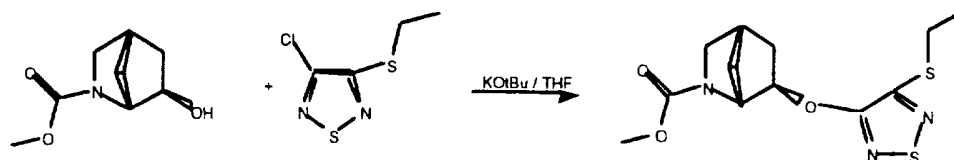
A three-neck round-bottom flask fitted with two addition
5 funnels was charged with NH_4Cl (146 g, 2.7 Mol), 37% aq.
formaldehyde (110 mL, 1.4 Mol) and H_2O (500 mL)
cyclopentadiene (60 g, 0.9 Mol) was added, and reaction was
stirred at room temperature under an atmosphere of N_2 .
After 6 h, K_2CO_3 (40 g, 0.30 Mol) was added. Reaction
10 cooled in an ice bath. One addition funnel was charged with
methyl chloroformate (70 mL, 0.9 Mol) and the second
addition funnel was charged with K_2CO_3 (125 g, 0.9 Mol) in
 H_2O (500 mL). The reagents from the two addition funnels
were added dropwise at such a rate that K_2CO_3 completed just
15 after methyl chloroformate, over a 30 min period. The
reaction was then stirred for 2 h, with ice bath cooling.
The reaction was then extracted with three 500 mL portions
of CH_2Cl_2 . The combined extracts were washed with a
saturated sodium chloride solution and dried over sodium
20 sulfate and evaporated under vacuum. Chromatography of 10 g
of the resulting brown oil (1:1 ethyl acetate, hexanes)
afforded 4.3 g of a colorless oil.

A solution of the product (4.3 g, 28 mMol) in 60 mL of
dry THF, under an N_2 atmosphere was cooled in an ice bath.
25 $\text{BH}_3\cdot\text{THF}$ (57 mL, 57 mMol) was added and the reaction was
stirred for 2 h with continued ice bath cooling. The
reaction was then quenched by addition of a mixture of 5 mL
 H_2O combined with 5 mL THF, followed by 10 mL of 5 N NaOH
and careful addition of 10 mL 30% H_2O_2 . The resulting
30 mixture was stirred vigorously for 1.5 h. The mixture was
then concentrated under vacuum to remove THF. The residue
was diluted with 50 mL brine and extracted with three 50 mL
portions of CH_2Cl_2 . The combined extracts were washed with
a saturated sodium chloride solution and dried over sodium
35 sulfate and evaporated. Chromatography (ethyl acetate)
afforded 2.8 g of the title compound.

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Exmample 41

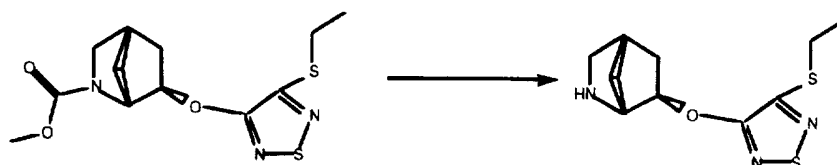
Synthesis of [exo] 2-Aza-2-(methoxycarbonyl)-6-((4-(ethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



- 5 Postassium t-butoxide (0.65g/5.8mmol) was added to a solution of [exo] 2-aza-2-(methoxycarbonyl)bicyclo[2.2.1]heptan-6-ol (1.0g/5.8mmol) in tetrahydrofuran (50mL). Stirred at room temperature for 45 minutes whereupon 3-chloro-4-(ethylthio)-1,2,5-
- 10 thiadiazole (0.95g/5.3mmol) was added to the reaction. Stirred overnight at room temperature. Poured the reaction into brine and extracted with ethyl acetate (3x75mL). The organic extracts were dried over magnesium sulfate then evaporated. The residue was purified by radial
- 15 chromatography on silica gel eluting with 25% ethyl acetate in hexanes to yield [exo] 2-aza-2-(methoxycarbonyl)-6-((4-(ethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (500mg/1.7mmol).

Exmample 42

- 20 **Synthesis of [exo] 2-Aza-6-((4-(ethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane**



- Trimethylsilyl iodide (0.4mL/2.0mmol) was added to a solution of [exo] 2-aza-2-(methoxycarbonyl)-6-((4-(ethylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (500mg/1.7mmol) in dichloromethane (25mL). The reaction was refluxed for 16 hours. The reaction was poured into methanol then evaporated. The residue was purified by radial chromatography over silica gel eluting with 0.5% conc. ammonium hydroxide / 5.0% ethanol in chloroform to
- 30 yield [exo] 2-Aza-6-((4-(ethylthio)-1,2,5-thiadiazol-3-

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yl)oxy)bicyclo[2.2.1]heptane (145mg/0.56mmol) which was isolated as the oxalate salt, **LY338327** (dec 182_C).

The following compounds were made using substantially the same procedure.

[exo] 2-Aza-6-((4-butoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane oxlate, **LY335838**, mp 162-164_C.

10 [exo] 2-Aza-6-((4-hexoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane oxlate, **LY333582**, mp 171-173_C.

Exmample 43

To a solution of an alcohol or an aliphatic thiol (0.5 mmol, 2 equiv.) in 4.0 mL of anhydrous THF contained in a 8 mL vial was added 1 mL of a 0.5 M mixture of potassium tert-butoxide (0.5 mmol, 2 equiv.) in THF. The vial was capped, briefly shaken and then cooled to around 0°C in an aluminum block. The vial was uncapped, a solution of sulfone (0.25 mmol, 1 equiv.) in THF was quickly added and then the vial was immediately recapped. The reaction mixture was shaken at ambient temperature overnight and was then added directly to 12 mL of a 30% solution of TFA in chloroform. After shaking overnight and concentrated under vacuum, the resulting residue was placed overnight in a vacuum oven with light heating (50°C). The residue was then re dissolved in a 15% solution of methanol in chloroform and passed through a Varion SAX ion exchange column (1 g, 6 mL column) which had been pretreated by washing with 1 N NaOH (20 mL) and methanol (8 mL). The resulting filtrate (total volume 12 mL) was then passed through a Varion SCX ion exchange column (1 g, 3 mL column). The column was washed 3-4 X with 3.0 mL portions of MeOH and the product eluted from the column using four 2 mL portions (8 mL total) of a 20% solution of sat. HCl·MeOH (or sat. HCl ethanol)/ CHCl₃. Concentration in a speed vac provided the hydrochloride salts of the

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products which were submitted for testing without further purification.

5 The following compounds were prepared using the same procedure as described above by using the appropriate starting materials.

(1R,4S,6R)-2-Aza-((4-(2-(4-chlorophenyl)-2-cyclopentylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362818**, MW = 442.4g/mol, MF = C₂₀ H₂₅ Cl₂ N₃ O₂ S, m/z + 1 = 406.2, 408.2.

(1R,4S,6R)-2-Aza-((4-(4-chlorobenzyl)thio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362819**, MW = 390.5g/mol, MF = C₁₅ H₁₇ Cl₂ N₃ O S₂, m/z + 1 = 354.

(1R,4S,6R)-2-Aza-((4-(3-(4-fluorophenyl)propoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362820**, MW = 385.9g/mol, MF = C₁₇ H₂₁ Cl F N₃ O S₂, m/z + 1 = 350.1.

(1R,4S,6R)-2-Aza-((4-(3-phenyl)prop-2-ynyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362821**, MW = 363.9g/mol, MF = C₁₇ H₁₈ Cl N₃ O₂ S, m/z + 1 = 328.3.

(1R,4S,6R)-2-Aza-((4-(hexyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362822**, MW = 333.9g/mol, MF = C₁₄ H₂₄ Cl N₃ O₂ S, m/z + 1 = 298.3.

(1R,4S,6R)-2-Aza-((4-but-2-ynyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362823**, MW = 301.8g/mol, MF = C₁₂ H₁₆ Cl N₃ O₂ S, m/z + 1 = 266.4.

(1R,4S,6R)-2-Aza-((4-(2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362824**, MW = 303.8g/mol, MF = C₁₂ H₁₇ Cl N₃ O₂ S, m/z + 1 = 268.

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- (1R,4S,6R)-2-Aza-((4-(4-fluorobenzyl)thio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY362826**, MW = 357.8g/mol, MF = C₁₅ H₁₇ Cl F N₃ O₂ S, m/z + 1 = 322.5.
- 5 (1S,4R,6S)-2-Aza-((4-(2-cyclohexyl-cyclohexoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368363**, MW = 414.0g/mol, MF = C₂₀ H₃₂ Cl N₃ O₂ S, m/z + 1 = 378.2.
- 10 (1S,4R,6S)-2-Aza-((4-(4-phenylbenzyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368364**, MW = 415.9g/mol, MF = C₂₁ H₂₂ Cl N₃ O₂ S, m/z + 1 = 380.1.
- (1S,4R,6S)-2-Aza-((4-(2-(4-chlorophenylthio)ethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368365**, MW = 420.4g/mol, MF = C₁₆ H₁₉ Cl N₃ O₂ S₂, m/z + 1 = 384.1.
- 15
- (1S,4R,6S)-2-Aza-((4-(2-phenyl-2-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368366**, MW = 379.9g/mol, MF = C₁₈ H₂₂ Cl N₃ O₂ S, m/z + 1 = 344.
- 20
- (1S,4R,6S)-2-Aza-((4-(3-(benzyloxy)propoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368367**, MW = 397.9g/mol, MF = C₁₈ H₂₄ Cl N₃ O₃ S, m/z + 1 = 362.1.
- 25
- (1S,4R,6S)-2-Aza-((4-(2-diphenyethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368368**, MW = 429.9g/mol, MF = C₂₂ H₂₄ Cl N₃ O₂ S, m/z + 1 = 394.1.
- 30
- (1S,4R,6S)-2-Aza-((4-(1-(2-thienyl)-2-propoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368370**, MW = 373.9g/mol, MF = C₁₅ H₂₀ Cl N₃ O₂ S₂, m/z + 1 = 338.1.
- 35

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(1S,4R,6S)-2-Aza-((4-(2-phenyl-2-cyclopentylethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368371**, MW = 421.9g/mol, MF = C₂₁ H₂₈ Cl N₃ O₂ S, m/z + 1 = 386.2.

5

(1S,4R,6S)-2-Aza-((4-(3-(methylthio)-1-hexoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368374**, MW = 379.9g/mol, MF = C₁₅ H₂₆ Cl N₃ O₂ S₂, m/z + 1 = 344.

10

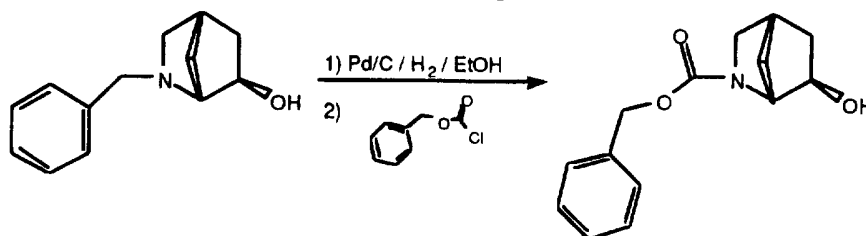
(1S,4R,6S)-2-Aza-((4-(2,3-pentafluoro-1-propoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY368376**, MW = 381.8g/mol, MF = C₁₁ H₁₃ Cl F₅ N₃ O₂ S, m/z + 1 = 346.1.

15

Example 44

Preparation

[*exo*] 2-Aza-2-benzylcarbonyl-bicyclo[2.2.1]heptan-6-ol



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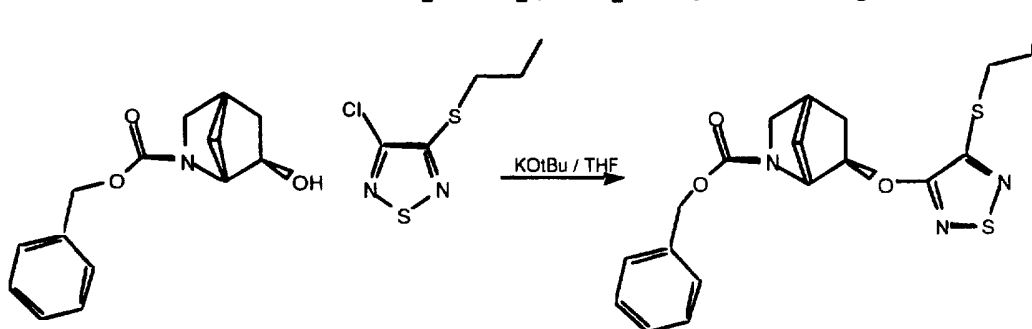
A solution of 2-benzyl-2-azabicyclo[2.2.1]heptan-6-ol (5.0mmol) in ethanol (75mL) and ethyl acetate (75mL) was hydrogenated with 5% Pd/C (10g) at 60 PSIG of hydrogen at room temperature for 16 hours. The catalyst was filtered off and the filtrate was evaporated. A solution of the filtrate in tetrahydrofuran (100mL) and H₂O (50mL) was cooled to 0°C. The pH was adjusted to 10 with 5N aqueous sodium hydroxide. Benzylchloroformate (5.1mmol) was added to the reaction solution while the pH was maintained between 9 and 10 with 5N aqueous sodium hydroxide. The reaction was stirred at 0°C for three hours, poured into ethyl acetate, washed with 1N HCl_(aq), dried over sodium sulfate, then

30

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evaporated to yield [exo] 2-aza-2-(benzylcarbonyl)-bicyclo[2.2.1]heptan-6-ol (4.9mmol).

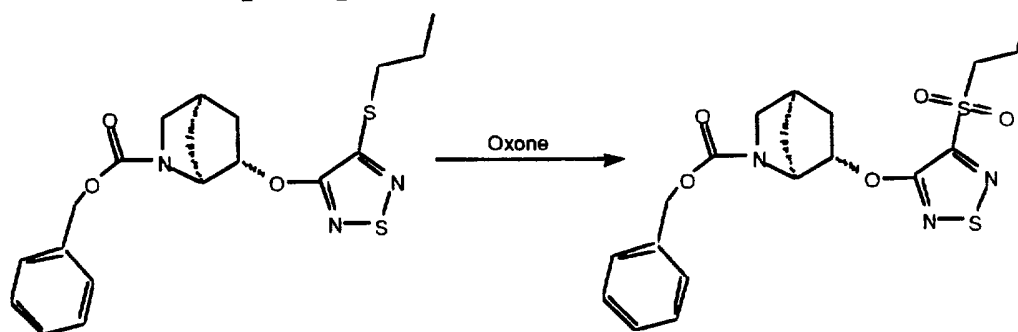
5 **[exo] 2-Aza-2-benzylcarbonyl-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane**



Potassium t-butoxide (2.6mmol) was added to a solution of [exo] 2-aza-2-benzylcarbonyl-bicyclo[2.2.1]heptan-6-ol (2.6mmol) in tetrahydrofuran (250mL). Stirred at -10_C
 10 for 30 minutes whereupon 3-chloro-4-(propylthio)-1,2,5-thiadiazole (2.6mmol) in tetrahydrofuran (50mL) was added to the reaction. Stirred for two hours at -10_C then room temperature for sixteen hours. The reaction mixture was poured into water and extracted with ethyl acetate. The
 15 organic extracts were dried and evaporated. The residue was purified by preparative HPLC using silica gel eluting with 30% ethyl acetate in hexanes to yield [exo] 2-aza-2-benzylcarbonyl-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.8g/2.0mmol).

20

[exo] 2-Aza-2-benzylcarbonyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



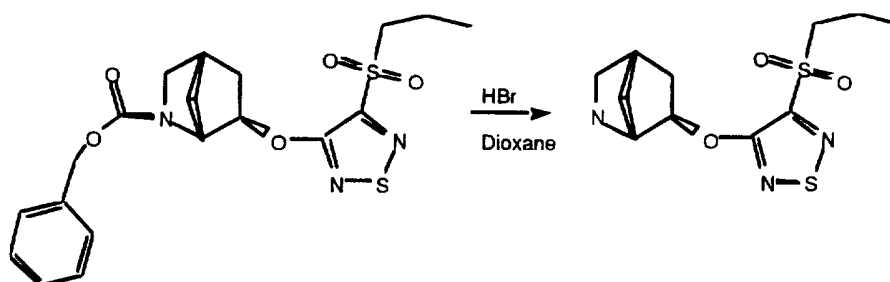
-73-

A solution of Oxone® (1.9g/3.2mmol) in water (10mL) was added to a solution of [exo] 2-aza-2-benzylcarbonyl-6-((4-(propylthio)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.8g/2.0mmol), water (4mL), 1N HCl_(aq) (2.9ml), and

5 tetrahydrofuran (20mL). Stirred at room temperature for four hours. The reaction was poured into water then extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, then evaporated to yield [exo] 2-aza-2-(benzylcarbonyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.7g/1.6mmol).

10

[exo] 2-Aza-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane



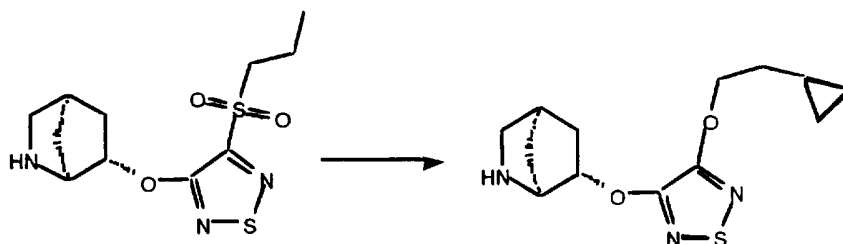
15 Hydrobromic acid was added (three minutes) above the surface of a solution of [exo] 2-aza-2-(benzylcarbonyl-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (2.2mmol) in dioxane (50mL). The reaction was stirred at room temperature for about two

20 hours. The reaction was poured into ethyl acetate, the aqueous layer was basified with aqueous sodium hydroxide, then extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate then evaporated to yield [exo] 2-aza-6-((4-propylsulfonyl-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane (0.57mg/1.9mmol).

25

[exo] 2-Aza-6-((4-cyclopropylethoxy-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane

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Potassium butoxide (6mmol) was added to a solution of cyclopropylethanol (6mmol) and tetrahydrofuran (70mL) at 0_C. The reaction was stirred for 45 minutes at 0_C. [exo] 2-Aza-2-benzylcarbonyl-6-((4-propylsulfonyl)-1,2,5-thiadiazol-3-yl)oxybicyclo[2.2.1]heptane (2.0mmol) was added to the reaction. The reaction was stirred for 3 hours while warming to room temperature. The reaction was poured into ethyl acetate then washed with water. The extracts were basified, dried over sodium sulfate then evaporated to yield [exo] 2-aza-6-((4-cyclopropylethoxy)-1,2,5-thiadiazol-3-yl)oxybicyclo[2.2.1]heptane which was isolated as the maleate salt to yield 400mg of **LY344171** (mp = 103-131_C).

The following compounds were made by following substantially the same procedure described above, except that the corresponding starting materials were selected to provide the desired compounds.

[exo] 2-Aza-((4-(cyclopropylmethoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344180**, mp 129-130_C.

[exo] 2-Aza-((4-(4-fluorobutoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344734**, mp 136-139_C.

[exo] 2-Aza-((4-(4-fluorobenzyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344735**, mp 164-165_C.

[exo] 2-Aza-((4-((2-thienyl)methoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344736**, mp 148-149_C.

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- [exo] 2-Aza-((4-(2-(2-thienyl)ethoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344737**, mp 140-142_C.
- 5 Z, [exo] 2-Aza-((4-(2-butenyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY34739**, mp 122-123_C.
- [exo] 2-Aza-((4-(3-butenyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344740**, mp
10 169-170_C.
- [exo] 2-Aza-((4-(3-butynyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344876**, mp
15 183-185_C.
- [exo] 2-Aza-((4-(2-butenyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344740**, mp
169-170_C.
- 20 E, [exo] 2-Aza-((4-(2-butenyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344877**, mp
169-170_C.
- [exo] 2-Aza-((4-(2-(3-thienyl)ethoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY344878**, mp 139-140_C.
- 25 [exo] 2-Aza-((4-(2-(4-fluorophenyl)ethoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344883**, mp
30 184-185_C.
- [exo] 2-Aza-((4-(cyclobutylmethoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344896**, mp
166-167_C.
- 35 [exo] 2-Aza-((4-(2-(4-chlorophenyl)-2-cyclopropylethoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane
hydrochloride, **LY344911**, mp 119-120_C.
- 40 [exo] 2-Aza-((4-((methylcyclopropyl)methoxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride,
LY344912 mp 155-156_C.
- [exo] 2-Aza-((4-(2-propynyloxy))-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344967**, mp
45 158-160_C.

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[exo] 2-Aza-((4-(4-(trifluoromethyl)benzyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY344968**, mp 180-183_C.

5 [exo] 2-Aza-((4-benzyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane hydrochloride, **LY348066**, mp 175-176_C.

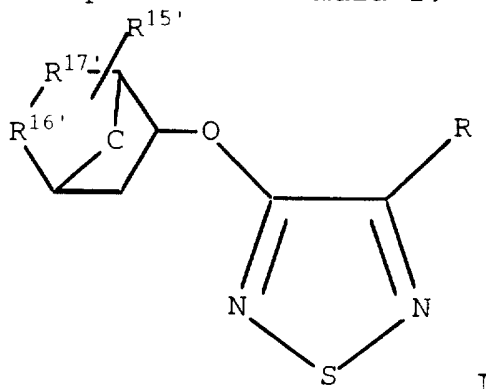
10 [exo] 2-Aza-((4-(3-thienyl)methoxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY348630**, mp 148-148.5_C.

15 [exo] 2-Aza-((4-(2-propenyloxy)-1,2,5-thiadiazol-3-yl)oxy)bicyclo[2.2.1]heptane maleate, **LY349390**, mp 129-131_C.

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We Claim:

1. A compound of formula I:



R is selected from the group consisting of -OR⁴, -SR⁴ and SO₂R⁴;

R⁴ is selected from the group consisting of C₁-15-alkyl, C₂-15-alkenyl, C₂-15-alkynyl, fused aromatic, and 5-membered heterocycle; each of which is optionally substituted with one or more independently selected from the group consisting of C₃-C₈ cycloalkyl, halogen(s), -CF₃, -CN, C₁-4 alkoxy, fused aromatic, 5-membered heterocycle, phenyl and phenoxy wherein phenyl, fused aromatic, and phenoxy is optionally substituted with one or more independently selected from the group consisting of halogen, -CN, C₁-4-alkyl, C₁-4-alkoxy, -OCF₃, -CF₃, -CONH₂ and -CSNH₂;

R^{16'} is carbon or nitrogen;

R^{17'} is carbon or nitrogen;

provided that one, and only one, of R^{16'} and R^{17'} must be nitrogen and when R^{16'} is nitrogen then R^{17'} is carbon and when R^{17'} is nitrogen then R^{16'} is carbon;

R^{15'} is selected from the group consisting of hydrogen, C₁-4 alkyl, C₁-4 alkenyl, C₁-4 alkynyl, -C(O)OR^{20'} and C₃-C₈ cycloalkyl;

R^{20'} is C₁-C₆ alkyl; or

a pharmaceutically acceptable salt or solvate thereof.

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2. A compound of **Claim 1** wherein R is -OR⁴.
3. A compound of **Claim 1** wherein R is -SR⁴.
4. A compound of **Claim 1** wherein R^{15'} is
hydrogen.
- 5 5. A compound of **Claim 1** wherein R^{16'} is
nitrogen.
6. A compound of **Claim 1** wherein R^{17'} is
nitrogen.
7. A compound of **Claim 1** wherein the
10 substitution is EXO.
8. A compound of **Claim 5** wherein R^{15'} is at the
R^{16'} position.
9. A compound of **Claim 6** wherein R^{15'} is at the
R^{17'} position.
- 15 10. A formulation comprising a compound of
Claim 1 associated with one or more carriers, diluents,
or excipients therefor.
11. A method for modulating a muscarinic
receptor comprising administering an effective amount of
20 a compound of **Claim 1** to a patient in need thereof.
12. A method of **Claim 11** wherein the compound
acts as a muscarinic receptor antagonist.
13. A method of **Claim 11** wherein the compound
acts as a muscarinic receptor agonist.
- 25 14. A method for treating a condition
associated with the malfunctioning of the muscarinic
cholinergic system comprising administering an effective
amount of a compound as claimed by **Claim 1** to a mammal in
need thereof.
- 30 15. A compound of **Claim 1** for use in the
manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US97/06675
A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 221/22, 285/10, 417/00, 417/12, 471/00

US CL : 546/84, 85, 97, 268.7; 548/135

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)

U.S. : 546/84, 85, 97, 268.7; 548/135

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 practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,043,345 A (SAUERBERG et al.) 27 August 1991, column, 4 lines 1-35.	1-11

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*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
A document defining the general state of the art which is not considered to be of particular relevance	*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
E earlier document published on or after the international filing date	*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
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)	* & * document member of the same patent family
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	

Date of the actual completion of the international search 02 JULY 1997	Date of mailing of the international search report 22 JUL 1997
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