QUATERNARY AMMONIUM DIPHENYLMETHYL COMPOUNDS USEFUL AS MUSCARINIC RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to quaternary ammonium compounds having muscarinic receptor antagonist or anticholinergic activity. The invention also relates to pharmaceutical compositions comprising these compounds, processes for preparing them and methods of use to treat pulmonary disorders.

STATE OF THE ART

Pulmonary or respiratory disorders, such as chronic obstructive pulmonary disease (COPD) and asthma, afflict many millions of people worldwide and such disorders are a leading cause of morbidity and mortality.

Muscarinic receptor antagonists are known to provide bronchoprotective effects and therefore, such compounds are useful for treating respiratory disorders, such as COPD and asthma. When used to treat such disorders, muscarinic receptor antagonists are typically administered by inhalation. However, even when administered by inhalation, a significant amount of the muscarinic receptor antagonist is often absorbed into the systemic circulation resulting in systemic side effects, such as dry mouth, mydriasis and cardiovascular side effects.

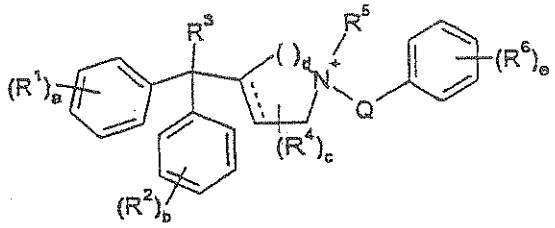
Additionally, many inhaled muscarinic receptor antagonists have a relatively short duration of action requiring that they be administered several times per day. Such a multiple-daily dosing regime is not only inconvenient but also creates a significant risk of inadequate treatment due to patient non-compliance with the required frequent dosing schedule.

Accordingly, a need exists for new muscarinic receptor antagonists. In particular, a need exists for muscarinic receptor antagonists having high potency, reduced systemic side effects when administered by inhalation, and a long duration of action thereby allowing for once-daily or even once-weekly dosing. In addition, a need exists for muscarinic receptor antagonists having high affinity for the receptor and a long receptor half life. Such compounds are expected to be particularly effective for treating pulmonary disorders, such as COPD and asthma, while reducing or eliminating side effects, such as dry-mouth and constipation.

SUMMARY

The present disclosure provides novel quaternary ammonium compounds which have muscarinic receptor antagonist or anticholinergic activity. Among other properties, compounds of the present disclosure have been found to possess improved binding affinity for hM_2 and hM_3 muscarinic receptor subtypes, have longer receptor half-lives, have a larger therapeutic window, or have greater potency compared to related compounds. Accordingly, compounds of the present disclosure are expected to be useful and advantageous as therapeutic agents for treating pulmonary disorders.

One embodiment of the present disclosure relates to compounds having formula I:



(I)

in salt or zwitterionic form, wherein:

a and b are independently 0 or an integer of from 1 to 5;

each R^1 and R^2 is independently selected from $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl, $-C_{3-6}$cycloalkyl, cyano, halo, $-OR^a$, $-CH_2OH$, -COOH, $-C(O)O-C_{1-4}$alkyl, $-C(O)NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, and $-NR^bR^c$; where each R^a is independently selected from hydrogen, $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl and $-C_{3-6}$cycloalkyl; each R^b and R^c is independently selected from hydrogen, $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl or $-C_{3-6}$cycloalkyl; or R^b and R^c together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle; or two adjacent R^1 groups or two adjacent R^2 groups are joined together to form $-C_{3-6}$alkylene, $-C_{2-4}$alkylene-O- or $-O-C_{1-4}$alkylene-O-;

R^3 is selected from $-C(O)NR^{3a}R^{3b}$, $-C(O)O-C_{1-4}$alkyl, -CN, -OH, $-CH_2OH$, and $-CH_2NH_2$;

R^{3a} and R^{3b} are independently selected from hydrogen, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-6}$cycloalkyl, $-C_{6-10}$aryl, $-C_{2-9}$heteroaryl, $-C_{3-6}$heterocycle, and $-(CH_2)_{1-2}-R^{3c}$, where R^{3c} is selected from -OH, $-O-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-C_{6-10}$aryl, $-C_{2-9}$heteroaryl, and $-C_{3-6}$heterocycle; or R^{3a} and R^{3b} together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle optionally containing one additional heteroatom selected from nitrogen, oxygen or sulfur;

c is 0 or an integer of from 1 to 3;

each R^4 is independently fluoro or -C_{1-4}alkyl;

d is 1 or 2, and ⎓ depicts an optional double bond;

R^5 is selected from -C_{1-6}alkyl, -CH_2-C_{2-6}alkenyl, -CH_2-C_{2-6}alkynyl, and -CH_2COR^{5a}; where R^{5a} is selected from -OH, -O-C_{1-6}alkyl, and -$NR^{5b}R^{5c}$; and R^{5b} and R^{5c} are independently selected from H and -C_{1-6}alkyl;

Q is -C_{0-5}alkylene-Q'-C_{0-1}alkylene-, wherein Q' is selected from -CH_2-, -CH=CH-, -C≡C-, -O-, -S-, -S(O)-, -SO_2-, -SO_2-NR^{Q1}-, -NR^{Q1}-SO_2-, -C(O)-, -OC(O)-, -C(O)O-, -NR^{Q1}C(O)-, -C(O)NR^{Q1}-, -NR^{Q2}-C(O)-NR^{Q3}-, -NR^{Q2}-C(S)-NR^{Q3}-, -C=N-O-, -S-S-, and-C(=N-O-R^{Q4})-, where R^{Q1} is hydrogen or -C_{1-4}alkyl, R^{Q2} and R^{Q3} are independently selected from hydrogen, -C_{1-4}alkyl, and -C_{3-6}cycloalkyl, or R^{Q2} and R^{Q3} are taken together to form -C_{2-4}alkylene or -C_{2-3}alkenylene, and R^{Q4} is -C_{1-4}alkyl or benzyl;

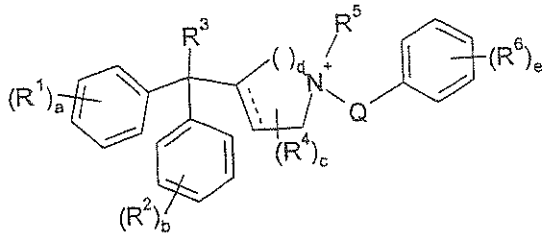
e is 0 or an integer of from 1 to 5;

each R^6 is independently selected from halo, -C_{1-4}alkyl, -C_{0-4}alkylene-OH, cyano, -C_{0-2}alkylene-COOH, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -$N(C_{1-4}alkyl)_2$, and -$N^+(O)O^-$;

wherein each alkyl, alkenyl, alkylene, alkynyl and cycloalkyl group in R^{1-3}, R^{3a-3c}, R^{4-6}, and R^a-R^c is optionally substituted with 1 to 5 fluoro atoms; wherein each alkyl, alkenyl, and alkynyl group in R^5 is optionally substituted with 1 to 2 substituents independently selected from -O-C_{1-6}alkyl, -OH and phenyl; each cycloalkyl, aryl, heteroaryl and heterocycle group in R^{1-2}, R^{3a-3c}, and R^{a-c} is optionally substituted with 1 to 3 substituents independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, cyano, halo, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -S(O)(C_{1-4}alkyl), -$S(O)_2$(C_{1-4}alkyl), -NH_2, -NH(C_{1-4}alkyl) and -$N(C_{1-4}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl group is optionally substituted with 1 to 5 fluoro substituents; and each -CH_2- group in Q is optionally substituted with 1 or 2 substituents independently selected from -C_{1-2}alkyl, -OH and fluoro;

or a pharmaceutically acceptable salt thereof.

According to a first aspect of the invention, there is provided a compound of formula I:



(I)

in salt or zwitterionic form, wherein:

a and b are independently 0 or an integer of from 1 to 5;

each R^1 and R^2 is independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C_{3-6}cycloalkyl, cyano, halo, -OR^a, -CH_2OH, -COOH, -C(O)-O-C_{1-4}alkyl, -$C(O)NR^bR^c$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, and -NR^bR^c; where each R^a is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl and -C_{3-6}cycloalkyl; each R^b and R^c is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl or -C_{3-6}cycloalkyl; or R^b and R^c together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle; or two adjacent R^1 groups or two adjacent R^2 groups are joined together to form -C_{3-6}alkylene, -C_{2-4}alkylene-O- or -O-C_{1-4}alkylene-O-;

R^3 is selected from -$C(O)NR^{3a}R^{3b}$, -C(O)O-C_{1-4}alkyl, -CN, -CH_2OH, and -CH_2NH_2; where R^{3a} and R^{3b} are independently selected from hydrogen, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, -C_{3-6}heterocycle, and -$(CH_2)_{1-2}$-R^{3c}, where R^{3c} is selected from -OH, -O-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, and -C_{3-6}heterocycle; or R^{3a} and R^{3b} together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle optionally containing one additional heteroatom selected from nitrogen, oxygen or sulfur;

c is 0 or an integer of from 1 to 3;

each R^4 is independently fluoro or -C_{1-4}alkyl;

d is 1 or 2, and ⎓ depicts an optional double bond;

R^5 is selected from -C_{1-6}alkyl, -CH_2-C_{2-6}alkenyl, -CH_2-C_{2-6}alkynyl, and -CH_2COR^{5a}; where R^{5a} is selected from -OH, -O-C_{1-6}alkyl, and -$NR^{5b}R^{5c}$; and R^{5b} and R^{5c} are independently selected from H and -C_{1-6}alkyl;

Q is -C_{0-5}alkylene-Q'-C_{0-1}alkylene-, wherein Q' is selected from -CH_2-, -CH=CH-, -C≡C-, -O-, -S-, -S(O)-, -SO_2-, -SO_2-NR^{Q1}-, -NR^{Q1}-SO_2-, -C(O)-, -OC(O)-, -C(O)O-, -NR^{Q1}C(O)-, -$C(O)NR^{Q1}$-, NR^{Q2}-C(O)-NR^{Q3}-, -NR^{Q2}-C(S)-NR^{Q3}-, -C=N-O-, -S-S-, and-C(=N-O-R^{Q4})-, where R^{Q1} is hydrogen or -C_{1-4}alkyl, R^{Q2} and R^{Q3} are independently selected from hydrogen, -C_{1-4}alkyl, and -C_{3-6}cycloalkyl, or R^{Q2} and R^{Q3} are taken together to form -C_{2-4}alkylene or -C_{2-3}alkenylene, and R^{Q4} is -C_{1-4}alkyl or benzyl;

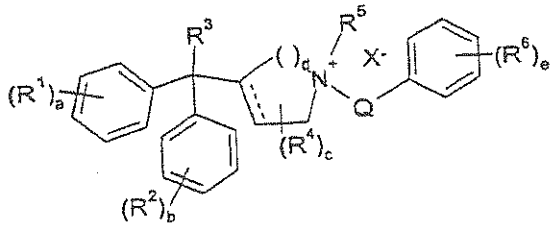
e is 0 or an integer of from 1 to 5;

each R^6 is independently selected from halo, -C_{1-4}alkyl, -C_{0-4}alkylene-OH, cyano, -C_{0-2}alkylene-COOH, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -$N(C_{1-4}alkyl)_2$, and -$N^+(O)O$;

wherein each alkyl, alkenyl, alkylene, alkynyl and cycloalkyl group in R^{1-3}, R^{3a-3c}, R^{4-6}, and R^{a-c} is optionally substituted with 1 to 5 fluoro atoms; wherein each alkyl, alkenyl, and alkynyl group in R^5 is optionally substituted with 1 to 2 substituents independently selected from -O-C_{1-6}alkyl, -OH and phenyl; each cycloalkyl, aryl, heteroaryl and heterocycle group in R^{1-2}, R^{3a-3c}, and R^{a-c} is optionally substituted with 1 to 3 substituents independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, cyano, halo, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -S(O)(C_{1-4}alkyl), -$S(O)_2$(C_{1-4}alkyl), -NH_2, -NH(C_{1-4}alkyl) and -N(C_{1-4}alkyl)$_2$, wherein each alkyl, alkenyl and alkynyl group is optionally substituted with 1 to 5 fluoro substituents; and each -CH_2- group in Q is optionally substituted with 1 or 2 substituents independently selected from -C_{1-2}alkyl, -OH and fluoro;

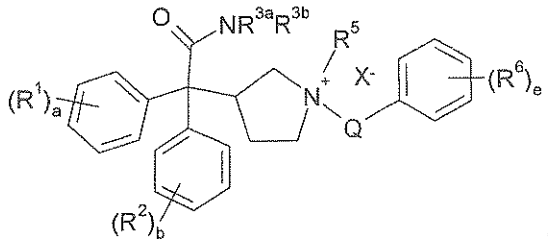
or a pharmaceutically acceptable salt thereof, wherein when said compound is in salt form, said compound comprises an anion of a pharmaceutically acceptable acid.

One embodiment of the present disclosure relates to quaternary ammonium compounds having formula I':



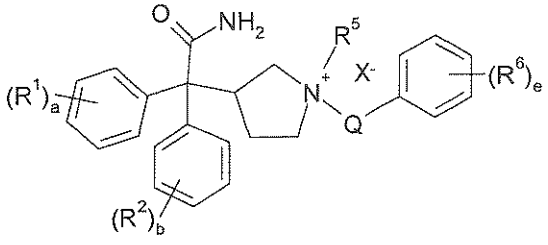
(I')

or a pharmaceutically acceptable salt thereof, where X^- is an anion of a pharmaceutically acceptable acid; and R^{1-6}, a-e, and Q are as defined above. Another embodiment of the present disclosure relates to quaternary ammonium compounds having formula I'a:



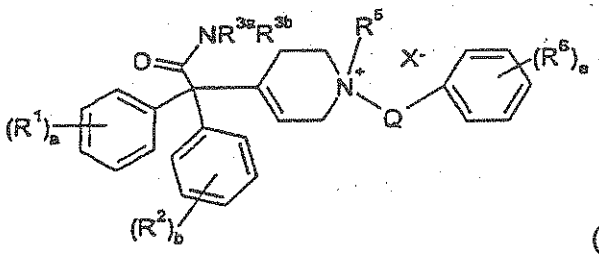
(I'a)

or a pharmaceutically acceptable salt thereof, where R^{1-2}, R^{3a-3b}, R^{5-6}, a, b, e, Q and X^- are as defined above. In one particular embodiment of formula I'a, Q is -C_{2-5}alkylene-Q'-. Still another embodiment of the present disclosure relates to quaternary ammonium compounds having formula I'b:



(I'b)

or a pharmaceutically acceptable salt thereof, where R^6, e, Q and X^- are as defined above. In one particular embodiment of formula I'b, Q is -C_{2-5}alkylene-Q'-. Another embodiment of the present disclosure relates to quaternary ammonium compounds having formula I'c:



(I'c)

or a pharmaceutically acceptable salt thereof, where R^{1-2}, R^{3a-3b}, R^{5-6}, a, b, e, Q and X^- are as defined above. In one particular embodiment of formula I'c, Q is -C_{2-5}alkylene-Q'-.

Among the compounds of formula I, compounds of particular interest are those having an inhibition dissociation constant (K_i) for binding to the M_3 receptor subtype of less than or equal to 100 nM; in particular having a K_i less than or equal to 50 nM; more particularly having a K_i less than or equal to 10 nM; and even more particularly having a K_i less than or equal to 1.0 nM.

According to a second aspect of the invention, there is provided a pharmaceutical composition comprising the compound as defined above and a pharmaceutically acceptable carrier.

Another embodiment of the present disclosure relates to pharmaceutical compositions comprising

a pharmaceutically acceptable carrier and a compound of the present disclosure. Such compositions may optionally contain other therapeutic agents such as steroidal anti-inflammatory agents (e.g., corticosteroids), β_2 adrenergic receptor agonists, phosphodiesterase-4 inhibitors, and combinations thereof. Accordingly, in yet another embodiment of the present disclosure, a pharmaceutical composition comprises a compound of the present disclosure, a second active agent, and a pharmaceutically acceptable carrier. Another embodiment of the present disclosure pertains to a combination of active agents, comprising a compound of the present disclosure and a second active agent. The compound of the present disclosure can be formulated together or separately from the additional agent(s). When formulated separately, a pharmaceutically acceptable carrier may be included with the additional agent(s). Thus, yet another embodiment of the present disclosure relates to a combination of pharmaceutical compositions, the combination comprising: a first pharmaceutical composition comprising a compound of the present disclosure and a first pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising a second active agent and a second pharmaceutically acceptable carrier. This present disclosure also relates to a kit containing such pharmaceutical compositions, for example where the first and second pharmaceutical compositions are separate pharmaceutical compositions.

Compounds of the present disclosure possess muscarinic receptor antagonist activity, and are therefore expected to be useful as therapeutic agents for treating patients suffering from a disease or disorder that is treated by blocking the muscarinic receptor. Thus, one embodiment of the present disclosure is directed to a method of producing bronchodilation in a patient, comprising administering to the patient a bronchodilation-producing amount of a compound of the present disclosure. The present disclosure is also directed to method of treating a pulmonary disorder such as chronic obstructive pulmonary disease or asthma, comprising administering to a patient a therapeutically effective amount of a compound of the present disclosure. Another embodiment of the present disclosure relates to a method for antagonizing a muscarinic receptor in a mammal comprising administering to the mammal, a muscarinic receptor-antagonizing amount of a compound of the present disclosure.

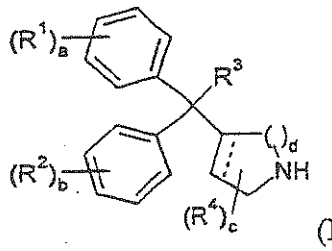
Since compounds of the present disclosure possess muscarinic receptor antagonist activity, such compounds are also useful as research tools. Accordingly, one embodiment of the present disclosure pertains to a method of using a compound of the present disclosure as a research tool, the method comprising conducting a biological assay using a compound of the present disclosure. Compounds of the present disclosure can also be used to evaluate new chemical compounds. Thus another

embodiment of the present disclosure relates to a method of evaluating a test compound in a biological assay, comprising: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the present disclosure to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include a muscarinic receptor binding assay and a bronchoprotection assay in a mammal. Still another embodiment of the present disclosure is directed to a method of studying a biological system or sample comprising a muscarinic receptor, the method comprising: (a) contacting the biological system or sample with a compound of the present disclosure; and (b) determining the effects caused by the compound on the biological system or sample.

The present disclosure is also directed to processes and intermediates useful for preparing compounds of the present disclosure. Accordingly, another embodiment of the present disclosure relates to a process of preparing compounds of the present disclosure, comprising: (a) reacting a compound of formula II with a compound of formula III to produce a compound of formula IV, and reacting the compound of formula IV with an organic substrate containing an R^5 group; or (b) reacting a compound of formula V with a compound of formula III; or (c) reacting a compound of formula V with a compound of formula VI to produce a compound of formula VII, and reacting the compound of formula VII with a compound of formula VIII; and recovering the product in salt or zwitterionic form, to provide a compound of formula I or I'; wherein compounds of formula II-VIII are as defined herein.

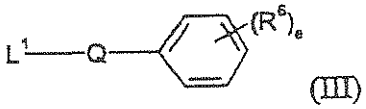
According to a third aspect of the invention, there is provided a process for preparing the compound as defined above, comprising:

(a) reacting a compound of formula II:



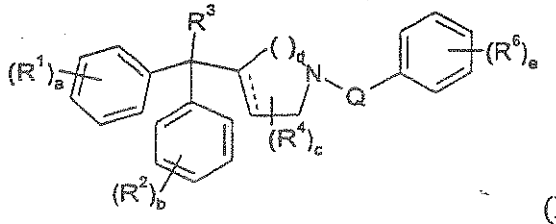
(II)

with a compound of formula III:



(III)

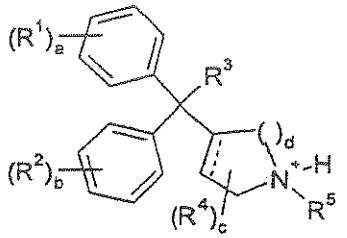
where L^1 represents a leaving group, to produce a compound of formula IV:



(IV)

and reacting the compound of formula IV with an organic substrate containing an R^5 group; or

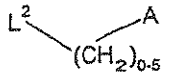
(b) reacting a compound of formula V:



(V)

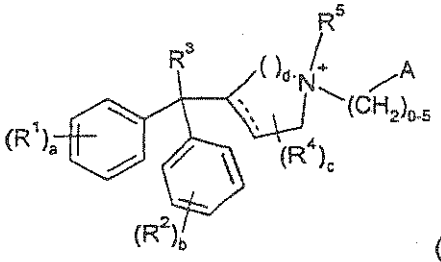
with a compound of formula III; or

(c) reacting a compound of formula V with a compound of formula VI:



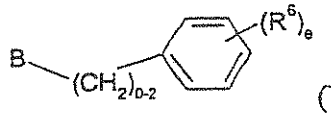
(VI)

where L^2 represents a leaving group, to produce a compound of formula VII:



(VII)

and reacting the compound of formula VII with a compound of formula VIII:



(VIII)

wherein L^3 represents a leaving group, and Q', A and B are defined as:

Q'	A	B
$-CH_2-$	$-CH_3$	L^3-alkylene-
-CH=CH-	H	L^3-alkenylene-
-C≡C-	H	L^3-alkynylene -
-O-	$-L^3$	HO-
-S-	$-L^3$	HS-
$-SO_2-NR^{Q1}-$	$-SO_2-OH$ or $-SO_2Cl$	$R^{Q1}HN-$
$-NR^{Q1}-SO_2-$	$-NHR^{Q1}$	HOO_2S-
-OC(O)-	-OH	HO(O)C-
-C(O)O-	-C(O)OH or -C(O)Cl	HO-
$-NR^{Q1}C(O)-$	$-NHR^{Q1}$	HO(O)C- or Cl(O)C-
$-NR^{Q2}-C(O)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=C=O	H_2N-
$-NR^{Q2}-C(S)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=S=O	H_2N-
-C=N-O-	-CHO	H_2NO-
-S-S-	-SH	HS-

and recovering the product in salt or zwitterionic form.

In other embodiments, the present disclosure is directed to products prepared by any of the processes described herein.

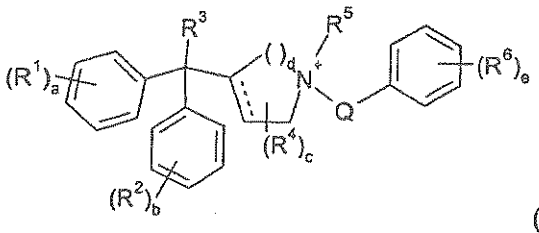
According to a fourth aspect of the invention, there is provided a compound prepared by the process as defined above.

According to a fifth aspect of the invention, there is provided use of the compound as defined above for the manufacture of a medicament.

Yet another embodiment of the present disclosure is directed to the use of a compound of the present disclosure for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating a pulmonary disorder or for antagonizing a muscarinic receptor in a mammal. Still another embodiment of the present disclosure pertains to the use of a compound of the present disclosure as a research tool. Other embodiments of the present disclosure are disclosed herein.

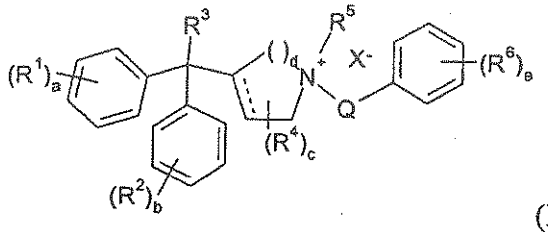
DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to compounds having formula I:



(I)

in salt or zwitterionic form, or a pharmaceutically acceptable salt thereof. More specifically, the invention is directed to quaternary ammonium compounds having formula I':



(I')

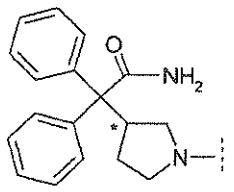
or a pharmaceutically acceptable salt thereof, where X^- is an anion of a pharmaceutically acceptable acid. The term "quaternary ammonium compound" refers to a compound that is derived from ammonium hydroxide or from an ammonium salt, wherein all four hydrogen atoms of the NH_4^+ ion have been replaced by organic groups.

As used herein, the term "compound of the invention" is intended to include compounds of formula I as well as the species embodied in formulas I', I'a, I'b, I'c, I'd, and I'e. The compounds of the invention are quaternary ammonium salts and may be converted between different salt forms using state of the art methodologies, for example, using ion exchange chromatography. Also, the compounds can be obtained in the form of solvates, and such solvates are included within the scope of this invention. Accordingly, those skilled in the art will recognize that reference to a compound herein, for example, reference to a "compound of the invention" includes reference to a compound of formula I as well as to any pharmaceutically acceptable salt forms and pharmaceutically acceptable solvates of that compound unless otherwise indicated.

The compounds of the invention may contain one or more chiral centers and so may exist in a number of stereoisomeric forms. When such chiral centers are present, this invention is directed to racemic mixtures, pure stereoisomers (i.e., enantiomers or diastereomers), stereoisomer-enriched mixtures, and the like unless otherwise indicated. When a chemical structure is depicted without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Thus, for example, the term "compound of formula I" is intended to include all possible stereoisomers of the

compound. Similarly, when a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of this invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual enantiomers may be obtained by numerous methods that are well known in the art, including chiral chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereomers, separating the diastereomers by conventional means such as chromatography or recrystallization, then regenerating the original enantiomers. Additionally, where applicable, all cis-trans or E/Z isomers (geometric isomers), tautomeric forms and topoisomeric forms of the compounds of this invention are included within the scope of this invention unless otherwise specified.

In particular, when d is 1, the compounds of formula I contain a chiral center at the carbon atom indicated by the symbol * in the following partial formula (shown without optional substituents for clarity):



In one embodiment of this invention, the carbon atom identified by the symbol * has the *(R)* configuration. In this embodiment, compounds of formula I have the *(R)* configuration at the carbon atom identified by the symbol * or are enriched in a stereoisomeric form having the *(R)* configuration at this carbon atom. In another embodiment, the carbon atom identified by the symbol * has the *(S)* configuration. In this embodiment, compounds of formula I have the *(S)* configuration at the carbon atom identified by the symbol * or are enriched in a stereoisomeric form having the *(S)* configuration at this carbon atom.

The compounds of the invention, as well as those compounds used in their synthesis, may also include isotopically-labeled compounds, *i.e.*, where one or more atoms have been enriched with atoms having an atomic mass different from the atomic mass predominately found in nature. Examples of isotopes that may be incorporated into the compounds of formula I, for example, include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O and ^{17}O.

The compounds of the invention have been found to possess muscarinic receptor antagonist activity. Among other properties, compounds of the invention have been found

to possess improved binding affinity for hM_2 and hM_3 muscarinic receptor subtypes, have longer receptor half-lives, and have greater potency compared to related compounds, and are expected to be useful as therapeutic agents for treating pulmonary disorders.

The nomenclature used herein to name the compounds of the invention is illustrated in the Examples herein. This nomenclature has been derived using the commercially-available AutoNom software (MDL, San Leandro, California).

REPRESENTATIVE EMBODIMENTS

The following substituents and values are intended to provide representative examples of various aspects and embodiments of the invention. These representative values are intended to further define and illustrate such aspects and embodiments and are not intended to exclude other embodiments or to limit the scope of the invention. In this regard, the representation that a particular value or substituent is preferred is not intended in any way to exclude other values or substituents from the invention unless specifically indicated.

The values for a and b are independently 0, 1, 2, 3, 4 or 5; particularly independently 0, 1 or 2; and even more particularly 0 or 1. In one embodiment, a is 0 or 1. In another embodiment, b is 0. In one embodiment, both a and b are 0. In another embodiment, a is 1 and b is 0.

When present, each R^1 and R^2 may be at the 2, 3, 4, 5 or 6-position of the phenyl ring to which it is attached. Each R^1 and R^2 is independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C_{3-6}cycloalkyl, cyano, halo, -OR^a, -CH_2OH, -COOH, -C(O)-O-C_{1-4}alkyl, -$C(O)NR^bR^c$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, and -NR^bR^c. Each R^a is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl and -C_{3-6}cycloalkyl. Each R^b and R^c is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl or -C_{3-6}cycloalkyl. Alternatively, R^b and R^c together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle. In another embodiment, two adjacent R^1 groups or two adjacent R^2 groups are joined together to form -C_{3-6}alkylene, -C_{2-4}alkylene-O- or -O-C_{1-4}alkylene-O-. In one embodiment, R^1 or R^2 are independently selected from -C_{1-4}alkyl (e.g. methyl, ethyl, *n*-propyl, isopropyl), fluoro, chloro, -OR^a (e.g., hydroxy, methoxy, ethoxy), -CH_2OH, -COOH, -C(O)-O-C_{1-4}alkyl (e.g., -$COOCH_3$), and -NR^bR^c (e.g., NH_2). In another specific embodiment, R^1 is selected from -C_{1-4}alkyl and -OR^a.

Each of the aforementioned alkyl, alkenyl, alkylene, alkynyl and cycloalkyl groups in R^1, R^2, R^a, R^b and R^c may be substituted with 1 to 5 fluoro atoms. For example, R^1 or R^2

can be -C_{1-4}alkyl such as difluoromethyl, trifluoromethyl, and 2,2,2-trifluoroethyl, or -OR^a, where R^a is difluoromethyl or trifluoromethyl. In addition, each cycloalkyl group in R^1, R^2, R^a, R^b and R^c may be substituted with 1 to 3 substituents independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, cyano, halo, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -S(O)(C_{1-4}alkyl), -$S(O)_2$(C_{1-4}alkyl), -NH_2, -NH(C_{1-4}alkyl) and -N(C_{1-4}alkyl)$_2$, where each of these alkyl, alkenyl and alkynyl groups can be substituted with 1 to 5 fluoro substituents.

R^3 is selected from -C(O)$NR^{3a}R^{3b}$, -C(O)O-C_{1-4}alkyl, -CN, -OH, -CH_2OH, and -CH_2NH_2. R^{3a} and R^{3b} are independently selected from hydrogen, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, -C_{3-6}heterocycle, and -$(CH_2)_{1-2}$-R^{3c}. R^{3c} is selected from -OH, -O-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, and -C_{3-6}heterocycle. In one embodiment, R^3 is -C(O)$NR^{3a}R^{3b}$. In one embodiment, R^{3a} and R^{3b} are independently hydrogen or -C_{1-4}alkyl. In another embodiment R^{3a} and R^{3b} are independently hydrogen or -C_{1-2}alkyl, such as methyl and ethyl. In yet another embodiment, R^{3a} and R^{3b} are both hydrogen. Alternatively, R^{3a} and R^{3b} together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle optionally containing one additional heteroatom selected from nitrogen, oxygen or sulfur. Representative heterocyclic rings include, but are not limited to, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-C_{1-4}alkylpiperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl.

Each of the aforementioned alkyl, alkenyl, alkynyl and cycloalkyl groups in R^3 and R^{3a-3c} may be substituted with 1 to 5 fluoro atoms. For example, R^3 can be -CF_3. In addition, each aryl, cycloalkyl, heteroaryl and heterocycle group in R^{3a-3c} may be substituted with 1 to 3 substituents independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, cyano, halo, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -S(O)(C_{1-4}alkyl), -$S(O)_2$(C_{1-4}alkyl), -NH_2, -NH(C_{1-4}alkyl) and -N(C_{1-4}alkyl)$_2$, where each of these alkyl, alkenyl and alkynyl groups can be substituted with 1 to 5 fluoro substituents.

The value for c is 0, 1, 2, or 3; particularly 0, 1 or 2; and even more particularly 0 or 1. In one embodiment, c is 0. In another embodiment, each of a, b and c represents 0.

When present, each R^4 is independently selected fluoro or -C_{1-4}alkyl. When more than one R^4 substituent is present, i.e., c is 2 or 3, the substituents can be on the same or on different carbon atoms. Exemplary R^4 groups include, but are not limited to, methyl, ethyl, and fluoro. The alkyl group in R^4 may be substituted with 1 to 5 fluoro atoms. For example, R^4 can be difluoromethyl or trifluoromethyl.

The value for d is 1 or 2, and ⁻⁻ depicts an optional double bond. In one embodiment, d is 1 and the double bond is absent, i.e., when the ring defined by "d" is a pyrrolidine ring. In one embodiment, the stereocenter at the 3-position of the pyrrolidine ring (i.e., the carbon atom bearing the 1-carbamoyl-1,1-diphenylmethyl group) has the *(S)* stereochemistry. In another embodiment, this stereocenter has the (*R*) stereochemistry. In one embodiment, d is 1 and the double bond is present, i.e., when the ring defined by "d" is a tetrahydropyridine ring.

R^5 is selected from -C_{1-6}alkyl, -CH_2-C_{2-6}alkenyl, -CH_2-C_{2-6}alkynyl, and -CH_2COR^{5a}. In some embodiments, R^5 may be absent. R^{5a} is selected from -OH, -O-C_{1-6}alkyl, and -$NR^{5b}R^{5c}$, where R^{5b} and R^{5c} are independently selected from H and -C_{1-6}alkyl. In one embodiment, R^5 is -C_{1-6}alkyl such as -CH_3 or -CH_2CH_3; and in a particular embodiment R^5 is -CH_3. Each of the aforementioned alkyl, alkenyl, and alkynyl groups in R^5 may be substituted with 1 to 5 fluoro atoms. For example, R^5 can be -CF_3. Each of the aforementioned alkyl, alkenyl, and alkynyl groups in R^5 may also be substituted with 1 to 2 -O-C_{1-6}alkyl, -OH and phenyl groups.

Q is -C_{0-5}alkylene-Q'-C_{0-1}alkylene-. Q' is selected from -CH_2-, -CH=CH-, -C≡C-, -O-, -S-, -S(O)-, -SO_2-, -SO_2-NR^{Q1}-, -NR^{Q1}-SO_2-, -C(O)-, -OC(O)-, -C(O)O-, -NR^{Q1}C(O)-, -C(O)NR^{Q1}-, -NR^{Q2}-C(O)-NR^{Q3}-, -NR^{Q2}-C(S)-NR^{Q3}-, -C=N-O-, -S-S-, and-C(=N-O-R^{Q4})-. R^{Q1} is hydrogen or -C_{1-4}alkyl. In one particular embodiment, R^{Q1} is hydrogen. R^{Q2} and R^{Q3} are independently selected from hydrogen, -C_{1-4}alkyl, and -C_{3-6}cycloalkyl, or they can be taken together to form -C_{2-4}alkylene or -C_{2-3}alkenylene. In one particular embodiment, R^{Q2} and R^{Q3} are both hydrogen. R^{Q4} is -C_{1-4}alkyl or benzyl. In one embodiment, R^{Q4} is -C_{1-4}alkyl such as -CH_3. In one particular embodiment, R^{Q4} is benzyl. In one particular embodiment, Q' is selected from -CH_2-, -O-, -S-, -S(O)-, -C(O)-, -OC(O)-, -C(O)O-, -NR^{Q1}C(O)-, -C(O)NR^{Q1}-, -NR^{Q2}-C(O)-NR^{Q3}-, -NR^{Q2}-C(S)-NR^{Q3}-, and-C(=N-O-R^{Q4})-. In another particular embodiment, Q' is selected from -O-, -S-, -C(O)-, and -OC(O)-.

The linker connecting Q' to the N^+ atom, -C_{0-5}alkylene-, may be a bond (0 carbon atoms) or have 1, 2, 3, 4, or 5 carbon atoms. In one particular embodiment, this linker is -C_{2-5}alkylene-; in another particular embodiment, -C_{1-3}alkylene-; and in yet another embodiment -C_3alkylene-. Each -CH_2- group in the -C_{0-5}alkylene- linker may be substituted with 1 or 2 substituents independently selected from -C_{1-2} alkyl, -OH and fluoro. In one particular embodiment, the linker is -$(CH_2)_3$- and one -CH_2- group is

substituted with -OH, for example -CH_2-CH(OH)-CH_2-.

The linker connecting Q' to the phenyl ring, -C_{0-1}alkylene-, may be a bond (0 carbon atoms) or have 1 carbon atom. In one particular embodiment, this linker is a bond. Each -CH_2- group in the -C_{0-1}alkylene- linker may be substituted with 1 or 2 substituents independently selected from -C_{1-2} alkyl, -OH and fluoro.

In specific embodiments, -C_{0-5}alkylene-Q'-C_{0-1}alkylene- is one of the following: -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_2$-CH=CH-, -$(CH_2)_2$-C≡C-, -$(CH_2)_2$-O-CH_2-, -$(CH_2)_3$-O-, -CH_2-CH(OH)-CH_2-O-, -$(CH_2)_3$-O-CH_2-, -$(CH_2)_3$-S-, -$(CH_2)_3$-S(O)-, -$(CH_2)_3$-SO_2-, -$(CH_2)_3$-C(O)-, -$(CH_2)_2$-OC(O)-, -$(CH_2)_2$-C(O)O-, -CH_2-C(O)O-CH_2-, -$(CH_2)_2$-NR^{Q1}C(O)-, -CH_2-C(O)NR^{Q1}-CH_2, -$(CH_2)_2$-NR^{Q2}-C(O)-NR^{Q3}-, -CH_2-C=N-O-, -$(CH_2)_2$-S-S-, and -$(CH_2)_3$-C(=N-O-R^{Q4})-, where R^{Q1}, R^{Q2} and R^{Q3} are hydrogen, and R^{Q4} is -C_{1-4}alkyl or benzyl.

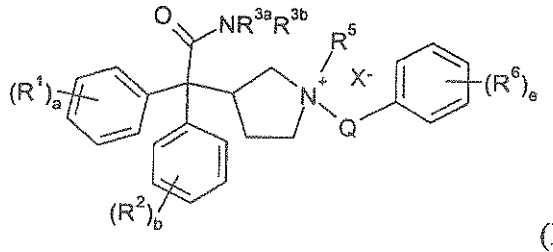
The value for e is 0, 1, 2, 3, 4 or 5. In one embodiment, e is 0, 1 or 2.

When present, each R^6 is independently selected from halo, -C_{1-4}alkyl, -C_{0-4}alkylene-OH, cyano, -C_{0-2}alkylene-COOH, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, and -N^+(O)O. In one particular embodiment, R^6 is selected from halo, -C_{1-4}alkyl, -OH, cyano, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -N(CH_3)$_2$, and -N^+(O)O. In one embodiment, R^6 is halo such as fluoro, chloro and bromo. In a particular embodiment e is 1 and R^6 is fluoro or chloro; in another embodiment, e is 2 and both R^6 groups are fluoro, or both R^6 groups are chloro, or one R^6 group is fluoro and the other R^6 group is chloro. In another embodiment, R^6 is -C_{1-4}alkyl such as -CH_3. In one embodiment, R^6 is -OH. In one embodiment, R^6 is -C_{1-4}alkylene-OH. In one embodiment, R^6 is cyano. In one embodiment, R^6 is -C_{0-2}alkylene-COOH such as -COOH. In one embodiment, R^6 is -C(O)O-C_{1-4}alkyl such as -C(O)O-CH_3. In one embodiment, R^6 is -O-C_{1-4}alkyl such as -O-CH_3. In one embodiment, R^6 is -S-C_{1-4}alkyl such as -S-CH_3. In one embodiment, R^6 is -NH-C(O)-C_{1-4}alkyl such as -NH-C(O)-CH_3. In yet another embodiment, R^6 is -N(C_{1-4}alkyl)$_2$ such as -N(CH_3)$_2$. In one embodiment, R^6 is -N^+(O)O. The alkyl group in R^6 may be substituted with 1 to 5 fluoro atoms. For example, R^6 can be -CF_3 or -OCF_3.

X^- is an anion of a pharmaceutically acceptable acid. The term "anion of a pharmaceutically acceptable acid" is used to refer to an anionic counterion of a pharmaceutically acceptable acid. Examples of pharmaceutically acceptable inorganic acids include, by way of illustration and not limitation, boric, carbonic, hydrohalic

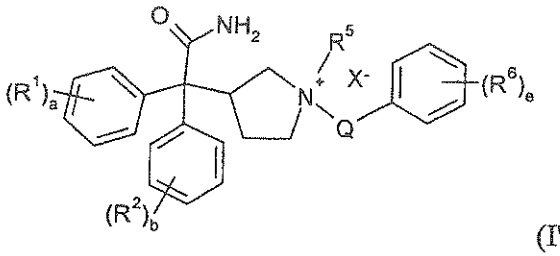
(hydrobromic, hydrochloric, hydrofluoric or hydroiodic), nitric, phosphoric, sulfamic and sulfuric acids, and hydroxide. Examples of pharmaceutically acceptable organic acids include, by way of illustration and not limitation, aliphatic hydroxyl acids (e.g., citric, gluconic, glycolic, lactic, lactobionic, malic, and tartaric acids), aliphatic monocarboxylic acids (e.g., acetic, butyric, formic, propionic and trifluoroacetic acids), aromatic carboxylic acids (e.g., benzoic, p-chlorobenzoic, diphenylacetic, gentisic, hippuric, and triphenylacetic acids), amino acids (e.g., aspartic and glutamic acids), aromatic hydroxyl acids (e.g., o-hydroxybenzoic, p-hydroxybenzoic, 1-hydroxynaphthalene-2-carboxylic and 3-hydroxynaphthalene-2-carboxylic acids), ascorbic, dicarboxylic acids (e.g., fumaric, maleic, oxalic and succinic acids), glucoronic, mandelic, mucic, nicotinic, orotic, pamoic, pantothenic, sulfonic acids (e.g., benzenesulfonic, camphosulfonic, edisylic, ethanesulfonic, isethionic, methanesulfonic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic and p-toluenesulfonic acids), xinafoic acid, and the like. In one embodiment, the pharmaceutically acceptable acid is selected from acetic, benzenesulfonic, benzoic, butyric, p-chlorobenzoic, citric, diphenylacetic, formic, hydrobromic, hydrochloric, hydrofluoric, hydroiodic, o-hydroxybenzoic, p-hydroxybenzoic, 1-hydroxynaphthalene-2-carboxylic, 3-hydroxynaphthalene-2-carboxylic, lactic, malic, maleic, methanesulfonic, nitric, phosphoric, propionic, succinic, sulfuric, tartaric, trifluoroacetic, and triphenylacetic acids. In another embodiment the pharmaceutically acceptable acid is selected from hydrobromic, hydroiodic, and trifluoroacetic acids. In one embodiment, the anion is selected from acetate, benzenesulfonate, benzoate, bromide, butyrate, chloride, p-chlorobenzoate, citrate, diphenylacetate, formate, fluoride, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, iodide, lactate, malate, maleate, methanesulfonate, nitrate, phosphate, propionate, succinate, sulfate, tartrate, trifluoroacetate, bi- and triphenylacetate. In yet another embodiment, the anion is selected from bromide, iodide and trifluoroacetate.

In one embodiment, R^3 is $-C(O)NR^{3a}R^{3b}$, c is 0 and d is 1. Thus, the invention is also directed to quaternary ammonium compounds having formula I'a:



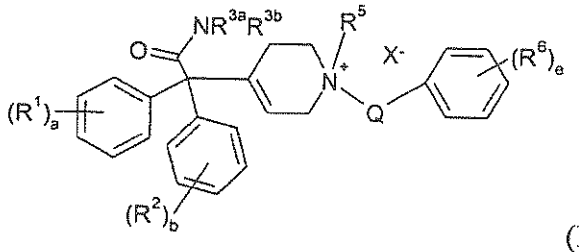
(I'a)

or a pharmaceutically acceptable salt thereof; where R^{1-2}, R^{3a-3b}, R^{5-6}, a, b, e, Q and X^- are as defined for formula I. In another embodiment, R^3 is $-C(O)NH_2$, R^5 is $-CH_3$, a, b and c are 0 and d is 1. Thus, the invention is also directed to quaternary ammonium compounds having formula I'b:



(I'b)

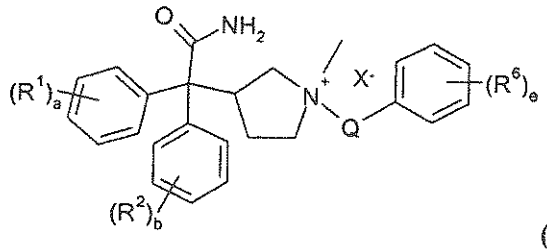
or a pharmaceutically acceptable salt thereof; where R^6, e, Q and X^- are as defined for formula I. In another embodiment, R^3 is $-C(O)NH_2$, R^5 is $-CH_3$, a, b and c are 0 and d is 2. Thus, the invention is also directed to quaternary ammonium compounds having formula I'c:



(I'c)

or a pharmaceutically acceptable salt thereof; where R^{1-2}, R^{3a-3b}, R^{5-6}, a, b, e, Q and X^- are as defined for formula I.

The invention is also directed to quaternary ammonium compounds having formula I'd:

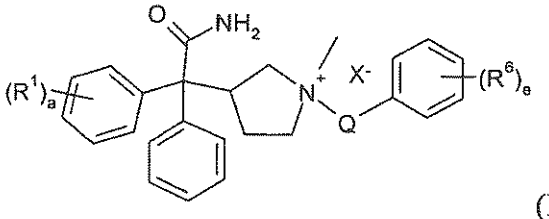


(I'd)

or a pharmaceutically acceptable salt thereof; where: a and b are independently 0 or 1; each

R^1 and R^2 is $-OR^a$, where R^a is hydrogen; Q is selected from: $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_2-CH=CH-$, $-(CH_2)_2-C\equiv C-$, $-(CH_2)_2-O-CH_2-$, $-(CH_2)_3-O-$, $-CH_2-CH(OH)-CH_2-O-$, $-(CH_2)_3-O-CH_2-$, $-(CH_2)_3-S-$, $-(CH_2)_3-S(O)-$, $-(CH_2)_3-SO_2-$, $-(CH_2)_3-C(O)-$, $-(CH_2)_2-OC(O)-$, $-(CH_2)_2-C(O)O-$, $-CH_2-C(O)O-CH_2-$, $-(CH_2)_2-NR^{Q1}C(O)-$, $-CH_2-C(O)NR^{Q1}-CH_2$, $-(CH_2)_2-NR^{Q2}-C(O)-NR^{Q3}-$, $-CH_2-C=N-O-$, $-(CH_2)_2-S-S-$, and $-(CH_2)_3-C(=N-O-R^{Q4})-$, where R^{Q1}, R^{Q2} and R^{Q3} are hydrogen, and R^{Q4} is $-C_{1-4}$alkyl or benzyl; e is 0, 1 or 2; each R^6 is independently selected from halo, $-C_{1-4}$alkyl, $-C_{0-4}$alkylene-OH, cyano, $-C(O)O-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-S-C_{1-4}$alkyl, $-NH-C(O)-C_{1-4}$alkyl, $-N(C_{1-4}$alkyl$)_2$, and $-N^+(O)O$. The moieties may be optionally substituted as described for formula I, and in one particular embodiment, the alkyl in R^6 is optionally substituted with 3 fluoro atoms, and one $-CH_2-$ group in Q is optionally substituted with -OH.

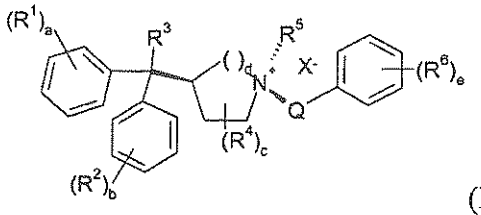
In another embodiment, the invention is directed to quaternary ammonium compounds having formula I'e:



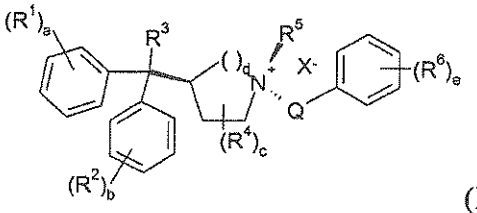
(I'e)

or a pharmaceutically acceptable salt thereof; where a is 0 or 1; R^1 is $-OR^a$, where R^a is hydrogen; Q is selected from: $-(CH_2)_4-$, $-(CH_2)_2-CH=CH-$, $-(CH_2)_2-C\equiv C-$, $-(CH_2)_3-O-$, $-(CH_2)_3-S-$, $-(CH_2)_3-C(O)-$, and $-(CH_2)_2-OC(O)-$; e is 0, 1 or 2; each R^6 is independently selected from halo, $-C_{1-4}$alkyl, -OH, and $-S-C_{1-4}$alkyl. While all of the moieties may be optionally substituted as described for formula I, in one particular embodiment, the compound is not optionally substituted.

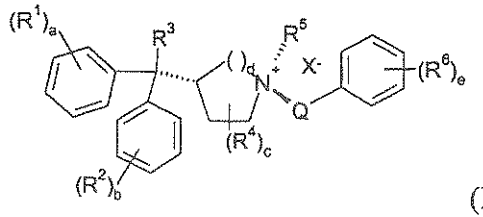
In still another embodiment, the invention is directed to quaternary ammonium compounds having formula I"a, I"b, I"c, or I"d:



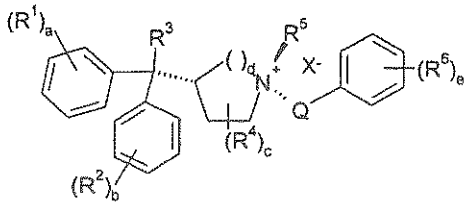
(I"a)



(I"b)



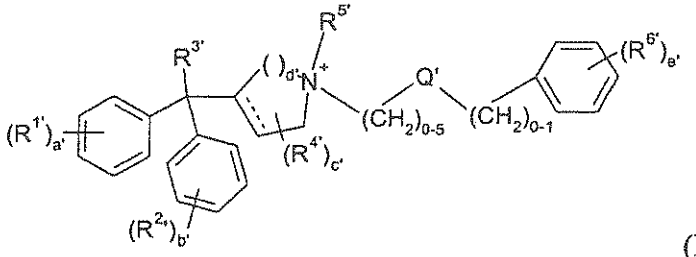
(I"c)



(I"d)

or a pharmaceutically acceptable salt thereof, where X^- is an anion of a pharmaceutically acceptable acid. In one particular embodiment, the invention is directed to compounds of formula I"a.

A particular group of compounds of formula I are those disclosed in U.S. Provisional Application No. 60/903,110, filed on February 23, 2007. This group includes compounds of formula I''':



(I''')

in salt or zwitterionic form, wherein: a' and b' are independently 0 or an integer of from 1 to 5; each $R^{1'}$ and $R^{2'}$ is independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C_{3-6}cycloalkyl, cyano, halo, -$OR^{a'}$, -$SR^{a'}$, -$S(O)R^{a'}$, -$S(O)_2R^{a'}$, and -$NR^{b'}R^{c'}$; where each $R^{a'}$ is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl and -C_{3-6}cycloalkyl; each $R^{b'}$ and $R^{c'}$ is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl or -C_{3-6}cycloalkyl; or $R^{b'}$ and $R^{c'}$ together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle; or two adjacent $R^{1'}$ groups or two adjacent $R^{2'}$ groups are joined together to form -C_{3-6}alkylene, -C_{2-4}alkylene-O- or -O-C_{1-4}alkylene-O-; $R^{3'}$ is selected from -$C(O)NR^{3a'}R^{3b'}$, -$C(O)O$-C_{1-4}alkyl, -CN, -OH, -CH_2OH, and -CH_2NH_2; where $R^{3a'}$ and $R^{3b'}$ are independently selected from hydrogen, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, -C_{3-6}heterocycle, and -$(CH_2)_{1-2}$-$R^{3c'}$, where $R^{3c'}$ is selected from -OH, -O-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, and -C_{3-6}heterocycle; or $R^{3a'}$ and $R^{3b'}$ together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle optionally containing one additional heteroatom selected from nitrogen, oxygen or sulfur; c' is 0 or an integer of from 1 to 3; each $R^{4'}$ is independently fluoro or -C_{1-4}alkyl; d' is 1 or 2, and ⎓ depicts an optional double bond; $R^{5'}$ is selected from -C_{1-6}alkyl, -CH_2-C_{2-6}alkenyl,

-CH_2-C_{2-6}alkynyl, and -$CH_2COR^{5a'}$; where $R^{5a'}$ is selected from -OH, -O-C_{1-6}alkyl, and -$NR^{5b'}R^{5c'}$; and $R^{5b'}$ and $R^{5c'}$ are independently selected from H and -C_{1-6}alkyl; Q' is selected from -CH_2-, -O-, -S-, -S(O)-, -SO_2-, -SO_2-$NR^{Q1'}$-, -$NR^{Q1'}$-SO_2-, -C(O)-, -OC(O)-, -C(O)O-, -$NR^{Q1'}$C(O)-, -C(O)$NR^{Q1'}$-, $NR^{Q2'}$-C(O)-$NR^{Q3'}$-, -$NR^{Q2'}$-C(S)-$NR^{Q3'}$-, -CH(OH)-, and-C(=N-O-$R^{Q4'}$)-, where $R^{Q1'}$ is hydrogen or -C_{1-4}alkyl, $R^{Q2'}$ and $R^{Q3'}$ are independently selected from hydrogen, -C_{1-4}alkyl, and -C_{3-6}cycloalkyl, or $R^{Q2'}$ and $R^{Q3'}$ are taken together to form -C_{2-4}alkylene or -C_{2-3}alkenylene, and $R^{Q4'}$ is -C_{1-4}alkyl or benzyl; e' is 0 or an integer of from 1 to 5; each $R^{6'}$ is independently selected from halo, -C_{1-4}alkyl, -OH, -C_{1-4}alkyl-OH, cyano, -COOH, -C(O)O-C_{1-4}alkyl, -C_{1-4}alkoxy, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, and -N^+(O)O; wherein each alkyl, alkenyl, alkylene, alkynyl and cycloalkyl group in $R^{1a'-3'}$, $R^{3a'-3c'}$, $R^{4'-6'}$, and $R^{a'-c'}$ is optionally substituted with 1 to 5 fluoro atoms; wherein each alkyl, alkenyl, and alkynyl group in $R^{5'}$ is optionally substituted with 1 to 2 substituents independently selected from -C_{1-4}alkoxy, -OH and phenyl; each cycloalkyl, aryl, heteroaryl and heterocycle group in $R^{1a'-2'}$, $R^{3a'-3c'}$, and $R^{a'-c'}$ is optionally substituted with 1 to 3 substituents independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, cyano, halo, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -S(O)(C_{1-4}alkyl), -$S(O)_2$(C_{1-4}alkyl), -NH_2, -NH(C_{1-4}alkyl) and -N(C_{1-4}alkyl)$_2$, wherein each alkyl, alkenyl and alkynyl group is optionally substituted with 1 to 5 fluoro substituents; and each -CH_2- group in -$(CH_2)_{0-5}$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-2}alkyl, -OH and fluoro; or a pharmaceutically acceptable salt thereof.

In addition, particular compounds of formula I that are of interest include those set forth in the Examples below, as well as the pharmaceutically acceptable salts thereof.

DEFINITIONS

When describing the compounds, compositions, methods and processes of the invention, the following terms have the following meanings unless otherwise indicated. Additionally, as used herein, the singular forms "a," "an" and "the" include the corresponding plural forms unless the context of use clearly dictates otherwise. The terms "comprising", "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms and include, for example -C_{1-2}alkyl, -C_{1-4}alkyl, and -C_{1-6}alkyl. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl,

isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

When a specific number of carbon atoms is intended for a particular term used herein, the number of carbon atoms is shown preceding the term as subscript. For example, the term "-C_{1-6}alkyl" means an alkyl group having from 1 to 6 carbon atoms, where the carbon atoms are in any acceptable configuration.

The term "alkylene" means a divalent saturated hydrocarbon group that may be linear or branched. Unless otherwise defined, such alkylene groups typically contain from 1 to 10 carbon atoms and include, for example, C_{0-1}alkylene, C_{0-5}alkylene, C_{1-4}alkylene, C_{2-4}alkylene, C_{2-5}alkylene, and C_{3-6}alkylene. Representative alkylene groups include, by way of example, methylene, ethane-1,2-diyl ("ethylene"), propane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl and the like. It is understood that when the alkylene term include zero carbons such as C_{0-1}alkylene or C_{0-5}alkylene, such terms are intended to include a single bond.

The term "alkenyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon double bonds. Unless otherwise defined, such alkenyl groups typically contain from 2 to 10 carbon atoms and include, for example, -C_{2-4}alkenyl and -C_{2-6}alkenyl. Representative alkenyl groups include, by way of example, ethenyl, *n*-propenyl, isopropenyl, *n*-but-2-enyl, *n*-hex-3-enyl and the like. The term "alkenylene" means a divalent alkenyl group, and exemplary alkenylene groups include -C_{2-3}alkenylene.

The term "alkoxy" means a monovalent group of the formula -O-alkyl, where alkyl is as defined herein. Unless otherwise defined, such alkylene groups typically contain from 1 to 10 carbon atoms and include, for example, -O-C_{1-4}alkyl and -O-C_{1-6}alkyl. Representative alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy and the like.

The term "alkynyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon triple bonds. Unless otherwise defined, such alkynyl groups typically contain from 2 to 10 carbon atoms and include, for example, -C_{2-4}alkynyl and -C_{2-6}alkynyl. Representative alkynyl groups include, by way of example, ethynyl, *n*-propynyl, *n*-but-2-ynyl, *n*-hex-3-ynyl and the like. The term "alkynylene" means a divalent alkynyl group, and exemplary alkynylene groups include -C_{2-3}alkenylene.

The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino group. Representative amino-protecting groups include, but are not limited to, *tert*-butoxycarbonyl (BOC), trityl (Tr), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), formyl, trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), and the like.

The term "aryl" means a monovalent aromatic hydrocarbon having a single ring (i.e., phenyl) or fused rings (i.e., naphthalene). Unless otherwise defined, such aryl groups typically contain from 6 to 10 carbon ring atoms and include, for example, -C_{6-10}aryl. Representative aryl groups include, by way of example, phenyl and naphthalene-1-yl, naphthalene-2-yl, and the like.

The term "cycloalkyl" means a monovalent saturated carbocyclic hydrocarbon group. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms and include, for example, -C_{3-6}cycloalkyl. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "divalent hydrocarbon group" means a divalent hydrocarbon group which is composed primarily of carbon and hydrogen atoms and which optionally contains one or more heteroatoms. Such divalent hydrocarbon groups may be branched or unbranched, saturated or unsaturated, acyclic or cyclic, aliphatic or aromatic, or combinations thereof. The divalent hydrocarbon group can optionally contain heteroatoms incorporated into the hydrocarbon chain or as substituents attached to the hydrocarbon chain.

The term "halo" means fluoro, chloro, bromo and iodo.

The term "heteroaryl" means a monovalent aromatic group having a single ring or two fused rings and containing in the ring at least one heteroatom (typically 1 to 3 heteroatoms) selected from nitrogen, oxygen or sulfur. Unless otherwise defined, such heteroaryl groups typically contain from 5 to 10 total ring atoms and include, for example, -C_{2-9}heteroaryl. Representative heteroaryl groups include, by way of example, monovalent species of pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole, isothiazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzothiophene, benzoimidazole, benzthiazole, quinoline, isoquinoline, quinazoline, quinoxaline and the like, where the point of attachment is at any available carbon or nitrogen ring atom.

The term "heterocycle" or "heterocyclic" means a monovalent saturated or unsaturated (non-aromatic) group having a single ring or multiple condensed rings and

containing in the ring at least one heteroatom (typically 1 to 3 heteroatoms) selected from nitrogen, oxygen or sulfur. Unless otherwise defined, such heterocyclic groups typically contain from 2 to 9 total ring carbon atoms and include, for example, -C_{3-6}heterocycle. Representative heterocyclic groups include, by way of example, monovalent species of pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,4-dioxane, morpholine, thiomorpholine, piperazine, 3-pyrroline and the like, where the point of attachment is at any available carbon or nitrogen ring atom.

The term "leaving group" means a functional group or an atom that can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include, but are not limited to, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "optionally substituted" means that group in question may be unsubstituted or it may be substituted one or several times, such as 1 to 3 times or 1 to 5 times. For example, an alkyl group that is "optionally substituted" with 1 to 5 fluoro atoms, may be unsubstituted, or it may contain 1, 2, 3, 4, or 5 fluoro atoms.

The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise undesirable. For example, the term "pharmaceutically acceptable carrier" refers to a material that can be incorporated into a composition and administered to a patient without causing undesirable biological effects or interacting in a deleterious manner with other components of the composition. Such pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug administration.

The term "solvate" means a complex or aggregate formed by one or more molecules of a solute, e.g., a compound of formula I or a pharmaceutically acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include, by way of example, water, methanol, ethanol, isopropanol, acetic acid and the like. When the solvent is water, the solvate formed is a hydrate.

The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need of treatment. In particular, an "effective"

amount is that amount needed to obtain the desired result, and a "therapeutically effective" amount is that amount needed to obtain the desired therapeutic effect. For example, for antagonizing a muscarinic receptor, an "effective amount" is a muscarinic-receptor-antagonizing amount. Similarly, a therapeutically effective amount for treating chronic obstructive pulmonary disease (COPD) is that amount that will achieve the desired therapeutic result, which may be disease prevention, amelioration, suppression or alleviation.

The term "treating" or "treatment" as used herein means the treating or treatment of a disease or medical condition (such as COPD) in a patient, such as a mammal (particularly a human) that includes: (a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient; (b) ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient; (c) suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or (d) alleviating the symptoms of the disease or medical condition in a patient. For example, the term "treating COPD" would include preventing COPD from occurring, ameliorating COPD, suppressing COPD, and alleviating the symptoms of COPD. The term "patient" is intended to include those animals, such as humans, that are in need of treatment or disease prevention, that are presently being treated for disease prevention or treatment of a specific disease or medical condition, as well as test subjects in which compounds of the invention are being evaluated or being used in a assay, for example an animal model.

All other terms used herein are intended to have their ordinary meaning as understood by those of ordinary skill in the art to which they pertain.

General Synthetic Procedures

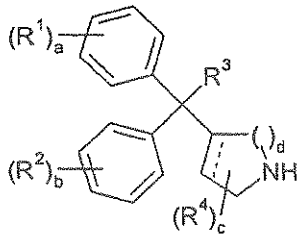
Compounds of the invention can be prepared from readily available starting materials using the following general methods, the procedures set forth in the Examples, or by using other methods, reagents, and starting materials that are known to those of ordinary skill in the art. Although the following procedures may illustrate a particular embodiment of the invention, it is understood that other embodiments of the invention can be similarly prepared using the same or similar methods or by using other methods, reagents and starting materials known to those of ordinary skill in the art. It will also be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used

unless otherwise stated. While optimum reaction conditions will typically vary depending on various reaction parameters such as the particular reactants, solvents and quantities used, those of ordinary skill in the art can readily determine suitable reaction conditions using routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary or desired to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions and reagents for protection and deprotection of such functional groups are well-known in the art. Functional groups that may be protected so as to prevent undesired reactions include, by way of example, carboxy groups, amino groups, hydroxyl groups, thiol groups, carbonyl groups and the like. Representative carboxy-protecting groups include, but are not limited to, esters, such as methyl, ethyl, *tert*-butyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluroenylmethyl (Fm), trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), diphenylmethyl (benzhydryl, DPM) and the like; amides and hydrazides. Representative protecting groups for amino groups include carbamates (such as *tert*-butoxycarbonyl) and amides. Representative hydroxyl-protecting groups include, but are not limited to, silyl groups including triC_{1-6}alkylsilyl groups, such as trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS) and the like; esters (acyl groups) including C_{1-6}alkanoyl groups, such as formyl, acetyl and the like; arylmethyl groups, such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), diphenylmethyl (benzhydryl, DPM) and the like; and ethers. Representative protecting groups for thiol groups include thioethers and thioesters. Representative protecting groups for carbonyl groups include acetals and ketals. Protecting groups other than those described herein may be used, if desired. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

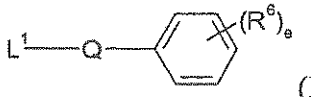
By way of illustration, compounds of formula I can be prepared by one or more of the following exemplary processes:

(a) reacting a compound of formula II:



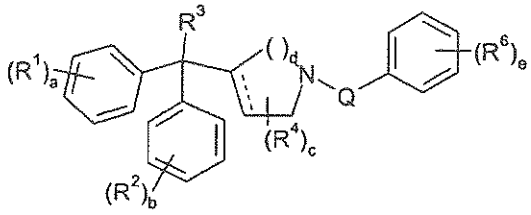
(II)

with a compound of formula III:



(III)

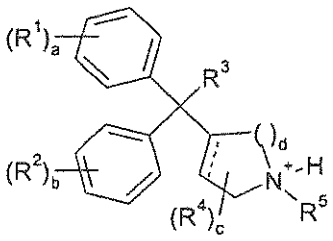
where L^1 represents a leaving group, to produce a compound of formula IV:



(IV)

and reacting the compound of formula IV with an organic substrate containing an R^5 group; or

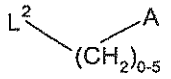
(b) reacting a compound of formula V:



(V)

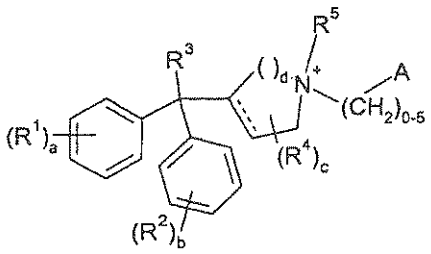
with a compound of formula III; or

(c) reacting a compound of formula V with a compound of formula VI:



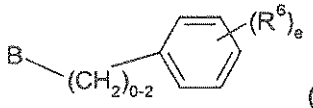
(VI)

where L^2 represents a leaving group and A is defined below, to produce a compound of formula VII:



(VII)

and reacting the compound of formula VII with a compound of formula VIII:



(VIII)

wherein L^3 represents a leaving group, and Q', A and B are defined as set forth in the following table:

Q'	A	B
$-CH_2-$	$-CH_3$	L^3-alkylene-
-CH=CH-	H	L^3-alkenylene-
-C≡C-	H	L^3-alkynylene -
-O-	$-L^3$	HO-
-S-	$-L^3$	HS-
$-SO_2-NR^{Q1}-$	$-SO_2-OH$ or $-SO_2Cl$	$R^{Q1}HN-$
$-NR^{Q1}-SO_2-$	$-NHR^{Q1}$	HOO_2S-
-OC(O)-	-OH	HO(O)C-
-C(O)O-	-C(O)OH or -C(O)Cl	HO-
$-NR^{Q1}C(O)-$	$-NHR^{Q1}$	HO(O)C- or Cl(O)C-
$-NR^{Q2}-C(O)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=C=O	H_2N-
$-NR^{Q2}-C(S)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=S=O	H_2N-
-C=N-O-	-CHO	H_2NO-
-S-S-	-SH	HS-

and recovering the product in salt or zwitterionic form.

The resulting reaction product, a compound of formula I, is a quaternary ammonium compound, which is readily crystallized in suitable solvents, such as are well known in the art. Such crystals are quaternary ammonium salts.

In these reactions, depending upon the particular substituents present, one or more protecting groups may be employed. If such protecting groups are used, they are removed using conventional procedures to provide the compound of formula I.

Process (a)

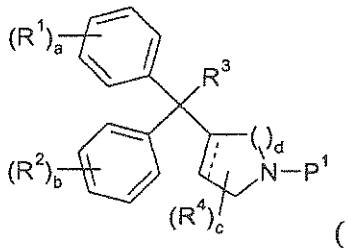
In process (a), the reaction between the compounds of formula II and III, the leaving group represented by L^1 can be, for example, halo, such as chloro, bromo or iodo,

or a sulfonic ester group, such as mesylate or tosylate. In one embodiment, L^1 is bromo. The reaction is conveniently performed in the presence of a base, for example, a tertiary amine such as diisopropylethylamine. Convenient solvents include nitriles, such as acetonitrile, dimethylformamide (DMF), and dimethylacetamide (DMA). The reaction is conveniently conducted at a temperature in the range of from 0°C to 100°C. The reaction product is then isolated using conventional procedures, such as extraction, recrystallization, chromatography and the like.

The compound of formula IV, the free base form of the desired product, is dissolved in a suitable solvent then contacted with an organic substrate. Exemplary solvents include toluene, DMA, and CH_3CN. The organic substrate is typically a pharmaceutically acceptable acid such as an organic halide. The substrate contains an R^5 group, for example, -C_{1-6}alkyl, which may be substituted with 1-5 fluoro atoms and/or 1 to 2 -O-C_{1-6}alkyl, -OH and phenyl groups, and a leaving group, examples of which include halides such as iodide or bromide. Exemplary substrates include methyl iodide, methyl bromide, ethyl iodide, propyl iodide, benzyl bromide and benzyl iodide.

In some situations, process (a) can be followed by a second reaction to yield a different compound of formula I. For example, compounds where Q' is -S(O)- or -SO_2- can be made by forming a compound of formula I where Q' is -S-, and subjecting such compound to an oxidation reaction. In addition, compounds where Q' is -C(=N-O-R^{Q4})- can be made by forming a compound of formula I where Q' is -C(O)-, and subjecting such compound to an imine formation reaction with H_2N-O-R^{Q4}.

Compounds of formula II are generally known in the art or can be prepared from commercially available starting materials and reagents using well-known procedures. For example, they may be prepared as described in U.S. Patent No. 5,096,890 to Cross et al., the disclosure of which is incorporated herein by reference in its entirety. Alternatively, compounds of formula II can be prepared by deprotecting a compound of formula 1:

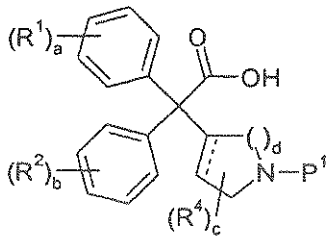


(1)

in which P^1 represents an amino-protecting group, such as a benzyl group. Benzyl groups are conveniently removed by reduction, for example, using a hydrogen or ammonium

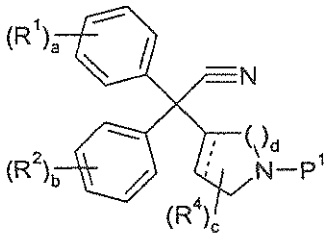
formate and a Group VIII metal catalyst, such as palladium. Optionally, this reaction is conducted in the presence of an acid, such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid and the like.

Compounds of formula 1 in which R^3 is $-C(O)NR^{3a}R^{3b}$ can be prepared by reacting a carboxylic acid of formula 2:



(2)

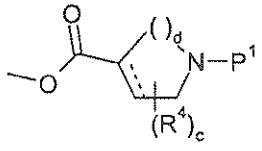
with an amine of formula $HNR^{3a}R^{3b}$ under amide bond forming conditions, where compounds of formula 2 may be prepared by hydrolyzing a compound of formula 3 using an aqueous solution of a acid, preferably hydrochloric acid, hydrobromic acid or sulfuric acid:



(3)

Compounds of formula 3 can be prepared as described in U.S. Patent No. 5,096,890 to Cross et al.

Compounds of formula 1 in which R^3 is $-C(O)O-C_{1-4}$alkyl can be prepared by reacting a carboxylic acid of formula 2 with a C_{1-4}alkyl alcohol in the presence of a catalytic amount of an acid, preferably hydrochloric acid, hydrobromic acid or sulfuric acid. Compounds of formula 1 in which R^3 is -CN can be prepared as described in U.S. Patent No. 5,096,890 to Cross et al. Compounds of formula 1 in which R^3 is -OH can be prepared by reacting an ester of formula 4 with a nucleophilic source of phenyl; such as phenyl lithium or phenyl magnesium bromide:



(4)

Compounds of formula 1 in which R^3 is $-CH_2OH$ can be prepared by reacting a

carboxylic acid of formula 2 with a reducing agent such as sodium borohydride, lithium aluminum hydride or borane.

Compounds of formula 1 in which R^3 is $-CH_2NH_2$ can be prepared by reacting a nitrile of formula 3 with a reducing agent such as lithium aluminum hydride or diisobutyl aluminum hydride.

Compounds of formula III are generally known or can be prepared from readily available starting materials using well-known synthetic methods.

Process (b)

In process (b), the reaction between the compounds of formula V and III can be conducted using known procedures for reacting pyrrolidines with halogenated compounds. The reaction is typically conducted in an organic solvent at a temperature in the range of from about 20 to 120°C, more typically in the range of about from about 20 to 80°C. Suitable organic solvents include acetonitrile, dimethylsulfoxide, dimethylacetamide, ether, and acetone. Compounds of formula V can be prepared by reacting compounds of formula II with an organic substrate containing an R^5 group as described in process (a).

Process (c)

In process (c), the reaction conditions between the compounds of formula V, VI and VIII will vary depending upon the respective A and B groups. The leaving group represented by L^3 can be, for example, a halo, typically bromo. Compounds of formula VI and VIII are generally known or can be prepared from readily available starting materials using well-known synthetic methods.

Some reactions in process (c) are coupling reactions, for example, when Q' is $-NR^{Q1}C(O)-$. In those reactions, the acidic moiety-containing compound may be in the form of a reactive derivative. For example, the carboxylic acid may be activated, for example, by forming an anhydride or carboxylic acid halide, such as a carboxylic acid chloride. Thus the carboxylic acid chloride is a reactive derivative of carboxylic acid. Alternatively, the carboxylic acid can be activated using conventional carboxylic acid/amine coupling reagents, such carbodiimides, *O*-(7-azabenzotriazol-1-yl-*N,N,N',N'* tetramethyluronium hexafluorophosphate (HATU) and the like. The sulfonic acid and thio acid moieties can be similarly derivatized. The reactions are conducted under conventional conditions using suitable coupling agents such as carbonyldiimidazole. The reaction is typically conducted in the presence of solvents such as trifluoroacetic acid and dichloromethane, and conveniently conducted at a temperature in the range of from -10°C

to 100°C.

The remaining reactions in process (c) are alkylation reactions, for example, when Q' is-O-. The reactions are conducted under conventional conditions using suitable solvents such as DMF or DMA, and conveniently conducted at a temperature in the range of from room temperature to 100 °C.

In addition, process (c) illustrates formation compounds of formula I where the R^{Q2} and/or R^{Q3} moieties are hydrogen. Such compounds are readily converted to compounds of formula 1 where R^{Q2} and/or R^{Q3} are a C_{1-4}alkyl or C_{3-6}cycloalkyl moiety, or are taken together to form an alkylene or alkenylene linkage.

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediates thereof are described in the Examples set forth below.

PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

Compounds of the invention are typically administered to a patient in the form of a pharmaceutical composition or formulation. Such pharmaceutical compositions may be administered to the patient by any acceptable route of administration including, but not limited to, inhaled, oral, nasal, topical (including transdermal) and parenteral modes of administration. Further, the compounds of the invention may be administered, for example orally, in multiple doses per day, in a single daily dose or a single weekly dose. It will be understood that any form of the compounds of the invention, (i.e., free base, pharmaceutically acceptable salt, solvate, etc.) that is suitable for the particular mode of administration can be used in the pharmaceutical compositions discussed herein.

Accordingly, in one embodiment, the invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the invention. The compositions may contain other therapeutic and/or formulating agents if desired. A "compound of the invention" may also be referred to herein as the "active agent."

The pharmaceutical compositions of this invention typically contain a therapeutically effective amount of a compound of the invention. Those skilled in the art will recognize, however, that a pharmaceutical composition may contain more than a therapeutically effective amount, i.e., bulk compositions, or less than a therapeutically effective amount, i.e., individual unit doses designed for multiple administration to achieve a therapeutically effective amount. In one embodiment, the composition will contain from

about 0.01-95 wt% of active agent, including, from about 0.01-30 wt%, such as from about 0.01- 10 wt%, with the actual amount depending upon the formulation itself, the route of administration, the frequency of dosing, and so forth. In another embodiment, a composition suitable for inhalation, for example, comprises from about 0.01-30 wt% or active agent with yet another embodiment comprises from about 0.01-10 wt% active agent.

Any conventional carrier or excipient may be used in the pharmaceutical compositions of the invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts. Additionally, carriers or excipients used in such compositions are commercially available. By way of further illustration, conventional formulation techniques are described in *Remington: The Science and Practice of Pharmacy*, 20th Edition, Lippincott Williams & White, Baltimore, Maryland (2000); and H. C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; compressed propellant gases, such as chlorofluorocarbons and hydrofluorocarbons; and other non-toxic compatible substances employed in pharmaceutical compositions.

Pharmaceutical compositions are typically prepared by thoroughly and intimately mixing or blending the active agent with a pharmaceutically acceptable carrier and one or more optional ingredients. The resulting uniformly blended mixture may then be shaped or loaded into tablets, capsules, pills, canisters, cartridges, dispensers and the like using

conventional procedures and equipment.

In one embodiment, the pharmaceutical compositions are suitable for inhaled administration. Suitable compositions for inhaled administration will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a nebulizer inhaler, a dry powder inhaler, or a metered-dose inhaler, examples of which are described below.

In a specific embodiment of the invention, a composition comprising the active agent is administered by inhalation using a nebulizer inhaler. Such nebulizer devices typically produce a stream of high velocity air that causes the composition to spray as a mist that is carried into a patient's respiratory tract. Accordingly, when formulated for use in a nebulizer inhaler, the active agent is typically dissolved in a suitable carrier to form a solution. Alternatively, the active agent can be micronized and combined with a suitable carrier to form a suspension of micronized particles of respirable size, where micronized is typically defined as having particles in which at least about 90 percent of the particles have a mass median diameter of less than about 10 μm. The term "mass median diameter" means the diameter such that half the mass of the particles is contained in particles with larger diameter and half is contained in particles with smaller diameter.

Suitable nebulizer devices include the Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim), the AERx® Pulmonary Delivery System (Aradigm Corp.), and the PARI LC Plus Reusable Nebulizer (Pari GmbH). An exemplary composition for use in a nebulizer inhaler comprises an isotonic aqueous solution comprising from about 0.05 μg/mL to about 10 mg/mL of a compound of the invention. In one embodiment, such a solution has a pH of about 4-6.

In another specific embodiment of the invention, a composition comprising the active agent is administered by inhalation using a dry powder inhaler (DPI). Such DPIs typically administer the active agent as a free-flowing powder that is dispersed in a patient's air-stream during inspiration. In order to achieve a free flowing powder, the active agent is typically formulated with a suitable excipient such as lactose, starch, mannitol, dextrose, polylactic acid, polylactide-co-glycolide, and combinations thereof. Typically, the active agent is micronized and combined with an excipient to form a blend suitable for inhalation. Accordingly, in one embodiment of the invention, the active agent is in micronized form. For example, a representative composition for use in a DPI comprises dry lactose having a particle size between about 1 μm and about 100 μm (e.g.,

dry milled lactose) and micronized particles of the active agent. Such a dry powder formulation can be made, for example, by combining lactose with the active agent and then dry blending the components. Alternatively, if desired, the active agent can be formulated without an excipient. The composition is then typically loaded into a DPI, or into inhalation cartridges or capsules for use with a DPI. DPIs are well known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including Aerolizer® (Novartis), airmax™ (IVAX), ClickHaler® (Innovata Biomed), Diskhaler® (GlaxoSmithKline), Diskus® or Accuhaler (GlaxoSmithKline), Easyhaler® (Orion Pharma), Eclipse™ (Aventis), FlowCaps® (Hovione), Handihaler® (Boehringer Ingelheim), Pulvinal® (Chiesi), Rotahaler® (GlaxoSmithKline), SkyeHaler™ or Certihaler™ (SkyePharma), Twisthaler (Schering-Plough), Turbuhaler® (AstraZeneca), Ultrahaler® (Aventis), and the like.

In yet another specific embodiment of the invention, the composition comprising the active agent is administered by inhalation using a metered-dose inhaler (MDI). Such MDIs typically discharge a measured amount of the active agent using compressed propellant gas. Metered-dose formulations thus typically comprise a solution or suspension of the active agent in a liquefied propellant, such as a chlorofluorocarbon such as CCl_3F or a hydrofluoroalkane (HFA) such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoro-*n*-propane (HFA 227), although HFAs are generally preferred due to concerns about chlorofluorocarbons affecting the ozone layer. Additional optional components of HFA formulations include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, and glycerin. See, for example, U.S. Patent No. 5,225,183 to Purewal et al., EP 0717987 A2 (Minnesota Mining and Manufacturing Company), and WO 92/22286 (Minnesota Mining and Manufacturing Company). A representative composition for use in an MDI comprises from about 0.01-5 wt% of active agent; from about 0-20 wt% ethanol; and from about 0-5 wt% surfactant; with the remainder being an HFA propellant. Such compositions are typically prepared by adding a chilled or pressurized hydrofluoroalkane to a suitable container containing the active agent, ethanol (if present) and the surfactant (if present). To prepare a suspension, the active agent is micronized and then combined with the propellant. The formulation is then loaded into an aerosol canister, which forms a portion of the MDI. MDIs are well known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including AeroBid Inhaler System (Forest

Pharmaceuticals), Atrovent Inhalation Aerosol (Boehringer Ingelheim), Flovent® (GlaxoSmithKline), Maxair Inhaler (3M), Proventil® Inhaler (Schering), Serevent® Inhalation Aerosol (GlaxoSmithKline), and the like. Alternatively, a suspension formulation can be prepared by spray drying a coating of surfactant on micronized particles of the active agent. See, for example, WO 99/53901 (Glaxo Group Ltd.) and WO 00/61108 (Glaxo Group Ltd.).

Additional examples of processes of preparing respirable particles, and formulations and devices suitable for inhalation dosing are described in U.S. Patent Nos. 5,874,063 to Briggner et al.; 5,983,956 to Trofast; 6,221,398 to Jakupovic et al.; 6,268,533 to Gao et al.; 6,475,524 to Bisrat et al.; and 6,613,307 to Cooper.

In another embodiment, the pharmaceutical compositions are suitable for oral administration. Suitable compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; solutions or suspensions in an aqueous or non-aqueous liquid; oil-in-water or water-in-oil liquid emulsions; elixirs or syrups; and the like; each containing a predetermined amount of the active agent.

When intended for oral administration in a solid dosage form (i.e., as capsules, tablets, pills and the like), the composition will typically comprise the active agent and one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate. Solid dosage forms may also comprise: fillers or extenders, such as starches, microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as cetyl alcohol and/or glycerol monostearate; absorbents, such as kaolin and/or bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; coloring agents; and buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may also be present in the pharmaceutical compositions. Exemplary coating agents for tablets, capsules, pills and like, include those used for enteric coatings, such as cellulose acetate phthalate, polyvinyl acetate phthalate,

hydroxypropyl methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, hydroxypropyl methyl cellulose acetate succinate, and the like. Examples of pharmaceutically acceptable antioxidants include: water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfate sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, alpha-tocopherol, and the like; and metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid, sorbitol, tartaric acid, phosphoric acid, and the like.

Compositions may also be formulated to provide slow or controlled release of the active agent using, by way of example, hydroxypropyl methyl cellulose in varying proportions or other polymer matrices, liposomes and/or microspheres. In addition, the pharmaceutical compositions of the invention may contain opacifying agents and may be formulated so that they release the active agent only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active agent can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Liquid dosage forms typically comprise the active agent and an inert diluent, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

When intended for oral administration, the pharmaceutical compositions of the invention may be packaged in a unit dosage form. The term "unit dosage form" refers to a physically discrete unit suitable for dosing a patient, i.e., each unit containing a predetermined quantity of the active agent calculated to produce the desired therapeutic

effect either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like.

Compounds of the invention can also be administered parenterally (e.g., by subcutaneous, intravenous, intramuscular, or intraperitoneal injection). For such administration, the active agent is provided in a sterile solution, suspension, or emulsion. Exemplary solvents for preparing such formulations include water, saline, low molecular weight alcohols such as propylene glycol, polyethylene glycol, oils, gelatin, fatty acid esters such as ethyl oleate, and the like. A typical parenteral formulation is a sterile pH 4-7 aqueous solution of the active agent. Parenteral formulations may also contain one or more solubilizers, stabilizers, preservatives, wetting agents, emulsifiers, and dispersing agents. These formulations may be rendered sterile by use of a sterile injectable medium, a sterilizing agent, filtration, irradiation, or heat.

Compounds of the invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, the compound can be admixed with permeation enhancers, such as propylene glycol, polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

If desired, the compounds of this invention may be administered in combination with one or more other therapeutic agents. Thus, in one embodiment, compositions of the invention may optionally contain other drugs that are co-administered with a compound of the invention. For example, the composition may further comprise one or more drugs (also referred to as "secondary agents(s)") selected from the group of other bronchodilators (e.g., PDE_3 inhibitors, adenosine 2b modulators and β_2 adrenergic receptor agonists); anti-inflammatory agents (e.g., steroidal anti-inflammatory agents such as corticosteroids and glucocorticoids; non-steroidal anti-inflammatory agents (NSAIDs); and PDE_4 inhibitors); other muscarinic receptor antagonists (i.e., antichlolinergic agents); antiinfective agents (e.g., Gram positive and Gram negative antibiotics, and antiviral agents); antihistamines; protease inhibitors; afferent blockers (e.g., D_2 agonists and neurokinin modulators); and combinations thereof. Numerous examples of such therapeutic agents are well known in the art, and examples are described below. By combining a compound of the invention with a secondary agent, double therapy can be achieved, i.e., muscarinic receptor antagonist activity and activity associated with the secondary agent (e.g., β_1 adrenergic

receptor agonist), in some cases by administering two compositions and in some cases by administering a single composition containing the active agent and the secondary agent. Accordingly, in yet another aspect of the invention, a pharmaceutical composition comprises a compound of the invention, a second active agent, and a pharmaceutically acceptable carrier. Third, fourth etc. active agents may also be included in the composition. For example, a composition may comprise a compound of the invention; a secondary agent selected from corticosteroids, β_2 adrenergic receptor agonists; phosphodiesterase-4 inhibitors, and combinations thereof; and a pharmaceutically acceptable carrier. In a specific embodiment, the composition comprises a compound of the invention, a β_2 adrenergic receptor agonist, and a steroidal anti-inflammatory agent. In combination therapy, the amount of compound of the invention that is administered, as well as the amount of secondary agents, may be less than the amount typically administered in monotherapy.

A compound of the invention may be either physically mixed with the second active agent to form a composition containing both agents; or each agent may be present in separate and distinct compositions which are administered to the patient simultaneously or sequentially. For example, a compound of the invention can be combined with a second active agent using conventional procedures and equipment to form a combination of active agents comprising a compound of the invention and a second active agent. Additionally, the active agents may be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition comprising a compound of the invention, a second active agent and a pharmaceutically acceptable carrier. In this embodiment, the components of the composition are typically mixed or blended to create a physical mixture. The physical mixture is then administered in a therapeutically effective amount using any of the routes described herein.

Alternatively, the active agents may remain separate and distinct before administration to the patient. In this embodiment, the agents are not physically mixed together before administration but are administered simultaneously or at separate times as separate compositions. Such compositions can be packaged separately or may be packaged together in a kit. When administered at separate times, the secondary agent will typically be administered less than 24 hours after administration of the compound of the invention. In other embodiments this timed relationship is less than 12 hours, less than 8 hours, less than 6 hours, less than 4 hours, less than 3 hours, less than 1 hour, less than thirty minutes,

less than ten minutes, less than one minute, or immediately after administration of the compound of the invention. This is also referred to as sequential administration. Thus, a compound of the invention can be administered by inhalation simultaneously or sequentially with another active agent using an inhalation delivery device that employs separate compartments (e.g. blister packs) for each active agent, where sequential may mean being administered immediately after administration of the compound of the invention or at some predetermined time later (e.g., one hour later or three hours later). Alternatively, the combination may be administered using separate delivery devices, i.e., one delivery device for each agent. Additionally, the agents can be delivered by different routes of administration, i.e., one by inhalation and the other by oral administration.

In one embodiment, the kit comprises a first dosage form comprising a compound of the invention and at least one additional dosage form comprising one or more of the secondary agents set forth herein, in quantities sufficient to carry out the methods of the invention. The first dosage form and the second (or third, etc,) dosage form together comprise a therapeutically effective amount of active agents for the treatment or prevention of a disease or medical condition in a patient.

Secondary agent(s), when included, are present in a therapeutically effective amount. i.e., are typically administered in an amount that produces a therapeutically beneficial effect when co-administered with a compound of the invention. The secondary agent can be in the form of a pharmaceutically acceptable salt, solvate, optically pure stereoisomer, and so forth. Thus, secondary agents listed below are intended to include all such forms, and are commercially available or can be prepared using conventional procedures and reagents. Suitable doses for a secondary agent are typically in the range of about 0.05 μg/day to about 500 mg/day.

In a particular embodiment, a compound of the invention is administered in combination with a β_2 adrenergic receptor agonist. Representative β_2 adrenergic receptor agonists include, but are not limited to, albuterol, bitolterol, fenoterol, formoterol, indacaterol, isoetharine, levalbuterol, metaproterenol, pirbuterol, salbutamol, salmefamol, salmeterol, terbutaline, and the like. Other β_2 adrenergic receptor agonists that can be used in combination with compounds of the invention include, but are not limited to, 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)-hexyl]oxy}butyl)benzenesulfonamide and 3-(-3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}-propyl)benzenesulfonamide and related

compounds disclosed in WO 02/066422 (Glaxo Group Ltd.); 3-[3-(4-{[6-([(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl} amino)hexyl]oxy}butyl)-phenyl]imidazolidine-2,4-dione and related compounds disclosed in WO 02/070490 (Glaxo Group Ltd.); 3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)-benzenesulfonamide, 3-(4-{[6-({(2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)-benzenesulfonamide, 3-(4-{[6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)-benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]-oxy}butyl)benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{[6-({(2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)-hexyl]oxy}butyl)-benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{[6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino) hexyl]-oxy}butyl)benzenesulfonamide and related compounds disclosed in WO 02/076933 (Glaxo Group Ltd.); 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and related compounds disclosed in WO 03/024439 (Glaxo Group Ltd.); *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl] ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine and related compounds disclosed in U.S. Patent No. 6,576,793 to Moran et al.; *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine and related compounds disclosed in U.S. Patent No. 6,653,323 to Moran et al. In a particular embodiment, the β_2-adrenoreceptor agonist is a crystalline monohydrochloride salt of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine. Typically, the β_2-adrenoreceptor agonist will be administered in an amount sufficient to provide from about 0.05-500 μg per dose.

In a particular embodiment, a compound of the invention is administered in combination with a steroidal anti-inflammatory agent. Representative steroidal anti-inflammatory agents include, but are not limited to, beclomethasone dipropionate; budesonide; butixocort propionate; 20*R*-16α,17α-[butylidenebis(oxy)]-6α,9α-difluoro-11β-hydroxy-17β-(methylthio)androsta-4-en-3-one (RPR-106541); ciclesonide; dexamethasone; 6α,9α-difluoro-17α -[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester; 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxoandrosta-1,4-

diene-17β-carbothioic acid *S*-fluoromethyl ester; 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioic acid (*S*)-(2-oxotetrahydrofuran-3*S*-yl) ester; flunisolide; fluticasone propionate; methyl prednisolone; mometasone furoate; prednisolone; prednisone; rofleponide; ST-126; triamcinolone acetonide; and the like. Typically, the steroidal anti-inflammatory agent will be administered in an amount sufficient to provide from about 0.05-500 μg per dose.

An exemplary combination is a compound of the invention co-administered with salmeterol as the β_2 adrenergic receptor agonist, and fluticasone propionate as the steroidal anti-inflammatory agent. Another exemplary combination is a compound of the invention co-administered with a crystalline monohydrochloride salt of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine as the β_2-adrenoreceptor agonist, and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester as the steroidal anti-inflammatory agent.

Other suitable combinations include, for example, other anti-inflammatory agents, e.g., NSAIDs (such as sodium cromoglycate; nedocromil sodium; phosphodiesterase (PDE) inhibitors (e.g., theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors); leukotriene antagonists (e.g., monteleukast); inhibitors of leukotriene synthesis; iNOS inhibitors; protease inhibitors, such as tryptase and elastase inhibitors; beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g., adenosine 2a agonists); cytokine antagonists (e.g., chemokine antagonists such as, an interleukin antibody (αIL antibody), specifically, an αIL-4 therapy, an αIL-13 therapy, or a combination thereof); or inhibitors of cytokine synthesis.

In a particular embodiment, a compound of the invention is administered in combination with a phosphodiesterase-4 (PDE4) inhibitors or mixed PDE3/PDE4 inhibitors. Representative PDE4 or mixed PDE3/PDE4 inhibitors include, but are not limited to, *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one; *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid and the like, or pharmaceutically acceptable salts thereof. Other representative PDE4 or mixed PDE4/PDE3 inhibitors include AWD-12-281 (elbion); NCS-613 (INSERM); D-4418 (Chiroscience and Schering-

Plough); CI-1018 or PD-168787 (Pfizer); benzodioxole compounds disclosed in WO99/16766 (Kyowa Hakko); K-34 (Kyowa Hakko); V-11294A (Napp); roflumilast (Byk-Gulden); pthalazinone compounds disclosed in WO99/47505 (Byk-Gulden); Pumafentrine (Byk-Gulden, now Altana); arofylline (Almirall-Prodesfarma); VM554/UM565 (Vernalis); T-440 (Tanabe Seiyaku); and T2585 (Tanabe Seiyaku).

In a particular embodiment, a compound of the invention is administered in combination with a muscarinic antagonist (i.e., anticholinergic agent). Representative muscarinic antagonists include, but are not limited to, atropine, atropine sulfate, atropine oxide, methylatropine nitrate, homatropine hydrobromide, hyoscyamine (*d, l*) hydrobromide, scopolamine hydrobromide, ipratropium bromide, oxitropium bromide, tiotropium bromide, methantheline, propantheline bromide, anisotropine methyl bromide, clidinium bromide, copyrrolate (Robinul), isopropamide iodide, mepenzolate bromide, tridihexethyl chloride (Pathilone), hexocyclium methylsulfate, cyclopentolate hydrochloride, tropicamide, trihexyphenidyl hydrochloride, pirenzepine, telenzepine, AF-DX 116 and methoctramine and the like.

In a particular embodiment, a compound of the invention is administered in combination with an antihistamine (i.e., H_1-receptor antagonist). Representative antihistamines include, but are not limited to, ethanolamines, such as carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride and dimenhydrinate; ethylenediamines, such as pyrilamine amleate, tripelennamine hydrochloride and tripelennamine citrate; alkylamines, such as chlorpheniramine and acrivastine; piperazines, such as hydroxyzine hydrochloride, hydroxyzine pamoate, cyclizine hydrochloride, cyclizine lactate, meclizine hydrochloride and cetirizine hydrochloride; piperidines, such as astemizole, levocabastine hydrochloride, loratadine or its descarboethoxy analogue, terfenadine and fexofenadine hydrochloride; azelastine hydrochloride; and the like.

The following formulations illustrate representative pharmaceutical compositions of the invention.

Exemplary Compositions For Administration By a DPI

A compound of the invention (0.2 mg) is micronized and then blended with lactose (25 mg). This blended mixture is then loaded into a gelatin inhalation cartridge. The contents of the cartridge are administered using a DPI, for example.

A micronized compound of the invention (100 mg) is blended with milled lactose (25 g) (e.g., lactose in which not greater than about 85% of the particles have a MMD of

about 60 μm to about 90 μm and not less than 15% of the particles have a MMD of less then 15 μm). The blended mixture is then loaded into individual blisters of a peelable blister pack in an amount sufficient to provide about 10-500 μg of the compound of the invention per dose. The contents of the blisters are administered using a DPI.

Alternately, a micronized compound of the invention (1 g) is blended with milled lactose (200 g) to form a bulk composition having a weight ratio of compound to milled lactose of 1:200. The blended composition is packed into a DPI capable of delivering between about 10-500 μg of the compound of the invention per dose.

Alternately, a micronized compound of the invention (100 mg) and a micronized β_2 adrenergic receptor agonist (500 mg) are blended with milled lactose (30 g). The blended mixture is then loaded into individual blisters of a peelable blister pack in an amount sufficient to provide about 10 μg to about 500 μg of the compound of the invention per dose. The contents of the blisters are administered using a DPI.

Exemplary Compositions For Use In An MDI

A micronized compound of the invention (10 g) is dispersed in a solution prepared by dissolving lecithin (0.2 g) in demineralized water (200 mL). The resulting suspension is spray dried and then micronized to form a micronized composition comprising particles having a mean diameter less than about 1.5 μm. The micronized composition is then loaded into MDI cartridges containing pressurized 1,1,1,2-tetrafluoroethane in an amount sufficient to provide about 10 μg to about 500 μg of the compound of the invention per dose when administered by the MDI.

Alternately, a suspension containing 5 wt% compound of the invention, 0.5 wt% lecithin, and 0.5 wt% trehalose is prepared by dispersing 5 g of a compound of the invention as micronized particles with mean size less than 10 μm in a colloidal solution formed from 0.5 g of trehalose and 0.5 g of lecithin dissolved in 100 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5 μm. The particles are loaded into canisters with pressurized 1,1,1,2-tetrafluoroethane.

Exemplary Composition For Use In A Nebulizer Inhaler

A compound of the invention (25 mg) is dissolved in citrate buffered (pH 5) isotonic saline (125 mL). The mixture is stirred and sonicated until the compound is dissolved. The pH of the solution is checked and adjusted, if necessary, to pH 5 by slowly

adding aqueous 1N sodium hydroxide. The solution is administered using a nebulizer device that provides about 10 μg to about 500 μg of the compound of the invention per dose.

Exemplary Hard Gelatin Capsules For Oral Administration

A compound of the invention (50 g), spray-dried lactose (440 g) and magnesium stearate (10 g) are thoroughly blended. The resulting composition is then loaded into hard gelatin capsules (500 mg of composition per capsule).

Exemplary Suspension For Oral Administration

The following ingredients are mixed to form a suspension containing 100 mg of compound per 10 mL of suspension:

Ingredients	Amount
Compound of the invention	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum® K (magnesium aluminum silicate)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Exemplary Injectable Formulation For Administration By Injection

compound of the invention (0.2 g) is blended with 0.4 M sodium acetate buffer solution (2.0 mL). The pH of the resulting solution is adjusted to pH 4 using 0.5 N aqueous hydrochloric acid or 0.5 N aqueous sodium hydroxide, as necessary, and then sufficient water for injection is added to provide a total volume of 20 mL. The mixture is then filtered through a sterile filter (0.22 micron) to provide a sterile solution suitable for administration by injection.

UTILITY

Compounds of the invention possess muscarinic receptor antagonist activity, and in one embodiment, at nanomolar potencies. In one embodiment, compounds of the invention are selective for inhibition of M_3 muscarinic receptor subtype activity over M_2 muscarinic receptor subtype activity. In another embodiment, compounds of the invention are selective for inhibition of M_3 and M_2 muscarinic receptor subtype activity over M_1, M_4, and M_5 muscarinic receptor subtype activity. Additionally, compounds of the invention

are expected to possess a desirable duration of action. Accordingly, in another specific embodiment, the invention is directed to compounds having a duration of action greater than about 24 hours. Moreover, compounds of the invention are also expected to possess reduced side effects, such as dry mouth, at efficacious doses when administered by inhalation compared to other known muscarinic receptor antagonists administered by inhalation (such as tiotropium).

One measure of the affinity of a compound for the M_3 receptor subtype is the inhibition dissociation constant (K_i) for binding to the receptor. Compounds of the invention are expected to have a K_i for the M_3 receptor subtype of less than or equal to 100 nM, as determined, for example, by an *in vitro* radioligand displacement assay. Compounds of particular interest include those having a K_i less than or equal to 50 nM, and in another embodiment, the compounds have a K_i less than or equal to 10 nM, and in yet another embodiment, the compounds have a K_i less than or equal to 1.0 nM. Compounds of even more particular interest include those having a K_i less than or equal to 500 pM, and in another embodiment, the compounds have a K_i less than or equal to 200 pM. It is noted that in some cases, compounds of the invention may possess weak muscarinic receptor antagonist activity. In such cases, those of skill in the art will recognize that these compounds still have utility as research tools.

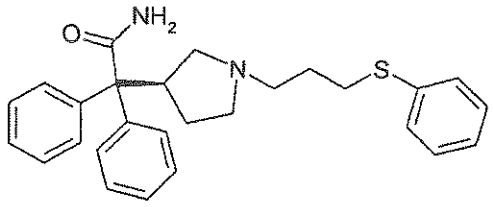
Also of particular interest are those compounds having an ID_{50} of less than or equal to 100 μg/mL at 24 hours post dosing, more particularly those compounds having an ID_{50} of less than or equal to 30 μg/mL at 24 hours post dosing.

Exemplary assays to determine properties of compounds of the invention, such as the muscarinic receptor antagonizing activity, are described in the Examples and include by way of illustration and not limitation, assays that measure hM_1, hM_2, hM_3, hM_4, and hM_5 muscarinic receptor binding (for example, as described in Assay 1). Useful functional assays to determine the muscarinic receptor antagonizing activity of compounds of the invention include by way of illustration and not limitation, assays that measure ligand-mediated changes in intracellular cyclic adenosine monophosphate (cAMP), ligand-mediated changes in activity of the enzyme adenylyl cyclase (which synthesizes cAMP), ligand-mediated changes in incorporation of guanosine 5'-O-(γ-thio)triphosphate ([^{35}S]GTPγS) into isolated membranes via receptor catalyzed exchange of [^{35}S]GTPγS for GDP, ligand-mediated changes in free intracellular calcium ions (measured, for example, with a fluorescence-linked imaging plate reader or FLIPR® from Molecular Devices, Inc.),

and the like. Exemplary assays are described in Assay 2. Compounds of this invention are expected to antagonize or decrease the activation of muscarinic receptors in any of the assays listed above, or assays of a similar nature, and will typically be used in these studies at a concentration ranging from about 0.1-100 nanomolar. Thus, the aforementioned assays are useful in determining the therapeutic utility, for example, the bronchodilating activity, of compounds of the invention.

Other properties and utilities of compounds of the invention can be demonstrated using various *in vitro* and *in vivo* assays well-known to those skilled in the art. For example, the *in vivo* potency of compounds of the invention can be measured in an animal model such as the Einthoven model. Briefly, the bronchodilator activity of a compound is evaluated in an anesthetized animal (the Einthoven model), which uses ventilation pressure as a surrogate measure of airway resistance. See, for example, Einthoven (1892) *Pfugers Arch.* 51:367-445; and Mohammed et al. (2000) *Pulm Pharmacol Ther.*13(6):287-92, as well as Assay 3 which describes a rat Einthoven model. In one embodiment, a compound of the invention administered at a dose of 100 μg/ml in the rat Einthoven model exhibits greater than or equal to 35% inhibition of the bronchoconstrictor response at 24 hours, and in another embodiment exhibits greater than or equal to 70 % inhibition at 24 hours. Another useful *in vivo* assay is the rat antisialagogue assay (for example, as described in Assay 4).

The quaternary compounds of the invention also provide surprising advantages over the corresponding non-quaternary compounds, as manifested, for example, in improved *in vitro* potency or improved *in vivo* potency at 24 hours post-dosing. For example, both enantiomers of the non-quaternary compound:



and

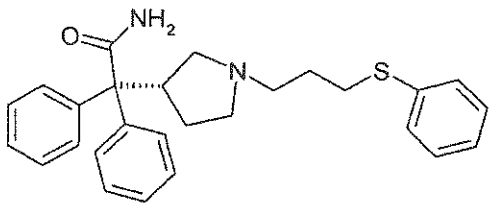
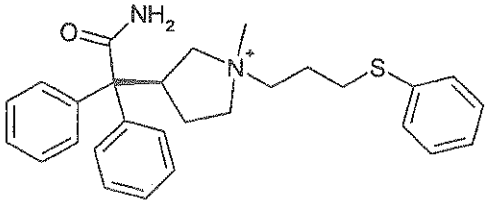


exhibit a hM_3 K_i value of 1.5 and 2.9 nM (measured at 6 hours), respectively, while quaternary compounds of the invention, such as (*S*)-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenylsulfanylpropyl)pyrrolidinium (Example 2) and *(R)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenylsulfanylpropyl)pyrrolidinium (Example 5-11):



and

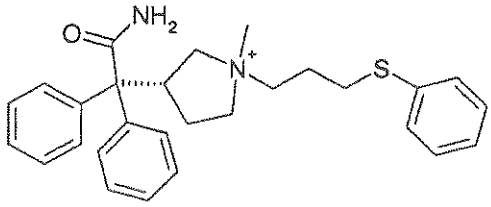


exhibit a hM_3 K_i value of less than 0.5 nM (measured at 6 hours).

Compounds of the invention are expected to be useful as therapeutic agents for treating medical conditions mediated by muscarinic receptors. Thus it is expected that patients suffering from a disease or disorder that is treated by blocking the muscarinic receptor can be treated by administering a therapeutically effective amount of a muscarinic receptor antagonist of the invention. Such medical conditions include, by way of example, pulmonary disorders or diseases including those associated with reversible airway obstruction, such as chronic obstructive pulmonary disease (e.g., chronic and wheezy bronchitis and emphysema), asthma, pulmonary fibrosis, allergic rhinitis, rhinorrhea, and the like. Other medical conditions that can be treated with muscarinic receptor antagonists are genitourinary tract disorders, such as overactive bladder or detrusor hyperactivity and their symptoms; gastrointestinal tract disorders, such as irritable bowel syndrome, diverticular disease, achalasia, gastrointestinal hypermotility disorders and diarrhea; cardiac arrhythmias, such as sinus bradycardia; Parkinson's disease; cognitive disorders, such as Alzheimer's disease; dismenorrhea; and the like.

The amount of active agent administered per dose or the total amount administered per day may be predetermined or it may be determined on an individual patient basis by taking into consideration numerous factors, including the nature and severity of the patient's condition, the condition being treated, the age, weight, and general health of the patient, the tolerance of the patient to the active agent, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the active agent and any secondary agents being administered, and the like. Treatment of a patient suffering from a disease or medical condition (such as COPD) can begin with a predetermined dosage or a dosage determined by the treating physician, and will continue for a period of time necessary to prevent, ameliorate, suppress, or alleviate the symptoms of the disease or medical condition. Patients undergoing such treatment will typically be monitored on a routine basis to determine the effectiveness of therapy. For example, in treating COPD, significant improvement in forced expiratory

volume (measured in one second) may be used to determine the effectiveness of treatment. Similar indicators for the other diseases and conditions described herein, are well-known to those skilled in the art, and are readily available to the treating physician. Continuous monitoring by the physician will insure that the optimal amount of active agent will be administered at any given time, as well as facilitating the determination of the duration of treatment. This is of particular value when secondary agents are also being administered, as their selection, dosage, and duration of therapy may also require adjustment. In this way, the treatment regimen and dosing schedule can be adjusted over the course of therapy so that the lowest amount of active agent that exhibits the desired effectiveness is administered and, further, that administration is continued only so long as is necessary to successfully treat the disease or medical condition.

Accordingly, in one embodiment, compounds of the invention are useful for treating smooth muscle disorders in mammals, including humans and their companion animals (e.g., dogs, cats etc.). Such smooth muscle disorders include, by way of illustration, overactive bladder, chronic obstructive pulmonary disease and irritable bowel syndrome. Typically, suitable doses for treating smooth muscle disorders or other disorders mediated by muscarinic receptors will range from about 0.14 μg/kg/day to about 7 mg/kg/day of active agent; including from about 0.15 μg/kg/day to about 5 mg/kg/day. For an average 70 kg human, this would amount to about 10 μg per day to about 500 mg per day of active agent.

In a specific embodiment, compounds of the invention are useful for treating pulmonary or respiratory disorders, such as COPD or asthma, in mammals including humans, by administering to a patient a therapeutically effective amount of the compound. Generally, the dose for treating a pulmonary disorder will range from about 10-1500 μg/day. The term "COPD" is understood by those of ordinary skill in the art to include a variety of respiratory conditions, including chronic obstructive bronchitis and emphysema, as exemplified by the teachings of Barnes (2000) *N. Engl. J. Med.* 343:269-78, and references cited therein. When used to treat a pulmonary disorder, compounds of the invention are optionally administered in combination with other therapeutic agents such as a β_2-adrenoreceptor agonist; a corticosteroid, a non-steroidal anti-inflammatory agent, or combinations thereof.

When administered by inhalation, compounds of the invention typically have the effect of producing bronchodilation. Accordingly, in another of its method aspects, the

invention is directed to a method of producing bronchodilation in a patient, comprising administering to a patient a bronchodilation-producing amount of a compound of the invention. Generally, the therapeutically effective dose for producing bronchodilation will range from about 10-1500 μg/day.

In another embodiment, compounds of the invention are used to treat overactive bladder. When used to treat overactive bladder, a typical dose will range from about 1.0-500 mg/day. In yet another embodiment, compounds of the invention are used to treat irritable bowel syndrome. When used to treat irritable bowel syndrome, compounds of the invention will typically be administered orally or rectally, and a typical dose will range from about 1.0-500 mg/day.

Since compounds of this invention possess muscarinic receptor antagonist activity, such compounds are also useful as research tools for investigating or studying biological systems or samples having muscarinic receptors. Any suitable biological system or sample having M_1, M_2, M_3, M_4 and/or M_5 muscarinic receptors may be employed in such studies which may be conducted either *in vitro* or *in vivo*. Representative biological systems or samples suitable for such studies include, but are not limited to, cells, cellular extracts, plasma membranes, tissue samples, isolated organs, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, humans, and so forth), and the like, with mammals being of particular interest. In one particular embodiment of the invention a muscarinic receptor in a mammal is antagonized by administering a muscarinic receptor-antagonizing amount of a compound of the invention. Compounds of the invention can also be used as research tools by conducting biological assays using such compounds.

When used as a research tool, a biological system or sample comprising a muscarinic receptor is typically contacted with a muscarinic receptor-antagonizing amount of a compound of the invention. After the biological system or sample is exposed to the compound, the effects of antagonizing the muscarinic receptor are determined using conventional procedures and equipment, such as by measuring binding in a radioligand binding assays or ligand-mediated changes in a functional assay or by determining the amount of bronchoprotection provided by the compound in a bronchoprotection assay in a mammal. Exposure encompasses contacting cells or tissue with the compound, administering the compound to a mammal, for example by i.p. or i.v. administration, and so forth. This determining step may comprise measuring a response, i.e., a quantitative analysis or may comprise an observation, i.e., a qualitative analysis. Measuring a response

involves, for example, determining the effects of the compound on the biological system or sample using conventional procedures and equipment, such as radioligand binding assays and measuring ligand-mediated changes in functional assays. The assay results can be used to determine the activity level as well as the amount of compound necessary to achieve the desired result, i.e., a muscarinic-antagonizing amount. Typically, the determining step will involve determining the muscarinic receptor ligand-mediated effects.

Additionally, compounds of the invention can be used as research tools for evaluating other chemical compounds, and thus are also useful in screening assays to discover, for example, new compounds having muscarinic receptor binding activity. In this manner, a compound of the invention is used as a standard in an assay to allow comparison of the results obtained with a test compound and with compounds of the invention to identify those test compounds that have about equal or superior binding, if any. For example, muscarinic receptor binding data (as determined, for example, by *in vitro* radioligand displacement assays) for a test compound or a group of test compounds is compared to the muscarinic receptor binding data for a compound of the invention to identify those test compounds that have the desired properties, e.g., test compounds having binding about equal or superior to a compound of the invention, if any. Alternatively, for example, bronchoprotective effects can be determined for test compounds and a compound of the invention in a bronchoprotection assay in a mammal and this data compared to identify test compounds providing about equal or superior bronchoprotective effects. This aspect of the invention includes, as separate embodiments, both the generation of comparison data (using the appropriate assays) and the analysis of the test data to identify test compounds of interest. Thus, a test compound can be evaluating in a biological assay, by a method comprising the steps of: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the invention to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include muscarinic receptor binding assays.

EXAMPLES

The following Preparations and Examples are provided to illustrate specific embodiments of the invention. These specific embodiments, however, are not intended to limit the scope of the invention in any way unless specifically indicated.

The following abbreviations have the following meanings unless otherwise indicated and any other abbreviations used herein and not defined have their standard meaning:

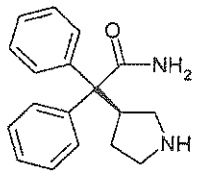
AC	adenylyl cyclase
ACN	acetonitrile
BSA	bovine serum albumin
cAMP	3'-5' cyclic adenosine monophosphate
CHO	Chinese hamster ovary
cM_5	cloned chimpanzee M_5 receptor
DCM	dichloromethane (i.e., methylene chloride)
DIPEA	*N,N*-diisopropylethylamine
dPBS	Dulbecco's phosphate buffered saline
DMA	*N,N*-dimethylacetamide
EDTA	ethylenediamine tetraacetic acid
EtOAc	ethyl acetate
EtOH	ethanol
FBS	fetal bovine serum
FLIPR	fluorometric imaging plate reader
HBSS	Hank's Buffered Salt Solution
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
hM_1	cloned human M_1 receptor
hM_2	cloned human M_2 receptor
hM_3	cloned human M_3 receptor
hM_4	cloned human M_4 receptor
hM_5	cloned human M_5 receptor
IPAc	isopropyl acetate
MCh	methylcholine
MeOH	methanol
MTBE	methyl *t*-butyl ether
TFA	trifluoroacetic acid
TFA salt	trifluoroacetate salt
THF	tetrahydrofuran

Any other abbreviations used herein but not defined have their standard, generally

accepted meaning. Unless noted otherwise, all materials, such as reagents, starting materials and solvents, were purchased from commercial suppliers (such as Sigma-Aldrich, Fluka Riedel-de Haën, and the like) and were used without further purification. Reactions were run under nitrogen atmosphere, unless noted otherwise. Progress of reaction mixtures was monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of which are given below and separately in specific examples of reactions. Reaction mixtures were worked up as described specifically in each reaction; commonly they were purified by extraction and other purification methods such as temperature-, and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC.

Preparation 1

2,2-Diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide



(*S*)-1-Benzyl-3-(*p*-toluenesulfonyloxy)pyrrolidine (1a): To a stirred solution of (*S*)-1-benzyl-3-pyrrolidinol (44.3 g, 0.25 mol) and 1,4-diazabicyclo[2.2.2]octane (33.7 g, 0.3 mol) in 250 mL of MTBE under nitrogen at 0°C, was added *p*-toluenesulfonyl chloride (52.4 g, 0.275 mol) portion-wise over 20 minutes. The mixture was stirred at 0 °C for 1 hour. The ice bath was removed and the mixture was stirred at ambient temperature overnight (20±5 hours). EtOAc (100 mL) was added, followed by saturated aqueous sodium bicarbonate solution (250 mL). The resulting mixture was stirred at ambient temperature for 1 hour. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate solution (250 mL); saturated aqueous NH_4Cl solution (250 mL); saturated aqueous NaCl solution (250 mL); and then dried over sodium sulfate (80 g). The sodium sulfate was filtered off and washed with EtOAc (20 mL) and the solvent was removed *in vacuo* to give 78.2 g of intermediate (1a) as an off-white solid (94% yield). HPLC analysis was conducted using a YMC ODSA C18 4.6 x 50 mm column, having a 5.0 micron particle size. Detection was by UV absorbance at 220 nm. The mobile phases employed were as follows (percentage by volume): A: MeOH/water/TFA (10/90/0.1; and B: MeOH/water/TFA (90/10/0.1). Using a flow rate of 4.0 mL/min of 0 to 100% B in A over 5 minutes, this intermediate was determined to have

a purity of 95%.

(*S*)-1-Benzyl-3-(1-cyano-1,1-diphenylmethyl)-pyrrolidine (1b): To a stirred solution of diphenylacetonitrile (12.18 g, 61.8 mmol) in anhydrous THF (120 mL) at 0°C, potassium *tert*-butoxide (10.60 g, 94.6 mmol) was added over 5 min. The mixture was stirred at 0 °C for 1 hour. To the mixture at 0 °C was added intermediate (1a) (20.48 g, 61.3 mmol) in one portion. The cold bath was removed and the mixture was stirred for 5-10 minutes at which time the mixture had become a brown homogeneous solution. The mixture was then heated at 40 °C overnight (20±5 hours). The mixture (bright yellow suspension) was allowed to cool to ambient temperature before adding water (150 mL). Most of the THF was then removed *in vacuo* and IPAc (200 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous NH_4Cl solution (150 mL); saturated aqueous NaCl solution (150 mL); and then dried over sodium sulfate (50 g). The sodium sulfate was filtered off and washed with IPAc (20 mL) and the solvent was removed *in vacuo* to give 23.88 g of intermediate (1b) as a light brown oil (>99% yield). Intermediate (1b) was determined to have a purity of 75% (contaminated mainly with excess diphenylacetonitrile) using the HPLC method described above.

(*S*)-3-(1-Cyano-1,1-diphenylmethyl)pyrrolidine (1c): Intermediate (1b) was dissolved in IPAc (approximately 1 g/10 mL) and the solution was mixed with an equal volume of 1N aqueous HCl. The resulting layers were separated and the aqueous layer was extracted with an equal volume of IPAc. The organic layers were combined, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to afford (*S*)-1-benzyl-3-(1-cyano-1,1-diphenylmethyl)pyrrolidine hydrochloride as a light yellow foamy solid. To a stirred solution of (*S*)-1-benzyl-3-(1-cyano-1,1-diphenylmethyl)pyrrolidine hydrochloride (8.55 g, 21.98 mmol) in MeOH (44 mL) was added palladium on carbon (1.71 g) and ammonium formate (6.93 g, 109.9 mmol). The mixture was heated to 50 °C with stirring for 3 hours. The mixture was cooled to ambient temperature and water (20 mL) was added. The resulting mixture was filtered through a pad of Celite®, washing with MeOH (20 mL). The filtrate was collected and most of the MeOH was removed *in vacuo*. The residue was mixed with IPAc (100 mL) and 10% aqueous sodium carbonate (50 mL). The resulting layers were separated and the aqueous layer was extracted with IPAc (50 mL). The organic layers were combined and dried over sodium sulfate (20 g). The sodium sulfate was filtered off and washed with IPAc (20 mL). The solvent was removed *in vacuo* to afford 5.75 g of intermediate (1c) as a light yellow oil (99.7% yield, 71% purity by

HPLC).

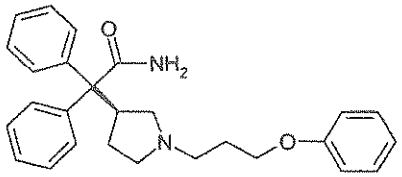
2,2-Diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide: A 200 mL flask with a magnetic stir bar and a nitrogen inlet was charged with intermediate (1c) (2.51 g) and 80% H_2SO_4 (19.2 mL; pre-prepared with 16 mL of 96% H_2SO_4 and 3.2 mL of H_2O). The mixture was then heated at 90 °C for 24 hours or until the starting material was consumed as indicated by HPLC. The mixture was allowed to cool to ambient temperature and then poured onto ice (approximately 50 mL by volume). A 50% aqueous NaOH solution was added slowly to the mixture with stirring over an ice bath until the pH was about 12. DCM (200 mL) was added and mixed with the aqueous solution at which time sodium sulfate precipitated out and was filtered off. The filtrate was collected and the layers were separated. The aqueous layer was extracted with DCM (100 mL) and the organic layers were combined and dried with over sodium sulfate (5 g). The sodium sulfate was filtered off and washed with DCM (10 mL). The solvent was removed *in vacuo* to give the crude product as a light yellow foamy solid (ca. 2.2 g, 86% purity by HPLC).

The crude product was dissolved in EtOH (18 mL) with stirring. To this solution was added a warm solution of L-tartaric acid (1.8 g) in EtOH (14 mL) and the resulting mixture was stirred overnight (15±5 hours). The resulting precipitate was isolated by filtration to give an off-white solid (ca. 3.2 g, >95% purity by HPLC). MeOH (15 mL) was added to this solid and the resulting slurry was stirred at 70 °C overnight (15 hours). The slurry was allowed to cool to ambient temperature and a white solid (~ 2.6 g, >99% purity by HPLC) was obtained after filtration. To this solid was added EtOAc (30 mL) and 1 N aqueous NaOH (25 mL). This mixture was mixed until two distinct layers formed and then the layers were separated and the aqueous layer was extracted with EtOAc (20 mL). The organic layers were combined and dried over sodium sulfate (10 g). The sodium sulfate was removed by filtration and the solvent was evaporated *in vacuo* to afford 1.55 g of the title compound as an off-white foamy solid (58% yield).

HPLC analysis was conducted using an Inertsil OCD-2 C18 column. Detection was by UV absorbance at 254 nm. The mobile phases employed were as follows (percentage by volume): A: MeOH/water/TFA (5/95/0.1); and B: MeOH/water/TFA (95/5/0.1). Using a flow rate of 1.0 mL/min of 0 to 100% B in A over 15 minutes, this compound was determined to have a purity of >99%.

Preparation 2

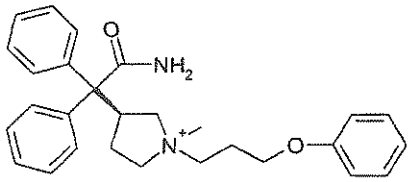
2-[*(S)*-1-(3-Phenoxypropyl)pyrrolidin-3-yl]-2,2-diphenylacetamide



Into a vial was added 2,2-diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide (42.0 mg, 0.15 mmol; prepared as described in Preparation 1) and 3-bromopropoxybenzene (23.7 μL, 0.15 mmol) in ACN (1 mL) and DIPEA (78 μL, 0.45 mmol). The mixture was heated to 70 °C overnight. After overnight, the reaction was cooled to room temperature and concentrated. The mixture was chromatographed on reverse-phase HPLC (gradient elution, 10-50% ACN/H_2O) to afford 49.0 mg (92% purity) of the title compound (56% yield) as a trifluoroacetate salt. MS *m/z*: [M + H^+] calcd for $C_{27}H_{30}N_2O_2$, 415.23; found 415.2.

EXAMPLE 1

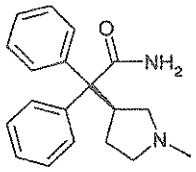
(*S*)-3-(Carbamoyldiphenylmethyl)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium



Into a vial was added 2-[*(S)*-1-(3-phenoxypropyl)pyrrolidin-3-yl]-2,2-diphenylacetamide (79mg, 0.15mmol; prepared as described in Preparation 2) in DMA (1 mL) and methyl iodide (0.093 mL, 1.5 mmol) and the mixture was stirred for 2hours at 80 °C. The mixture was then cooled to room temperature and concentrated. The mixture was chromatographed on reverse-phase HPLC (gradient elution, 10-50% ACN/H_2O) to afford 35.0 mg (85% purity) of the title compound (36% yield) as a TFA salt. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2$, 429.25; found 429.6. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.29 (2H, m), 2.68 (1H, s), 2.90 (5H, s), 2.98 (5H, s), 3.37 (2H, m), 3.59 (2H, m)3.95 (H, m), 4.06 (2H, t), 5.93 (2H, s), 6.9 (4H, m), 7.28 (7H, m).

Preparation 3

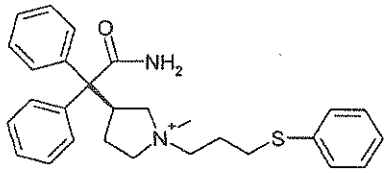
2-((*S*)-1-Methylpyrrolidin-3-yl)-2,2-diphenylacetamide



To a round-bottom flask was added 2,2-diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide (2.8 g, 10.0 mmol; prepared as described in Preparation 1), MeOH (30 mL) and then formaldehyde (2 mL, 30% in water, 24.6 mmol) with stirring. The solution was then purged with nitrogen and then with hydrogen. The mixture was stirred overnight under hydrogen. The mixture was then filtered through a pad of Celite®, concentrated *in vacuo*, then taken up in H_2O/ACN (1:1 mixture, 1g solid/20 mL solvent mixture). The mixture was stirred overnight at room temperature. Finally the mixture was filtered and then allowed to dry to afford 2.7 g of the title compound as an off-white foamy solid (96.4% yield). MS *m/z*: [M + H^+] calcd for $C_{19}H_{22}N_2O$, 294.39; found 295.0. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.73 (1H, s), 1.97 (2H, m), 2.27 (3H, s), 2.42 (1H, q), 2.55 (1H, m), 2.67 (1H, t), 2.75 (1H, m), 3.46 (1H, m), 5.63 (1H, br s), 7.26 (8H, m), 7.41 (2H, m).

EXAMPLE 2

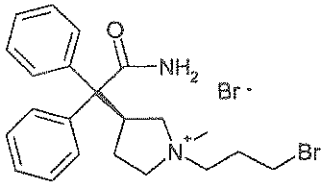
(*S*)-3-(Carbamoyldiphenylmethyl)-1-methyl-1-(3-phenylsulfanylpropyl)pyrrolidinium



Into a vial was added 2-((*S*)-1-methylpyrrolidin-3-yl)-2,2-diphenylacetamide (300 mg, 1.0 mmol; prepared as described in Preparation 3) in DMA (10 mL) and 3-chloropropylsulfanylbenzene (200 mg, 1.0 mmol). Sodium iodide (30 mg, 0.2 mmol) was added to the mixture. The mixture was degassed under nitrogen and then was heated to 90 °C overnight. The mixture was then concentrated and chromatographed on reverse-phase HPLC (gradient elution, 10-50% ACN/H_2O) to afford 49.0 mg (92% purity) of the title compound as a TFA salt. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2OS$: 445.23; found: 445.1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.97 (1H, m), 2.20 (1H, m), 2.70 (2H, s), 2.88 (2H, s), 2.93 (2H, s), 3.3 (1H, m), 3.4 (1H, m), 3.52 (1H, m), 3.89 (2H, m), 4.03 (2H, m), 4.30 (1H, t), 5.63 (1H, d) 5.94 (1H, s) 7.20 (2H, m), 7.35 (13H, m).

Preparation 4

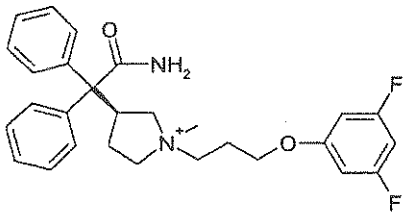
(S)-1-(3-Bromopropyl)-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidinium Bromide



To a round-bottom flask was dissolved 2,2-diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide (2.8 g, 10 mmol; prepared as described in Preparation 1) and 1,3-dibromopropane (6.8 mL, 50 mmol) in DMA (30 mL). The mixture was stirred and placed in an oil bath at 80 °C for 2 hours. The mixture was cooled to room temperature and ethyl ether (200 mL) was added with stirring. Immediate formation of white precipitate occurred. The mixture was stirred overnight. The white precipitate was filtered and dried in a vacuum dessicator to afford 6.6 g of the title compound as a white solid (Yield = 95%). MS *m/z*: [M^+] calcd for $C_{22}H_{28}BrN_2O_2$, 415.14; found 417.2. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.86 (3H, s), 2.20 (2H, m), 2.40 (1H, m), 2.73 (1H, m), 2.78 (1H, s), 3.49 (6H, m), 3.89 (1H, m), 4.06 (2H, m), 4.38 (1H, t), 5.80 (1H, br d), 6.32 (1H, br s), 7.34 (10H, m).

EXAMPLE 3

(S)-3-(Carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenoxy) propyl]-1-methyl-pyrrolidinium

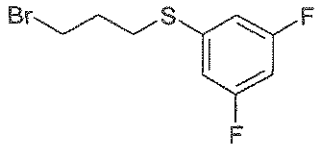


To a round-bottom flask was added *(S)*-1-(3-bromopropyl)-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidinium bromide (900 mg, 2.2 mmol; prepared as described in Preparation 4) in DMA (10 mL). To the mixture was added 3,5-difluorophenol (288 mg, 2.2mmol), followed by potassium carbonate (0.5 g, 3.6 mmol), which was stirred vigorously. The mixture was stirred overnight at room temperature. The mixture was then concentrated and chromatographed on reverse-phase HPLC (gradient elution, 10-50% ACN/H_2O) to afford 75.0 mg (99% purity) of the title compound (6% yield) as a TFA salt. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$: 465.24; found: 465.2. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.10 (1H, s), 2.19 (2H, s), 2.67 (3H, s), 2.80 (1H, s),

3.25 (3H, s), 3.53 (1H, t), 3.67 (2H, s), 3.87 (2H, s), 4.01 (2H, s), 4.20 (1H, t), 5.80 (1H, d), 6.38 (3H, m), 6.53 (1H, d).

Preparation 5

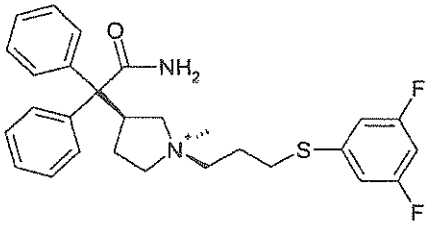
1-(3-Bromopropylsulfanyl)-3,5-difluorobenzene



To a round-bottom flask was added 3,5-difluorobenzenethiol (4.9 g, 33.8 mmol) in ACN (50 mL). 3-Bromo-1-propanol (4.7 g, 34.0 mmol) and potassium carbonate (6.4 g, 46 mmol) were added, and the mixture was stirred at room temperature for 3 hours. The mixture was then filtered through a pad of Celite® and the solvent was removed under reduced pressure. The crude material was then dissolved in anhydrous DCM (100 mL). Triphenylphosphine dibromide (25 g, 59 mmol) was added to the mixture, which was then stirred for 2 hours. The solvent was removed under reduced pressure. The residue was suspended in EtOAc (200 mL), stirred for 1 hour, and filtered to remove solids. The filtrate was concentrated under reduced pressure, then diluted in 50% EtOAc/hexanes (200 mL), and filtered through a pad of Celite® and silica gel. The solution was then concentrated under reduced pressure to afford the title compound (5.8 g).

EXAMPLE 4

(1R,3S)-3-(Carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium

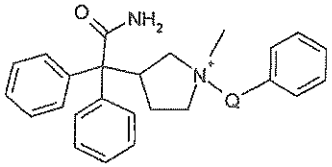


2,2-Diphenyl-2-(*S*)-pyrrolidin-3-ylacetamide (3.5 g, 12.5 mmol; prepared as described in Preparation 1) in DMA (33 mL) was combined with DIPEA (3.5 mL, 20 mmol), followed by the addition o f 1-(3-bromopropylsulfanyl)-3,5-difluorobenzene (3.5 g, 13.1 mmol; prepared as described in Preparation 5). The mixture was stirred for 14 hours at room temperature. Methyl iodide (3.1 mL, 50 mmol) was added and the mixture was stirred at 70 °C for 2 hours. The mixture was then concentrated *in vacuo*. The resulting product was a mixture of 2 diastereomers at the quaternary amine center. The

diastereomers were separated by reverse phase HPLC on a LUNA C-18 Column using a 37% (ACN/H_2O/0.1% TFA) isocratic gradient over 45 minutes, to afford 1.5 g of the title compound as a TFA salt. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2OS$, 481.21; found 481.2.

EXAMPLE 5

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 5-1 to 5-23, having the following formula were also prepared as TFA salts:



Ex.	Q
5-1	-$(CH_2)_2$-
5-2	-$(CH_2)_3$-
5-3	-$(CH_2)_6$-
5-4	-$(CH_2)_2$-C(O)O-
5-5	-$(CH_2)_2$-O-CH_2-
5-6	-$(CH_2)_2$-NHC(O)-
5-7	-$(CH_2)_4$-
5-8	-$(CH_2)_2$-OC(O)-
5-9	-$(CH_2)_4$-
5-10	-$(CH_2)_3$-O-
5-11	-$(CH_2)_3$-S-
5-12	-$(CH_2)_2$-OC(O)-
5-13	-$(CH_2)_3$-C(O)-

Ex.	Q
5-14	-$(CH_2)_5$-
5-15	-$(CH_2)_2$-NHC(O)NH-
5-16	-CH_2-C(O)NH-CH_2-
5-17	-CH_2-C(O)O-CH_2-
5-18	-$(CH_2)_3$-C(N-O-CH_3)-
5-19	-$(CH_2)_3$-C(N-O-benzyl)-
5-20	-$(CH_2)_3$-S-
5-21	-$(CH_2)_3$-S-
5-22	-$(CH_2)_2$-C≡C-
5-23	-$(CH_2)_2$-CH=CH-
5-24	-CH_2-C=N-O-
5-25	-$(CH_2)_2$-S-S-

(5-1) 3-(carbamoyldiphenylmethyl)-1-methyl-1-phenethylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{27}H_{31}N_2O$, 399.24; found 399.0.

(5-2) 3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenylpropyl)pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O$, 413.26; found 413.0.

(5-3) 3-(carbamoyldiphenylmethyl)-1-methyl-1-(6-phenylhexyl)pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{31}H_{39}N_2O$, 455.31; found 455.4.

(5-4) 3-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]-propionic acid phenyl ester. MS *m/z*: [M^+] calcd for $C_{28}H_{31}N_2O_3$, 443.23; found 443.2.

(5-5) 2-[*(S)*-1-(2-benzyloxyethyl)-1-methylpyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2$, 429.25; found 429.2.

(5-6) N-{2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]ethyl}benzamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}N_3O_2$, 442.25; found 442.2.

(5-7) 2-[*(S)*-1-methyl-1-(4-phenylbutyl)pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O$, 427.28; found 427.2.

(5-8) benzoic acid 2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]ethyl ester. MS *m/z*: [M^+] calcd for $C_{28}H_{31}N_2O_3$, 443.23; found 443.2.

(5-9) *(R)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(4-phenylbutyl)pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O$, 427.28; found 427.2.

(5-10) *(R)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenoxypropyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2$, 429.25; found 429.2.

(5-11) *(R)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenylsulfanylpropyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2OS$, 445.23; found 445.2.

(5-12) *(R)*-1-(2-benzoyloxyethyl)-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}N_2O_3$, 443.23; found 443.2.

(5-13) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(4-oxo-4-phenylbutyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{33}N_2O_2$, 441.25; found 441.2.

(5-14) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(5-phenylpentyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{30}H_{37}N_2O$, 441.29; found 441.2.

(5-15) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-[2-(3-phenylureido)ethyl] pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_4O_2$, 457.26; found 457.2.

(5-16) *(S)*-1-(benzylcarbamoylmethyl)-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}N_3O_2$, 442.25; found 442.2.

(5-17) *(S)*-1-benzyloxycarbonylmethyl-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}N_2O_3$, 443.23; found 443.2.

(5-18) 2-(*(S)*-1-{4-[(E)-methoxyimino]-4-phenylbutyl}-1-methylpyrrolidin-3-yl)-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{30}H_{36}N_3O_2$, 470.28; found 470.2.

(5-19) 2-(*(S)*-1-{4-[(E)-benzyloxyimino]-4-phenylbutyl}-1-methylpyrrolidin-3-yl)-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{36}H_{40}N_3O_2$, 546.31; found 546.4.

(5-20) 2-[(1S,3S)-1-methyl-1-(3-phenylsulfanylpropyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2OS$, 445.23; found 445.2.

(5-21) 2-[(1R,3S)-1-methyl-1-(3-phenylsulfanylpropyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2OS$, 445.23; found 445.2.

(5-22) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(4-phenyl-but-3-ynyl)pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{31}N_2O$, 423.24; found 423.2.

(5-23) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(*(E)*-4-phenyl-but-3-

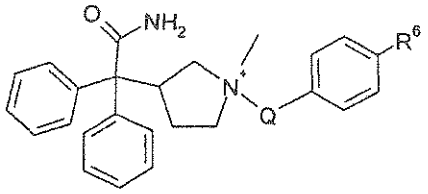
enyl)pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{33}N_2O$, 425.26; found 425.2.

(5-24) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(2-phenoxyiminoethyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{27}H_{30}N_3O_2$, 429.23; found 428.2.

(5-25) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-phenyldisulfanylpropyl) pyrrolidinium MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2OS_2$, 478.20; found 477.2.

EXAMPLE 6

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 6-1 to 6-30, having the following formula were also prepared as TFA salts:



Ex.	Q	R^6
6-1	$-(CH_2)_2-$	$-N^+(O)O$
6-2	$-(CH_2)_3-O-$	-F
6-3	$-(CH_2)_2-$	-OH
6-4	$-(CH_2)_2-OC(O)-$	$-OCF_3$
6-5	$-(CH_2)_2-NHC(O)-$	$-OCH_3$
6-6	$-(CH_2)_2-OC(O)-$	$-N(CH_3)_2$
6-7	$-(CH_2)_2-OC(O)-$	$-OCH_3$
6-8	$-(CH_2)_4-$	$-OCH_3$
6-9	$-(CH_2)_3-O-$	$-CH_3$
6-10	$-(CH_2)_3-O-$	$-C(O)OCH_3$
6-11	$-CH_2-CH(OH)-CH_2-O-$	F
6-12	$-(CH_2)_3-O-$	-OH
6-13	$-(CH_2)_3-O-$	-Cl
6-14	$-(CH_2)_3-S-$	-Br
6-15	$-(CH_2)_3-S-$	-Cl
6-16	$-(CH_2)_3-S-$	$-OCH_3$
6-17	$-(CH_2)_3-C(O)-$	-Br
6-18	$-(CH_2)_3-O-$	$-N^+(O)O$
6-19	$-(CH_2)_3-O-$	$-OCH_3$
6-20	$-(CH_2)_3-C(O)-$	-F
6-21	$-(CH_2)_3-C(O)-$	-OH
6-22	$-(CH_2)_3-C(O)-$	$-OCH_3$
6-23	$-(CH_2)_3-C(O)-$	$-CH_3$
6-24	$-(CH_2)_3-S-$	$-NHC(O)CH_3$
6-25	$-(CH_2)_3-S-$	$-S-CH_3$
6-26	$-(CH_2)_3-S-$	-F
6-27	$-(CH_2)_3-S-$	$-CH_3$

Ex.	Q	R^6
6-28	$-(CH_2)_3-O-$	$-S-CH_3$
6-29	$-(CH_2)_3-C(O)-$	-Cl
6-30	$-(CH_2)_3-S-$	-OH

(6-1) 3-(carbamoyldiphenylmethyl)-1-methyl-1-[2-(4-nitrophenyl)ethyl] pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{27}H_{30}N_3O_3$, 444.23; found 444.0.

(6-2) 3-(carbamoyldiphenylmethyl)-1-[3-(4-fluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2O_2$, 447.24; found 447.0. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.20 (3H, m), 2.73 (4H, d), 2.90 (1H, m), 3.35 (5H, s), 3.53 (1H, t), 3.68 (2H, t) 4.29 (1H, t), 4.31 (1H, t), 5.74 (1H, s), 6.15 (1H, d), 6.77 (2H, m) 6.79 (2H, m) 7.26 (11H, m).

(6-3) 3-(carbamoyldiphenylmethyl)-1-[2-(4-hydroxyphenyl)ethyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{27}H_{31}N_2O_2$, 415.24; found 415.0.

(6-4) 4-trifluoromethoxybenzoic acid 2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]ethyl ester. MS *m/z*: [M^+] calcd for $C_{29}H_{30}F_3N_2O_4$, 527.22; found 527.2.

(6-5) N-{2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]ethyl}-4-methoxybenzamide. MS *m/z*: [M^+] calcd for $C_{29}H_{34}N_3O_3$, 472.26; found 472.2.

(6-6) 4-dimethylaminobenzoic acid 2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl]ethyl ester. MS *m/z*: [M^+] calcd for $C_{30}H_{36}N_3O_3$, 486.28; found 486.2.

(6-7) 4-methoxybenzoic acid 2-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl] ethyl ester. MS *m/z*: [M^+] calcd for $C_{29}H_{33}N_2O_4$, 473.24; found 473.2.

(6-8) 2-{*(S)*-1-[4-(4-methoxyphenyl)butyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_30H_{37}N_2O_2$, 457.29; found 457.4.

(6-9) 2-[*(S)*-1-methyl-1-(3-p-tolyloxypropyl)pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2$, 443.27; found 443.2.

(6-10) 4-{3-[*(S)*-3-(carbamoyldiphenylmethyl)-1-methylpyrrolidin-1-yl] propoxy}benzoic acid methyl ester. MS *m/z*: [M^+] calcd for $C_{30}H_{35}N_2O_4$, 487.26; found 487.2.

(6-11) 2-{*(S)*-1-[*(S)*-3-(4-fluorophenoxy)-2-hydroxypropyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_32FN_2O_3$, 463.24; found 463.2.

(6-12) 2-{*(S)*-1-[3-(4-hydroxyphenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_3$, 445.25; found 445.2.

(6-13) 2-{*(S)*-1-[3-(4-chlorophenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}ClN_2O_2$, 463.22; found 463.2.

(6-14) 2-{*(S)*-1-[3-(4-bromophenylsulfanyl)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}BrN_2OS$, 523.14; found 523.2.

(6-15) 2-{*(S)*-1-[3-(4-chlorophenylsulfanyl)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}ClN_2OS$, 479.19; found 479.2.

(6-16) 2-{*(S)*-1-[3-(4-methoxyphenylsulfanyl)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2S$, 475.24; found 475.2.

(6-17) 2-{1-[4-(4-bromophenyl)-4-oxo-butyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{32}BrN_2O_2$, 519.16; found 519.2.

(6-18) 2-{1-methyl-1-[3-(4-nitrophenoxy)propyl]pyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}N_3O_4$, 474.24; found 474.2.

(6-19) 2-{1-[3-(4-methoxyphenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_3$, 459.26; found 459.2.

(6-20) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{32}FN_2O_2$, 459.24; found 459.2.

(6-21) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(4-hydroxyphenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{33}N_2O_3$, 457.25; found 457.2.

(6-22) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(4-methoxyphenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{30}H_{35}N_2O_3$, 471.26; found 471.2.

(6-23) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(4-oxo-4-p-tolylbutyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{30}H3_5N_2O_2$, 455.27; found 455.2.

(6-24) *(S)*-1-[3-(4-acetylaminophenylsulfanyl)propyl]-3-(carbamoyldiphenyl methyl)-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{30}H_{36}N_3O_2S$, 502.25; found 502.2.

(6-25) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-[3-(4-methylsulfanylphenyl sulfanyl)propyl]pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2OS_2$, 491.22; found 491.2.

(6-26) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(4-fluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2OS$, 463.22; found 463.6.

(6-27) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-p-tolylsulfanylpropyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2OS$, 459.25; found 459.2.

(6-28) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-[3-(4-methylsulfanylphenoxy)

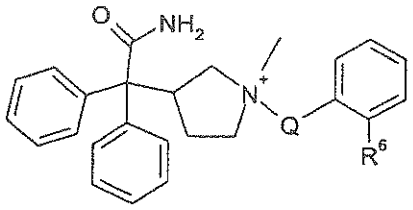
propyl]pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2S$, 475.24; found 475.2.

(6-29) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(4-chlorophenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{32}ClN_2O_2$, 475.22; found 475.2.

(6-30) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(4-hydroxyphenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2S$, 461.23; found 461.2.

EXAMPLE 7

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 7-1 to 7-8, having the following formula were also prepared as TFA salts:



Ex.	Q	R^6
7-1	$-(CH_2)_3-O-$	$-CH_3$
7-2	$-(CH_2)_3-O-$	-Br
7-3	$-(CH_2)_3-O-$	-F
7-4	$-(CH_2)_3-S-$	-F
7-5	$-(CH_2)_3-S-$	-Cl
7-6	$-(CH_2)_3-C(O)-$	-Cl
7-7	$-(CH_2)_3-O-$	-OH
7-8	$-(CH_2)_3-S-$	-OH

(7-1) 2-[*(S)*-1-methyl-1-(3-o-tolyloxypropyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2$, 443.27; found 443.2.

(7-2) 2-{*(S)*-1-[3-(2-bromophenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}BrN_2O_2$, 507.16; found 507.2.

(7-3) 2-{*(S)*-1-[3-(2-fluorophenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2O_2$, 447.24; found 447.2.

(7-4) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2-fluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2OS$, 463.22; found 463.2.

(7-5) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2-chlorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}ClN_2OS$, 479.19; found 479.2.

(7-6) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(2-chlorophenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{32}ClN_2O_2$, 475.22; found 475.2.

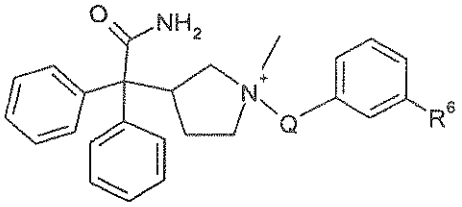
(7-7) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2-hydroxyphenoxy)propyl]-1-

methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_3$, 445.25; found 445.2.

(7-8) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2-hydroxyphenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2S$, 461.23; found 461.2.

EXAMPLE 8

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 8-1 to 8-17, having the following formula were also prepared as TFA salts:



Ex.	Q	R^6
8-1	$-(CH_2)_3-O-$	$-CH_3$
8-2	$-(CH_2)_3-O-$	-Cl
8-3	$-(CH_2)_3-O-$	-CN
8-4	$-(CH_2)_3-S-$	-Cl
8-5	$-(CH_2)_3-S-$	-F
8-6	$-(CH_2)_3-S-$	$-CF_3$
8-7	$-(CH_2)_3-S-$	$-OCF_3$
8-8	$-CH_2-C(O)NH-CH_2-$	-F
8-9	$-(CH_2)_3-O-$	$-OCH_3$
8-10	$-(CH_2)_3-O-$	-F
8-11	$-(CH_2)_3-S-$	$-CH_3$
8-12	$-(CH_2)_3-C(O)-$	$-OCH_3$
8-13	$-(CH_2)_3-O-$	-OH
8-14	$-(CH_2)_2-OC(O)-$	-F
8-15	$-(CH_2)_3-S-$	-OH
8-16	$-(CH_2)_3-O-$	-F
8-17	$-(CH_2)_2-C\equiv C-$	-F

(8-1) 2-[*(S)*-1-methyl-1-(3-m-tolyloxypropyl)pyrrolidin-3-yl]-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2$, 443.27; found 443.2.

(8-2) 2-{*(S)*-1-[3-(3-chlorophenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}ClN_2O_2$, 463.22; found 463.2.

(8-3) 2-{*(S)*-1-[3-(3-cyanophenoxy)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{29}H_{32}N_3O_2$, 454.25; found 454.2.

(8-4) 2-{*(S)*-1-[3-(3-chlorophenylsulfanyl)propyl]-1-methylpyrrolidin-3-yl}-2,2-diphenylacetamide. MS *m/z*: [M^+] calcd for $C_{28}H_{32}ClN_2OS$, 479.19; found 479.2.

(8-5) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-fluoro-phenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2OS$, 463.22; found 463.2. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.90 (2H, m), 2.05 (1H, m), 2.14 (2H, br m), 2.62 (3H, s), 2.86 (2H, t), 3.02 (2H, m), 3.22 (1H, s), 3.33 (1H, s), 3.45 (1H, t), 3.59 (1H, d), 3.70 (1H, t), 3.87 (2H, m), 4.18 (1H, m), 5.87 (1H, d), 6.35 (1H, s), 7.0 (4H, m), 7.3 (10H, m).

(8-6) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-[3-(3-trifluoromethylphenyl sulfanyl)propyl]pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{32}F_3N_2OS$, 513.22; found 513.2.

(8-7) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-[3-(3-trifluoromethoxyphenyl sulfanyl)propyl]pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{32}F_3N_2O_2S$, 529.21; found 529.2.

(8-8) *(S)*-3-(carbamoyldiphenylmethyl)-1-[(3-fluorobenzylcarbamoyl)methyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}FN_3O_2$, 460.24; found 460.2.

(8-9) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-methoxyphenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_3$, 459.26; found 459.2.

(8-10) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-fluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2O_2$, 447.24; found 447.2. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.06 (1H, s), 2.18 (2H, s), 2.67 (2H, s), 2.79 (1H, s), 3.26 (3H, s), 3.38 (1H, s), 3.53 (1H, t), 3.68 (1H, s), 3.88 (2H, t), 4.03 (2H, t), 4.16 (1H, m), 5.82 (1H, d), 6.6 (3H, m), 6.51 (1H, s), 7.18 (1H, m), 7.3 (10H, m).

(8-11) *(S)*-3-(carbamoyldiphenylmethyl)-1-methyl-1-(3-m-tolylsulfanylpropyl) pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2OS$, 459.25; found 459.2.

(8-12) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(3-methoxyphenyl)-4-oxobutyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{30}H_{35}N_2O_3$, 471.26; found 471.2.

(8-13) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-hydroxyphenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_3$, 445.25; found 445.2.

(8-14) *(S)*-3-(carbamoyldiphenylmethyl)-1-[2-(3-fluorobenzoyloxy)ethyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{30}FN_2O_3$, 461.22; found 461.2.

(8-15) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-hydroxyphenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{33}N_2O_2S$, 461.23; found 461.2.

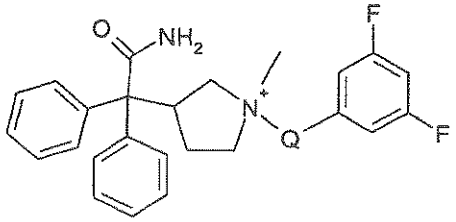
(8-16) *(R)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-fluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{32}FN_2O_2$, 448.24; found 447.2.

(8-17) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(3-fluorophenyl)but-3-ynyl]-1-

methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{30}FN_2O$, 442.23; found 441.2.

EXAMPLE 9

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 9-1 to 9-10, having the following formula were also prepared as TFA salts:



Ex.	Q
9-1	-$(CH_2)_3$-S-
9-2	-$(CH_2)_2$-NHC(O)NH-
9-3	-CH_2-C(O)O-CH_2-
9-4	-$(CH_2)_3$-O-CH_2-
9-5	-$(CH_2)_3$-S(O)-
9-6	-$(CH_2)_3$-SO_2-
9-7	-$(CH_2)_3$-S-
9-8	-$(CH_2)_3$-O-
9-9	-$(CH_2)_2$-C≡C-
9-10	-$(CH_2)_3$-O-

(9-1) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2OS$, 481.21; found 481.2. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.02 (3H, m), 2.63 (s, 3H), 2.78 (1H, s), 2.88 (1H, s), 3.05 (1H, m), 3.24 (1H, s), 3.34 (1H, s), 3.48 (1H, s), 3.61 (1H, s), 3.72 (1H, s), 3.86 (2H, m), 4.14 (1H, m), 5.80 (2H, d), 6.22 (1H, s), 6.62 (1H, q), 6.79 (2H, dd), 7.35 (10H, m).

(9-2) *(S)*-3-(carbamoyldiphenylmethyl)-1-{2-[3-(3,5-difluorophenyl)ureido]ethyl}-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_4O_2$, 493.24; found 493.2.

(9-3) *(S)*-3-(carbamoyldiphenylmethyl)-1-(3,5-difluorobenzyloxycarbonylmethyl)-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{29}F_2N_2O_3$, 479.21; found 479.2.

(9-4) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,5-difluorobenzyloxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{33}F_2N_2O_2$, 479.25; found 479.2.

(9-5) *(S)*-3-(Carbamoyldiphenylmethyl)-1-[3-(3,5-difluorobenzenesulfinyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2S$, 497.21; found 497.2.

(9-6) *(S)*-3-(Carbamoyldiphenylmethyl)-1-[3-(3,5-difluorobenzenesulfonyl)propyl]-1-methyl-pyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_3S$, 513.20; found 513.2.

(9-7) *(1S,3S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenylsulfanyl) propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2OS$, 482.21; found 482.2.

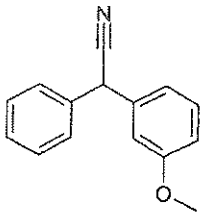
(9-8) *(1S,3S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 466.24; found 465.2.

(9-9) *(S)*-3-(carbamoyldiphenylmethyl)-1-[4-(3,5-difluorophenyl)but-3-ynyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{29}F_2N_2O$, 460.22; found 459.2.

(9-10) *(R)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,5-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 466.24; found 465.2.

Preparation 6

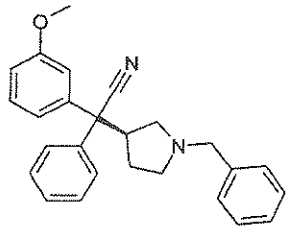
(3-Methoxyphenyl)phenylacetonitrile



A solution of 1-(chlorophenylmethyl)-3-methoxybenzene (5.5 g, 24 mmol) in DCM (100 mL) was cooled to 0 °C. Trimethylsilyl cyanide (3.5 mL, 26 mmol) was added to the stirred solution. 1.0 M of tin tetrachloride in heptane (0.75 mL, .75 mmol) was then added. The solution was stirred for 2 hours, then quenched with MeOH (50 mL). The solvent was removed under reduced pressure. The crude material was then purified via silica gel chromatography to obtain the title compound (2.2 g, 10 mmol).

Preparation 7

((S)-1-Benzylpyrrolidin-3-yl)(3-methoxyphenyl)phenylacetonitrile

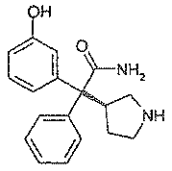


To a stirred solution of (3-methoxyphenyl)phenylacetonitrile (5.2 g, 23 mmol; prepared as described in Preparation 6) in THF (100 mL) was added toluene-4-sulfonic acid *(S)*-1-benzylpyrrolidin-3-yl ester (7.2 g, 22 mmol), followed by the addition of potassium *t*-butoxide (4.0 g, 36 mmol). The mixture was heated to 80 °C for 1 hour, then allowed to cool and H_2O (10 mL) was added. The mixture was filtered through a pad of

Celite®. The mixture was washed with a saturated aqueous NaCl solution (100 mL) and the organic phase was separated, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure. The crude material was purified via silica gel chromatography to afford the title compound (6.2 g, 17 mmol). MS *m/z*: {M + H^+] calcd for $C_{26}H_{26}N_2O$, 382.5; found 383.4.

Preparation 8

2-(3-Hydroxyphenyl)-2-phenyl-2-*(S)*-pyrrolidin-3-yl-acetamide

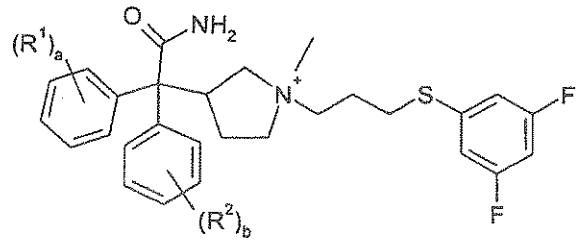


To a stirred solution of *(S)*-1-benzylpyrrolidin-3-yl)-(3-methoxyphenyl) phenylacetonitrile (6.2 g, 16 mmol; prepared as described in Preparation 7) in *t*-butyl alcohol (150 mL) was added KOH (35 g, 620 mmol). The reaction flask was equipped with a reflux condenser and nitrogen inlet and stirred at 110 °C for 14 days. The mixture was allowed to cool to room temperature. Water (120 mL) and ether (100 mL) were added to the mixture. The organic phase was then separated, and the aqueous phase was extracted 2 times with ether (100 mL each). The organic layers were combined, dried over $MgSO_4$, then filtered. The solvent was removed under reduced pressure and the crude material was then taken in DCM (250 mL) and cooled to 0 °C. To this stirred solution was added 1.0 M of boron tribromide in DCM (30 mL, 30 mmol) and the mixture was stirred at 0 °C for 90 minutes. The mixture was then added to a stirred solution of 30% ammonia & ice. The mixture was then filtered through a pad of Celite®, then washed with a saturated aqueous NaCl solution (200 mL). The organic phase was dried over $MgSO_4$, then filtered. The solvent was removed under reduced pressure. The crude material was then subjected to normal hydrogenation conditions to obtain the title compound. MS *m/z*: {M + H^+] calcd for $C_{18}H_{20}N_2O_2$, 296.36; found 297.6.

This material was used to prepare the compound of Example 10-3.

EXAMPLE 10

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 10-1 to 10-3, having the following formula were also prepared as TFA salts:



Ex.	a	R^1	b	R^2
10-1	1	4-hydroxy	1	4-hydroxy
10-2	1	4-hydroxy	0	-
10-3	1	3-hydroxy	0	-

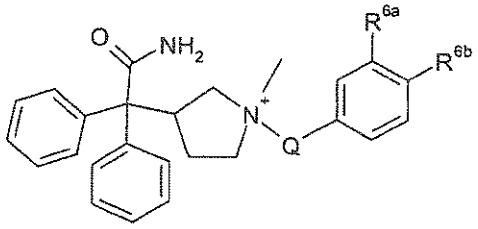
(10-1) *(S)*-3-[carbamoyl-bis-(4-hydroxyphenyl)methyl]-1-[3-(3,5-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_3S$, 514.20; found 513.2.

(10-2) *(S)*-3-[(S)-carbamoyl-(4-hydroxyphenyl)phenylmethyl]-1-[3-(3,5-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2S$, 498.21; found 497.2.

(10-3) *(S)*-3-[carbamoyl-(3-hydroxyphenyl)phenylmethyl]-1-[3-(3,5-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2S$, 498.21; found 497.2.

EXAMPLE 11

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 11-1 to 11-3, having the following formula were also prepared as TFA salts:



Ex.	Q	R^{6a}	R^{6b}
11-1	$-(CH_2)_3-S-$	-F	$-OCH_3$
11-2	$-(CH_2)_3-O-$	-F	-F
11-3	$-(CH_2)_3-S-$	-F	-F

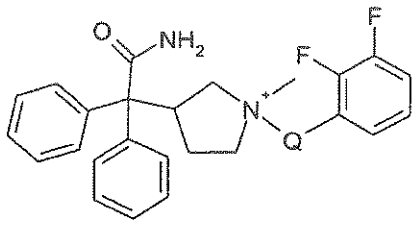
(11-1) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3-fluoro-4-methoxyphenylsulfanyl) propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{29}H_{34}FN_2O_2S$, 493.23; found 493.2.

(11-2) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,4-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 465.24; found 465.2.

(11-3) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(3,4-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2OS$, 481.21; found 481.2.

EXAMPLE 12

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 12-1 to 12-2, having the following formula were also prepared as TFA salts:



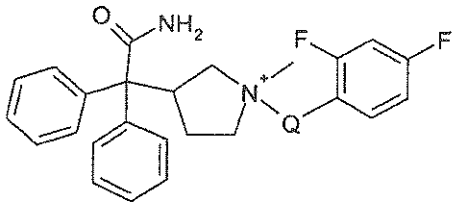
Ex.	Q
12-1	$-(CH_2)_3-O-$
12-2	$-(CH_2)_2-OC(O)-$

(12-1) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2,3-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 465.24; found 465.2.

(12-2) *(S)*-3-(carbamoyldiphenylmethyl)-1-[2-(2,3-difluorobenzoyloxy)ethyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{29}F_2N_2O_3$, 479.21; found 479.2.

EXAMPLE 13

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 13-1 to 13-2, having the following formula were also prepared as TFA salts:



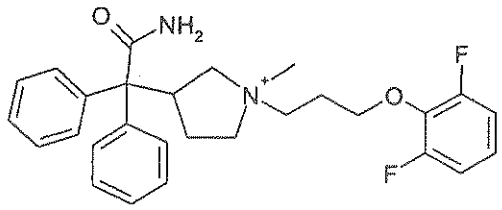
Ex.	Q
13-1	$-(CH_2)_3-O-$
13-2	$-(CH_2)_3-S-$

(13-1) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2,4-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 465.24; found 465.2.

(13-2) *(S)*-3-(carbamoyldiphenylmethyl)-1-[3-(2,4-difluorophenylsulfanyl)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2OS$, 481.21; found 481.2.

EXAMPLE 14

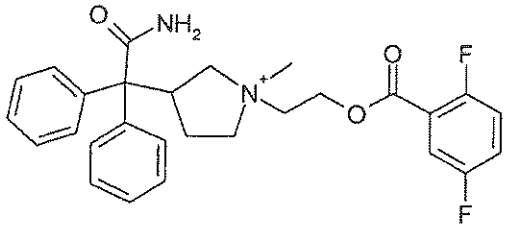
Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compound 14, having the following formula was also prepared as a TFA salt:



(S)-3-(carbamoyldiphenylmethyl)-1-[3-(2,6-difluorophenoxy)propyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{31}F_2N_2O_2$, 465.24; found 465.2.

EXAMPLE 15

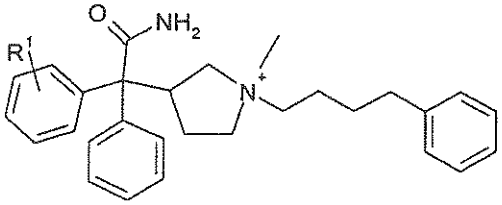
Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compound 15, having the following formula was also prepared as a TFA salt:



(S)-3-(carbamoyldiphenylmethyl)-1-[2-(2,5-difluorobenzoyloxy)ethyl]-1-methylpyrrolidinium. MS *m/z*: [M^+] calcd for $C_{28}H_{29}F_2N_2O_3$, 479.21; found 479.2.

EXAMPLE 16

Following the procedures described in the previous examples, and substituting the appropriate starting materials and reagents, compounds 16-1 to 16-3, having the following formula were also prepared as TFA salts:



(16-1) *(S)*-3-(carbamoylphenyl-*m*-tolylmethyl)-1-methyl-1-(4-phenylbutyl) pyrrolidinium (R^1=3-methyl). MS *m/z*: [M^+] calcd for $C_{30}H_{37}N_2O$, 441.29; found 441.2.

(16-2) *(S)*-3-(carbamoylphenyl-*p*-tolylmethyl)-1-methyl-1-(4-phenylbutyl) pyrrolidinium (R^1=4-methyl). MS *m/z*: [M^+] calcd for $C_{30}H_{37}N_2O$, 441.29; found 441.2.

(16-3) *(S)*-3-[carbamoyl(4-hydroxyphenyl)phenylmethyl]-1-methyl-1-(4-phenylbutyl)pyrrolidinium (R^1=4-hydroxy). MS *m/z*: [M^+] calcd for $C_{29}H_{35}N_2O_2$, 443.27; found 443.2.

Assay 1

Radioligand Binding Assay

Membrane Preparation from Cells Expressing

hM_1, hM_2, hM_3 and hM_4 Muscarinic Receptor Subtypes

CHO cell lines stably expressing cloned human hM_1, hM_2, hM_3 and hM_4 muscarinic receptor subtypes, respectively, were grown to near confluency in medium consisting of HAM's F-12 supplemented with 10% FBS and 250 μg/mL Geneticin. The cells were grown in a 5% CO_2, 37°C incubator and lifted with 2 mM EDTA in dPBS. Cells were collected by 5 minute centrifugation at 650 x g, and cell pellets were either stored frozen at -80 °C or membranes were prepared immediately. For membrane preparation, cell pellets were resuspended in lysis buffer and homogenized with a Polytron PT-2100 tissue disrupter (Kinematica AG; 20 seconds x 2 bursts). Crude membranes were centrifuged at 40,000 x g for 15 minutes at 4°C. The membrane pellet was then resuspended with resuspension buffer and homogenized again with the Polytron tissue disrupter. The protein concentration of the membrane suspension was determined by the method described in Lowry, O. et al., *Journal of Biochemistry* 193:265 (1951). All membranes were stored frozen in aliquots at -80°C or used immediately. Aliquots of prepared hM_5 receptor membranes were purchased directly from Perkin Elmer and stored at -80°C until use.

Radioligand Binding Assay on Muscarinic Receptor

Subtypes hM_1, hM_2, hM_3, hM_4 and hM_5

Radioligand binding assays were performed in 96-well microtiter plates in a total assay volume of 1000 μL. CHO cell membranes stably expressing either the hM_1, hM_2, hM_3, hM_4 or hM_5 muscarinic subtype were diluted in assay buffer to the following specific target protein concentrations (μg/well): 10 μg for hM_1, 10-15 μg for hM_2, 10-20 μg for hM_3, 10-20 μg for hM_4, and 10-12 μg for hM_5. The membranes were briefly homogenized using a Polytron tissue disruptor (10 seconds) prior to assay plate addition. Saturation binding studies for determining K_D values of the radioligand were performed using L-[*N*-methyl-^{3}H]scopolamine methyl chloride ([^{3}H]-NMS) (TRK666, 84.0 Ci/mmol, Amersham

Pharmacia Biotech, Buckinghamshire, England) at concentrations ranging from 0.001 nM to 20 nM. Displacement assays for determination of K_i values of test compounds were performed with [^{3}H]-NMS at 1 nM and eleven different test compound concentrations. The test compounds were initially dissolved to a concentration of 40 μM in dilution buffer and then serially diluted 5x with dilution buffer to final concentrations ranging from 400 fM to 4 μM. The addition order and volumes to the assay plates were as follows: 825 μL assay buffer with 0.1% BSA, 25 μL radioligand, 100 μL diluted test compound, and 50 μL membranes. Assay plates were incubated for 6 hours at 37°C. Binding reactions were terminated by rapid filtration over GF/B glass fiber filter plates (Perkin Elmer Inc., Wellesley, MA) pre-treated in 0.3% polyethyleneimine (PEI). Filter plates were rinsed three times with wash buffer (10 mM HEPES) to remove unbound radioactivity. Plates were then air dried, and 50 μL Microscint-20 liquid scintillation fluid (PerkinElmer Inc., Wellesley, MA) was added to each well. The plates were then counted in a PerkinElmer Topcount liquid scintillation counter (PerkinElmer Inc., Wellesley, MA). Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the one-site competition model. K_i values for test compounds were calculated from observed IC_{50} values and the K_D value of the radioligand using the Cheng-Prusoff equation (Cheng Y; Prusoff W.H. *Biochemical Pharmacology* 22(23):3099-108 (1973)). K_i values were converted to pK_i values to determine the geometric mean and 95% confidence intervals. These summary statistics were then converted back to K_i values for data reporting.

In this assay, a lower K_i value indicates that the test compound has a higher binding affinity for the receptor tested. Exemplary compounds of the invention that were tested in this assay, were found to have a K_i value of less than about 120 nM for the M_3 muscarinic receptor subtype in this assay. More typically, these compounds were found to have K_i values of less than about 50 nM, with some compounds having K_i values of less than about 10 nM or less than about 1.0 nM.

Assay 2

Muscarinic Receptor Functional Potency Assays

Blockade of Agonist-Mediated Inhibition of cAMP Accumulation

In this assay, the functional potency of a test compound is determined by measuring the ability of the test compound to block oxotremorine-inhibition of forskolin-mediated cAMP accumulation in CHO-K1 cells expressing the hM_2 receptor.

cAMP assays are performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with ^{125}I-cAMP (NEN SMP004B, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturer's instructions.

Cells are rinsed once with dPBS and lifted with Trypsin-EDTA solution (0.05% trypsin/0.53 mM EDTA) as described in Assay 1. The detached cells are washed twice by centrifugation at 650 x g for five minutes in 50mLs dPBS. The cell pellet is then re-suspended in 10 mL dPBS, and the cells are counted with a Coulter Z1 Dual Particle Counter (Beckman Coulter, Fullerton, CA). The cells are centrifuged again at 650 x g for five minutes and re-suspended in stimulation buffer to an assay concentration of 1.6 x 10^6 - 2.8 x 10^6 cells/mL.

The test compound is initially dissolved to a concentration of 400 μM in dilution buffer (dPBS supplemented with 1 mg/mL BSA (0.1%)), and then serially diluted with dilution buffer to final molar concentrations ranging from 100 μM to 0.1 nM. Oxotremorine is diluted in a similar manner.

To measure oxotremorine inhibition of AC activity, 25 μL forskolin (25 μM final concentration diluted in dPBS), 25 μL diluted oxotremorine, and 50 μL cells are added to agonist assay wells. To measure the ability of a test compound to block oxotremorine-inhibited AC activity, 25 μL forskolin and oxotremorine (25 μM and 5 μM final concentrations, respectively, diluted in dPBS) 25 μL diluted test compound, and 50 μL cells are added to remaining assay wells.

Reactions are incubated for 10 minutes at 37°C and stopped by addition of 100 μL ice-cold detection buffer. Plates are sealed, incubated overnight at room temperature and counted the next morning on a PerkinElmer TopCount liquid scintillation counter (PerkinElmer Inc., Wellesley, MA). The amount of cAMP produced (pmol/well) is calculated based on the counts observed for the samples and cAMP standards, as described in the manufacturer's user manual. Data are analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the non-linear regression, one-site competition equation. The Cheng-Prusoff equation is used to calculate the K_i, using the EC_{50} of the oxotremorine concentration-response curve and the oxotremorine assay concentration as the K_D and [L], respectively. The K_i values are converted to pK_i values to determine the geometric mean and 95% confidence intervals. These summary statistics are then converted back to K_i values for data reporting.

In this assay, a lower K_i value indicates that the test compound has a higher

functional activity at the receptor tested. The exemplified compounds of the invention are expected to have a K_i value of less than about 100 nM for blockade of oxotremorine-inhibition of forskolin-mediated cAMP accumulation in CHO-K1 cells expressing the hM_2 receptor.

Blockade of Agonist-Mediated [^{35}S]GTPγS Binding

In a second functional assay, the functional potency of test compounds can be determined by measuring the ability of the compounds to block oxotremorine-stimulated [^{35}S]GTPγS binding in CHO-K1 cells expressing the hM_2 receptor.

At the time of use, frozen membranes are thawed and then diluted in assay buffer with a final target tissue concentration of 5-10 μg protein per well. The membranes are briefly homogenized using a Polytron PT-2100 tissue disrupter and then added to the assay plates.

The EC_{90} value (effective concentration for 90% maximal response) for stimulation of [^{35}S]GTPγS binding by the agonist oxotremorine is determined in each experiment.

To determine the ability of a test compound to inhibit oxotremorine-stimulated [^{35}S]GTPγS binding, the following is added to each well of 96 well plates: 25 μL of assay buffer with [^{35}S]GTPγS (0.4nM), 25 μL of oxotremorine (EC_{90}) and GDP (3 μM), 25 μL of diluted test compound and 25 μL CHO cell membranes expressing the hM_2 receptor. The assay plates are then incubated at 37°C for 60 minutes. The assay plates are filtered over 1% BSA-pretreated GF/B filters using a PerkinElmer 96-well harvester. The plates are rinsed with ice-cold wash buffer for 3 x 3 seconds and then air or vacuum dried. Microscint-20 scintillation liquid (50 μL) is added to each well, and each plate is sealed and radioactivity counted on a topcounter (PerkinElmer). Data are analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the non-linear regression, one-site competition equation. The Cheng-Prusoff equation is used to calculate the K_i, using the IC_{50} values of the concentration-response curve for the test compound and the oxotremorine concentration in the assay as the K_D and [L], ligand concentration, respectively.

In this assay, a lower K_i value indicates that the test compound has a higher functional activity at the receptor tested. The exemplified compounds of the invention are expected to have a K_i value of less than about 100 nM for blockade of oxotremorine-stimulated [^{35}S]GTPγS binding in CHO-K1 cells expressing the hM_2 receptor.

Blockade of Agonist-Mediated Calcium Release via FLIPR Assays

Muscarinic receptor subtypes (M_1, M_3 and M_5 receptors), which couple to G_q proteins, activate the phospholipase C (PLC) pathway upon agonist binding to the receptor. As a result, activated PLC hydrolyzes phosphatyl inositol diphosphate (PIP_2) to diacylglycerol (DAG) and phosphatidyl-1,4,5-triphosphate (IP_3), which in turn generates calcium release from intracellular stores, i.e., endoplasmic and sarcoplasmic reticulum. The FLIPR (Molecular Devices, Sunnyvale, CA) assay capitalizes on this increase in intracellular calcium by using a calcium sensitive dye (Fluo-4AM, Molecular Probes, Eugene, OR) that fluoresces when free calcium binds. This fluorescence event is measured in real time by the FLIPR, which detects the change in fluorescence from a monolayer of cells cloned with human M_1 and M_3, and chimpanzee M_5 receptors. Antagonist potency can be determined by the ability of antagonists to inhibit agonist-mediated increases in intracellular calcium.

For FLIPR calcium stimulation assays, CHO cells stably expressing the hM_1, hM_3 and cM_5 receptors are seeded into 96-well FLIPR plates the night before the assay is done. Seeded cells are washed twice by Cellwash (MTX Labsystems, Inc.) with FLIPR buffer (10 mM HEPES, pH 7.4, 2 mM calcium chloride, 2.5 mM probenecid in HBSS without calcium and magnesium) to remove growth media and leaving 50 µL/well of FLIPR buffer. The cells are then incubated with 50 µL/well of 4 µM FLUO-4AM (a 2X solution was made) for 40 minutes at 37°C, 5% carbon dioxide. Following the dye incubation period, cells are washed two times with FLIPR buffer, leaving a final volume of 50 µL/well.

To determine antagonist potency, the dose-dependent stimulation of intracellular Ca^{2+} release for oxotremorine is first determined so that antagonist potency can later be measured against oxotremorine stimulation at an EC_{90} concentration. Cells are first incubated with compound dilution buffer for 20 minutes, followed by agonist addition, which is performed by the FLIPR. An EC_{90} value for oxotremorine is generated according to the method detailed in the FLIPR measurement and data reduction section below, in conjunction with the formula $EC_F = ((F/100\text{-}F)\text{^}1/H) * EC_{50}$. An oxotremorine concentration of 3 x EC_F is prepared in stimulation plates such that an EC_{90} concentration of oxotremorine is added to each well in the antagonist inhibition assay plates.

The parameters used for the FLIPR are: exposure length of 0.4 seconds, laser strength of 0.5 watts, excitation wavelength of 488 nm, and emission wavelength of

550 nm. Baseline is determined by measuring the change in fluorescence for 10 seconds prior to addition of agonist. Following agonist stimulation, the FLIPR continuously measures the change of fluorescence every 0.5 to 1 second for 1.5 minutes to capture the maximum fluorescence change.

The change of fluorescence is expressed as maximum fluorescence minus baseline fluorescence for each well. The raw data is analyzed against the logarithm of drug concentration by nonlinear regression with GraphPad Prism (GraphPad Software, Inc., San Diego, CA) using the built-in model for sigmoidal dose-response. Antagonist K_i values are determined by Prism using the oxotremorine EC_{50} value as the K_D and the oxotremorine EC_{90} for the ligand concentration according to the Cheng-Prusoff equation (Cheng & Prusoff, 1973).

In this assay, a lower K_i value indicates that the test compound has a higher functional activity at the receptor tested. The exemplified compounds of the invention are expected to have a K_i value of less than about 100 nM for blockade of agonist-mediated calcium release in CHO cells stably expressing the hM_3 receptor.

Assay 3

Rat Einthoven Assay

This *in vivo* assay is used to assess the bronchoprotective effects of test compounds exhibiting muscarinic receptor antagonist activity.

All test compounds are diluted in sterile water and are dosed via the inhalation route (IH). The rats (Sprague-Dawley, male, 250-350 g) are exposed to the aerosol generated from an LC Star Nebulizer Set and driven by a mixture of gases (5% CO_2/95% atmospheric air). Each test compound solution is nebulized over a 10 minute time period in a pie shaped dosing chamber capable of holding six rats. At predetermined time points after inhalation of compound, the Einthoven assay is performed.

Thirty minutes prior to the start of pulmonary evaluation, the animals are anesthetized with inactin (thiobutabarbital, 120 mg/kg IP). The jugular vein is catheterized with saline filled polyethylene catheters (PE-50) and used to infuse MCh. The trachea is then dissected and cannulated with a 14G needle and used for rat ventilation during pulmonary evaluation. Once surgery is complete, rats are ventilated using a piston respirator set at a stroke volume of 1 ml/100 g body weight but not exceeding 2.5 ml volume, and at a rate of 90 strokes per minute.

The changes in pressure that occur with each breath are measured. Baseline values

are collected for at least 2.5 minutes then rats are challenged non-cumulatively with 2-fold incremental increases of the bronchoconstrictor MCh (5, 10, 20, 40 and 80 μg/ml). The MCh is infused for 2.5 minutes from a syringe pump at a rate of 2 mL/kg/min. The animals are euthanized upon completion of the studies.

Changes in ventilation pressure (cm H_20) in treated animals are expressed as % inhibition of MCh response relative to control animals. In this assay, a higher % inhibition value indicates that the test compound has a bronchoprotective effect. Exemplary compounds of the invention that are tested in this assay at a dose of 100 μg/ml are expected to exhibit greater than 35% inhibition, some are expected to exhibit greater than 70% inhibition, and some are expected to exhibit greater than 90% inhibition.

1.5 hr ID_{50} Determination

Standard muscarinic antagonists were evaluated in the rat Einthoven assay 1.5 hrs post -dose. The order of potency (ID_{50}s) for the five standards tested was determined to be: ipratropium (4.4 μg/ml)> tiotropium (6 μg/ml)> des-methyl-tiotropium (12 μg/ml) > glycopyrrolate (15 μg/ml) > LAS-34237 (24 μg/ml). The potency of the test compound is similarly determined at 1.5 hrs post-dose.

6 and 24 hr ID_{50} Determination

Standards tiotropium and ipratropium were also evaluated 24 hr and/or 6 hr post-dose in the rat Einthoven assay. Ipratropium (10 and 30 μg/ml) was about 3-fold less potent 6-hr post-dose compared to its 1.5 hr potency. The observed loss of activity at this time point (6 hr) is consistent with its relatively short duration of action in the clinic. Tiotropium showed a slow onset of effect with peak bronchoprotection being achieved 6-hr post-dose. Its 6 hr and 24 hr potency values were not significantly different from each other and were about 2-fold more potent compared to its 1.5 hr potency. The onset of action of the test compound, as well as the 6 and 24 hr potency values, is similarly determined.

Assay 4

Rat Antisialagogue Assay

Rats (Sprague-Dawley, male, 250-350 g) are dosed, anesthetized and cannulated as described for Assay 3. At predetermined time points and after surgery, animals are placed on their dorsal side at a 20° incline with their head in a downward slope. A pre-weighed gauze pad is inserted in the animal's mouth and the muscarinic agonist pilocarpine (PILO) (3 mg/kg, iv.) is administered. Saliva produced during 10 minutes

post-PILO is measured gravimetrically by determining the weight of the gauze pad before and after PILO. Antisialagogue effects are expressed as % inhibition of salivation relative to control animals.

1, 6 and 24 hr ID_{50} Determination

The rat antisialagogue assay was developed to assess systemic exposure and calculate the lung selectivity index (LSI) of test compounds. The standard, tiotropium, was evaluated in this model at 1, 6, and 24 hr post-dose. Tiotropium was found to be most potent at inhibiting pilocarpine-induced salivation 6 hrs post dose. This finding is consistent with the peak effects observed in the Einthoven assay.

This model is a modified version of the procedure described in Rechter, "Estimation of anticholinergic drug effects in mice by antagonism against pilocarpine-induced salivation" *Ata Pharmacol Toxicol* 24:243-254 (1996). The mean weight of saliva in vehicle-treated animals, at each pre-treatment time, is calculated and used to compute % inhibition of salivation, at the corresponding pre-treatment time, at each dose.

Exemplary compounds of the invention that are tested in this assay are expected to exhibit ID_{50} values less than 100 μg/ml (measured at 24 hours), with some compounds expected to exhibit an ID_{50} value less than 30 μg/ml, some less than 20 μg/ml, and some less than 15 μg/ml.

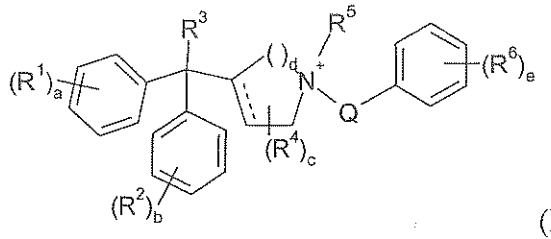
The ratio of the anti-sialagogue ID_{50} to bronchoprotective ID_{50} is used to compute the apparent lung selectivity index of the test compound. Generally, compounds having an apparent lung selectivity index greater than about 5 are preferred.

While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statues and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each document had been individually incorporated by reference herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

in salt or zwitterionic form, wherein:

a and b are independently 0 or an integer of from 1 to 5;

each R^1 and R^2 is independently selected from -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C_{3-6}cycloalkyl, cyano, halo, -OR^a, -CH_2OH, -COOH, -C(O)-O-C_{1-4}alkyl, -$C(O)NR^bR^c$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, and -NR^bR^c; where each R^a is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl and -C_{3-6}cycloalkyl; each R^b and R^c is independently selected from hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl or -C_{3-6}cycloalkyl; or R^b and R^c together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle; or two adjacent R^1 groups or two adjacent R^2 groups are joined together to form -C_{3-6}alkylene, -C_{2-4}alkylene-O- or -O-C_{1-4}alkylene-O-;

R^3 is selected from -$C(O)NR^{3a}R^{3b}$, -C(O)O-C_{1-4}alkyl, -CN, -CH_2OH, and -CH_2NH_2; where R^{3a} and R^{3b} are independently selected from hydrogen, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, -C_{3-6}heterocycle, and -$(CH_2)_{1-2}$-R^{3c}, where R^{3c} is selected from -OH, -O-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -C_{6-10}aryl, -C_{2-9}heteroaryl, and -C_{3-6}heterocycle; or R^{3a} and R^{3b} together with the nitrogen atom to which they are attached form a C_{3-6}heterocycle optionally containing one additional heteroatom selected from nitrogen, oxygen or sulfur;

c is 0 or an integer of from 1 to 3;

each R^4 is independently fluoro or -C_{1-4}alkyl;

d is 1 or 2, and ⋯ depicts an optional double bond;

R^5 is selected from -C_{1-6}alkyl, -CH_2-C_{2-6}alkenyl, -CH_2-C_{2-6}alkynyl, and -CH_2COR^{5a}; where R^{5a} is selected from -OH, -O-C_{1-6}alkyl, and -$NR^{5b}R^{5c}$; and R^{5b} and R^{5c} are independently selected from H and -C_{1-6}alkyl;

Q is -C_{0-5}alkylene-Q'-C_{0-1}alkylene-, wherein Q' is selected from -CH_2-, -CH=CH-, -C≡C-, -O-, -S-, -S(O)-, -SO_2-, -SO_2-NR^{Q1}-, -NR^{Q1}-SO_2-, -C(O)-, -OC(O)-, -C(O)O-,

$-NR^{Q1}C(O)-$, $-C(O)NR^{Q1}-$, $NR^{Q2}-C(O)-NR^{Q3}-$, $-NR^{Q2}-C(S)-NR^{Q3}-$, -C=N-O-, -S-S-, and-$C(=N-O-R^{Q4})-$, where R^{Q1} is hydrogen or $-C_{1-4}$alkyl, R^{Q2} and R^{Q3} are independently selected from hydrogen, $-C_{1-4}$alkyl, and $-C_{3-6}$cycloalkyl, or R^{Q2} and R^{Q3} are taken together to form $-C_{2-4}$alkylene or $-C_{2-3}$alkenylene, and R^{Q4} is $-C_{1-4}$alkyl or benzyl;

e is 0 or an integer of from 1 to 5;

each R^6 is independently selected from halo, $-C_{1-4}$alkyl, $-C_{0-4}$alkylene-OH, cyano, $-C_{0-2}$alkylene-COOH, $-C(O)O-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, $-S-C_{1-4}$alkyl, $-NH-C(O)-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, and $-N^+(O)O$;

wherein each alkyl, alkenyl, alkylene, alkynyl and cycloalkyl group in R^{1-3}, R^{3a-3c}, R^{4-6}, and R^a-R^c is optionally substituted with 1 to 5 fluoro atoms; wherein each alkyl, alkenyl, and alkynyl group in R^5 is optionally substituted with 1 to 2 substituents independently selected from $-O-C_{1-6}$alkyl, -OH and phenyl; each cycloalkyl, aryl, heteroaryl and heterocycle group in R^{1-2}, R^{3a-3c}, and R^{a-c} is optionally substituted with 1 to 3 substituents independently selected from $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl, cyano, halo, $-O-C_{1-4}$alkyl, $-S-C_{1-4}$alkyl, $-S(O)(C_{1-4}alkyl)$, $-S(O)_2(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-4}alkyl)$ and $-N(C_{1-4}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl group is optionally substituted with 1 to 5 fluoro substituents; and each $-CH_2-$ group in Q is optionally substituted with 1 or 2 substituents independently selected from $-C_{1-2}$alkyl, -OH and fluoro;

or a pharmaceutically acceptable salt thereof, wherein when said compound is in salt form, said compound comprises an anion of a pharmaceutically acceptable acid.

2. The compound of Claim 1, wherein a is 0 or 1.

3. The compound of Claim 1, wherein b is 0.

4. The compound of Claim 1, wherein R^3 is $-C(O)NR^{3a}R^{3b}$.

5. The compound of Claim 4, wherein R^{3a} and R^{3b} are independently selected from hydrogen and $-C_{1-4}$alkyl.

6. The compound of Claim 5, wherein R^{3a} and R^{3b} are hydrogen.

7. The compound of Claim 1, wherein c is 0.

8. The compound of Claim 7, wherein a and b are 0.

9. The compound of Claim 7, wherein a is 1 and b is 0.

10. The compound of Claim 1, wherein d is 1 and the double bond is absent.

11. The compound of Claim 1, wherein d is 2 and the double bond is present.

12. The compound of Claim 1, wherein R^5 is $-C_{1-6}$alkyl.

13. The compound of Claim 12, wherein R^5 is $-CH_3$.

14. The compound of Claim 1, wherein $-C_{0-5}$alkylene-Q'-C_{0-1}alkylene- is

-C_{1-3}alkylene-Q'-C_{0-1}alkylene-.

15. The compound of Claim 14, wherein -C_{0-5}alkylene-Q'-C_{0-1}alkylene- is -C_3alkylene-Q'-C_{0-1}alkylene-.

16. The compound of Claim 1, wherein Q' is selected from -CH_2-, -O-, -S-, -S(O)-, -C(O)-, -OC(O)-, -C(O)O-, -NR^{Q1}C(O)-, -NR^{Q2}-C(O)-NR^{Q3}-, -NR^{Q2}-C(S)-NR^{Q3}-, and -C(=N-O-R^{Q4})-.

17. The compound of Claim 16, wherein Q' is -NR^{Q1}C(O)- and R^{Q1} is hydrogen.

18. The compound of Claim 16, wherein Q' is selected from -NR^{Q2}-C(O)-NR^{Q3}- and -NR^{Q2}-C(S)-NR^{Q3}-, and R^{Q2} and R^{Q3} are hydrogen.

19. The compound of Claim 16, wherein Q' is -C(=N-O-R^{Q4})- and R^{Q4} is -CH_3 or benzyl.

20. The compound of Claim 16, wherein Q' is selected from -O-, -S-, -C(O)-, and -OC(O)-.

21. The compound of Claim 1, wherein -C_{0-5}alkylene-Q'-C_{0-1}alkylene- is selected from -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_2$-CH=CH-, -$(CH_2)_2$-C≡C-, -$(CH_2)_2$-O-CH_2-, -$(CH_2)_3$-O-, -CH_2-CH(OH)-CH_2-O-, -$(CH_2)_3$-O-CH_2-, -$(CH_2)_3$-S-, -$(CH_2)_3$-S(O)-, -$(CH_2)_3$-SO_2-, -$(CH_2)_3$-C(O)-, -$(CH_2)_2$-OC(O)-, -$(CH_2)_2$-C(O)O-, -CH_2-C(O)O-CH_2-, -$(CH_2)_2$-NR^{Q1}C(O)-, -CH_2-C(O)NR^{Q1}-CH_2, -$(CH_2)_2$-NR^{Q2}-C(O)-NR^{Q3}-, -CH_2-C=N-O-, -$(CH_2)_2$-S-S-, and -$(CH_2)_3$-C(=N-O-R^{Q4})-, where R^{Q1}, R^{Q2} and R^{Q3} are hydrogen, and R^{Q4} is -C_{1-4}alkyl or benzyl.

22. The compound of Claim 1, wherein -C_{0-5}alkylene-Q'-C_{0-1}alkylene- is -C_{0-5}alkylene-Q'-.

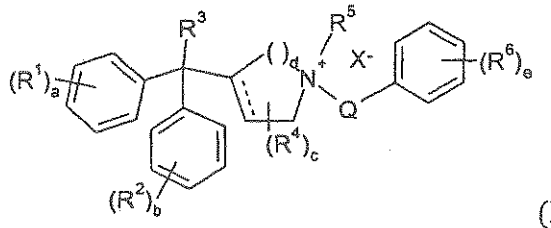
23. The compound of Claim 1, wherein e is 0.

24. The compound of Claim 1, wherein e is 1.

25. The compound of Claim 24, wherein R^6 is selected from halo, -C_{1-4}alkyl, -OH, cyano, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, and -N^+(O)O.

26. The compound of Claim 1, wherein e is 2, one R^6 is halo and the second R^6 is selected from halo and -O-C_{1-4}alkyl.

27. The compound of Claim 1, having the formula I':



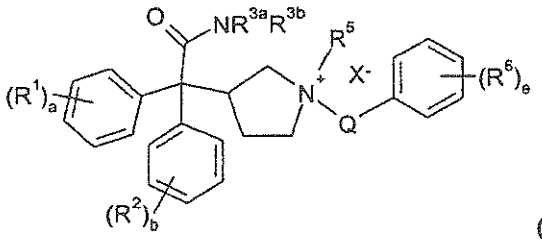
(I')

where X is an anion of a pharmaceutically acceptable acid.

28. The compound of Claim 27, wherein X is selected from acetate, benzenesulfonate, benzoate, bromide, butyrate, chloride, p-chlorobenzoate, citrate, diphenylacetate, formate, fluoride, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, iodide, lactate, malate, maleate, methanesulfonate, nitrate, phosphate, propionate, succinate, sulfate, tartrate, trifluoroacetate, and triphenylacetate.

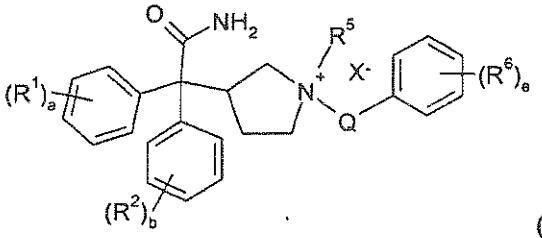
29. The compound of Claim 28, wherein X is selected from bromide, iodide and trifluoroacetate.

30. The compound of Claim 27, having the formula I'a:



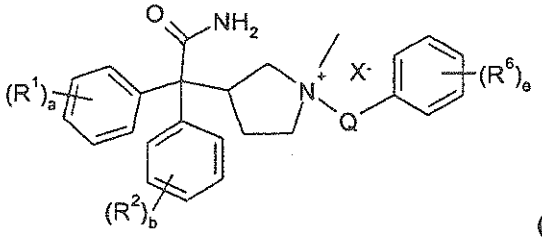
(I'a).

31. The compound of Claim 30, having the formula I'b:



(I'b).

32. The compound of Claim 31, having the formula I'd:



(I'd)

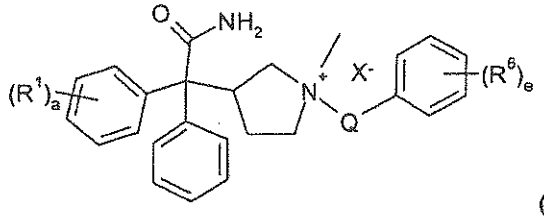
wherein a and b are independently 0 or 1; each R^1 and R^2 is $-OR^a$, where R^a is hydrogen;

Q is selected from: $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$,

-$(CH_2)_2$-CH=CH-, -$(CH_2)_2$-C≡C-, -$(CH_2)_2$-O-CH_2-, -$(CH_2)_3$-O-, -CH_2-CH(OH)-CH_2-O-, -$(CH_2)_3$-O-CH_2-, -$(CH_2)_3$-S-, -$(CH_2)_3$-S(O)-, -$(CH_2)_3$-SO_2-, -$(CH_2)_3$-C(O)-, -$(CH_2)_2$-OC(O)-, -$(CH_2)_2$-C(O)O-, -CH_2-C(O)O-CH_2-, -$(CH_2)_2$-NR^{Q1}C(O)-, -CH_2-C(O)NR^{Q1}-CH_2, -$(CH_2)_2$-NR^{Q2}-C(O)-NR^{Q3}-, -CH_2-C=N-O-, -$(CH_2)_2$-S-S-, and -$(CH_2)_3$-C(=N-O-R^{Q4})-, where R^{Q1}, R^{Q2} and R^{Q3} are hydrogen, and R^{Q4} is -C_{1-4}alkyl or benzyl; e is 0, 1 or 2; each R^6 is independently selected from halo, -C_{1-4}alkyl, -C_{0-4}alkylene-OH, cyano, -C(O)O-C_{1-4}alkyl, -O-C_{1-4}alkyl, -S-C_{1-4}alkyl, -NH-C(O)-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, and -N^+(O)O.

33. The compound of Claim 32 wherein the alkyl in R^6 is optionally substituted with 3 fluoro atoms; and one -CH_2- group in Q is optionally substituted with -OH.

34. The compound of Claim 32, having the formula I'e:

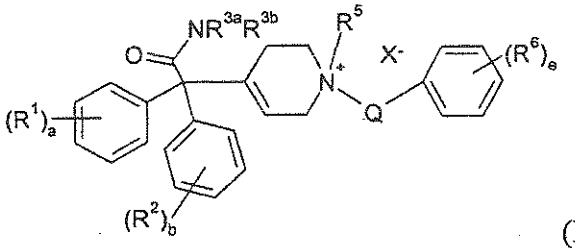


(I'e)

wherein a is 0 or 1; R^1 is -OR^a, where R^a is hydrogen; Q is selected from: -$(CH_2)_4$-, -$(CH_2)_2$-CH=CH-, -$(CH_2)_2$-C≡C-, -$(CH_2)_3$-O-, -$(CH_2)_3$-S-, -$(CH_2)_3$-C(O)-, and -$(CH_2)_2$-OC(O)-; e is 0, 1 or 2; each R^6 is independently selected from halo, -C_{1-4}alkyl, -OH, and -S-C_{1-4}alkyl.

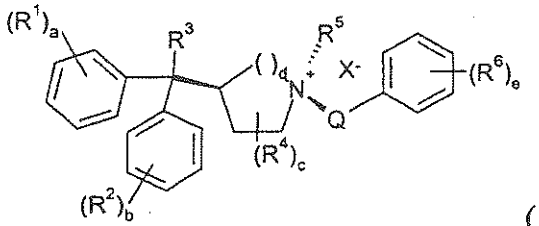
35. The compound of Claim 34, which is not optionally substituted.

36. The compound of Claim 27, having the formula I'c:



(I'c).

37. The compound of Claim 1, having the formula I"a:



(I"a)

where X^- is an anion of a pharmaceutically acceptable acid.

38. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

39. The composition of Claim 38, wherein the compound is in micronized form.

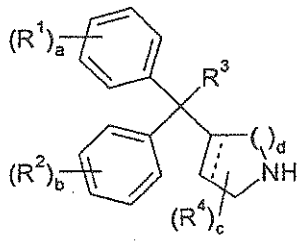
40. The composition of Claim 38, further comprising a second therapeutic agent.

41. The composition of Claim 40, wherein the second therapeutic agent is selected from β_2 adrenergic receptor agonists, steroidal anti-inflammatory agents, phosphodiesterase-4 inhibitors, and combinations thereof.

42. The composition of Claim 38, further comprising a β_2 adrenergic receptor agonist and a steroidal anti-inflammatory agent.

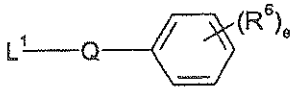
43. A process for preparing the compound of Claim 1, comprising:

(a) reacting a compound of formula II:



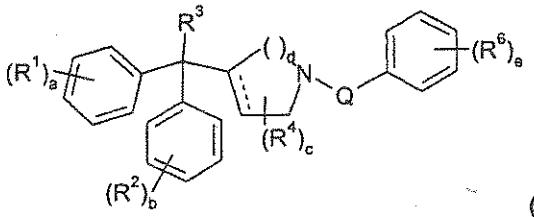
(II)

with a compound of formula III:



(III)

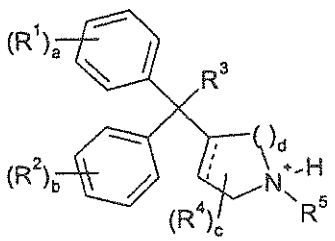
where L^1 represents a leaving group, to produce a compound of formula IV:



(IV)

and reacting the compound of formula IV with an organic substrate containing an R^5 group; or

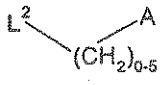
(b) reacting a compound of formula V:



(V)

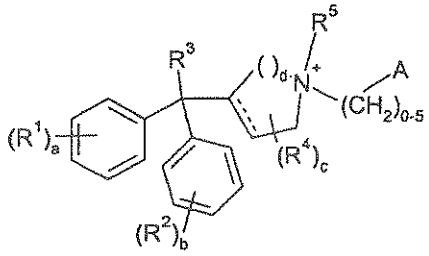
with a compound of formula III; or

(c) reacting a compound of formula V with a compound of formula VI:



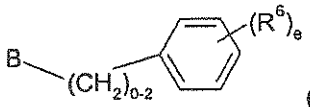
(VI)

where L^2 represents a leaving group, to produce a compound of formula VII:



(VII)

and reacting the compound of formula VII with a compound of formula VIII:



(VIII)

wherein L^3 represents a leaving group, and Q', A and B are defined as:

Q'	A	B
$-CH_2-$	$-CH_3$	L^3-alkylene-
-CH=CH-	H	L^3-alkenylene-
-C≡C-	H	L^3-alkynylene -
-O-	$-L^3$	HO-
-S-	$-L^3$	HS-
$-SO_2-NR^{Q1}-$	$-SO_2$-OH or $-SO_2Cl$	$R^{Q1}HN-$
$-NR^{Q1}-SO_2-$	$-NHR^{Q1}$	HOO_2S-
-OC(O)-	-OH	HO(O)C-
-C(O)O-	-C(O)OH or -C(O)Cl	HO-
$-NR^{Q1}C(O)-$	$-NHR^{Q1}$	HO(O)C- or Cl(O)C-
$-NR^{Q2}-C(O)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=C=O	H_2N-
$-NR^{Q2}-C(S)-NR^{Q3}-$ where R^{Q2} and R^{Q3} are H	-N=S=O	H_2N-
-C=N-O-	-CHO	H_2NO-
-S-S-	-SH	HS-

and recovering the product in salt or zwitterionic form.

44. A compound prepared by the process of Claim 43.

45. Use of the compound of Claim 1 for the manufacture of a medicament.

46. The use of Claim 45, wherein the medicament is useful for treating a pulmonary disorder.

47. The use of Claim 46, wherein the pulmonary disorder is chronic obstructive pulmonary disease or asthma.

48. The use of Claim 45, wherein the medicament is useful for producing bronchodilation.

49. The use of Claim 45, wherein the medicament is useful for antagonizing a muscarinic receptor in a mammal.