Muscarinic receptor antagonists (also known as antimuscarinics or anticholinergics) such as Detrol® LA (tolterodine), Ditropan XL® (oxybutynin), and Vesicare® (solifenacin succinate) currently represent the major pharmacological options approved and marketed for the treatment of OAB. Antimuscarinics are believed to reduce bladder overactivity by inhibiting bladder smooth muscle contractility. Physicians and patients remain unsatisfied with the current therapies and desire medicines with improved efficacy and tolerability. In particular there is an unacceptably high incidence of dry mouth and constipation associated with these medications. Also, current medications do not adequately treat urgency, one of the most bothersome symptoms of OAB.

Accordingly, there remains a need for new medicines and methods of treatment which offer improved efficacy and tolerability in the treatment of symptoms associated with overactive bladder, above and beyond the currently available therapies.

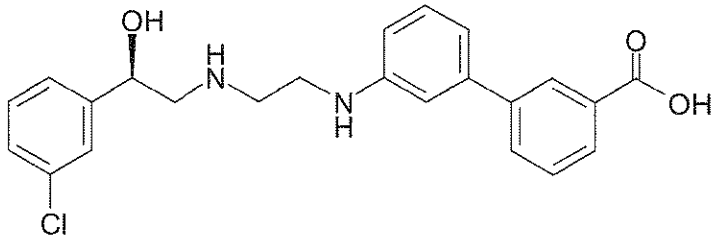
SUMMARY ~~OF THE INVENTION~~

A method of treating one or more symptoms associated with overactive bladder using a new synergistic treatment combination has now been discovered. The disclosed treatment combination ~~according to the invention~~ comprises a beta-3 adrenergic receptor agonist and a muscarinic receptor antagonist. The inventors have shown that this combination has unexpectedly increased efficacy for the treatment of one or more symptoms associated with OAB.

In one aspect, there is provided a combination comprising: (i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist selected from the group consisting of solabegron and pharmaceutically acceptable salts thereof; and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist selected from the group consisting of tolterodine, oxybutynin, trospium, solifenacin, darifenacin, propiverine, fesoterodine, and pharmaceutically acceptable salts thereof; said combination being useful for relieving one or more symptoms associated with overactive bladder (OAB) in a synergistic manner, versus the individual components (i) and (ii), wherein said one or more symptoms of overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

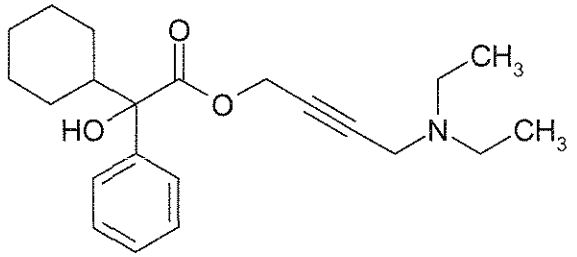
In another aspect, there is provided a pharmaceutical composition comprising the combination disclosed herein, further comprising one or more pharmaceutically acceptable carriers, diluents or excipients.

In yet another aspect, there is provided a combination comprising: (i) a therapeutically effective amount of a compound of Formula (I),



Formula (I)

or a pharmaceutically acceptable salt thereof; and(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a compound of Formula (II),



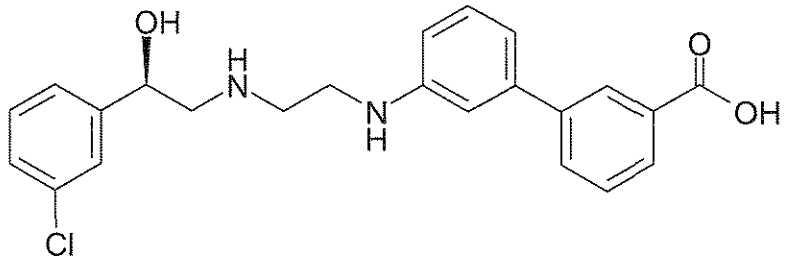
Formula (II)

or a pharmaceutically acceptable thereof; said combination being useful for relieving one or more symptoms associated with overactive bladder in a synergistic manner, versus the individual components (i) and (ii), wherein said one or more symptoms of overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

Accordingly, the ~~invention~~ disclosure encompasses treatment combinations comprising (i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist, and (ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a muscarinic receptor antagonist. The ~~invention~~ disclosure also encompasses methods of treating one or more symptoms associated with overactive bladder in a mammal using (i) and (ii), either in a single dosage form or separately. Use of the combinations in medical therapy and use of the combinations in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder, are also provided.

In a one ~~aspect~~ embodiment of the present ~~invention~~disclosure, there is provided a method of treating one or more symptoms associated overactive bladder in a mammal, comprising administering to said mammal:

(i) a therapeutically effective amount of a compound of Formula (I),

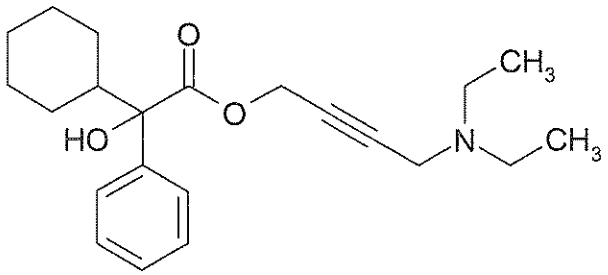


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

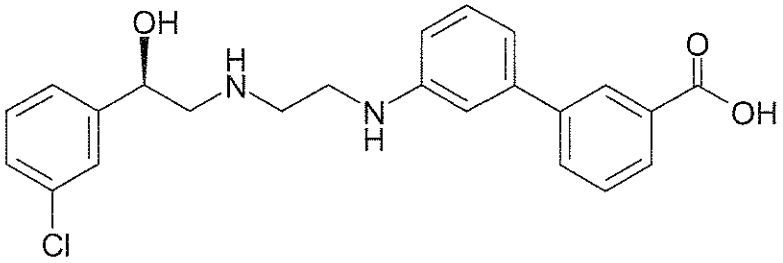


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In another ~~aspect of the present invention~~embodiment, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

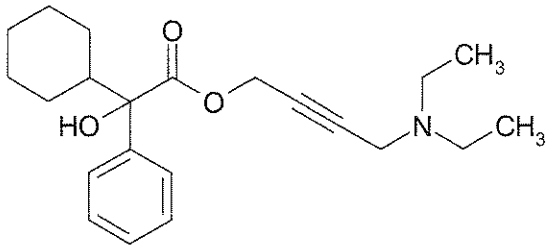


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

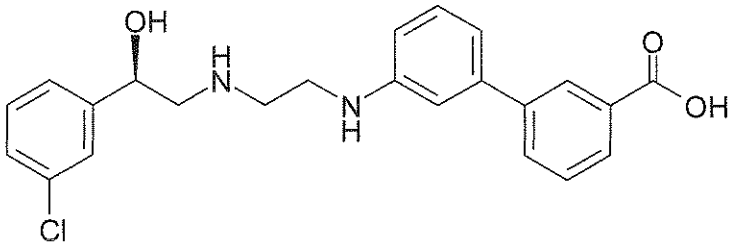


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

In an additional ~~aspect of the present invention~~embodiment, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

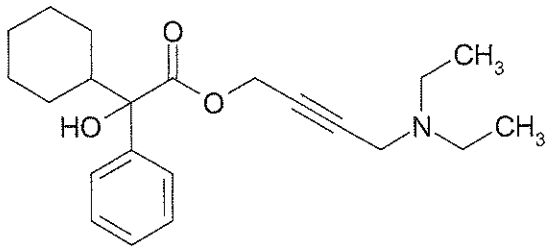


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

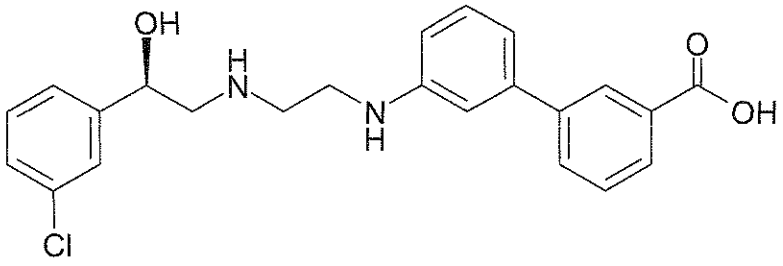


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, for use in medical therapy.

In an additional ~~aspect of the present invention~~embodiment, there is provided a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

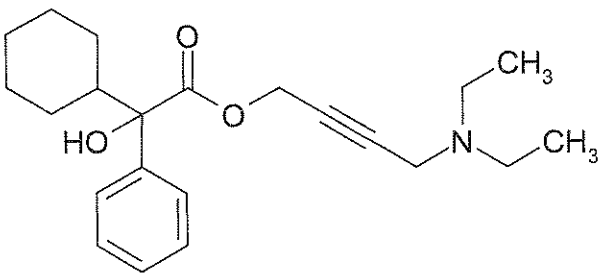


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),

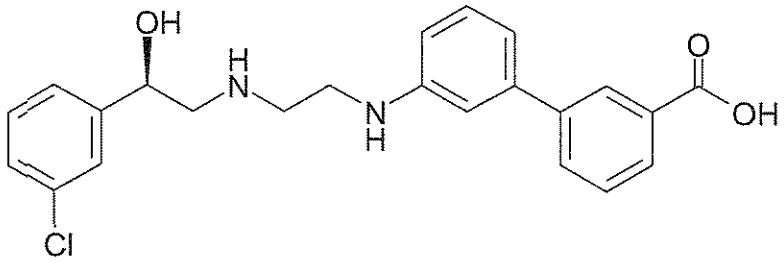


Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, for use in the treatment of one or more symptoms associated with overactive bladder.

In another ~~aspect of the present invention~~embodiment, there is provided the use of a combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

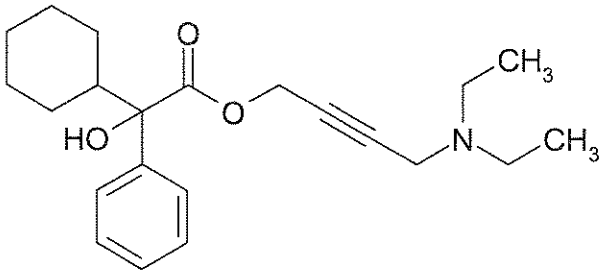


Formula (I)

or pharmaceutically acceptable salts (for example, the hydrochloride salt), solvates, or solvated pharmaceutically acceptable salts thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount, of a compound of Formula (II),



Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof, in the preparation of a medicament useful in the treatment of one or more symptoms associated with overactive bladder.

DETAILED DESCRIPTION OF THE INVENTION

Unexpectedly, new synergistic drug combinations have been discovered which are useful in treating one or more symptoms associated with OAB. These combinations

What is claimed is:

1. A combination comprising:

(i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist; and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist,

said combination being useful for relieving one or more symptoms associated with overactive bladder (OAB) in a synergistic manner, versus the individual components (i) and (ii).

2. The combination of claim 1, wherein said one or more symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

3. The combination of claims 1 or 2, wherein said beta-3 adrenergic receptor agonist comprises solabegron, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

4. The combination of any of claims 1-3, wherein said muscarinic receptor antagonist comprises oxybutynin, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or a pharmaceutically acceptable salt solvated with pharmaceutically acceptable solvent thereof.

5. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising administering to said mammal:

(i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist; and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist.

6. The method of claim 5, wherein said one or more symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

7. The method of claim 5 or 6, wherein components (i) and (ii) are co-administered.

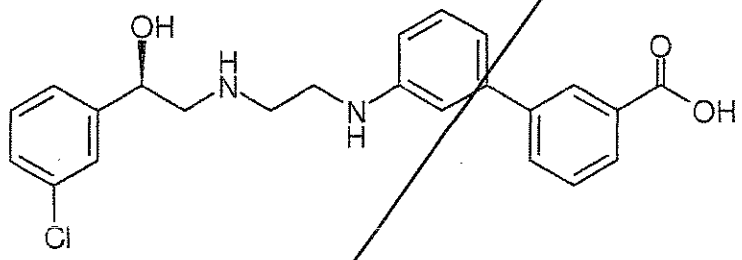
8. The method of any of claims 5-7, wherein components (i) and (ii) are contained in a single dosage form.

9. The method of claim 5 or 6, wherein components (i) and (ii) are administered separately.

10. The method of any of claims 5, 6 or 9, wherein there is a time delay between the administration of components (i) and (ii).

11. A combination comprising:

(i) a therapeutically effective amount of a compound of Formula (I),

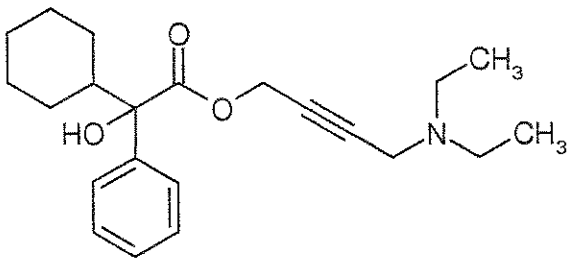


Formula (I)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a compound of Formula (II),



Formula (II)

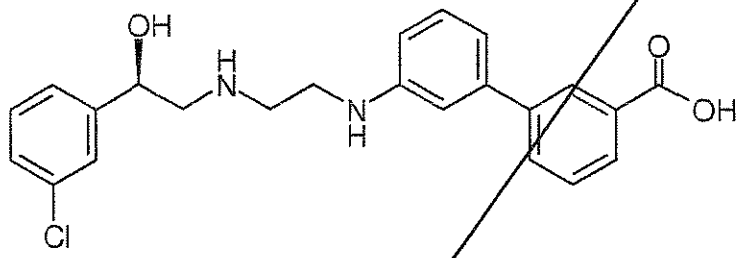
or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

12. The combination according to claim 11, wherein the salt of the compound of Formula (I) comprises the hydrochloride salt.

13. A pharmaceutical composition comprising the combination of claim 11 or 12, further comprising one or more pharmaceutically acceptable carriers, diluents, or excipients.

14. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising administering to said mammal:

(i) a therapeutically effective amount of a compound of Formula (I),

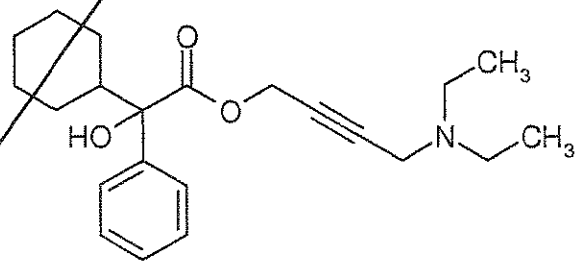


Formula (I)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a compound of Formula (II),



Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof.

15. The method of claim 14, wherein said one or more symptoms associated with overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

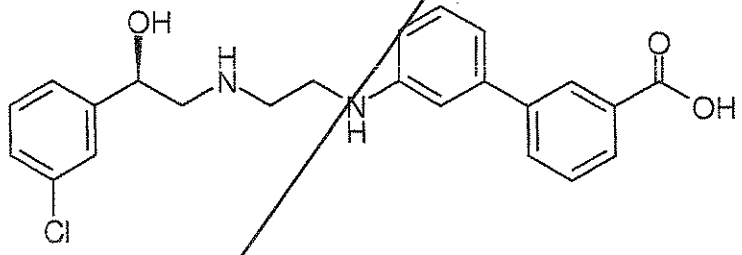
16. The method of claim 14 or 15, wherein components (i) and (ii) are co-administered.

17. The method of any of claims 14-16, wherein components (i) and (ii) are contained in a single dosage form.

18. The method of claim 14 or 15, wherein components (i) and (ii) are administered separately.

19. The method of any of claims 14, 15 or 18, wherein there is a time delay between the administration of components (i) and (ii).

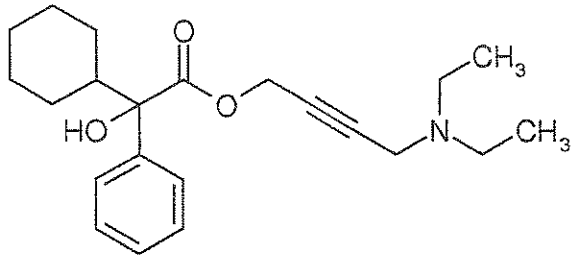
20. Use of a compound of Formula (I),



Formula (I)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

in combination with a compound of Formula (II),



Formula (II)

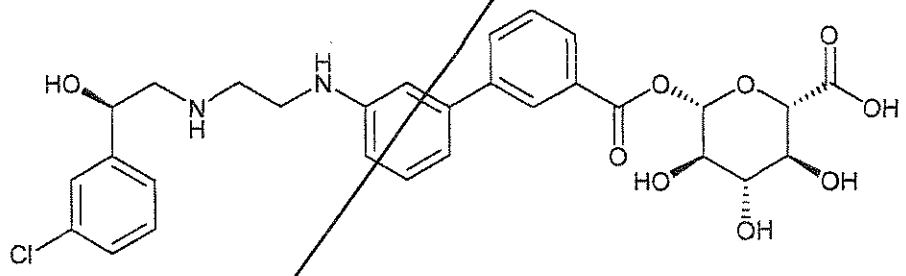
or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

in the preparation of a medicament for the treatment of one or more symptoms associated with overactive bladder.

21. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising the step of administering to a mammal in need thereof, a therapeutically effective amount of the combination of claim 11.

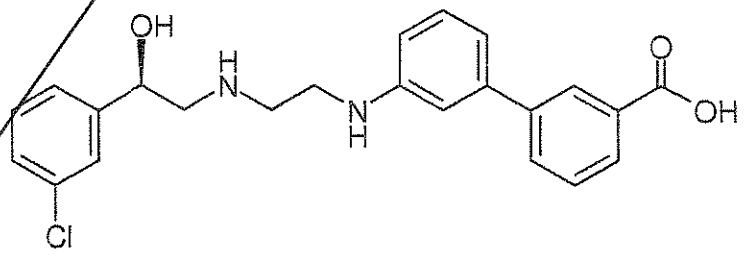
22. A method of treating one or more symptoms associated with overactive bladder in a mammal, comprising the step of administering to a mammal in need thereof, a therapeutically effective amount of the pharmaceutical composition of claim 13.

23. The method of any of claims 14-19, wherein component (i) further comprises the compound of Formula (III)



Formula (III).

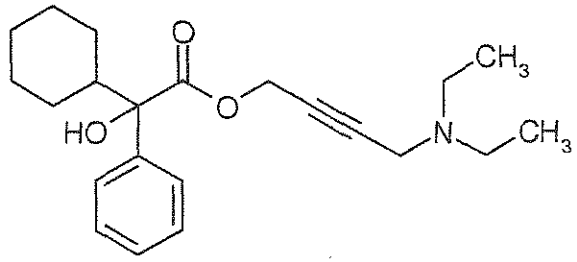
24. A compound of Formula (I),



Formula (I)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

in combination with a compound of Formula (II),



Formula (II)

or pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or pharmaceutically acceptable salts solvated with pharmaceutically acceptable solvents thereof;

for use in the treatment of one or more symptoms associated with overactive bladder.

What is claimed is:

1. A combination comprising:

(i) a therapeutically effective amount of a beta-3 adrenergic receptor agonist selected from the group consisting of solabegron and pharmaceutically acceptable salts thereof; and

(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a muscarinic receptor antagonist selected from the group consisting of tolterodine, oxybutynin, trospium, solifenacin, darifenacin, propiverine, fesoterodine, and pharmaceutically acceptable salts thereof;

said combination being useful for relieving one or more symptoms associated with overactive bladder (OAB) in a synergistic manner, versus the individual components (i) and (ii), wherein said one or more symptoms of overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

2. The combination of claim 1, wherein said muscarinic receptor antagonist is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of tolterodine, oxybutynin, and solifenacin.

3. The combination of claim 2, comprising a therapeutically effective amount of said muscarinic receptor antagonist.

4. The combination of claim 1, wherein said muscarinic receptor antagonist is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of tolterodine and oxybutynin.

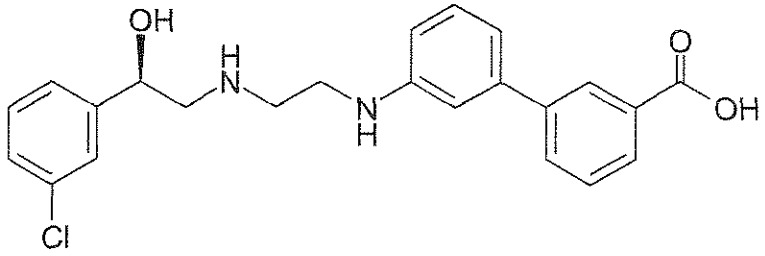
5. The combination of claim 4, comprising a therapeutically effective amount of said muscarinic receptor antagonist.

6. The combination of claim 1, wherein said muscarinic receptor antagonist is oxybutynin or a pharmaceutically acceptable salt thereof.

7. The combination of claim 1, comprising a subtherapeutic effective amount of said muscarinic receptor antagonist.

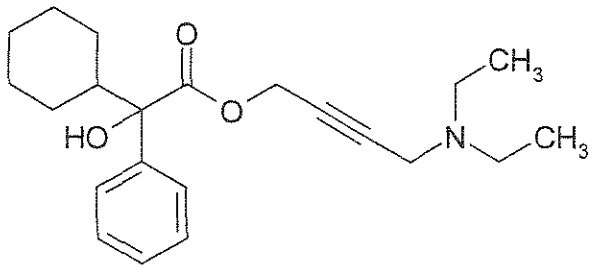
8. A pharmaceutical composition comprising the combination of claim 1, further comprising one or more pharmaceutically acceptable carriers, diluents or excipients.

9. A combination comprising:
(i) a therapeutically effective amount of a compound of Formula (I),



Formula (I)

or a pharmaceutically acceptable salt thereof; and
(ii) a therapeutically effective amount, or a sub-therapeutically effective amount of a compound of Formula (II),



Formula (II)

or a pharmaceutically acceptable thereof; said combination being useful for relieving one or more symptoms associated with overactive bladder in a synergistic manner, versus the individual components (i) and (ii), wherein said one or more symptoms of overactive bladder are selected from the group consisting of frequency of urgency, nocturia, and urinary incontinence.

10. The combination according to claim 9, wherein the salt of the compound of Formula (I) is the hydrochloride salt.