biphenyl compounds having both muscarinic receptor antagonist and β_2 adrenergic receptor agonist activities.

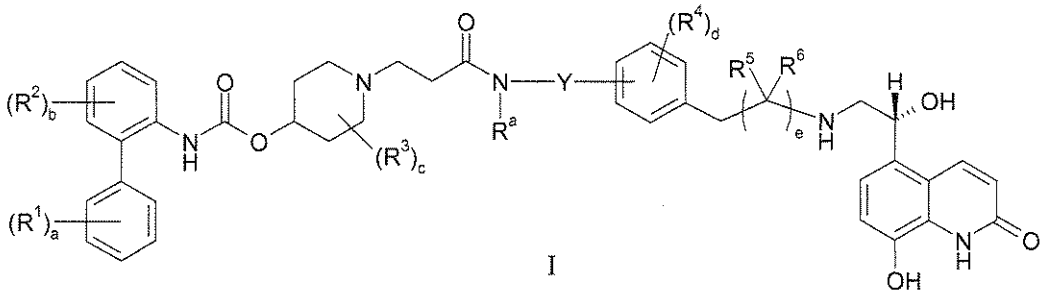
Dual-acting MABA compounds are expected to be particularly useful for treating pulmonary disorders because such compounds can be formulated and administered as a single therapeutic agent but, once administered, they provide bronchodilation through two distinct, and possibly synergistic, modes of action. Additionally, MABA compounds have the potential to be combined with an anti-inflammatory agent, such as an inhaled corticosteroid (ICS), to provide triple therapy in a single inhaler using only two therapeutic agents (MABA + ICS).

Thus, a need exists for new MABA compounds. In particular, a need exists for new MABA compounds that are highly effective as both a muscarinic receptor antagonist and a β_2 adrenergic receptor agonist. Additionally, MABA compounds having a long duration of action, i.e., compounds that provide significant bronchodilation for at least about 24 hours after administration by inhalation, may be particularly useful for treating certain pulmonary disorders where once-daily administration of a bronchodilating agent is desired.

SUMMARY ~~OF THE INVENTION~~

This disclosure~~invention~~ relates to novel diamide compounds having both muscarinic receptor antagonist and β_2 adrenergic receptor agonist activities. Such compounds produce bronchodilation when administered to a mammal by inhalation. In some cases, compounds of this disclosure~~invention~~ have been found to possess a long duration of action, i.e., to produce bronchodilation for at least about 24 hours after administration. Accordingly, compounds of this disclosure~~invention~~ are expected to be useful and advantageous as bronchodilating agents for treating pulmonary disorders.

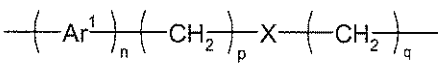
In one embodiment~~aspect~~, this disclosure~~invention~~ relates to a compound of formula I:



I

wherein

Y is a group of formula (a):



(a)

and Y is attached at the 3- or 4-position of the phenylene ring relative to the $-CH_2-(CR^5R^6)_e-$ group;

X is selected from –C(O)NH- and –NHC(O)-;

Ar^1 is selected from phen-1,3-ylene and phen-1,4-ylene, wherein the phenylene group is unsubstituted or substituted with 1 to 3 substituents selected independently from C_{1-3} alkyl, -O-(C_{1-3} alkyl) and halo;

each R^1 is selected independently from C_{1-3} alkyl, -O-(C_{1-3} alkyl), hydroxyl and halo;

each R^2 is selected independently from C_{1-3} alkyl, -O-(C_{1-3} alkyl) and halo;

each R^3 is selected independently from C_{1-3} alkyl; or two R^3 groups are joined to form C_{1-3} alkylene, C_{2-3} alkenylene or oxiran-2,3-diyl;

each R^4 is selected independently from C_{1-3} alkyl, -O-(C_{1-3} alkyl) and halo;

R^5 is selected from hydrogen, methyl and ethyl;

R^6 is selected from hydrogen, methyl and ethyl;

R^a is selected from C_{1-6} alkyl;

a is 0, 1, 2 or 3;

b is 0, 1, 2 or 3;

c is 0, 1, 2, 3 or 4;

d is 0, 1, 2 or 3;

e is 0 or 1;

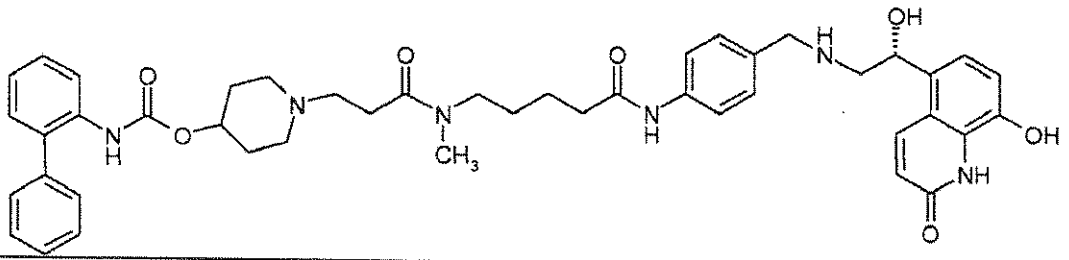
n is 0 or 1;

p is 0, 1, 2, 3, 4, 5 or 6; provided that when *n* is 0, *p* is 1, 2, 3, 4, 5 or 6;

q is 0, 1, 2, 3, 4, 5 or 6;

or a pharmaceutically acceptable salt thereof.

In a first aspect, there is provided the compound of formula



or a pharmaceutically acceptable salt thereof.

As used hereinafter, the phrase "compound of formula I" means a compound of formula I or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula I in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

In a second~~another~~ aspect, this disclosure~~invention~~ relates to a pharmaceutical composition comprising (a) a compound as defined in the first aspect~~of formula I~~; and (b) a pharmaceutically acceptable carrier. ~~This~~

An embodimentaspect of the invention includes, for example, pharmaceutical compositions suitable for administration by inhalation.

In yet another embodimentaspect, this disclosureinvention relates to a composition comprising (a) a compound of formula I, and (b) a steroidal anti-inflammatory agent (e.g., a corticosteroid). The term "steroidal anti-inflammatory agent" as used herein includes pharmaceutically acceptable salts and/or solvates of such agents unless otherwise indicated. This disclosureinvention also relates to a pharmaceutical composition comprising (a) a compound of formula I; (b) a steroidal anti-inflammatory agent; and (c) a pharmaceutically acceptable carrier. These embodimentsaspects of the invention include, for example, compositions suitable for administration by inhalation. In a particular embodiment, the steroidal anti-inflammatory agent is a corticosteroid (e.g., a glucocorticoid), such as fluticasone propionate or a solvate thereof; or fluticasone furoate or a solvate thereof.

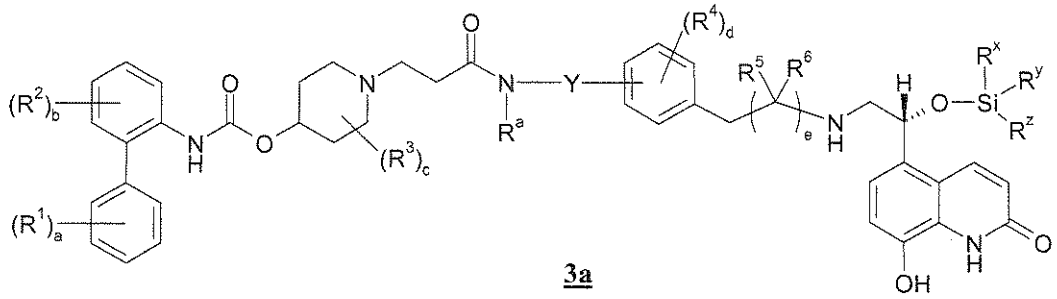
In still another embodimentaspect, this disclosureinvention relates to a method for treating a pulmonary disorder in a patient comprising administering a compound of formula I to the patient. This embodimentaspect of the invention includes, for example, treating chronic obstructive pulmonary disease or asthma. Also included are methods in which a steroidal anti-inflammatory agent is administered simultaneously or sequentially with compound of formula I to treat a pulmonary disorder.

In another embodimentaspect, this disclosureinvention relates to a method for producing bronchodilation in a mammal comprising administering a bronchodilation-producing amount of a compound of formula I to the mammal. This embodimentaspect includes, for example, producing bronchodilation in a human.

In yet another embodimentaspect, this disclosureinvention relates to a method for antagonizing a muscarinic receptor and agonizing a β_2 adrenergic receptor in a biological system or sample comprising a muscarinic receptor and a β_2 adrenergic receptor, the method comprising treating the biological system or sample with a compound of formula I. This embodimentaspect includes both *in vivo* and *in vitro* methods.

In a third aspect, there is provided a compound as defined above, for use in therapy.

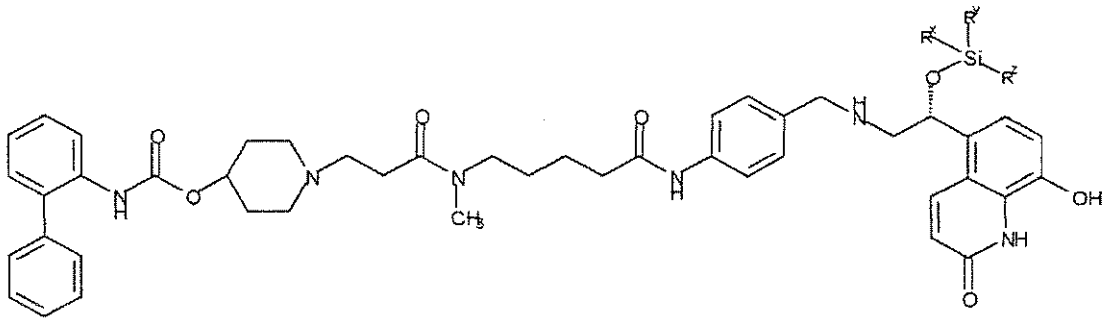
This disclosureinvention also relates to processes and novel intermediates useful for preparing compounds of formula I. In one such embodiment, this disclosureinvention relates to a compound of formula **3a**:



3a

or a salt thereof, wherein R^x and R^y are independently selected from C_{1-4} alkyl, phenyl, and -C_{1-4} alkyl-(phenyl); and R^z is selected from C_{1-4} alkyl, phenyl, -C_{1-4} alkyl-(phenyl) and –O-(C_{1-4} alkyl).

In a fourth aspect, there is provided an intermediate compound for preparing a compound as defined above, the intermediate compound having the formula:



wherein

R^x and R^y are independently selected from C_{1-4} alkyl, phenyl, and -C_{1-4} alkyl-(phenyl);

R^z is selected from C_{1-4} alkyl, phenyl, -C_{1-4} alkyl-(phenyl) and -O-(C_{1-4} alkyl);

or a salt thereof.

In a fifth~~yet another of its method~~ aspect~~s~~, this disclosure~~invention~~ relates to a process of preparing a compound as defined in the first aspect~~of formula I~~, the process comprising deprotecting a compound as defined in the fourth aspect~~of formula 3a to provide a compound of formula I~~.

Other ~~aspects and~~ embodiments of this disclosure~~invention~~ are described herein.

DETAILED DESCRIPTION OF THE INVENTION

In one of its composition aspects, this invention relates to compounds of formula I. Such compounds contain one or more chiral centers and therefore, such compounds (and intermediates thereof) can exist as racemic mixtures; pure stereoisomers (i.e., enantiomers or diastereomers); stereoisomer-enriched mixtures and the like. Chiral compounds shown or named herein without a defined stereochemistry at a chiral center are intended to include any or all possible stereoisomer variations at the undefined stereocenter unless otherwise indicated. The depiction or naming of a particular stereoisomer means the indicated stereocenter has the designated stereochemistry with the understanding that minor amounts of other stereoisomers may also be present unless otherwise indicated, provided that the utility of the depicted or named compound is not eliminated by the presence of another stereoisomer.

Compounds of formula I also contain several basic groups (e.g., amino groups) and therefore, such compounds can exist as the free base or in various salt forms, such a mono-protonated salt form or a di-protonated salt form or mixtures thereof. All such forms are included within the scope of this invention, unless otherwise indicated.

This invention also includes isotopically-labeled compounds of formula I, i.e., compounds of formula I where an atom has been replaced or enriched with an atom having the same atomic number but an atomic mass different from the atomic mass that