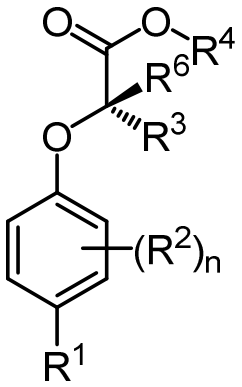
It has been found that a set of novel compounds that inhibit ClC-1 ion channels are capable of restoring neuromuscular transmission, as evidenced by the data generated by investigation of the compound set in biological models described herein. These compounds thus constitute a new group of potential drugs that can be used to treat or ameliorate muscle weakness and muscle fatigue in neuromuscular junction disorders caused by disease or by neuromuscular blocking agents.

The present disclosure thus concerns the discovery of new ClC-1 ion channel inhibitors with application in the treatment of a range of conditions, such as reversal of block, ALS and myasthenic conditions, in which muscle activation by the nervous system is compromised and symptoms of weakness and fatigue are prominent.

In one example, the present disclosure refers to a compound of Formula (IIa):



Formula (IIa)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br, I, -CN, $-CF_3$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_4 cycloalkyl and $–S-CH_3$;
- R^2 is independently selected from the group consisting of hydrogen, deuterium, F, Cl, Br, I, -CN, $-CF_3$ and –oxime optionally substituted with C_1 alkyl;
- R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl and C_5 cycloalkenyl, each of which may be optionally substituted with one or more, identical or different, substituents R^5;

- R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8;
- R^5 is independently selected from the group consisting of deuterium, F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, and OH;
- R^6 is independently selected from the group consisting of hydrogen and deuterium;
- R^7 is independently selected from the group consisting of deuterium and F;
- R^8 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, 3 or 4;

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

with the proviso that:

when R^1 is Cl, R^2 is Cl, R^4 is H, R^5 is H, R^6 is H and n is 1 or 2, then R^3 is not methyl;

when R^1 is Cl, R^2 is Cl, R^4 is H, R^5 is H, R^6 is H and n is 1, then R^3 is not ethyl;

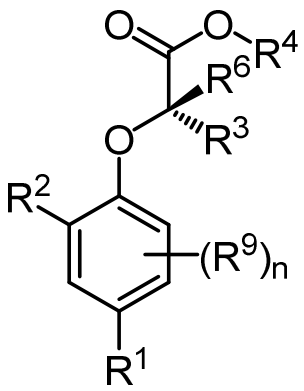
when R^1 is Cl, R^4 is H or Me or 4-methoxyphenyl or 4-nitrophenyl, R^5 is H, R^6 is H and n is 0, then R^3 is not methyl;

when R^1 is Br, R^4 is H, R^5 is H, R^6 is H and n is 0, then R^3 is not methyl or isopropyl;

when R^1 is Br, R^4 is Me, R^5 is H, R^6 is H and n is 0, then R^3 is not isopropyl; and

when R^1 is I, R^4 is H, R^5 is H, R^6 is H and n is 0, then R^3 is not methyl.

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



Formula (VII)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br, I, -CN, -CF_3, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_4 cycloalkyl and –S-CH_3;
- R^2 is independently selected from the group consisting of hydrogen, deuterium, F, Cl, Br, I, -CN, -CF_3 and –oxime optionally substituted with C_1 alkyl;
- R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R^5, and C_{2-5} alkynyl which may be optionally substituted with one or more, identical or different, substituents R^5;
- R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8;
- R^5 is independently selected from the group consisting of F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, and OH;
- R^6 is independently selected from the group consisting of hydrogen and deuterium;
- R^7 is independently selected from the group consisting of deuterium and F;

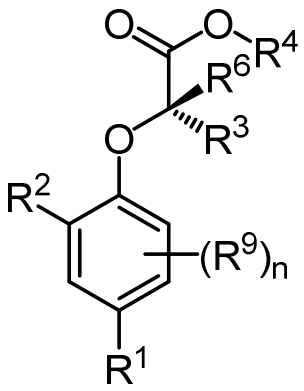
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;
- R^9 is deuterium; and
- n is an integer 0, 1, 2, 3 or 4;

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

In another aspect, the present disclosure refers to a use of the compound as disclosed herein for the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or reversing and/or ameliorating a neuromuscular blockade. In one example, the disclosure concerns a composition comprising a compound as defined herein and uses thereof, such as in treating, ameliorating and/or preventing a neuromuscular disorder, and/or for use in reversing and/or ameliorating a neuromuscular blockade.

Claims

1. A compound of Formula (VII):



Formula (VII)

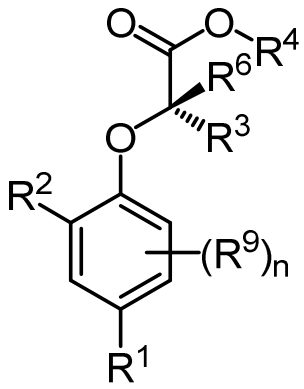
wherein:

- R^1 is selected from the group consisting of F, Cl, Br, I, -CN, -CF_3, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_4 cycloalkyl and –S-CH_3;
- R^2 is independently selected from the group consisting of hydrogen, deuterium, F, Cl, Br, I, -CN, -CF_3 and –oxime optionally substituted with C_1 alkyl;
- R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R^5, and C_{2-5} alkynyl which may be optionally substituted with one or more, identical or different, substituents R^5;
- R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8;
- R^5 is independently selected from the group consisting of F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, and OH;

- R^6 is independently selected from the group consisting of hydrogen and deuterium;
- R^7 is independently selected from the group consisting of deuterium and F;
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;
- R^9 is deuterium; and
- n is an integer 0, 1, 2, 3 or 4;

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

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



Formula (VII)

wherein:

R^1 is selected from the group consisting of F, Cl, Br, and I;

R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl and Br;

R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R^5, and C_{2-5} alkynyl, which may be optionally substituted with one or more, identical or different, substituents R^5;

R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and

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

R^5 is independently selected from the group consisting of F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 and OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;

R^6 is selected from the group consisting of hydrogen and deuterium;

R^7 is independently selected from the group consisting of deuterium and F; and

R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;

R^9 is deuterium; and

n is 0, 1, 2 or 3;

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

3. The compound according to any one of the preceding claims, wherein
   - R^1 is selected from the group consisting of Cl and Br;
   - R^2 is selected from the group consisting of F, Cl and Br;
   - R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl each of which is substituted with one or more, identical or different, substituents R^5, and C_{2-5} alkynyl, which may be optionally substituted with one or more, identical or different, substituents R^5;
   - R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7 and phenyl optionally substituted with one or more, identical or different, substituents R^8;
   - R^5 is independently selected from the group consisting of F, -OC_{1-5} alkyl optionally substituted with one or more, identical or different,

substituents R^7 and -OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;

- R^6 is selected from the group consisting of hydrogen and deuterium;
- R^7 is independently selected from the group consisting of deuterium and F;
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;
- R^9 is deuterium; and
- n is 0, 1, 2 or 3

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

4. The compound according to any one of the preceding claims, wherein

- R^1 is Br;
- R^2 is selected from the group consisting of F, Cl and Br;
- R^3 is methyl substituted with one or more, identical or different, substituents R^5, C_{2-3} alkyl substituted with one or more, identical or different, substituents R^5 or C_{3-4} cycloalkyl substituted with one or more, identical or different, substituents R^5;
- R^4 is H;
- R^5 is independently selected from the group consisting of F, -OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 and -OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;
- R^6 is selected from the group consisting of hydrogen and deuterium;
- R^7 is independently selected from the group consisting of deuterium and F;
- R^9 is deuterium; and
- n is 0, 1, 2 or 3.

5. The compound according to any one of claims 1 or 2, wherein:

R^1 is selected from the group consisting of F, Cl, Br, I;

R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl, Br, I;

R^3 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl and C_5 cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R^5;

- R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl

optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8;

R^5 is independently selected from the group consisting of F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 and OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;

R^6 is selected from the group consisting of hydrogen and deuterium;

R^7 is independently selected from the group consisting of deuterium and F; and

R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;

R^9 is deuterium; and

n is 0, 1, 2 or 3;

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

6. The compound according to any one of the preceding claims, wherein:

R^1 is Br;

R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl and Br;

R^3 is C_{1-3} alkyl substituted with one or more, identical or different, substituents R^5;

R^4 is H;

R^5 is independently selected from the group consisting of F, $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^7 and $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;

R^6 is selected from the group consisting of hydrogen and deuterium;

R^7 is independently selected from the group consisting of deuterium and F; and

n is 0;

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

7. The compound according to any one of claims 1 or 2, wherein:

R^1 is selected from the group consisting of F, Cl, Br, I;

R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl, Br, I;

R^3 is selected from the group consisting of C_{1-5} alkyl and C_{3-5} cycloalkyl each of which is substituted with one or more, identical or different, substituents R^5;

R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8;

R^5 is independently selected from the group consisting of F, OC_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 and OC_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7;

R^6 is deuterium;

R^7 is independently selected from the group consisting of deuterium and F;

R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;

R^9 is deuterium; and

n is 0, 1, 2 or 3;

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

8. The compound according to claim 1, wherein:

R^1 is selected from the group consisting of F, Cl, Br, I, -CN, $-CF_3$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-4} cycloalkyl and $–S-CH_3$;

R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl, Br and I;

R^3 is selected from the group consisting of fluoromethyl, fluoroethyl and fluoropropyl;

R^4 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7, phenyl optionally substituted with one or more, identical

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

R^6 is selected from the group consisting of hydrogen and deuterium;

R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;

R^9 is deuterium; and

n is 0, 1, 2 or 3;

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

9. The compound according to any one of claims 1 or 2, wherein the compound is selected from the group consisting of:

(2*R*)-2-[4-bromo(3,5-$^2H_2$)phenoxy]-3-fluoropropanoic acid*;*

(2*R*)-2-[4-bromo(2,6-$^2H_2$)phenoxy]-3-fluoropropanoic acid*;*

(2*R*)-2-(4-bromo-2-fluorophenoxy)-3,3-difluoropropanoic acid*;*

(2*R*)-2-(4-bromo-2-fluorophenoxy)-3-fluoropropanoic acid*;*

(2*R*)-2-(2-bromo-4-chlorophenoxy)-3-fluoropropanoic acid*;*

(2*R*)-2-(4-chlorophenoxy)-3-fluoropropanoic acid*;*

(2*R*)-2-(4-chloro-2-fluorophenoxy)-3-fluoropropanoic acid*;*

(2*R*)-2-(2,4-dibromophenoxy)-3-fluoropropanoic acid*;*

(2*S*)-2-(4-bromophenoxy)-3-hydroxypropanoic acid*;*

(2*R*)-2-(4-bromophenoxy)-3-fluoropropanoic acid*;*

(2*S*,3*E*)-2-(4-bromophenoxy)-4-fluorobut-3-enoic acid;

(2*S*)-2-(4-bromophenoxy)pent-4-ynoic acid;

(2*S*)-2-(2,4-dibromophenoxy)pent-4-ynoic acid;

(2*S*)-2-(4-bromo-2-chlorophenoxy)pent-4-ynoic acid;

(2*S*)-2-(4-bromo-2-fluorophenoxy)pent-4-ynoic acid;

(2*S*)-2-(2,4-dibromophenoxy)-3-methoxypropanoic acid;

(2*R*)-2-(4-bromo-2-chlorophenoxy)-3-fluoropropanoic acid;

(2*S*)-2-(4-bromo-2-chlorophenoxy)-4-fluorobutanoic acid;

(2*R*)-2-(4-bromophenoxy)-3-fluoro(2-^{2}H)propanoic acid;

(2*S*)-2-(4-bromo-2-iodophenoxy)-4-fluorobutanoic acid;

(2*S*)-2-(4-bromo-2-fluorophenoxy)-4-fluorobutanoic acid;

(2*S*)-2-(4-bromophenoxy)-4-fluorobutanoic acid;

(2*R*,3*R*)-2-(4-bromophenoxy)-3-fluorobutanoic acid, and

(2*R*,3*R*)-2-(4-bromo-2-fluorophenoxy)-3-fluorobutanoic acid.

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

11. Use of the compound according to any one of the preceding claims for the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or reversing and/or ameliorating a neuromuscular blockade.

12. The use according to claim 11 wherein the neuromuscular disorder is selected from the group consisting of myasthenia gravis (such as autoimmune and congenital 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, and hyperkalemic periodic paralysis.

13. The use according to claim 11 wherein the neuromuscular disorder is amyotrophic lateral sclerosis (ALS).

14. The use according to claim 11, wherein the neuromuscular disorder is myasthenia gravis.

15. The use according to claim 11 wherein the neuromuscular disorder has been induced by a neuromuscular blocking agent.