- R^6 is independently selected from the group consisting of deuterium, F, -CN, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^7 is independently selected from the group consisting deuterium, F, Cl, -CN, C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^8 is independently selected from the group consisting of deuterium and F;
- R^9 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- X is a bond or selected from the group consisting of -O-, -S-, -CH_2-, -CHR^6-, and -$C(R^6)_2$-; and
- n is an integer 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In another aspect, the disclosure refers to the use of the compound as disclosed herein or composition as disclosed herein in the manufacture of a medicament for treatment of symptoms of an indication selected from the group consisting of myasthenia gravis, Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), reversal diabetic polyneuropathy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, periodic paralysis, sarcopenia, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy and Duchenne muscular dystrophy.

In another aspect, the disclosure refers to the use of the compound as disclosed herein or composition as disclosed herein in the manufacture of a medicament for reversing and/or ameliorating a neuromuscular blockade.

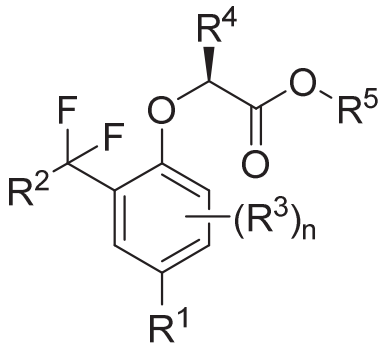
In another example, the disclosure concerns a compound as defined herein for use in treating, ameliorating and/or preventing a neuromuscular disorder, and/or for use in reversing and/or ameliorating a neuromuscular blockade. In yet another example, the disclosure concerns a composition comprising a compound as defined herein.

Description of Drawings

Figure 1. Panel A shows a schematic representation of the positioning of the three microelectrodes (V_1, V_2 and V_3) when inserted in a single skeletal muscle fibre for G_m determination. Please note that the drawing illustrates only the impaled fibre although it is part of an intact muscle that contains many such fibres. All electrodes recorded the membrane potential of the fibre and the two peripheral electrodes were used to inject current (-30 nA, 50 ms). The electrodes were inserted with known inter-electrode distances (X_1, X_2 and X_3). After insertion, current was passed first via the V_1 electrode and then via the V_3 electrode. The resulting deflections in the membrane voltage were measured by the other electrodes. The steady state deflections in membrane potential were measured and divided by the magnitude of the injected current (-30 nA) to obtain

Claims

1. A compound of Formula (II)



Formula (II)

wherein:

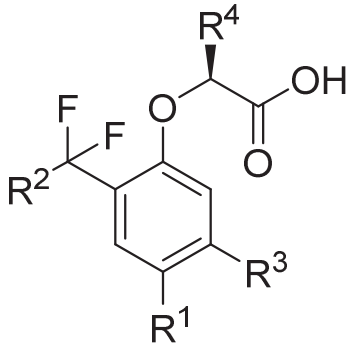
- R^1 is selected from the group consisting of C_{1-2} alkyl, C_2 alkenyl, C_2 alkynyl, CN, CF_3, NO_2, F, Cl, Br, and I;
- R^2 is selected from the group consisting of C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6, C_{2-5} alkenyl optionally be substituted with one or more, identical or different, substituents R^6, C_{2-5} alkynyl optionally be substituted with one or more, identical or different, substituents R^6, C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6, phenyl optionally substituted with one or more, identical or different, substituents R^9, and 5-6 membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R^7;
- R^3 is selected from the group consisting of deuterium, Cl and F;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, and C_{3-5} cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R^7;
- R^5 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^8, C_{2-5} alkenyl optionally substituted with one or more, identical or different, substituents R^8, C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^8, C_{3-6} cycloalkyl optionally

substituted with one or more, identical or different, substituents R^8, phenyl optionally substituted with one or more, identical or different, substituents R^9, and benzyl optionally substituted with one or more, identical or different, substituents R^9;

- R^6 is independently selected from the group consisting of deuterium, F, -CN, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^7 is independently selected from the group consisting deuterium, F, Cl, -CN, C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^8 is independently selected from the group consisting of deuterium and F;
- R^9 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F; and
- n is an integer 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

2. The compound according to claim 1, wherein the compound is of Formula (III):



Formula (III)

wherein:

- R^1 is selected from the group consisting of C_2 alkenyl, C_2 alkynyl, NO_2, F, Cl, Br, and I;

- R^2 is C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6;
- R^3 is selected from the group consisting of H, deuterium, Cl and F;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl and C_{2-5} alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R^7;
- R^6 is independently selected from the group consisting of deuterium, F, -CN, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^7 is independently selected from the group consisting of deuterium, F, Cl, -CN, C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl, wherein the C_{3-5} cycloalkyl, -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, -S-C_{1-5} alkyl, and -S-C_{3-5} cycloalkyl may optionally be substituted with one or more, identical or different, substituents R^8;
- R^8 is independently selected from the group consisting of deuterium and F;

or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

3. The compound according to any of claims 1 to 2, wherein R^1 is Cl or Br.

4. The compound according to any of claims 1 to 3, wherein R^2 is C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^6.

5. The compound according to any of claims 1 to 4, wherein R^3 is F.

6. The compound according to any of claims 1 to 5, wherein R^4 is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6.

7. The compound according to any of claims 1 to 6, wherein R^4 is Me or CH_2F.

8. The compound according to any of claims 1 to 5, wherein R^4 is C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^6.

9. The compound according to any of claims 1 or 3 to 8, wherein R^5 is H.

10. The compound according to any one of claims 1 to 11, wherein the compound is selected from the group consisting of:

(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-cyclopropylpropanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]butanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]propanoic acid;
(2*S*)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]propanoic acid;
2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]acetic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]propanoic acid;
(2*S*)-2-{4-bromo-2-[difluoro(phenyl)methyl]phenoxy}propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-2-cyclopropylacetic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluorobutyl)phenoxy]propanoic acid;
(2*R*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[4-bromo-2-(cyclopropyldifluoromethyl)phenoxy]propanoic acid;
(2*S*)-2-{4-bromo-2-[difluoro(1,3-thiazol-2-yl)methyl]phenoxy}propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]pent-4-ynoic acid;
(2*S*)-2-[4-bromo-2-(cyclobutyldifluoromethyl)phenoxy]propanoic acid;
(2*R*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropanoic acid;
(2*R*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-3-chloropropanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]pent-4-ynoic acid;
(2*S*)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]pent-4-ynoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-iodophenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy](2-^{2}H)propanoic acid;
(2*R*)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-ethynylphenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)-6-fluorophenoxy]propanoic acid;
(2*S*)-2-[4-cyano-2-(1,1-difluoropropyl)phenoxy]propanoic acid;
(2*R*)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)(3,5,6-$^{2}H_{3}$)phenoxy]propanoic acid;
2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
(2*S*)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]propanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-(trifluoromethyl)phenoxy]propanoic acid;

(2*R*)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-ethenylphenoxy]propanoic acid;
2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]acetic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-methylphenoxy]propanoic acid;
2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]acetic acid;
2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
(2*S*)-2-[2-(1,1-difluoroethyl)-4-ethynylphenoxy]propanoic acid;
(2*R*)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[4,5-dichloro-2-(1,1-difluoropropyl)phenoxy]propanoic acid;
(2*R*)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]-3-fluoropropanoic acid;
(2*R*)-2-[4,5-dichloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-fluorobutanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]butanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-ethenyl-5-fluorophenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]butanoic acid;
(2*S*)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]butanoic acid;
(2*R*)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4-nitrophenoxy]propanoic acid;
(2*S*)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-methoxybutanoic acid;
(2*R*)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]-3-fluoropropanoic acid;
(2*S*)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]propanoic acid; and
(2*S*)-2-[4-bromo-2-(1,1-difluoro-3-methoxypropyl)phenoxy]propanoic acid.

11. The compound according to any one of claims 1 to 10, wherein the compound is an inhibitor of the ClC-1 ion channel.

12. A composition comprising the compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

13. The compound according to any one of claims 1 to 11 or composition according to claim 12 for use as a medicament.

14. Use of the compound according to any one of claims 1 to 11 or composition according to claim 12 in the manufacture of a medicament for treatment of symptoms of an indication selected from the group consisting of myasthenia gravis, Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), reversal diabetic polyneuropathy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, periodic paralysis, sarcopenia, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy and Duchenne muscular dystrophy.

15. Use of the compound according to any one of claims 1 to 11 or composition according to claim 12 in the manufacture of a medicament for reversing and/or ameliorating a neuromuscular blockade.