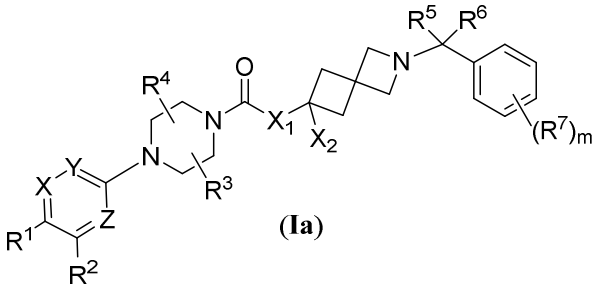
the muscarinic receptor pan antagonist trihexyphenidyl (M_1 (K_i = 1 nM), M_2 (K_i = 20 nM), M_3 (K_i = 10 nM), M_4 (K_i = 10 nM) and M_5 (K_i = 30 nM)) is thought to have use-limiting side effects, such as, cognitive impairment, tachycardia, and gastrointestinal tract function associated with antagonism of M_1, M_2, and M_3. Therefore, selective M_4 antagonists may provide treatment for parkinsonism or dystonia without side effects from inhibiting other muscarinic receptor subtypes (see, https://doi.org/10.1101/2020.10.12.324152).

Despite the advances that have been made in this field, a need remains in the art for improved M_4 antagonists, including compounds, compositions, and methods related thereto. The present disclosure fulfills these and other needs, as evident in reference to the following disclosure.

SUMMARY

In one aspect, the present disclosure refers to a compound of Formula (**Ia**):



(**Ia**)

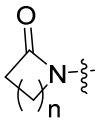
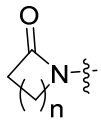
,

or a pharmaceutically acceptable salt thereof:

wherein:

each of X, Y, Z is independently CR^8 or N, wherein R^8 is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 alkoxy, or cyano;

R^1 is R^9-$S(=O)_2$-;

R^2 is hydrogen, halogen, amino, $R^{10}NH$-$S(=O)_2$-, R^9-$S(=O)_2$-, R^9-S(=O)-, R^9-S-, R^9-S(=O)(=NR^{10})-, R^9-O-,  (n = 1, 2, or 3), cyano or C_1-C_4 alkyl, wherein R^9 is selected from C_1-C_4 alkyl, C_3-C_7-cycloalkyl, and 3-7 membered heterocyclyl, wherein R^9 or  is optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, -OH, -NHR^{10}, halogen, or cyano, and wherein R^{10} is hydrogen, C_1-C_4 alkyl, or C_3-C_7 cycloalkyl; or R^1, R^2 and the carbon atoms they are attached to form a 3-7 membered ring with one or more heteroatoms selected from N, O, and S;

X_1 is O or NH;

X_2 is hydrogen or C_1-C_4 alkyl;

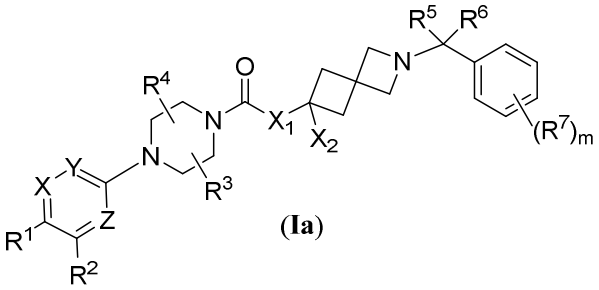
R^3 and R^4 are each independently selected from hydrogen and C_1-C_4 alkyl, and R^3 and R^4 are bonded to different ethylene groups of the piperazine ring;

each of R^5 and R^6 is independently hydrogen or C_1-C_4 alkyl, or R^5, R^6 and the carbon atom they are attached to form a C_3-C_7 cycloalkyl or a 3-7 membered heterocyclyl, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, -OH, -NHR^{10}, halogen, and cyano;

R^7 is hydrogen, halogen, or C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with halogen, amino, -OH, C_1-C_4 alkoxy, or cyano; and

m is 0, 1, or 2.

One example of the present disclosure encompasses, *inter alia*, certain 2-azaspiro[3.3]heptane derivatives of Formula (**Ia**):



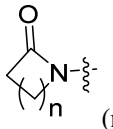
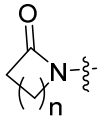
(**Ia**)

;

or a pharmaceutically acceptable salt thereof,

wherein:

each of X, Y, Z is independently CR^8 or N, wherein R^8 is hydrogen, C_1-C_4 alkyl, halogen, C_1-C_4 alkoxy, or cyano;

each of R^1 and R^2 is independently hydrogen, halogen, amino, $R^{10}NH$-$S(=O)_2$-,R^9-$S(=O)_2$-, R^9-S(=O)-, R^9-S-, R^9-S(=O)(=NR^{10})-, R^9-O-,  (n= 1, 2, or 3), cyano or C_1-C_4 alkyl, wherein R^9 is selected from C_1-C_4 alkyl, C_3-C_7 cycloalkyl, and 3-7 membered heterocyclyl, wherein R^9 or  is optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, -OH, -NHR^{10}, halogen, or cyano, and wherein R^{10} is hydrogen, C_1-C_4 alkyl, or C_3-C_7 cycloalkyl; or R^1, R^2 and the carbon atoms they are attached to form a 3-7 membered ring with one or more heteroatoms selected from N, O, and S;

X_1 is O or NH;

X_2 is hydrogen or C_1-C_4 alkyl;

R^3 and R^4 are each independently selected from H and C_1-C_4 alkyl, and R^3 and R^4 are bonded to different ethylene groups of the piperazine ring;

each of R^5 and R^6 is independently hydrogen or C_1-C_4 alkyl, or R^5, R^6 and the carbon atom they are attached to form a C_3-C_7 cycloalkyl or a 3-7 membered heterocyclyl, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, -OH, -NHR^{10}, halogen, and cyano;

R^7 is hydrogen, halogen, or C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with halogen, amino, -OH, C_1-C_4 alkoxy, or cyano; and

m is 0, 1, or 2.

One example of the present disclosure relates to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound of the present disclosure or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to a pharmaceutical product selected from a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

One example of the present disclosure relates to pharmaceutical compositions comprising a compound of the present disclosure or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

One example of the present disclosure relates to methods for preparing a pharmaceutical composition comprising the step of admixing a compound according of the present disclosure or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a method for preparing a pharmaceutical composition comprising the step of admixing a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier

One example of the present disclosure relates to methods for antagonizing a muscarinic receptor 4 (M_4) of a cell comprising contacting the cell with the compound according of the present disclosure or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to an *in vitro* method for antagonizing a muscarinic receptor 4 (M_4) of a cell, comprising contacting the cell with the compound disclosed herein, or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for antagonizing a muscarinic receptor 4 (M_4) of a cell *in vivo.*

One example of the present disclosure relates to methods for treating or preventing a neurological disease, disorder, or symptom in an individual, comprising administering to the individual in need thereof, a therapeutically effective amount of a compound according of the present disclosure or a pharmaceutically acceptable salt thereof; a pharmaceutical product of the present disclosure; or a pharmaceutical composition of the present disclosure.

One example of the present disclosure relates to methods for treating or preventing a muscarinic receptor 4 (M_4) mediated disease, disorder, or symptom in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according of the present disclosure or a pharmaceutically acceptable salt thereof; a pharmaceutical product of the present disclosure; or a pharmaceutical composition of the present disclosure.

One example of the present disclosure relates to uses of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a neurological disease, disorder, or symptom in an individual. In one aspect, the present disclosure refers to use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein, or a pharmaceutical product disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a neurological disease, disorder, or symptom in an individual.

One example of the present disclosure relates to uses of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a muscarinic receptor 4 (M_4) mediated disease, disorder, or symptom in an individual. In one aspect, the present disclosure refers to use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein, or a pharmaceutical product disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a muscarinic receptor 4 (M_4) mediated disease, disorder, or symptom in an individual.

One example of the present disclosure relates to compounds of the present disclosure or a pharmaceutically acceptable salt thereof; pharmaceutical products of the present disclosure; or pharmaceutical compositions of the present disclosure; for use in a method of treatment or prophylaxis of the human or animal body by therapy. In one aspect, the present disclosure refers to a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical product disclosed herein, or a pharmaceutical composition disclosed herein, for use in treatment or prophylaxis of a human or animal body by therapy.

One example of the present disclosure relates to compounds of the present disclosure or a pharmaceutically acceptable salt thereof; pharmaceutical products of the present disclosure; or pharmaceutical compositions of the present disclosure; for use in a method for treating or preventing a neurological disease, disorder, or symptom in an individual. In one aspect, the present disclosure refers to a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical product disclosed herein, or a pharmaceutical composition disclosed herein, for use in treating or preventing a neurological disease, disorder, or symptom in an individual.

One example of the present disclosure relates to compounds of the present disclosure or a pharmaceutically acceptable salt thereof; pharmaceutical products of the present disclosure; or pharmaceutical compositions of the present disclosure; for use in a method for treating or preventing a muscarinic receptor 4 (M_4) mediated disease, disorder, or symptom in an individual. In one aspect, the present disclosure refers to a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical product disclosed herein, or a pharmaceutical composition disclosed herein, for use in treating or preventing a muscarinic receptor 4 (M_4) mediated disease, disorder, or symptom in an individual.

These and other aspects of the disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

As used herein, "**administering**" refers to providing a compound of the invention or other therapy, remedy or treatment to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as, tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as, IV, IM, IP, and the like; transdermal dosage forms, including creams, jellies, powders, and patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories. A health care practitioner can directly provide a compound to an individual in the form of a sample or can indirectly provide a compound to an individual by providing an oral or written prescription for the compound. Also, for example, an individual can obtain a compound by themselves without the involvement of a health care practitioner. When the compound is administered to the individual, the body is transformed by the compound in some way. When a compound of the invention is provided in combination with one or more other agents, "administration" is understood to include the compound and other agents are administered at the same time or at different times. When the agents of a combination are