MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel derivatives of 8-azoniabicyclo[3,2,1]octanes, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72 /id} {Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-

muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

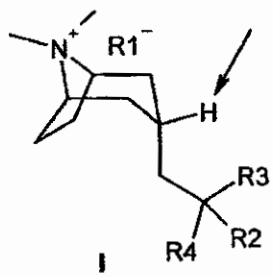
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M_3 mAChR and which method comprises administering an effective amount of a compound of Formula (I) or Formula (II) [except the compound of Formula (II) with R2 and R3 as 2-thiophene and R4 as $-OC(O)CH_3$] or a pharmaceutically acceptable salt thereof.

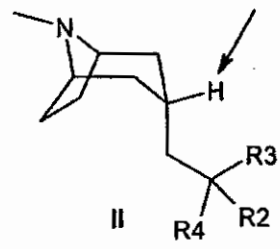
This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I) or Formula (II).

The present invention also provides for the novel compounds of Formula (I) or Formula (II), and pharmaceutical compositions comprising a compound of Formula (I) or Formula (II), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) or Formula (II) useful in the present invention are represented by the structure:



I



II

wherein:

the H atom indicated is in the exo position;

$R1^-$ represents an anion associated with the positive charge of the N atom. $R1^-$ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate;

R2 and R3 are independently selected from the group consisting of straight or branched chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups (having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms), heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom, heterocycloalkyl-alkyl (having 6 to10 carbon atoms) and N or O as the heteroatom, aryl, optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

R4 is slected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl, -OR5, $-CH_2OR5$, $-CH_2OH$, -CN, $-CF_3$, $-CH_2O(CO)R6$, $-CO_2R7$, $-CH_2NH_2$, $-CH_2N(R7)SO_2R5$, $-SO_2N(R7)(R8)$, $-CON(R7)(R8)$, $-CH_2N(R8)CO(R6)$, $-CH_2N(R8)SO_2(R6)$, $-CH_2N(R8)CO_2(R5)$, $-CH_2N(R8)CONH(R7)$;

R5 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl;

R6 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, aryl, heteroaryl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-heteroaryl;

R7 and R8 are, independently, selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{12})$cycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_7)$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl-aryl, and $(C_1\text{-}C_6)$alkyl-heteroaryl.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II) may also be formed with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine,

tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

• "wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as cyclopentene.

Preferred compounds useful in the present invention include:

(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;

(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;

3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;

N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;
[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and
(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

More preferred compounds useful in the present invention include:
(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and
(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

Methods of Preparation.

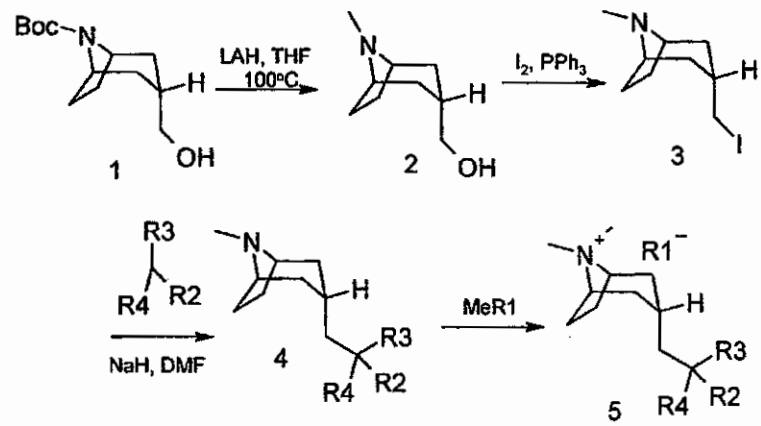
Preparation

The compounds of Formula (I) and Formula (II) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) and Formula (II) having a variety of different R1, R2, R3 and R4 which are

reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some schemes are shown with compounds only of Formula (II), this is merely for illustration purpose only.

The general preparation method is shown in **Scheme I**. The synthesis started with compound **1**. Reduction with lithium aluminium hydride (LAH) afforded alcohol **2**. Displacement with iodine provided **3**. Coupling reaction with the anion derived from HCR2(R3)(R4) then furnished compound **4**, which was easily converted to ammonium salt **5**.

Scheme I.

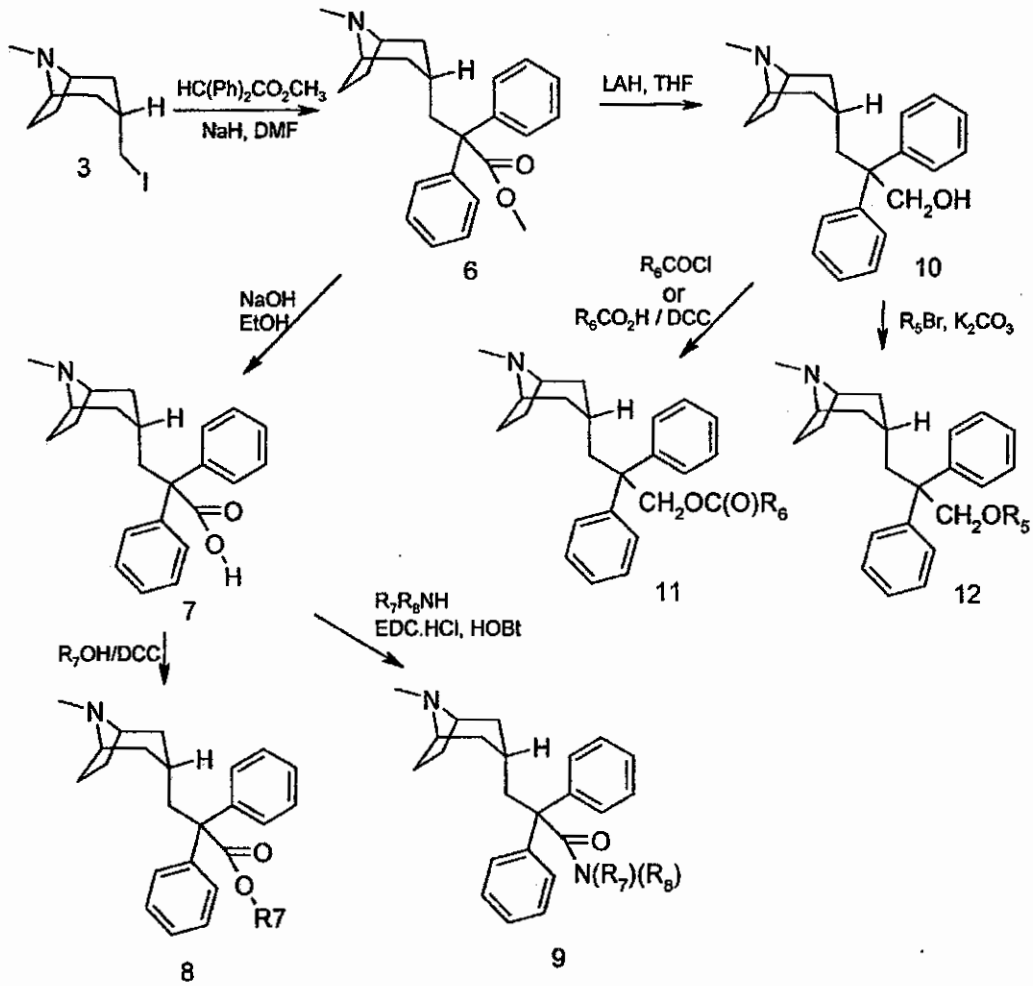


A more specific preparation method leading to compounds with Formula (II) is outlined in **Scheme II**. Alkylation of ester $HC(Ph)_2CO_2CH_3$ with **3** afforded compound **6**. Hydrolysis of **6** generated acid **7**. 1,3-Dicyclohexylcarbodiimide (DCC) mediated condensation of the acid with alcohol (R7)OH then furnished ester **8**. Condensation of acid **7** with amine (R7)(R8)NH under suitable amide coupling conditions well known to those skilled in the art such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole hydrate (HOBt) provided amide **9**. Reduction of **6** generated alcohol **10**. Reaction of **10** with acid chloride (R6)COCl or acid $(R6)CO_2H$ afforded ester **11**. Alkylation of **10** with appropriate reagents such as (R5)Br then furnished **12**.

Compounds with structures similar to **6, 7, 8, 9, 10, 11** and **12** were converted to corresponding ammonium salts by reacting with appropriate reaction reagents such as

MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

Scheme II.

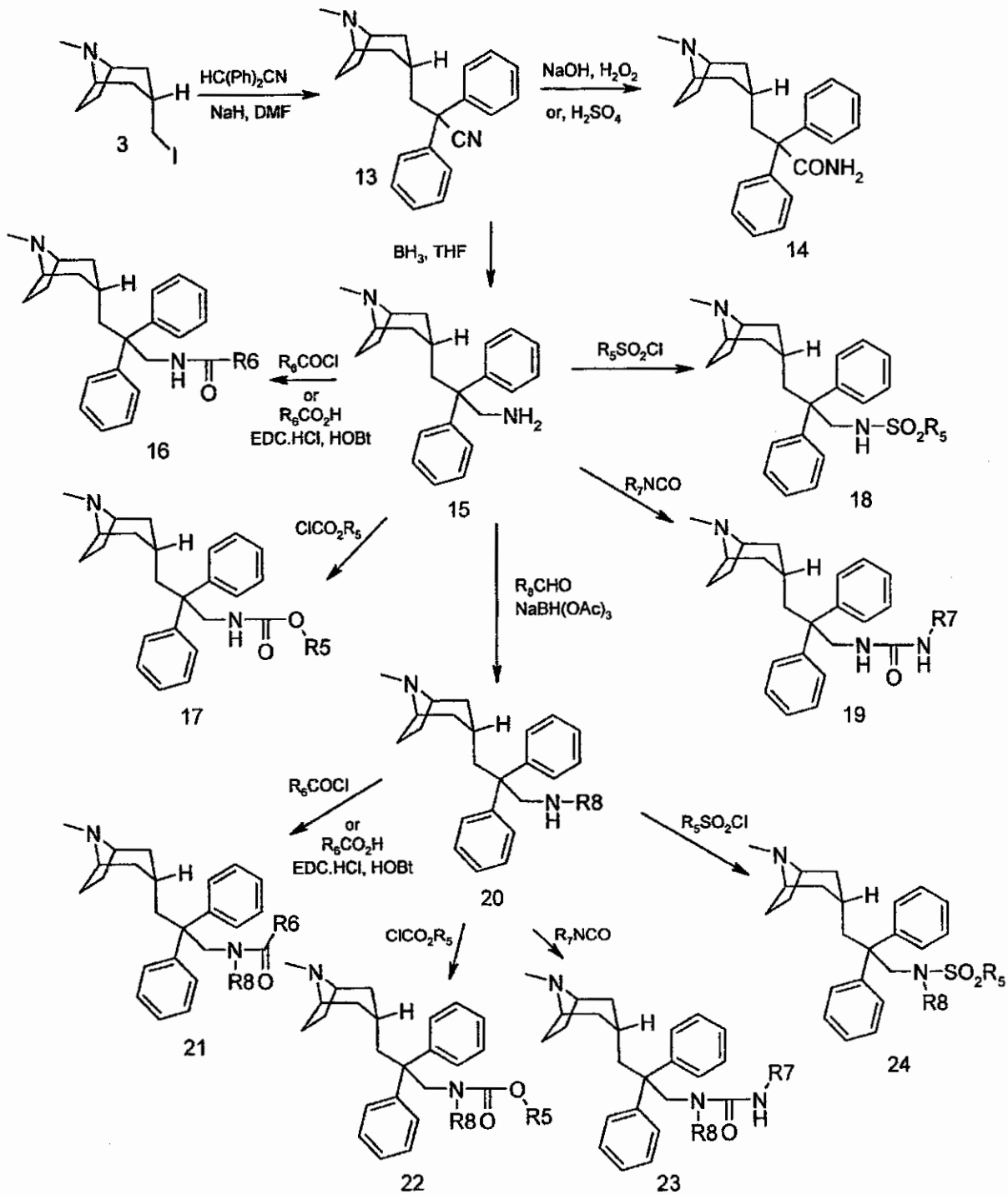


A more specific preparation method leading to compounds with Formula (II) is outlined in **Scheme III.** Alkylation of $HC(Ph)_2CN$ with **3** provided nitrile **13**. Hydrolysis of **13** under either basic conditions (e.g., NaOH and H_2O_2) or acidic conditions (e.g., H_2SO_4) afforded amide **14**. Reduction of **13** led to amine **15** that was conviently transfromed to amide **16**, carbamide **17**, sulfonamide **18** and urea **19**. Condensation of **15** with aldehyde (R8)CH(O) followed by reduction with $NaBH(OAc)_3$ furnished amine **20** that was easily converted to amide **21**, carbamide **22**, urea **23** and sulfonamide **24**.

Compounds with structures similar to **13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23** and **24** were converted to corresponding ammonium salts by reacting with appropriate

reaction reagents such as MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

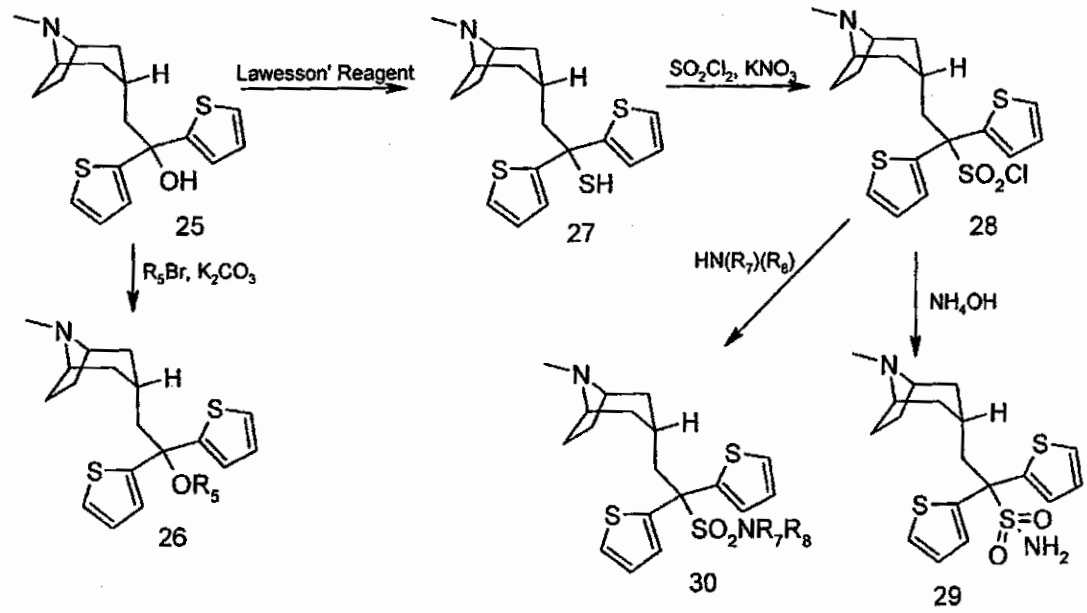
Scheme III.



A more specific preparation method leading to compounds with Formula (II) is outlined in **Scheme IV.** Alkylation of **25** with (R5)Br provided **26.** Reaction of **25** with Lawesson's reagent afforded **27.** Oxidation of **27** with SO_2Cl_2 and KNO_3 furnished **28** that was converted to either **29** or sulfonamide **30.**

Compounds with structures similar to **26, 27, 29** and **30** were easily converted to the corresponding ammonium salts by reacting with appropriate reaction reagents such as MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

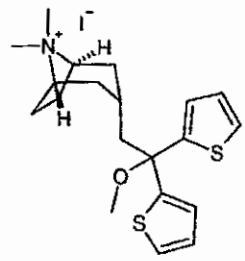
Scheme IV



SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

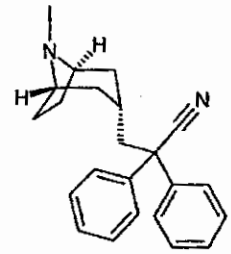
Example 1



(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

To a solution of 2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,1-dithiophen-2-yl-ethanol (prepared according to US2800482) (212mg, 0.64mmol) in 5 mL methylenechloride and iodomethane (0.40mL, 6.4 mmol), 50% aqueous potassium hydroxide (0.25mL, 3.2 mmol) and tetrabutylammonium chloride (5mg, 3 mol%) was added. The reaction mixture was heated to reflux for 5 d. Each day, an additional 0.2mL iodomethane and 0.1mL potassium hydroxide was added. Upon completion, the reaction mixture was cooled to room temperature, diluted with methylenechloride and washed with water. The aqueous layer was extracted with methylenechloride and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was recrystallized from methylenechloride/ethyl acetate to give 109mg of the title compound: LCMS (ES) *m/z* 362 $(M)^+$.

Example 2



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile

2a) Preparation of ((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanol

A mixture of 1,1-dimethylethyl (endo)-3-(hydroxymethyl)-8-azabicyclo[3.2.1] octane-8-carboxylate (0.50 g, 2.05 mmol) and $LiAlH_4$ (6.16 mL, 1.0 M in THF, 6.16 mmol) was heated at 80°C with a microwave reactor for 60 min. The solution was then mixed with saturated Na_2SO_4 solution, filtered through celite and concentrated to afford the title compound (0.31 g, 97 %): LCMS (ES) *m/z* 156 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.28 (s, 1H), 1.59 (m, 4H), 1.90 (m, 1H), 2.13 (m, 4H), 2.32 (s, 3H), 3.17 (s, 2H), 3.59 (d, 2H).

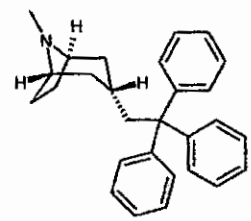
2b) Preparation of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane

A solution of iodine (6.67 g, 25.8 mmol) and ((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanol (2.0 g, 12.9 mmol) in CH_2Cl_2 (120 mL) was mixed with PPh_3 (on resin, 8.6 g, 3 mmol/g, 25.8 mmol). The resultant mixture was stirred for 17 hours, filtered and concentrated to afford the title compound (2.63 g, 77 %): LCMS (ES) *m/z* 266 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 2.05 (m, 4H), 2.39 (m, 3H), 2.79 (d, 3H), 2.98 (m, 2H), 3.45 (d, 2H), 3.81 (s, 2H).

2c) Preparation of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile

A solution of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane(1.06 g, 4.0 mmol) and Ph_2CHCN (2.32 g, 12.0 mmol) in DMF (20 mL) was mixed with NaH (0.288 g, 12.0 mmol). The resultant mixture was stirred at room temperature for 60 minutes. Filtration and purification via a reverse phase HPLC (Gilson) then afforded the title compound (1.16 g, 93 %): LCMS (ES) *m/z* 331 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.64 (m, 2H), 2.14 (m, 1H), 2.26 (m, 2H), 2.34 (m, 2H), 2.52 (m, 2H), 2.75 (m, 5H), 3.83 (s, 2H), 7.39 (d, 10H).

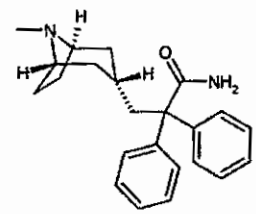
Example 3



(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane

A solution of triphenylmethane (0.276 g, 1.13 mmol) in THF (0.5 mL) was mixed with *n*-BuLi (0.706 mL, 1.6 M in Hexane, 1.13 mmol). The solution was stirred for 10 minutes and added by a solution of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane (100 mg, 0.377 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature for 60 minutes, mixed with H_2O (0.1 mL), concentrated and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (23.8 mg, 17 %): LCMS (ES) *m/z* 382 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.07 (d, 2H), 2.12 (m, 1H), 2.22 (m, 4H), 2.31 (m, 2H), 2.65 (d, 3H), 2.97 (d, 2H), 3.63 (s, 2H), 7.21 (m, 3H), 7.30 (d, 12H).

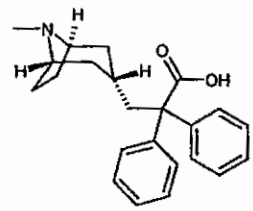
Example 4



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (53 mg, 0.16 mmol) in CH_2Cl_2 (0. 25 mL) was mixed with H_2SO_4 (0.28 mL, 96 %) and stirred at 40°C for 30 hours. The mixture was then poured into ice, neutralized with $NH_3.H_2O$, extracted with EtOAc and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) provided the title compound (17.2 mg, 30 %): MS (ES) *m/z* 347 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.31 (d, 2H), 1.98 (m, 1H), 2.28 (m, 4H), 2.39 (m, 2H), 2.67 (d, 3H), 2.79 (d, 2H), 3.66 (s, 2H), 5.82 (s, br, 1H), 6.88 (s, br, 1H), 7.37 (m, 10H).

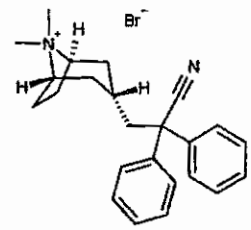
Example 5



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid

A solution of 2-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-1,1-diphenylethanol (100 mg, 1.56 mmol) in HCOOH (0.25 mL) was quickly added by H_2SO_4 (2.73 mL, 90 %) at 0°C. The reaction vial was capped immediately and stored in a refrigerator at –20°C for 7 days. The solution was poured into ice, neutralized with $NH_3.H_2O$, extracted with EtOAc and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (52 mg, 48 %): LCMS (ES) *m/z* 350 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.39 (d, 2H), 1.86 (m, 1H), 1.97 (m, 2H), 2.30 (m, 4H), 2.69 (s, 3H), 2.84 (d, 2H), 3.69 (s, 2H), 7.28 (m, 2H), 7.36 (m, 8H).

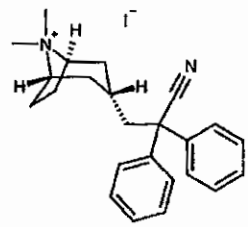
Example 6



(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (310 mg, 0.938 mmol) in acetone (6.0 mL) was mixed with MeBr (4.69 mL, 2.0 M in *t*-BuOMe, 9.38 mmol). The resultant mixture was stirred at room temperature for 60 minutes and filtered. The solid was washed with acetone (2 x 3 mL) to afford the title compound (333 mg, 83 %): LCMS (ES) *m/z* 345 $(M)^+$; ^{1}H-NMR(MeOD) δ 1.82 (d, 2H), 2.17 (m, 1H), 2.35 (m, 2H), 2.49 (m, 4H), 3.01 (d, 2H), 3.07 (s, 3H), 3.10 (s, 3H), 3.79 (s, 2H), 7.36 (m, 2H), 7.43 (m, 4H), 7.49 (m, 4H).

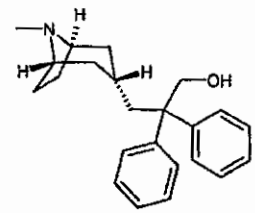
Example 7



(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (26.5 mg, 0.080 mmol) in CH_2Cl_2 (0.5 mL) and MeCN (0.5 mL) was mixed with MeI (0.125 mL, 2.00 mmol). The resultant mixture was stirred at room temperature for 3 hours, diluted with DMSO (0.3 mL) and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (22.9 mg, 60 %): LCMS (ES) *m/z* 345 $(M)^+$; ^{1}H-NMR($CDCl_3$) δ 1.83 (d, 2H), 2.17 (m, 1H), 2.35 (m, 2H), 2.49 (m, 4H), 3.01 (d, 2H), 3.07 (s, 3H), 3.10 (s, 3H), 3.79 (s, 2H), 7.36 (m, 2H), 7.43 (m, 4H), 7.49 (m, 4H).

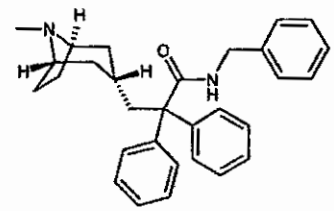
Example 8



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol

A mixture of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid (42.5 mg, 0.122 mmol) and $LiAlH_4$ (0.488 mL, 1.0 M in THF, 0.488 mmol) was heated with a microwave reactor at 100°C for 1 hour. It was diluted with saturated Na_2SO_4 solution, filtered through celite and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (29.1 mg, 71 %): LCMS (ES) *m/z* 336$(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.40 (d, 2H), 1.92 (m, 1H), 2.29 (m, 6H), 2.59 (m, 2H), 2.68 (d, 3H), 3.72 (s, 2H), 4.16 (s, 2H), 7.13 (m, 3H), 7.30 (m, 7H).

Example 9

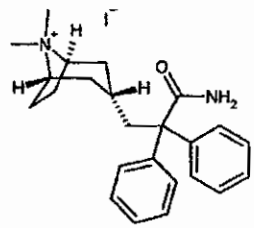


N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid (82.0 mg, 0.235 mmol) in CH_2Cl_2 (3.0 mL) was mixed with $PhCH_2NH_2$ (28.2 µL, 0.258 mmol), EDC (49.5 mg, 0.258 mmol), HOBt (3.2 mg, 0.024 mmol) and $(CH_3CH_2)_3N$ (0.232 mL, 1.65 mmol). The mixture was stirred at room temperature for 60 hours and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (29.8 mg, 30 %): LCMS (ES) *m/z* 439$(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.34 (d, 2H), 1.96 (m,

1H), 2.23 (m, 2H), 2.38 (m, 4H), 2.63 (d, 3H), 2.83 (d, 2H), 3.66 (s, 2H), 4.41 (d, 2H), 6.93 (m, 2H), 7.22 (m, 3H), 7.38 (m, 10H).

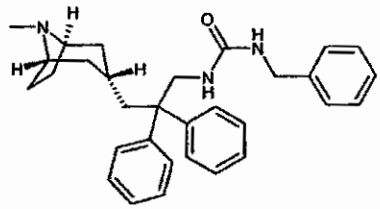
Example 10



(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide by following the procedure of Example 7 (33 % yield): LCMS (ES) *m/z* 363 $(M)^+$; ^{1}H-NMR($CDCl_3$) δ 1.49 (d, 2H), 1.95 (m, 1H), 2.25 (m, 2H), 2.42 (m, 4H), 2.84 (d, 2H), 3.17 (s, 3H), 3.23 (s, 3H), 3.93 (s, 2H), 5.65 (s, 1H), 5.91 (s, 1H), 7.39 (m, 10H).

Example 11



1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

11a) 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine

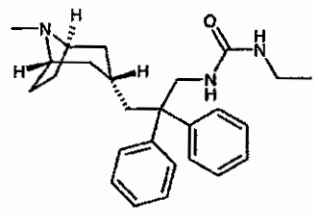
A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (250 mg, 0.758 mmol) in THF (2.5 mL) was mixed with BH_3 (2.53 mL, 1.5 M in THF, 3.79 mmol) at 0°C. The mixture was stirred at room temperature for 20 hours and diluted with H_2O (1.0 mL). The solution was then mixed with K_2CO_3 (0.1 g) and stirred at room temperature for 1 hour. Organic layers were separated and the aqueous part was extracted with EtOAc (2 x 3 mL). The organic layers were

combined, dried over Na_2SO_4 and concentrated. Purification via a reverse phase HPLC (Gilson) afforded the titled compound (159mg, 63%): LCMS (ES) *m/z* 335 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.35 (d, 2H), 2.01 (m, 3H), 2.34 (s, 4H), 2.55 (s, 2H), 2.68 (s, 3H), 3.73 (m, 5H), 7.26 (m, 4H), 7.33 (m, 2H), 7.43 (m, 4H).

11b) 1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (50.0 mg, 0.149 mmol) in CH_2Cl_2 (2.0 mL) was mixed with $PhCH_2NCO$ (20.4 μL, 0.164 mmol) and $(CH_3CH_2)_3N$ (62.8 μL, 0.447 mmol). The result mixture was stirred at room temperature for 1 hours and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the titled compound (13.0mg, 19%): LCMS (ES) *m/z* 468 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.24 (d, 2H), 1.94 (m, 3H), 2.25 (m, 4H), 2.49 (d, 2H), 2.67 (s, 3H), 3.62 (s, 2H), 3.97 (s, 2H), 4.23 (s, 2H), 7.22 (m, 6H), 7.33 (m, 4H).

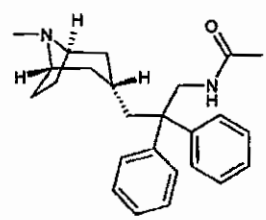
Example 12



1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and CH_3CH_2NCO by following the procedure in Example 11 (45% yield): LCMS (ES) *m/z* 406 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.03 (t, 3H), 1.33 (d, 2H), 1.94 (m, 3H), 2.25 (m, 4H), 2.55 (d, 2H), 2.67 (s, 3H), 3.07 (q, 2H), 3.68 (s, 2H), 3.94 (s, 2H), 7.24 (m, 6H), 7.34 (m, 4H).

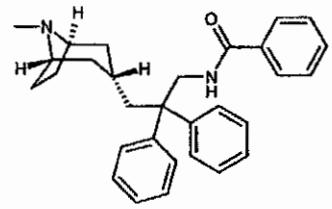
Example 13



N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (33.4 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was mixed with Ac_2O (18.9 μL, 0.20 mmol) and pyridine (16.2 μL, 0.20 mmol). The mixture was stirred at room temperature for 1 hour and concentrated. Purification *via* a reverse phase HPLC (Gilson) then afforded the title compound (10.7mg, 29%): LCMS (ES) *m/z* 377 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.26 (d, 2H), 1.82 (s, 3H), 1.96 (m, 3H), 2.26 (s, 4H), 2.53 (d, 2H), 2.67 (s, 3H), 3.66 (s, 2H), 4.00 (s, 2H), 7.24 (m, 6H), 7.33 (m, 4H).

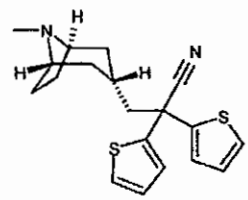
Example 14



N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and $(PhCO)_2O$ by following the procedure in Example 13 (8% yield): LCMS (ES) *m/z* 439 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.28 (d, 2H), 2.00 (m, 3H), 2.24 (s, 4H), 2.59 (d, 2H), 2.67 (s, 3H), 3.65 (s, 2H), 4.21 (s, 2H), 7.31 (m, 6H), 7.39 (m, 6H), 7.50 (m, 3H).

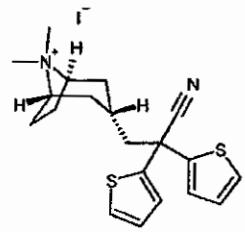
Example 15



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile

The title compound was prepared from (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane and 2,2-di-thiophen-2-yl-acetonitrile by following the procedure in Example 2C (34 % yield): LCMS (ES) *m/z* 343 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.79 (m, 2H), 2.21 (m, 2H), 2.33 (m, 2H), 2.62 (m, 2H), 2.73 (m, 4H), 3.80 (m, 2H), 4.35 (s, 2H), 7.02 (m, 2H), 7.23 (m, 2H), 7.37 (m, 2H).

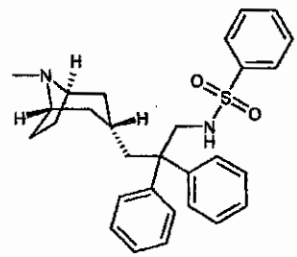
Example 16



(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile by following the procedure in Example 7 (43 %): LCMS (ES) *m/z* 345 $(M)^+$; ^{1}H-NMR($CDCl_3$) δ 1.82 (d, 2H), 2.35 (m, 2H), 2.23 (m, 3H), 2.58 (m, 4H), 2.82 (m, 2H), 3.37 (s, 6H), 4.25 (s, 2H), 7.02 (m, 2H), 7.24 (m, 2H), 7.36 (m, 2H).

Example 17

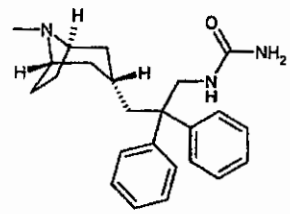


N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (67.0 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was mixed with $PhSO_2Cl$ (28.2 μL, 0.22 mmol) and $(CH_3CH_2)_3N$ (84.3 μL, 0.60 mmol). The result mixture was stirred at room temperature for 1 hours and concentrated. Purification *via* a reverse phase HPLC (Gilson) then afforded the title compound (51.5mg, 54%): LCMS (ES) *m/z* 475

$(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.39 (d, 2H), 2.01 (m, 3H), 2.30 (s, 4H), 2.69 (s, 5H), 3.60 (s, 2H), 3.68 (s, 2H), 7.12 (m, 4H), 7.27 (m, 6H), 7.55 (m, 2H), 7.63(m, 1H), 7.78 (m, 2H).

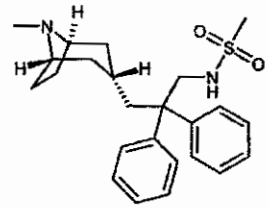
Example 18



[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

To a solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (50.0 mg, 0.149 mmol) in CH_2Cl_2 (4.0 mL), $ClSO_2NCO$ (31.2 μL, 0.358 mmol) was added. The mixture was stirred at room temperature for 2 days and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (21.6mg, 38%): LCMS (ES) *m/z* 378 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.33 (d, 2H), 2.01 (m, 3H), 2.29 (s, 4H), 2.57 (m, 2H), 2.68 (s, 3H), 3.69 (s, 2H), 4.01 (s, 2H), 7.25 (m, 6H), 7.34 (m, 4H).

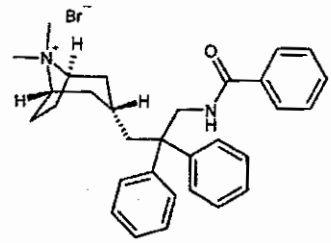
Example 19



N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and $MeSO_2Cl$ by following the procedure in Example 17 (28% yield): LCMS (ES) *m/z* 413 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.39 (d, 2H), 1.97 (m, 3H), 2.30 (s, 4H), 2.68 (s, 3H), 2.76 (s, 3H), 3.68 (s, 2H), 3.84 (s, 2H), 7.23 (s, 6H), 7.33 (s, 4H).

Example 20



(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide

A solution of *N*-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide (29 mg, 0.0683 mmol) in CH_2Cl_2 (0.5 mL) and acetone (0.5 mL) was mixed with MeBr (0.342 mL, 2.0 M in *t*-butyl methyl ether, 0.683 mmol). The resultant mixture was stirred at room temperature for 3 hours and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (19.6 mg, 64 %): LCMS (ES) *m/z* 453 $(M)^+$; ^{1}H-NMR(MeOD) δ 1.20 (d, 2H), 2.32 (m, 7H), 2.65 (d, 2H), 2.98 (s, 3H), 3.02 (s, 3H), 3.60 (s, 2H), 4.22 (s, 2H), 7.30(m, 6H), 7.39(m, 6H), 7.50 (s, 3H).

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assay:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described[10]. CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10

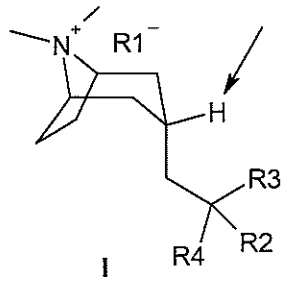
minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM NaH CO_3, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels [11]. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine[12]. Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

CLAIMS

1. A compound having structure I as indicated below



I

wherein:

the H atom indicated is in the exo position;

$R1^-$ represents an anion associated with the positive charge of the N atom;

R2 and R3 each represent phenyl; and

R4 represents –CN.

2. A compound according to claim 1 wherein $R1^-$ is selected from bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate.

3. A compound according to claim 1 which is (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide.

4. A compound according to claim 1 which is (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

5. A pharmaceutical composition comprising a compound according to any of claims 1 to 4 and a pharmaceutically acceptable carrier thereof.

6. A pharmaceutical composition comprising (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide.

7. A pharmaceutical composition comprising (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

8. Use of a compound according to any of claims 1 to 4 in the manufacture of a medicament for the treatment of a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor.

9. Use according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. Use according to claim 8 or 9 wherein the compound is to be administered via inhalation via the mouth or nose.

11. Use according to any of claims 8 to 10, wherein the compound is to be administered via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.