

CLC-1 INHIBITORS FOR USE IN THE TREATMENT OF MULTIPLE
SCLEROSIS AND NEUROMUSCULAR DISEASES**Technical field**

The present disclosure relates to compounds capable of inhibiting the CLC-1 ion
5 channel for use in treating, ameliorating and/or preventing multiple sclerosis and other
neuromuscular diseases.

Background

Multiple sclerosis (MS) is the most common demyelinating disease, in which the
10 insulating covers of nerve cells in the brain and spinal cord are damaged. This damage
disrupts the ability of parts of the nervous system to transmit signals, resulting in a
range of signs and symptoms, including physical, mental, and sometimes psychiatric
problems. Specific symptoms can include double vision, visual loss, muscle weakness,
and trouble with sensation or coordination. MS takes several forms, with new
15 symptoms either occurring in isolated attacks (relapsing forms) or building up over time
(progressive forms). In the relapsing forms of MS, between attacks, symptoms may
disappear completely, although some permanent neurological problems often remain,
especially as the disease advances.

20 Multiple sclerosis is the most common immune-mediated disorder affecting the central
nervous system. Nearly one million people have MS in the United States in 2022, and
in 2020, about 2.8 million people were affected globally, with rates varying widely in
different regions and among different populations. The disease usually begins between
the ages of 20 and 50 and is twice as common in women as in men.

25 Several phenotypes (commonly termed "types"), or patterns of progression, have been
described. Phenotypes use the past course of the disease in an attempt to predict the
future course. They are important not only for prognosis, but also for treatment
decisions.

30 The International Advisory Committee on Clinical Trials of MS describes four types of
MS in what is known as the Lublin classification:

- Clinically isolated syndrome (CIS)
- Relapsing-remitting MS (RRMS)
- 35 • Primary progressive MS (PPMS)

- Secondary progressive MS (SPMS)

RRMS is characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits that occur during attacks may either resolve or leave problems, the latter in about 40% of attacks and being more common the longer a person has had the disease. This describes the initial course of 80% of individuals with MS.

The relapsing-remitting subtype usually begins with a clinically isolated syndrome (CIS). In CIS, a person has an attack suggestive of demyelination, but does not fulfil the criteria for multiple sclerosis. 30 to 70% of persons who experience CIS, later develop MS.

PPMS occurs in roughly 10–20% of individuals with the disease, with no remission after the initial symptoms. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements. The usual age of onset for the primary progressive subtype is later than of the relapsing-remitting subtype. It is similar to the age that secondary progressive usually begins in RRMS, around 40 years of age.

SPMS occurs in around 65% of those with initial RRMS, who eventually have progressive neurologic decline between acute attacks without any definite periods of remission. Occasional relapses and minor remissions may appear. The most common length of time between disease onset and conversion from RRMS to SPMS is 19 years.

No cure for multiple sclerosis is known although several disease-modifying treatments have been approved by regulatory agencies of different countries. Medications approved by the FDA include interferons beta-1a and beta-1b, monoclonal antibodies (e.g. natalizumab, alemtuzumab and ocrelizumab), and immunomodulators (e.g. glatiramer acetate, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, diroximel fumarate. Siponimod, Cladribine, Ozanimod).

None of these treatments though directly target or improve muscle weakness or coordination even though there is evidence for peripheral nervous system (PNS)

involvement in multiple sclerosis (Weir et al, 1979; Hopf and Eysholdt, 1978). Hopf and Eysholdt (1978) showed that the relative refractory period (RRP) of median nerve sensory fibers was significantly prolonged in MS patients. Weir et al, (1979) showed that 6 of 15 MS patients had clearly abnormal jitter when measured using single fibre electromyography (SFEMG) and a further five patients had borderline abnormalities of SFEMG.

Jitter is the variability in the arrival time of muscle fibre action potentials to the recording electrode between consecutive electrical discharges when measuring neuromuscular function using single fiber electromyography (sfEMG). Blocking is complete NMJ transmission failure of muscle fibre action potentials to the recording electrode between consecutive electrical discharges when measuring neuromuscular function using sfEMG.

Normalisation of jitter and/or reduction of block could improve neuromuscular function by ensuring that an increased number of muscle fibres in a muscle respond together at the same time thereby improving muscle force and control.

Accordingly, there is a need for safe and efficacious therapies to improve muscle function in patients with all forms of multiple sclerosis.

Summary

The present invention relates to CIC-1 inhibitors for use in the treatment, prevention and/or amelioration of multiple sclerosis and other neuromuscular diseases.

Description of Drawings

Figure 1

CIC-1 channel inhibition with NMD712 ((S)-2-(p-bromophenoxy)butyric acid) restores muscle function and NMJ transmission in a pharmacological rat model of neuromuscular dysfunction. The figure displays stimulated muscle force (A), compound muscle action potentials (CMAP) (B), jitter (C) and block (D) from rats before (white, pre- neuromuscular blocking agent (NMBA)) and during a constant infusion of NMBA to reach a stable level of decreased neuromuscular function (Grey, Control) relative to pre-NMBA. NMD712 was administered orally (50 mg/kg) and the four parameters were measured 60 minutes post-dose (checked). NMD712 resulted in a restoration of all four

measured parameters: muscle force (A), CMAP (B), jitter (C) and block (D). N=4 animals, values are MEAN $\pm$ SEM. *statistical significance based on 2-way ANOVA with multiple comparisons (** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

5 Figure 2

Figure 2 depicts the study design of a clinical observational study that enrolled patients with CMT types 1 and 2 and healthy age-matched controls at two study sites. Clinical tests are listed in the order of testing. CMTES2: CMT Examination Score2. RNS: Repetitive Nerve Stimulation. SFEMG: Single Fibre EMG. *CMTES2 only performed at
10 visit 1.

Figure 3

Figure 3 depicts jitter and blocking from visit 1 of a clinical observational study of healthy subjects and Charcot-Marie-Tooth (CMT) patients displayed as individual data
15 with medians for healthy controls and CMT patients (A and B) and for CMT1 and CMT2 patients (C and D). Mean Consecutive Difference (MCD).

Definitions

The nomenclature used in the present application is based on IUPAC systematic
20 nomenclature, unless indicated otherwise.

The terms "C₁₋₂ alkyl", "C₁₋₃ alkyl" and "C₁₋₅ alkyl" refers to a branched or unbranched alkyl group having from one to two, one to three or one to five carbon atoms respectively, including but not limited to methyl, ethyl, prop-1-yl, prop-2-yl, 2-methyl-prop-1-yl, 2-methyl-prop-2-yl, 2,2-dimethyl-prop-1-yl, but-1-yl, but-2-yl, 3-methyl-but-1-yl, 3-methyl-but-2-yl, pent-1-yl, pent-2-yl and pent-3-yl.
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The term "C₂ alkenyl" and "C₂₋₅ alkenyl" refers to a branched or unbranched alkenyl group having two or from two to five carbon atoms respectively, two of which are connected by a double bond, including but not limited to ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl and isopentenyl.
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The term "C₂ alkynyl" and "C₂₋₅ alkynyl" refers to a branched or unbranched alkynyl group having two or from two to five carbon atoms respectively, two of which are connected by a triple bond, including but not limited to ethynyl, prop-1-ynyl, prop-2-
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ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, buta-1,3-diynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, penta-2,4-diynyl and penta-1,3-diynyl.

5 The term "C₃₋₅ cycloalkyl" and "C₃₋₆ cycloalkyl" refers to a group having three to five or three to six carbon atoms respectively including a monocyclic or bicyclic carbocycle, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of C₃₋₅ cycloalkyl wherein one -CH₂- is replaced by -O- are oxiran-2-yl, oxetan-2-yl, oxetan-3-yl, oxolan-2-yl and oxolan-3-yl.

10 The term "C₁₋₂ alkoxy" refers to an alkyl group having from one to two carbon atoms attached to an oxygen atom, and binding is to the oxygen atom. Examples of C₁₋₂ alkoxy are methoxy and ethoxy.

15 The term "C₁₋₂ alkylthio" refers to an alkyl group having from one to two carbon atoms attached to a sulfur atom, and binding is to the sulfur atom. Examples of C₁₋₂ alkthio are methylthio and ethylthio.

20 The term "4-6 membered heterocycle" refers to a group having four, five or six carbon atoms respectively wherein between 1 and 3 carbon atoms in the ring have been replaced with a heteroatom selected from the group comprising nitrogen, sulphur and oxygen. Binding to the heterocycle may be at the position of the heteroatom or via a carbon atom of the heterocycle.

25 4-membered heterocycles include but are not limited to oxetane, azetidine and thietane.

30 5-membered heterocycles include but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, dihydrofuran, dihydrothiophene, 3-pyrroline, 2-pyrroline, 2-imidazoline, 2-pyrazolidine, dihydro-oxazole, dihydro-thiazole, dihydro-isoxazole, dihydro-isothiazole, dihydro-1,2,3-triazole, dihydro-1,2,4-triazole, dihydro-1,2,5-oxadiazole, dihydro-1,2,3-oxadiazole, dihydro-1,2,4-oxadiazole, dihydro-1,3,4-oxadiazole, dihydro-1,2,5-thiadiazole, dihydro-1,2,3-thiadiazole, dihydro-1,2,4-thiadiazole, dihydro-1,3,4-thiadiazole, tetrahydrofuran,

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5 tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, thiazolidine, isoxazolidine, isothiazolidine, 1,2,3-triazolidine, 1,2,4-triazolidine, 1,2,5-oxadiazolidine, 1,2,3-oxadiazolidine, 1,3,4-oxadiazolidine, 1,2,5-thiadiazolidine, 1,2,3-thiadiazolidine, 1,3,4-thiadiazolidine, 1,2-oxathiolane, 1,3-oxathiolane, 2-oxazolidinone and 2-pyrrolidinone.

6-membered heterocycles include but are not limited to pyridine, pyrazine, pyrimidine, pyridazine, tetrahydropyran, thiane, piperidine, 1, 4-dioxane, morpholine, 1,4-oxathiane, 1,4-diathiane and piperazine.

10

The term "5 membered aromatic heterocycle" refers to an aromatic group having five carbon atoms wherein between 1 and 3 carbon atoms in the ring have been replaced with a heteroatom selected from the group comprising nitrogen, sulphur and oxygen. Binding to the heterocycle may be at the position of the heteroatom or via a carbon atom of the heterocycle.

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5-membered aromatic heterocycles include but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, 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.

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25 The term "half-life" as used herein is the time it takes for the compound to lose one-half of its pharmacologic activity. The term "plasma half-life" is the time that it takes the compound to lose one-half of its pharmacologic activity in the blood plasma.

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30 The term "treatment" refers to the combating of a disease or disorder. "Treatment" or "treating," as used herein, includes any desirable effect on the symptoms or pathology of a disease or condition as described herein, and may include even minimal changes or improvements in one or more measurable markers of the disease or condition being treated. "Treatment" or "treating" does not necessarily indicate complete eradication or cure of the disease or condition, or associated symptoms thereof. In some embodiments, the term "treatment" encompasses amelioration and prevention.

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The term "amelioration" refers to moderation in the severity of the symptoms of a disease or condition. Improvement in a patient's condition, or the activity of making an effort to correct, or at least make more acceptable, conditions that are difficult to endure related to patient's conditions is considered "ameliorative" treatment.

The term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action.

The term "jitter" refers to the variability in the arrival time of action potentials to the recording electrode between consecutive electrical discharges when measuring neuromuscular function using single fiber electromyography (sfEMG). For example, jitter can be measured by calculating, with a recording electrode, the variation in the time interval between two action potentials of a same motor unit.

The term "blocking" refers to complete NMJ transmission failure of action potentials to the recording electrode between consecutive electrical discharges when measuring neuromuscular function using sfEMG. Blocking of neuromuscular transmission can be detected by determining the percentage of paired successful action potentials, from different muscle fibers of a same motor unit in a neuromuscular tissue, to the total number voluntary activations of said motor unit. For example, blocking can be detected by (i) first counting the number of paired successful action potentials from different muscle fibers of a same motor unit in a neuromuscular tissue, (ii) dividing the number of paired successful action potentials by the total number of action potentials occurring in at least one of the motor unit's muscle fibers and (iii) multiplying the result of the division by 100. If, for example, different pairs of muscle fibers of the same motor unit undergo 100 voluntary activations and 90 of the activations result in a detectable action potential in one but not the other muscle fiber, then the degree of blocking that motor unit suffers from is 10%.

Detailed description

Skeletal muscle specific CIC-1 chloride ion channels carry the inhibitory currents that counteract neuromuscular transmission. Inhibition of CIC-1 reduces the inhibitory current and thereby increases muscle membrane excitability and enhances neuromuscular transmission (Pedersen et al 2021). Administration of a CIC-1 inhibitor

will both normalise jitter and increase the probability of an action potential firing (i.e. reducing block) by making the muscle membrane more excitable. Reduction of block and normalisation of jitter will reduce the incidence of NMJ transmission failure and enhance muscle function thereby resulting in increased muscle strength and control.

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Thus, in a primary aspect, the present invention relates to CIC-1 inhibitors for use in the treatment, prevention and/or amelioration of multiple sclerosis and other neuromuscular diseases.

10 The compounds for use of the present disclosure comprise compounds capable of inhibiting the CIC-1 channel thereby improving or restoring neuromuscular function, i.e. the compounds are CIC-1 inhibitors. In one embodiment, the EC₅₀ of the compound is <50 µM, such as <40 µM, such as <30 µM, such as <20 µM, such as <15 µM, such as <10 µM, and such as <5 µM. The EC₅₀ of the compound may for example be
15 determined as described in Example 1.

In one embodiment, the recovery of force in muscles with neuromuscular dysfunction is >5%, for example >10%, for example >15%, for example >20%, for example >25%, for example >30% and for example >35%. The recovery of force in muscles with
20 neuromuscular dysfunction may for example be determined as described in Example 2.

In one embodiment, the compound may result in a positive shift in the half activation voltage of CIC-1 channels, $\Delta V_{1/2}$. The half activation voltage of CIC-1 channels may for example be determined as described in Example 3.

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In one embodiment, the compound may increase the tetanic force in an *in situ* muscle contractile experiment. The increase the tetanic force may for example be determined as described in Example 4.

CIC-1 inhibitors are for example described in WO 2016/202341, WO 2019/115777, WO
30 2019/115780, WO 2019/115781, EP19181263, WO 2020/254553, WO 2020/254558 and WO 2020/254559.

All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

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In one aspect, the present disclosure relates to a method of treating, preventing and/or ameliorating multiple sclerosis, said method comprising administering a CIC-1 inhibitor to a subject in need thereof. In one aspect, the present disclosure relates to a method of treating, preventing and/or ameliorating multiple sclerosis, said method comprising
5 administering a therapeutically effective amount of the compound for use as defined herein to a subject in need thereof. In one embodiment, the subject is a human being.

In one aspect, the present disclosure relates to use of a CIC-1 inhibitor for the manufacture of a medicament for the treatment, prevention and/or amelioration of
10 multiple sclerosis. In one aspect, the present disclosure relates to use of a compound as defined herein, for the manufacture of a medicament for the treatment, prevention and/or amelioration of multiple sclerosis.

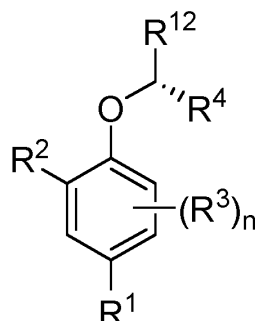
In one embodiment, the CIC-1 inhibitor restores contractile force in the muscles of the
15 subject. Contractile force *ex vivo* may for example be measured as described in Example 2 herein whilst contractile force in a clinical setting may for example be measured as described in Scott et al, 2011.

In one aspect, the present disclosure relates to a CIC-1 inhibitor for use in a method of
20 restoring contractile force in the muscles of a subject suffering from multiple sclerosis. In one aspect, the present disclosure relates to a method of restoring contractile force in the muscles of a subject suffering from multiple sclerosis, said method comprising administering a CIC-1 inhibitor to the subject in need thereof. In one aspect, the present disclosure relates to use of a CIC-1 inhibitor for the manufacture of a
25 medicament for restoring contractile force in the muscles of a subject suffering from multiple sclerosis. Contractile force *ex vivo* may for example be measured as described in Example 2 herein whilst contractile force in a clinical setting may for example be measured as described in Scott et al, 2011.

30 In one embodiment, the CIC-1 inhibitor reduces the incidence of NMJ transmission failure in the muscles of the subject. NMJ transmission failure may for example be measured as described in Example 5 herein whilst contractile force in a clinical setting may for example be measured as described in Scott et al, 2011.

- In one aspect, the present disclosure relates to a CIC-1 inhibitor for use in a method of reducing the incidence of NMJ transmission failure in the muscles of a subject suffering from multiple sclerosis. In one aspect, the present disclosure relates to a method of reducing the incidence of NMJ transmission failure in the muscles of a subject suffering from multiple sclerosis, said method comprising administering a CIC-1 inhibitor to the subject in need thereof. In one aspect, the present disclosure relates to use of a CIC-1 inhibitor for the manufacture of a medicament for reducing the incidence of NMJ transmission failure in the muscles of a subject suffering from multiple sclerosis.
- 10 In one embodiment, the CIC-1 inhibitor increases the probability of an action potential firing in the muscles of the subject. An increase in the probability of an action potential firing may be determined in a subject as described in Example 6 or as described by Weir et al, 1979.
- 15 In one aspect, the present disclosure relates to a CIC-1 inhibitor for use in a method of increasing the probability of an action potential firing in the muscles of a subject suffering from multiple sclerosis. In one aspect, the present disclosure relates to a method of increasing the probability of an action potential firing in the muscles of a subject suffering from multiple sclerosis, said method comprising administering a CIC-1 inhibitor to the subject in need thereof. In one aspect, the present disclosure relates to use of a CIC-1 inhibitor for the manufacture of a medicament for increasing the probability of an action potential firing in the muscles of a subject suffering from multiple sclerosis.
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- 25 In one embodiment, the CIC-1 inhibitor normalises jitter in the muscles of the subject. Normalisation of jitter in the muscles of the subject may be determined as described in Example 6.
- 30 In one aspect, the present disclosure relates to a CIC-1 inhibitor for use in a method of normalising jitter in the muscles of a subject suffering from multiple sclerosis. In one aspect, the present disclosure relates to a method of normalising jitter in the muscles of a subject suffering from multiple sclerosis, said method comprising administering a CIC-1 inhibitor to the subject in need thereof. In one aspect, the present disclosure relates to use of a CIC-1 inhibitor for the manufacture of a medicament for normalising jitter in the muscles of a subject suffering from multiple sclerosis.
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In some embodiments, the compound for use is a compound of Formula (I):



Formula (I)

5

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶,

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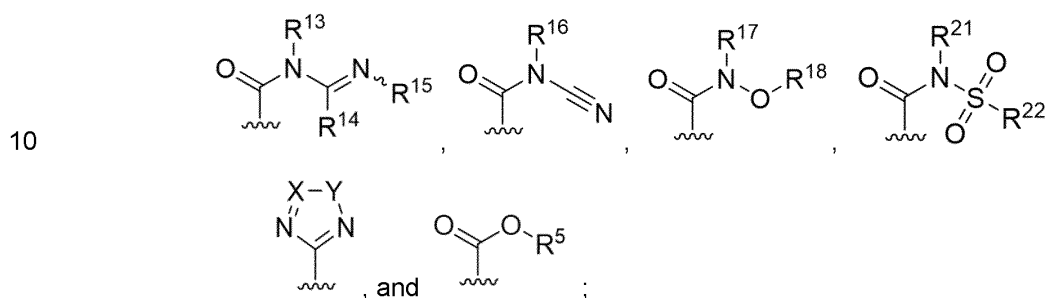
phenyl optionally substituted with one or more, identical or different, substituents R^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;

- R^6 is independently selected from the group consisting of deuterium and F;

5 - R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;

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

- R^{12} is selected from the group consisting of



- R^{13} is selected from the group consisting of H, C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;

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- R^{14} is selected from the group consisting of C_{1-5} alkyl optionally 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 and phenyl optionally substituted with one or more, identical or different, substituents R^8 ;

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- R^{15} is selected from the group consisting of $-OH$, $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;

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- R^{16} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different,

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- substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 5 - R^{17} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{20} , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl
- 10 optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{18} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{19} , C_{3-6} cycloalkyl optionally substituted with one or more, identical or different,
- 15 substituents R^{19} , phenyl optionally substituted with one or more, identical or different, substituents R^8 , and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- R^{19} is independently selected from the group consisting of F, Cl, Br, I, $-CN$, $=O$, C_{3-6} cycloalkyl optionally substituted with one or more, identical or
- 20 different, substituents R^6 , $-O-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-O-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-S-$
- 25 C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-S-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO-$
- 30 C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO_2-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different,
- 35 substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different substituents R^6 , $-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted

- with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{3-5}$ 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^8 , pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R^{20} and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- R^{20} is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{21} is selected from the group consisting of H, C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{22} is selected from the group consisting of C_{1-5} alkyl optionally 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 and phenyl optionally substituted with one or more, identical or different, substituents R^6 ;

- X is selected from the group consisting of N and CR^{23} ;

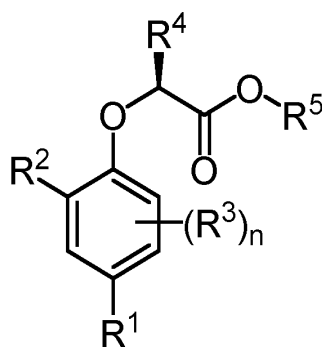
5 - Y is selected from the group consisting of NH, O and S;

- R^{23} is selected from the group consisting of H, NH_2 , C_{1-5} alkyl optionally 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 , $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 ;

15 - n is an integer 0, 1, 2, or 3;

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

In some embodiments, the compound for use is a compound of Formula (II):



20

Formula (II)

wherein:

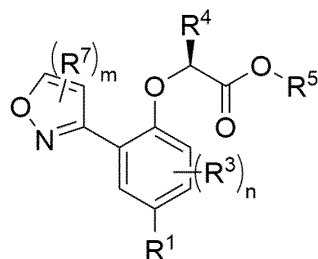
- R^1 is selected from the group consisting of F, Cl, Br and I;

25 - R^2 is a 5-membered aromatic heterocycle which may be optionally substituted with one or more, identical or different, substituents R^7 ;

- R^3 is selected from the group consisting of deuterium, F and Cl;

- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶,
- 10 phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- 15 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- n is an integer 0, 1, 2 or 3;
- 20 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In some embodiments, the compound for use is a compound of Formula (IX):



Formula (IX)

wherein:

- R¹ is selected from the group consisting of H, deuterium, F, Cl, Br and I, preferably Cl or Br;
- R³ is selected from the group consisting of deuterium, F, and Cl;

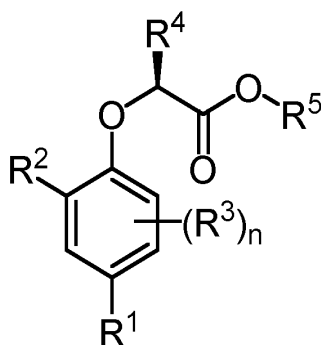
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₅ cycloalkenyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally
10 substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl and cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium,
15 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,
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or
solvate thereof.

20

In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, m is 2.

- In one embodiment, R¹ is selected from the group consisting of F, Cl, Br and I; R³ is selected from the group consisting of deuterium, F, and Cl; R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₅ cycloalkenyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶; R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl; R⁶ is independently selected from deuterium and F; and R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl, and
25 cyclopropyl.
30

In some embodiments, compound for use is a compound of Formula (II):

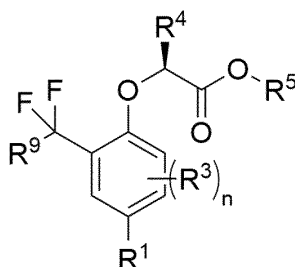


Formula (II)

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
 - R² is -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶
 - R³ is selected from the group consisting of deuterium, Cl and F
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁸ 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.

In some embodiments, the compound for use is a compound of Formula (X):



Formula (X)

wherein:

- 5 - R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F;
- 20 - R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- R⁹ is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶; and
- 25 - n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In one embodiment, the compound for use is of Formula (X) and:

- 30 - R¹ is selected from the group consisting of F, Cl, Br, and I;

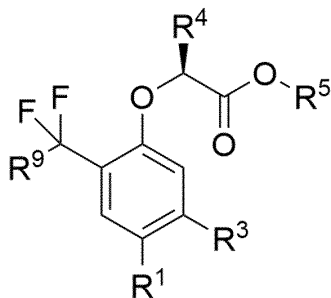
- R³ is selected from the group consisting of deuterium and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally
- 10 substituted with one or more, identical or different, substituents R^{B8}, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- 15 - R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- R⁹ is selected from the group consisting of C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶; and
- n is an integer 0, 1, 2, or 3;
- 20 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In one embodiment, the compound for use is of Formula (X) and:

- 25 - R¹ is selected from the group consisting of C₂ alkenyl, C₂ alkynyl, NO₂, F, Cl, Br, and I;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl and C₂₋₅ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 30 - R⁵ is H;
- R⁶ is independently selected from deuterium and F;
- R⁹ is C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶; and
- n is an integer 0, 1, 2, or 3;

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

In some embodiments, to the compound for use is a compound of Formula (XI):



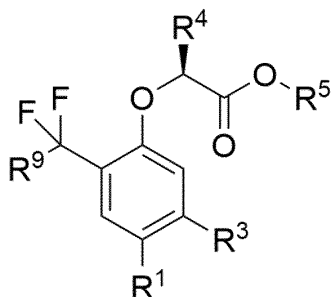
Formula (XI)

wherein:

- R¹ is selected from the group consisting of C₂ alkenyl, C₂ alkynyl, NO₂, F, Cl, Br, and I;
- R³ is selected from the group consisting of H, deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl and C₂₋₅ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R^{B8}, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from deuterium and F;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F; and
- R⁹ is C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶;

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

In some embodiments, the compound for use is a compound of Formula (XI):



Formula (XI)

5

wherein:

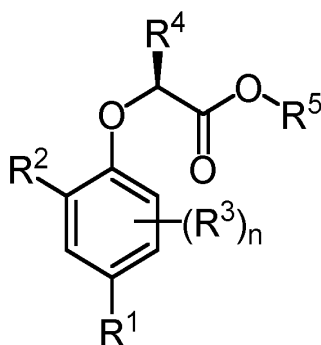
- R¹ is selected from the group consisting of C₂ alkynyl, NO₂, Cl, Br, and I;
 - R³ is selected from the group consisting of deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₃ alkyl and C₂₋₃ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is H;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - and
 - R⁹ is C₁₋₃ alkyl optionally be substituted with one or more, identical or different, substituents R⁶;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

15

In one embodiment, R⁹ is methyl. In one embodiment, R⁹ is ethyl. In one embodiment, R⁹ is n-propyl. In one embodiment, R⁹ is isopropyl. In one embodiment, R⁹ is cyclopropyl.

20

In some embodiments, the compound for use is a compound is of Formula (II):

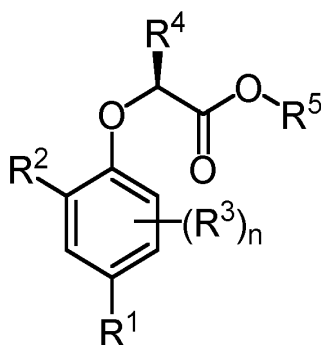


Formula (II)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br and I;
- R³ is selected from the group consisting of deuterium, Cl and F
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In some embodiments, the compound for use is a compound of Formula (II):

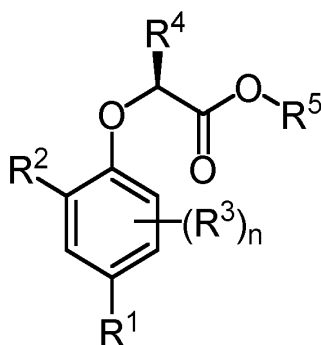


Formula (II)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br, and I;
- 5 - R² is selected from the group consisting of hydrogen, deuterium, F, Cl and Br;
- R³ is deuterium;
- R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₃₋₅ cycloalkyl, C₅ cycloalkenyl, each of which is substituted with one or
10 more, identical or different, substituents R⁶, and C₂₋₅ alkynyl, which may be optionally substituted with one or more, identical or different, substituents R⁶; and
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl
15 optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
20 and
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F; and
- n is 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or
25 solvate thereof.

In some embodiments, the compound for use is a compound of Formula (II):

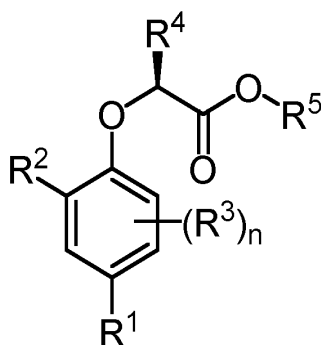


Formula (II)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br and I;
- 5 - R² is selected from the group consisting of hydrogen, deuterium, F, Cl, and Br;
- R³ is deuterium;
- R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, and C₅ cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R⁶; and
- 10 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F; and
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F; and
- 20 - n is 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

25 In some embodiments, the compound for use is a compound of Formula (II):

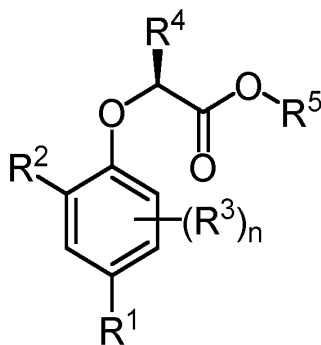


Formula (II)

wherein:

- R¹ is selected from the group consisting of H, Br, Cl, F and I;
 - R² is H;
 - R⁴ is selected from the group consisting of -CH₃, -CH₂-CH₃, -CH(CH₃)₂, -CH₂-F, -CH₂-CH₂F, and cyclopropyl;
 - R⁵ is H; and
 - n is 0,
- or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof.

In some embodiments, the compound for use is a compound of Formula (II):



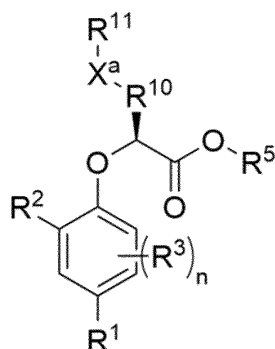
Formula (II)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br, I, -CN, and -CF₃;
- R² is selected from the group consisting of C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R³ is selected from the group consisting of deuterium, F, and Cl;

- R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ 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.

In some embodiments, the compound for use is a compound of Formula (XII):



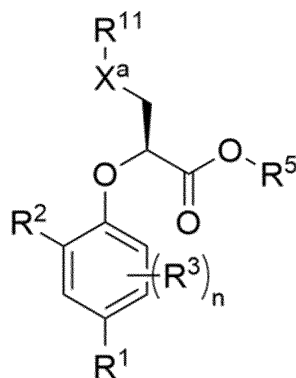
Formula (XII)

- wherein:
- R¹ is selected from the group consisting of F, Cl, Br and I;
 - R² is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;
 - R³ is selected from the group consisting of deuterium, Cl and F;
 - R¹⁰ is C₁₋₂ alkanediyl which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₆ cycloalkyl, each of which may be optionally substituted

with one or more, identical or different, substituents R^6 ; 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 ;

- 5 - R^{11} is C_{1-2} alkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^6 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
- 10 - n is an integer 0, 1, 2 or 3; and
- X^a is O or S;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

15 In some embodiments, the compound for use is a compound of Formula (XIII):



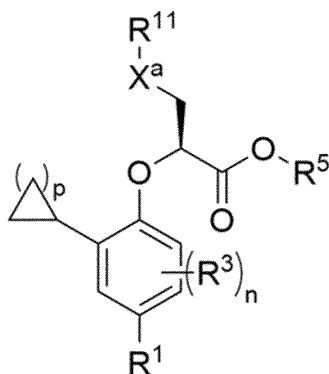
Formula (XIII)

wherein:

- 20 - R^1 is selected from the group consisting of Cl and Br;
- R^2 is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^3 is selected from the group consisting of deuterium and F;
- R^{11} is C_{1-2} alkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 25 - R^6 is independently selected from the group consisting of deuterium and F;
- n is an integer 0, 1, 2 or 3; and
- X^a is O or S;

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

In some embodiments, the compound for use is a compound of Formula (XIV):



Formula (XIV)

wherein:

- R¹ is selected from the group consisting of Cl and Br;
- R³ is selected from the group consisting of deuterium and F;
- R¹¹ is C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- p is an integer 1 or 2;
- n is an integer 0, 1, 2 or 3; and
- X^a is O or S;

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

In one embodiment, X^a is O. In one embodiment, X^a is S. In one embodiment, p is 1. In one embodiment, p is 2.

In one embodiment, R¹ is C₁₋₂ alkyl. In one embodiment, R¹ is C₂ alkenyl. In one embodiment, R¹ is C₂ alkynyl. In one embodiment, R¹ is CN. In one embodiment, R¹ is CF₃. In one embodiment, R¹ is NO₂. In one embodiment, R¹ is Cl or Br. In one embodiment, R¹ is F. In one embodiment, R¹ is Cl. In one embodiment, R¹ is Br. In one embodiment, R¹ is I.

In one embodiment, R² is H. In one embodiment, R² is deuterium. In one embodiment, R² is F. In one embodiment, R² is Cl. In one embodiment, R² is Br. In one embodiment, R² is I. In one embodiment, R² is C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R² is vinyl. In one
5 embodiment, R² is C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R² is ethynyl. In one embodiment, R² is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R² is cyclopropyl. In one embodiment, R² is cyclobutyl.

10 In one embodiment, R² is -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶. In one embodiment, R² is Me-CF₂-. In one embodiment, R² is Et-CF₂-. In one embodiment, R² is ⁿPr-CF₂-. In one embodiment, R² is ⁱPr-CF₂-. In one embodiment, R² is cyclopropyl-CF₂-.

15 In one embodiment, R² is 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷. In one embodiment, R² is selected from the group consisting of furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole. In one embodiment, R² is selected from the group consisting of thiophene, pyrrole, isoxazole, 1,2,4-oxadiazole and 1,3,4-oxadiazole. In one embodiment, R² 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 R⁷. In one embodiment, R² 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 R⁷. In one embodiment, R² is selected from isoxazol-5-yl and isoxazol-3-yl. In one embodiment, R² is 1,2-oxazol-3-yl. In one
25 embodiment, R² is 1,2-oxazol-4-yl. In one embodiment, R² is 1,2-oxazol-5-yl. In one
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embodiment, R² is 1,3-oxazol-2-yl. In one embodiment, R² is 1,3-oxazol-4-yl. In one embodiment, R² is 1,3-oxazol-5-yl. In one embodiment, R² is 1,2-thiazol-3-yl. In one embodiment, R² is 1,2-thiazol-4-yl. In one embodiment, R² is 1,2-thiazol-5-yl. In one embodiment, R² is 1,3-thiazol-2-yl. In one embodiment, R² is 1,3-thiazol-4-yl. In one embodiment, R² is 1,3-thiazol-5-yl. In one embodiment, R² is 1,2,3-thiadiazol-4-yl. In one embodiment, R² is 1,2,3-thiadiazol-5-yl. In one embodiment, R² is 1,2,4-thiadiazol-3-yl. In one embodiment, R² is 1,2,4-thiadiazol-5-yl. In one embodiment, R² is 1,3,4-thiadiazol-2-yl. In one embodiment, R² is 1,2,5-thiadiazol-3-yl. In one embodiment, R² is 1,2,3-oxadiazol-4-yl. In one embodiment, R² is 1,2,3-oxadiazol-5-yl. In one embodiment, R² is 1,2,4-oxadiazol-3-yl. In one embodiment, R² is 1,2,4-oxadiazol-5-yl. In one embodiment, R² is 1,3,4-oxadiazol-2-yl. In one embodiment, R² is 1,2,5-oxadiazol-3-yl.

In one embodiment, R³ is deuterium. In one embodiment, R³ is Cl. In one embodiment, R³ is F.

In one embodiment, R⁴ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is selected from the group consisting of methyl, ethyl, n-propyl and isopropyl. In one embodiment, R⁴ is selected from the group consisting of methyl, ethyl, n-propyl and isopropyl wherein the methyl, ethyl, n-propyl or isopropyl group is substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is Me. In one embodiment, R⁴ is Et. In one embodiment, R⁴ is -CH₂F. In one embodiment, R⁴ is -CH₂-CH₂F. In one embodiment, R⁴ is C₁₋₂ alkoxy-C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is C₁₋₂ alkylthio-C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is selected from the group consisting of MeOCH₂-, EtOCH₂-, MeSCH₂- and EtSCH₂-. In one embodiment, R⁴ is C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is prop-2-ynyl. In one embodiment, R⁴ is -CH₂-C₂₋₄ alkynyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R⁴ is selected from the group consisting of cyclopropyl and

cyclobutyl. In one embodiment, R⁴ is H. In one embodiment, R⁴ is deuterium. When R⁴ is H, the carbon to which R⁴ is bound is not a stereogenic centre.

5 In one embodiment, R⁵ is H. In one embodiment, R⁵ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁸. In one embodiment, R⁵ is C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁸. In one embodiment, R⁵ is phenyl optionally substituted with one or more, identical or different, substituents R⁸. In one embodiment, R⁵ is benzyl optionally substituted with one or more, identical or different, substituents R⁸.

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In one embodiment, R⁶ is deuterium. In one embodiment, R⁶ is F.

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In one embodiment, R⁷ is deuterium. In one embodiment, R⁷ is F. In one embodiment, R⁷ is selected from the group consisting of methyl, ethyl or cyclopropyl.

In one embodiment, R⁸ is deuterium. In one embodiment, R⁸ is methoxy. In one embodiment, R⁸ is nitro. In one embodiment, R⁸ is cyano. In one embodiment, R⁸ is Cl. In one embodiment, R⁸ is Br. In one embodiment, R⁸ is I. In one embodiment, R⁸ is F.

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In one embodiment, R¹³ is H. In one embodiment, R¹³ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹³ is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹³ is -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹³ is -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶.

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In one embodiment, R¹⁴ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁴ is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁴ is phenyl optionally substituted with one or more, identical or different, substituents R⁸.

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In one embodiment, R¹⁵ is -OH. In one embodiment, R¹⁵ is -OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment,

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R¹⁵ is -OC₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶.

5 In one embodiment, R¹⁶ is H. In one embodiment, R¹⁶ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁶ is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁶ is -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁶ is -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶.

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In one embodiment, R¹⁷ is H. In one embodiment, R¹⁷ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R²⁰. In one embodiment, R¹⁷ is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁷ is -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁷ is -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶.

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In one embodiment, R¹⁸ is H. In one embodiment, when R¹⁸ is H then R¹⁷ is not H. In one embodiment, R¹⁸ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R¹⁹. In one embodiment, R¹⁸ is C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R¹⁹. In one embodiment, R¹⁸ is phenyl optionally substituted with one or more, identical or different, substituents R⁸. In one embodiment, R¹⁸ is 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R²⁰.

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In one embodiment, R¹⁹ is F, Cl, Br or I. In one embodiment, R¹⁹ is -CN. In one embodiment, R¹⁹ is =O. In one embodiment, R¹⁹ is C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -O-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -O-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -S-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -S-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -SO-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -SO-C₃₋₅

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cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -SO₂-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -SO₂-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different substituents R⁶. In one embodiment, R¹⁹ is -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -NH-C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is -C(=O)-NH-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R¹⁹ is phenyl optionally substituted with one or more, identical or different, substituents R⁸. In one embodiment, R¹⁹ is pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R²⁰. In one embodiment, R¹⁹ is 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R²⁰.

In one embodiment, R²⁰ is F, Cl, Br or I. In one embodiment, R²⁰ is -CN. In one embodiment, R²⁰ is =O. In one embodiment, R²⁰ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶. In one embodiment, R²⁰ is -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶. In one

embodiment, R^{20} is $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .

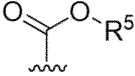
5 In one embodiment, R^{21} is H. In one embodiment, R^{21} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, R^{21} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, R^{21} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, R^{21} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .

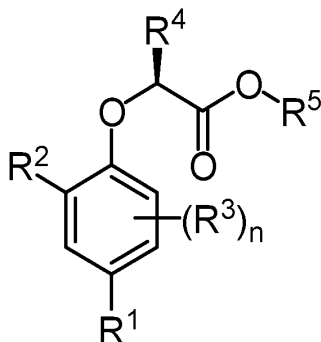
10 In one embodiment, R^{22} C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, R^{22} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, R^{22} is phenyl optionally substituted with one or more, identical or different, substituents R^8 .

15 In one embodiment, X is N. In one embodiment, X is CR^{23} wherein R^{23} is H. In one embodiment, X is CR^{23} wherein R^{23} is NH_2 . In one embodiment, X is CR^{23} wherein R^{23} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, X is CR^{23} wherein R^{23} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, X is CR^{23} wherein R^{23} is $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, X is CR^{23} wherein R^{23} is $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, X is CR^{23} wherein R^{23} is $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 . In one embodiment, X is CR^{23} wherein R^{23} is $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .

20 In one embodiment, Y is NH. In one embodiment, Y is O. In one embodiment, Y is S.

25 In one embodiment, n is 0. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3.

In one embodiment, R¹² is . In some embodiments, the compound for use is a compound of Formula (II):



Formula (II)

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wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more,

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identical or different, substituents R^6 , C_{3-6} 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^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;

- R^6 is independently selected from the group consisting of deuterium and F;

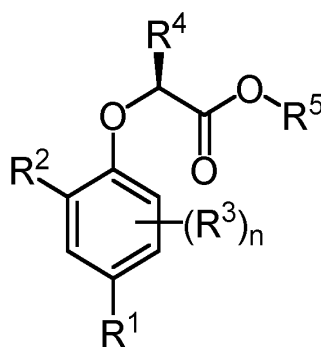
- R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;

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

- n is an integer 0, 1, 2, or 3;

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

In some embodiments, the compound for use is a compound of Formula (II):



Formula (II)

wherein:

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

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

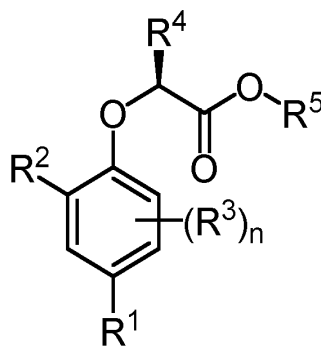
- R^3 is selected from the group consisting of deuterium, Cl and F

- R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{1-2} alkoxy- C_{1-2} alkyl, C_{1-2} alkylthio- C_{1-2} 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^6 ;

- 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^6 , C_{2-5} alkenyl

- optionally substituted with one or more, identical or different, substituents R^6 , C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-6} 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^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;
- 5 - R^6 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;
- 10 - n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
- 15 In one embodiment, R^1 is selected from the group consisting of Cl and Br, R^2 is selected from the group consisting of H, deuterium or F and R^4 is selected from the group consisting of Me, Et and $-CH_2F$.

In some embodiments, the compound for use is a compound of Formula (II):



Formula (II)

wherein:

- R^1 is selected from the group consisting of F, Cl, Br and I;
- R^2 is a 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R^7 ;
- 25 - R^3 is selected from the group consisting of deuterium, F, and Cl;

- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl and cyclopropyl;
 - R⁸ 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.

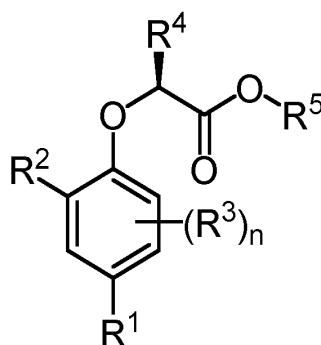
In some embodiments, when R¹ is F, Cl or Br, R² is 1,2-oxazol-5-yl, R⁴ is H, R⁵ is H and R⁶ is H then n is 1, 2 or 3.

In one embodiment, the compound for use is of Formula (II) and

- R¹ is selected from the group consisting of F, Cl, Br and I, preferably Cl or Br;
- R² 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 R⁷;
- R³ is selected from the group consisting of deuterium, F, and Cl;
- R⁴ is selected from the group consisting of C₁₋₅ alkyl and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, 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^7 is independently selected from the group consisting of H, deuterium, F, Cl, Br, I, C_{1-5} alkyl and C_{3-5} cycloalkyl;
 - 5 - R^6 is independently selected from 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 or 3;
 - or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or
 - 10 solvate thereof.

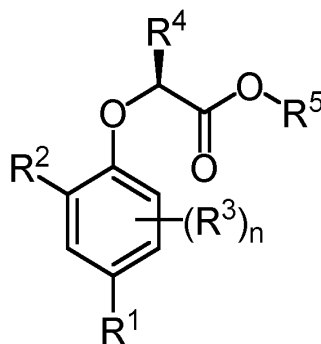
In some embodiments, the compound for use is a compound of Formula (II):



Formula (II)

- 15 wherein:
- R^1 is selected from the group consisting of F, Cl, Br and I;
 - R^2 is a 5-membered aromatic heterocycle which may be optionally substituted with one or more, identical or different, substituents R^7 ;
 - R^3 is selected from the group consisting of deuterium, F and Cl;
 - 20 - R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{1-2} alkoxy- C_{1-2} alkyl, C_{1-2} alkylthio- C_{1-2} 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^6 ;
 - R^5 is selected from the group consisting of H, C_{1-5} alkyl optionally substituted
 - 25 with one or more, identical or different, substituents R^6 , C_{2-5} alkenyl optionally substituted with one or more, identical or different, substituents R^6 , C_{2-5} alkynyl optionally substituted with one or more,

- identical or different, substituents R^6 , C_{3-6} 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^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;
- 5 - R^6 is independently selected from the group consisting of deuterium and F;
- R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- 10 - n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
- 15 In one embodiment, R^1 is selected from the group consisting of Cl and Br, R^2 is selected from the group consisting of 1,2-oxazol-3-yl, 1,2-oxazol-5-yl, 1,3-oxazol-4-yl and 1,2,3-thiadiazol-4-yl and R^4 is selected from the group consisting of Me, Et and -CH₂F.
- 20 In some embodiments, the compound for use is a compound of Formula (II):



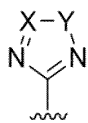
Formula (II)

wherein:

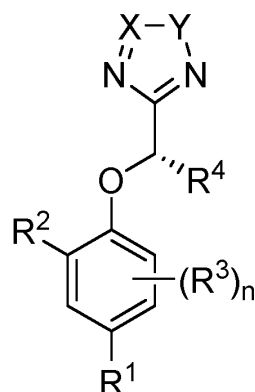
- R^1 is selected from the group consisting of C_{1-2} alkyl, C_2 alkenyl, C_2 alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- 25 - R^2 is -CF₂- C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6

- R³ is selected from the group consisting of deuterium, Cl and F
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
 - n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

In one embodiment, R¹ is selected from the group consisting of Cl and Br, R² is selected from the group consisting of -CF₂Me and -CF₂Et and R⁴ is selected from the group consisting of Me, Et and -CH₂F.



In one embodiment, R¹² is . In some embodiments, the compound for use is a compound of Formula (III):



Formula (III)

wherein:

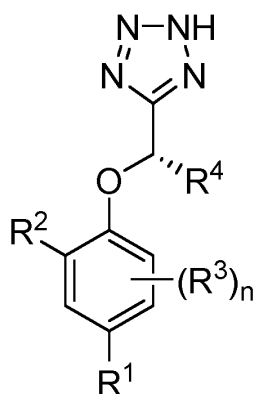
- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- X is selected from the group consisting of N and CR²³;
- Y is selected from the group consisting of NH, O and S;
- R²³ is selected from the group consisting of H, NH₂, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅

cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 ;

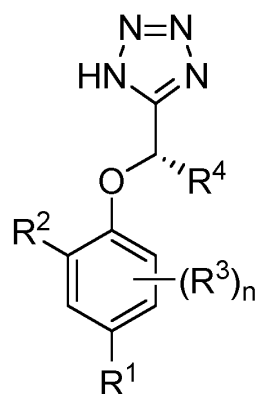
- n is an integer 0, 1, 2, or 3;

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

In one embodiment, the compound for use is of Formula (IVa) or Formula (IVb)



Formula (IVa)



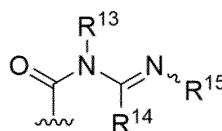
Formula (IVb)

wherein:

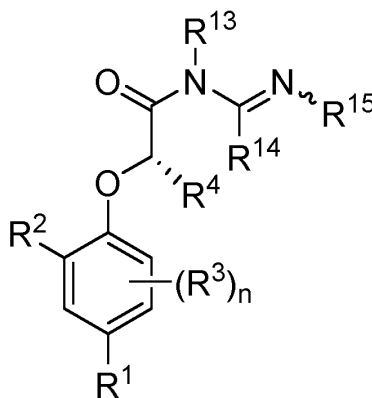
- R^1 is selected from the group consisting of C_{1-2} alkyl, C_2 alkenyl, C_2 alkynyl, CN, CF_3 , NO_2 , F, Cl, Br, and I;
- R^2 is selected from the group consisting of H, deuterium, F, Cl, Br, I, C_{2-5} alkenyl optionally be substituted with one or more, identical or different, substituents R^6 , 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 , $-CF_2-C_{1-5}$ alkyl optionally be substituted with one or more, identical or different, substituents R^6 , and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R^7 ;

- R³ is selected from the group consisting of deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
 - n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

It is understood by the skilled person that Formulas (IXa) and (IXb) are tautomers of each other.



In one embodiment, R¹² is . In some embodiments, the compound for use is a compound of Formula (V):



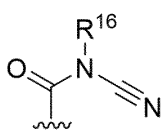
Formula (V)

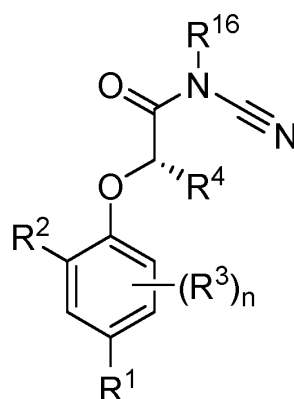
wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;

- 5 - R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 10 - R³ is selected from the group consisting of deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
 - R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- 20 - R¹³ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl
- 25 optionally substituted with one or more, identical or different, substituents R⁶;
- 30 - R¹⁴ is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶ and phenyl optionally substituted with one or more, identical or different, substituents R⁸;
- 35 - R¹⁵ is selected from the group consisting of -OH, -OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -OC₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;

- n is an integer 0, 1, 2, or 3;
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

5 In one embodiment, R¹² is . In some embodiments, the compound for use is a compound of Formula (VI):



Formula (VI)

wherein:

- 10 - R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 15
- 20 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and

C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;

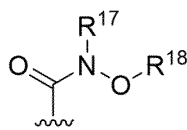
- R⁶ is independently selected from the group consisting of deuterium and F;

- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;

- R¹⁶ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;

- n is an integer 0, 1, 2, or 3;

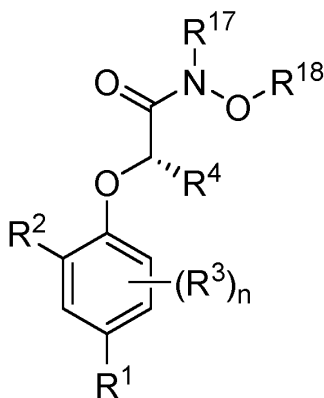
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.



In one embodiment, R¹² is

. In some embodiments, the compound for

use is a compound of Formula (VII)



Formula (VII)

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;

- 5 - R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 10 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- 20 - R¹⁷ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R²⁰, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl
- 25 optionally substituted with one or more, identical or different, substituents R⁶;
- 30 - R¹⁸ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R¹⁹, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R¹⁹, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R²⁰;
- 35 - R¹⁹ is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -O-C₁₋₅ alkyl optionally substituted with one or

more, identical or different, substituents R^6 , -O-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -S-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -S-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO₂-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO₂-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different substituents R^6 , -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₃₋₅ 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^8 , pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R^{20} and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;

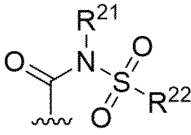
- R^{20} is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or

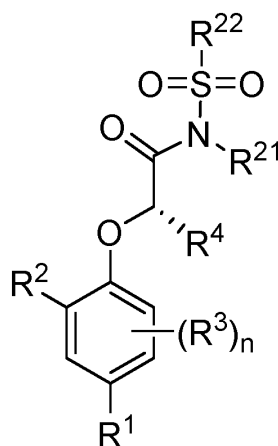
more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;

5 - n is an integer 0, 1, 2, or 3;

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

10

In one embodiment, R^{12} is . In some embodiments, the compounds for use is a compound of Formula (VIII)



Formula (VIII)

15

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 H, deuterium, F, Cl, Br, I, 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 , $-CF_2-$

20

- C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 5 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- 15 - R²¹ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl
- 20 optionally substituted with one or more, identical or different, substituents R⁶;
- R²² is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different,
- 25 substituents R⁶ and phenyl optionally substituted with one or more, identical or different, substituents R⁶;
- n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
- 30 In one embodiment, the compound for use is selected from the group consisting of:
- (S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
- (S)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]propionic acid;
- (R)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]-3-fluoropropionic acid;
- 35 (S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-methoxybutyric acid;

- (S)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-nitrophenoxy]propionic acid;
(R)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-(4-chloro-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
5 (S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
(S)-2-[2-(1,1-difluoropropyl)-5-fluoro-4-styrenyloxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-fluorobutyric acid;
10 (R)-2-[4,5-dichloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
(R)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-[4,5-dichloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-[2-(1,1-difluoroethyl)-4-ethynylphenoxy]propionic acid;
15 [4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]acetic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-tolyloxy]propionic acid;
[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]acetic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-styrenyloxy]propionic acid;
20 (R)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-(trifluoromethyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)(3,5,6-²H₃)phenoxy]propionic acid;
25 (S)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-cyano-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-ethynylphenoxy]propionic acid;
30 (R)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy](2-²H)propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-iodophenoxy]propionic acid;
(S)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-pentynoic acid;
35 (R)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;

- (S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
(S)-2-(4-bromo-2-cyclobutylphenoxy)-3-methoxypropionic acid;
(S)-2-[4-bromo-2-(cyclopropyldifluoromethyl)phenoxy]propionic acid;
(R)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
5 (S)-2-[4-bromo-2-(1,1-difluorobutyl)phenoxy]propionic acid;
(S)-[4-bromo-2-(1,1-difluoroethyl)phenoxy]cyclopropylacetic acid;
(S)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;
[4-bromo-2-(1,1-difluoropropyl)phenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]propionic acid;
10 (S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-3-methoxypropionic acid;
15 (S)-(4-bromo-2-cyclopropylphenoxy)cyclopropylacetic acid;
(S)-cyclopropyl(2,4-dibromophenoxy)acetic acid;
(S)-(4-bromo-2-chlorophenoxy)cyclopropylacetic acid;
(2R,3R)-2-(p-bromophenoxy)-3-fluorobutyric acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-ethoxypropionic acid;
20 [4-bromo-2-(1,3-oxazol-4-yl)phenoxy]acetic acid;
[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]acetic acid;
[4-chloro-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-[4-bromo-2-(5-isoxazolyl)phenoxy]cyclopropylacetic acid;
(S)-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]cyclopropylacetic acid;
25 (S,E)-2-(p-bromophenoxy)-4-fluoro-3-butenic acid;
(2R,3R)-2-(4-bromo-2-fluorophenoxy)-3-fluorobutyric acid;
(4-bromo-2-cyclopropylphenoxy)acetic acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-cyclopropylpropionic acid;
[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]acetic acid;
30 [4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-2-[4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclobutylpropionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
[4-bromo-2-(5-isoxazolyl)phenoxy]acetic acid;
35 (S)-2-(p-bromophenoxy)(2-²H)butyric acid;

- (S)-2-(p-bromophenoxy)-4-pentynoic acid;
[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]acetic acid;
(4-bromo-2-ethynylphenoxy)acetic acid;
(S)-2-(4-bromo-2-fluorophenoxy)valeric acid;
5 (S)-2-(2,4-dibromophenoxy)valeric acid;
(S)-2-(4-bromo-2-chlorophenoxy)valeric acid;
(S)-2-(p-bromophenoxy)-3-cyclopropylpropionic acid;
(S)-2-(2,4-dibromophenoxy)-4-pentynoic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-pentynoic acid;
10 (S)-(p-bromophenoxy)cyclopropylacetic acid;
(S)-2-(4-bromo-2-fluorophenoxy)-4-pentynoic acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]butyric acid;
(S)-2-(p-bromophenoxy)valeric acid;
(R)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-fluoropropionic acid;
15 (S)-2-[4-bromo-2-(1,3,4-thiadiazol-2-yl)phenoxy]propionic acid;
(S)-(4-bromo-2-chlorophenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-3-cyclopropylpropionic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-3-methylbutyric acid;
[4-bromo-2-(3-isoxazolyl)phenoxy]acetic acid;
20 (R)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
(S)-2-(p-bromophenoxy)-3-butenic acid;
(S)-2-[4-bromo-2-(1H-1,2,3-triazol-5-yl)phenoxy]propionic acid;
(2S)-2-(p-bromophenoxy)(3,4-²H₂)butyric acid;
25 (R)-2-(4-bromo-2-chlorophenoxy)-3-fluoropropionic acid;
(S)-2-(4-bromo-2-chlorophenoxy)butyric acid;
(S)-2-(4-bromo-3-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-fluorobutyric acid;
(S)-2-(p-ethynylphenoxy)-4-fluorobutyric acid;
30 (S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,3-oxazol-5-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
(R)-2-(p-bromophenoxy)-3-fluoro(2-²H)propionic acid;
35 (R)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;

- (S)-2-(4-bromo-5-fluoro-2-styrenyloxy)propionic acid;
(S)-2-[4-bromo-2-(1,3-thiazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-methylbutyric acid;
5 (S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(R)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)propionic acid;
(S)-2-[4-bromo-2-(2,2-difluoroethenyl)-5-fluorophenoxy]propionic acid;
10 (S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]butyric acid;
(S)-2-(4-bromo-2-iodophenoxy)-4-fluorobutyric acid;
(S)-(4-bromo-2-ethynylphenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-ethynyl-5-fluorophenoxy)propionic acid;
(S)-2-(4-chloro-2-ethynyl-5-fluorophenoxy)propionic acid;
15 (S)-2-[4-bromo-2-(4-isoxazolyl)phenoxy]propionic acid;
(R)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-(p-bromophenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-fluorophenoxy)-4-fluorobutyric acid;
20 (S)-2-(4-bromo-2-ethynylphenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-styrenyloxy)-4-fluorobutyric acid;
(S)-(4-bromo-2-fluorophenoxy)cyclobutylacetic acid;
(S)-2-[4-chloro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4,5-dichloro-2-(3-isoxazolyl)phenoxy]propionic acid;
25 (S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-(p-bromophenoxy)-4-fluorobutyric acid;
(S)-2-{2-[(E)-2-fluoroethenyl]-4-bromophenoxy}propionic acid;
(S)-2-[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
30 (S)-2-{2-[(E)-2-fluoroethenyl]-4-chlorophenoxy}propionic acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(R)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
35 (S)-2-[4-chloro-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;

- (S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]butyric acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
5 (S)-2-[4-chloro-2-(1,3-oxazol-2-yl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-iodophenoxy)-3-methylbutyric acid;
(S)-(4-bromo-2-fluorophenoxy)cyclopropylacetic acid;
(R)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(3-isothiazolyl)phenoxy]propionic acid;
10 (S)-2-(4-bromo-2-ethynylphenoxy)butyric acid;
(S)-2-(4-bromo-2-iodophenoxy)butyric acid;
(S)-2-(4-chloro-2-fluorophenoxy)butyric acid;
(S)-2-(p-bromophenoxy)butyric acid;
(S)-2-[4-bromo-2-(2,2-difluoroethenyl)phenoxy]propionic acid;
15 (S)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-fluorophenoxy)butyric acid;
20 (S)-2-[4-bromo-2-(5-methyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenoxy]propionic acid;
(R)-2-[p-bromo(3,5-²H₂)phenoxy]-3-fluoropropionic acid;
(S)-2-[p-bromo(3,5-²H₂)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;
25 ethyl (S)-2-(4-bromo-2-fluorophenoxy)-3-methyl-3-butenolate;
(R)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
(R)-2-[p-bromo(2,6-²H₂)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(1,3-thiazol-2-yl)phenoxy]propionic acid;
(S)-2-[p-bromo(2,6-²H₂)phenoxy]propionic acid;
30 (S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-methyl-5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-iodophenoxy)propionic acid;
(S)-2-[4-bromo-2-(2-imidazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(5-imidazolyl)phenoxy]propionic acid;
35 (R)-2-(4-bromo-2-cyclobutylphenoxy)-3-fluoropropionic acid;

- (*R*)-2-(4-bromo-2-fluorophenoxy)-3,3-difluoropropionic acid;
(*S*)-2-(4-bromo-2-ethynylphenoxy)propionic acid;
(*S*)-2-(2-bromo-4-chlorophenoxy)-3-methylbutyric acid;
(*S*)-2-(2-fluoro-4-iodophenoxy)propionic acid;
5 (*S*)-2-(2-bromo-4-iodophenoxy)propionic acid;
(*R*)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(*S*)-2-(2-chloro-4-iodophenoxy)propionic acid;
(*S*)-2-(2-bromo-4-chlorophenoxy)propionic acid;
(*S*)-2-(4-bromo-2-cyclopropylphenoxy)propionic acid;
10 (*S*)-2-(4-bromo-2-styrenyloxy)propionic acid;
(*S*)-2-[4-chloro-2-(1-methyl-3-methyl-4-pyrazolyl)phenoxy]propionic acid;
(*S*)-2-[4-chloro-2-(5-pyrazolyl)phenoxy]propionic acid;
(*S*)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]propionic acid;
(*S*)-2-(2-cyclopropyl-4-fluorophenoxy)propionic acid;
15 (*S*)-2-[4-chloro-2-(1-methyl-4-pyrazolyl)phenoxy]propionic acid;
(*S*)-2-(2-cyclobutyl-4-fluorophenoxy)propionic acid;
(*S*)-2-(4-bromo-2-cyclobutylphenoxy)propionic acid;
(*R*)-2-(4-bromo-2-fluorophenoxy)-3-fluoropropionic acid;
(*S*)-2-(4-chloro-2-fluorophenoxy)-3-methylbutyric acid;
20 (*S*)-2-(4-chloro-2-cyclobutylphenoxy)propionic acid;
(*S*)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]propionic acid;
(*R*)-2-(2-bromo-4-chlorophenoxy)-3-fluoropropionic acid;
(*R*)-2-(*p*-chlorophenoxy)-3-fluoropropionic acid;
(*R*)-2-(4-chloro-2-fluorophenoxy)-3-fluoropropionic acid;
25 (*R*)-2-(2,4-dibromophenoxy)-3-fluoropropionic acid;
(*S*)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]propionic acid;
(*R*)-2-(*p*-bromophenoxy)-3-fluoropropionic acid;
(*S*)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
(*S*)-2-(4-bromo-2-fluorophenoxy)propionic acid;
30 (*S*)-2-(4-chloro-2-fluorophenoxy)propionic acid;
(*S*)-2-(2,4-dibromophenoxy)propionic acid;
(*S*)-2-(4-chloro-2-ethynylphenoxy)propionic acid;
(*S*)-2-(4-chloro-2-styrenyloxy)propionic acid;
(*S*)-2-(4-chloro-2-cyclopropylphenoxy)propionic acid;
35 (*S*)-2-(*p*-chlorophenoxy)butyric acid;

- sodium (S)-2-(2,4-dichlorophenoxy)propionate;
(S)-2-(p-chlorophenoxy)-3-methylbutyric acid;
(S)-2-(p-cyanophenoxy)propionic acid;
methyl (S)-2-(p-bromophenoxy)propionate;
5 methyl (S)-2-(p-chlorophenoxy)butyrate;
isopropyl (S)-2-(p-chlorophenoxy)propionate;
methyl (S)-2-(p-chlorophenoxy)propionate,
(2S)-2-(4-bromo-2-fluorophenoxy)-N-{1-
[(cyclopropylmethoxy)imino]ethyl}propanamide;
10 (2S)-2-(4-bromophenoxy)-N-[1-(methoxyimino)ethyl]propanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[(4-fluorophenyl)(hydroxyimino)methyl]-3-
methylbutanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]-3-
methylbutanamide;
15 (2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;
(2S)-2-(4-bromophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-cyanopropanamide;
(2S)-N-cyano-2-(2,4-dibromophenoxy)propanamide;
(2S)-2-(4-bromophenoxy)-N-cyanopropanamide;
20 (2S)-2-(4-chlorophenoxy)-N-cyanopropanamide;
(2S)-2-(4-bromophenoxy)-N-cyano-3-methylbutanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-methoxypropanamide;
(2S)-N-acetyl-N-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
25 (2S)-N-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-N-(azetidin-3-yloxy)-2-(4-chlorophenoxy)propanamide;
(2S)-N-acetyl-N-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-
chlorophenoxy)propanamide;
(2S)-N-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-chlorophenoxy)propanamide;
30 (2S)-N-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
tert-butyl N-(2-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}propyl)carbamate;
(2S)-N-acetyl-2-(4-chlorophenoxy)-N-[(1-acetamidopropan-2-
yl)oxy]propanamide;
(2S)-2-(4-bromophenoxy)-N-(pyrrolidin-3-yloxy)propanamide;

- (2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
tert-butyl 3-([(2S)-2-(4-chlorophenoxy)propanamido]oxy)azetidine-1-carboxylate;
- 5 (2S)-2-(4-chlorophenoxy)-*N*-[(pyrrolidin-3-yl)methoxy]propanamide;
tert-butyl 3-([(2S)-2-(4-chlorophenoxy)propanamido]oxy)methyl)pyrrolidine-1-carboxylate;
(2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
- 10 (2S)-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(pyrrolidin-3-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2,2-dimethylpropyl)-*N*-hydroxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(pyrrolidin-1-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(2-oxopyrrolidin-1-yl)ethoxy]propanamide;
- 15 (2S)-*N*-acetyl-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(4,4,4-trifluoro-2-methylbutoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(3-cyclopentylpropyl)-*N*-hydroxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(2E)-2-methyl-3-phenylprop-2-en-1-
- 20 yl]oxy}propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-oxo-2-[2-(trifluoromethyl)pyrrolidin-1-yl]ethoxy]propanamide;
tert-butyl *N*-[2-([(2S)-2-(4-chlorophenoxy)propanamidyl]oxy)ethyl]carbamate;
(2S)-2-(4-chlorophenoxy)-*N*-[(2-methyl-1H-imidazol-4-
- 25 yl)methoxy]propanamide;
tert-butyl 4-([(2S)-2-(4-chlorophenoxy)propanamido]oxy)methyl)-2-methyl-1H-imidazole-1-carboxylate;
- (2S)-2-(4-bromo-2-fluorophenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-bromophenoxy)-*N*-cyclobutoxypropanamide;
- 30 (2S)-2-(4-chlorophenoxy)-*N*-[2-oxo-2-(pyrrolidin-1-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[1-(4-fluorophenyl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[1-(1,3-thiazol-2-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-{1-[4-(trifluoromethyl)phenyl]ethoxy}propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-methanesulfinylethoxy)propanamide;
- 35 (2S)-2-(4-chlorophenoxy)-*N*-(2-methanesulfonylethoxy)propanamide;

- (2S)-2-(4-chlorophenoxy)-*N*-[(1,2-oxazol-3-yl)methoxy]propanamide;
(2S)-2-(4-chloro-2-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-*N*-
(cyclopropylmethoxy)propanamide;
5 (2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-*N*-
(cyclopropylmethoxy)propanamide;
(2S)-*N*-(tert-butoxy)-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(methylsulfonyl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(1-phenylethoxy)propanamide;
10 (2S)-2-(4-chlorophenoxy)-*N*-[(1-methyl-1H-imidazol-2-
yl)methoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-methoxyethoxy)propanamide;
(2S)-2-(4-chloro-2-fluorophenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-*N*-methoxypropanamide;
15 (2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-*N*-methoxypropanamide;
(2S)-*N*-(benzyloxy)-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(2-methoxycyclopentyl)oxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-5-methylhexanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-*N*-methylpropanamide;
20 (2S)-2-(4-chloro-2-methylphenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-chloro-2-methylphenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-4-methylpentanamide;
25 (2S)-2-(4-chlorophenoxy)-*N*-[(3-methylbut-2-en-1-yl)oxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxyhexanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(1,3-oxazol-2-yl)methoxy]propanamide;
(2S)-2-(2,4-dibromophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-*N*-methoxypropanamide;
30 (2S)-2-(4-chlorophenoxy)-*N*-(oxan-2-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(1,3-thiazol-2-yl)methoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(3,3-difluorocyclobutoxy)propanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-methoxypropanamide;
35 (2S)-2-(4-chlorophenoxy)-*N*-(cyclopentylloxy)propanamide;

- (2S)-2-(4-chlorophenoxy)-N-(2-cyclopentylethoxy)propanamide;
(2S)-2-(4-bromo-2-chlorophenoxy)-N-methoxypropanamide;
(2S)-2-(4-bromo-2-methylphenoxy)-N-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-(cyclopropylmethoxy)propanamide;
5 (2S)-2-(4-chlorophenoxy)-N-(cyclobutylmethoxy)propanamide;
(2S)-N-(2-aminoethoxy)-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-bromophenoxy)-N-methoxy-3-methylbutanamide;
methyl 2-[[2-(2S)-2-(4-chlorophenoxy)propanamido]oxy]acetate;
(2S)-2-(4-chlorophenoxy)-N-[2-(2-methoxyethoxy)ethoxy]propanamide;
10 (2S)-2-(4-chlorophenoxy)-N-cyclobutoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-(2-hydroxyethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-ethoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-propoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-(propan-2-yloxy)propanamide;
15 (2S)-2-(4-chlorophenoxy)-N-methoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-(cyclopropanesulfonyl)propanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-(cyclopropanesulfonyl)propanamide;
20 (2S)-2-(4-chlorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromophenoxy)-N-methanesulfonyl-3-methylbutanamide;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)propyl]-2H-1,2,3,4-tetrazole;
25 5-[(1S)-1-(4-bromo-2-fluorophenoxy)-2-methylpropyl]-2H-1,2,3,4-tetrazole;
5-[(1R)-1-(4-bromophenoxy)-2-fluoroethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromophenoxy)propyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
30 5-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-cyclopropylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-ethenylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
35 5-[(1S)-1-(4-chloro-2-ethylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;

- 5-[(1S)-1-(4-chloro-2-methylphenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chlorophenoxy)ethyl]-1H-1,2,3,4-tetrazole;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-yl}acetamide;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-yl}methanesulfonamide;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-amine;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}acetamide;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}methanesulfonamide;
3-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4H-1,2,4-triazole;
3-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4H-1,2,4-triazole;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methoxy-1,2,4-oxadiazole;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-amine;
3-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4H-1,2,4-triazole;
3-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4H-1,2,4-triazole;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methyl-4H-1,2,4-triazole;
5-[(1S)-1-(4-chlorophenoxy)ethyl]-1H-1,2,4-triazole;
(2S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-*N*-cyanopropanamide;
(2S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-*N*-cyanopropanamide;
(2S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-methanesulfonylpropanamide;
(2S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-(cyclopropanesulfonyl)propenamide;
5-[(1S)-1-[4-bromo-2-(1,1-difluoroethyl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,1-difluoropropyl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-cyclobutylphenoxy)-2-methoxyethyl]-1H-1,2,3,4-tetrazole; and
5-[(1S)-1-(4-bromo-2-cyclopropylphenoxy)-2-methoxyethyl]-1H-1,2,3,4-tetrazole,

or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure relates to a method for treating a neuromuscular disorder comprising at least one or more of: subjecting different muscle fibers of the same motor unit in a neuromuscular tissue of a patient being examined for the neuromuscular disorder to a number of activations; detecting, with a medical device
5 and a recording electrode, the number of paired successful action potentials from the number of activations; determining whether the patient is suffering from or at risk of blocking by dividing the number of paired successful action potentials over a total number of activations; and, when the number of paired successful action potentials over the total number of activations is below a threshold of 95%, administering a CIC-1
10 inhibitor to the patient, wherein the administering of the CIC-1 inhibitor increases the number of paired successful action potentials over the total number of activations by at least 5%.

A 'paired successful action potential' is when voluntary activation of the muscle elicits
15 an action potential in two muscle fibers of the same motor unit with a recording electrode. It can be measured as time (jitter) and/or the success in eliciting an action potential in both muscle fibers (block). A motor unit can be defined as 'one motor neuron and all of its associated muscle fibers'.

20 Examples of a medical device and a recording electrode are a clinical electrodiagnostic system are the Cadwell Sierra Wave (Kennewick, WA, USA), a concentric needle recording electrode (25 mm X 30 gauge, Dantec) and 1–10 kHz for high- and low-pass filter settings.

25 Examples of neuromuscular tissue of a patient being examined are the abductor pollicis brevis muscle, the trapezius muscle, the frontalis muscle and the extensor digitorum muscle.

In exemplary embodiments, the method comprises administering the CIC-1 inhibitor to
30 the patient when the number of paired successful action potentials over the total number of activations is below a threshold of 90%, below a threshold of 85%, below a threshold of 80%, below a threshold of 75%, below a threshold of 70%, below a threshold of 65%, below a threshold of 60%, below a threshold of 55% or below a threshold of 50%.

35

In exemplary embodiments, the administering of the CIC-1 inhibitor increases the number of paired successful action potentials over the total number of activations by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 50%, at least 75%, any percentage or range of percentages between 5% and 75%, any percentage
5 or range of percentages between 10% and 50%, or any percentage or range of percentages between 10% and 30%.

In exemplary embodiments, the administering of the CIC-1 inhibitor to the patient restores contractile force of the patient's muscles by at least 5%, by at least 10%, at
10 least 15%, at least 20%, at least 25%, at least 30%, at least 50%, at least 75%, at least 100%, at least 150%, at least 200%, any percentage or range of percentages between 10% and 400%, any percentage or range of percentages between 15% and 200%, or any percentage or range of percentages between 20% and 100%.

15 In exemplary embodiments, the administering of the CIC-1 inhibitor to the patient reduces incidence of neuromuscular junction transmission failure in the patient's muscles by at least 5%, by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 50%, at least 75%, any percentage or range of percentages between 5% and 75%, any percentage or range of percentages between 10% and
20 50%, or any percentage or range of percentages between 10% and 30%.

In one aspect, the present disclosure relates to a method for treating a neuromuscular disorder comprising at least one or more of: acquiring, with a medical device and a recording electrode, a variation in a time interval between two action potentials of the
25 same motor unit in a neuromuscular tissue of a patient being examined for the neuromuscular disorder; determining whether the variation in the time interval between the two action potentials of the same motor unit exceeds or meets a threshold of 40 μ s; and administering a CIC-1 inhibitor to the patient when the variation in the time interval between the two action potentials exceeds or meets the threshold, wherein the
30 administering of the CIC-1 inhibitor reduces the variation in the time interval between the two action potentials between consecutive electrical discharges by at least 10%.

In exemplary embodiments, the method comprises determining whether the variation in the time interval between the two action potentials of the same motor unit exceeds or
35 meets a threshold of at least 40 μ s, of at least 45 μ s, of at least 50 μ s, of at least 55 μ s,

of at least 60 μ s, of at least 65 μ s, of at least 70 μ s, of at least 75 μ s, of at least 80 μ s, of at least 85 μ s, of at least 90 μ s, of at least 95 μ s, of at least 100 μ s, of at least 150 μ s, of at least 200 μ s or of at least 250 μ s.

- 5 In exemplary embodiments, the administering of the CIC-1 inhibitor reduces the variation in the time interval between the two action potentials between consecutive electrical discharges by at 5 μ s, at least 10 μ s, at least 15 μ s, at least 20 μ s, at least 25 μ s, at least 30 μ s, at least 40 μ s, at least 50 μ s, at least 75 μ s, at least 100 μ s, any point or range between 5 μ s and 200 μ s, any point or range between 5 μ s and 100 μ s
- 10 or any point or range between 10 μ s and 50 μ s.

In exemplary embodiments, the variation in the time interval between two action potentials is measured using single fiber electromyography (SFEMG).

- 15 In exemplary embodiments, the administering of the CIC-1 inhibitor to the patient reduces the variation in the time interval between the two action potentials between consecutive electrical discharges by at least 15%, at least 20%, at least 25%, at least 30%, at least 50%, at least 75%, at least 100%, at least 150%, at least 200%, any percentage or range of percentages between 10% and 400%, any percentage or range
- 20 of percentages between 15% and 200%, or any percentage or range of percentages between 20% and 100%.

In exemplary embodiments, the methods for treating a neuromuscular disorder can also be used to prevent and/or ameliorate the neuromuscular disorder.

- 25 In exemplary embodiments, the neuromuscular disorder is at least one of the following: sarcopenia, myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenic syndrome, seronegative myasthenia gravis, muscle specific kinase myasthenia gravis (MuSK-MG), Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM),
- 30 Charcot-Marie Tooth disease, diabetic polyneuropathy, periodic paralysis, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy, Duchenne muscular dystrophy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, metabolic myopathy,

Kennedy's disorder, multiple sclerosis and multifocal motor neuropathy. In other exemplary embodiments, the neuromuscular disorder is multiple sclerosis.

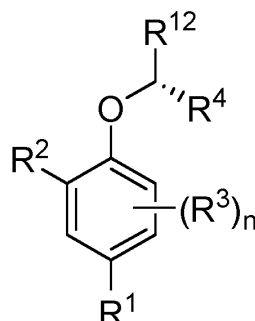
Any one of the CIC-1 inhibitors disclosed herein can be used in the disclosed methods.

5

Items

1. A compound for use in the treatment, prevention and/or amelioration of multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
- 10 2. A compound for use in a method of restoring contractile force in the muscles of a subject suffering from multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
3. A compound for use in a method of reducing the incidence of NMJ transmission failure in the muscles of a subject suffering from multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
- 15 4. A compound for use in a method of increasing the probability of an action potential firing in the muscles of a subject suffering from multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
- 20 5. A compound for use in a method of normalising jitter in the muscles of a subject suffering from multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
6. The compound for use according to item 1, wherein the CIC-1 inhibitor restores contractile force in the muscles of the subject.
7. The compound for use according to any one of the preceding items, wherein the CIC-1 inhibitor reduces the incidence of NMJ transmission failure in the muscles of the subject.
- 25 8. The compound for use according to any one of the preceding items, wherein the CIC-1 inhibitor increases the probability of an action potential firing in the muscles of the subject.
9. The compound for use according to any one of the preceding items, wherein the CIC-1 inhibitor normalises jitter in the muscles of the subject.
- 30

10. The compound for use according to any one of the preceding items, wherein the compound is of Formula (I):



Formula (I)

5

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶,

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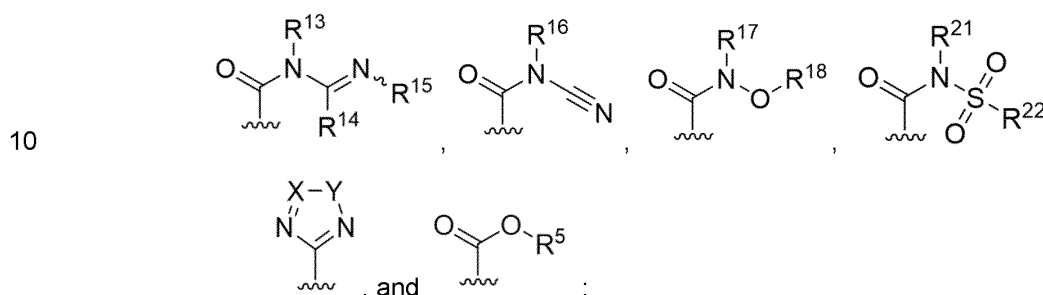
phenyl optionally substituted with one or more, identical or different, substituents R^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;

- R^6 is independently selected from the group consisting of deuterium and F;

5 - R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;

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

- R^{12} is selected from the group consisting of:



- R^{13} is selected from the group consisting of H, C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;

15

- R^{14} is selected from the group consisting of C_{1-5} alkyl optionally 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 and phenyl optionally substituted with one or more, identical or different, substituents R^8 ;

20

- R^{15} is selected from the group consisting of -OH, $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;

25

- R^{16} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different,

30

- substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 5 - R^{17} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{20} , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl
- 10 optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{18} is selected from the group consisting of H, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{19} , C_{3-6} cycloalkyl optionally substituted with one or more, identical or different,
- 15 substituents R^{19} , phenyl optionally substituted with one or more, identical or different, substituents R^8 , and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- R^{19} is independently selected from the group consisting of F, Cl, Br, I, $-CN$, $=O$, C_{3-6} cycloalkyl optionally substituted with one or more, identical or
- 20 different, substituents R^6 , $-O-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-O-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-S-$
- 25 C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-S-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO-$
- 30 C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-SO_2-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different,
- 35 substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different substituents R^6 , $-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted

- with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{3-5}$ 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^8 , pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R^{20} and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- R^{20} is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{21} is selected from the group consisting of H, C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- R^{22} is selected from the group consisting of C_{1-5} alkyl optionally 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 and phenyl optionally substituted with one or more, identical or different, substituents R^6 ;

- X is selected from the group consisting of N and CR^{23} ;

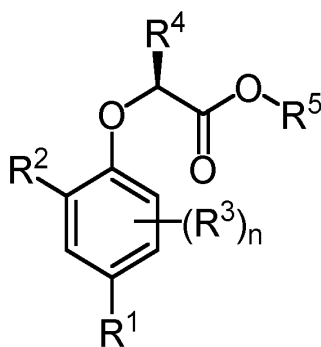
5 - Y is selected from the group consisting of NH, O and S;

- R^{23} is selected from the group consisting of H, NH_2 , C_{1-5} alkyl optionally 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 , $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 ;

15 - n is an integer 0, 1, 2, or 3;

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

11. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (II):



20

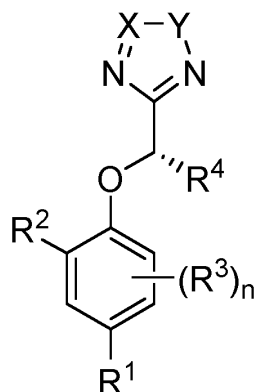
Formula (II)

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;

25 - R^2 is selected from the group consisting of H, deuterium, F, Cl, Br, I, 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 , $-CF_2-$ C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6 , and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R^7 ;
- 5
- 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_{1-2} alkoxy- C_{1-2} alkyl, C_{1-2} alkylthio- C_{1-2} 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^6 ;
 - 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^6 , C_{2-5} alkenyl optionally substituted with one or more, identical or different, substituents R^6 , C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-6} 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^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;
 - R^6 is independently selected from the group consisting of deuterium and F;
 - R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl and cyclopropyl;
 - R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
 - n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
12. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (III):



Formula (III)

wherein:

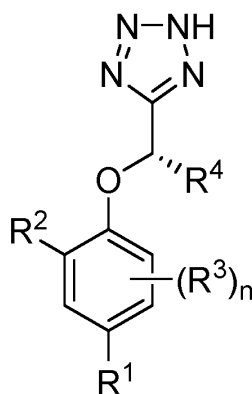
- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- X is selected from the group consisting of N and CR²³;
- Y is selected from the group consisting of NH, O and S;
- R²³ is selected from the group consisting of H, NH₂, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅

cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 ; and

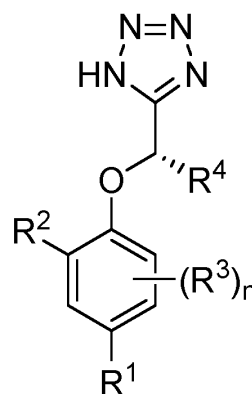
- n is an integer 0, 1, 2, or 3;

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

13. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (IVa) or Formula (IVb):



Formula (IVa)



Formula (IVb)

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 H, deuterium, F, Cl, Br, I, 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 , $-CF_2-C_{1-5}$ alkyl optionally be substituted with one or more, identical or different, substituents R^6 , and 5-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;

5 - R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{1-2} alkoxy- C_{1-2} alkyl, C_{1-2} alkylthio- C_{1-2} 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^6 ;

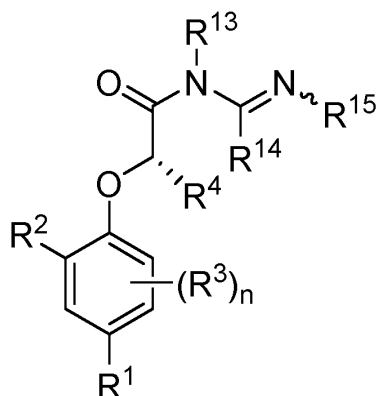
- R^6 is independently selected from the group consisting of deuterium and F;

10 - R^7 is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl; and

- n is an integer 0, 1, 2, or 3;

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

15 14. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (V):



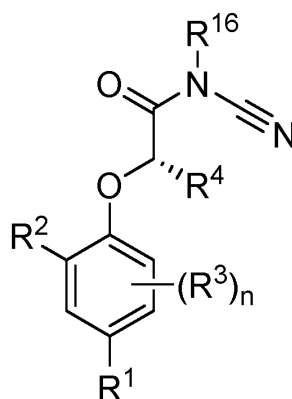
Formula (V)

wherein:

20 - 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;

25 - R^2 is selected from the group consisting of H, deuterium, F, Cl, Br, I, 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 , $-CF_2-$

- C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 5 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- 15 - R¹³ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl
- 20 optionally substituted with one or more, identical or different, substituents R⁶;
- R¹⁴ is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different,
- 25 substituents R⁶ and phenyl optionally substituted with one or more, identical or different, substituents R⁶;
- R¹⁵ is selected from the group consisting of -OH, -OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -OC₃₋₅ cycloalkyl optionally substituted with one or more, identical or
- 30 different, substituents R⁶; and
- n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
15. The compound for use according to any one of items 1 to 9, wherein the
- 35 compound is of Formula (VI):



Formula (VI)

wherein:

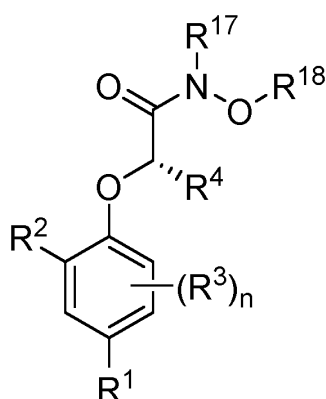
- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R¹⁶ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more,

identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ; and

- n is an integer 0, 1, 2, or 3;

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

16. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (VII):



Formula (VII)

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;

15 - R^2 is selected from the group consisting of H, deuterium, F, Cl, Br, I, 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 , $-CF_2-$ C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6 , and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R^7 ;

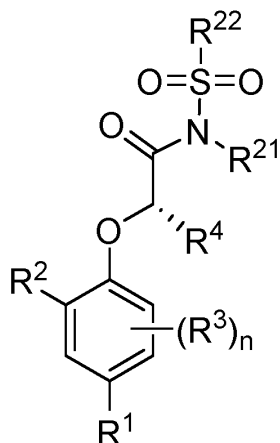
- R^3 is selected from the group consisting of deuterium, Cl and F;

25 - R^4 is selected from the group consisting of H, deuterium, C_{1-5} alkyl, C_{1-2} alkoxy- C_{1-2} alkyl, C_{1-2} alkylthio- C_{1-2} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, and

- C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F,
5 methyl, ethyl or cyclopropyl;
 - R⁸ is independently selected from the group consisting of deuterium,
methoxy, nitro, cyano, Cl, Br, I, and F;
 - R¹⁷ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted
with one or more, identical or different, substituents R²⁰, C₃₋₅ cycloalkyl
10 optionally substituted with one or more, identical or different,
substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more,
identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl
optionally substituted with one or more, identical or different,
substituents R⁶;
 - R¹⁸ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted
with one or more, identical or different, substituents R¹⁹, C₃₋₆ cycloalkyl
optionally substituted with one or more, identical or different,
substituents R¹⁹, phenyl optionally substituted with one or more, identical
or different, substituents R⁸, and 4-6 membered heterocycle optionally
20 substituted with one or more, identical or different, substituents R²⁰;
 - R¹⁹ is independently selected from the group consisting of F, Cl, Br, I, -CN,
=O, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or
different, substituents R⁶, -O-C₁₋₅ alkyl optionally substituted with one or
more, identical or different, substituents R⁶, -O-C₃₋₅ cycloalkyl optionally
25 substituted with one or more, identical or different, substituents R⁶, -S-
C₁₋₅ alkyl optionally substituted with one or more, identical or different,
substituents R⁶, -S-C₃₋₅ cycloalkyl optionally substituted with one or
more, identical or different, substituents R⁶, -SO-C₁₋₅ alkyl optionally
substituted with one or more, identical or different, substituents R⁶, -SO-
30 C₃₋₅ cycloalkyl optionally substituted with one or more, identical or
different, substituents R⁶, -SO₂-C₁₋₅ alkyl optionally substituted with one
or more, identical or different, substituents R⁶, -SO₂-C₃₋₅ cycloalkyl
optionally substituted with one or more, identical or different,
substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more,
35 identical or different substituents R⁶, -C(=O)-OC₁₋₅ alkyl optionally

- 5 substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₃₋₅ 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^8 , pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R^{20} and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- 10 - R^{20} is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 and -C(=O)-NH-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ; and
- 15 - n is an integer 0, 1, 2, or 3;
- 20 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

17. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (VIII):



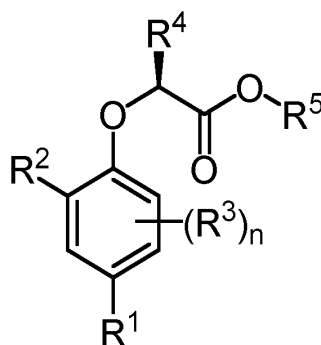
Formula (VIII)

wherein:

- 5 - R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- 10 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 20 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;

- 5 - R²¹ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶ and -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R²² is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶ and phenyl optionally substituted with one or more, identical or different, substituents R⁸; and
- n is an integer 0, 1, 2, or 3;
- 15 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

18. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (II):



Formula (II)

20 wherein:

- R¹ is selected from the group consisting of F, Cl, Br and I;
- R² is a 5-membered aromatic heterocycle which may be optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, F and Cl;
- 25 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and

- C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- 10 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- 15 - R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
- 20 19. The compound for use according to any one of the preceding items, wherein R² is 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷.
20. The compound for use according to item 11, wherein:
- 25 - R¹ is selected from the group consisting of F, Cl, Br and I;
- R² is a 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, F, and Cl;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 30 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or

- more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl and cyclopropyl;
- 5 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ 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.
- 10
21. The compound for use according to item 18, with the proviso that when R¹ is F, Cl or Br, R² is 1,2-oxazol-5-yl, R⁴ is H, R⁵ is H and R⁶ is H then n is 1, 2 or 3.
22. The compound for use according to any one of items 11 or 18 to 21,
- 15 wherein:
- R¹ is selected from the group consisting of F, Cl, Br and I, preferably Cl or Br;
- R² 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
- 20 more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, F, and Cl;
- R⁴ is selected from the group consisting of C₁₋₅ alkyl and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 25 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally
- 30 substituted with one or more, identical or different, substituents R⁸;
- R⁷ is independently selected from the group consisting of H, deuterium, F, Cl, Br, I, C₁₋₅ alkyl and C₃₋₅ cycloalkyl;
- R⁶ is independently selected from deuterium and F;

- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;

- n is an integer 0, 1, 2 or 3;

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

5

23. The compound for use according to any one of items 10 to 22, wherein R¹ is selected from the group consisting of Cl and Br, R² is selected from the group consisting of 1,2-oxazol-3-yl, 1,2-oxazol-5-yl, 1,3-oxazol-4-yl and 1,2,3-thiadiazol-4-yl and R⁴ is selected from the group consisting of Me, Et and -CH₂F.

10

24. The compound for use according to any one of items 10 to 22, wherein R² is selected from the group consisting of furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole.

15

25. The compound for use according to any one of items 10 to 21, wherein R² is selected from the group consisting of thiophene, pyrrole, isoxazole, 1,2,4-oxadiazole and 1,3,4-oxadiazole.

20

26. The compound for use according to any one of items 10 to 22, wherein R² 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 R⁷.

25

27. The compound for use according to any one of items 10 to 22, wherein R² 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

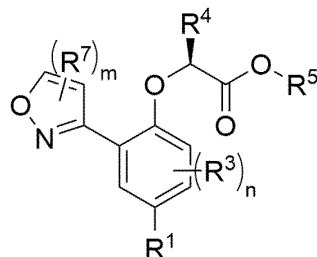
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each of which may be optionally substituted with one or more, identical or different, substituents R⁷.

28. The compound for use according to any one of items 10 to 22, wherein R² is selected from isoxazol-5-yl and isoxazol-3-yl.
- 5 29. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-oxazol-3-yl.
30. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-oxazol-4-yl.
- 10 31. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-oxazol-5-yl.
32. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-oxazol-2-yl.
33. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-oxazol-4-yl.
- 15 34. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-oxazol-5-yl.
35. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-thiazol-3-yl.
- 20 36. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-thiazol-4-yl.
37. The compound for use according to any one of items 10 to 22, wherein R² is 1,2-thiazol-5-yl.
38. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-thiazol-2-yl.
- 25 39. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-thiazol-4-yl.

40. The compound for use according to any one of items 10 to 22, wherein R² is 1,3-thiazol-5-yl.
41. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,3-thiadiazol-4-yl.
- 5 42. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,3-thiadiazol-5-yl.
43. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,4-thiadiazol-3-yl.
- 10 44. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,4-thiadiazol-5-yl.
45. The compound for use according to any one of items 10 to 22, wherein R² is 1,3,4-thiadiazol-2-yl.
46. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,5-thiadiazol-3-yl.
- 15 47. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,3-oxadiazol-4-yl.
48. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,3-oxadiazol-5-yl.
- 20 49. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,4-oxadiazol-3-yl.
50. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,4-oxadiazol-5-yl.
51. The compound for use according to any one of items 10 to 22, wherein R² is 1,3,4-oxadiazol-2-yl.
- 25 52. The compound for use according to any one of items 10 to 22, wherein R² is 1,2,5-oxadiazol-3-yl.

53. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (IX):



Formula (IX)

5 wherein:

- R¹ is selected from the group consisting of H, deuterium, F, Cl, Br and I, preferably Cl or Br;
- R³ is selected from the group consisting of deuterium, F, and Cl;
- R⁴ is selected from the group consisting of H, deuterium, C₁-₅ alkyl, C₂-₅ alkenyl, C₂-₅ alkynyl, C₃-₅ cycloalkyl, C₅ cycloalkenyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁-₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂-₅ alkenyl, C₂-₅ alkynyl, C₃-₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸ and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl and cyclopropyl;
- R⁶ is independently selected from deuterium and F;
- R⁸ 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.

54. The compound for use according to item 53, wherein m is 0.

55. The compound for use according to item 53, wherein m is 1.

56. The compound for use according to item 53, wherein m is 2.

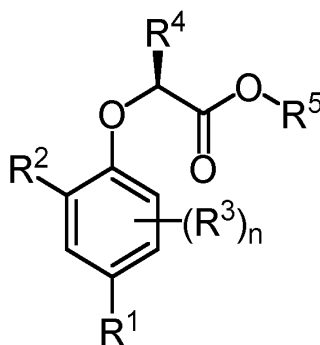
57. The compound for use according to any of items 53 to 56, wherein;

- R¹ is selected from the group consisting of F, Cl, Br and I;
- R³ is selected from the group consisting of deuterium, F, and Cl;
- 5 - R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₅ cycloalkenyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl and C₂₋₅ alkynyl;
- 10 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl, and cyclopropyl; and
- R⁶ is independently selected from deuterium and F.

58. The compound for use according to any one of items 10 to 17, wherein R² is

- CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or
- 15 different, substituents R⁶.

59. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (II):



Formula (II)

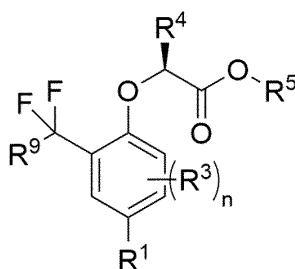
20 wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or
- 25 different, substituents R⁶;
- R³ is selected from the group consisting of deuterium, Cl and F;

- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶,
- 10 phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- n is an integer 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
- 20 60. The compound for use according to any one of items 10 to 17 or 59, wherein R² is Me-CF₂-.
- 61. The compound for use according to any one of items 10 to 17 or 59, wherein R² is Et-CF₂-.
- 62. The compound for use according to any one of items 10 to 17 or 59, wherein R² is ⁿPr-CF₂-.
- 25 63. The compound for use according to any one of items 10 to 17 or 59, wherein R² is ⁱPr-CF₂-.
- 64. The compound for use according to any one of items 10 to 17 or 59, wherein R² is cyclopropyl-CF₂-.
- 30 65. The compound for use according to any one of items 10 to 17 or 59, wherein R¹ is selected from the group consisting of Cl and Br, R² is selected

from the group consisting of -CF₂Me and -CF₂Et and R⁴ is selected from the group consisting of Me, Et and -CH₂F.

66. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (X):



5

Formula (X)

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- 10 - R⁹ is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 15 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- 20 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ 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;
- 25

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

67. The compound for use according to item 66, wherein:

- R¹ is selected from the group consisting of F, Cl, Br, and I;
- 5 - R³ is selected from the group consisting of deuterium and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R^{B8},
- 15 phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ is independently selected from the group consisting of deuterium,
- 20 methoxy, nitro, cyano, Cl, Br, I, and F;
- R⁹ is selected from the group consisting of C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶; and
- n is an integer 0, 1, 2, or 3;

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

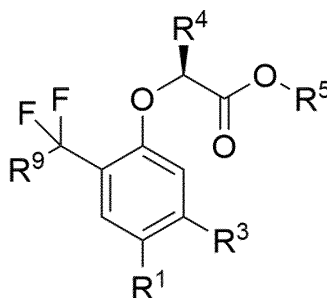
68. The compound for use according item 66, wherein:

- R¹ is selected from the group consisting of C₂ alkenyl, C₂ alkynyl, NO₂, F, Cl, Br, and I;
- R⁹ is C₁₋₅ alkyl optionally be substituted with one or more, identical or
- 30 different, substituents R⁶;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl and C₂₋₅ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶;

- R⁵ is H;
- R⁶ is independently selected from deuterium and F; and
- n is an integer 0, 1, 2, or 3;

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

69. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (XI):



Formula (XI)

wherein:

- R¹ is selected from the group consisting of C₂ alkynyl, NO₂, Cl, Br, and I;
- R³ is selected from the group consisting of H, deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl and C₂₋₅ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is H;
- R⁶ is independently selected from deuterium and F; and
- R⁹ is C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶;

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

70. The compound for use according to item 69, wherein:

- R¹ is selected from the group consisting of C₂ alkenyl, C₂ alkynyl, NO₂, F, Cl, Br, and I;
- R⁹ is C₁₋₃ alkyl optionally be substituted with one or more, identical or different, substituents R⁶;

- R³ is selected from the group consisting of deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₃ alkyl and C₂₋₃ alkynyl each of which may be optionally substituted with one or more, identical or different, substituents R⁶; and
 - R⁶ is independently selected from the group consisting of deuterium and F;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

71. The compound for use according to any one of items 66 to 70, wherein R⁹ is methyl.

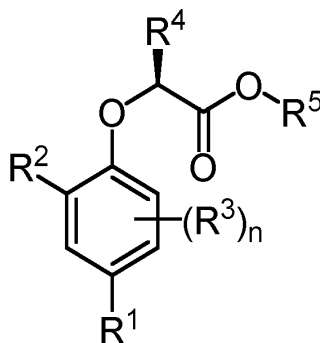
72. The compound for use according to any one of items 66 to 70, wherein R⁹ is ethyl.

73. The compound for use according to any one of items 66 to 70, wherein R⁹ is n-propyl.

74. The compound for use according to any one of items 66 to 70, wherein R⁹ is isopropyl.

75. The compound for use according to any one of items 66 to 70, wherein R⁹ is cyclopropyl.

76. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (II):



Formula (II)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br and I;

- R² is selected from the group consisting of H, deuterium, F, Cl, Br and I;
 - R³ is selected from the group consisting of deuterium, Cl and F
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁸ 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.
77. The compound for use according to item 11, wherein:
- R¹ is selected from the group consisting of F, Cl, Br, and I;
 - R² is selected from the group consisting of hydrogen, deuterium, F, Cl and Br;
 - R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₃₋₅ cycloalkyl, C₅ cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R⁶, and C₂₋₅ alkynyl, which may be optionally substituted with one or more, identical or different, substituents R⁶; and
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, 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 independently selected from the group consisting of deuterium and F;
- and
- 5 - R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;
- R^3 is deuterium; and
- n is 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or
- 10 solvate thereof.

78. The compound for use according to item 11, wherein:

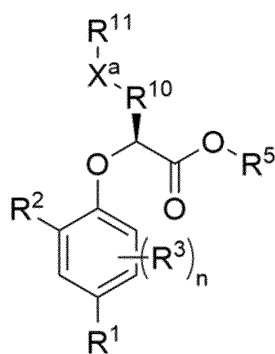
- R^1 is selected from the group consisting of F, Cl, Br and I;
- R^2 is selected from the group consisting of hydrogen, deuterium, F, Cl, and Br;
- 15 - R^4 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, and C_5 cycloalkenyl, each of which is substituted with one or more, identical or different, substituents R^6 ; and
- 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^6 , C_{3-6} cycloalkyl
- 20 optionally substituted with one or more, identical or different, substituents R^6 , 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 independently selected from the group consisting of deuterium and F;
- 25 and
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I and F;
- R^3 is deuterium; and
- n is 0, 1, 2 or 3;
- 30 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

79. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R^2 is H.

80. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R² is deuterium.
81. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R² is F.
- 5 82. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R² is Cl.
83. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R² is Br.
- 10 84. The compound for use according to any one of items 10 to 17, or 76 to 78, wherein R² is I.
85. The compound for use according to item 11, wherein:
- R¹ is selected from the group consisting of H, Br, Cl, F and I;
 - R² is H;
 - R⁴ is selected from the group consisting of -CH₃, -CH₂-CH₃, -CH(CH₃)₂, -CH₂F, -CH₂-CH₂F, -, and cyclopropyl;
 - 15 - R⁵ is H; and
 - n is 0,
- or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof.
86. The compound for use according to item 11, wherein:
- 20 - R¹ is selected from the group consisting of F, Cl, Br, I, -CN, and -CF₃;
 - R² is selected from the group consisting of C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R³ is selected from the group consisting of deuterium, F, and Cl;
 - 25 - R⁴ is selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or
 - 30

- more, identical or different, substituents R^8 and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;
- R^6 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 or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

87. The compound for use according to any one of items 10 to 17 or 86, wherein R^2 is C_{2-5} alkenyl optionally substituted with one or more, identical or different, substituents R^6 .
88. The compound for use according to any one of items 10 to 17 or 86, wherein R^2 is vinyl.
89. The compound for use according to any one of items 10 to 17 or 86, wherein R^2 is C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^6 .
90. The compound for use according to any one of items 10 to 17 or 86, wherein R^2 is ethynyl.
91. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (XII):

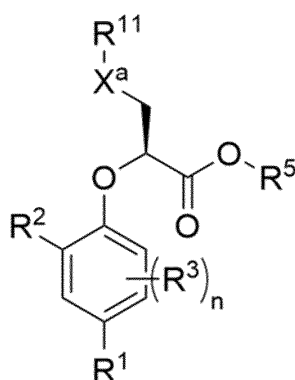


Formula (XII)

wherein:

- R¹ is selected from the group consisting of F, Cl, Br and I;
- R² is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;
- R³ is selected from the group consisting of deuterium, Cl and F;
- 5 - R¹⁰ is C₁₋₂ alkanediyl which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₆ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶; phenyl optionally substituted with one or more, identical or different, substituents R⁸; and
10 benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R¹¹ is C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶;
- 15 - R⁶ is independently selected from the group consisting of deuterium and F;
- R⁸ 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; and
- X^a is O or S;
- 20 or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

92. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (XIII):



Formula (XIII)

wherein:

- R¹ is selected from the group consisting of Cl and Br;
- R² is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶;
- 5 - R³ is selected from the group consisting of deuterium and F;
- R¹¹ is C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- n is an integer 0, 1, 2 or 3; and
- 10 - X^a is O or S;

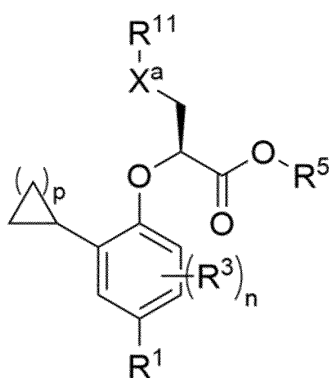
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

93. The compound for use according to any one of items 11 to 17, 86, 91 or 92, wherein R² is C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶.

94. The compound for use according to any one of items 11 to 17, 86, 91 or 92, wherein R² is cyclopropyl.

95. The compound for use according to any one of items 11 to 17, 86, 91 or 92, wherein R² is cyclobutyl.

- 20 96. The compound for use according to any one of items 1 to 9, wherein the compound is of Formula (XIV):



Formula (XIV)

wherein:

- R¹ is selected from the group consisting of Cl and Br;
- R³ is selected from the group consisting of deuterium and F;
- R¹¹ is C₁₋₂ alkyl optionally substituted with one or more, identical or different, substituents R⁶;
- R⁶ is independently selected from the group consisting of deuterium and F;
- p is an integer 1 or 2;
- n is an integer 0, 1, 2 or 3; and
- X^a is O or S;

5

10

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

97. The compound for use according to item any one of items 91 to 96, wherein X^a is O.

15

98. The compound for use according to any one of items 91 to 96, wherein X^a is S.

99. The compound for use according to any one of items 96 to 98, wherein p is 1.

100. The compound for use according to any one of items 96 to 98, wherein p is 2.

20

101. The compound for use according to any one of items 10, 11 or 18 to 100, wherein R⁵ is H.

102. The compound for use according to any one of items 10, 11 or 18 to 100, wherein R⁵ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁸.

25

103. The compound for use according to any one of items 10, 11 or 18 to 100, wherein R⁵ is C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁸.

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104. The compound for use according to any one of items 10, 11 or 18 to 100, wherein R⁵ is phenyl optionally substituted with one or more, identical or different, substituents R⁸.

105. The compound for use according to any one of items 10, 11 or 18 to 100, wherein R^5 is benzyl optionally substituted with one or more, identical or different, substituents R^8 .
- 5 106. The compound for use according to any one of items 10 or 12, wherein X is N.
107. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is H.
108. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is NH_2 .
- 10 109. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
110. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 111. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
112. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 113. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 25 114. The compound for use according to any one of items 10 or 12, wherein X is CR^{23} wherein R^{23} is $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
115. The compound for use according to any one of items 10, 12 or 106 to 114, wherein Y is NH.

116. The compound for use according to any one of items 10, 12 or 106 to 114, wherein Y is O.
117. The compound for use according to any one of items 10, 12 or 106 to 114, wherein Y is S.
- 5 118. The compound for use according to any one of items 10 or 14, wherein R^{13} is H.
119. The compound for use according to any one of items 10 or 14, wherein R^{13} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 10 120. The compound for use according to any one of items 10 or 14, wherein R^{13} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
121. The compound for use according to any one of items 10 or 14, wherein R^{13} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 122. The compound for use according to any one of items 10 or 14, wherein R^{13} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
123. The compound for use according to any one of items 10, 14 or 118 to 122, wherein R^{14} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 124. The compound for use according to any one of items 10, 14 or 118 to 122, wherein R^{14} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 25 125. The compound for use according to any one of items 10, 14 or 118 to 122, wherein R^{14} is phenyl optionally substituted with one or more, identical or different, substituents R^8 .
126. The compound for use according to any one of items 10, 14 or 118 to 125, wherein R^{15} is $-OH$.

127. The compound for use according to any one of items 10, 14 or 118 to 125, wherein R^{15} is $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 128. The compound for use according to any one of items 10, 14 or 118 to 125, wherein R^{15} is $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
129. The compound for use according to any one of items 10 or 15, wherein R^{16} is H.
- 10 130. The compound for use according to any one of items 10 or 15, wherein R^{16} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
131. The compound for use according to any one of items 10 or 15, wherein R^{16} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 132. The compound for use according to any one of items 10 or 15, wherein R^{16} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 133. The compound for use according to any one of items 10 or 15, wherein R^{16} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
134. The compound for use according to any one of items 10 or 16, wherein R^{17} is H.
- 25 135. The compound for use according to any one of items 10 or 16, wherein R^{17} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{20} .
136. The compound for use according to any one of items 10 or 16, wherein R^{17} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .

137. The compound for use according to any one of items 10 or 16, wherein R^{17} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 138. The compound for use according to any one of items 10 or 16, wherein R^{17} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
139. The compound for use according to any one of items 10, 16 or 134 to 138, wherein R^{18} is H.
- 10 140. The compound for use according to any one of items 10, 16 or 134 to 138, wherein when R^{18} is H then R^{17} is not H.
141. The compound for use according to any one of items 10, 16 or 134 to 138, wherein R^{18} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{19} .
- 15 142. The compound for use according to any one of items 10, 16 or 134 to 138, wherein R^{18} is C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^{19} .
143. The compound for use according to any one of items 10, 16 or 134 to 138, wherein R^{18} is phenyl optionally substituted with one or more, identical or different, substituents R^8 .
- 20 144. The compound for use according to any one of items 10, 16 or 134 to 138, wherein R^{18} is a 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} .
145. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is F, Cl, Br or I.
- 25 146. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-CN$.
147. The compound for use according to any one of items 10, 16 or 134 to 144, wherein, R^{19} is $=O$.

148. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 149. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-O-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
150. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-O-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 10 151. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-S-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
152. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-S-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 153. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-SO-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
154. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-SO-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 155. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 25 156. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-SO_2-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 30 157. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different substituents R^6 .

158. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 159. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-NH-C(=O)-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
160. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 10 161. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-NH-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
162. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 163. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
164. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 165. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is phenyl optionally substituted with one or more, identical or different, substituents R^8 .
- 25 166. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is pyrrolidine-1-yl optionally substituted with one or more, identical or different, substituents R^{20} .
- 30 167. The compound for use according to any one of items 10, 16 or 134 to 144, wherein R^{19} is 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} .

168. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is F, Cl, Br or I.
169. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -CN.
- 5 170. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is =O.
171. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 10 172. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
173. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -C(=O)- C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 174. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -C(=O)-OC $_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
175. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -C(=O)- C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 176. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -NH-C(=O)- C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 25 177. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is -NH-C(=O)- C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .

178. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 179. The compound for use according to any one of items 10, 16 or 134 to 167, wherein R^{20} is $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
180. The compound for use according to any one of items 10 or 17, wherein R^{21} is H.
- 10 181. The compound for use according to any one of items 10 or 17, wherein R^{21} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
182. The compound for use according to any one of items 10 or 17, wherein R^{21} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 15 183. The compound for use according to any one of items 10 or 17, wherein R^{21} is $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 .
184. The compound for use according to any one of items 10 or 17, wherein R^{21} is $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 20 185. The compound for use according to any one of items 10, 17 or 180 to 184, wherein R^{22} C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
186. The compound for use according to any one of items 10, 17 or 180 to 184, wherein R^{22} is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 25 187. The compound for use according to any one of items 10, 17 or 180 to 184, wherein R^{22} is phenyl optionally substituted with one or more, identical or different, substituents R^8 .

188. The compound for use according to any one of items 10 to 187, wherein R^1 is C_{1-2} alkyl.
189. The compound for use according to any one of items 10 to 187, wherein R^1 is C_2 alkenyl.
- 5 190. The compound for use according to any one of items 10 to 187, wherein R^1 is C_2 alkynyl.
191. The compound for use according to any one of items 10 to 187, wherein R^1 is CN.
- 10 192. The compound for use according to any one of items 10 to 187, wherein R^1 is CF_3 .
193. The compound for use according to any one of items 10 to 187, wherein R^1 is NO_2 .
194. The compound for use according to any one of items 10 to 187, wherein R^1 is Cl or Br.
- 15 195. The compound for use according to any one of items 10 to 187, wherein R^1 is F.
196. The compound for use according to any one of items 10 to 187, wherein R^1 is Cl.
- 20 197. The compound for use according to any one of items 10 to 187, wherein R^1 is Br.
198. The compound for use according to any one of items 10 to 187, wherein R^1 is I.
199. The compound for use according to any one of items 10 to 198, wherein R^3 is deuterium.
- 25 200. The compound for use according to any one of items 10 to 198, wherein R^3 is Cl.

201. The compound for use according to any one of items 10 to 198, wherein R^3 is F.
- 5 202. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
203. The compound for use according to any one of items 10 to 201, wherein R^4 is selected from the group consisting of methyl, ethyl, n-propyl and isopropyl.
- 10 204. The compound for use according to any one of items 10 to 201, wherein R^4 is selected from the group consisting of methyl, ethyl, n-propyl and isopropyl wherein the methyl, ethyl, n-propyl or isopropyl group is substituted with one or more, identical or different, substituents R^6 .
205. The compound for use according to any one of items 10 to 201, wherein R^4 is Me.
- 15 206. The compound for use according to any one of items 10 to 201, wherein R^4 is ethyl.
207. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{1-5} alkyl substituted with one or more F.
- 20 208. The compound for use according to any one of items 10 to 201, wherein R^4 is methyl substituted with one or more, identical or different, substituents R^6 .
209. The compound for use according to any one of items 10 to 201, wherein R^4 is selected from the group consisting of $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$ and $-CH_2CF_3$.
- 25 210. The compound for use according to any one of items 10 to 201, wherein R^4 is $-CH_2F$.
211. The compound for use according to any one of items 10 to 201, wherein R^4 is $-CH_2-CH_2F$.

212. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{1-2} alkoxy- C_{1-2} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
- 5 213. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{1-2} alkylthio- C_{1-2} alkyl optionally substituted with one or more, identical or different, substituents R^6 .
214. The compound for use according to any one of items 10 to 201, wherein R^4 is selected from the group consisting of $MeOCH_2-$, $EtOCH_2-$, $MeSCH_2-$ and $EtSCH_2-$.
- 10 215. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{2-5} alkenyl optionally substituted with one or more, identical or different, substituents R^6 .
216. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{2-5} alkynyl optionally substituted with one or more, identical or
15 different, substituents R^6 .
217. The compound for use according to any one of items 10 to 201, R^4 is prop-2-ynyl.
218. The compound for use according to any one of items 10 to 201, wherein R^4 is $-CH_2-C_{2-4}$ alkynyl optionally substituted with one or more, identical or
20 different, substituents R^6 .
219. The compound for use according to any one of items 10 to 201, wherein R^4 is C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 .
220. The compound for use according to any one of items 10 to 201, wherein R^4 is selected from the group consisting of cyclopropyl and cyclobutyl.
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221. The compound for use according to any one of items 10 to 201, wherein R^4 is deuterium.
222. The compound for use according to any one of items 10 to 201, wherein R^4 is H.

223. The compound for use according to any one of items 10 to 201, wherein when R^4 is H, the carbon to which R^4 is bound is not a stereogenic centre.
224. The compound for use according to any one of items 10 to 223, wherein R^6 is deuterium.
- 5 225. The compound for use according to any one of items 10 to 223, wherein R^6 is F.
226. The compound for use according to any one of items 10 to 225, wherein R^7 is deuterium.
- 10 227. The compound for use according to any one of items 10 to 225, wherein R^7 is F.
228. The compound for use according to any one of items 10 to 225, wherein R^7 is selected from the group consisting of methyl, ethyl or cyclopropyl.
229. The compound for use according to any one of items 10 to 227, wherein R^8 is deuterium.
- 15 230. The compound for use according to any one of items 10 to 227, wherein R^8 is methoxy.
231. The compound for use according to any one of items 10 to 227, wherein R^8 is nitro.
- 20 232. The compound for use according to any one of items 10 to 227, wherein R^8 is cyano.
233. The compound for use according to any one of items 10 to 227, wherein R^8 is Cl.
234. The compound for use according to any one of items 10 to 227, wherein R^8 is Br.
- 25 235. The compound for use according to any one of items 10 to 227, wherein R^8 is I.

236. The compound for use according to any one of items 10 to 227, wherein R^8 is F.
237. The compound for use according to any one of items 10 to 236, wherein n is 0.
- 5 238. The compound for use according to any one of items 10 to 236, wherein n is 1.
239. The compound for use according to any one of items 10 to 236, wherein n is 2.
- 10 240. The compound for use according to any one of items 10 to 236, wherein n is 3.
241. The compound for use according to item 1, wherein the compound is selected from the group consisting of:
- (S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
- (S)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]propionic acid;
- 15 (R)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]-3-fluoropropionic acid;
- (S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-methoxybutyric acid;
- (S)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]propionic acid;
- (S)-2-[2-(1,1-difluoropropyl)-4-nitrophenoxy]propionic acid;
- (R)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]-3-fluoropropionic acid;
- 20 (S)-2-(4-chloro-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
- (S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
- (S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
- (S)-2-[2-(1,1-difluoropropyl)-5-fluoro-4-styrenyloxy]propionic acid;
- (S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]butyric acid;
- 25 (S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-fluorobutyric acid;
- (R)-2-[4,5-dichloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
- (R)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]-3-fluoropropionic acid;
- (S)-2-[4,5-dichloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;
- (R)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
- 30 (S)-2-[2-(1,1-difluoroethyl)-4-ethynylphenoxy]propionic acid;
- [4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
- [4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]acetic acid;

- (S)-2-[2-(1,1-difluoropropyl)-4-tolyloxy]propionic acid;
[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]acetic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-styrenyloxy]propionic acid;
(R)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
5 (S)-2-[2-(1,1-difluoropropyl)-4-(trifluoromethyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)(3,5,6-²H₃)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]propionic acid;
10 (R)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-cyano-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-ethynylphenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
15 (S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy](2-²H)propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-iodophenoxy]propionic acid;
(S)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-pentynoic acid;
(R)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
20 (S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
(S)-2-(4-bromo-2-cyclobutylphenoxy)-3-methoxypropionic acid;
(S)-2-[4-bromo-2-(cyclopropyl)difluoromethyl]phenoxy]propionic acid;
(R)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,1-difluorobutyl)phenoxy]propionic acid;
25 (S)-[4-bromo-2-(1,1-difluoroethyl)phenoxy]cyclopropylacetic acid;
(S)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;
[4-bromo-2-(1,1-difluoropropyl)phenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-cyclopropylpropionic acid;
30 (S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-3-methoxypropionic acid;
(S)-(4-bromo-2-cyclopropylphenoxy)cyclopropylacetic acid;
35 (S)-cyclopropyl(2,4-dibromophenoxy)acetic acid;

- (S)-(4-bromo-2-chlorophenoxy)cyclopropylacetic acid;
(2R,3R)-2-(p-bromophenoxy)-3-fluorobutyric acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-ethoxypropionic acid;
[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]acetic acid;
5 [4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]acetic acid;
[4-chloro-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-[4-bromo-2-(5-isoxazolyl)phenoxy]cyclopropylacetic acid;
(S)-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]cyclopropylacetic acid;
(S,E)-2-(p-bromophenoxy)-4-fluoro-3-butenoic acid;
10 (2R,3R)-2-(4-bromo-2-fluorophenoxy)-3-fluorobutyric acid;
(4-bromo-2-cyclopropylphenoxy)acetic acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-cyclopropylpropionic acid;
[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]acetic acid;
[4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]acetic acid;
15 (S)-2-[4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclobutylpropionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
[4-bromo-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-2-(p-bromophenoxy)(2-²H)butyric acid;
20 (S)-2-(p-bromophenoxy)-4-pentynoic acid;
[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]acetic acid;
(4-bromo-2-ethynylphenoxy)acetic acid;
(S)-2-(4-bromo-2-fluorophenoxy)valeric acid;
(S)-2-(2,4-dibromophenoxy)valeric acid;
25 (S)-2-(4-bromo-2-chlorophenoxy)valeric acid;
(S)-2-(p-bromophenoxy)-3-cyclopropylpropionic acid;
(S)-2-(2,4-dibromophenoxy)-4-pentynoic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-pentynoic acid;
(S)-(p-bromophenoxy)cyclopropylacetic acid;
30 (S)-2-(4-bromo-2-fluorophenoxy)-4-pentynoic acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]butyric acid;
(S)-2-(p-bromophenoxy)valeric acid;
(R)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,3,4-thiadiazol-2-yl)phenoxy]propionic acid;
35 (S)-(4-bromo-2-chlorophenoxy)cyclobutylacetic acid;

- (S)-2-(4-bromo-2-chlorophenoxy)-3-cyclopropylpropionic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-3-methylbutyric acid;
[4-bromo-2-(3-isoxazolyl)phenoxy]acetic acid;
(R)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
5 (S)-2-[4-chloro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
(S)-2-(p-bromophenoxy)-3-butenic acid;
(S)-2-[4-bromo-2-(1H-1,2,3-triazol-5-yl)phenoxy]propionic acid;
(2S)-2-(p-bromophenoxy)(3,4-²H₂)butyric acid;
(R)-2-(4-bromo-2-chlorophenoxy)-3-fluoropropionic acid;
10 (S)-2-(4-bromo-2-chlorophenoxy)butyric acid;
(S)-2-(4-bromo-3-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-fluorobutyric acid;
(S)-2-(p-ethynylphenoxy)-4-fluorobutyric acid;
(S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
15 (S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,3-oxazol-5-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
(R)-2-(p-bromophenoxy)-3-fluoro(2-²H)propionic acid;
(R)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
20 (S)-2-(4-bromo-5-fluoro-2-styrenyloxy)propionic acid;
(S)-2-[4-bromo-2-(1,3-thiazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
25 (R)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)propionic acid;
(S)-2-[4-bromo-2-(2,2-difluoroethenyl)-5-fluorophenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]butyric acid;
30 (S)-2-(4-bromo-2-iodophenoxy)-4-fluorobutyric acid;
(S)-(4-bromo-2-ethynylphenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-ethynyl-5-fluorophenoxy)propionic acid;
(S)-2-(4-chloro-2-ethynyl-5-fluorophenoxy)propionic acid;
(S)-2-[4-bromo-2-(4-isoxazolyl)phenoxy]propionic acid;
35 (R)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;

- (S)-(p-bromophenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-fluorophenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-ethynylphenoxy)-4-fluorobutyric acid;
5 (S)-2-(4-bromo-2-styrenyloxy)-4-fluorobutyric acid;
(S)-(4-bromo-2-fluorophenoxy)cyclobutylacetic acid;
(S)-2-[4-chloro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4,5-dichloro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
10 (S)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-(p-bromophenoxy)-4-fluorobutyric acid;
(S)-2-{2-[(E)-2-fluoroethenyl]-4-bromophenoxy}propionic acid;
(S)-2-[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-{2-[(E)-2-fluoroethenyl]-4-chlorophenoxy}propionic acid;
15 (S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(R)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;
20 (S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]butyric acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-chloro-2-(1,3-oxazol-2-yl)phenoxy]propionic acid;
25 (S)-2-(4-bromo-2-iodophenoxy)-3-methylbutyric acid;
(S)-(4-bromo-2-fluorophenoxy)cyclopropylacetic acid;
(R)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(3-isothiazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-ethynylphenoxy)butyric acid;
30 (S)-2-(4-bromo-2-iodophenoxy)butyric acid;
(S)-2-(4-chloro-2-fluorophenoxy)butyric acid;
(S)-2-(p-bromophenoxy)butyric acid;
(S)-2-[4-bromo-2-(2,2-difluoroethenyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]butyric acid;
35 (S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]butyric acid;

- (S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-fluorophenoxy)butyric acid;
(S)-2-[4-bromo-2-(5-methyl-3-isoxazolyl)phenoxy]propionic acid;
5 (S)-2-[4-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenoxy]propionic acid;
(R)-2-[p-bromo(3,5-²H₂)phenoxy]-3-fluoropropionic acid;
(S)-2-[p-bromo(3,5-²H₂)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;
ethyl (S)-2-(4-bromo-2-fluorophenoxy)-3-methyl-3-butenate;
10 (R)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
(R)-2-[p-bromo(2,6-²H₂)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(1,3-thiazol-2-yl)phenoxy]propionic acid;
(S)-2-[p-bromo(2,6-²H₂)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]propionic acid;
15 (S)-2-[4-bromo-2-(3-methyl-5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-iodophenoxy)propionic acid;
(S)-2-[4-bromo-2-(2-imidazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(5-imidazolyl)phenoxy]propionic acid;
(R)-2-(4-bromo-2-cyclobutylphenoxy)-3-fluoropropionic acid;
20 (R)-2-(4-bromo-2-fluorophenoxy)-3,3-difluoropropionic acid;
(S)-2-(4-bromo-2-ethynylphenoxy)propionic acid;
(S)-2-(2-bromo-4-chlorophenoxy)-3-methylbutyric acid;
(S)-2-(2-fluoro-4-iodophenoxy)propionic acid;
(S)-2-(2-bromo-4-iodophenoxy)propionic acid;
25 (R)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-(2-chloro-4-iodophenoxy)propionic acid;
(S)-2-(2-bromo-4-chlorophenoxy)propionic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)propionic acid;
(S)-2-(4-bromo-2-styrenyloxy)propionic acid;
30 (S)-2-[4-chloro-2-(1-methyl-3-methyl-4-pyrazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-pyrazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(2-cyclopropyl-4-fluorophenoxy)propionic acid;
(S)-2-[4-chloro-2-(1-methyl-4-pyrazolyl)phenoxy]propionic acid;
35 (S)-2-(2-cyclobutyl-4-fluorophenoxy)propionic acid;

- (S)-2-(4-bromo-2-cyclobutylphenoxy)propionic acid;
(R)-2-(4-bromo-2-fluorophenoxy)-3-fluoropropionic acid;
(S)-2-(4-chloro-2-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-chloro-2-cyclobutylphenoxy)propionic acid;
5 (S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]propionic acid;
(R)-2-(2-bromo-4-chlorophenoxy)-3-fluoropropionic acid;
(R)-2-(p-chlorophenoxy)-3-fluoropropionic acid;
(R)-2-(4-chloro-2-fluorophenoxy)-3-fluoropropionic acid;
(R)-2-(2,4-dibromophenoxy)-3-fluoropropionic acid;
10 (S)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]propionic acid;
(R)-2-(p-bromophenoxy)-3-fluoropropionic acid;
(S)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-bromo-2-fluorophenoxy)propionic acid;
(S)-2-(4-chloro-2-fluorophenoxy)propionic acid;
15 (S)-2-(2,4-dibromophenoxy)propionic acid;
(S)-2-(4-chloro-2-ethynylphenoxy)propionic acid;
(S)-2-(4-chloro-2-styrenyloxy)propionic acid;
(S)-2-(4-chloro-2-cyclopropylphenoxy)propionic acid;
(S)-2-(p-chlorophenoxy)butyric acid;
20 sodium (S)-2-(2,4-dichlorophenoxy)propionate;
(S)-2-(p-chlorophenoxy)-3-methylbutyric acid;
(S)-2-(p-cyanophenoxy)propionic acid;
methyl (S)-2-(p-bromophenoxy)propionate;
methyl (S)-2-(p-chlorophenoxy)butyrate;
25 isopropyl (S)-2-(p-chlorophenoxy)propionate;
methyl (S)-2-(p-chlorophenoxy)propionate,
(2S)-2-(4-bromo-2-fluorophenoxy)-N-{1-
[(cyclopropylmethoxy)imino]ethyl}propanamide;
(2S)-2-(4-bromophenoxy)-N-[1-(methoxyimino)ethyl]propanamide;
30 (2S)-2-(4-bromo-2-fluorophenoxy)-N-[(4-fluorophenyl)(hydroxyimino)methyl]-3-
methylbutanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]-3-
methylbutanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;
35 (2S)-2-(4-bromophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;

- (2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-*N*-cyanopropanamide;
(2S)-*N*-cyano-2-(2,4-dibromophenoxy)propanamide;
(2S)-2-(4-bromophenoxy)-*N*-cyanopropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyanopropanamide;
5 (2S)-2-(4-bromophenoxy)-*N*-cyano-3-methylbutanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-*N*-methoxypropanamide;
(2S)-*N*-acetyl-*N*-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-*N*-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
10 (2S)-*N*-(azetidin-3-yloxy)-2-(4-chlorophenoxy)propanamide;
(2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-chlorophenoxy)propanamide;
(2S)-*N*-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-chlorophenoxy)propanamide;
(2S)-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
15 tert-butyl *N*-(2-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}propyl)carbamate;
(2S)-*N*-acetyl-2-(4-chlorophenoxy)-*N*-[(1-acetamidopropan-2-yl)oxy]propanamide;
(2S)-2-(4-bromophenoxy)-*N*-(pyrrolidin-3-yloxy)propanamide;
(2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
20 tert-butyl 3-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}azetidine-1-carboxylate;
(2S)-2-(4-chlorophenoxy)-*N*-[(pyrrolidin-3-yl)methoxy]propanamide;
tert-butyl 3-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}methyl)pyrrolidine-1-carboxylate;
25 (2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(pyrrolidin-3-yloxy)propanamide;
30 (2S)-2-(4-chlorophenoxy)-*N*-(2,2-dimethylpropyl)-*N*-hydroxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(pyrrolidin-1-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(2-oxopyrrolidin-1-yl)ethoxy]propanamide;
(2S)-*N*-acetyl-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
35 (2S)-2-(4-chlorophenoxy)-*N*-(4,4,4-trifluoro-2-methylbutoxy)propanamide;

- (2S)-2-(4-chlorophenoxy)-N-(3-cyclopentylpropyl)-N-hydroxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-[(2E)-2-methyl-3-phenylprop-2-en-1-yl]oxy}propanamide;
(2S)-2-(4-chlorophenoxy)-N-{2-oxo-2-[2-(trifluoromethyl)pyrrolidin-1-yl]ethoxy}propanamide;
5 tert-butyl N-(2-[(2S)-2-(4-chlorophenoxy)propanamidyl]oxy)ethyl)carbamate;
(2S)-2-(4-chlorophenoxy)-N-[(2-methyl-1H-imidazol-4-yl)methoxy]propanamide;
tert-butyl 4-([(2S)-2-(4-chlorophenoxy)propanamido]oxy)methyl)-2-methyl-1H-imidazole-1-carboxylate;
10 (2S)-2-(4-bromo-2-fluorophenoxy)-N-cyclobutoxypropanamide;
(2S)-2-(4-bromophenoxy)-N-cyclobutoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-[2-oxo-2-(pyrrolidin-1-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-N-[1-(4-fluorophenyl)ethoxy]propanamide;
15 (2S)-2-(4-chlorophenoxy)-N-[1-(1,3-thiazol-2-yl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-N-[1-[4-(trifluoromethyl)phenyl]ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-N-(2-methanesulfinylethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-(2-methanesulfonylethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-[(1,2-oxazol-3-yl)methoxy]propanamide;
20 (2S)-2-(4-chloro-2-fluorophenoxy)-N-methoxypropanamide;
(2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-N-(cyclopropylmethoxy)propanamide;
(2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-N-(cyclopropylmethoxy)propanamide;
25 (2S)-N-(tert-butoxy)-2-(4-chlorophenoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-[2-(methylsulfonyl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-N-(1-phenylethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-[(1-methyl-1H-imidazol-2-yl)methoxy]propanamide;
30 (2S)-2-(4-chlorophenoxy)-N-(2-methoxyethoxy)propanamide;
(2S)-2-(4-chloro-2-fluorophenoxy)-N-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-N-methoxypropanamide;
(2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-N-methoxypropanamide;
(2S)-N-(benzyloxy)-2-(4-chlorophenoxy)propanamide;
35 (2S)-2-(4-chlorophenoxy)-N-[(2-methoxycyclopentyl)oxy]propanamide;

- (2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-5-methylhexanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-*N*-methylpropanamide;
(2S)-2-(4-chloro-2-methylphenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-cyclobutoxypropanamide;
5 (2S)-2-(4-chloro-2-methylphenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-4-methylpentanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(3-methylbut-2-en-1-yl)oxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxyhexanamide;
10 (2S)-2-(4-chlorophenoxy)-*N*-[(1,3-oxazol-2-yl)methoxy]propanamide;
(2S)-2-(2,4-dibromophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(oxan-2-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(1,3-thiazol-2-yl)methoxy]propanamide;
15 (2S)-2-(4-chlorophenoxy)-*N*-(3,3-difluorocyclobutoxy)propanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclopentylloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-cyclopentylethoxy)propanamide;
20 (2S)-2-(4-bromo-2-chlorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-bromo-2-methylphenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclopropylmethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclobutylmethoxy)propanamide;
(2S)-*N*-(2-aminoethoxy)-2-(4-chlorophenoxy)propanamide;
25 (2S)-2-(4-bromophenoxy)-*N*-methoxy-3-methylbutanamide;
methyl 2-[[2-(2S)-2-(4-chlorophenoxy)propanamido]oxy]acetate;
(2S)-2-(4-chlorophenoxy)-*N*-[2-(2-methoxyethoxy)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-hydroxyethoxy)propanamide;
30 (2S)-2-(4-chlorophenoxy)-*N*-ethoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-propoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(propan-2-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-methoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-*N*-
35 (cyclopropanesulfonyl)propenamide;

- (2S)-2-(4-bromo-2-fluorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-(cyclopropanesulfonyl)propanamide;
(2S)-2-(4-chlorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromophenoxy)-N-methanesulfonyl-3-methylbutanamide;
- 5 5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropyl]-2H-1,2,3,4-tetrazole;
- 5-[(1S)-1-(4-bromo-2-fluorophenoxy)propyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)-2-methylpropyl]-2H-1,2,3,4-tetrazole;
5-[(1R)-1-(4-bromophenoxy)-2-fluoroethyl]-2H-1,2,3,4-tetrazole;
- 10 5-[(1S)-1-(4-bromophenoxy)propyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
- 15 5-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-cyclopropylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-ethenylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-ethylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-methylphenoxy)ethyl]-2H-1,2,3,4-tetrazole;
- 20 5-[(1S)-1-(4-chlorophenoxy)ethyl]-1H-1,2,3,4-tetrazole;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-yl}acetamide;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-yl}methanesulfonamide;
- 25 3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-amine;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}acetamide;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}methanesulfonamide;
- 30 3-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4H-1,2,4-triazole;
3-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4H-1,2,4-triazole;
- 35 3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methoxy-1,2,4-oxadiazole;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-amine;
3-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4H-1,2,4-triazole;

- 3-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4H-1,2,4-triazole;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methyl-4H-1,2,4-triazole;
5-[(1S)-1-(4-chlorophenoxy)ethyl]-1H-1,2,4-triazole;
5 (2S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-*N*-cyanopropanamide;
(2S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-*N*-cyanopropanamide;
(2S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-methanesulfonylpropanamide;
10 (2S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-(cyclopropanesulfonyl)propanamide;
5-[(1S)-1-[4-bromo-2-(1,1-difluoroethyl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,1-difluoropropyl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-cyclobutylphenoxy)-2-methoxyethyl]-1H-1,2,3,4-tetrazole; and
15 5-[(1S)-1-(4-bromo-2-cyclopropylphenoxy)-2-methoxyethyl]-1H-1,2,3,4-tetrazole,
or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

- 20 242. A method for treating a neuromuscular disorder comprising at least one or more of: subjecting different muscle fibers of the same motor unit in a neuromuscular tissue of a patient being examined for the neuromuscular disorder to a number of activations; detecting, with a medical device and a recording electrode, the number of paired successful action potentials from the number of activations; determining whether the patient is suffering from
25 or at risk of blocking by dividing the number of paired successful action potentials over a total number of activations; and, when the number of paired successful action potentials over the total number of activations is below a threshold of 95%, administering a CIC-1 inhibitor to the patient, wherein the administering of the CIC-1 inhibitor increases the number of
30 paired successful action potentials over the total number of activations by at least 5%.

243. The method of item 242, wherein the CIC-1 inhibitor is a compound according to any one of items 10 to 241.

244. The method of item 242, wherein the method is used in the treatment, prevention and/or amelioration of a neuromuscular disorder.
245. The method of item 243, wherein the neuromuscular disorder is at least one of the following: sarcopenia, myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenic syndrome, seronegative myasthenia gravis, muscle specific kinase myasthenia gravis (MuSK-MG), Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), Charcot-Marie Tooth disease, diabetic polyneuropathy, periodic paralysis, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy, Duchenne muscular dystrophy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, metabolic myopathy, Kennedy's disorder, multiple sclerosis and multifocal motor neuropathy.
246. The method of item 245, wherein the neuromuscular disorder is multiple sclerosis.
247. The method of item 242, wherein the administering of the CIC-1 inhibitor restores contractile force of the patient's muscles by at least 5%.
248. The method of item 242, wherein the administering of the CIC-1 inhibitor reduces incidence of neuromuscular junction transmission failure in the patient's muscles by at least 5%.
249. The method of item 242, wherein the variation in the time interval between two action potentials is measured using single fiber electromyography.
250. A method for treating a neuromuscular disorder comprising at least one or more of: acquiring, with a medical device and a recording electrode, a variation in a time interval between two action potentials of the same motor unit in a neuromuscular tissue of a patient being examined for the neuromuscular disorder; determining whether the variation in the time interval between the two action potentials of the same motor unit exceeds or meets a threshold of 40 μ s; and administering a CIC-1 inhibitor to the

patient when the variation in the time interval between the two action potentials exceeds or meets the threshold, wherein the administering of the CIC-1 inhibitor reduces the variation in the time interval between the two action potentials between consecutive electrical discharges by at least 10%.

- 5 251. The method of item 250, wherein the CIC-1 inhibitor is a compound according to any one of items 10 to 241.
252. The method of item 250, wherein the method is used in the treatment, prevention and/or amelioration of a neuromuscular disorder.
- 10 253. The method of item 250, wherein the neuromuscular disorder is at least one of the following: sarcopenia, myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenic syndrome, seronegative myasthenia gravis, muscle specific kinase myasthenia gravis (MuSK-MG), Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy
- 15 (CIM), Charcot-Marie Tooth disease, diabetic polyneuropathy, periodic paralysis, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy, Duchenne muscular dystrophy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, metabolic myopathy, Kennedy's disorder,
- 20 multiple sclerosis and multifocal motor neuropathy.
254. The method of item 253, wherein the neuromuscular disorder is multiple sclerosis.
255. The method of item 250, wherein the administering of the CIC-1 inhibitor restores contractile force of the patient's muscles by at least 5%.
- 25 256. The method of item 250, wherein the administering of the CIC-1 inhibitor reduces incidence of neuromuscular junction transmission failure in the patient's muscles by at least 5%.
257. The method of item 250, wherein the variation in the time interval
- 30 between two action potentials is measured using single fiber electromyography.

Results

Example 1: Electrophysiological measurement of compound inhibition of CIC-1 in rat muscle

The investigatory goal of these experiments was to evaluate whether compounds
5 inhibit CIC-1 channels in native tissue of rat skeletal muscle fibres. Apparent CIC-1
affinity was reported by the concentration of compound at which 50% of the
compound's full inhibition of CIC-1 was observed (EC_{50}) (see also WO2019/115777).

Experimentally, G_m was measured in individual fibres of whole rat soleus muscles
10 using a three micro-electrodes technique described in this example and in full detail
elsewhere (Riisager *et al.*, Determination of cable parameters in skeletal muscle fibres
during repetitive firing of action potentials. *Journal of Physiology*, **2014**, 592, 4417-
4429). Briefly, intact rat soleus muscles were dissected out from 12-14 week old Wistar
rats and placed in an experimental chamber that was perfused with a standard Krebs
15 Ringer solution containing 122 mM NaCl, 25 mM $NaHCO_3$, 2.8 mM KCl, 1.2 mM
 KH_2PO_4 , 1.2 mM $MgSO_4$, 1.3 mM $CaCl_2$, 5.0 mM D-glucose. During experiments, the
solution was kept at approx. 30°C and continuously equilibrated with a mixture of 95%
 O_2 and 5% CO_2 , pH ~7.4. The experimental chamber was placed in Nikon upright
microscope that was used to visualize individual muscle fibres and the three electrodes
20 (glass pipettes filled with 2 M potassium citrate). For G_m measurements, the electrodes
were inserted into the same fibre with known inter-electrode distances of 0.35 - 0.5 mm
(V1-V2, X1) and 1.1-1.5 mm (V1-V3, X3). The membrane potential of the impaled
muscle fibre was recorded by all electrodes. Two of the electrodes were furthermore
used to inject 50 ms current pulses of -30 nA. Given the positions of the electrodes,
25 three different inter-electrode distances could be identified (X1-X2, X1-X3, X2-X3) and
hence the membrane potential responses to the current injections could be obtained at
three distances from the point of current injection. The steady state voltage deflection
at each distance was divided by the magnitude of current injected (-30 nA) and the
resulting transfer resistances were plotted against inter-electrode distance and the data
30 was fitted to a mono-exponential function from which G_m could be calculated using
linear cable theory.

To establish a dose response relationship, G_m was first determined in 10 muscle fibres
in the absence of compound and then at four increasing compound concentrations with
35 G_m determinations in 5-10 fibres at each concentration. The average G_m values at each

concentration were plotted against compound concentration and the data was fitted to sigmoidal function to obtain an EC₅₀ value.

5 The EC₅₀ value for various CIC-1 inhibitors are given in WO 2019/115777, WO 2019/115780, WO 2019/115781, WO 2020/254553, WO 2020/254558 and WO 2020/254559.

Example 2: Measurement of force in an *in vitro* model

10 The current disclosure relates to compounds that inhibit CIC-1 ion channels and increase muscle excitability and thereby improve muscle function in clinical conditions where muscle activation is failing. Such conditions result in loss of contractile function of skeletal muscle, weakness and excessive fatigue. In this series of experiments the compounds were tested for their ability to restore contractile function of isolated rat muscle when the neuromuscular transmission had been compromised akin to
15 neuromuscular disorders.

Experimentally, soleus muscles from 4-5 wk old rats were isolated with the motor nerve remaining attached. The nerve-muscle preparations were mounted in experimental setups that enabled electrical stimulation of the motor nerve. Stimulation of the motor
20 nerve led to activation of the muscle fibres and ensuing force production that was recorded. The nerve-muscle preparations were also in these experiments incubated in the standard Krebs Ringer (see example 15) and the solution was heated to 30°C and continuously equilibrated with a mixture of 95% O₂ and 5% CO₂, pH ~7.4.

25 After mounting the nerve-muscle preparation in the experimental setup, the contractile function of the muscle was initially assessed under the control conditions. Sub-maximal concentration of tubocurarine (115 nM), an acetylcholine receptor antagonist, was then added to the experimental bath to impose partial inhibition of the ability of the motor nerve to activate the muscle fibres. The experimental condition mimics the failing
30 neuromuscular transmission in a range of neuromuscular disorders. After addition of tubocurarine the contractile force declined over the next 90 minutes to 10-50 % of the control force. The test compound was then added to obtain the required compound concentration in the bath and the contractile force recovered was measured. To quantify the ability of the compound to restore force the percentage of the initial force
35 that was restored was determined after 40 mins of compound exposure.

The percentage increase of initial force that was restored for various CIC-1 inhibitors are given in WO 2016/202341, WO 2019/115777, WO 2019/115780, WO 2019/115781, EP19181253, WO 2020/254553, WO 2020/254558 and WO 2020/254559.

Example 3: Screening of compounds on the human isoform of CIC-1 expressed in CHO cells using automated patch-clamp

The investigatory goal of these experiments was to evaluate how compounds affect the open probability and current amplitude of human CIC-1 channels expressed in CHO cells. Experiments were performed using an automated patch clamp system that allowed high throughput testing of whole cell patches together with both intracellular and extracellular addition of compound.

Automated voltage clamp measurements

Automated whole cell patch clamp experiments were performed with the Qpatch 16 system (Sophion Bioscience, Ballerup, Denmark) at room temperature. Data acquisition and analysis were performed in the Qassay software (ver. 5.6, Odense).

Voltage protocol and analysis of whole cell CIC-1 currents

To evoke CIC-1 currents in whole cell patches, the membrane potential was initially stepped from a holding potential of -30 mV to +60 mV for 100 ms and then to various test voltages (sweeps) ranging from +120 mV to -140 mV in steps of 20 mV for 300 ms. To obtain tail currents, the membrane potential was stepped to -100 mV after each test voltage for 300 ms and then relaxed to -30 mV for 2 sec between sweeps.

I/V relationships for whole cell instant and steady state current amplitudes were obtained by plotting average current densities at the beginning and at the end of the 300 ms step against the membrane potential.

In order to determine the relative overall open probability (P_o), the instantaneous tail currents were normalized to the maximal tail current obtained following the most positive voltage step and plotted against the test voltage. Plots of normalized tail currents from each whole cell patch were then fitted to a Boltzmann function allowing determination of half activation voltages ($V_{1/2}$).

Solutions

For automated patch clamp experiments extracellular solutions contained: 2 mM CaCl_2 , 1 mM MgCl_2 , 10 mM HEPES, 4 mM KCl, 145 mM NaCl, 10 mM Glucose, pH adjusted to 7.4 with NaOH (2 M). Osmolality adjusted to ~320 using sucrose.

- 5 Intracellular solutions contained: 80 mM CsF, 60 mM CsCl, 5/1 mM KOH/EGTA, 10 mM HEPES, 10 mM NaCl, pH adjusted to 7.2 with NaOH (2 M). Osmolality adjusted to ~320 mOsm using sucrose.

Cell line information:

- 10 Cells used in patch clamp experiments were Chinese hamster ovary cells (CHO) constitutively expressing human CIC-1 channels. The amino acid sequence encoded by the cDNA used to create this cell line was identical to the translated sequence for GenBank accession number NM_000083.2. Cells were produced by Charles River (Catalogue CT6175, Cleveland OH, USA) in a cryopreserved format. Experiments were
- 15 performed on the cells directly after thawing (3×10^6 cells used in each experiment).

Test protocol

- To evaluate the compound effect on CIC-1, when applied directly to the intracellular side of the cell membrane, the half activation voltage, $V_{1/2}$, was determined from whole
- 20 cell patches with compound added to the intracellular solution and then compared to $V_{1/2}$ determined from control cell patches with only vehicle added to the intracellular solution. Additionally, the effect of extracellular added compound was evaluated by determine $V_{1/2}$ and steady state current amplitudes before and after exchanging the extracellular solution to contain compound.
- 25 The difference in half activation voltage of CIC-1 channels, $\Delta V_{1/2}$, was determined as the difference between the cell patches treated intracellularly with compound and control cells patches and is reported for various CIC-1 inhibitors in WO 2019/115777, WO 2019/115780, WO 2019/115781, EP19181253, WO 2020/254554 and WO 2020/254558. A positive shift in $\Delta V_{1/2}$ is reflecting CIC-1 channel inhibition by the tested
- 30 compound. P-values of <0.05 is considered significant.

Example 4: Measurement of *In Situ* Muscle Contractile Characteristics

Isometric hindlimb force was measured in 12-week old female Lewis rats in the presence and absence of compound.

Rats were placed under anesthesia with isoflurane (2–4%), intubated and subsequently connected to a micro ventilator (Microvent 1, Hallowell EMC, US). Two stimulation electrodes were inserted through the skin to stimulate the sciatic nerve. A small incision was made proximal to the ankle, to expose the Achilles tendon, which was tied by cotton string, and connected to a force transducer (Fort250, World Precision Instruments) with adjustable position (Vernier control). The Achilles tendon was then cut distal to the attached cotton string. The rat was placed on a heated pad, and to prevent movement artefacts from contraction of the ankle dorsiflexors, the foot was fixated by tape on a footplate.

Muscle contractile properties were assessed by applying an electrical current (under supramaximal voltage conditions) to the nerve and recording the force generated by the muscle. The muscle was stretched until maximal force was obtained, when assessed by 2 Hz stimulation. Isometric force was measured every 30 seconds at 12 Hz (Twitch), 10 pulses, and at every 5 minutes at 80 Hz (Tetanic) for 1 second (80 pulses). This stimulation pattern was employed throughout the experiment, except in few cases where 80 Hz stimulation was replaced by 12 Hz (10 pulses). Neuromuscular transmission was partially inhibited by constant infusion of Cisatracurium (Nimbex, GlaxoSmithKline) at a concentration of 0.1 mg/kg at an adjustable infusion speed, adjusted individually for each animal to obtain a level of inhibition of ca. 50% of the forced generated at 12 Hz stimulation on the 4th pulse. When the level of neuromuscular inhibition was stable, the test article was injected i.v., i.p. or per oral at the chosen concentration. The effect of test article was assessed on its ability to increase force generated from the stimulation pattern applied. The effect was assessed in the ability to increase force per se (tetanic, 80 Hz, stimulation), and the ratio between individual twitch peaks (12 Hz stimulation). The effect was monitored for at least 1 hour after injection of test article. In addition, the time from injection of test article to maximal effect on force (both twitch and tetanic) was noted and the time for the effect to disappear (return to baseline), if possible. When appropriate the infusion of neuromuscular blocking agent was ceased, with the stimulation pattern continued, and the return of force to control levels was monitored. Animals were sacrificed by cervical dislocation while still fully sedated.

The percentage increase in tetanic force that was restored for various CIC-1 inhibitors are given in WO 2019/115777, WO 2019/115780, WO 2019/115781, WO 2020/254553, WO 2020/254554, WO 2020/254558 and WO 2020/254559.

Example 5: Pharmacological model of neuromuscular dysfunction in sedated WT rats

An experimental setup

5 Experiments were performed in sedated and mechanically ventilated female wistar rats in a pharmacological model of neuromuscular dysfunction. The setup was designed to enable co-temporal measurements of electromyographic recordings of compound muscle action potentials (CMAP, EMG) and stimulated muscle force in combination with stimulated single fiber EMG (SSFEMG; to evaluate jitter and block) from *triceps*
10 *surae* muscles. Neuromuscular dysfunction was induced pharmacologically by intravenous infusion of a neuromuscular blocking agent (NMBA); cisatracurium.

Animal surgery

Anaesthesia was introduced with a 1:1 mix of Fentanyl (Hypnorm) and Midazolam
15 (Dormicum 5mg/mL) (Hameln Pharma Plus gmbh, DE) at dose volume 1 mL/kg subcutaneously. Following, rats were intubated and mechanically ventilated to ensure adequate pulmonary gas exchange (Hallowell MicroVent 1 Rodent Anesthesia Ventilator, Dre Veterinary, KY, USA), and anaesthesia was maintained by mixing isoflurane (2-3 %) in the ventilation gas. A gastric tube was inserted through the
20 oesophagus to the ventricle to allow per oral (PO) dosing. The jugular vein was cannulated for acquisition of blood samples to verify an efficacious plasma exposure level. The animals' core body temperature was continuously monitored and maintained at 37 °C by the heating pad upon which the animal was positioned.

Stimulated muscle force and CMAP

When the animal was under stable anaesthesia, preparations for measuring CMAP
25 (EMG) and force from the right hind leg were made: The distal part of the *triceps surae* muscle was surgically exposed and a string was tied firmly to the Achilles' tendon after which the tendon was cut distally to the string. The string was connected to a force
30 transducer (FORT 1000, World Precision Instruments, FL, USA). Two stimulation electrodes (Monopolar EMG Needle Electrode 25 mm x 27 g, Chalgren, London, UK) were then inserted in the vicinity of the sciatic nerve to elicit nerve-stimulated contractile responses of the *triceps surae* muscle upon electrical stimulation of the nerve. The force generation elicited by stimulation was in turn recorded and quantified
35 by the force transducer. Lastly, two EMG electrodes (subdermal needle electrode,

Cadwell Kennewick, WA, USA) were placed subcutaneously with the active recording electrode placed distal to the knee joint over the proximal portion of the *triceps surae* muscle and the reference electrode was placed over the metatarsal region of the foot. The acquisition program (Signal version 6.4, Cambridge Electronics Design Ltd,
5 Cambridge, UK) was used to control stimulation, delivered by an isolated stimulator (isostim 01D NPI electronics, DE) and to record the data via an analogue-digital converter (Micro 1401 Cambridge Electronics Design Ltd, Cambridge, UK).

After set-up, the sciatic nerve was stimulated with 10 pulses of 12 Hz (12-15 V) every
10 30 s. After 9 stimulations (5 min) the 12 Hz stimulation was substituted by 80 Hz stimulation for 1 second, and 9 stimulations later again substituted by 80 Hz stimulation for 1 second. This cycle was repeated until the end of the experiment. Muscle force data from 80 Hz stimulation was quantified as the Area Under the Curve (AUC) of the active force (g*s). For CMAP analysis the amplitude of the 1st peak in trains of 12 Hz
15 stimulation, and amplitudes of the 10th peak were used, and the ratio of 10th/1st is depicted in Figure 1 A and B.

Stimulated Single Fiber EMG (SSFEMG)

SSFEMG was performed in the same rats simultaneously with force and CMAP to
20 assess jitter and NMJ blocking in the presence and absence of CIC-1 inhibitor compound. SSFEMG was performed in the gastrocnemius muscle (left leg) using a Sierra Summit clinical electrodiagnostic system (Cadwell, Kennewick, WA, USA)¹⁸. Hair of the left hind leg was shaved, and the foot of the left hindlimb leg was secured with tape with the hip joint in an abducted position and the ankle in plantarflexion. Two
25 stimulation electrodes (Monopolar EMG Needle Electrode 25mm x 27 g, Chalgren, London, UK) were then placed transcutaneously at various positions at the Gastrocnemius muscle to stimulate branches from the sciatic nerve to muscle fibers. One ground electrode (subdermal needle electrode, Cadwell Kennewick, WA, USA) was inserted subcutaneously at the root of the tail. A highly selective SFEMG recording
30 needle (25 x 0.30 mm, SEI EMG s.r.l., Cittadella, IT) was inserted into the gastrocnemius muscle to record single fiber APs elicited upon stimulation. The nerve branch was stimulated with a frequency of 10 Hz, pulse duration of 50 μ s, and varying current intensity (mA) that were adapted to each rat. Criteria for the captured APs were a minimum amplitude of 200 μ V and a rise time <500 μ s together with an all-or-nothing
35 response. One hundred (100) potentials were captured from each synapse. Jitter

(mean consecutive delay, MCD) was reported as an average per animal and blocking was reported as the percentage of synapses with blocking out of the total number of synapses for each animal. SSFEMG parameters of jitter, which is the variability in the arrival time of APs to the recording electrode between consecutive electrical
5 discharges, and intermittent impulse blocking (i.e., complete NMJ transmission failure) were quantified (Figure 1 C and D).

After stable recordings of all four read-outs (force, CMAP, jitter and block) (White bar, Figure 1 A-D), NMBA was introduced as a constant iv infusion to a stable
10 neuromuscular block level resulting in approximately 30% force relative to pre-NMBA (grey bar, Figure 1 A-D) and NMD712 ((S)-2-(p-bromophenoxy)butyric acid) was administered orally (50 mg/kg). 60 minutes after compound administration recordings were made (checked bar, Figure 1 A-D). The NMD compound resulted in a restoration of all 4 parameters, suggesting an improvement in neuromuscular transmission and
15 muscle function.

Example 6: Method of determining jitter and block in a clinical setting

Single fibre electromyography (SFEMG) was performed using a clinical
electrodiagnostic system [Ohio State University: Cadwell Sierra Wave (Kennewick,
20 WA, USA)] a concentric needle recording electrode (25 mm X 30 gauge, Dantec) and 1–10 kHz for high- and low-pass filter settings to record and analysed up to 22 apparent single muscle fibre action potential pairs during voluntary contraction. A total of 50-100 consecutive discharges were analysed for each apparent single muscle fiber pair to determine parameters of jitter (variability of NMJ transmission) and blocking
25 (i.e., Failure of NMJ transmission). Repetitive Nerve Stimulation (RNS) at 3 Hz stimulation rate was performed on trapezius and abductor pollicis brevis muscles. Compound muscle action potential (CMAP) decrement of amplitude and area of 1st to 5th and 1st to 10th stimuli was quantified. See also Weir et al, 1979.

30 Example 7: Observational Clinical Trial

I. Introduction

An observational clinical trial was run to determine and characterize the presence of NMJ transmission abnormalities in patients with CMT1 or CMT2. The primary aim was to investigate NMJ transmission deficits in CMT types 1 and 2 patients compared with
35 age-matched healthy controls.

II.1. Study Overview and Timeline

The study protocol was reviewed and approved by The Ohio State University Wexner Medical Center Institutional Review Board and The Central Denmark region Committees on Health Research Ethics. All participants, both CMT patients and healthy controls, provided written informed consent before study participation. CMT participants underwent 4 clinic evaluations. After the baseline visit the between visit interval was 2 weeks +/-10 days (Figure 2). Each visit involved clinical and electrophysiological testing. Healthy controls underwent electrophysiological testing at a single visit (Visit 1). (Figure 2). The study was conducted in accordance with the Declaration of Helsinki and registered in the database Clinicaltrials.gov (NCT04980807)

II.2. Participants

Study enrolment included participants with CMT types 1 and 2 and aged-matched healthy controls. The inclusion and exclusion criteria for CMT participants and healthy controls are listed in Tables 1 and 2 respectively. The inclusion and exclusion criteria were defined to ensure that the CMT diagnosis was certain, that participants could complete the physical tests, and that their condition was stable in order to eliminate factors that could potentially influence NMJ function.

Table 1: Inclusion and exclusion criteria for CMT participants

CMT Participants	
Inclusion criteria	Exclusion criteria
Age ≥18 years	Ulceration that would interfere with functional ability
Diagnosis of CMT Type 1 or 2 via: - genetic testing; or - a combination of clinical presentation and electrodiagnostic testing	Severe deformity or ankle contracture that would sufficiently limit passive range of motion to affect assessment of dorsiflexion strength
Physical ability (all must apply): - ambulate 10 meters without bracing - bilateral ankle plantarflexion strength between 2- and 5 (inclusive) on the	Significant change in physical activity or exercise (e.g. significant in- or decrease in intensity or frequency) within 8 weeks before Study Day 1 or

Medical Research Council (MRC) scale • bilateral ankle dorsiflexion strength between 2- and 4+ (inclusive) on the MRC scale	inability to maintain the baseline level of physical activity throughout the study
Ability to adhere to study schedule and procedures	Moderate to severe neuropathic or inflammatory/musculoskeletal pain that would interfere with performance of the tests
Stable concomitant medications for 2 months prior to enrolment	A diagnosis of a primary NMJ disorder such as myasthenia gravis, Lambert Eaton Myasthenic Syndrome or congenital myasthenic disorder
Ability to provide written informed consent	Any disability or condition that would prevent completion of the study tasks
	Recent major surgery

Table 2: Inclusion and exclusion criteria for healthy control participants

Healthy Control Participants	
Inclusion criteria	Exclusion criteria
Age ≥18 years	Pregnant
Healthy male or female volunteers	Requiring prescription medicines likely to interfere with electromyography (EMG) recordings
Ability to provide written informed consent	Presence of current or previous medical condition which might interfere with participation in the study

II.3. Study Outcomes

5 Outcome measures included NMJ electrophysiological testing, isometric dynamometry, Manual Muscle Testing, 10-meter walk/run time, Timed Up and Go, 6-minute walk test, Berg Balance Scale (total score), Six-Spot Step Test, 9-hole peg test, and CMT Examination Score (CMTES2). Adverse events (AEs) were collected throughout the

10 (electrophysiological tests) and CMT participants (electrophysiological and clinical

tests) at all study visits using on a scale from 0-9 with 0 indicating no discomfort and 9 indicating worst possible discomfort.

II.3.A. NMJ Electrophysiology.

5 Single fibre electromyography (SFEMG) was performed using a clinical
electrodiagnostic system [Ohio State University: Cadwell Sierra Wave (Kennewick,
WA, USA)] a concentric needle recording electrode (25 mm X 30 gauge, Dantec) and
1–10 kHz for high- and low-pass filter settings to record and analysed up to 22
10 apparent single muscle fibre action potential pairs during voluntary contraction. A total
of 50-100 consecutive discharges were analysed for each apparent single muscle fiber
pair to determine parameters of jitter (variability of NMJ transmission) and blocking
(i.e., Failure of NMJ transmission). Repetitive Nerve Stimulation (RNS) at 3 Hz
stimulation rate was performed on trapezius and abductor pollicis brevis muscles.
Compound muscle action potential (CMAP) decrement of amplitude and area of 1st to
15 5th and 1st to 10th stimuli was quantified.

Manual Muscle Testing (MMT)

Manual muscle testing (MMT) was performed on 15 muscle groups, including shoulder
abduction, elbow flexion/extension, wrist flexion/extension, long thumb flexors, hip
20 flexors/extensors, hip abductors, knee flexors/extensors, ankle dorsi flexors/plantar
flexors, and neck flexors/extensors. All but the neck muscle groups were tested
bilaterally. Positioning and grading were standardized and applied as previously
described (Personius, 1994; Kendall, 2005). The modified Medical Research Council
(MRC) scale was translated into a 0-10 ordinal scale that was used for analysis (Table
25 3).

Table 3: Translation table for converting MRC score into ordinal scale score

MRC Grade	Value for Analysis
5	10
4+	9
4	8
4-	7
3+	6
3	5

3-	4
2+	3
2	2
2-	1
1	0
0	0

Isometric Dynamometry

Isometric dynamometry was performed using each site's respective available equipment. The Ohio State University utilized the Accurate Test of Limb Isometric Strength (ATLIS) chair, which is a fixed frame apparatus with an adjustable wireless loadcell. Ankle dorsiflexion was tested in an upright seated position; positioning was otherwise standardized and applied as previously described (Andres et al, 2012). Aarhus University Hospital utilized a Biodex Isokinetic Dynamometer, SYSTEM 3 PRO (Biodex Medical Systems, Inc.). Ankle dorsiflexion was tested on the non-dominant side. Positioning was standardized and applied as previously described (Harbo et al, 2012). A minimum of two trials were performed; additional trials were performed if there was greater than 15% variability. Since different methods were used, data collected for the two sites were not combined for analysis. The highest value for each muscle group was recorded.

II.3.B. Functional and Assessments

Nine-hole Peg Test (9HPT)

The nine-hole peg test (9HPT) is a timed test of finger dexterity and hand function. Participants place 9 pegs from a reservoir into holes aligned in a 3-by-3 grid and then move them back to the reservoir again one at a time. The 9HPT has been shown to be reliable and responsive in people with CMT (Svensson et al, 2006; Solari et al, 2008; Piscoquito et al, 2015). Set up and procedure were standardized as previously described (Mathiowetz et al, 1985). Two trials were performed with each hand; trials were averaged and used for analysis.

Six-spot Step Test (SSST)

The Six-spot Step Test (SSST) is a timed test of lower extremity function and balance. Participants walk in a standardized zig-zag pattern through a 1 x 5-meter course,

sliding cylindrical blocks with their tested foot out of the course as they move through it (Nieuwenhuis et al, 2006). This test has been shown to be valid and reliable in neurodegenerative conditions and older adults (Sandroff et al, 2015; Brincks et al, 2019; Kondori et al, 2020); it has also shown responsiveness in polyneuropathy (Kreutzfeldt et al, 2017). Two trials were performed with each foot; trials were averaged and used for analysis. Participants were permitted to use their typical bracing and/or assistive devices, which was documented at each visit.

Ten-meter Walk/Run Test (10mWRT)

The 10-meter Walk/Run Test (10mWRT) is a timed assessment meant to capture maximal performance over a short distance and does not suffer from the same ceiling effects as a test that permits only walking regardless of the person's ability (Krosschell et al, 2022). It has been shown to be reliable in CMT (Bray et al, 2020). Two trials were performed and averaged for analysis. Participants were permitted to use their typical bracing and/or assistive devices, which was documented at each visit.

Timed Up and Go (TUG)

The Timed Up and Go (TUG) is a timed mobility assessment involving rising from a chair, walking 3 meters at a comfortable pace, and returning to sit in the chair (Podsiadlo et al, 1991). It has been validated neurologic, neuromuscular, and geriatric populations (Dunaway et al, 2014). Two trials were performed and averaged for use in data analysis. Participants were permitted to use their typical bracing and/or assistive devices, which was documented at each visit.

Six-minute Walk Test (6MWT)

The Six-minute Walk Test (6MWT) is a measure of endurance and can also provide an index of fatigability (Montes et al, 2010). Validity has been established in people with CMT (Mori et al, 2020). The test was administered according to the American Thoracic Society guidelines on a 30-meter course with standardized cues (ATS, 2002). Participants were permitted to use their typical bracing and/or assistive devices, which was documented at each visit. A 10-minute rest was required prior to the start of the test. Total distance as well as percent change in distance walked between the first and sixth minutes were used for analyses.

Berg Balance Scale (BBS)

The Berg Balance Scale (BBS) is a 14-item assessment of balance during functional tasks. Each item is scored on a 0 to 4 scale where higher scores indicate better performance. The total score used for analysis is the sum of the individual scores for each item with a maximum score of 56. It has demonstrated validity in CMT (Bragadin et al, 2015). Participants were permitted to wear bracing but could not use mobility devices. Items were administered as previously described (Berg et al, 1989).

CMT Examination Score (CMES2)

The CMT Examination Score version 2 is a composite scoring system to assess sensory and motor impairment in subjects with CMT. It is a subscore of the CMT Neuropathy Score. Each item is scored on a 0-4 ordinal scale where higher scores indicate greater severity of impairment. It has demonstrated excellent inter- and intra-rate reliability in people with CMT (Murphy et al, 2011).

II.4. Statistical Analysis

Statistical analyses were performed using SAS by an independent statistical consultancy group, Phastar. Statistical coding was performed prior to database lock and in accordance with the statistical analysis plan for the study. For the primary aim comparing NMJ transmission in CMT patients and controls, data that followed parametric (normal) distribution was analysed with unpaired t-tests. For data with unequal variances, Welch's test was used. For data that did not follow parametric distribution, a Mann Whitney test was applied. For the secondary aim of test-retest reliability interclass correlation coefficient (ICC) were calculated. For the exploratory analysis investigating associations between electrophysiological and clinical outcomes, Spearman correlation coefficients were calculated. No corrections for multiple testing were performed due to the exploratory nature of the study.

III. Results

III.1. Study Participants, Demographics, Baseline Characteristics, and Adverse Events

A total of 23 CMT patients and 10 healthy controls were screened for participation. A total of 21 CMT patients and 10 healthy controls were enrolled. Of those, 18 CMT patients and 10 healthy controls completed all visits while 2 CMT patients dropped out after visit 3 (1 patient was unable to make the final visit within the allowed time-period

and another enrolled in a drug study), and 1 patient withdrew consent before first visit for personal reasons. For these 3 subjects, available data are included in the analyses. Demographic and baseline characteristics are presented in Table 4. No AEs were reported for the healthy controls. A total of 4 AEs were reported in CMT patients: 1

5 patient fell during 6MWT – graded mild, 1 patient fell during 10MWT – graded mild, 1 patient experienced knee pain following isometric dynamometry – graded moderate, and 1 patient had a syncope – graded mild.

Table 4: Demographics and Clinical Baseline Characteristics

	HC	CMT	CMT1	CMT2
N	10	21	16	5
Age (Years)	43.3 ± 12.68	46.4 ± 14.4	43 ± 11.7	56 ± 19.3
Gender (M/F)	4/6	5/16	3/13	2/3
CMTES2 Total Score	NA	10.1 ± 3.2 N=20	10.3 ± 2.7 N=15	9.4 ± 3.4 N=5
9 Hole Peg Test (s)	NA	21.6 ± 4.7 N=20	21.9 ± 5.3 N=15	21.0 ± 2.2 N=5
6 Spot Step Test (s)	NA	9.9 ± 2.6 N=20	9.5 ± 2.7 N=15	10.9 ± 1.8 N=5
10 Meter Walk/Run Test (s)	NA	6.1 ± 2.1 N=20	5.8 ± 1.8 N=15	6.9 ± 3.1 N=5
Timed Up and Go (s)	NA	7.9 ± 1.9 N=20	7.4 ± 1.6 N=15	9.4 ± 2.2 N=5
Berg Balance Scale Total Score	NA	51.3 ± 5.0 N=20	52.1 ± 4.8 N=15	49.0 ± 5.6 N=5
Manual Muscle Testing Total Score	NA	249.6 ± 17.3 N=19	251.2 ± 15.6 N=14	245.2 ± 23.0 N=5
Non-Dominant Ankle Dorsi Flexor Strength – Aarhus (Nm)	NA	12.0 ± 4.5 N=9	12.1 ± 4.8 N=8	11.3 N=1
Right Ankle Dorsi Flexor Strength – Ohio (N)	NA	95.9 ± 58.9 N=7	96.9 ± 65.5 N=4	94.6 ± 62.9 N=3
6 Minute Walk Test Total Distance (m)	NA	455.3 ± 102.8 N=20	464.9 ± 93.7 N=15	426.7 ± 134.8 N=5
6 Minute Walk Test 6th/1st minute (%)	NA	-6.6 ± 13.9 N=20	-5.2 ± 14.7 N=15	-10.8 ± 11.2 N=5

Data are mean ± SD.

III.2.CMT patients demonstrate notable NMJ transmission deficits compared with healthy controls

For the primary aim, comparing NMJ transmission on SFEMG and RNS between CMT patients and healthy controls, data from study visit 1 (baseline) was used. Median SFEMG jitter, a measure of NMJ transmission reliability, was increased by >90% in CMT patients compared with healthy controls [CMT: median jitter 56.3 μ s (range: 35.3; 196.6) versus Healthy controls: median 29.4 μ s (range: 18.6; 35.6), $p<0.05$] (Figure 3A). Similarly, SFEMG blocking, a measure of NMJ transmission failure, was increased in CMT patients [CMT: median blocking 13.39 % (range: 0; 90.9) versus Healthy controls: median 0 % (range: 0; 4.5), $p<0.05$]. In addition to comparing CMT patients to healthy controls, SFEMG jitter was also compared between CMT1 and CMT2. Jitter was increased in CMT2 versus CMT1 [CMT2: median jitter 100.2 μ s (range: 62.2; 152.2) versus CMT1: median jitter 49.3 μ s (range: 35.3; 196.6), $p<0.05$] (Figure 3C). Similarly, SFEMG blocking was increased in CMT2 versus CMT1 [CMT2: median blocking 75.0% (range: 12.5; 87.5) versus CMT1: median blocking 10.0% (range: 0.0; 90.9), $p<0.05$] (Figure 3D).

Compound muscle action potential (CMAP) amplitude was assessed following a single supramaximal stimulation and following a train of 10 stimulations at 3 Hz. CMAP amplitude following a single stimulation demonstrated ~40% reduction in CMT patients compared with healthy controls recording from the abductor pollicis brevis (APB) muscle and ~35% reduction in CMT patients compared with healthy controls recording from the trapezius muscle. In contrast to SFEMG, RNS at 3 Hz demonstrated no significantly increased decrement when comparing the 1st stimulation to both the 5th and 10th stimulation in a train of 10 stimulations and recording from both the APB and trapezius muscles. Neither CMAP amplitude following a single stimulation nor decrement following a train of stimuli showed differences between CMT1 and CMT2 for the APB or trapezius muscles.

IV.3. Secondary Analysis – Test-Retest Reliability

Test-retest reliability was assessed for both electrophysiological and clinical outcomes by calculating interclass correlation coefficient (ICC) values based on data from study visit 1-4 from CMT patients. Test-retest reliability estimates between visits are summarised in Table 5.

Table 5: Test-Retest Reliability

Outcome Measure	ICC	Visit 1	Visit 2	Visit 3	Visit 4
Electrophysiological Outcomes					
Jitter (μ s)	0.50	75.6 $\pm$ 47.7	76.2 $\pm$ 47.7	66.3 $\pm$ 33.4	71.2 $\pm$ 38.5
Blocking (%)	0.48	29.9 $\pm$ 33.2	32.0 $\pm$ 30.3	25.2 $\pm$ 26.9	23.8 $\pm$ 23.4
CMAP Decrement of Area Stim 1-10 APB (%)	0.14	-9.9 $\pm$ 8.7	-10.1 $\pm$ 4.4	-7.5 $\pm$ 4.2	-7.4 $\pm$ 5.5
CMAP Decrement of Area Stim 1-10 Trapezius (%)	0.01	-7.8 $\pm$ 4.8	-8.3 $\pm$ 4.7	-9.0 $\pm$ 4.6	-6.5 $\pm$ 3.6
Clinical Outcomes					
10 Meter Walk/Run Test (s)	0.97	6.1 $\pm$ 2.1	5.9 $\pm$ 2.2	5.8 $\pm$ 2.3	5.5 $\pm$ 2.0
9 Hole Peg Test (s)	0.92	21.6 $\pm$ 4.7	21.3 $\pm$ 5.2	20.2 $\pm$ 5.0	20.0 $\pm$ 3.0
Right Ankle Dorsi Flexor Strength – Ohio (N)	0.88	95.9 $\pm$ 58.8	83.7 $\pm$ 46.3	93.4 $\pm$ 48.6	100.8 $\pm$ 60.7
Non-Dominant Ankle Dorsi Flexor Strength – Aarhus (Nm)	0.87	12.0 $\pm$ 4.5	13.5 $\pm$ 4.3	13.7 $\pm$ 4.1	13.8 $\pm$ 5.8
6 Minute Walk Test Total Distance (m)	0.81	455.3 $\pm$ 102.9	474.4 $\pm$ 101.0	481.3 $\pm$ 103.9	490.4 $\pm$ 90.8
6 Spot Step Test (s)	0.79	9.9 $\pm$ 2.6	9.1 $\pm$ 2.8	8.8 $\pm$ 2.6	8.3 $\pm$ 2.5
Timed Up and Go (s)	0.76	7.9 $\pm$ 1.9	7.6 $\pm$ 1.8	7.6 $\pm$ 1.9	7.3 $\pm$ 1.6
Berg Balance Scale	0.72	51.3 $\pm$ 5.1	53.2 $\pm$ 3.4	53.9 $\pm$ 3.3	54.0 $\pm$ 3.3
Manual Muscle Testing	0.69	249.6 $\pm$ 17.3	256.3 $\pm$ 12.4	256.5 $\pm$ 13.2	259.7 $\pm$ 10.2
6 Minute Walk Test 6th/1st minute (%)	0.52	-6.6 $\pm$ 13.9	-6.5 $\pm$ 12.5	-3.0 $\pm$ 7.7	-3.3 $\pm$ 6.0

Data are mean $\pm$ SD and interclass correlation coefficient (ICC).

IV.4. Secondary Analysis - Tolerability of Electrophysiological and Clinical Outcomes

Tolerability scores for the different procedures at each visit for CMT patients and healthy controls are summarised in Table 6. Tolerability was evaluated on a scale from 0-9 with 0 indicating no discomfort and 9 indicating worst possible discomfort.

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Table 6: Tolerability of Electrophysiological and Clinical Outcomes

Outcome Measure	HC Visit 1	CMT Visit 1	CMT Visit 2	CMT Visit 3	CMT Visit 4
Electrophysiological Outcomes					
SFEMG	2 (1-6)	3.5 (0-6)	2.5 (0-9)	3 (0-9)	2.5 (0-8)
RNS – Trapezius	2 (0-7)	4.5 (0-8)	4 (0-8)	5 (0-9)	4(0-9)
RNS – APB	3 (0-6)	4 (1-8)	5 (1-9)	3 (0-9)	3 (0-8)
Clinical Outcomes					
CMTES2	NA	0 (0-2)	NA	NA	NA
9 Hole Peg Test	NA	0 (0-4)	0 (0-4)	0 (0-4)	0 (0-4)
6 Spot Step Test	NA	0 (0-4)	0 (0-4)	0 (0-4)	0 (0-4)
10 Meter Walk/Run Test	NA	0.5 (0-4)	1 (0-4)	1 (0-4)	0 (0-4)
Timed Up and Go	NA	0 (0-4)	0 (0-4)	0 (0-4)	0 (0-4)
Berg Balance Scale	NA	1 (0-7)	0 (0-5)	0 (0-6)	0.5 (0-3)
Manual Muscle Testing	NA	0.5 (0-5)	1 (0-3)	0 (0-4)	1 (0-4)
Isometric Dynamometry	NA	1.5 (0-5)	2 (0-5)	2 (0-4)	0.5 (0-4)
6 Minute Walk Test	NA	2 (0-5)	1 (0-6)	1.5 (0-5)	1 (0-5)

Data are medians with range

IV.5. NMJ transmission defects are correlated with measures of strength and function in CMT

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Associations between electrophysiological and clinical endpoints are summarized in Table 7. Clinical parameters related to strength, balance and mobility were associated with jitter and blocking. 6 Spot Step Test, 10 Meter Walk/Run Test and Timed Up and Go were positively associated with jitter and blocking indicating that longer time to complete these tasks (worse performance) are associated with higher levels of jitter and blocking (worse NMJ transmission). Isometric ankle dorsi flexor strength, the total score of the Berg Balance Scale, and 6 Minute Walk Test were negatively associated with jitter and blocking indicating that lower performance in these tasks were

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associated with higher levels of jitter and blocking. CMTES2, Manual Muscle Testing and 9 Hole Peg Test were not associated with jitter and blocking. In general, and in contrast to SFEMG measurements, clinical endpoints were not associated with CMAP decrement assessed with RNS (data not shown).

5

Table 7: Association of clinical outcomes with jitter and blocking

Clinical Outcome Measure	Association with Jitter	Association with Blocking
Right Ankle Dorsi Flexor Strength – Ohio	-0.893 (p=0.007)	-0.750 (p=0.052)
Non-Dominant Ankle Dorsi Flexor Strength – Aarhus	-0.783 (p=0.013)	-0.630 (p=0.069)
6 Spot Step Test	0.674 (p=0.001)	0.533 (p=0.015)
Berg Balance Scale Total Score	-0.608 (p=0.004)	-0.548 (p=0.012)
Timed Up and Go	0.606 (p=0.005)	0.457 (p=0.043)
6 Minute Walk Test Total Distance	-0.598 (p=0.005)	-0.484 (p=0.030)
10 Meter Walk/Run Test	0.541 (p=0.014)	0.333 (p=0.137)
6 Minute Walk Test 6th / 1st minute	-0.474 (p=0.035)	-0.616 (p=0.004)
9 Hole Peg Test	0.284 (p=0.225)	0.016 (p=0.947)
Manual Muscle Testing Total Score	-0.190 (p=0.437)	-0.067 (p=0.784)
CMTES2 Total Score	0.081 (p=0.733)	0.018 (p=0.940)

Associations between SFEMG parameters and clinical outcomes are Spearman’s correlations. Isometric dynamometry was performed by separate procedures by Aarhus and Ohio and hence these data were analysed by site.

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V. Discussion and Conclusions

As the final link between the nervous system and skeletal muscle, reliable NMJ transmission is critical for neural control of muscle contraction. Based on sparse animal studies and findings in other motor axonal and motor neuronal disorders, we hypothesized that patients with CMT would demonstrate features of NMJ transmission deficits. We further hypothesized that NMJ transmission deficits would be correlated with assessments of disease severity and function. Using SFEMG, we confirmed that CMT patients have notable NMJ transmission deficits compared with healthy age-matched controls. Furthermore, NMJ transmission deficits showed significant correlations with clinical outcome measures of strength, mobility, and balance.

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This study further provides reliability and tolerability estimates for clinical and electrophysiological outcomes in CMT patients. In general, clinical outcome measures were well tolerated and showed moderate to excellent reliability. SFEMG showed
5 better reliability and tolerability than RNS, but both tests were associated with stronger discomfort in a subset of patients.

Notably, SFEMG demonstrated clear evidence for NMJ transmission deficits. The fact that jitter and blocking showed significant correlations with clinical outcomes raises the
10 possibility of targeting NMJ transmission dysfunction to improve symptoms in patients with CMT.

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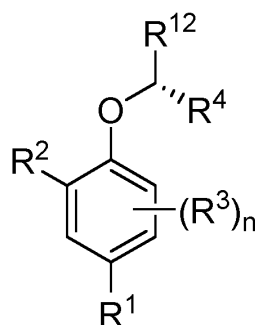
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Hopf and Eysholdt, 1978. Hopf HC, Eysholdt M. Impaired refractory periods of peripheral sensory nerves in multiple sclerosis. *Ann Neurol*. 1978 Dec;4(6):499-501. PMID: 742849. The entire content of the foregoing document is incorporated by
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30 reference herein.

Claims

1. A compound for use in the treatment, prevention and/or amelioration of multiple sclerosis, wherein the compound is a CIC-1 inhibitor.
- 5 2. The compound for use according to claim 1, wherein the CIC-1 inhibitor restores contractile force in the muscles of the subject.
3. The compound for use according to claim 1, wherein the CIC-1 inhibitor reduces the incidence of NMJ transmission failure in the muscles of the subject.
4. The compound for use according to claim 1, wherein the CIC-1 inhibitor increases
10 the probability of an action potential firing in the muscles of the subject.
5. The compound for use according to claim 1, wherein the CIC-1 inhibitor normalises jitter in the muscles of the subject.
6. The compound for use according to any of claims 1 to 5, wherein the compound is of Formula (I):



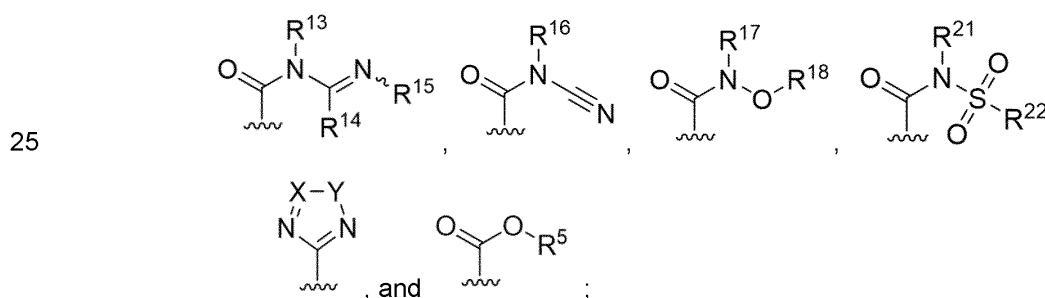
Formula (I)

wherein:

- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- 20 - R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-

C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;

- 5 - R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- 10 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶,
- 15 phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from the group consisting of deuterium and F;
- 20 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
- R⁸ is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F;
- R¹² is selected from the group consisting of:



- R¹³ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -C(=O)-C₁₋₅ alkyl optionally substituted with one or more,
- 30

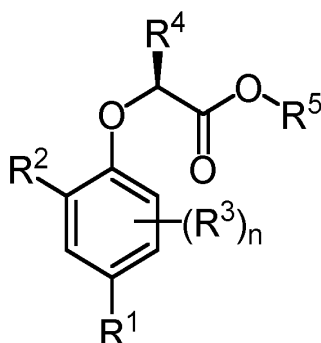
- identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 5 - R^{14} is selected from the group consisting of C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 and phenyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 10 - R^{15} is selected from the group consisting of $-OH$, $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 15 - R^{16} is selected from the group consisting of H , C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 20 - R^{17} is selected from the group consisting of H , C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{20} , C_{3-5} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl
- 25 optionally substituted with one or more, identical or different, substituents R^6 ;
- 30 - R^{18} is selected from the group consisting of H , C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{19} , C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^{19} , phenyl optionally substituted with one or more, identical or different, substituents R^6 , and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;
- 35 - R^{19} is independently selected from the group consisting of F , Cl , Br , I , $-CN$, $=O$, C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-O-C_{1-5}$ alkyl optionally substituted with one or

more, identical or different, substituents R^6 , -O-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -S-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -S-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO₂-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -SO₂-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different substituents R^6 , -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-NH-C₃₋₅ 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^8 , pyrrolidin-1-yl optionally substituted with one or more, identical or different, substituents R^{20} and 4-6 membered heterocycle optionally substituted with one or more, identical or different, substituents R^{20} ;

- R^{20} is independently selected from the group consisting of F, Cl, Br, I, -CN, =O, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-OC₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R^6 , -C(=O)-C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , -NH-C(=O)-C₁₋₅ alkyl optionally substituted with one or

- more, identical or different, substituents R^6 , $-NH-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-C(=O)-NH-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-NH-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 5
- R^{21} is selected from the group consisting of H, C_{1-5} alkyl optionally 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 , $-C(=O)-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-C(=O)-C_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 10
- R^{22} is selected from the group consisting of C_{1-5} alkyl optionally 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 and phenyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 15
- X is selected from the group consisting of N and CR^{23} ;
- 20
- Y is selected from the group consisting of NH, O and S;
- R^{23} is selected from the group consisting of H, NH_2 , C_{1-5} alkyl optionally 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 , $-OC_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 , $-OC_{3-5}$ cycloalkyl optionally substituted with one or more, identical or different, substituents R^6 , $-NH-C(=O)C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 and $-NH-SO_2-C_{1-5}$ alkyl optionally substituted with one or more, identical or different, substituents R^6 ;
- 25
- 30
- n is an integer 0, 1, 2, or 3;
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.

7. The compound for use according to claim 6, wherein the compound is of Formula (II):



Formula (II)

wherein:

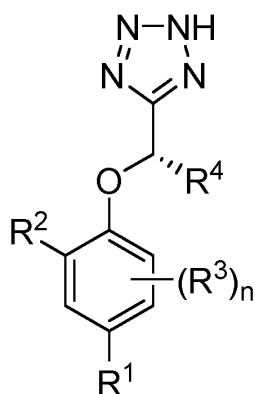
- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
- R² is selected from the group consisting of H, deuterium, F, Cl, Br, I, C₂₋₅ alkenyl optionally be substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally be substituted with one or more, identical or different, substituents R⁶, C₃₋₅ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶, and 5-membered aromatic heterocycle optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
- R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
- R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different,

- substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
- R⁶ is independently selected from deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
 - R⁸ 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.
8. The compound for use according to any one of claims 6 to 7, wherein:
- R¹ is selected from the group consisting of F, Cl, Br and I;
 - R² is selected from the group consisting of H, deuterium, F, Cl, Br and I;
 - R³ is selected from deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁸ 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.
9. The compound for use according to any one of claims 6 to 7, wherein:
- R¹ is selected from the group consisting of F, Cl, Br and I;

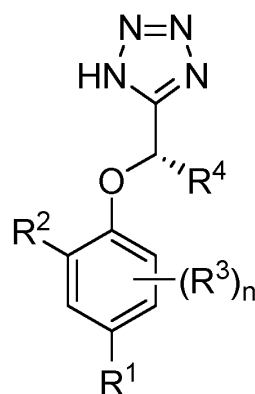
- R² is a 5-membered aromatic heterocycle which may be optionally substituted with one or more, identical or different, substituents R⁷;
 - R³ is selected from the group consisting of deuterium, F and Cl;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkynyl optionally substituted with one or more, identical or different, substituents R⁶, C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁶, phenyl optionally substituted with one or more, identical or different, substituents R⁸, and benzyl optionally substituted with one or more, identical or different, substituents R⁸;
 - R⁶ is independently selected from deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl;
 - R⁸ 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.
10. The compound for use according to any one of claims 6 to 7, wherein:
- R¹ is selected from the group consisting of C₁₋₂ alkyl, C₂ alkenyl, C₂ alkynyl, CN, CF₃, NO₂, F, Cl, Br, and I;
 - R² is -CF₂-C₁₋₅ alkyl optionally be substituted with one or more, identical or different, substituents R⁶;
 - R³ is selected from the group consisting of deuterium, Cl and F
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁵ is selected from the group consisting of H, C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R⁶, C₂₋₅ alkenyl optionally substituted with one or more, identical or different,

- substituents R^6 , C_{2-5} alkynyl optionally substituted with one or more, identical or different, substituents R^6 , C_{3-6} 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^8 , and benzyl optionally substituted with one or more, identical or different, substituents R^8 ;
- 5 - R^6 is independently selected from deuterium and F;
- R^8 is independently selected from the group consisting of deuterium, methoxy, nitro, cyano, Cl, Br, I, and F; and
- 10 - n is an integer 0, 1, 2 or 3.

11. The compound for use according to claim 6, wherein the compound is of Formula (IVa) or Formula (IVb):



Formula (IVa)



Formula (IVb)

15 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 H, deuterium, F, Cl, Br, I, 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 , $-CF_2-$ C_{1-5} alkyl optionally be substituted with one or more, identical or different, substituents R^6 , and 5-membered aromatic heterocycle
- 20

- optionally substituted with one or more, identical or different, substituents R⁷;
- R³ is selected from the group consisting of deuterium, Cl and F;
 - R⁴ is selected from the group consisting of H, deuterium, C₁₋₅ alkyl, C₁₋₂ alkoxy-C₁₋₂ alkyl, C₁₋₂ alkylthio-C₁₋₂ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and C₃₋₅ cycloalkyl, each of which may be optionally substituted with one or more, identical or different, substituents R⁶;
 - R⁶ is independently selected from the group consisting of deuterium and F;
 - R⁷ is independently selected from the group consisting of deuterium, F, methyl, ethyl or cyclopropyl; and
 - n is an integer 0, 1, 2, or 3
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
12. The compound for use according to any one of claims 6 to 12, wherein R¹ is selected from the group consisting of Br and Cl.
13. The compound for use according to any one of claims 6 to 13, wherein R⁴ is selected from the group consisting of methyl, -CH₂F, ethyl, -CH₂CH₂F, n-propyl and isopropyl.
14. The compound for use according to any one of claims 6 to 14, wherein n is 0 or 1.
15. The compound for use according to claim 1, wherein the compound is selected from the group consisting of:
- (S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
 - (S)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]propionic acid;
 - (R)-2-[2-(1,1-difluoropropyl)-4,5-difluorophenoxy]-3-fluoropropionic acid;
 - (S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-methoxybutyric acid;
 - (S)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]propionic acid;
 - (S)-2-[2-(1,1-difluoropropyl)-4-nitrophenoxy]propionic acid;
 - (R)-2-[5-chloro-2-(1,1-difluoropropyl)-4-fluorophenoxy]-3-fluoropropionic acid;
 - (S)-2-(4-chloro-2-cyclopropyl-5-fluorophenoxy)-3-methoxypropionic acid;
 - (S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
 - (S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]butyric acid;
 - (S)-2-[2-(1,1-difluoropropyl)-5-fluoro-4-styrenyloxy]propionic acid;

- (S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]butyric acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-fluorobutyric acid;
(R)-2-[4,5-dichloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
(R)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]-3-fluoropropionic acid;
5 (S)-2-[4,5-dichloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-[2-(1,1-difluoroethyl)-4-ethynylphenoxy]propionic acid;
[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]acetic acid;
10 (S)-2-[2-(1,1-difluoropropyl)-4-tolyloxy]propionic acid;
[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]acetic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-styrenyloxy]propionic acid;
(R)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-3-fluoropropionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-(trifluoromethyl)phenoxy]propionic acid;
15 (S)-2-[4-chloro-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)(3,5,6-²H₃)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)-5-fluorophenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
20 (S)-2-[4-cyano-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]propionic acid;
(S)-2-[2-(1,1-difluoropropyl)-4-ethynylphenoxy]propionic acid;
(R)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy](2-²H)propionic acid;
25 (S)-2-[2-(1,1-difluoropropyl)-4-iodophenoxy]propionic acid;
(S)-2-[4-chloro-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
(S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-4-pentynoic acid;
(R)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-4-pentynoic acid;
30 (S)-2-(4-bromo-2-cyclobutylphenoxy)-3-methoxypropionic acid;
(S)-2-[4-bromo-2-(cyclopropyldifluoromethyl)phenoxy]propionic acid;
(R)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,1-difluorobutyl)phenoxy]propionic acid;
(S)-[4-bromo-2-(1,1-difluoroethyl)phenoxy]cyclopropylacetic acid;
35 (S)-2-[4-chloro-2-(1,1-difluoropropyl)phenoxy]propionic acid;

- [4-bromo-2-(1,1-difluoropropyl)phenoxy]acetic acid;
(S)-2-[4-bromo-2-(1,1-difluoro-2-methylpropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]butyric acid;
5 (S)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-3-methoxypropionic acid;
(S)-(4-bromo-2-cyclopropylphenoxy)cyclopropylacetic acid;
(S)-cyclopropyl(2,4-dibromophenoxy)acetic acid;
10 (S)-(4-bromo-2-chlorophenoxy)cyclopropylacetic acid;
(2R,3R)-2-(p-bromophenoxy)-3-fluorobutyric acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-ethoxypropionic acid;
[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]acetic acid;
[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]acetic acid;
15 [4-chloro-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-[4-bromo-2-(5-isoxazolyl)phenoxy]cyclopropylacetic acid;
(S)-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]cyclopropylacetic acid;
(S,E)-2-(p-bromophenoxy)-4-fluoro-3-butenoic acid;
(2R,3R)-2-(4-bromo-2-fluorophenoxy)-3-fluorobutyric acid;
20 (4-bromo-2-cyclopropylphenoxy)acetic acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-cyclopropylpropionic acid;
[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]acetic acid;
[4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-2-[4-bromo-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;
25 (S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclobutylpropionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
[4-bromo-2-(5-isoxazolyl)phenoxy]acetic acid;
(S)-2-(p-bromophenoxy)(2-²H)butyric acid;
(S)-2-(p-bromophenoxy)-4-pentynoic acid;
30 [4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]acetic acid;
(4-bromo-2-ethynylphenoxy)acetic acid;
(S)-2-(4-bromo-2-fluorophenoxy)valeric acid;
(S)-2-(2,4-dibromophenoxy)valeric acid;
(S)-2-(4-bromo-2-chlorophenoxy)valeric acid;
35 (S)-2-(p-bromophenoxy)-3-cyclopropylpropionic acid;

- (S)-2-(2,4-dibromophenoxy)-4-pentynoic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-pentynoic acid;
(S)-(p-bromophenoxy)cyclopropylacetic acid;
(S)-2-(4-bromo-2-fluorophenoxy)-4-pentynoic acid;
5 (S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]butyric acid;
(S)-2-(p-bromophenoxy)valeric acid;
(R)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(1,3,4-thiadiazol-2-yl)phenoxy]propionic acid;
(S)-(4-bromo-2-chlorophenoxy)cyclobutylacetic acid;
10 (S)-2-(4-bromo-2-chlorophenoxy)-3-cyclopropylpropionic acid;
(S)-2-(4-bromo-2-chlorophenoxy)-3-methylbutyric acid;
[4-bromo-2-(3-isoxazolyl)phenoxy]acetic acid;
(R)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
15 (S)-2-(p-bromophenoxy)-3-butenic acid;
(S)-2-[4-bromo-2-(1H-1,2,3-triazol-5-yl)phenoxy]propionic acid;
(2S)-2-(p-bromophenoxy)(3,4-²H₂)butyric acid;
(R)-2-(4-bromo-2-chlorophenoxy)-3-fluoropropionic acid;
(S)-2-(4-bromo-2-chlorophenoxy)butyric acid;
20 (S)-2-(4-bromo-3-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-bromo-2-chlorophenoxy)-4-fluorobutyric acid;
(S)-2-(p-ethynylphenoxy)-4-fluorobutyric acid;
(S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
(S)-2-[4-bromo-2-(1,2,3-thiadiazol-4-yl)phenoxy]propionic acid;
25 (S)-2-[4-bromo-2-(1,3-oxazol-5-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-4-fluorobutyric acid;
(R)-2-(p-bromophenoxy)-3-fluoro(2-²H)propionic acid;
(R)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-(4-bromo-5-fluoro-2-styrenyloxy)propionic acid;
30 (S)-2-[4-bromo-2-(1,3-thiazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-bromo-5-fluoro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-methylbutyric acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(R)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
35 (S)-2-[4-chloro-5-fluoro-2-(5-isoxazolyl)phenoxy]propionic acid;

- (S)-2-(4-bromo-2-cyclopropyl-5-fluorophenoxy)propionic acid;
(S)-2-[4-bromo-2-(2,2-difluoroethenyl)-5-fluorophenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]butyric acid;
(S)-2-(4-bromo-2-iodophenoxy)-4-fluorobutyric acid;
5 (S)-(4-bromo-2-ethynylphenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-ethynyl-5-fluorophenoxy)propionic acid;
(S)-2-(4-chloro-2-ethynyl-5-fluorophenoxy)propionic acid;
(S)-2-[4-bromo-2-(4-isoxazolyl)phenoxy]propionic acid;
(R)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
10 (S)-(p-bromophenoxy)cyclobutylacetic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-fluorophenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-ethynylphenoxy)-4-fluorobutyric acid;
(S)-2-(4-bromo-2-styrenyloxy)-4-fluorobutyric acid;
15 (S)-(4-bromo-2-fluorophenoxy)cyclobutylacetic acid;
(S)-2-[4-chloro-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-[4,5-dichloro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-5-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
20 (S)-2-(p-bromophenoxy)-4-fluorobutyric acid;
(S)-2-{2-[(E)-2-fluoroethenyl]-4-bromophenoxy}propionic acid;
(S)-2-[4-bromo-2-(1,3-oxazol-4-yl)phenoxy]propionic acid;
(S)-2-{2-[(E)-2-fluoroethenyl]-4-chlorophenoxy}propionic acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
25 (S)-2-[4-fluoro-2-(3-isoxazolyl)phenoxy]propionic acid;
(R)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(S)-2-[4-chloro-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
30 (S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]butyric acid;
(S)-2-[4-chloro-2-(3-isoxazolyl)phenoxy]propionic acid;
(S)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-cyclopropylpropionic acid;
(S)-2-[4-chloro-2-(1,3-oxazol-2-yl)phenoxy]propionic acid;
(S)-2-(4-bromo-2-iodophenoxy)-3-methylbutyric acid;
35 (S)-(4-bromo-2-fluorophenoxy)cyclopropylacetic acid;

- (*R*)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-fluoropropionic acid;
(*S*)-2-[4-chloro-2-(3-isothiazolyl)phenoxy]propionic acid;
(*S*)-2-(4-bromo-2-ethynylphenoxy)butyric acid;
(*S*)-2-(4-bromo-2-iodophenoxy)butyric acid;
5 (*S*)-2-(4-chloro-2-fluorophenoxy)butyric acid;
(*S*)-2-(*p*-bromophenoxy)butyric acid;
(*S*)-2-[4-bromo-2-(2,2-difluoroethenyl)phenoxy]propionic acid;
(*S*)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]butyric acid;
(*S*)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]butyric acid;
10 (*S*)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]-3-methylbutyric acid;
(*S*)-2-[4-bromo-2-(4-methyl-3-isoxazolyl)phenoxy]propionic acid;
(*S*)-2-(4-bromo-2-fluorophenoxy)butyric acid;
(*S*)-2-[4-bromo-2-(5-methyl-3-isoxazolyl)phenoxy]propionic acid;
(*S*)-2-[4-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenoxy]propionic acid;
15 (*R*)-2-[*p*-bromo(3,5-²H₂)phenoxy]-3-fluoropropionic acid;
(*S*)-2-[*p*-bromo(3,5-²H₂)phenoxy]propionic acid;
(*S*)-2-[4-bromo-2-(5-cyclopropyl-3-isoxazolyl)phenoxy]propionic acid;
ethyl (*S*)-2-(4-bromo-2-fluorophenoxy)-3-methyl-3-butenolate;
(*R*)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
20 (*R*)-2-[*p*-bromo(2,6-²H₂)phenoxy]-3-fluoropropionic acid;
(*S*)-2-[4-chloro-2-(1,3-thiazol-2-yl)phenoxy]propionic acid;
(*S*)-2-[*p*-bromo(2,6-²H₂)phenoxy]propionic acid;
(*S*)-2-[4-bromo-2-(3-isoxazolyl)phenoxy]propionic acid;
(*S*)-2-[4-bromo-2-(3-methyl-5-isoxazolyl)phenoxy]propionic acid;
25 (*S*)-2-(4-bromo-2-iodophenoxy)propionic acid;
(*S*)-2-[4-bromo-2-(2-imidazolyl)phenoxy]propionic acid;
(*S*)-2-[4-bromo-2-(5-imidazolyl)phenoxy]propionic acid;
(*R*)-2-(4-bromo-2-cyclobutylphenoxy)-3-fluoropropionic acid;
(*R*)-2-(4-bromo-2-fluorophenoxy)-3,3-difluoropropionic acid;
30 (*S*)-2-(4-bromo-2-ethynylphenoxy)propionic acid;
(*S*)-2-(2-bromo-4-chlorophenoxy)-3-methylbutyric acid;
(*S*)-2-(2-fluoro-4-iodophenoxy)propionic acid;
(*S*)-2-(2-bromo-4-iodophenoxy)propionic acid;
(*R*)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]-3-fluoropropionic acid;
35 (*S*)-2-(2-chloro-4-iodophenoxy)propionic acid;

- (S)-2-(2-bromo-4-chlorophenoxy)propionic acid;
(S)-2-(4-bromo-2-cyclopropylphenoxy)propionic acid;
(S)-2-(4-bromo-2-styrenyloxy)propionic acid;
(S)-2-[4-chloro-2-(1-methyl-3-methyl-4-pyrazolyl)phenoxy]propionic acid;
5 (S)-2-[4-chloro-2-(5-pyrazolyl)phenoxy]propionic acid;
(S)-2-[4-chloro-2-(5-isoxazolyl)phenoxy]propionic acid;
(S)-2-(2-cyclopropyl-4-fluorophenoxy)propionic acid;
(S)-2-[4-chloro-2-(1-methyl-4-pyrazolyl)phenoxy]propionic acid;
(S)-2-(2-cyclobutyl-4-fluorophenoxy)propionic acid;
10 (S)-2-(4-bromo-2-cyclobutylphenoxy)propionic acid;
(R)-2-(4-bromo-2-fluorophenoxy)-3-fluoropropionic acid;
(S)-2-(4-chloro-2-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-chloro-2-cyclobutylphenoxy)propionic acid;
(S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]propionic acid;
15 (R)-2-(2-bromo-4-chlorophenoxy)-3-fluoropropionic acid;
(R)-2-(p-chlorophenoxy)-3-fluoropropionic acid;
(R)-2-(4-chloro-2-fluorophenoxy)-3-fluoropropionic acid;
(R)-2-(2,4-dibromophenoxy)-3-fluoropropionic acid;
(S)-2-[4-bromo-2-(5-isoxazolyl)phenoxy]propionic acid;
20 (R)-2-(p-bromophenoxy)-3-fluoropropionic acid;
(S)-2-(4-bromo-2-fluorophenoxy)-3-methylbutyric acid;
(S)-2-(4-bromo-2-fluorophenoxy)propionic acid;
(S)-2-(4-chloro-2-fluorophenoxy)propionic acid;
(S)-2-(2,4-dibromophenoxy)propionic acid;
25 (S)-2-(4-chloro-2-ethynylphenoxy)propionic acid;
(S)-2-(4-chloro-2-styrenyloxy)propionic acid;
(S)-2-(4-chloro-2-cyclopropylphenoxy)propionic acid;
(S)-2-(p-chlorophenoxy)butyric acid;
sodium (S)-2-(2,4-dichlorophenoxy)propionate;
30 (S)-2-(p-chlorophenoxy)-3-methylbutyric acid;
(S)-2-(p-cyanophenoxy)propionic acid;
methyl (S)-2-(p-bromophenoxy)propionate;
methyl (S)-2-(p-chlorophenoxy)butyrate;
isopropyl (S)-2-(p-chlorophenoxy)propionate;
35 methyl (S)-2-(p-chlorophenoxy)propionate,

- (2S)-2-(4-bromo-2-fluorophenoxy)-N-{1-[(cyclopropylmethoxy)imino]ethyl}propanamide;
(2S)-2-(4-bromophenoxy)-N-[1-(methoxyimino)ethyl]propanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[(4-fluorophenyl)(hydroxyimino)methyl]-3-methylbutanamide;
5 (2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]-3-methylbutanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;
(2S)-2-(4-bromophenoxy)-N-[1-(hydroxyimino)ethyl]propanamide;
10 (2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-cyanopropanamide;
(2S)-N-cyano-2-(2,4-dibromophenoxy)propanamide;
(2S)-2-(4-bromophenoxy)-N-cyanopropanamide;
(2S)-2-(4-chlorophenoxy)-N-cyanopropanamide;
(2S)-2-(4-bromophenoxy)-N-cyano-3-methylbutanamide;
15 (2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-methoxypropanamide;
(2S)-N-acetyl-N-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-N-[(1-acetylazetidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
(2S)-N-(azetidin-3-yloxy)-2-(4-chlorophenoxy)propanamide;
20 (2S)-N-acetyl-N-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-chlorophenoxy)propanamide;
(2S)-N-[(1-acetylpyrrolidin-3-yl)methoxy]-2-(4-chlorophenoxy)propanamide;
(2S)-N-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
tert-butyl N-(2-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}propyl)carbamate;
25 (2S)-N-acetyl-2-(4-chlorophenoxy)-N-[(1-acetamidopropan-2-yl)oxy]propanamide;
(2S)-2-(4-bromophenoxy)-N-(pyrrolidin-3-yloxy)propanamide;
(2S)-N-acetyl-N-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-bromophenoxy)propanamide;
30 tert-butyl 3-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}azetidine-1-carboxylate;
(2S)-2-(4-chlorophenoxy)-N-[(pyrrolidin-3-yl)methoxy]propanamide;
tert-butyl 3-[(2S)-2-(4-chlorophenoxy)propanamido]oxy}methyl)pyrrolidine-1-carboxylate;

- (2S)-*N*-acetyl-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
- (2S)-*N*-[(1-acetylpyrrolidin-3-yl)oxy]-2-(4-chlorophenoxy)propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-(pyrrolidin-3-yloxy)propanamide;
- 5 (2S)-2-(4-chlorophenoxy)-*N*-(2,2-dimethylpropyl)-*N*-hydroxypropanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[2-(pyrrolidin-1-yl)ethoxy]propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[2-(2-oxopyrrolidin-1-yl)ethoxy]propanamide;
- (2S)-*N*-acetyl-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-(2-acetamidoethoxy)propanamide;
- 10 (2S)-2-(4-chlorophenoxy)-*N*-(4,4,4-trifluoro-2-methylbutoxy)propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-(3-cyclopentylpropyl)-*N*-hydroxypropanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-{[(2E)-2-methyl-3-phenylprop-2-en-1-yl]oxy}propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[2-oxo-2-[2-(trifluoromethyl)pyrrolidin-1-yl]ethoxy]propanamide;
- 15 tert-butyl *N*-(2-[[2-(4-chlorophenoxy)propanamidyl]oxy]ethyl)carbamate;
- (2S)-2-(4-chlorophenoxy)-*N*-[(2-methyl-1H-imidazol-4-yl)methoxy]propanamide;
- tert-butyl 4-({[(2S)-2-(4-chlorophenoxy)propanamido]oxy)methyl}-2-methyl-1H-imidazole-1-carboxylate;
- 20 (2S)-2-(4-bromo-2-fluorophenoxy)-*N*-cyclobutoxypropanamide;
- (2S)-2-(4-bromophenoxy)-*N*-cyclobutoxypropanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[2-oxo-2-(pyrrolidin-1-yl)ethoxy]propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[1-(4-fluorophenyl)ethoxy]propanamide;
- 25 (2S)-2-(4-chlorophenoxy)-*N*-[1-(1,3-thiazol-2-yl)ethoxy]propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-{1-[4-(trifluoromethyl)phenyl]ethoxy}propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-(2-methanesulfinylethoxy)propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-(2-methanesulfonylethoxy)propanamide;
- (2S)-2-(4-chlorophenoxy)-*N*-[(1,2-oxazol-3-yl)methoxy]propanamide;
- 30 (2S)-2-(4-chloro-2-fluorophenoxy)-*N*-methoxypropanamide;
- (2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-*N*-(cyclopropylmethoxy)propanamide;
- (2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-*N*-(cyclopropylmethoxy)propanamide;
- 35 (2S)-*N*-(tert-butoxy)-2-(4-chlorophenoxy)propanamide;

- (2S)-2-(4-chlorophenoxy)-*N*-[2-(methylsulfanyl)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(1-phenylethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(1-methyl-1H-imidazol-2-yl)methoxy]propanamide;
5 (2S)-2-(4-chlorophenoxy)-*N*-(2-methoxyethoxy)propanamide;
(2S)-2-(4-chloro-2-fluorophenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,3,4-oxadiazol-2-yl)phenoxy]-*N*-methoxypropanamide;
(2S)-2-[4-chloro-2-(trifluoromethyl)phenoxy]-*N*-methoxypropanamide;
(2S)-*N*-(benzyloxy)-2-(4-chlorophenoxy)propanamide;
10 (2S)-2-(4-chlorophenoxy)-*N*-[(2-methoxycyclopentyl)oxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-5-methylhexanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-*N*-methylpropanamide;
(2S)-2-(4-chloro-2-methylphenoxy)-*N*-cyclobutoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-cyclobutoxypropanamide;
15 (2S)-2-(4-chloro-2-methylphenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chloro-3-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxy-4-methylpentanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(3-methylbut-2-en-1-yl)oxy]propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-cyclobutoxyhexanamide;
20 (2S)-2-(4-chlorophenoxy)-*N*-[(1,3-oxazol-2-yl)methoxy]propanamide;
(2S)-2-(2,4-dibromophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(oxan-2-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-[(1,3-thiazol-2-yl)methoxy]propanamide;
25 (2S)-2-(4-chlorophenoxy)-*N*-(3,3-difluorocyclobutoxy)propanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-cyclobutoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclopentylloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(2-cyclopentylethoxy)propanamide;
30 (2S)-2-(4-bromo-2-chlorophenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-bromo-2-methylphenoxy)-*N*-methoxypropanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclopropylmethoxy)propanamide;
(2S)-2-(4-chlorophenoxy)-*N*-(cyclobutylmethoxy)propanamide;
(2S)-*N*-(2-aminoethoxy)-2-(4-chlorophenoxy)propanamide;
35 (2S)-2-(4-bromophenoxy)-*N*-methoxy-3-methylbutanamide;

- methyl 2-[[2-(2-(4-chlorophenoxy)propanamido]oxy}acetate;
(2S)-2-(4-chlorophenoxy)-N-[2-(2-methoxyethoxy)ethoxy]propanamide;
(2S)-2-(4-chlorophenoxy)-N-cyclobutoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-(2-hydroxyethoxy)propanamide;
5 (2S)-2-(4-chlorophenoxy)-N-ethoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-propoxypropanamide;
(2S)-2-(4-chlorophenoxy)-N-(propan-2-yloxy)propanamide;
(2S)-2-(4-chlorophenoxy)-N-methoxypropanamide;
(2S)-2-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-N-
10 (cyclopropanesulfonyl)propanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromo-2-fluorophenoxy)-N-(cyclopropanesulfonyl)propanamide;
(2S)-2-(4-chlorophenoxy)-N-methanesulfonylpropanamide;
(2S)-2-(4-bromophenoxy)-N-methanesulfonyl-3-methylbutanamide;
15 5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]-3-fluoropropyl]-2H-1,2,3,4-
tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)propyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)-2-methylpropyl]-2H-1,2,3,4-tetrazole;
5-[(1R)-1-(4-bromophenoxy)-2-fluoroethyl]-2H-1,2,3,4-tetrazole;
20 5-[(1S)-1-(4-bromophenoxy)propyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-[4-bromo-2-(1,2-oxazol-5-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
25 5-[(1S)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-2H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-cyclopropylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-ethenylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-ethylphenoxy)ethyl]-1H-1,2,3,4-tetrazole;
5-[(1S)-1-(4-chloro-2-methylphenoxy)ethyl]-2H-1,2,3,4-tetrazole;
30 5-[(1S)-1-(4-chlorophenoxy)ethyl]-1H-1,2,3,4-tetrazole;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-yl}acetamide;
N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-
yl}methanesulfonamide;
3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-thiadiazol-5-amine;
35 N-{3-[(1S)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}acetamide;

- N*-{3-[(1*S*)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-yl}methanesulfonamide;
- 3-[(1*S*)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4*H*-1,2,4-triazole;
- 5 3-[(1*S*)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-(trifluoromethyl)-4*H*-1,2,4-triazole;
- 3-[(1*S*)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methoxy-1,2,4-oxadiazole;
- 3-[(1*S*)-1-(4-bromo-2-fluorophenoxy)ethyl]-1,2,4-oxadiazol-5-amine;
- 3-[(1*S*)-1-[4-bromo-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4*H*-1,2,4-triazole;
- 10 3-[(1*S*)-1-[4-chloro-2-(1,2-oxazol-3-yl)phenoxy]ethyl]-5-methyl-4*H*-1,2,4-triazole;
- 3-[(1*S*)-1-(4-bromo-2-fluorophenoxy)ethyl]-5-methyl-4*H*-1,2,4-triazole;
- 5-[(1*S*)-1-(4-chlorophenoxy)ethyl]-1*H*-1,2,4-triazole;
- 15 (2*S*)-2-[4-bromo-2-(1,1-difluoroethyl)phenoxy]-*N*-cyanopropanamide;
- (2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)-5-fluorophenoxy]-*N*-cyanopropanamide;
- (2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-methanesulfonylpropanamide;
- (2*S*)-2-[4-bromo-2-(1,1-difluoropropyl)phenoxy]-*N*-(cyclopropanesulfonyl)propenamide;
- 20 5-[(1*S*)-1-[4-bromo-2-(1,1-difluoroethyl)phenoxy]ethyl]-1*H*-1,2,3,4-tetrazole;
- 5-[(1*S*)-1-[4-bromo-2-(1,1-difluoropropyl)phenoxy]ethyl]-1*H*-1,2,3,4-tetrazole;
- 5-[(1*S*)-1-(4-bromo-2-cyclobutylphenoxy)-2-methoxyethyl]-1*H*-1,2,3,4-tetrazole; and
- 25 5-[(1*S*)-1-(4-bromo-2-cyclopropylphenoxy)-2-methoxyethyl]-1*H*-1,2,3,4-tetrazole,
- or a pharmaceutically acceptable salt, hydrate, polymorph, tautomer, or solvate thereof.
16. A method for treating a neuromuscular disorder:
- 30 subjecting different muscle fibers of the same motor unit in a neuromuscular tissue of a patient being examined for the neuromuscular disorder to a number of activations;
- detecting, with a medical device and a recording electrode, the number of paired successful action potentials from the number of activations;

- determining whether the patient is suffering from or at risk of blocking by dividing the number of paired successful action potentials over a total number of activations; and
- when the number of paired successful action potentials over the total number of activations is below a threshold of 95%, administering a CIC-1 inhibitor to the patient, wherein the administering of the CIC-1 inhibitor increases the number of paired successful action potentials over the total number of activations by at least 5%.
- 5
17. The method of claim 16, wherein the CIC-1 inhibitor is a compound according to any one of claims 1-15.
- 10
18. The method of claim 16, wherein the method is used in the treatment, prevention and/or amelioration of a neuromuscular disorder.
19. The method of claim 16, wherein the neuromuscular disorder is selected from one of the following: sarcopenia, myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenic syndrome, seronegative myasthenia gravis, muscle specific kinase myasthenia gravis (MuSK-MG), Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), Charcot-Marie Tooth disease, diabetic polyneuropathy, periodic paralysis, hypokalemic periodic paralysis, hyperkalemic periodic paralysis, myotubular myopathy, Duchenne muscular dystrophy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, critical illness polyneuropathy, metabolic myopathy, Kennedy's disorder, multiple sclerosis and multifocal motor neuropathy.
- 15
20. The method of claim 19, wherein the neuromuscular disorder is multiple sclerosis.
- 25
21. The method of claim 16, wherein the administering of the CIC-1 inhibitor restores contractile force of the patient's muscles by at least 5%.
22. The method of claim 16, wherein the administering of the CIC-1 inhibitor reduces incidence of neuromuscular junction transmission failure in the patient's muscles by at least 5%.
- 30

23. A method for treating a neuromuscular disorder comprising:
acquiring, with a medical device and a recording electrode, a variation in a
time interval between two action potentials of the same motor unit in a
neuromuscular tissue of a patient being examined for the neuromuscular
disorder;
5 determining whether the variation in the time interval between the two action
potentials of the same motor unit exceeds or meets a threshold of 40 μ s;
and
administering a CIC-1 inhibitor to the patient when the variation in the time
10 interval between the two action potentials exceeds or meets the
threshold, wherein the administering of the CIC-1 inhibitor reduces the
variation in the time interval between the two action potentials between
consecutive electrical discharges by at least 10%.
24. The method of claim 23, wherein the CIC-1 inhibitor is a compound
15 according to any one of claims 1-15.
25. The method of claim 23, wherein the method is used in the treatment,
prevention and/or amelioration of a neuromuscular disorder.
26. The method of claim 25, wherein the neuromuscular disorder is selected
from one of the following: sarcopenia, myasthenia gravis, autoimmune
20 myasthenia gravis, congenital myasthenic syndrome, seronegative
myasthenia gravis, muscle specific kinase myasthenia gravis (MuSK-MG),
Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral
sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy
(CIM), Charcot-Marie Tooth disease, diabetic polyneuropathy, periodic
25 paralysis, hypokalemic periodic paralysis, hyperkalemic periodic paralysis,
myotubular myopathy, Duchenne muscular dystrophy, Guillain-Barré
syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome,
critical illness polyneuropathy, metabolic myopathy, Kennedy's disorder,
multiple sclerosis and multifocal motor neuropathy.
27. The method of claim 26, wherein the neuromuscular disorder is multiple
30 sclerosis.

28. The method of claim 23, wherein the administering of the CIC-1 inhibitor restores contractile force of the patient's muscles by at least 5%.
29. The method of claim 23, wherein the administering of the CIC-1 inhibitor reduces incidence of neuromuscular junction transmission failure in the patient's muscles by at least 5%.
- 5
30. The method of claim 23, wherein the variation in the time interval between two action potentials is measured using single fiber electromyography.