In FR 1 451 171, Logeais Bonnert described 2-(1,3,4-oxadiazol-2-yl)phenoxy derived compounds having antiinflammatory activity.

In the article *Journal of Medicinal Chemistry,* **2004**, *47*, 6160-73, Gentili *et al* describe using 2-(thiophen-3-yl)phenoxy)acetic acid derivates as adreno receptors.

In the article *Journal of Medicinal Chemistry,* **2010**, *53*, 7825-35, Del Bello *et al* describe using 2-(thiophen-3-yl)phenoxy)acetic acid derivates as adreno receptors.

In US 2006/0211765, Pairaudeau *et al*. reported a further series of substituted biphenyloxy acetic acids for treatment of respiratory disorders

In WO 2016/202341, Pedersen *et al*. reported a series of of phenoxypropionic acids and related compounds that appear to block the ClC-1 ion channel for use in treating, ameliorating and/or preventing neuromuscular disorders. However, they possess alternative structural features to those in the current invention.

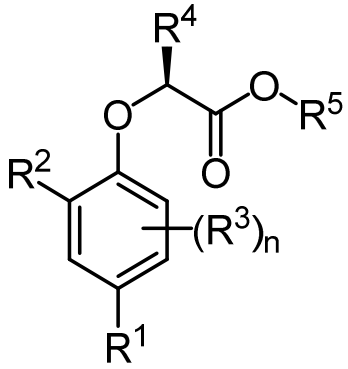
Summary

The present disclosure comprises a new series of compounds that alleviate disorders of the neuromuscular junction through inhibition of ClC-1 channels.

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 aspect, the present disclosure refers to a use of a compound of Formula (I):



Formula (I)

wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^2 is a 5-membered aromatic heterocycle, wherein each of which may be optionally substituted with one or more, identical or different, substituents R^6;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-

C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;

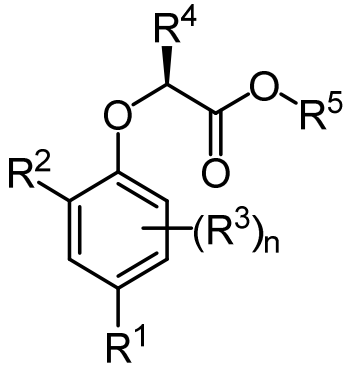
- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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,

with the proviso that when R^1 is F, Cl or Br, R^2 is 1,2-oxazol-5-yl, R^4 is H, R^5 is H and R^6 is H then n is 1, 2 or 3;

for the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or for reversing and/or ameliorating a neuromuscular blockade.

In another aspect, the present disclosure refers to a compound of Formula (I):



Formula (I)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br and I;
- R^2 is a 5-membered aromatic heterocycle, wherein each of which may be optionally substituted with one or more, identical or different, substituents R^6
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;
- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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, with the proviso that when R^4 is H then R^2 is 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2-thiazol-3-yl, 1,2-oxazol-3-yl or 1,3-oxazol-4-yl.

In one example, the disclosure concerns a compound of Formula (I):

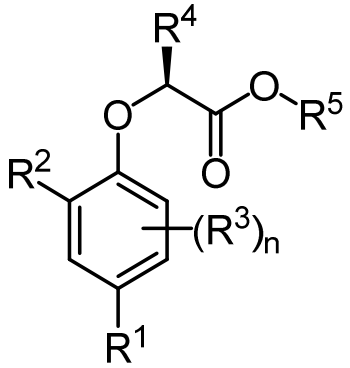
C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;

- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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,

for use in treating, ameliorating and/or preventing a neuromuscular disorder, and/or for use in reversing and/or ameliorating a neuromuscular blockade.

In another example, the disclosure concerns a compound of Formula (I):



Formula (I)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br and I;
- R^2 is a 5-6 membered aromatic heterocycle or an 8-10 membered aromatic bicyclic heterocycle each of which may be optionally substituted with one or more, identical or different, substituents R^6;

or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof, with the proviso that when R^4 is H then R^2 is 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2-thiazol-3-yl, 1,2-oxazol-3-yl or 1,3-oxazol-4-yl.

In yet another example, the disclosure concerns a composition comprising a compound as defined herein.

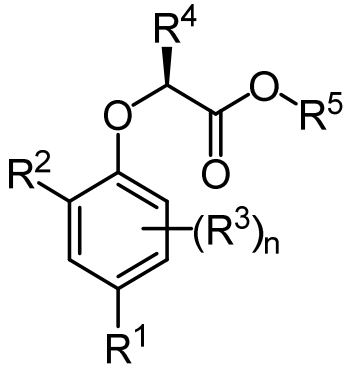
Description of Drawings

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 transfer resistances. These were next plotted against inter-electrode distances, and fitted to an exponential function (Panel B), from which G_m could be calculated using linear cable theory. The approach described in panel A and B, was repeated for several muscle fibres in the muscle during exposure at increasing concentrations of compound A-19, with approx. 10 fibres at each concentration. Average G_m at each concentration was plotted as a function of compound concentration in panel C, and fitted to a 4-parameter sigmoidal function from which the EC_{50} value for the compound was obtained (dashed line)

Figure 2. Panel A shows representative force traces before and after exposure to compound A-22. Force traces from a representative muscle stimulated to contract in 1) control condition before addition of neuromuscular blocking agent, 2) the force response to stimulation after 90 minutes incubation with Tubocurarine. Here the muscle displays severe neuromuscular transmission impediment, and 3) The muscle force response after addition of 50 µM compound A-22. Panel B shows average force (AUC) from 3 muscles relative to their initial force. The traces presented in panel A (1, 2, 3), correspond to the dotted lines in panel B, respectively. Thus, force is lost due to 90 min

Claims

1. Use of a compound of Formula (I):



Formula (I)

wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^2 is a 5-membered aromatic heterocycle, wherein each of which may be optionally substituted with one or more, identical or different, substituents R^6;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-

C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;

- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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;

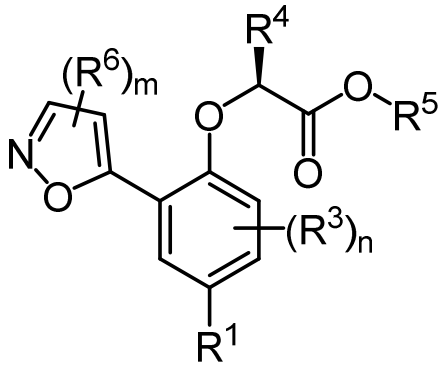
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof,

with the proviso that when R^1 is F, Cl or Br, R^2 is 1,2-oxazol-5-yl, R^4 is H, R^5 is H and R^6 is H then n is 1, 2 or 3;

for the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or for reversing and/or ameliorating a neuromuscular blockade.

2. The use according claim 1, wherein R^2 is selected from the group consisting of 1,2-oxazol-3-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2-thiazol-3-yl, 1,2-thiazol-4-yl, 1,2-thiazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-3-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl and 1,2,5-oxadiazol-3-yl each of which may be optionally substituted with one or more, identical or different, substituents R^6.

3. The use according to any one of claims 1 to 2, wherein the compound is of Formula (II):



Formula (II)

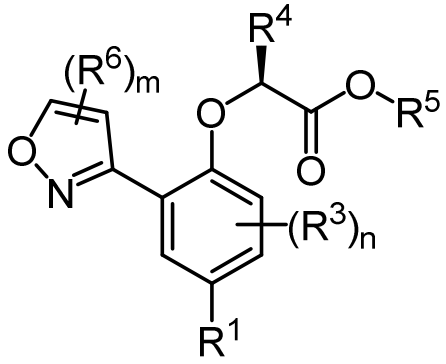
wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl

and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;

- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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,
- m is an integer 0, 1 or 2; and
- n is an integer 0, 1, 2 or 3.

4. The use according to any one of claims 1 to 2, wherein the compound is of Formula (III):



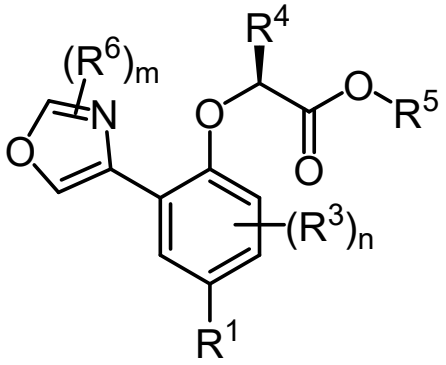
Formula (III)

wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;
- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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;
- m is an integer 0, 1 or 2; and
- n is an integer 0, 1, 2 or 3.

5. The use according to any one of claims 1 to 2, wherein the compound is of Formula (XVI):



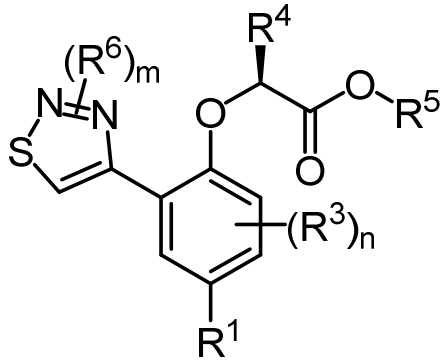
Formula (XVI)

wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;

- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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;
- m is an integer 0, 1 or 2; and
- n is an integer 0, 1, 2 or 3.

6. The use according to any one of claims 1 to 2, wherein the compound is of Formula (XVII):



Formula (XVII)

wherein:

- R^1 is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;
- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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;
- m is an integer 0 or 1; and
- n is an integer 0, 1, 2 or 3.

7. The use according to any of claims 1 to 6, wherein n is 0 or 1.

8. The use according to any one of claims 1 to 7, wherein R^4 is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 or C_{1-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7.

9. The use according to any one of claims 1 to 8, wherein R^1 is selected from the group consisting of F, Cl, Br and I.

10. The use according to any one of claims 1 to 9, wherein R^5 is hydrogen.

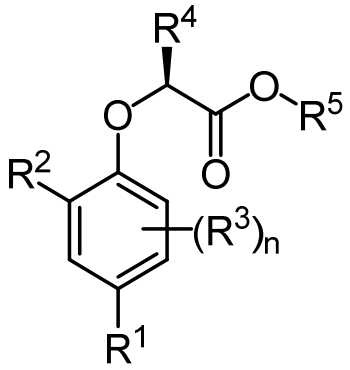
11. The use according to any one of claims 1 to 10, wherein m is 0.

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

13. The use according to any one of claims 1 to 12, wherein the neuromuscular disorder is selected from the group consisting of myasthenia gravis, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), Charcot-Marie tooth disease (CMT) and sarcopenia.

14. The use according to any one of claims 1 to 13, wherein the neuromuscular disorder has been induced by a neuromuscular blocking agent.

15. A compound of Formula (I):



Formula (I)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br and I;
- R^2 is a 5-membered aromatic heterocycle, wherein each of which may be optionally substituted with one or more, identical or different, substituents R^6
- R^3 is selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, CF_3, CCl_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, OCF_3, $OCCl_3$ and isocyanide;
- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, 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, C_{2-5} alkynyl, 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 H, deuterium, tritium, F, Cl, Br, I, CN, isocyanide, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl, and wherein C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, C_5 cycloalkenyl, O-C_{1-5} alkyl, O-C_{2-5} alkenyl, O-C_{2-5} alkynyl, O-C_{3-5} cycloalkyl, O-C_5 cycloalkenyl, -C(=O)-C_{1-5} alkyl, -C(=O)-C_{2-5} alkenyl, -C(=O)-C_{2-5} alkynyl, -C(=O)-C_{3-5} cycloalkyl, -CH_2-O-C_{1-3} alkyl and -CH_2-S-C_{1-3} alkyl may be optionally substituted with one or more halogens;
- R^7 is independently selected from the group consisting of deuterium, tritium, F, Cl, Br, I, CN, isocyanide, O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, S-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8, CH_2-O-C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^8 and CH_2-S-C_{1-3} alkyl optionally 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, with the proviso that when R^4 is H then R^2 is 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2-thiazol-3-yl, 1,2-oxazol-3-yl or 1,3-oxazol-4-yl.

16. The compound according to claim 15, wherein R^1 is Cl or Br.

17. The compound according to any one of claims 15 to 16, wherein R^2 is selected from the group consisting of 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2-thiazol-3-yl, 1,2-oxazol-3-yl, 1,2-oxazol-5-yl and 1,3-oxazol-4-yl each of which may be optionally substituted with one or more, identical or different, substituents R^6.

18. The compound according to any one of claims 15 to 17, wherein R^4 is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^7 or C_{1-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7.

19. The compound according to any one of claims 15 to 17, wherein R^4 is H or deuterium.

20. The compound according to any one of claims 15 to 19, wherein R^5 is hydrogen.

21. The compound according to any one of claims 15 to 20, wherein m is 0.

22. The compound according to any of claims 15 to 21, wherein n is 0 or 1.

23. The compound according to any of claims 15 to 22, wherein the compound is selected from the group consisting of:

(*2S*)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]butanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]butanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-methylbutanoic acid;
(*2S*)-2-{4-bromo-2-[3-(propan-2-yl)-1,2-oxazol-5-yl]phenoxy}propanoic acid;
(*2S*)-2-[4-bromo-2-(4-methyl-1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-chloro-6-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(5-methyl-1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(5-cyclopropyl-1,2-oxazol-3-yl)phenoxy]propanoic acid;

(*2S*)-2-[4-chloro-2-(1,3-thiazol-2-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(3-methyl-1,2-oxazol-5-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1H-imidazol-2-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1H-imidazol-4-yl)phenoxy]propanoic acid;

(*2R*)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-chloro-2-(1,3-dimethyl-1H-pyrazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1H-pyrazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(thiophen-2-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-5-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1-methyl-1H-pyrazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1H-pyrazol-1-yl)phenoxy]propanoic acid;
(*2S*)-2-[4,5-dichloro-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]-3-cyclopropylpropanoic acid;
(*2S*)-2-[4-fluoro-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2R*)-2-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-chloro-2-(4-methyl-1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(5-cyclopropyl-1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]-3-methylbutanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]butanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-cyclopropylpropanoic acid;
(*2S*)-2-[4-chloro-2-(1,3-oxazol-2-yl)phenoxy]propanoic acid;
(*2R*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-bromo-2-(2H-1,2,3-triazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]-4-fluorobutanoic acid;
(*2S*)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-4-fluorobutanoic acid;
(*2R*)-2-[4-chloro-5-fluoro-2-(1,2-oxazol-5-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-bromo-2-(1,3-thiazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,3-oxazol-4-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-5-yl)phenoxy]-3-methylbutanoic acid;
(*2S*)-2-[4-chloro-2-(1,2-oxazol-5-yl)phenoxy]-3-cyclopropylpropanoic acid;
(*2R*)-2-[4-chloro-2-(1,2-oxazol-5-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-chloro-5-fluoro-2-(1,2-oxazol-5-yl)phenoxy]propanoic acid;

(*2S*)-2-[4-chloro-2-(1,2-oxazol-5-yl)phenoxy]butanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-4-yl)phenoxy]propanoic acid;
(*2R*)-2-[4-chloro-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-chloro-2-(1,3-oxazol-4-yl)phenoxy]propanoic acid;
2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]acetic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-2-cyclopropylacetic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]-2-cyclopropylacetic acid;
(*2S*)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-cyclopropylpropanoic acid;
2-[4-bromo-2-(4-methyl-1,2-oxazol-3-yl)phenoxy]acetic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,2-oxazol-5-yl)phenoxy]propanoic acid;
(*2S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-cyclobutylpropanoic acid;
(*2S*)-2-[4-bromo-5-fluoro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propanoic acid;
2-[4-bromo-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]acetic acid;
(*2S*)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]butanoic acid;
(*2R*)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-bromo-2-(1,3,4-thiadiazol-2-yl)phenoxy]propanoic acid;
2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]acetic acid;
(*2R*)-2-[4-bromo-5-fluoro-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropanoic acid;
(*2S*)-2-[4-chloro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,3-oxazol-5-yl)phenoxy]propanoic acid;
(2*S*)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-ethoxypropanoic acid;
2-[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]acetic acid; and
(2*S*)-2-[4-chloro-2-(1,2-thiazol-3-yl)phenoxy]propanoic acid.