Compounds for use in treating neuromuscular disorders

Field of invention

The present invention relates to compositions comprising compounds for use in treating, ameliorating and/or preventing neuromuscular disorders. The compounds as defined herein preferably inhibit the ClC-1 ion channel. The invention further relates to methods of treating, preventing and/or ameliorating neuromuscular disorders, by administering said composition to a person in need thereof.

Background of invention

Walking, breathing, and eye movement are examples of essential everyday physiological activities that are powered by contractile activity of skeletal muscle. Skeletal muscles are inherently resting and contractile activity exclusively occurs in response to commands from the central nervous system. Such neuronal commands take the form of action potentials that travel from the brain to the muscle fibers in several steps. The neuromuscular junction (NMJ) is the highly specialized membrane area on muscle fibers where motor neurons come into close contact with the muscle fibers, and it is at NMJ that neuronal action potentials are transmitted to muscular action potentials in a one-to-one fashion via synaptic transmission.

Neuromuscular transmission refers to the sequence of cellular events at the NMJ whereby an action potential in the lower motor neuron is transmitted to a corresponding action potential in a muscle fiber[1]: When a neuronal action potential arrives at the pre-synaptic terminal it triggers influx of Ca^{2+} through voltage gated P/Q-type Ca^{2+} channels in the nerve terminal membrane. This influx causes a rise in cytosolic Ca^{2+} in the nerve terminal that triggers exocytosis of acetylcholine (ACh). Released ACh next diffuses across the synaptic cleft to activate nicotinic ACh receptors in the post-synaptic, muscle fiber membrane. Upon activation, ACh receptors convey an excitatory current flow of Na^{+} into the muscle fiber, which results in a local depolarization of the muscle fiber at the NMJ that is known as the endplate potential (EPP). If the EPP is sufficiently large, voltage gated Na^{+} channels in the muscle fiber will activate and an action potential in the muscle fiber will ensue. This action potential then propagates from NMJ throughout the muscle fiber and triggers the Ca^{2+} release from the sarcoplasmic

reticulum. The released Ca^{2+} activates the contractile proteins within the muscle fibers thus resulting in contraction of the fiber.

Failure in the neuromuscular transmission can arise from both pre-synaptic dysfunction (Lambert Eaton syndrome[2], amyotrophic lateral sclerosis[11], spinal muscular atrophy[12]) and as a result of post-synaptic dysfunction as occurs in myasthenia gravis[3]. Failure to excite and/or propagate action potentials in muscle can also arise from reduced muscle excitability such as in critical illness myopathy (CIM)[4]. In Lambert Eaton syndrome, an autoimmune attack against the pre-synaptic P/Q-type Ca^{2+} channels results in markedly reduced Ca^{2+} influx into the nerve terminal during the pre-synaptic action potential and, consequently, a reduced release of ACh into the synaptic cleft. In myasthenia gravis the most common finding is an autoimmune attack on the post-synaptic membrane either against the nicotinic ACh receptors or the musk-receptor in the muscle fiber membrane[3]. Congenital forms of myasthenia are also known[5]. Common to disorders with neuromuscular transmission failure (Lambert Eaton syndrome, amyotrophic lateral sclerosis, spinal muscular atrophy and myasthenia gravis) is that the current flow generated by ACh receptor activation is markedly reduced, and EPPs therefore become insufficient to trigger muscle fiber action potentials. Neuromuscular blocking agents also reduce EPP by antagonizing ACh receptors. In CIM with reduced muscle excitability, the EPP may be of normal amplitude but they are still insufficient to trigger muscle fiber action potentials because the membrane potential threshold for action potential excitation has become more depolarized because of loss-of-function of voltage gated Na^+ channels in the muscle fibers.

While ACh release (Lambert Eaton, amyotrophic lateral sclerosis, spinal muscular atrophy), ACh receptor function (myasthenia gravis, neuromuscular blockade) and function of voltage gated Na^+ channels (CIM) are essential components in the synaptic transmission at NMJ, the magnitude of the EPP is also affected by inhibitory currents flowing in the NMJ region of muscle fibers. These currents tend to outbalance excitatory current through ACh receptors and, expectedly, they thereby tend to reduce EPP amplitude. The most important ion channel for carrying such inhibitory membrane currents in muscle fibers is the muscle-specific ClC-1 Cl^- ion channel[6-8].

ACh esterase (AChE) inhibitors are traditionally used in the treatment of myasthenia gravis. This treatment leads to improvement in most patients but it is associated with side effects, some of which are serious[9]: Because ACh is an import neurotransmitter in

the autonomic nervous system, delaying it's breakdown can lead to gastric discomfort, diarrhea, salivation and muscle cramping. Overdosing is a serious concern as it can lead to muscle paralysis and respiratory failure, a situation commonly referred to as cholinergic crisis. Despite the serious side effects of AChE inhibitors, these drugs are today the treatment of choice for a number of disorders involving neuromuscular impairment. In patients where pyridostigmine (a parasympathomimetic and a reversible ACHE inhibitor) is insufficient, corticosteroid treatment (prednisone) and immunosuppressive treatment (azathioprine) is used. Plasma exchange can be used to obtain a fast but transient improvement[9].

Unfortunately, all of the currently employed myasthenia gravis drug regimens are associated with deleterious long-term consequences. In addition, the otherwise safe use of common drugs such as anti-infectives, cardiovascular drugs, anticholinergics, anticonvulsants, antirheumatics and others have been reported to worsen the symptoms of myasthenia gravis patients[10].

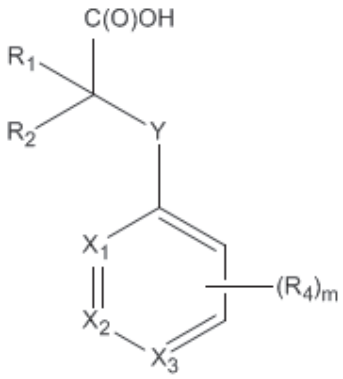
Summary

The present inventors have identified a group of compounds that alleviate neuromuscular junction disorders through inhibition of CIC-1 channels.

Thus, for the first time, it has been found that compounds that inhibit the CIC-1 ion channels are capable of restoring neuromuscular transmission. These compounds thus constitute a new group of drugs that can be used to treat or ameliorate muscle weakness and muscle fatigue in neuromuscular junction disorders caused by disease or by neuromuscular blocking agents.

The present disclosure thus concerns the use of CIC-1 ion channel inhibitors in the treatment of a range of conditions in which muscle activation by the nervous system is compromised and symptoms of weakness and fatigue are prominent.

In one aspect, the present disclosure provides use of a composition comprising a compound of Formula (II):



Formula (II)

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

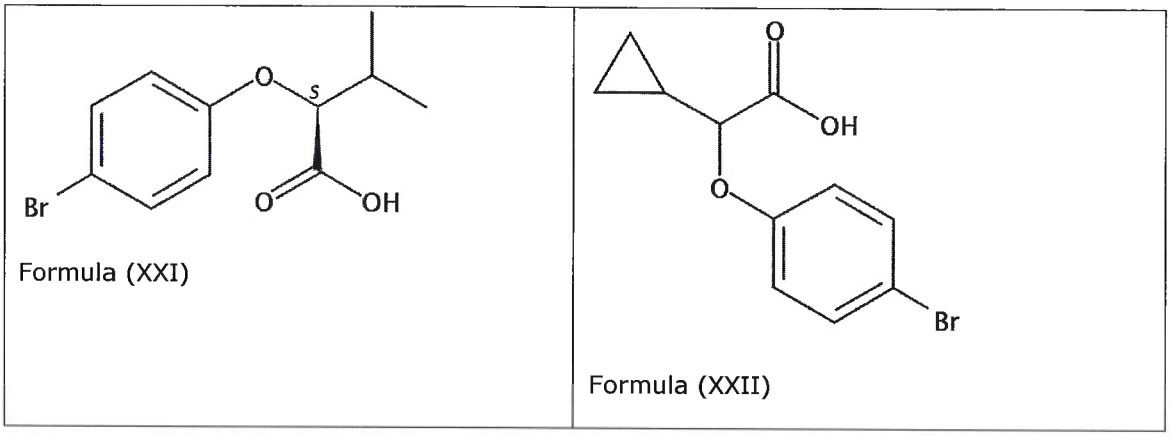
- m is 0, 1 or 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from CH;
- R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;;
- R_4 is selected from the group consisting H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;

R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;
in the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or reversing and/or ameliorating a neuromuscular blockade after surgery,
wherein the neuromuscular disorder is selected from the group consisting of myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenia gravis, Lambert-Eaton Syndrome, critical illness myopathy (CIM), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), diabetic polyneuropathy, Guillain-Barré

syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, and critical illness polyneuropathy.

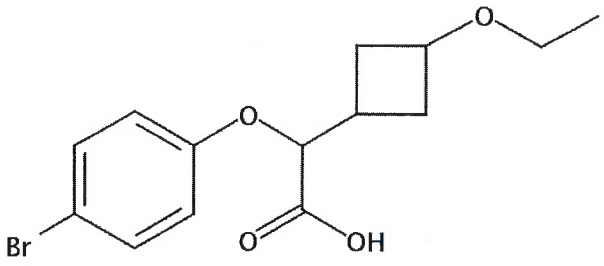
In another aspect, the present disclosure provides use of a composition as defined herein in the manufacture of a medicament for recovery of neuromuscular transmission.

In another aspect, the present disclosure provides a compound selected from the group consisting of formulas (XXI), (XXII), (XXVII), (XX), (XXVIII), (XXIII), (XXIV), (LIII), (LII), (XXXIII), (XLVI), (LXXIV), (LXXV), (LXXVI), (LXXVII), (LXXVIII), (LXXIX), and (LXXX):

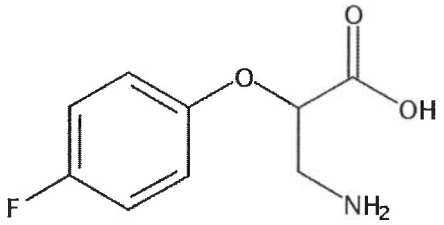


Formula (XXI)

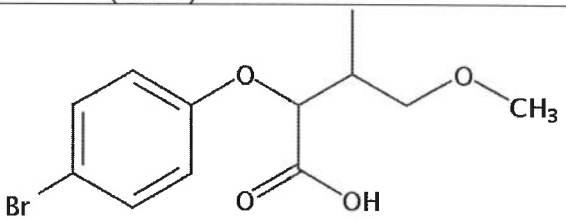
Formula (XXII)



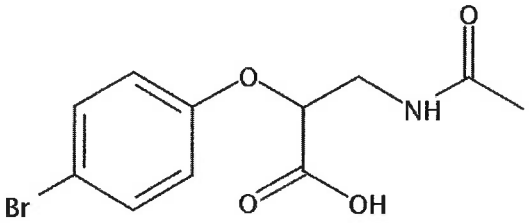
Formula (XXVII)



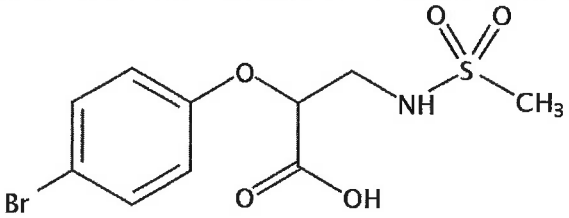
Formula (XX)



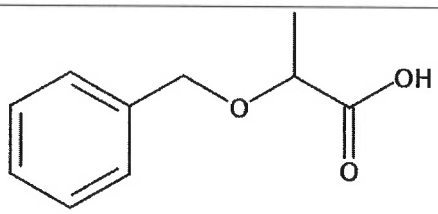
Formula (XXVIII)



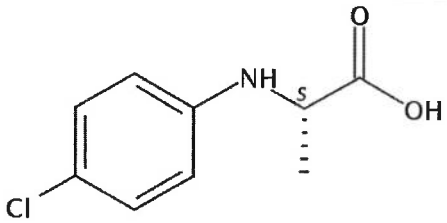
Formula (XXIII)



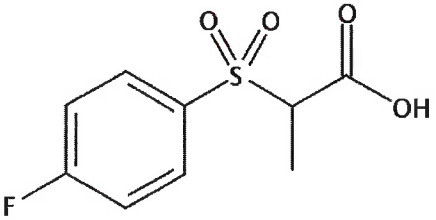
Formula (XXIV)



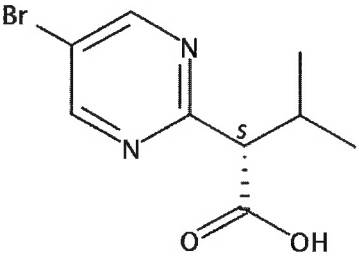
Formula (LIII)



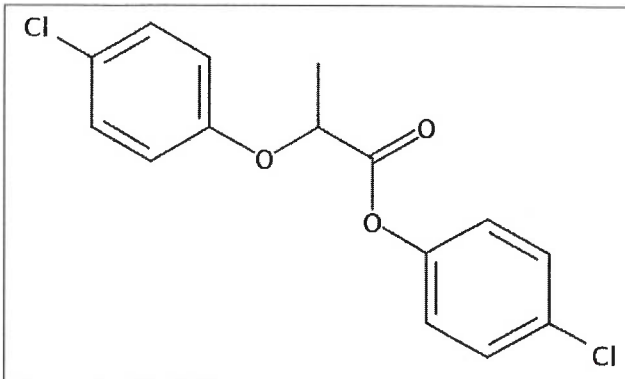
Formula (LII)



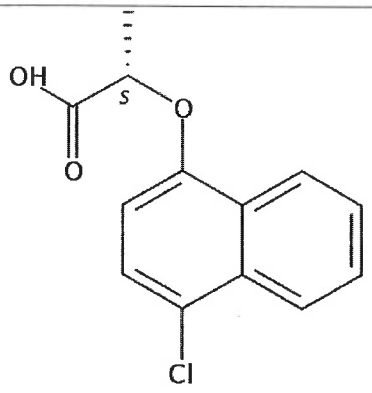
Formula (XXXIII)



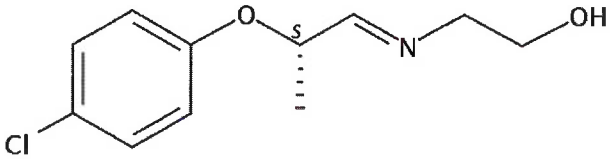
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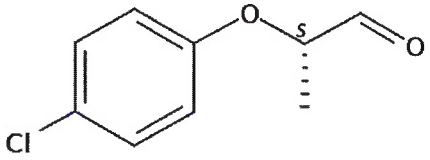
Formula (LXXVI)



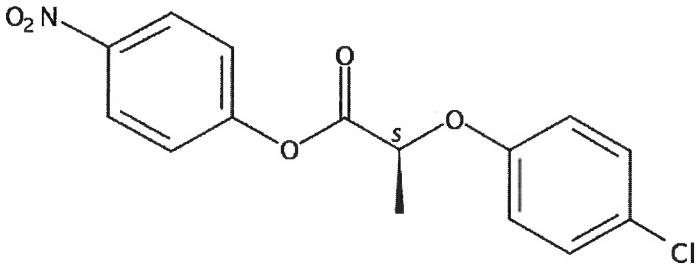
Formula (XLVI)



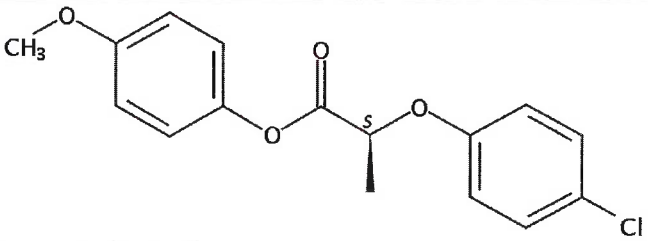
Formula (LXXV)



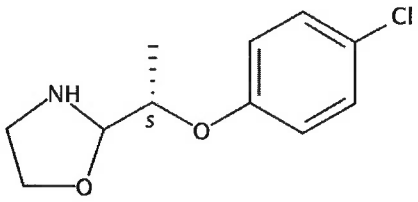
Formula (LXXVII)



Formula (LXXVIII)

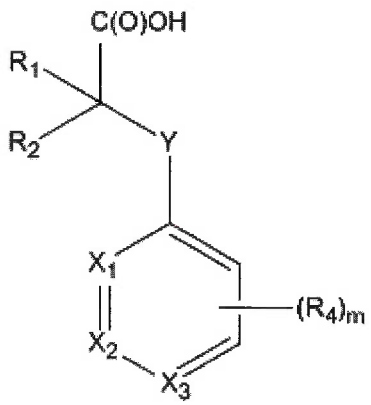


Formula (LXXIX)



Formula (LXXX)

In one example, the disclosure describes a composition comprising a compound of Formula (II):



Formula (II)

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

- m is 0, 1, 2, 3, 4 or 5;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from the group consisting of CH and N;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo ; or R_1 and R_2 are linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9

R_{10}, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;

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

In another example, the disclosure describes a method of treating, preventing and/or ameliorating a neuromuscular disorder, said method comprising administering a therapeutically effective amount of the composition as defined herein to a person in need thereof.

In one example, the disclosure describes the use of a composition as defined herein, for the manufacture of a medicament for the treatment, prevention and/or amelioration of a neuromuscular disorder, and/or for reversing and/or amelioration of a neuromuscular blockade after surgery.

In one example, the disclosure describes a method of reversing and/or ameliorating a neuromuscular blockade after surgery, said method comprising administering a therapeutically effective amount of the composition as defined herein to a person in need thereof.

In one example, the disclosure describes a method for recovery of neuromuscular transmission, said method comprising administering a therapeutically effective amount of the composition as defined herein to a person in need thereof.

In one example, the disclosure describes a composition as defined herein for use in recovery of neuromuscular transmission.

In one example, the disclosure describes use of a composition as defined herein for the manufacture of a medicament for the recovery of neuromuscular transmission.

Description of Drawings

Figure 1: Experimental methods for compromising neuromuscular transmission and the approaches employed to selectively activate contractions either via stimulation of the motor nerve or by directly exciting the rat muscle fibers. Soleus muscles were stimulated to contract using three different methods: In panel A, the muscle was stimulated to contract either directly using field stimulation with pulses of 0.2 ms duration or indirectly through stimulation of the nerve using a suction electrode. In panel B and C, muscles were stimulated directly as described above or indirectly via the nerve using field stimulation with short pulses of 0.02 ms. Two different methods of compromising neuromuscular transmission were applied: In panel A and B, a sub-maximal concentration of tubocurarine (0.2 µM) was used to inhibit ACh receptors in the post-synaptic muscle fiber membrane. In panel C, neuromuscular transmission was reduced by elevating extracellular Mg^{2+} to 3.5 mM. In experiments were nerve-stimulation was conducted using a suction electrode, the electrical activity of the muscle could be recorded as M-waves (Inserts in panel A). The entire M-wave train is shown with the first and the last M-waves in the trains enlarged above.

Figure 2. Effect of ClC-1 channel inhibition with 9-AC on nerve-stimulated force in rat soleus muscles exposed to tubocurarine or elevated extracellular Mg^{2+}. Muscles were stimulated to contract by activation of the motor nerve using a suction electrode. During experiments, the muscles contracted every 10 min for 2 s in response to 60 Hz stimulation. A) shows representative recordings of tetani from a soleus muscle from a 4-week-old animal that first contracted in control conditions, then during the pre-incubation with tubocurarine and, finally, in the presence of both tubocurarine and 9-AC. At the end of the experiment, tubocurarine was washed out to ensure full recovery of contractile force. M-wave recordings from the muscle have been included for the force responses indicated by *i*, *ii* and *iii*. The entire M-wave train is shown with the first and the last M-waves in the trains enlarged above. To depress any myotonia with the pronounced ClC-1 channel inhibition with 9-AC, 10 nM TTX was added together with tubocurarine. B) shows representative recordings of tetani from a soleus muscle from a 4-week-old animal that first contracted in control conditions, then during the pre-incubation with 3.5 mM Mg^{2+} and, finally, at 3.5 mM Mg^{2+} in the presence of 9-AC. When returned to normal extracellular Mg^{2+} of 1.2 mM, full contractile force ensued. M-

wave recordings from the muscle have been included for the force responses indicated by *i*, *ii* and *iii* as described in A.

Figure 3 Example of recovery of nerve-stimulated force with a clofibric acid derivative, C8, in muscles exposed to 150 nM tubocurarine. The motor nerve was stimulated every 10 min for 2 s with 30 Hz with field stimulation using short duration pulses. A) shows force recordings from two muscles with the traces being overlaid to illustrate the effect of C8 clearly. Traces are shown before addition tubocurarine, after 40 min with tubocurarine, and after 110 min tubocurarine. After 40 min with tubocurarine, 50 µM C8 was added to the muscle that is presented by black traces. B) shows average observations from 5 muscles treated with C8 and 5 control muscles exposed to only tubocurarine. Dotted lines indicate the recovery of nerve-stimulated force in the muscles treated with C8 compared to their force production after 40 min with tubocurarine. This recovery of force was used in Table 1.

Figure 4. A three-electrode technique was used to determine the effect of clofibric acid derivatives on the resting membrane conductance, G_m. Three electrodes were inserted into the same muscle fiber enabling recordings of the membrane potential response to the injection of square current pulses at three inter-electrode distances (dist1<dist2<dist3). A) shows the voltage responses at three inter-electrode distances in a control muscle fiber, and in a fiber exposed to 10 µM C8. B) to determine G_m the steady state deflection of the membrane potential was measured at each of the three inter-electrode distances. The magnitude of these steady state deflections were next plotted against the inter-electrode distance, and the data was fitted to a two-parameter exponential function (lines). From these parameters the fiber length constant and input resistance were obtained enabling G_m to be calculated. C) shows G_m at a range of C8 concentrations. By fitting a sigmoidal function to this data the concentration of C8 that reduced G_m by 50 % was obtained and this has been presented in Table 3.

Figure 5. Effect of C8 and neostigmine on the tubocurarine concentration required to reduce nerve-stimulated force in soleus muscles. Muscles from 4-week-old rats were stimulated to contract by activating the motor nerve with short duration pulses in field stimulation. Muscles contracted every 10 min for 2 s in response to 30 Hz stimulation. Four different experimental conditions were used. Thus, muscles were initially incubated for 30 min in either *i*) control conditions, *ii*) with 50 µM C8, *iii*) in the presence

of 10 nM neostigmine, or *iv*) with the combination of neostigmine and C8. After this pre-incubation, increasing concentrations of tubocurarine were added to the bath solutions with 60 min (corresponding to six contractions) between each increase in tubocurarine. A) shows representative recordings of force at different concentrations of tubocurarine in a control muscle. B) similar to A) but this muscle had been pre-incubated with C8. C) similar to A) but this muscle had been pre-incubated with neostigmine. D) similar to A) but this muscle had been pre-incubated with the combination of C8 and neostigmine. The force integral (AUC) was determined at each tubocurarine concentration. Such AUC determinations were plotted against tubocurarine concentration for each muscle. E) shows such plots of AUC for muscles in A-D. The lines connecting the symbols are fits of the data to a sigmoidal function from which the tubocurarine concentration that was required to reduce AUC to 50 % could be obtained (Tub_{50}). The averages of Tub_{50} in the four groups of muscles are given in Table 4.

Figure 6. Effect of a C8 and 3,4-AP on the extracellular Mg^{2+} concentration required to reduce nerve-stimulated force in soleus muscles. Muscles from 4-week-old rats were stimulated to contract by activating the motor nerve with short duration pulses in field stimulation. Muscles contracted every 10 min for 2 s in response to 30 Hz stimulation. Four different experimental conditions were used. Thus, muscles were initially incubated for 30 min in either *i*) control conditions, *ii*) with 50 µM C8, *iii*) in the presence of 10 µM 3,4-AP, or *iv*) with the combination of 3,4-AP and C8. After this pre-incubation, the extracellular Mg^{2+} was progressively increased in the bath solutions every 60 min resulting in six contractions between each increase in extracellular Mg^{2+}. A) shows representative recordings of force at different concentrations of Mg^{2+} in a control muscle. B) similar to A) but this muscle had been pre-incubated with C8. C) similar to A) but this muscle had been pre-incubated with 3,4-AP. B) similar to A) but this muscle had been pre-incubated with the combination of C8 and 3,4-AP. The force integral (AUC) was determined at each extracellular Mg^{2+} concentration. AUC was plotted against Mg^{2+} concentration and the data was fitted to a sigmoidal function. This provided the extracellular Mg^{2+} concentration that was required to reduce the nerve-stimulated force to 50 % (Mg_{50}) under the four different conditions (see Table 5).

Figure 7. Effects of C8 on EPP amplitude in rat soleus muscle. Intracellular electrodes were inserted near visible nerve branches in the muscle. The solution contained 1 µM µ-conotoxin GiiiB to block NaV1.4. Under these conditions nerve-stimulation only

resulted in EPP formation in the fibers and it did not trigger muscle fiber action potentials. A) shows representative EPPs under control conditions and with two concentrations of C8. B) shows average EPP amplitudes in the fibers. *Indicates significantly different from control as evaluated using a student t-test.

Figure 8. Effects of C8 on contractile force in human muscles depressed by elevated extracellular K^+ and low dose of TTX. A) shows effect of adding 150 μM C8 on force in a muscle at elevated K^+ and with TTX. B) shows the average force at elevated K^+ in the presence or absence of C8. *Indicates significant different as evaluated using a one-tailed student t-test.

Figure 9. Effects of I.P. C8 injection (20 mg/kg) on running performance of rats after I.P. injection of tubocurarine (0.13 mg/kg). A) illustrates the design of the experiments. Prior to Day One the animals had been familiarized to the rotarod in three training sessions distributed over two days. B) shows the distance covered by the rats on the two days 21-26 mins after injection of tubocurarine. C) shows the increase in performance on Day Two when compared to performance on Day One. D) shows the number of animals that on Day Two had an increased performance of more than 100 % compared to performance on Day One.

Figure 10. Effects of C8 on running performance after inducing passive myasthenia gravis in rats using MAB35 monoclonal antibody. Prior to I.P. injection of MAB35 the animals had been familiarized to the rotarod over three training sessions distributed over two days. After I.P. injection of MAB35 the running performance of the animals was monitored regularly and if a stable reduction in performance developed, the animals were given either sham, 20 mg/kg C8 or 30 mg/kg C8. After this treatment performance was monitored every second hour. *Indicates significant different as evaluated using student t-test.

Detailed description of the invention

Definitions

The term “halogen” means fluoro, chloro, bromo or iodo. “Halo” means halogen.

The term "C_{1-8}-alk(en/yn)yl" means C_{1-8}-alkyl, C_{2-8}-alkenyl or C_{2-6}-alkynyl; wherein:

- The term "C_{1-8}-alkyl" refers to a branched or unbranched alkyl group having from one to eight carbon atoms, 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-l-yl, but-l-yl, but- 2-yl, 3-methyl-but-1-yl, 3-methyl-but-2-yl, pent-1-yl, pent-2-yl, pent-3-yl, hex-1- yl, hex-2-yl, hex-3-yl, 2-methyl-4,4-dimethyl-pent- 1 -yl and hept- 1 – yl;
- The term "C_{2-8}-alkenyl" refers to a branched or unbranched alkenyl group having from two to eight carbon atoms and one double bond, including but not limited to ethenyl, propenyl, and butenyl; and
- The term "C_{2-8}-alkynyl" refers to a branched or unbranched alkynyl group having from two to eight carbon atoms and one triple bond, including but not limited to ethynyl, propynyl and butynyl.

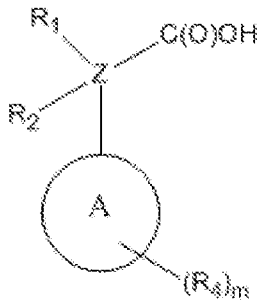
The term "C_{3-6}-cycloalk(en)yl" means C_{3-6}-cycloalkyl or C_{3-6}-cycloalkenyl, wherein:

- The term "C_{3-6}-cycloalkyl" refers to a group having three to six carbon atoms including a monocyclic or bicyclic carbocycle, including but not limited to cyclopropyl, cyclopentyl, cyclopropylmethyl and cyclohexyl;
- The term "C_{3-6}-cycloalkenyl" refers to a group having three to six carbon atoms including a monocyclic or bicyclic carbocycle having three to six carbon atoms and at least one double bond, including but not limited to cyclobutenylmethyl, cyclopentenyl, cyclohexenyl

Composition

It is within the scope of the present invention to provide a composition for use in treating, ameliorating and/or preventing neuromuscular disorders characterized in that the neuromuscular function is reduced. As disclosed herein, inhibition of ClC-1 surprisingly improves or restores neuromuscular function. The compositions of the present invention comprise compounds capable of inhibiting the ClC-1 channel thereby improving or restoring neuromuscular function.

In one aspect, the invention relates to a composition comprising a compound of Formula (I):



Formula (I)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;

  wherein
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, --R_{13}-O-R_{11}, NR_9 R_{10}, -$S(O)R_{12}$, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group

consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}, nitro and halo;

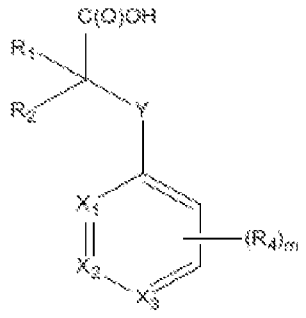
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

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

In one embodiment A is a monocyclic or bicyclic aromatic or heteroaromatic ring. A may for example be a monocyclic ring comprising 5 to 6 carbon atoms or a bicyclic ring comprising 8 to 10 C-atoms. In one embodiment A is five-membered or six-membered aromatic ring. A can also be a five-membered or six-membered heteroaromatic ring. In a preferred embodiment A is phenyl or naphthyl.

The heteroaromatic ring may for example comprise S, O or N atoms. In one embodiment A is a five or six-membered aromatic ring comprising at least one N. In one embodiment A is a five-membered heteroaromatic ring comprising an S and four C atoms. In another embodiment A is a five-membered heteroaromatic ring comprising an O and four C atoms.

In one embodiment, the invention relates to a composition comprising a compound of Formula (II):



Formula (II)

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

- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;

- X_1, X_2 and X_3 are selected from the group consisting of, CH and N;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl;
- R_4 is as defined in numbered paragraph 1 below;
- m is as defined in numbered paragraph 1 below;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}, nitro and halo;

R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl for use in treating, ameliorating and/or preventing a neuromuscular disorder.

Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2. Thus Y may be O, NH, N-CH_3, CH_2, CH_2-O, S or SO_2. In one preferred embodiment Y is selected from the group consisting of O, NH, CH_2, S, and SO_2. In a particular embodiment Y is O.

X_1, X_2 and X_3 are selected from the group consisting of, CH and N. In one embodiment X_1 is N, X_2 is N or X_3 is N. In another preferred embodiment X_1 is N. In particular embodiment X_2 is N.

R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, cyano, O- R_{11}, fluorinated C_{1-3}, nitro and halo, wherein R_9, R_{10} and R_{11} are independently

selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl

In one embodiment R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl. In an embodiment thereof R_4 is selected from the group consisting of H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, from the group consisting of H, C_{1-4}-alk(en)yl and C_{3-6}-cycloalk(en)yl or from the group consisting of H, C_{1-4}-alkyl and C_{3-6}-cycloalk(en)yl. In one embodiment R_4 is selected from the group consisting of H and C_{1-4}-alkyl.

In another embodiment R_4 is selected from the group consisting of NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10} or O-R_{11}, wherein R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl. R_9, R_{10} and R_{11} may for example be independently selected from H and C_{1-4}-alkyl or from the group consisting of H and C_{1-3}-alkyl. In one embodiment R_9, R_{10} and R_{11} are independently selected from H and -CH_3.

In another embodiment R_4 is selected from the group consisting of cyano, fluorinated C_{1-3}, nitro and halo. In one embodiment R_4 is selected from the group consisting of Cl, Br, I or F. In one embodiment R_4 is selected from the group consisting of Cl and Br.

R_4 can be located in either ortho- meta or para-position with respect to Y.

m can be 0, 1, 2, 3, 4 or 5. In one embodiment m is 0, 1, 2, 3 or 4, such as 0, 1, 2 or 3 or such as 0, 1 or 2. In another embodiment m is 0 or 1.

In one embodiment R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$, wherein

- R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -$S(O)R_{12}$, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be

substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; and

- R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

In one embodiment R_3 and/or R_5 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl. In another embodiment R_3 is selected from the group consisting of H, C_{1-6}-alkyl and C_{3-7}-cycloalkyl. In yet another embodiment R_3 is selected from the group consisting of H, C_{1-6}-alkyl, such as from the group consisting of H and C_{1-4}-alkyl. In another embodiment R_3 is selected from the group consisting of H and CH_3.

In another embodiment R_1 and R_2 are independently selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl. C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, --R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo.

R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl It is appreciated that R_1 is different from R_2.

In a preferred embodiment R_1 is selected from the group consisting of H and -CH_3. In a more preferred embodiment R_1 is H.

In one embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl. C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

In another embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

In yet another embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl, C_{3-6}-cycloalkyl and amino-C_{1-4}-alkyl, wherein said C_{1-4}-alkyl and C_{3-6}-cycloalkyl may be substituted with O-R_{11}, wherein R_{11} is as defined above. In a specific embodiment R_{11} is -CH_3.

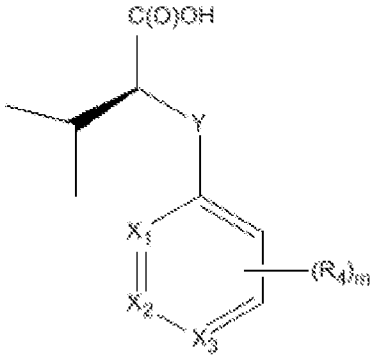
In one embodiment R_1 and R_2 are independently selected from the group consisting of H and CH_3. In a preferred embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-6}-alkyl and C_{3-7}-cycloalkyl. For example, R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl and C_{3-5}-cycloalkyl. In a further preferred embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl. In a particular embodiment, R_1 is H and R_2 is selected from the group consisting of H, -CH_3, -$CH(CH_3)_2$ and cyclopropyl. In an embodiment thereof R_1 is H and R_2 is -$CH(CH_3)_2$.

In a specific embodiment R_2 is -$CH(CH_3)CH_2$-O-CH_3. In particular, R_1 is H and R_2 is -$CH(CH_3)CH_2$-O-CH_3.

In a preferred embodiment the compound is the S-enantiomer with respect to the C-atom to which R_2 is bound.

R_1 and R_2 are in one embodiment linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl. In one particular embodiment R_1 and R_2 are linked to form a C_{3-5}-cycloalk(en)yl or a halo-C_{3-5}-cycloalk(en)yl. In another embodiment R_1 and R_2 are linked to form a C_{3-4}-cycloalk(en)yl or a halo-C_{3-4}-cycloalk(en)yl. In a preferred embodiment R_1 and R_2 are linked to form a cyclopropyl or a halo-cyclopropyl. In a more preferred embodiment R_1 and R_2 are linked to form a cyclopropyl.

In a particular embodiment R_1 is H and R_2 is -$CH(CH_3)_2$ and wherein said compound is the S-enantiomer with respect to the C-atom to which R_2 is bound as shown in formula (III):

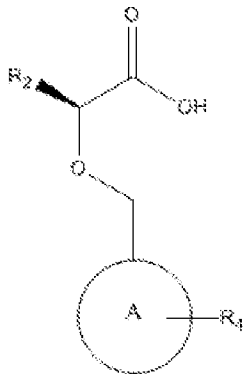


Formula (III)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein, m, Y, X_1, X_2 and X_3 and R_4 are as defined above. For example X_1 is N, X_2 is N or X_3 is N. In another embodiment X_1, X_2 and X_3 is C. R_4 may for example be selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl

In a preferred embodiment m is 0, 1 or 2. In one embodiment m is 0 or 1. For example m is 1.

In an embodiment of the present invention the compound of Formula (I) is further defined by Formula (IV):

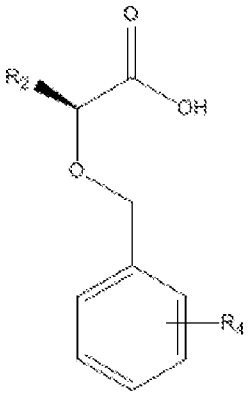


Formula (IV)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein A, R_2 and R_4 are as defined above. In one embodiment R_2 is C_{1-6}-alkyl or C_{3-7}-

cycloalkyl. For example A is a monocyclic ring such as a phenyl. It is preferred that R_4 is in ortho- or meta position.

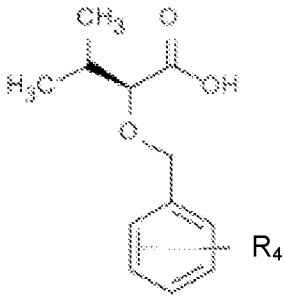
Thus, in an embodiment thereof, the compound of Formula (IV) is further defined by Formula (V):



Formula (V)

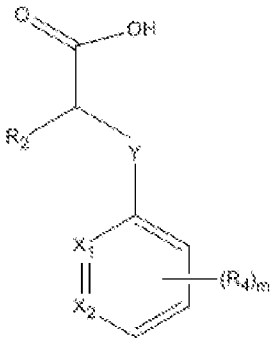
wherein R_2 and R_4 are as defined above.

In one embodiment thereof, the compound of Formula (V) is further defined by Formula (VI):



Formula (VI)

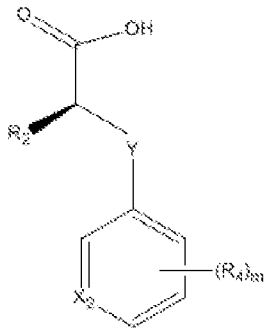
wherein R_4 is as defined above. It is preferred the R_4 is in ortho- or meta position.
In another embodiment of the present invention the compound of Formula (I) is further defined by Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein m is 2 and X_1, X_2, Y, R_2 and R_4 are as defined above.

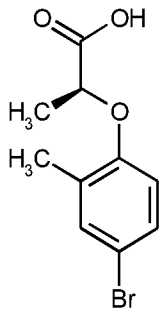
In one embodiment thereof Formula (VII) is further defined by Formula (VIII)



Formula (VIII)

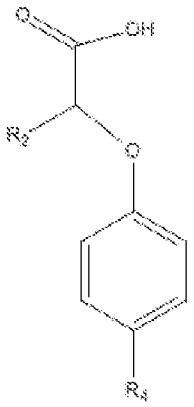
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein m, X_2, Y, R_2 and R_4 are as defined above. For example, in a preferred embodiment Y is O. Further, it is preferred that R_2 is selected from the group consisting of H and C_{1-4}-alkyl. R_4 is in one embodiment selected from the group consisting of H, -CH_3 and halogen.

In a specific embodiment the compound of Formula (VIII) is further defined by Formula (IX):



Formula (IX)

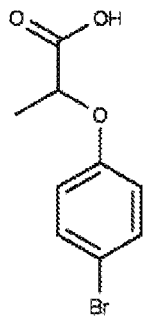
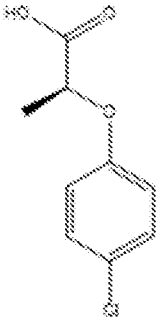
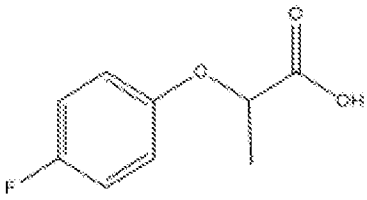
In one embodiment of the present invention the compound of Formula (VII) is further defined by Formula (X):

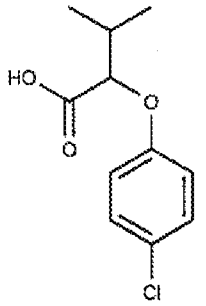


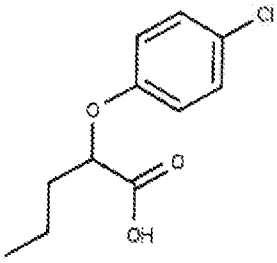
Formula (X)

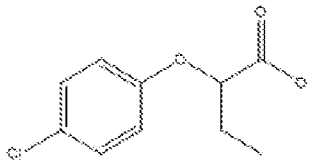
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2-O-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-NH_2$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-NH-CO-CH_3$ and $-CH_2-NH-SO_2-CH_3$ and cyclopropyl, and R_4 is selected from the group consisting of H, Br, Cl, F and I. In a preferred embodiment R_2 is $-CH_3$ or $-CH(CH_3)_2$; and R_4 is selected from the group consisting of H, Br, Cl, F and I. In particular, R_2 is $-CH(CH_3)_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

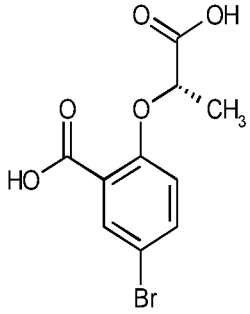
In specific embodiments Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII):

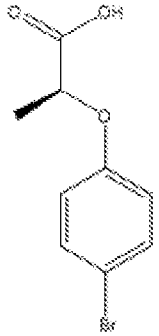
 Formula (XI)	 Formula (XII)	 Formula (XIII)

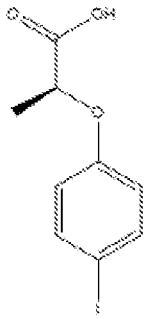

Formula (XIV)

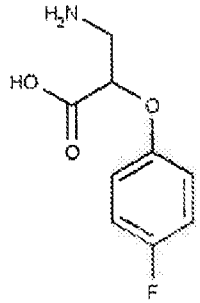

Formula (XV)

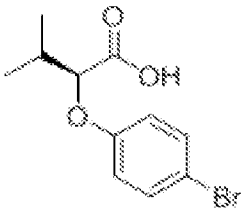

Formula (XVI)

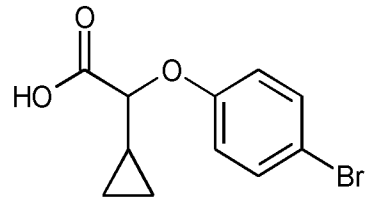

Formula (XVII)

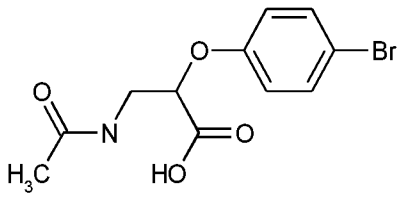

Formula (XVIII)

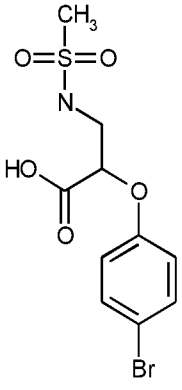

Formula (XIX)

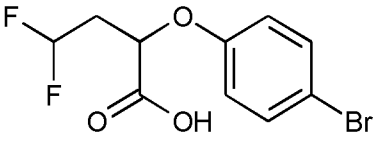

Formula (XX)

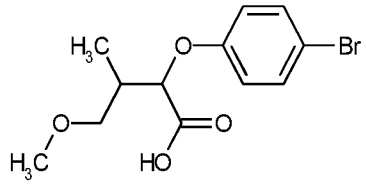

Formula (XXI)


Formula (XXII)

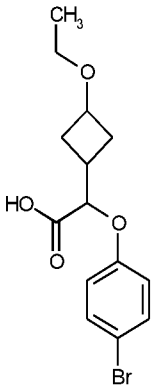

Formula (XXIII)


Formula (XXIV)

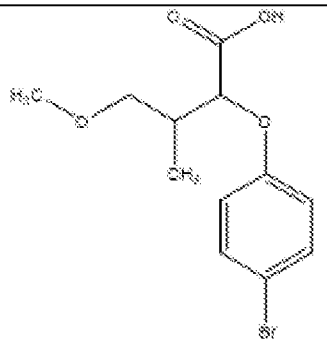

Formula (XXV)



Formula (XXVI)

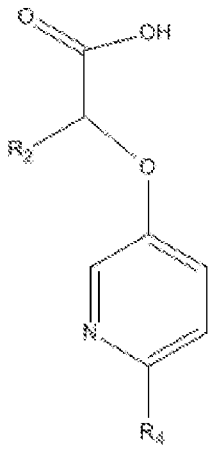


Formula (XXVII)



Formula (XXVIII)

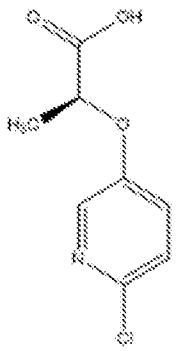
In another embodiment of the present invention the compound of Formula (VII) is further defined by Formula (XXIX):



Formula (XXIX)

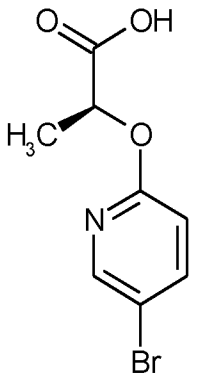
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I. In a preferred embodiment R_2 is $-CH_3$ or $-CH(CH_3)_2$; and R_4 is selected from the group consisting of H, Br, Cl, F and I. In another preferred embodiment R_2 is $-CH_3$ or $-CH(CH_3)_2$ and R_4 is selected from the group consisting of H, Br, Cl and F. It is further preferred that the compound of Formula (X) is the S-enantiomer with respect to the C-atom to which R_2 is bound. This embodiment is exemplified by Formulas (XXIII) and (XXIV), where R_2 is $-CH_3$ and R_4 is Cl or Br.

Thus, in one embodiment the compound of Formula (XXIX) is further defined by Formula (XXX):



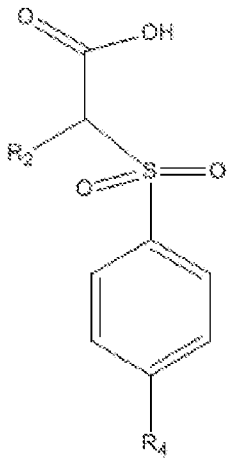
Formula (XXX)

In another specific embodiment the compound of Formula (VII) is further defined by Formula (XXXI):



Formula (XXXI)

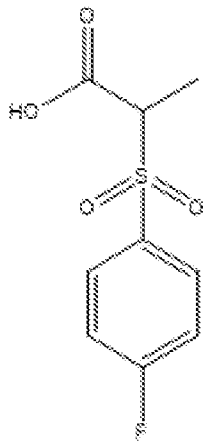
In one embodiment of the present invention Y is SO_2. In particular, the compound of Formula (VII) can be further defined by Formula (XXXII):



Formula (XXXII)

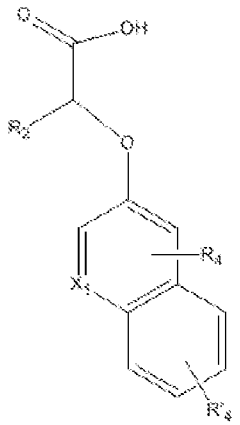
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I. In a preferred embodiment R_2 is $-CH_3$ or $-CH(CH_3)_2$; and R_4 is selected from the group consisting of H, Br, Cl, F and I. In another preferred embodiment R_2 is $-CH_3$ or $-CH(CH_3)_2$ and R_4 is selected from the group consisting of H, Br, Cl and F.

In a specific embodiment the compound of Formula (XXXII) is defined by Formula (XXXIII):



Formula (XXXIII)

As mentioned above, in one embodiment of the present A can be a naphthyl. In one embodiment Y is O. Thus, in a preferred embodiment of the present invention the compound of Formula (I) is further defined by Formula (XXXIV):

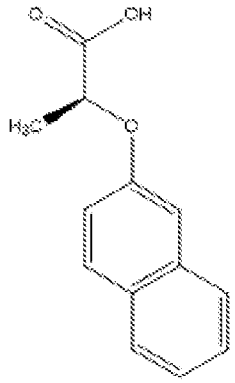


Formula (XXXIV)

or a salt or tautomer thereof;

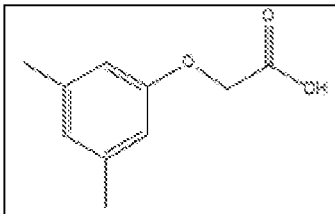
wherein R_2 and X_1 are as defined above; and R_4 and R'_4 are independently selected from the group consisting of H, halo, cyano, hydroxy, -CHO, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, O- C_{1-6}-alk(en/yn)yl. In a preferred embodiment R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$. Preferably R_2 is CH_3 or $-CH(CH_3)_2$. It is preferred that R_4 and R'_4 are individually selected from the group consisting of H, Br, Cl, F and I. In another preferred embodiment R_4 and/or R'_4 are H. It is further preferred that X_1 is N or C.

In a particular embodiment R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$; X_1 is N or C; and R_4 and R'_4 are individually selected from the group consisting of H, Br, Cl, F and I. In a particular embodiment Formula (XXXIV) is further defined by Formula (XXXV):

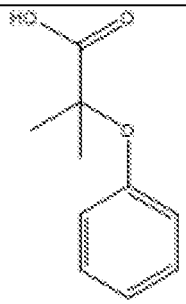


Formula (XXXV)

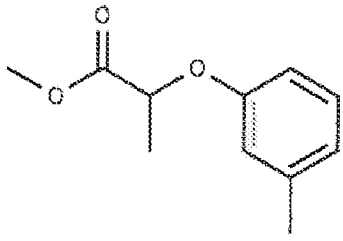
In specific embodiments of the present invention the compound of Formula (I) is further defined by any one of Formulas (XXXVI) to (LIX):



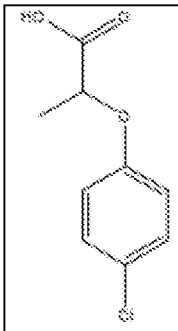
Formula (XXXVI)



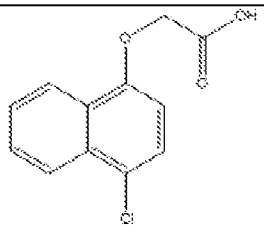
Formula (XXXVII)



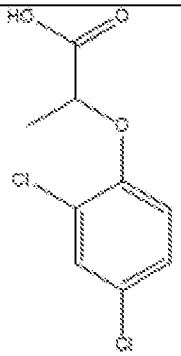
Formula (XXXVIII)



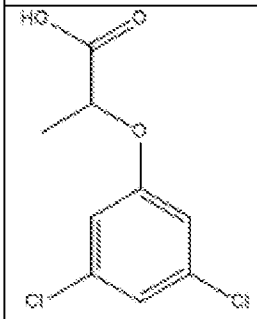
Formula (XXXIX)



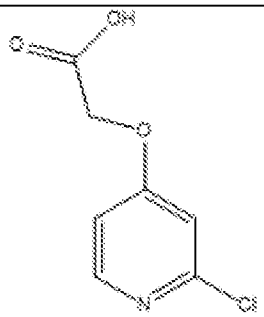
Formula (XL)



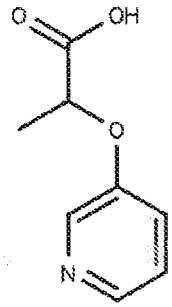
Formula (XLII)



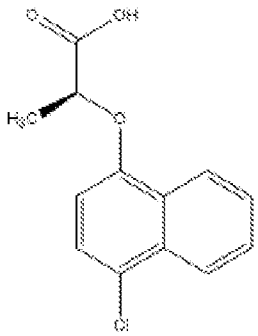
Formula (XLIII)



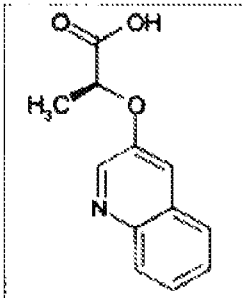
Formula (XLIV)



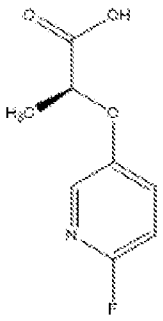
Formula (XLV)



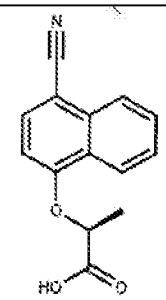
Formula (XLVI)



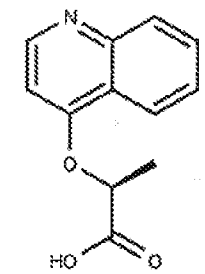
Formula (XLVII)



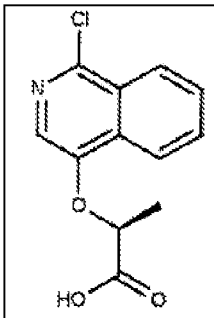
Formula (XLVIII)



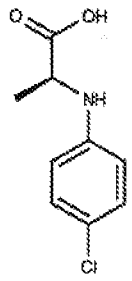
Formula (XLIX)



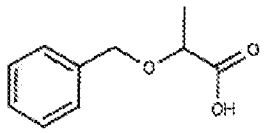
Formula (L)



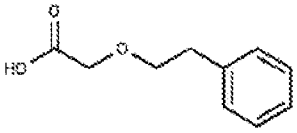
Formula (LI)



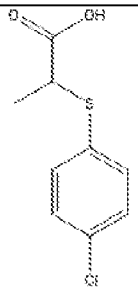
Formula (LII)



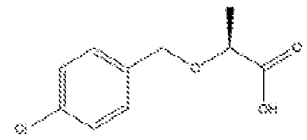
Formula (LIII)



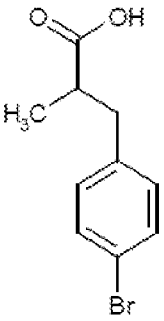
Formula (LIV)



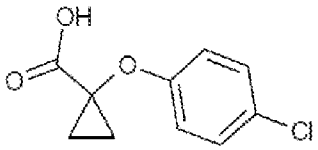
Formula (LV)



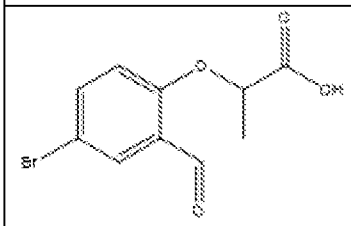
Formula (LVI)



Formula (LVII)



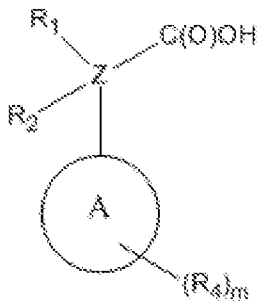
Formula (LVIII)



Formula (LIX)

Compound

Another aspect of the present invention relates to a compound of Formula (I):



Formula (I)

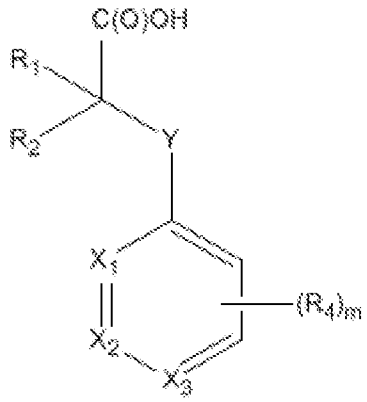
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
  wherein
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, $-S(O)R_{12}$, $S(O)_2R_{12}$, cyano, $O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo;

- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, $-S(O)R_{12}$, $S(O)_2R_{12}$, cyano, $O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

In one embodiment thereof, A is a monocyclic or bicyclic aromatic or heteroaromatic ring. For example, A can be a five-membered or six-membered aromatic ring. In one embodiment A is phenyl, or naphthyl.

In another embodiment of the present invention, the compound of Formula (I) is further defined by Formula (II):



Formula (II)

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

- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are selected from the group consisting of, CH and N;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl,

wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo ; or R_1 and R_2 are linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl;

- R_4 is as defined in numbered paragraph 1 below;
- m is as defined in numbered paragraph 1 below;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;

R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl; for use in treating, ameliorating and/or preventing a neuromuscular disorder.

In a preferred embodiment R_1 is selected from the group consisting of H and -CH_3. In a particular embodiment R_1 is H.

Thus, in one embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, NR_9 R_{10}, -S(O)R_{12}, $S(O)_2R_{12}$, cyano, O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10} and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl

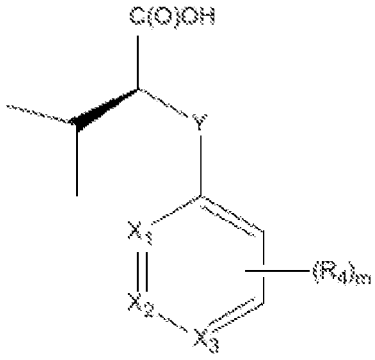
Thus, in another embodiment R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl, C_{3-6}-cycloalkyl and amino-C_{1-4}-alkyl, wherein said C_{1-4}-alkyl and C_{3-6}-cycloalkyl may be substituted with O-R_{11}, wherein R_{11} is as defined above. In one embodiment R_{11} is -CH_3. In another embodiment R_2 is -$CH(CH_3)CH_2$-O-CH_3.

In a preferred embodiment of the present invention R_1 is H and R_2 is selected from the group consisting of H, C_{1-6}-alkyl and C_{3-7}-cycloalkyl. For example, R_1 is H and R_2 is selected from the group consisting of H, $-CH_3$, $-CH(CH_3)_2$ and cyclopropyl. In a particular embodiment, R_1 is H and R_2 is $-CH(CH_3)_2$.

It is preferred that R_1 is different from R_2.

It is appreciated that the compound as defined herein is the S-enantiomer with respect to the C-atom to which R_2 is bound.

In one embodiment thereof, R_1 is H and R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl and wherein said compound is the S-enantiomer with respect to the C-atom to which R_2 is bound as shown in Formula (III):



Formula (III)

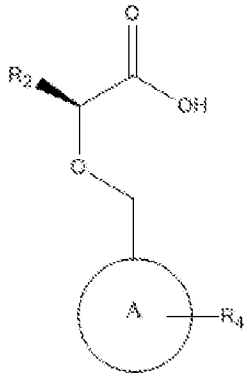
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein, Y, X_1, X_2 and X_3 and R_4 are as defined above.

In one preferred embodiment of the invention, R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl.

In one embodiment m is 0, 1 or 2. For example m is 1.

In one embodiment of the invention X_1 is N, X_2 is N or X_3 is N. In another embodiment X1, X_2 and X_3 is C.

The compound may in one embodiment be defined by Formula (I), which is further defined by Formula (IV):

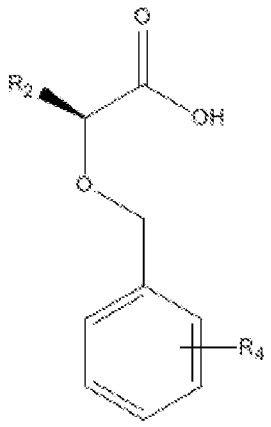


Formula (IV)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein A, R_2 and R_4 are as defined above.

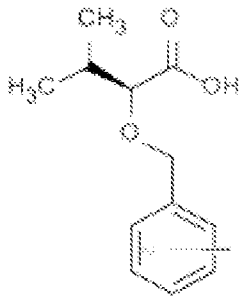
Also, the compound of Formula (IV) can be further defined by Formula (V):

wherein R_2 and R_4 are as defined above. It is preferred that R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl.



Formula (V)

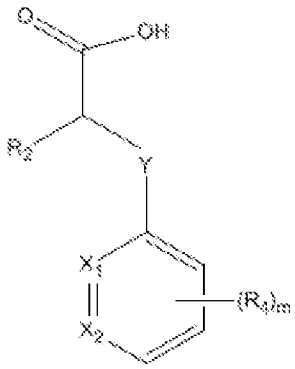
In one embodiment thereof, the compound of Formula (V) is further defined by Formula (VI):



Formula (VI)

wherein R_4 is as defined above. Preferably, R_4 is in ortho- or meta position.

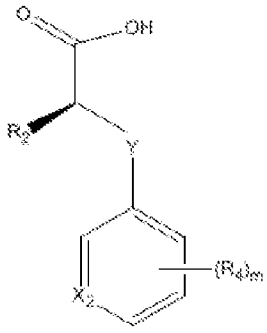
In one embodiment of the present invention the compound of Formula (I) is further defined by Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein m is 2 and X_1, X_2, Y, R_2 and R_4 are as defined above.

In an embodiment thereof, the compound of Formula (VII) is further defined by Formula (VIII)

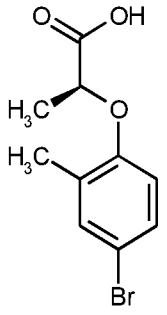


Formula (VIII)

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

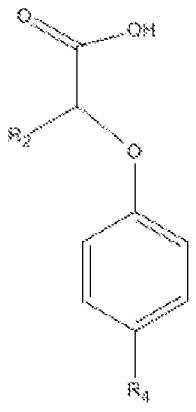
wherein m, X_2, Y, R_2 and R_4 are as defined above.

In one preferred embodiment Y is O. It is further preferred that R_2 is selected from the group consisting of H and C_{1-4}-alkyl. Preferably, R_4 is selected from the group consisting of H, $-CH_3$ and halogen. Thus, in one embodiment the compound is further defined by Formula (IX):



Formula (IX)

In one embodiment the compound of Formula (VII) is further defined by Formula (X):

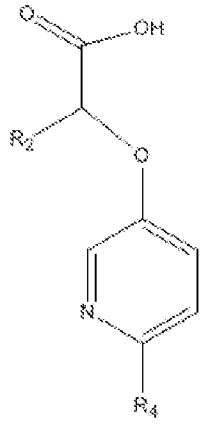


Formula (X)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2-O-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-NH_2$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-NH-CO-CH_3$ and $-CH_2-NH-SO_2-CH_3$ and cyclopropyl, and R_4 is selected from the group consisting of H, Br, Cl, F and I.

In specific embodiments, the compound of Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII) as defined herein.

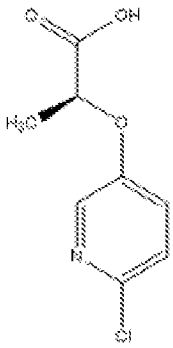
Another embodiment of the present invention relates to a compound of Formula (VII) that is further defined by Formula (XXIX):



Formula (XXIX)

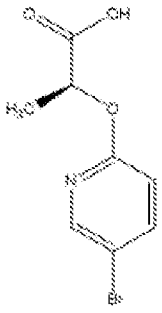
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

In particular, the compound of Formula (XXIX) is further defined by Formula (XXX):



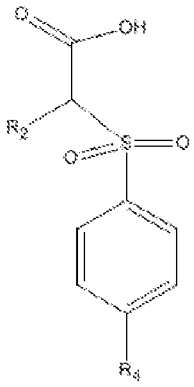
Formula (XXX)

In one embodiment, the compound of Formula (VII) is further defined by Formula (XXXI):



Formula (XXXI)

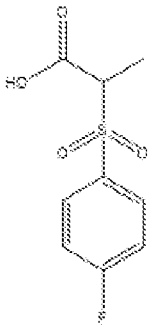
Also, the compound of Formula (VII) can be further defined by Formula (XXXII):



Formula (XXXII)

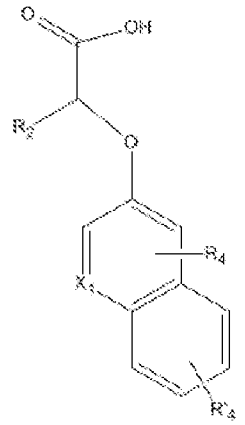
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

Preferably, the compound of Formula (XXXII) is further defined by Formula (XXXIII):



Formula (XXXIII)

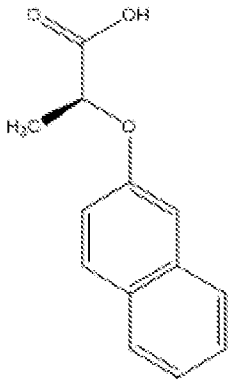
In another embodiment of the present invention the compound of Formula (I) is further defined by Formula (XXXIV):



Formula (XXXIV)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$; X_1 is N or C; and R_4 and R'_4 are individually selected from the group consisting of H, Br, Cl, F and I.

In particular, Formula (XXXIV) can be further defined by Formula (XXXV):



Formula (XXXV)

In specific embodiments of the present invention, the compound of Formula (I) is further defined by any one of Formulas (XXXVI) to (LIX).

Neuromuscular disorders

The composition of the present invention is used for treating, ameliorating and/or preventing a neuromuscular disorder.

The inventors of the present invention have shown that inhibition of ClC-1 channels recovers neuromuscular transmission. ClC-1 function may therefore contribute to muscle weakness in conditions of compromised neuromuscular transmission.

Thus, in one embodiment of the present invention, the composition for use as described herein inhibits ClC-1 channels. Thus, it is appreciated that compounds of Formula (I) inhibit ClC-1 channels.

The neuromuscular disorder may also include neuromuscular dysfunctions.

Neuromuscular disorders include for example disorders with symptoms of muscle weakness and fatigue. Such disorders may include conditions with reduced neuromuscular transmission safety factor. In one embodiment the neuromuscular disorders are motor neuron disorders. Motor neuron disorders are disorders with reduced safety in the neuromuscular transmission. In one embodiment motor neuron disorders are selected from the group consisting of amyotrophic lateral sclerosis[11] (ALS), spinal muscular atrophy[12] (SMA), X-linked spinal and bulbar muscular atrophy[13], Kennedy´s disorder[14], multifocal motor neuropathy[15], Guillain-Barré syndrome[16], poliomyelitis[17] and post-polio syndrome[18].

Thus, in one preferred embodiment of the present invention the neuromuscular disorder is ALS. In another preferred embodiment the neuromuscular disorder is SMA.

As stated above the neuromuscular disorders include for example disorders with symptoms of muscle weakness and fatigue. Such disorder may for example include diabetes[19].

In one embodiment the composition of the present invention is used to prevent neuromuscular disorder. The composition may for example be used prophylactically against nerve gas that is known to cause symptoms of muscle weakness and fatigue[20].

In another embodiment the neuromuscular disorders is chronic fatigue syndrome. Chronic fatigue syndrome[21] (CFS) is the common name for a medical condition characterized by debilitating symptoms, including fatigue that lasts for a minimum of six months in adults. CFS may also be referred to as systemic exertion intolerance disorder (SEID), myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS), chronic fatigue immune dysfunction syndrome (CFIDS), or by several other terms. Symptoms of CFS include malaise after exertion; unrefreshing sleep, widespread muscle and joint pain, physical exhaustion, and muscle weakness.

In a further embodiment the neuromuscular disorder is a critical illness polyneuropathy[22] or CIM[4]. Critical illness polyneuropathy and CIM are overlapping syndromes of widespread muscle weakness and neurological dysfunction developing in critically ill patients.

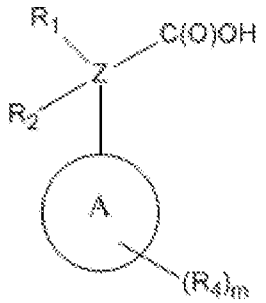
The neuromuscular disorder may also include metabolic myopathy[23] and mitochondrial myopathy[24]. Metabolic myopathies result from defects in biochemical metabolism that primarily affects muscle. These may include glycogen storage disorders, lipid storage disorder and 3-phosphocreatine stores disorder. Mitochondrial myopathy is a type of myopathy associated with mitochondrial disorder. Symptoms of mitochondrial myopathies include muscular and neurological problems such as muscle weakness, exercise intolerance, hearing loss and trouble with balance and coordination.

In a preferred embodiment the neuromuscular disorder is a myasthenic condition. Myasthenic conditions are characterized by muscle weakness and neuromuscular transmission failure. Congenital myasthenia gravis[5] is an inherited neuromuscular disorder caused by defects of several types at the neuromuscular junction. Myasthenia gravis[3] and Lambert–Eaton[2] syndrome are also examples of myasthenic condition. Myasthenia gravis is either an autoimmune or congenital neuromuscular disorder that leads to fluctuating muscle weakness and fatigue. In the most common cases, muscle weakness is caused by circulating antibodies that block ACh receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter ACh on nicotinic Ach-receptors at neuromuscular junctions. Lambert–Eaton myasthenic syndrome (also known as LEMS, Lambert–Eaton syndrome, or Eaton–Lambert syndrome) is a rare autoimmune disorder that is characterized by

muscle weakness of the limbs. It is the result of an autoimmune reaction in which antibodies are formed against presynaptic voltage-gated calcium channels, and likely other nerve terminal proteins, in the neuromuscular junction.

Thus, in one preferred embodiment of the present invention the neuromuscular disorder is myasthenia gravis. In another preferred embodiment the neuromuscular disorder is Lambert–Eaton syndrome.

Neuromuscular blockade is used in connection with surgery under general anaesthesia. Reversing agents are used for more rapid and safer recovery of muscle function after such blockade. Complications with excessive muscle weakness after blockade during surgery can result in delayed weaning from mechanical ventilation and respiratory complications after the surgery. Since such complications have pronounced effects on outcome of the surgery and future quality of life of patients, there is a need for improved reversing agents[25]. Thus, in a preferred embodiment the neuromuscular disorder is muscle weakness caused by neuromuscular blockade after surgery. In another preferred embodiment of the present invention the composition is used for reversing and/or ameliorating neuromuscular blockade after surgery. Thus, one aspect of the present invention relates to a composition comprising a compound of Formula (I):



Formula (I)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or

substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
wherein

- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, $-S(O)R_{12}$, $S(O)_2R_{12}$, cyano, $O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, $-S(O)R_{12}$, $S(O)_2R_{12}$, cyano, $O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

for use in reversing and/or ameliorating a neuromuscular blockade after surgery.

Another aspect of the invention relates to a method of reversing and/or ameliorating a neuromuscular blockade after surgery, said method comprising administering a therapeutically effective amount of the composition as defined in any one of the numbered paragraphs herein below to a person in need thereof.

In yet another aspect, the present invention relates to use of a composition as defined herein, for the manufacture of a medicament for reversing and/or amelioration of a neuromuscular blockade after surgery.

Combination therapy

The composition of the present invention may comprise further active ingredients/agents or other components to increase the efficiency of the composition. Thus, in one embodiment the composition further comprises at least one further active agent. It is appreciated that the active agent is suitable for treating, preventing or ameliorating said neuromuscular disorder.

The active agent is in a preferred embodiment an acetylcholine esterase inhibitor. Said acetylcholine esterase inhibitor may for example be selected from the group consisting of delta-9-tetrahydrocannabinol, carbamates, physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, rivastigmine, phenanthrene derivatives, galantamine, caffeine – noncompetitive, piperidines, donepezil, tacrine, edrophonium, huperzine, ladostigil, ungeremine and lactucopicrin.

Preferably the acetylcholine esterase inhibitor is selected from the group consisting of neostigmine, physostigmine and pyridostigmine. It is preferred that the acetylcholine esterase inhibitor is neostigmine or pyridostigmine.

The active agent may also be an immunosuppressive drug. Iimmunosuppressive drugs are drugs that suppress or reduce the strength of the body's immune system. They are also known as anti-rejection drugs. Immunosuppressive drugs include but are not limited to glucocorticoids, corticosteroids, cytostatics, antibodies and drugs acting on immunophilins. In one embodiment the active agent is prednisone.

The active agent may also be an agent that is used in anti-myotonic treatment. Such agents include for example blockers of voltage gated Na^+ channels, and aminoglycosides.

The active agent may also be an agent for reversing a neuromuscular blockade after surgery. Such agents include for example neostigmine or suggammadex.

The active agent may also be an agent for increasing the Ca^{2+} sensitivity of the contractile filaments in muscle. Such agent includes tirasemtiv.

The active agent may also be an agent for increasing ACh release by blocking voltage gated K^+ channels in the pre-synaptic terminal. Such agent includes 3,4-aminopyridine. As illustrated in example 5, combination therapy using C8 and 3,4-diaminopyridine resulted in an unexpected synergistic effect on recovery of neuromuscular transmission.

Pharmaceutical formulations

The composition according to the present invention is used for treating, ameliorating and/or preventing a neuromuscular disorder. Thus, it is preferred that the compositions and compounds described herein are pharmaceutically acceptable. In one embodiment the composition as described herein is in the form of a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation, which comprises a compound of Formula (I) and a pharmaceutically acceptable salt or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof, as herein defined, and a pharmaceutically acceptable carrier. Thus, in one embodiment the composition of the present invention further comprises a pharmaceutically acceptable carrier. The pharmaceutical formulations may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 2005, Lippincott, Williams & Wilkins.

The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more excipients which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compositions of the present invention may be formulated for parenteral administration and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers, optionally with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or non-aqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

In a preferred embodiment the compositions of the present invention is formulated for oral administration. Oral administration forms include solid form preparations including powders, tablets, drops, capsules, cachets, lozenges, and dispersible granules. Other forms suitable for oral administration may include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, toothpaste, gel dentrifrice, chewing gum, or solid form preparations which are intended to be converted shortly before use to liquid form preparations, such as solutions, suspensions, and emulsions. In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component.

In a preferred embodiment the composition as described herein is formulated in a tablet or capsule. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers are magnesium carbonate, magnesium stearate, talc,

sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like.

Drops according to the present invention may comprise sterile or non-sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

The compositions of the present invention may also be formulated in a wide variety of formulations for parenteral administration.

For injections and infusions the formulations may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Alternatively, the composition may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules, vials, pre-filled syringes, infusion bags, or can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

Examples of oily or non-aqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils, and injectable organic esters, and

may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents.

The formulations for injection will typically contain from about 0.5 to about 25% by weight of the active ingredient in solution.

Topical delivery

The compounds may also be administered topically. Regions for topical administration include the skin surface and also mucous membrane tissues of the vagina, rectum, nose, mouth, and throat.

The topical composition will typically include a pharmaceutically acceptable carrier adapted for topical administration. Thus, the composition may take the form of a suspension, solution, ointment, lotion, sexual lubricant, cream, foam, aerosol, spray, suppository, implant, inhalant, tablet, capsule, dry powder, syrup, balm or lozenge, for example. Methods for preparing such compositions are well known in the pharmaceutical industry.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin or a fatty acid. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Lotions according to the present invention also include those suitable for application to the eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide.

Nasal, pulmonary and bronchial administration

Formulations for use in nasal, pulmonary and/or bronchial administration are normally administered as aerosols in order to ensure that the aerosolized dose actually reaches the mucous membranes of the nasal passages, bronchial tract or the lung. The term "aerosol particle" is used herein to describe the liquid or solid particle suitable for nasal, bronchial or pulmonary administration, i.e., that will reach the mucous membranes.

Typically aerosols are administered by use of a mechanical devices designed for pulmonary and/or bronchial delivery, including but not limited to nebulizers, metered dose inhalers, and powder inhalers. With regard to construction of the delivery device, any form of aerosolization known in the art, including but not limited to spray bottles, nebulization, atomization or pump aerosolization of a liquid formulation, and aerosolization of a dry powder formulation, can be used.

Liquid Aerosol Formulations in general contain a compound of the present invention in a pharmaceutically acceptable diluent. Pharmaceutically acceptable diluents include but are not limited to sterile water, saline, buffered saline, dextrose solution, and the like.

Formulations for dispensing from a powder inhaler device will normally comprise a finely divided dry powder containing pharmaceutical composition of the present invention (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device. Dry powder formulations for inhalation may also be formulated using powder-filled capsules, in particularly capsules the material of which is selected from among the synthetic plastics.

The formulation is formulated to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy and known to the person skilled in the art. The propellant may be any propellant generally used in the art. Specific non-limiting examples of such useful propellants are a chlorofluorocarbon, a hydrofluorocarbon, a hydrochlorofluorocarbon, or a hydrocarbon.

The formulations of the present embodiment may also include other agents useful for pH maintenance, solution stabilization, or for the regulation of osmotic pressure.

The formulations of the present embodiment may also include other agents useful for pH maintenance, solution stabilization, or for the regulation of osmotic pressure.

Transdermal Delivery

The pharmaceutical agent-chemical modifier complexes described herein can be administered transdermally. Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient. The skin sites include anatomic regions for transdermally administering the drug and include the forearm, abdomen, chest, back, buttock, mastoidal area, and the like.

Transdermal delivery is accomplished by exposing a source of the complex to a patient's skin for an extended period of time. Transdermal patches have the added advantage of providing controlled delivery of a pharmaceutical agent-chemical modifier complex to the body. Such dosage forms can be made by dissolving, dispersing, or otherwise incorporating the pharmaceutical agent-chemical modifier complex in a proper medium, such as an elastomeric matrix material. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel. For example, a simple adhesive patch can be prepared from a backing material and an acrylate adhesive.

Administration forms

As described herein above administration forms include but are not limited to oral, parental, topical, enteral, rectal or buccal administration.

In one embodiment the composition is administered or adapted for administration enterally, topically, parenterally or as part of a sustained release implant.

The parenteral administration may for example be intravenous, subcutaneous, intramuscular, intracranial or intraperitoneal. In a preferred embodiment the parental administration is intramuscular. Enteral administration includes oral, rectal, or buccal administration. In one embodiment topical administration is dermal, epicutaneous, vaginal, intravesical, pulmonary, intranasal, intratracheal or as eye drops.

In another embodiment the composition is administered or adapted for administration subcutaneously or intravenously.

It is appreciated that the composition of the present invention comprises at least 30 wt. % compound, such as at least 25 wt. % compound, such as for example at least 20 wt. % compound, at least 15 wt. % compound, such as at least 25 wt. % compound, such as for example at least 20 wt. % compound, at least 15 wt. % compound, such as at least 10 wt. % compound, such as for example at least 8 wt. % compound, at least 5 wt. % compound, such as at least 4 wt. % compound, such as for example at least 3 wt. % compound, at least 2 wt. % compound, such as at least 1 wt. % compound, such as for example at least 0,5 wt. % compound or at least 0,5 wt. % compound.
Wt. % is an abbreviation for weight percent.

The compound is any compound defined by Formula (I). Thus, the active ingredient can be any of the compounds defined by the formulas or embodiments presented herein.

In one embodiment the compound as described herein is to be administered in a dosage of from 1 µg/kg - 30,000 µg/kg body weight, such as 1 µg/kg - 7,500 µg/kg, such as 1 µg/kg - 5,000 µg/kg, such as 1 µg/kg - 2,000 µg/kg, such as 1 µg/kg - 1,000 µg/kg, such as 1 µg/kg - 700 µg/kg, such as 5 µg/kg - 500 µg/kg, such as 10 µg/kg to 100 µg/kg bodyweight.

In another embodiment the compound as described herein is to be administered in a dosage of from 1 µg/kg -1,000 µg/kg body weight, such as 1 µg/kg - 500 µg/kg, such as 1 µg/kg - 250 µg/kg, such as 1 µg/kg - 100 µg/kg, such as 1 µg/kg - 50 µg/kg, such as 1 µg/kg to 10 µg/kg bodyweight.

In yet another embodiment the compound as described herein is to be administered in a dosage of from 10 µg/kg - 30,000 µg/kg body weight, such as 10 µg/kg - 7,500 µg/kg, such as 10 µg/kg - 5,000 µg/kg, such as 10 µg/kg - 2,000 µg/kg, such as 10 µg/kg - 1,000 µg/kg, such as 10 µg/kg - 700 µg/kg, such as 10 µg/kg - 500 µg/kg, such as 10 µg/kg to 100 µg/kg bodyweight.

In one embodiment the administration of the composition as described herein is repeated at least 1, 2, 3, 4, 5 or 6 times weekly.

In another embodiment the administration is repeated at least 1-3 times weekly, such as 2-5 times weekly, such as 3-6 times weekly.

In a further embodiment the administration is repeated daily. The administration of the composition may for example be repeated 1, 2, 3, 4, 5, 6, 7 or 8 times daily. In one embodiment the administration is repeated 1 to 8 times daily, such as 2 to 5 times daily.

The compound as defined herein can be modified in order to increase its half-life when administered to a patient, in particular its plasma half-life.

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.

Modification of the compound to increase its half-life may for example include conjugation of a moiety that increases the half-life of the compound. Thus, in an embodiment the compound further comprises a moiety conjugated to said compound, thus generating a moiety-conjugated compound. It is preferred that the moiety-conjugated compound has a plasma and/or serum half-life being longer than the plasma and/or serum half-life of the non-moiety conjugated compound.

The moiety conjugated to the compound can for example be one or more type(s) of moieties selected from the group consisting of albumin, fatty acids, polyethylene glycol (PEG), acylation groups, antibodies and antibody fragments.

Methods

In one aspect the present invention relates to a method of treating, preventing and/or ameliorating a neuromuscular disorder, said method comprising administering a therapeutically effective amount of the composition as defined herein to a person in need thereof.

The person in need thereof may be a person having a neuromuscular disorder or a person at risk of developing a neuromuscular disorder or a person having symptoms of muscle weakness and/or fatigue. In another embodiment the person in need thereof is a person with reduced neuromuscular transmission safety with prolonged recovery after neuromuscular blockade. Types of neuromuscular disorders are defined herein above. In a preferred embodiment the person has, amyotrophic lateral sclerosis, spinal muscular atrophy, myasthenia gravis or Lambert–Eaton syndrome.

A therapeutically effective amount is an amount that produces a therapeutic response or desired effect in the person taking it. Administration forms and dosages are as defined herein above.

The method of treatment may be combined with other methods that are known to treat, prevent and/or ameliorate neuromuscular disorders. The treatment method may for example be combined with administration of any of the agents mentioned herein above. In one embodiment the treatment is combined with administration of acetylcholine esterase inhibitor such as for example neostigmine or pyridostigmine.

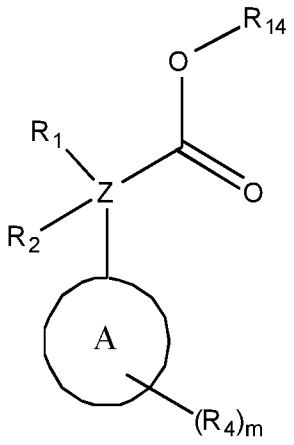
Another aspect of the invention relates to use of a composition as defined herein, for the manufacture of a medicament for the treatment, prevention and/or amelioration of a neuromuscular disorder.

Another aspect relates to use of a composition as defined herein, for the manufacture of a medicament or a reversal agent for reversing and/or ameliorating a neuromuscular blockade after surgery.

Prodrugs

The compounds of formula (I) may be administered as a prodrug to modify the distribution, duration of efficacy or other properties. Conversion of the carboxylic acid group of compounds of formula (I) to an ester using ethanol to form the ethyl ester is an example of such prodrug. Preferred alcohols include low molecular weight alcohols, phenols and other aromatic alcohols, and fluorinated alcohols. In some cases, it is preferable to use an enol as the alcohol, for example 4-hydroxy-pent-3-ene-2-one. Alternatively, the prodrug may be the corresponding aldehyde, or an imine thereof. Again, these precursors can be expected to transform to the carboxylic acid *in vivo*. The prodrugs are administered using the same formulations and in the same dosage ranges as the compounds of formula (I).

In one aspect, said prodrug is defined by Formula (LX):



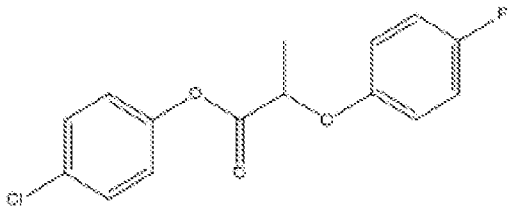
Formula (LX)

or a salt of tautomer thereof

wherein m, A, Z, R_1, R_2 and R_4 are as defined above and wherein R_{14} is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, pyrimidyl, pyridinyl, thiazolyl, oxadiazolyl and quinolyl, all aromatic and heteroaromatic groups optionally substituted by one or more R_4

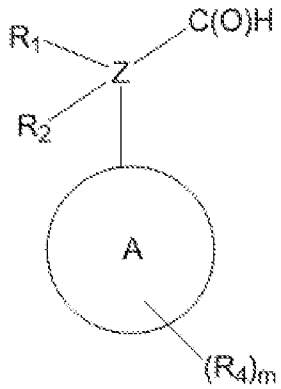
In one embodiment R_{14} is a phenyl substituted with methoxy, nitro, cyano, Cl, Br, I and/or F.

In one embodiment Formula (LX) is further defined by Formula (LXI):



Formula (LXI)

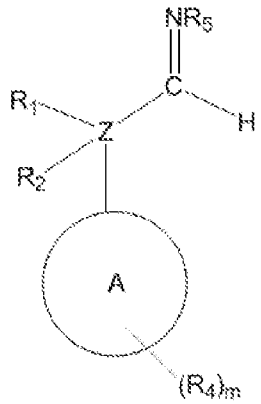
In another embodiment of the present invention the prodrug is defined by Formula (LXII):



Formula (LXII)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof, wherein m, A, Z, R_1, R_2 and R_4 are as defined above.

The prodrug can also be defined by Formula (LXIII):



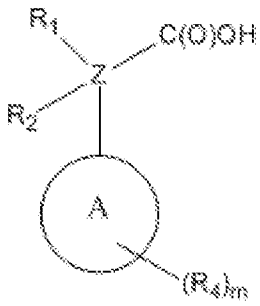
Formula (LXII)

wherein m, A, Z, R_1, R_2 and R_4 are as defined above, and B is a 5- to 7-membered heterocyclic.

Paragraphs

The present application provides embodiments as described by the following numbered paragraphs:

1. A composition comprising a compound of Formula (I):



Formula (I)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;

- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;

wherein

- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

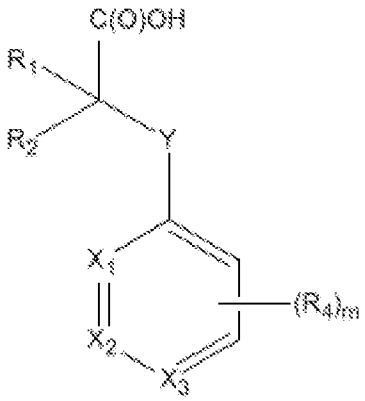
for use in treating, ameliorating and/or preventing a neuromuscular disorder.

2. The composition according to paragraph 1, wherein A is a monocyclic or bicyclic aromatic or heteroaromatic ring.

3. The composition according to any of paragraphs 1 and 2, wherein A is five-membered or six-membered aromatic ring.

4. The composition according to any one of paragraphs 1 to 3, wherein A is phenyl, or naphthyl.

5. The composition according to any of the preceding paragraphs, wherein said compound is a compound of Formula (II):



Formula (II)

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

- m is 0, 1, 2, 3, 4 or 5;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from the group consisting of CH and N;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo ; or R_1 and R_2 are linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl;

- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;

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

6. The composition for use according to any one of the preceding paragraphs, wherein R_1 is selected from the group consisting of H and -CH_3.

7. The composition according to any one of the preceding paragraphs, wherein R_1 is H.

8. The composition for use according to any of the preceding paragraphs, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

9. The composition for use according to any of the preceding paragraphs, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl, C_{3-6}-cycloalkyl and amino-C_{1-4}-alkyl, wherein said C_{1-4}-alkyl and C_{3-6}-cycloalkyl may

be substituted with O-R_{11}, wherein R_{11} is selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

10. The composition for use according to paragraph 9, wherein R_{11} is -CH_3.

11. The composition for use according to paragraph 9, wherein R_2 is -$CH(CH_3)CH_2$-O-CH_3.

12. The composition for use according to any of paragraphs 1 to 7, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-6}-alkyl and C_{3-7}-cycloalkyl.

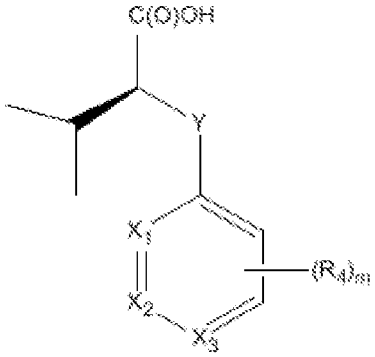
13. The composition for use according to any of the preceding paragraphs, wherein R_1 is H and R_2 is selected from the group consisting of H, -CH_3, -$CH(CH_3)_2$ and cyclopropyl.

14. The composition for use according to any of the preceding paragraphs, wherein R_1 is H and R_2 is -$CH(CH_3)_2$.

15. The composition for use according to any one of the preceding paragraphs, wherein R_1 is different from R_2.

16. The composition for use according to any one of the preceding paragraphs, wherein said compound is an S-enantiomer with respect to the C-atom to which R_2 is bound.

17. The composition for use according to any paragraphs 1 to 16, wherein R_1 is H and R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl and wherein said compound is an S-enantiomer with respect to the C-atom to which R_2 is bound as shown in Formula (III):



Formula (III)

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

- wherein Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are selected from the group consisting of, CH and N;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo.

18. The composition for use according to any one of the preceding paragraphs wherein R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl.

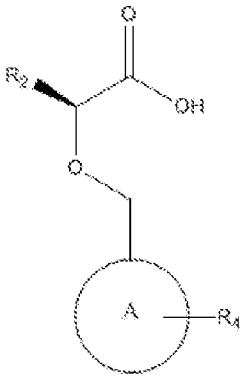
19. The composition for use according to any one of the preceding paragraphs wherein m is 0, 1 or 2.

20. The composition for use according to any one of the preceding paragraphs wherein m is 1.

21. The composition for use according to any paragraphs, wherein X_1 is N, X_2 is N or X_3 is N.

22. The composition for use according to any one of paragraphs 5 to 20, wherein X_1, X_2 and X_3 is C.

23. The composition for use according to any one of paragraphs 1 to 4, wherein the compound of Formula (I) is further defined by Formula (IV):



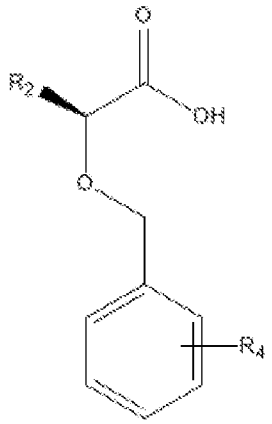
Formula (IV)

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

- wherein A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9$-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9$-CO- R_{10}, $-NR_{10}$-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo.

- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

24. The composition for use according to paragraph 23, wherein the compound of Formula (IV) is further defined by Formula (V):



Formula (V)

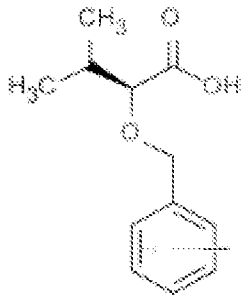
wherein

- R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

25. The composition for use according to paragraph 23, wherein R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl.

26. The composition for use according paragraph 25, wherein the compound of Formula (V) is further defined by Formula (VI):



R_4 Formula (VI)

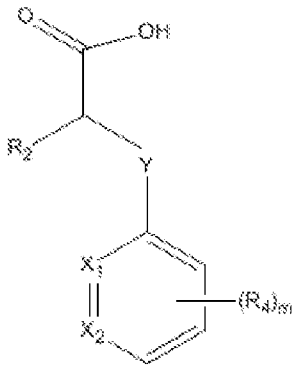
wherein R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2-NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;

- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl

- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

27. The composition for use according to any one of paragraphs 24 to 26, wherein R_4 is in ortho- or meta position.

28. The composition for use according to paragraph 1, wherein the compound of Formula (I) is further defined by Formula (VII):



Formula (VII)

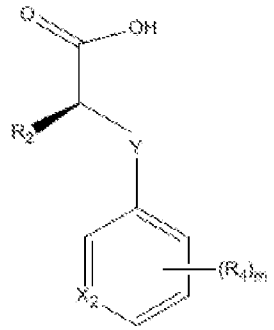
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein

- m is 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1 and X_2 are independently selected from the group consisting of CH and N;
- R_2 is selected from the group consisting of -OR_3, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -NR_3, -$NR_3C(O)R_9$ or -R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;

R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

29. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by Formula (VIII)



Formula (VIII)

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

- m is 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_2 is selected from the group consisting of, CH and N;

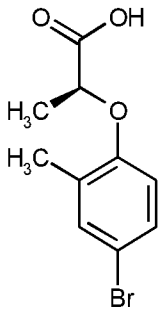
- R_2 is selected from the group consisting of -OR_3, -SR_5, -$S(O)R_5$, -$S(O)_2R_5$, -NR_3, -$NR_3C(O)R_9$ or -R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo; R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

30. The composition for use according to any one of paragraphs 5 to 29, wherein Y is O.

31. The composition for use according to any one of paragraphs 28 to 30, wherein R_2 is selected from the group consisting of H and C_{1-4}-alkyl.

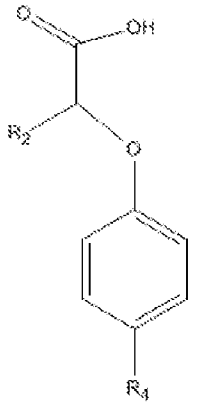
32. The composition for use according to any one of paragraphs 28 to 31, wherein R_4 is selected from the group consisting of H, $-CH_3$ and halogen.

33. The composition for use according to paragraph 32, wherein said compound is further defined by Formula (IX):



Formula (IX)

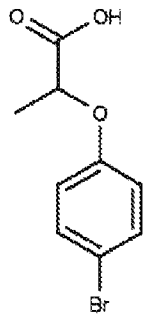
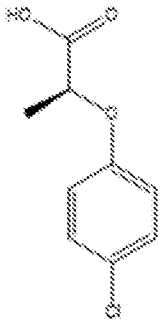
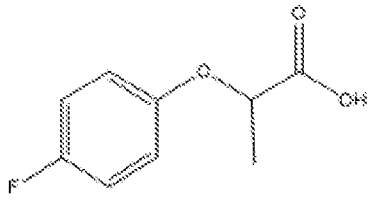
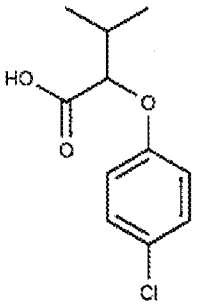
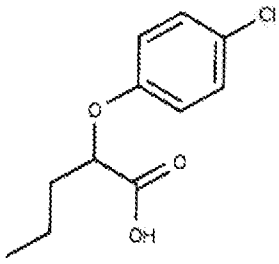
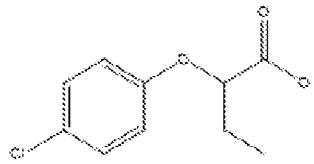
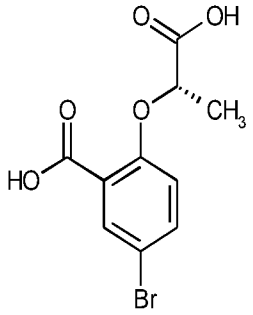
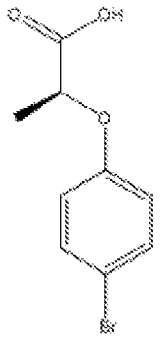
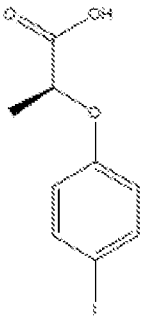
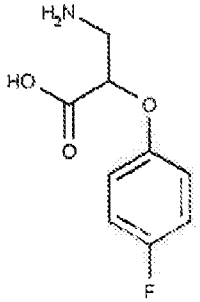
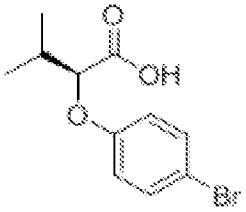
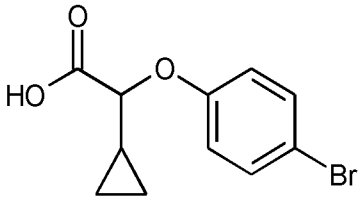
34. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by Formula (X):

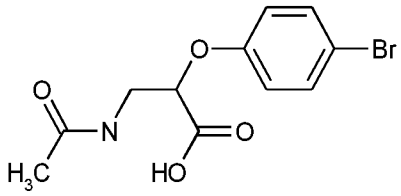
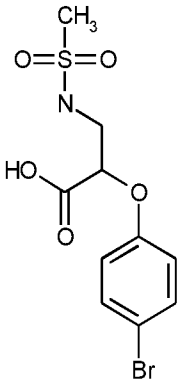
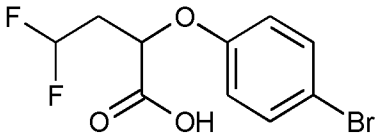
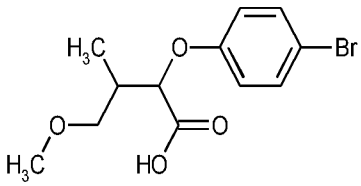
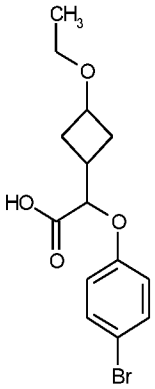
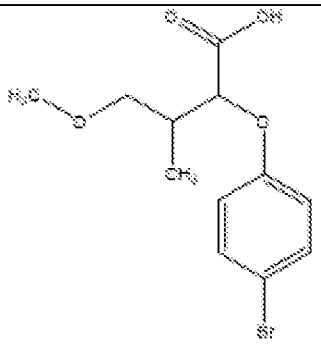


Formula (X)

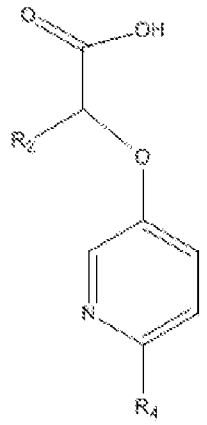
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2-O-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-NH_2$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-NH-CO-CH_3$ and $-CH_2-NH-SO_2-CH_3$ and cyclopropyl, and R_4 is selected from the group consisting of H, Br, Cl, F and I.

35. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII):

 Formula (XI)	 Formula (XII)	 Formula (XIII)
 Formula (XIV)	 Formula (XV)	 Formula (XVI)
 Formula (XVII)	 Formula (XVIII)	 Formula (XIX)
 Formula (XX)	 Formula (XXI)	 Formula (XXII)

 Formula (XXIII)	 Formula (XXIV)	 Formula (XXV)
 Formula (XXVI)	 Formula (XXVII)	 Formula (XXVIII)

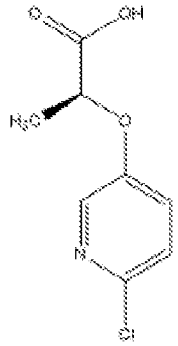
36. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by Formula (XXIX):



Formula (XXIX)

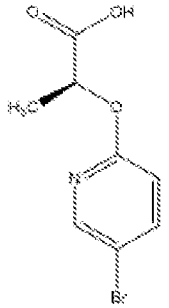
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

37. The composition for use according to paragraph 36, wherein the compound of Formula (XXIX) is further defined by Formula (XXX):



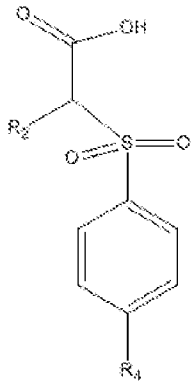
Formula (XXX)

38. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by Formula (XXXI):



Formula (XXXI)

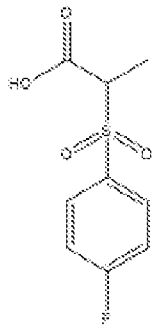
39. The composition for use according to paragraph 28, wherein the compound of Formula (VII) is further defined by Formula (XXXII):



Formula (XXXII)

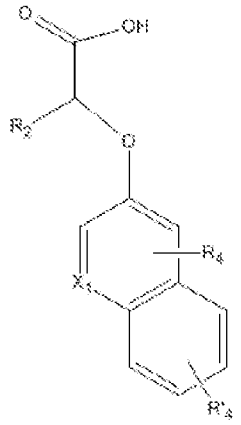
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

40. The composition for use according to paragraph 39, wherein the compound of Formula (XXXII) is further defined by Formula (XXXIII):



Formula (XXXIII)

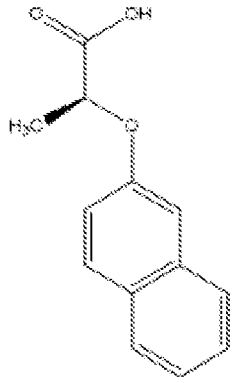
41. The composition for use according to paragraph 1, wherein the compound of Formula (I) is further defined by Formula (XXXIV):



Formula (XXXIV)

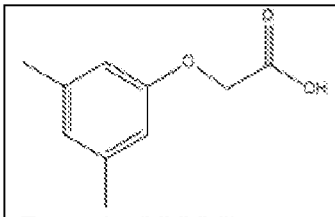
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$; X_1 is N or C; and R_4 and R'_4 are independently selected from the group consisting of H, Br, Cl, F and I.

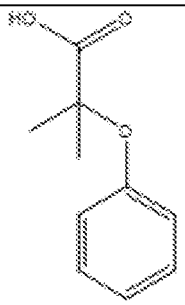
42. The composition for use according to paragraph 41, wherein Formula (XXXIV) is further defined by Formula (XXXV):

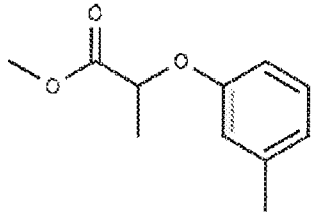


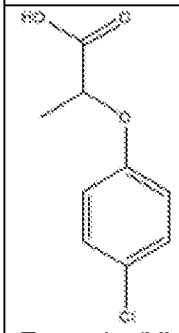
Formula (XXXV)

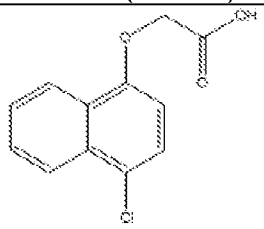
43. The composition for use according to paragraph 1, wherein the compound of Formula (I) is further defined by any one of Formulas (XXXVI) to (LIX)

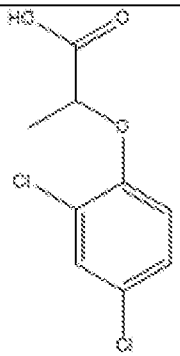

Formula (XXXVI)

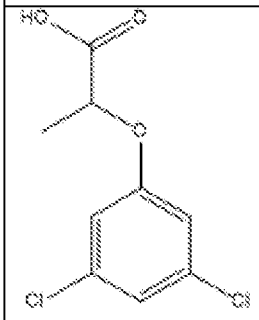

Formula (XXXVII)

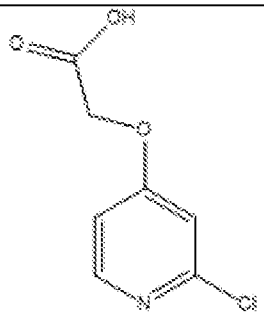

Formula (XXXVIII)

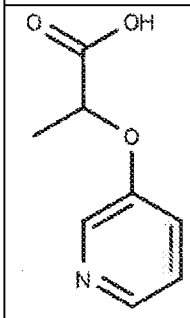

Formula (XXXIX)

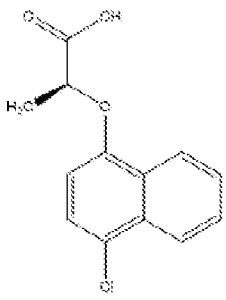

Formula (XL)

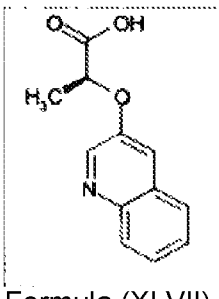

Formula (XLII)

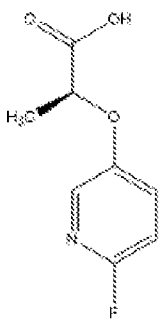

Formula (XLIII)

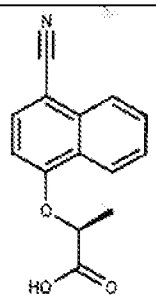

Formula (XLIV)

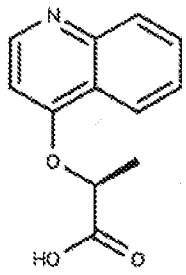

Formula (XLV)

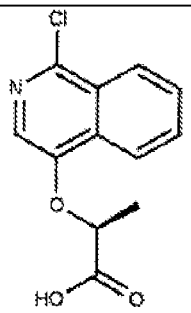

Formula (XLVI)

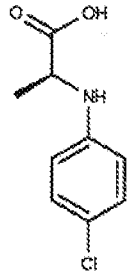

Formula (XLVII)

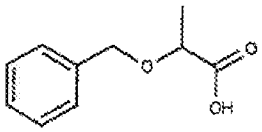

Formula (XLVIII)

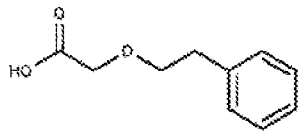

Formula (XLIX)

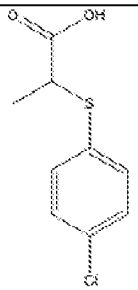

Formula (L)

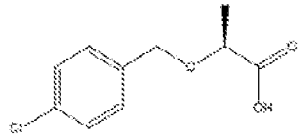

Formula (LI)

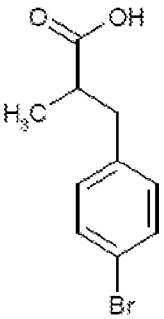

Formula (LII)

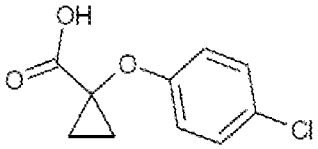

Formula (LIII)

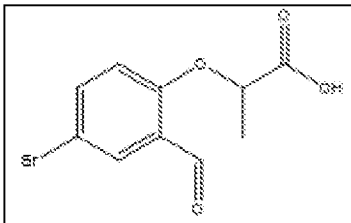

Formula (LIV)


Formula (LV)

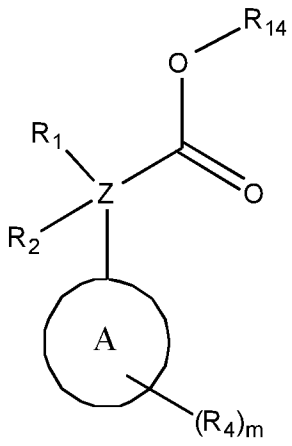

Formula (LVI)


Formula (LVII)


Formula (LVIII)

 Formula (LIX)		

44. The composition for use according to any one of the preceding paragraphs wherein said prodrug is defined by Formula (LX):



Formula (LX)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N,

$NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;

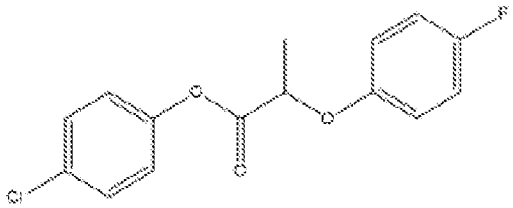
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo; R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo.
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

- R_{14} is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, pyrimidyl, pyridinyl, thiazolyl, oxadiazolyl and quinolyl, all aromatic and heteroaromatic groups optionally substituted by one or more R_4.

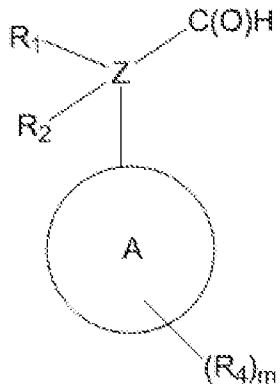
45. The prodrug according to paragraph 44, wherein R_{14} is a phenyl substituted with methoxy, nitro, cyano, Cl, Br, I and/or F.

46. The prodrug according to paragraph 44, wherein Formula (LX) is further defined by Formula (LXI):



Formula (LXI)

47. The composition for use according to any one of paragraphs 1 to 43, wherein said prodrug is defined by Formula (LXII):



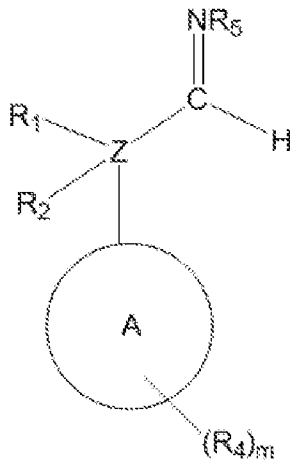
Formula (LXII)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;

- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo.

48. The composition for use according to any one of paragraphs 1 to 43, wherein



Formula (LXIII)

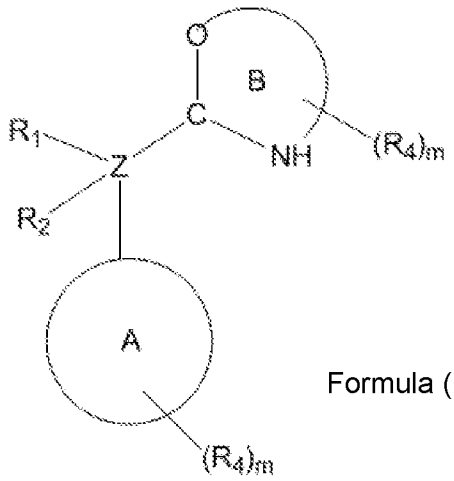
said prodrug is defined by Formula (LXIII):

wherein

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;

- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

49. The composition for use according to any one of paragraphs 1 to 43, wherein said prodrug is defined by Formula (LXIV):



Formula (LXIV)

wherein

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo;
- B is a 5- to 7-membered heterocyclic.

50. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is myasthenia gravis.

51. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is autoimmune myasthenia gravis.

52. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is congenital myasthenia gravis.

53. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is Lambert-Eaton Syndrome.

54. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is critical illness myopathy.

55. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is amyotrophic lateral sclerosis (ALS).

56. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is spinal muscular atrophy (SMA).

57. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is critical illness myopathy (CIM).

58. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is diabetic polyneuropathy.

59. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder is selected from the group consisting of Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, and critical illness polyneuropathy.

60. The composition for use according to any one of the preceding paragraphs, wherein the composition is for use in the treatment of symptoms of an indication selected from the group consisting of myasthenia gravis (such as autoimmune and congenital myasthenia gravis), Lambert-Eaton Syndrome, critical illness myopathy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), critical illness myopathy (CIM), diabetic polyneuropathy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, and critical illness polyneuropathy.

61. The composition for use according to any one of the preceding paragraphs wherein the neuromuscular disorder has been induced by a neuromuscular blocking agent.

62. The composition for use according to any one of the preceding paragraphs further comprising a pharmaceutically acceptable carrier.

63. The composition for use according to any one of the preceding paragraphs further comprising at least one further active agent.

64. The composition for use according to any one of the preceding paragraphs wherein said further active agent is suitable for treating, preventing or ameliorating said neuromuscular disorder.

65. The composition for use according to any one of the preceding paragraphs, wherein said further active agent is an acetylcholine esterase inhibitor.

66. The composition for use according to paragraph 65, wherein said acetylcholine esterase inhibitor is selected from the group consisting of delta-9-tetrahydrocannabinol, carbamates, physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, rivastigmine, phenanthrene derivatives, galantamine, caffeine – noncompetitive, piperidines, donepezil, tacrine, edrophonium, huperzine, ladostigil, ungeremine and lactucopicrin.

67. The composition for use according paragraph 65, wherein said acetylcholine esterase inhibitor is neostigmine or pyridostigmine.

68. The composition for use according to any one of the preceding paragraphs, wherein said further active agent is suggamadex.

69. The composition for use according to any one of the preceding paragraphs, wherein said further active agent is tirasemtiv.

70. The composition for use according to any one of the preceding paragraphs, wherein said further active agent is 3,4-aminopyridine.

71. The composition for use according to any one of the preceding paragraphs, wherein the composition is administered or adapted for administration enterally, topically, parenterally or as part of a sustained release implant.

72. The composition for use according to any one of the preceding paragraphs, wherein the parenteral administration is intravenous, subcutaneous, intramuscular, intracranial or intraperitoneal.

73. The composition for use according to any one of the preceding paragraphs, wherein the enteral administration is oral, rectal, or buccal.

74. The composition for use according to any one of the preceding paragraphs, wherein the topical administration is dermal, epicutaneous, vaginal, intravesical, pulmonary, intranasal, intratracheal or as eye drops.

75. The composition for use according to any one of the preceding paragraphs, wherein the composition is administered or adapted for administration subcutaneously or intravenously.

76. The composition for use according to any one of the preceding paragraphs, wherein the composition is formulated for oral administration.

77. The composition for use according to any one of the preceding paragraphs, wherein the composition is formulated in a tablet or capsule.

78. The composition for use according to any one of the preceding paragraphs, wherein said composition is to be administered in a dosage of from 1 µg/kg - 10,000 µg/kg body weight, such as 1 µg/kg - 7,500 µg/kg, such as 1 µg/kg - 5,000 µg/kg, such as 1 µg/kg - 2,000 µg/kg, such as 1 µg/kg - 1,000 µg/kg, such as 1 µg/kg - 700 µg/kg, such as 5 µg/kg - 500 µg/kg, such as 10 µg/kg to 100 µg/kg bodyweight.

79. The composition for use according to any one of the preceding paragraphs, wherein said administration is repeated daily.

80. The composition for use according to any one of the preceding paragraphs, wherein said administration is repeated at least 1-3 times weekly, such as 2-5 times weekly, such as 3-6 times weekly.

81. The composition for use according to any one of the preceding paragraphs, wherein said administration is repeated 1 to 8 times daily, such as 2 to 5 times daily.

82. The composition for use according to any one of the preceding paragraphs, wherein said compound further has been modified in order to increase its half-life when administered to a patient, in particular its plasma half-life.

83. The composition for use according to any one of the preceding paragraphs, wherein said compound further comprises a moiety conjugated to said compound, thus generating a moiety-conjugated compound.

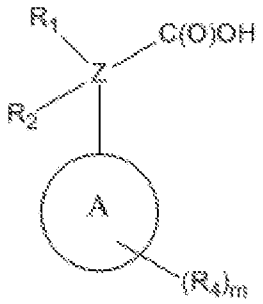
84. The composition for use according to any one of the preceding paragraphs, wherein the moiety-conjugated compound has a plasma and/or serum half-life being longer than the plasma and/or serum half-life of the non-moiety conjugated compound.

85. The composition for use according to any one of the preceding paragraphs, wherein the moiety conjugated to the compound is one or more type(s) of moieties selected from the group consisting of albumin, fatty acids, polyethylene glycol (PEG), acylation groups, antibodies and antibody fragments.

86. A method of treating, preventing and/or ameliorating a neuromuscular disorder, said method comprising administering a therapeutically effective amount of the composition as defined in any one of the preceding paragraphs to a person in need thereof.

87. Use of a composition as defined in any one of paragraphs 1 to 85, for the manufacture of a medicament for the treatment, prevention and/or amelioration of a neuromuscular disorder.

88. A composition comprising a compound of Formula (I):



Formula (I)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;

  wherein
- R_1 and R_2 are independently selected from the group consisting of $-OR_3$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-NR_3$, $-NR_3C(O)R_9$ or $-R_3$, wherein R_3 is selected from the group consisting of -H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9$-CO- R_{10}, $-N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, $-SO_2$- NR_9 R_{10}, $-R_{13}$-O-R_{11}, $-NR_9$ R_{10}, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of -H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9$-CO- R_{10}, $-NR_{10}$-SO_2-R_{11}, -CO-NR_9R_{10}, $-SO_2$- NR_9 R_{10}, $-R_{13}$-O-R_{11}, $-NR_9R_{10}$, cyano, -O-R^{11}, fluorinated C_{1-3}, nitro and halo;

- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from -H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl

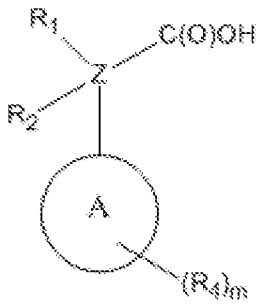
for use in reversing and/or ameliorating a neuromuscular blockade after surgery.

89. A method of reversing and/or ameliorating a neuromuscular blockade after surgery, said method comprising administering a therapeutically effective amount of the composition as defined in paragraph 88 to a person in need thereof.

90. A method for recovery of neuromuscular transmission, said method comprising administering a therapeutically effective amount of the composition as defined in paragraph 88 to a person in need thereof.

91. Use of a composition as defined in paragraph 88, for the manufacture of a medicament for recovery of neuromuscular transmission.

92. A compound of Formula (I):



Formula (I)

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

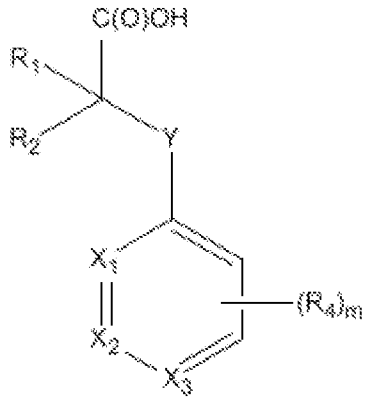
- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- m is 0, 1, 2, 3, 4 or 5;
- Z is a 2-5 atom chain comprising at least one carbon atom and optionally one heteroatom or substituted heteroatom, wherein the heteroatom or substituted heteroatom is selected from the group consisting of O, N, $NC(O)R_3$, S, $S(O)R_5$ and $S(O)_2R_5$, wherein each atom of said 2-5 atom chain is optionally substituted with R_1 and R_2;
  wherein
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, NR_9R_{10}, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $-O-R^{11}$, fluorinated C_{1-3}, nitro and halo;
- R_5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

93. The compound according to paragraph 92, wherein A is a monocyclic or bicyclic aromatic or heteroaromatic ring.

94. The compound according to any of paragraphs 92 and 93, wherein A is five-membered or six-membered aromatic ring.

95. The compound according to any one of paragraphs 92 to 93, wherein A is phenyl, or naphthyl.

96. The compound according to any of paragraphs 92 to 95, wherein said compound is a compound of Formula (II):



Formula (II)

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

- m is 0, 1, 2, 3, 4 or 5;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from the group consisting of CH and N;
- R_1 and R_2 are independently selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -

NR_9 R_{10}, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo ; or R_1 and R_2 are linked to form a C_{3-6}-cycloalk(en)yl or a halo-C_{3-6}-cycloalk(en)yl;

- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, $-NR_9-CO-R_{10}$, $-NR_{10}-SO_2-R_{11}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, cyano, $O-R^{11}$, fluorinated C_{1-3}, nitro and halo;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $-S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

97. The compound according to any one of paragraphs 92 to 96, wherein R_1 is selected from the group consisting of -H and $-CH_3$.

98. The compound according to any one of paragraphs 92 to 96, wherein R_1 is H.

99. The compound according to any of paragraphs 92 to 98, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of $-NR_9-CO-R_{10}$, $-N(R_{10})_2-SO_2-R_{12}$, $-CO-NR_9R_{10}$, $-SO_2-NR_9R_{10}$, $-R_{13}-O-R_{11}$, $-NR_9R_{10}$, $-S(O)R_{12}$, $S(O)_2R_{12}$, cyano, $-O-R_{11}$, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

100. The compound according to any of paragraphs 92 to 98, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl, C_{3-6}-cycloalkyl and amino-C_{1-4}-alkyl, wherein said C_{1-4}-alkyl and C_{3-6}-cycloalkyl may be substituted

with
O-R_{11}, wherein R_{11} is selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

101. The compound according to paragraph 100, wherein R_{11} is -CH_3.

102. The compound according to paragraph 100, wherein R_2 is -$CH(CH_3)CH_2$-O-CH_3.

103. The compound according to any of paragraphs 92 to 102, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-6}-alkyl and C_{3-7}-cycloalkyl.

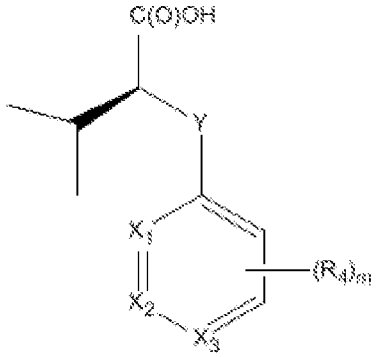
104. The compound according to any of paragraphs 92 to 102, wherein R_1 is H and R_2 is selected from the group consisting of H, -CH_3, -$CH(CH_3)_2$ and cyclopropyl.

105. The compound according to any one of paragraphs 92 to 104, wherein R_1 is H and R_2 is -$CH(CH_3)_2$.

106. The compound according to any one of paragraphs 92 to 105, wherein R_1 is different from R_2.

107. The compound according to any one of paragraphs 92 to 106, wherein said compound is an S-enantiomer with respect to the C-atom to which R_2 is bound.

108. The compound according to any paragraphs 92 to 107, wherein R_1 is H and R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl and wherein said compound is an S-enantiomer with respect to the C-atom to which R_2 is bound as shown in Formula (III):



Formula (III)

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

- m is 0, 1, 2, 3, 4 or 5
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from the group consisting of CH and N;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo, wherein R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl; R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl and R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, -S(O)R_{12}, -S$(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;

- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

109. The compound according to any one of paragraphs 92 to 108, wherein R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl.

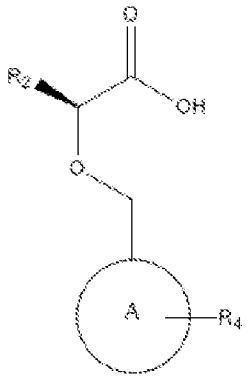
110. The compound according to any one of paragraphs 92 to 109, wherein m is 0, 1 or 2.

111. The compound according to any one of paragraphs 92 to 110, wherein m is 1.

112. The compound according to any one of paragraphs 92 to 111, wherein X_1 is N, X_2 is N or X_3 is N.

113. The compound according to any one of paragraphs 92 to 111, wherein X_1, X_2 and X_3 is C.

114. The compound according to any one of paragraphs 92 to 113, wherein the compound of Formula (I) is further defined by Formula (IV):

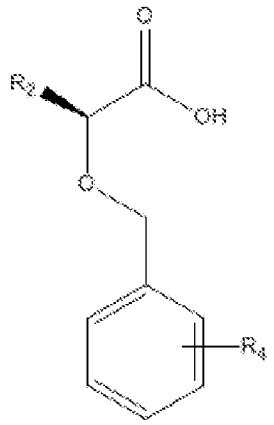


Formula (IV)

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

- A is an aromatic or heteroaromatic ring selected from the group consisting of phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazyl, and pyridazinyl;
- R_2 is selected from the group consisting of OR_3, SR_5, $S(O)R_5$, $S(O)_2R_5$, NR_3, $NR_3C(O)R_9$ or R_3, wherein R_3 is selected from the group consisting of H, C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_4 is selected from the group consisting of H, C_{1-6}-alk(en/yn)yl, C_{3-6}-cycloalk(en)yl, -NR_9-CO- R_{10}, -NR_{10}-SO_2-R_{11}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, cyano, O-R^{11}, fluorinated C_{1-3}, nitro and halo, wherein R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl; R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl and R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;
- R^5 is selected from the group consisting of C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, wherein said C_{1-8}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to three substituents selected from the group consisting of -NR_9-CO-R_{10}, -$N(R_{10})_2SO_2$-R_{12}, -CO-NR_9 R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9R_{10}, -$S(O)R_{12}$, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}, nitro and halo; or R_1 and R_2 are linked to form a ring;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

115. The compound according to paragraph 114, wherein the compound of Formula (IV) is further defined by Formula (V):

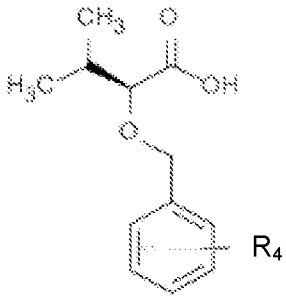


Formula (V)

wherein R_2 and R_4 are as defined above.

116. The compound according to paragraph 114 or paragraph 115, wherein R_2 is C_{1-6}-alkyl or C_{3-7}-cycloalkyl.

117. The compound according paragraph 115, wherein the compound of Formula (V) is further defined by Formula (VI):

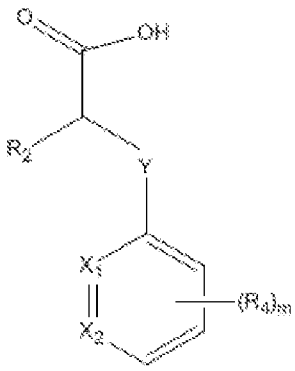


Formula (VI)

wherein R_4 is as defined above

118. The compound according to any one of paragraphs 115 to 117, wherein R_4 is in ortho- or meta position.

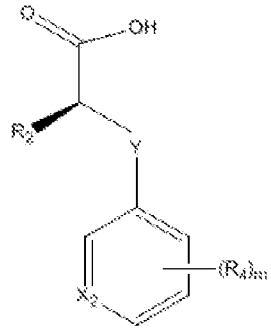
119. The compound according to paragraph 92, wherein the compound of Formula (I) is further defined by Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein m is 2 and X_1, X_2, Y, R_2 and R_4 are as defined above.

120. The compound according to paragraph 119, wherein the compound of Formula (VII) is further defined by Formula (VIII)



Formula (VIII)

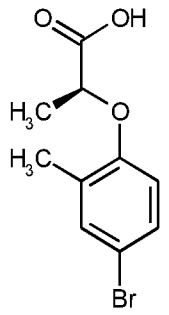
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein m, X_2, Y, R_2 and R_4 are as defined above.

121. The compound according to any one of paragraphs 92 to 120, wherein Y is O.

122. The compound according to any one of paragraphs 92 to 121, wherein R_2 is selected from the group consisting of H and C_{1-4}-alkyl.

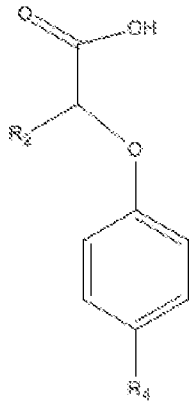
123. The compound according to any one of paragraphs 92 to 122, wherein R_4 is selected from the group consisting of H, $-CH_3$ and halogen.

124. The compound according to any one of paragraphs paragraph 92 to 123, wherein said compound is further defined by Formula (IX):



Formula (IX)

125. The compound according to paragraph 119, wherein the compound of Formula (VII) is further defined by Formula (X):



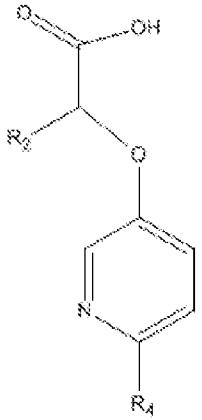
Formula (X)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2-O-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-NH_2$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-NH-CO-CH_3$ and $-CH_2-NH-SO_2-CH_3$ and cyclopropyl, and R_4 is selected from the group consisting of H, Br, Cl, F and I.

126. The compound se according to paragraph 119, wherein the compound of Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII) as

defined in paragraph 35.

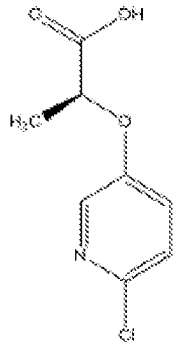
127. The compound according to paragraph 119, wherein the compound of Formula (VII) is further defined by Formula (XXIX):



Formula (XXIX)

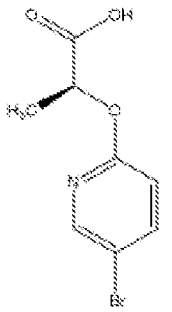
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

128. The compound according to paragraph 127, wherein the compound of Formula (XXIX) is further defined by Formula (XXX):



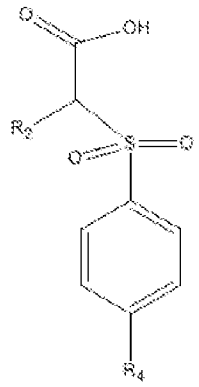
Formula (XXX)

129. The compound according to paragraph 119, wherein the compound of Formula (VII) is further defined by Formula (XXXI):



Formula (XXXI)

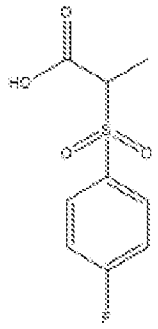
130. The compound according to paragraph 119, wherein the compound of Formula (VII) is further defined by Formula (XXXII):



Formula (XXXII)

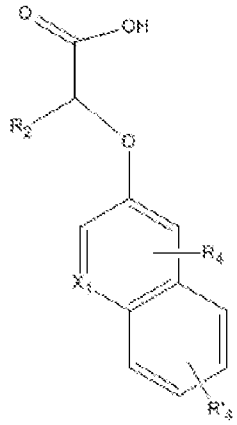
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

131. The compound according to paragraph 130, wherein the compound of Formula (XXXII) is further defined by Formula (XXXIII):



Formula (XXXIII)

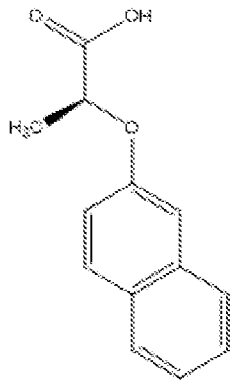
132. The compound according to paragraph 92, wherein the compound of Formula (I) is further defined by Formula (XXXIV):



Formula (XXXIV)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$; X_1 is N or C; and R_4 and R'_4 are independently selected from the group consisting of H, Br, Cl, F and I.

133. The compound according to paragraph 132, wherein Formula (XXXIV) is further defined by Formula (XXXV):



Formula (XXXV)

134. The compound according to paragraph 92, wherein the compound of Formula (I) is further defined by any one of Formulas (XXXVI) to (LIX) as defined in paragraph 43.

EXAMPLES

Materials and Methods

Isolation of muscles from rats and human, ethical approval, dissection of muscles, solutions, and chemicals

Experiments were performed using rat soleus muscles from either young (4-wk-old) or adult Wistar rats (12-14-week-old). Animal handling, killing and isolation of muscle is described elsewhere[26] All experiments were performed using normal Krebs-Ringer bicarbonate solution[26] (NKR). In solutions with elevated Mg^{2+}, $MgCl_2$ was added to NKR-solution causing minor increases in osmolarity and ionic strength. In solutions with elevated K^+, 4 mM NaCl was replaced by 4 mM KCl in the NKR.

For experiments conducted using human abdominal muscle, details on patients, approval and the approaches for isolation, transportation, and experimentation are available elsewhere[27].

Electrical stimulation, contractile force and M-waves

In all contraction experiments, isometric force production was determined and force produced during contractions was quantified by measuring the integral of the force response (AUC). Stimulation and force recordings have been described elsewhere[26]. Briefly, muscles were stimulated to contract in three different ways (Fig. 1): i) When using field stimulation (25-30 V/cm) and pulses with a duration of 0.2 ms, the muscles could be stimulated directly without requirements of a functional motor nerve. ii) If the duration of the pulses used in the field stimulation was only 0.02 ms, the contractile force could be completely suppressed by the nicotinic ACh receptor antagonist tubocurarine. This shows that stimulation with short pulses activates the muscles indirectly through stimulation of the attached motor nerve. iii) Stimulation could be isolated to the motor nerve after it had been sucked into a glass capillary. In these latter experiments, extracellular recordings of action potentials (M-waves) could be measured without temporal overlap with stimulation artefacts.

Cable properties and endplate potentials

Isolated soleus muscles from adult rats or human abdominal muscles preparations were placed in a chamber and the resting membrane conductance (G_m) was measured in individual fibers using electrophysiological techniques described in detail elsewhere

(Fig. 4)[28]. G_m reflects function of ion channels that are open at the resting membrane potential. In skeletal muscle, G_m is dominated by ClC-1 Cl^- channels and for this reason an effect of a compound on G_m predominantly reflects alterations in ClC-1 function. To ensure that the compound indeed affected ClC-1 function, recordings were in some cases repeated in the presence of the ClC-1 inhibitor 9-AC (100 µM) to quantify for effects of the compounds on K^+ channels. To determine affinity of ClC-1 channels for a particular compound, G_m was plotted against compound concentration and a Boltzmann sigmoidal function was fitted to the data to obtain Kd of the compound (Table 3).

To measure endplate potentials (EPPs), soleus muscles from adult rats were placed in a chamber and the motor nerve was stimulated. To only measure EPPs, 1 µM of µ-conotoxin GiiiB was added to solution. All recordings were corrected for variation in resting membrane potential using -80 mV as the standard[29].

Pharmacokinetic analysis and test of C8 in rat models of myasthenia gravis

The pharmacokinetic analysis of a single, intraperitoneal (I.P.) dose of C8 (10 mg/kg) was studied in young (4 weeks old) Sprague-Dawley rats. This part of the study was performed by Pipeline Biotech A/S (Spørring, Denmark). 24 animals were injected with C8 and three animals were sacrificed at times 15 min, 30 min, 1hr, 2hr, 4 hr, 6 hr, 8hr, 24 hr after injection and plasma concentrations of C8 was determined using Liquid Chromatography Mass Spectrometry (LC-MS). Plasma concentrations (free and bound) were determined by OnTarget Chemistry (Uppsala, Sweden, Project No.: PB243-001).

Two sets of *in vivo* experiments were performed with C8: In the first series of experiments I.P. tubocurarine at (0.13 mg/kg) was used to induce a myasthenia like phenotype while in the second series of experiments a passive immunization model of myasthenia gravis was used in which rats were injected I.P. with a monoclonal antibody against the acetylcholine receptors at the neuromuscular endplate (MAB35, GTX14187, Genetex, 0.4-0.6 mg/kg). In both series of experiments, running performance was tested on a rotarod using a protocol where the rod was accelerated gradually over a 5 min period, and the running time and covered distance before falling off the rod were measured. To accustom the animals to the rotarod, the animals were tested three times on two consecutive days and animals that failed to complete the 5 min of running on the last day of familiarization period were not used in experiments.

Experiments with tubocurarine were carried out over two days, and on each day the effect of tubocurarine on running performance was tested. On the first day only tubocurarine was injected. Animals that failed to respond to tubocurarine were not used on the next day of experimentation. On the second day, the animals were first allowed to run on the rotarod, and all animals performed normally. This shows that effects of the tubocurarine that had been injected on the day before had completely disappeared. Animals were then divided into two groups: One group was injected with 20 mg/kg C8 while the other group received sham treatment. 2 hrs after the C8 or sham injection, the second injection of tubocurarine was administered and the animals running performance on the rotarod was tested. The allocation of the animals into the two groups (C8 or sham) was random and unknown to the experimenter (blinded experimental design).

In experiments with MAB35, animals were first familiarized with the rotarod over two consecutive days and then injected I.P. with MAB35. After injection, rotarod performance was then again monitored regularly over the consecutive two days. Performance generally started to decline within 21-43 hrs after MAB35 injection, and if a stable reduction in performance was obtained, the animals were administered either C8 or sham. A considerable number of animals, however, became moribund failing to walk and they had altered ventilation (rapid) and pronounced ptosis. These animals were not included in experiments. Animals with a stable reduction in performance were injected with C8 (20 or 30 mg/kg) or sham treated and their performance were again monitored 2, 4, and 6 hrs after C8 or sham injection.

Chemicals

Compounds for testing were obtained from different suppliers including Enamine, Vitas, and CanAm Bioresearch. For synthesis of particular compounds please see below.

Statistics

All data are expressed as mean with SEM. Significant difference between groups was ascertained using a Students t-test (paired for contra-lateral muscles). Statistical analysis was performed using Sigmaplot 12.0 including fitting of data (Fig. 4C, Fig. 5E, Fig. 6E) to a four parameter sigmoidal function to get Kd values for Tables 3-5. Categorical data was tested using Fishers Exact test. Groups were considered significantly different for P-values < 0.05.

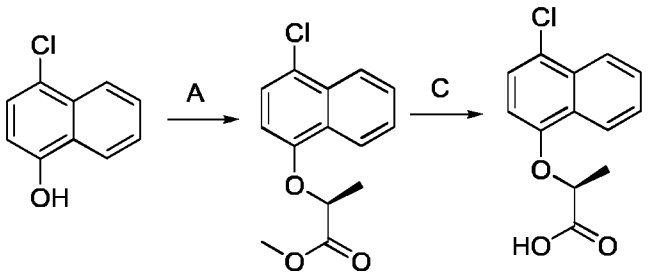
Synthesis of compounds

Example number	IUPAC name	Preparation method	NMR
C1	(2S)-2-(4-chlorophenoxy) propanoic acid	A	1H-NMR (400MHz, DMSO-d6): δ 13.2 (s, 1H), 7.35 (m, 2H), 6.9 (m, 2H), 4.85 (q, 1H), 1.45 (d, 3H).
C2	(2S)-2-[(4-chlorophenyl)amino]propanoic acid	B	1H-NMR (500MHz, DMSO-d6): δ 7.15 (m, 2H), 6.58 (m, 2H), 3.95 (q, 1H), 1.35 (d, 3H).
C3	2-(benzyloxy)propanoic acid	B	1H-NMR (400MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.35 (m, 5H), 4.7 (d, 1H), 4.5 (d, 1H), 4.05 (q, 1H), 1.47 (d, 3H).
C4	2-(4-fluorophenoxy)propanoic acid	A	1H-NMR (400MHz, DMSO-d6): δ 12.68 (s, 1H), 6.9 (m, 4H), 4.68 (q, 1H), 1.62 (d, 3H).
C5	(2S)-2-(benzyloxy)propanoic acid	B	1H-NMR (400MHz, $CDCl_3$): δ 11.3 (bs, 1H), 7.4 (m, 5H), 4.71 (d, 1H), 4.52 (d, 1H), 4.08 (q, 1H), 1.47 (d, 3H).
C6	2-(4-fluorobenzenesulfonyl)propanoic acid	D	1H-NMR (500MHz, DMSO-d6): δ 13.4 (s, 1H), 7.96 (m, 2H), 7.51 (m, 2H), 4.38 (q, 1H), 1.35 (d, 3H).
C7	2-(4-chlorophenoxy)butanoic acid	A	1H-NMR (400MHz, DMSO-d6): δ 12.72 (bs, 1H), 7.23 (m, 2H), 6.83 (m, 2H), 4.52 (m, 1H), 1.9 (m, 2H), 1.05 (m, 3H).
C8	(2S)-2-(4-bromophenoxy)propanoic acid	A	1H-NMR (300MHz, $CDCl_3$): δ 8.42 (bs, 1H), 7.35 (m, 2H), 6.78 (m, 2H), 4.71 (q, 1H), 1.62 (d, 3H).
C9	3-amino-2-(4-fluorophenoxy)propanoic acid hydrochloride	E	1H-NMR (400MHz, DMSO-d6): δ 13.7 (bs, 1H), 8.25 (s, 2H), 7.18 (m, 2H), 7.02 (m, 2H), 5.05 (q, 1H), 3.15 (bs, 2H).
C10	(2S)-2-[(4-chloronaphthalen-1-yl)oxy]propanoic acid	A	1H-NMR (400MHz, DMSO-d6): δ 13.2 (bs, 1H), 8.25 (d, 1H), 8.0 (d, 1H), 7.6 (m, 3H), 6.90 (d, 1H), 4.98 (q, 1H), 1.58 (d, 3H).
C11	4-chlorophenyl 2-(4-chlorophenoxy) propanoate	F	1H-NMR (300MHz, DMSO/CCl_4): δ 7.41 (m, 2H), 7.08 (m, 6H), 5.14 (m, 1H), 1.71 (d, 3H).
C12	(2S)-2-(5-bromopyrimidin-2-yl)-3-methylbutanoic acid	C	1H-NMR (300MHz, $CDCl_3$): δ 9.65 (bs, 1H), 8.42 (m, 2H), 5.05 (dd, 1H), 2.44 (m, 1H), 1.2 (m, 6H).
C13	2-[(1S)-1-(4-chlorophenoxy)ethyl]-1,3-oxazolidine	H	1H-NMR (300MHz, $CDCl_3$): δ 7.24 (m, 2H), 6.9 (m, 2H), 4.62 (m, 1H), 4.41 (m, 1H), 3.8 (m, 2H), 3.3 (m, 1H), 3.1 (m, 1H), 1.4 (m, 3H).
C14	2-(4-bromophenoxy)-2-cyclopropylactic acid	B	1H-NMR (500MHz, DMSO-d6): δ 13.1 (s, 1H), 7.48 (m, 2H), 6.8 (m, 2H), 4.08 (d, 1H), 1.12 (m,1H), 0.5 (m, 4H).
C15	2-(4-bromophenoxy)-3acetamidopropanoic acid	B	1H-NMR (500MHz, DMSO-d6): δ 13.3 (s, 1H), 8.15 (s, 1H), 7.48 (m, 2H), 6.85 (m, 2H), 4.70 (q, 1H), 3.61 (m, 1H), 3.31 (m, 1H), 1.72 (s, 3H).
C16	2-(4-bromophenoxy)-3-methanesulfonamidopropanoic acid	B	1H-NMR (500MHz, DMSO-d6): δ 13.4 (bs, 1H), 7.5 (m, 3H), 6.92 (m, 2H), 4.85 (m, 1H), 3.52 (m, 1H), 3.35 (m, 1H) 2.9 (s, 3H).
C17	(2S)-2-(4-chlorophenoxy) propanal	G	1H-NMR (300MHz, CDCl3): δ 9.7 (d, 1H), 7.25 (m, 2H), 6.81 (m, 2H), 4.61 (q, 1H), 1.45 (m, 3H).
C18	4-nitrophenyl (2S)-2-(4-	F	1H-NMR (300MHz, $CDCl_3$): δ 8.28 (m, 2H),

	chlorophenoxy) propanoate		7.25 (m, 4H), 6.84 (m, 2H), 5.02 (m, 1H), 1.82 (m, 3H).
C19	4-methoxyphenyl (2S)-2-(4-chlorophenoxy) propanoate	F	1H-NMR (300MHz, $CDCl_3$): δ 7.3 (m, 2H), 6.92 (m, 6H), 4.9 (q, 1H), 3.81 (s, 3H), 1.78 (dd, 3H).
C20	2-(4-bromophenoxy)-2-(3-ethoxycyclobutyl)acetic acid	B	1H-NMR (400MHz, DMSO-d6): δ 13.1 (bs, 1H), 7.42 (m, 2H), 6.81 (m, 2H), 4.65 (dd, 1H), 3.44 (m, 1H), 3.30 (m, 1H), 3.24 (m, 3H), 2.36 (m , 1H), 0.9 (dd, 3H).
C21	2-(4-bromophenoxy)-4-methoxy-3-methylbutanoic acid	B	1H-NMR (400MHz, DMSO-d6): δ 13.1 (s, 1H), 7.42 (m, 2H), 6.82 (m, 2H), 4.61 (d, 1H), 3.80 (m, 1H), 3.28 (m, 2H), 2.31 (m , 3H), 1.80 (m , 2H), 1.05 (t, 3H).
C22	(2S)-2-(4-bromophenoxy)-3methylbutanoic acid	A	1H-NMR (500MHz, $CDCl_3$): δ 7.41 (m, 2H), 6.78 (m, 2H), 4.41 (d, 1H), 2.38 (q, 1H), 1.11 (d, 6H).

Compounds of formula (I) may be synthesized by one of the following methods:

Synthetic Method A, Mitsunobu coupling, exemplified by (2S)-2-[(4-chloronaphthalen-1-yl)oxy]propanoic acid:



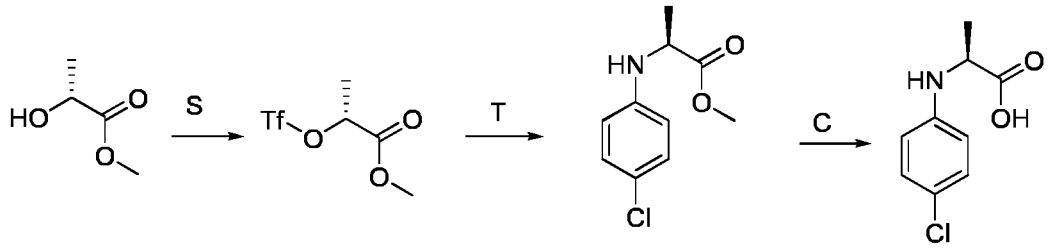
Procedure for the Step A

To a solution of starting compound, Ph_3P, and ((R)-methyl 2-hydroxypropanoate in a solvent like DCM was added DEAD at 0 °C. After stirring for 1 to 24 h at room temperature, the reaction completion was observed by NMR testing of a sample. Aqueous workup was performed. The compound was purified by chromatography.

Procedure for the Step C

To a solution of the product of Step A in ethanol was added an aqueous solution of an alkali like KOH. The resulting mixture was refluxed for 1-12h, and reaction was monitored by TLC. At the end of reaction, the mixture was subjected to an aqueous/acidic work up using a solvent like DCM or an ether. The compound was purified by chromatography if necessary.

Synthetic Method B, displacement coupling, exemplified by (2S)-2-[(4-chlorophenyl)amino]propanoic acid:



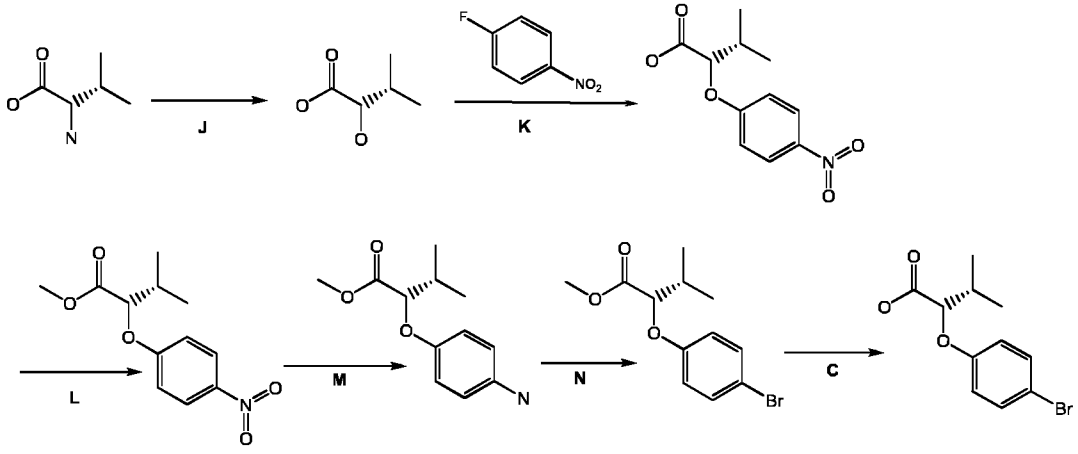
Step S

To a cold solution of pyridine in a solvent like DCM was added trifluoromethanesulfonic anhydride at below 0 °C. After stirring for 5-60 min, (R)-methyl 2-hydroxypropanoate was added. The mixture was stirred for 1-10h at room temperature, filtered, and the filtrate was partially evaporated.

Step T

To a mixture of 4-chloroaniline, a base like TEA and a solvent like DCM or DMF was added freshly prepared compound of step S at 0-5 °C. The resulting mixture was stirred at 35 °C for 4h, diluted with water, and extracted with DCM when the phases do not separate. Removal of the solvent yields the compound.

Synthetic Method C, SN_{Ar} displacement coupling, exemplified by (2S)-2-(4-bromophenoxy)-3-methylbutanoic acid:



Step J

To a solution of acid amino acid in 1N H_2SO_4, a solution of $NaNO_2$ in minimal quantity of water was added under cooling. The resulted mixture was stirred at room temperature for 1-3 days, saturated with Na_2SO_4, and extracted with a solvent like methyl-tert-butyl ether or DCM. The organic layer was evaporated.

Step K

To a suspension of NaH in DMF a solution of the product of step J in DMF was added. After stirring, p-fluoronitrobenzene or the desired electrophile was added and stirring continued at 100 °C for 3-48h. The mixture was diluted a solution of NH_4Cl and K_2CO_3 at room temperature, and extracted with a solvent like methyl-tert-butyl ether or ethyl acetate. The water layer was acidified with 3N HCl and extracted with methyl-tert-butyl ether or ethyl acetate. The organic layer was evaporated.

Step L

To a 0 °C solution of the product of step K in methanol, a catalytic amount of acetyl chloride was added. The mixture was heated under reflux for 3-9 h and the solvent was evaporated. The residue was extracted with a solvent like methyl-tert-butyl ether or DCM. The organic layer was evaporated.

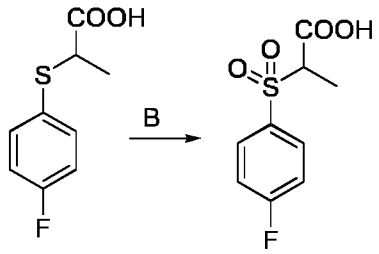
Step M

To a solution of the product of step L in methanol, 10% Pd/C was added and hydrogenated under ambient pressure for 24h. The mixture was filtered through silica gel and evaporated.

Step N

To a solution of *t*-$BuNO_2$ in acetonitrile, $CuBr_2$ was added. To the reaction mixture the product of step M in acetonitrile was added and the mixture was heated under reflux for 2-9 h. To the room temperature mixture, 20% aq. HCl was added and then extracted with a suitable solvent like methyl-tert-butyl ether or ethyl acetate. The organic layer was washed with water and evaporated. The oily residue was chromatographed.

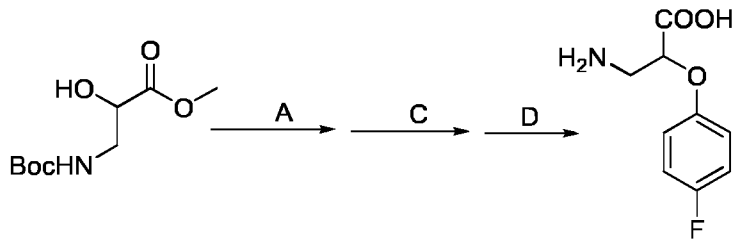
Synthesis Method D, exemplified by 2-(4-fluorobenzenesulfonyl)propanoic acid



Step B

The thioether obtained by Method A or B in a suitable solvent like DCM or ethyl acetate is treated with m-CPBA or another peracid at room temperature for 1-48 h and the reaction is monitored by TLC. After aqueous workup, the product is purified by chromatography.

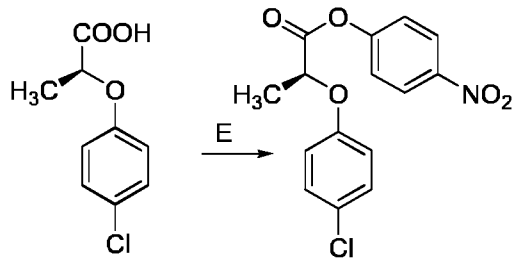
Synthesis Method E, exemplified by 3-amino-2-(4-fluorophenoxy)propanoic acid hydrochloride



Step D

The protected compound obtained from Step C in a suitable solvent like DCM is treated with TFA at room temperature for 1-18 h. After evaporation, the product is purified by reversed-phase chromatography with an HCl containing eluent.

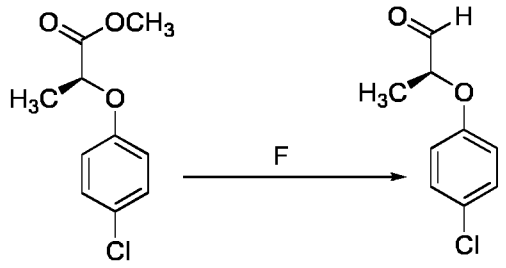
Synthesis Method F, exemplified by 4-nitrophenyl (2S)-2-(4-chlorophenoxy) propanoate



Step E

The acid obtained by the previous methods in a suitable solvent like DCM or acetonitrile is treated DCC and the desired phenol, like p-nitrophenol, with a suitable catalyst like DMAP at room temperature for 1-48 h. After aqueous workup at acidic pH, the product is purified by rapid chromatography.

Synthesis Method G, exemplified by (2S)-2-(4-chlorophenoxy)propanal

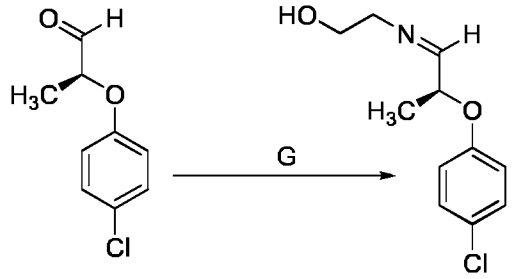


Step F

The ester obtained by the previous methods in a suitable solvent like toluene is treated DIBAL-H at -78°C for 1 h. After aqueous workup, the product is purified by rapid chromatography.

Synthesis Method H, exemplified by

[[(2S)-2-(4-chlorophenoxy)propylidene]amino]ethan-1-ol



Step G

The aldehyde obtained by the step F in a suitable solvent like DCM is treated at room temperature with the desired primary amine like 2-aminoethanol. Evaporation, redilution with DCM and re-evaporation yielded the desired product.

Example 1: Experimental approach for testing compounds

The aim was to find compounds that by inhibition of ClC-1 channels can recover nerve-stimulated force under conditions of fatigue including conditions where fatigue is caused by compromised neuromuscular transmission. Neuromuscular transmission dysfunction can develop because of both pre- and/or post-synaptic complications in connection with a disorder or as part of neuromuscular blockade during/after surgery. In the initial series of drug testing, experiments were performed with isolated muscles in the presence of sub-maximal ACh receptor antagonist tubocurarine. Since the inclusion of tubocurarine caused a partial loss of neuromuscular transmission this experiment mimics the conditions in myasthenia gravis[3,5] and neuromuscular blockade[25]. To mimic conditions with pre-synaptic complication (Lambert Eaton syndrome[2], motor neuron disorder[11,12], polyneuropathy[19]) the intact nerve-muscle preparations were incubated at elevated extracellular Mg^{2+}, which is known to suppress release of ACh from nerve terminals of motor neurons[31,32].

Experiments shown in Fig. 1 were performed to confirm that tubocurarine and elevated extracellular Mg^{2+} specifically suppressed neuromuscular transmission without affecting the capacity of the muscle fibers to generate force. The experiments also illustrate that field stimulation of the entire nerve-muscle preparation selectively activates the motor nerve when short-duration pulses (0.02 vs 0.2 ms) were used. In Fig. 1A the preparation was stimulated either via field stimulation or via nerve-stimulation using a

suction electrode. With the suction electrode only the nerve could be stimulated. When exposed to a submaximal concentration of the ACh receptor antagonist tubocurarine (0.2 µM) a clear drop in peak force and a further decline (or fade) in force during the stimulation developed. This drop in force clearly reflected compromised neuromuscular transmission, as the decline in peak force and fading were not seen with direct stimulation of the muscle. Recordings of M-waves in the muscle in Fig. 1A show that tubocurarine caused marked decline in M-wave signal during the stimulation (compare inserts *i* and *ii* in Fig. 1A). Thus, loss of M-wave and force with tubocurarine reflected partial blockade of neuromuscular function. Such fading of force and M-waves during stimulation represent clinical hallmarks of both myasthenia gravis and neuromuscular blockade in connection with surgery. In Fig. 1B, observations with normal (0.2 ms) and short-duration (0.02 ms) pulses have been compared. It can be seen that only with short-duration pulses did tubocurarine cause a decline in peak force and fading (Fig. 1B). This confirms that short-duration pulses in field stimulation could be used as specific nerve-stimulation. Fig. 1C shows that also elevated extracellular Mg^{2+} primarily affected nerve-stimulated force while it did not affect force when the muscle was stimulated directly. Elevated extracellular Mg^{2+} could thus be used to partially block neuromuscular transmission and thus be used as a model of conditions with compromised pre-synaptic function (Lambert Eaton syndrome, amyotrophic lateral sclerosis, spinal muscular atrophy).

Example 2: Proof-of-concept that ClC-1 inhibition can overcome loss of neuromuscular transmission in conditions mimicking neuromuscular disorders

To initially confirm that inhibition of ClC-1 ion channels can be used to recover contractile force in muscle with reduced neuromuscular transmission, isolated nerve-muscle preparations were first exposed to either tubocurarine (Fig. 2A) or elevated Mg^{2+} (Fig. 2B) and then a specific ClC-1 inhibitor (9-AC) was added. It can be seen that ClC-1 inhibition caused a marked recovery of both force and M-wave signal in both conditions. This demonstrates the novel concept that ClC-1 channel inhibition can alleviate loss of force induced by compromised neuromuscular transmission. Similar observations were seen in EDL and diaphragm muscles from both young and adult rats (data not shown). 9-AC does not have the potential to be used as a pharmaceutical.

Example 3: Identification of useful compounds for improving neuromuscular transmission

To identify ClC-1 inhibitors that could be used for treatment of neuromuscular disorders we repeated the experiment shown in Fig. 2A but instead of adding 9-AC we added the compounds of interest in different concentrations within the range from 10 to 500 µM. The starting point for finding ClC-1 inhibitors was derivatives of clofibrate that have been shown to have ClC-1 inhibiting actions[33] (Table 1). Fig. 3A shows representative nerve-stimulated force in two muscles during such an experiment before and during exposure to tubocurarine. In one of the muscles (black trace), 50 µM of a test compound (C8) was added after 40 mins in tubocurarine. For comparison with the muscle only exposed to tubocurarine (grey trace), the two traces have been overlaid. It can be seen that while tubocurarine affected the two muscles equally before C8 addition (middle traces), the muscle receiving C8 recovered markedly when compared to its force before C8 addition and especially when compared to the other muscle that did not get C8 (right traces). To quantify the recovery of force with compounds such as C8, the force integrals (AUC) were determined for each contraction during an experiment and these AUC values were related to AUC before addition of tubocurarine. Fig. 3B shows average AUC observations of force during experiments in which muscles at tubocurarine were exposed to C8. For comparison, muscles only exposed to tubocurarine have been included. The dotted line indicates the recovery of force with C8 when compared to the force production before its addition. This value was used in Table 1 for evaluation of the efficacy of the different compounds in recovering force. Please note that force produced by the muscles only exposed to tubocurarine continued to fall after C8 had been added to the other group of muscles. This shows that C8 is able to recover force despite a progressively stronger suppressive action of tubocurarine.

Table 1. Recovery of nerve-stimulated force by some compounds in isolated rat soleus muscles exposed to sub-maximal tubocurarine concentration. AUC force was first determined after 40 min in tubocurarine (column 3) and related to nerve-stimulated force prior to addition of tubocurarine. The AUC at the different concentrations of compounds (columns 4-6) is the % change in AUC compared to the AUC before addition (column 3).

	IUPAC	Force before addition of compound % of control	50 µM % change after addition	150 µM % change after addition	500 µM % change after addition	*n*
C5	(2S)-2-(benzyloxy)propanoic acid	24	-7	1	42	2
C6	2-(4-fluorobenzenesulfonyl)propanoic acid	39	-11	-8	9	5
C7	2-(4-chlorophenoxy)butanoic acid	41	-12	0	40	2
C8	(2S)-2-(4-bromophenoxy)propanoic acid	36	16	23	NT	10
C9	3-amino-2-(4-fluorophenoxy)propanoic acid hydrochloride	57	-14	-13	5	2
C11	4- chlorophenyl 2- (4-fluorophenoxy)propanoate	38	46	54	NT	4
C21	2-(4-bromophenoxy)-4-methoxy-3-methylbutanoic acid	54	-3	7	36	2
C22	(2S)-2-(4-bromophenoxy)-3methylbutanoic acid	42	16	NT	NT	2
NT: Not Tested						

In a separate series of experiments with 8 isolated rat soleus muscles, ACh receptors were inhibited using 2 µM rocuronium, which is a clinically used neuromuscular blocking agent. Under these conditions the nerve-stimulated force was reduced to 51±5 % of force before rocuronium. When 50 µM C8 was subsequently added nerve-stimulated contractile force was significantly recovered to 81±4 % of force before rocuronium ($p<0.01$). This illustrates the potential of these compounds to be used as reversal agents.

The next series of experiments determined whether the compounds that recovered nerve-stimulated force in the presence of tubocurarine could also recover nerve-stimulated force at elevated extracellular Mg^{2+}. To do this the experiment depicted in Fig. 2B was repeated with C8. As in Fig. 3, AUC was quantified for each contraction and the capacity of C8 to recover force at elevated Mg^{2+} was evaluated from the recovery of AUC compared to AUC immediately before application of the compound (Table 2).

Table 2. Recovery of nerve-stimulated force with compounds in isolated rat soleus muscles exposed to 3.5 mM Mg^{2+}. AUC force was first determined after 70 min at elevated extracellular Mg^{2+} (column 3) and related to nerve-stimulated force prior to addition of additional Mg^{2+}. The AUC at the different concentrations of compounds (columns 4 and 5) is the % change in AUC compared to the AUC before Mg^{2+} elevation (column 3). As in experiments with tubocurarine, please note that force kept dropping in muscles only exposed to elevated Mg^{2+}.

	IUPAC	**Force before addition of compound % of control**	**50 µM % change after addition**	**100 µM % change after addition**	***n***
C8	(2S)-2-(4-bromophenoxy)propanoic acid	38±6	13±4	26±5	2

Example 4: Effect of compounds on ClC-1 channels - target validation

The effect of compounds on ClC-1 ion channels was determined in muscle from adult rats using electrophysiological techniques described elsewhere[31]. With this technique, three electrodes were placed in the same muscle fiber and by injecting small current pulses through two electrodes it was possible to obtain the voltage responses to this current injection at three inter-electrode distances. Examples of voltage responses at the three inter-electrode distances in a control fiber and in a fiber at 10 µM C8 are presented in Fig. 4A. By plotting the steady state deflection of the voltage responses against inter-electrode distance, G_m can be determined from fits of the data to a two-parameter exponential function (Fig. 4B). The lines connecting data points in Fig. 4B show fits of data to the two-parameter exponential function. Such recordings were performed for relevant compounds for a range of compound concentrations, and in Fig. 4C the observations of G_m at the different concentrations of C8 have been plotted. A Kd for a particular compound was obtained by fitting the data of G_m in Fig. 4C to a sigmoidal function (line in Fig. 4C). Such Kd values have been included in Table 3 for relevant compounds. The observations in Table 3 show that compounds that were

particular effective in recovering nerve-stimulated force in muscle with compromised neuromuscular transmission (Tables 1 and 2) were also potent inhibitors of G_m (Table 3).

Also included are Kd values for compounds when tested in human muscle using an approach identical to that in rat muscle.

Table 3. Effect of different compounds on G_m in isolated rat and human muscles.

	G_m No Compound	Kd for ClC-1 inhibition
C8 Rat	642±25, n=33	9 µM
C8 Human	430±41, n=5	5.5 µM
C22 rat	642±25, n=33	4.1 µM

Example 5: Combination treatments

ClC-1 is a novel target in treatment of neuromuscular complications and it was therefore explored whether this approach for symptomatic treatment could be used in combination with existing symptomatic treatment approaches. In myasthenia gravis, which in isolated muscles was mimicked by tubocurarine, the symptoms of muscle fatigue are most commonly treated with inhibitors of acethylcholineesterase[3] of which neostigmine and pyridostigmine are examples. Also, neostigmine is the most commonly used reversal agent of neuromuscular blocked after surgery[25]. To test if ClC-1 inhibitors and neostigmine or pyridsostigmine can be used in combination, the concentration of tubocurarine that was required to depress nerve-stimulated force by 50% (Kd,tub) was determined in four experimental conditions: *i*) control conditions, *ii*) with ClC-1 inhibitor alone, *iii*) with neostigmine or pyridostigmine alone, and *iv*) with neostigmine or pyridostigmine and ClC-1 inhibitor together. Fig. 5A-D show recordings of nerve-stimulated force production at different tubocurarine concentrations when tested under the four experimental conditions. It can be seen that C8 (Fig. 5B) and neostigmine (Fig. 5C) both resulted in elevated nerve-stimulated force when compared to control (Fig. 5A). The force was, however, best maintained when both neostigmine and C8 were used (Fig. 5D). To quantify the effect of compounds on tubocurarine sensitivity, the force at the different tubocurarine concentrations was determined. In plots of nerve-stimulated force against tubocurarine concentration (Fig. 5E) Kd,tub was

determined by fitting four parameter sigmoidal functions to the data and the Kd,tub for the different compounds have been collected in Table 4.

Table 4: Effect of neostigmine, pyridostigmine, ClC-1 inhibitor, and combination of neostigmine or pyridostigmine and ClC-1 inhibitor on Kd,tub. *Indicates significantly different from control. **Significantly different from the combination of neostigmine and compound.

Compound	Control	Neostigmine (10 nM)	Pyridostigmine (100 nM)	Compound (50 µM)	Compound (50 µM) + Neostigmine (10 nM)	Compound (50 µM) + Pyridostigmine (100 nM)
C8	118±5 nM	166±13 nM*,**		177±7 nM*,**	218±18 nM*	
C8	118±5 nM		127±15 nM	177±7 nM*,**		186±5 nM*

While the use of tubocurarine mimics conditions with reduced neuromuscular transmission due to post-synaptic dysfunction (myasthenia gravis, neuromuscular blockade), the experiments with elevated extracellular Mg^{2+} mimics conditions with pre-synaptic dysfunction akin to a range of neuromuscular disorders including Lambert Eaton syndrome[26], motor neuron disorders[6-9] and polyneuropathy[18,19]. Patients with Lambert Eaton syndrome are commonly treated with inhibitors of voltage gated K^+ channels such as 3,4-diaminopyridine (3,4-AP). Based on this it was determined whether recovery of nerve-stimulated force at elevated extracellular Mg^{2+} with ClC-1 inhibiting compounds could be added to force recovery with 3,4-AP. This was done by determining the concentration of Mg^{2+} that was required to depress nerve-stimulated force by 50 % (Kd,Mg^{2+}) in four experimental conditions: *i*) in control conditions, *ii*) with 3,4-AP alone, *iii*) with C8 alone, and *iv*) with 3,4-AP and C8 together. Fig. 6A-D show recordings of nerve-stimulated force production at different Mg^{2+} concentrations when tested under these four experimental conditions. It can be seen that with both 3,4-AP and ClC-1 inhibitor did the nerve-stimulated force at elevated Mg^{2+} remain elevated when compared to control. The force was, however, best maintained when the combination of both 3,4-AP and ClC-1 inhibitor was used. To quantify the effect of compounds on Mg^{2+} sensitivity the force at the different Mg^{2+} concentrations was determined. In plots of nerve-stimulated force against Mg^{2+} concentration (Fig. 6E) the Kd,Mg^{2+} was determined by fitting four parameter sigmoidal function to the data. Kd, Mg^{2+} for the different compounds have been collected in Table 5.

Table 5. Effect of 3,4-AP, ClC-1 inhibitor and combination of 3,4-AP and ClC-1 inhibitor on Kd,Mg^{2+} *Indicates significantly different from control. **Significantly different from the combination of 3,4-AP and compound.

Com-pound	**IUPAC**	Control	3,4-AP (10 µM)	Compound (50 µM)	Compound (50 µM) + 3,4-AP (10 µM)
C8	(2S)-2-(4-bromophenoxy)propanoic acid	3.5±0.1 mM *n*=6	5.8±0.3 mM*,** *n*=3	4.0±0.1 mM*,** *n*=7	7.8±0.5 mM* *n=4*

As illustrated in table 5, combination therapy using C8 and 3,4-diaminopyridine results in an unexpected synergistic effect on recovery of neuromuscular transmission.

Example 6: Effect of ClC-1 inhibitor on endplate potentials (EPPs)

Experiments with intracellular electrodes inserted near visible nerves in rat soleus muscles enabled recordings of EPPs upon nerve stimulation. To prevent action potential initiation upon nerve stimulation, µ-conotoxin GiiiB (1 µM) was included in the incubation solution to inhibit voltage gated Na^+ channels in the muscle fibers (NaV1.4). As shown by representative recordings in Fig. 7A the EPP amplitude became larger when C8 was used to inhibit ClC-1 channels. Fig. 7B show summarized data from all fibers. Both 10 and 25 µM C8 caused significantly larger EPPs when compared to control conditions.

Example 7: ClC-1 inhibition can recover contractile force in human muscles under conditions that mimic critical illness myopathy

Critical illness myopathy (CIM) is a condition that develops in around 30 % of critically ill patients in intensive care units[4]. The condition is diagnosed from a loss of muscle excitability as evaluated from reduction in compound muscle action potentials. The associated muscle weakness prevents patients from weaning from mechanical ventilation and therefore increases the stay in intensive care units. At the cellular level, CIM is associated with loss of NaV1.4 function and muscle fibers become depolarized[4]. To evaluate whether ClC-1 inhibition can recover muscle function in such conditions, depolarization and loss of NaV1.4 function in CIM were mimicked in experiments with isolated human muscles. Fibers were depolarized by raised extracellular K^+, and loss of NaV1.4 function was induced by a small dose of NaV1.4 inhibitor TTX. As shown by Fig. 8, the contractile force declined upon introducing the elevated K^+ and TTX. However, contractile force was markedly recovery upon addition of C8. This confirms

that compounds that inhibit ClC-1 such as C8 can prevent loss of force due to depolarization and NaV1.4 loss of function – the mechanisms underlying CIM.

Example 8: Pharmacokinetic analysis of C8 in rats and effect of ClC-1 inhibition in animal models of myasthenia gravis

Before conducting *in vivo* experiments with animal models of myasthenia gravis, some pharmacokinetic details were obtained for C8 in response to one-bolus I.P. injection. The details from these experiments have been summarized in Table 6:

Table 6. PK parameters for C8 tested in rats.

Parameter	Unit	Value
t1/2	h	3.70
Tmax	h	0.5
Cmax	ng/ml	44600
C0	ng/ml	24533
AUC 0-t	ng/ml*h	203635
AUC 0-inf_obs	ng/ml*h	205381
AUC 0-t/0-inf_obs		0.9915
VD_obs	ml	259.62
Cl_obs	ml/h	48.69

In the first series of *in vivo* experiments, myasthenia gravis was simply mimicked by I.P. injection of tubocurarine (0.13 mg/kg) in animals that had been familiarized to running on the rotarod. On the first of two consecutive days, tubocurarine was injected I.P. and the running performance of the animal was tested 21 minutes after this injection. On the second day of experimentation, the animals first performed a test run to ensure that they were no longer affected by the tubocurarine injected the day before. Then C8 (20 mg/kg) or sham treatment were injected I.P. and allowed to act for 2 hrs before again injecting tubocurarine. Animals were again tested 21 minutes after this second tubocurarine treatment. This experimental design enabled a paired analysis of whether the sham or C8 injections on the second day changed the response of the animals to tubocurarine. It should also be noted that the experimenter did not know which animals had been given C8 or sham treatment. The design of the experiments has been illustrated in Fig. 9A and the results from the experiments are illustrated in Fig. 9B-D. As can be seen from Fig. 9B, the animals that were administered sham-treatment covered almost identical distances on the two days. C8 treated animals, however, were able to cover significantly longer distance on the rotarod on the second day when compared to their own performance on the first day. Thus, C8 treated

animals ran around 150 % longer on the second day (Fig. 9C) clearly contrasting that sham-treated animals only ran around 2 % longer. To demonstrate that the marked improvement upon C8 administration was a general response of the animals and not just a rare observation in a few animals, Fig. 9D shows the number of animals in the two groups (sham and C8) that had a performance increase of at least 100 % on the second day.

In the last series of experiments, myasthenia gravis was mimicked in rats by inducing an immunological reaction against the motor endplate of muscle fibers using monoclonal antibody against the nicotinic ACh receptor in muscle fibers. Again the animals had been familiarized to the rotarod before the MAB35 injection. As shown in Fig. 10, symptoms of reduced performance developed 21-43 hrs after injection of MAB35. When a stable reduction in performance was observed, the animals were administered either C8 or sham. From Fig. 10 it can be seen that upon injection sham treatment the performance further declined. This decline was reduced when 20 mg/kg C8 was injected and with the larger dose of C8 (30 mg/kg) there was a clear recovery of performance. While there was no difference in performance between the three groups of animals before sham or C8 injections, the performance in the groups of animals treated with C8 was significantly better than sham-treated animals after injection.

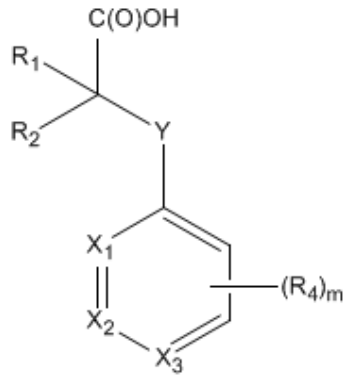
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Claims

1. Use of a composition comprising a compound of Formula (II):



Formula (II)

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

- m is 0, 1 or 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1, X_2 and X_3 are independently selected from CH;
- R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;;
- R_4 is selected from the group consisting H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl;

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

wherein the neuromuscular disorder is selected from the group consisting of myasthenia gravis, autoimmune myasthenia gravis, congenital myasthenia gravis, Lambert-Eaton Syndrome, critical illness myopathy (CIM), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), diabetic polyneuropathy, Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, and critical illness polyneuropathy.

2. The use according to claim 1, wherein R_1 is H and R_2 is selected from the group consisting of H, C_{1-4}-alkyl, C_{3-6}-cycloalkyl and amino-C_{1-4}-alkyl, wherein said C_{1-4}-alkyl and C_{3-6}-cycloalkyl may be substituted with O-R_{11}, wherein R_{11} is selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl.

3. The use according to claim 2, wherein R_{11} is -CH_3.

4. The use according to claim 2, wherein R_2 is -$CH(CH_3)CH_2$-O-CH_3.

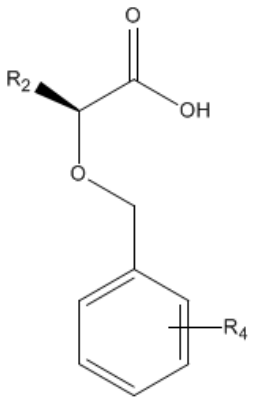
5. The use according to any of the preceding claims, wherein R_1 is H and R_2 is selected from the group consisting of H, -CH_3, -$CH(CH_3)_2$ and cyclopropyl.

6. The use according to any of the preceding claims, wherein R_1 is H and R_2 is -$CH(CH_3)_2$.

7. The use according to any one of the preceding claims, wherein R_1 is different from R_2.

8. The use according to any one of the preceding claims wherein m is 1.

9. The use according to any one of the preceding claims, wherein the compound of Formula (II) is further defined by Formula (V):



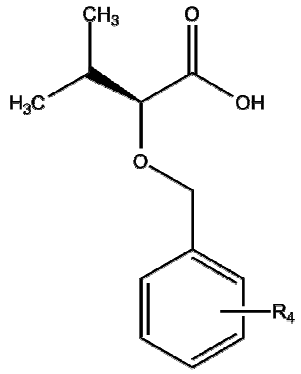
Formula (V)

wherein

- R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

10. The use according claim 9, wherein the compound of

Formula (V) is further defined by Formula (VI):

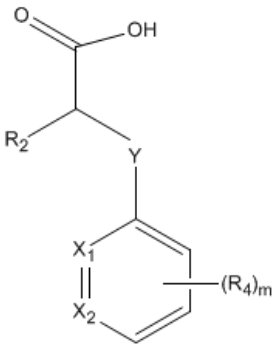


Formula (VI)

wherein R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl

11. The use according to any one of claims 9 to 10, wherein R_4 is in ortho- or meta position.

12. The use according to claim 1, wherein the compound of Formula (II) is further defined by Formula (VII):



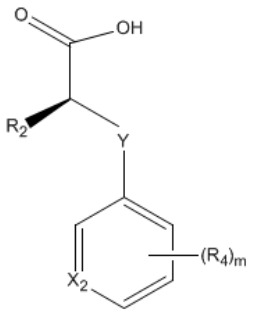
Formula (VII)

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

- m is 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_1 and X_2 are independently selected from CH;

- R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo, wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

13. The use according to claim 12, wherein the compound of Formula (VII) is further defined by Formula (VIII)



Formula (VIII)

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

- m is 2;
- Y is selected from the group consisting of O, NH, N-CH_3, CH_2, CH_2-O, S and SO_2;
- X_2 is selected from CH;
- R_2 is selected from the group consisting of H, C_{1-4}-alk(en)yl, C_{3-6}-cycloalk(en)yl, wherein said C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl may be substituted with up to two substituents selected from the group consisting of -NR_9-CO- R_{10}, -$N(R_{10})_2$-SO_2-R_{12}, -CO-NR_9R_{10}, -SO_2- NR_9 R_{10}, -R_{13}-O-R_{11}, -NR_9 R_{10}, -S(O)R_{12}, -$S(O)_2R_{12}$, cyano, -O-R_{11}, fluorinated C_{1-3}-alkyl, nitro and halo,

wherein R_9, R_{10}, and R_{11} are independently selected from H, C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl, whereas R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;

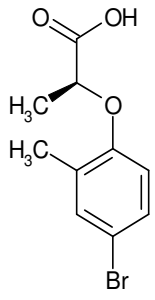
- R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl
- R_{13} is selected from C_{1-4}-alk(an/en/yn)diyl and C_{3-6}-cycloalk(an/en)diyl.

14. The use according to any one of claims 1 to 13, wherein Y is O.

15. The use according to any one of claims 13 to 14, wherein R_2 is selected from the group consisting of H and C_{1-4}-alkyl.

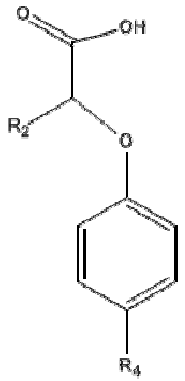
16. The use according to any one of claims 13 to 15, wherein R_4 is selected from the group consisting of H, $-CH_3$ and halogen.

17. The use according to claim 16, wherein said compound is further defined by Formula (IX):



Formula (IX)

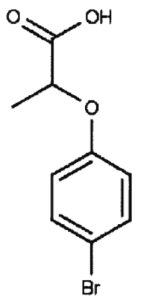
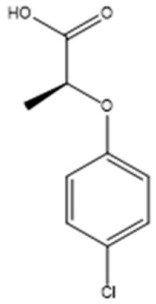
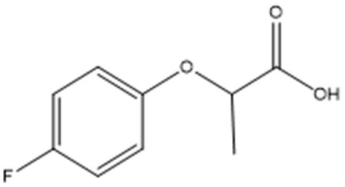
18. The use according to claim 1, wherein the compound of Formula (VII) is further defined by Formula (X):

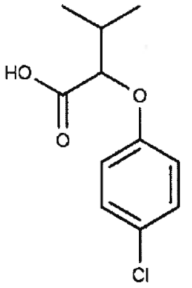
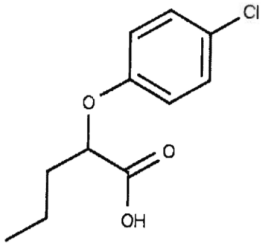
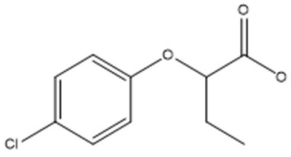
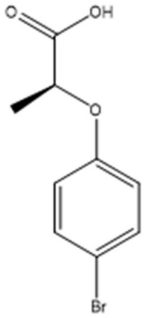
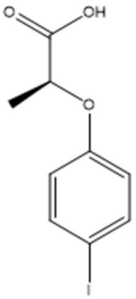
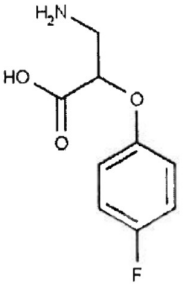
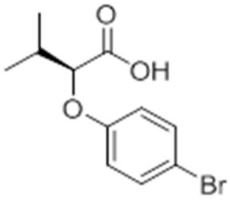
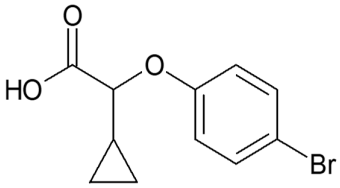
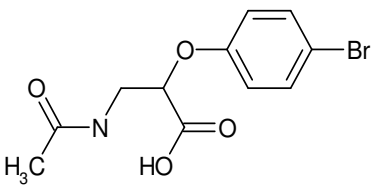
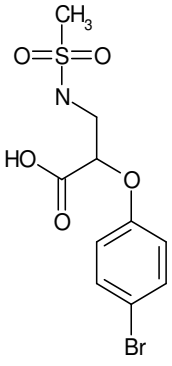
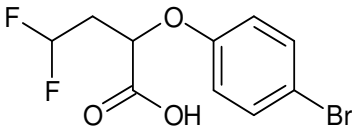


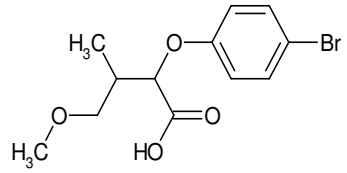
Formula (X)

or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2-O-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-NH_2$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-NH-CO-CH_3$ and $-CH_2-NH-SO_2-CH_3$ and cyclopropyl, and R_4 is selected from the group consisting of H, Br, Cl, F and I.

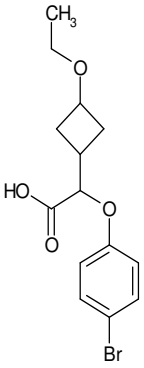
19. The use according to claim 1, wherein the compound of Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII):

 Formula (XI)	 Formula (XII)	 Formula (XIII)

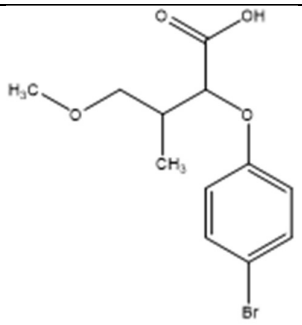
 Formula (XIV)	 Formula (XV)	 Formula (XVI)
	 Formula (XVIII)	 Formula (XIX)
 Formula (XX)	 Formula (XXI)	 Formula (XXII)
 Formula (XXIII)	 Formula (XXIV)	 Formula (XXV)



Formula (XXVI)

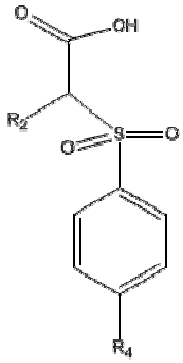


Formula (XXVII)



Formula (XXVIII)

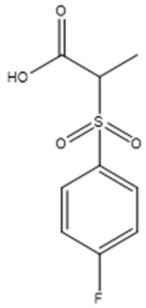
20. The use according to claim 1, wherein the compound of Formula (VII) is further defined by Formula (XXXII):



Formula (XXXII)

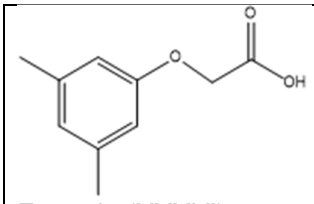
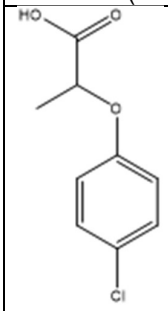
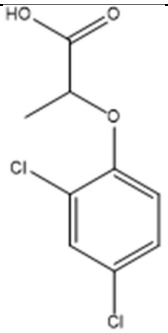
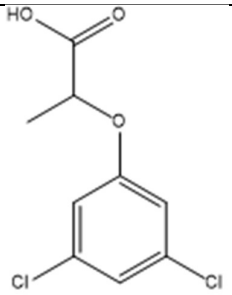
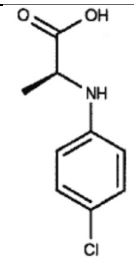
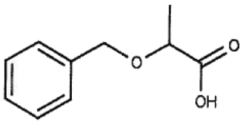
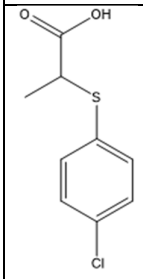
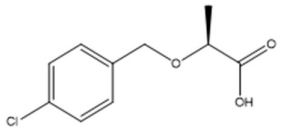
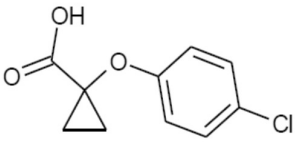
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

21. The use according to claim 20, wherein the compound of Formula (XXXII) is further defined by Formula (XXXIII):



Formula (XXXIII)

22. The use according to claim 1, wherein the compound of Formula (II) is further defined by any one of Formulas (XXXVI) to (LIX)

 Formula (XXXVI)		
 Formula (XXXIX)	 Formula (XLII)	 Formula (XLIII)
	 Formula (LII)	 Formula (LIII)
 Formula (LV)	 Formula (LVI)	 Formula (LVIII)

23. The use according to any one of the preceding claims wherein the neuromuscular disorder is myasthenia gravis, autoimmune myasthenia gravis or congenital myasthenia gravis.

24. The use according to any one of the preceding claims wherein the neuromuscular disorder is Lambert-Eaton Syndrome, critical illness myopathy (CIM), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) or diabetic polyneuropathy.

25. The use according to any one of the preceding claims wherein the neuromuscular disorder is selected from the group consisting of Guillain-Barré syndrome, poliomyelitis, post-polio syndrome, chronic fatigue syndrome, and critical illness polyneuropathy.

26. The use according to any one of the preceding claims wherein the neuromuscular disorder has been induced by a neuromuscular blocking agent.

27. The use according to any one of the preceding claims further comprising at least one further active agent.

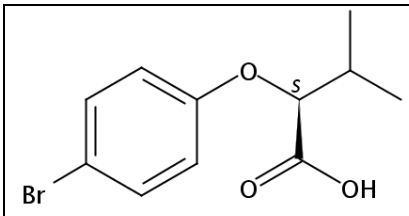
28. The use according to claim 27, wherein said further active agent is an acetylcholine esterase inhibitor, suggamadex, tirasemtiv or 3,4-aminopyridine.

29. The use according to claim 28, wherein said acetylcholine esterase inhibitor is selected from the group consisting of Delta9-tetrahydrocannabinol, carbamates, physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, rivastigmine, phenanthrene derivatives, galantamine, caffeine – noncompetitive, piperidines, donepezil, tacrine, edrophonium, huperzine, ladostigil, ungeremine and lactucopicrin.

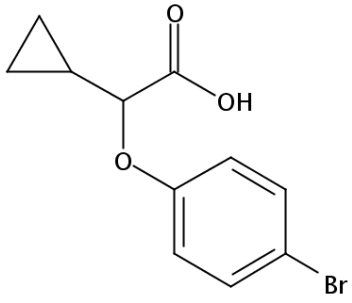
30. The use according to any one of the preceding claims, wherein said compound further comprises a moiety selected from the group consisting of albumin, fatty acids, polyethylene glycol (PEG), acylation groups, antibodies and antibody fragments conjugated to said compound, thus generating a moiety-conjugated compound.

31. Use of a composition as defined in any one of claims 1 to 30 in the manufacture of a medicament for recovery of neuromuscular transmission.

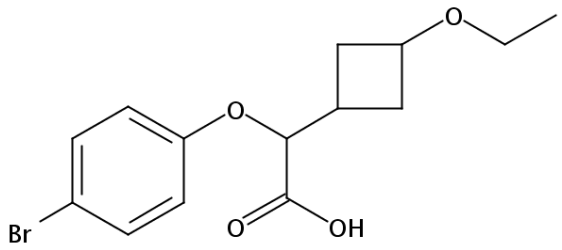
32. A compound selected from the group consisting of formulas (XXI), (XXII), (XXVII), (XX), (XXVIII), (XXIII), (XXIV), (LIII), (LII), (XXXIII), (XLVI), (LXXIV), (LXXV), (LXXVI), (LXXVII), (LXXVIII), (LXXIX), and (LXXX):



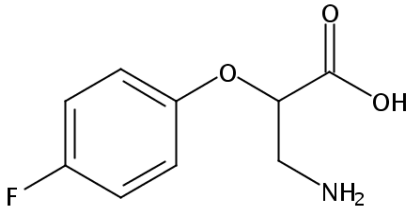
Formula (XXI)



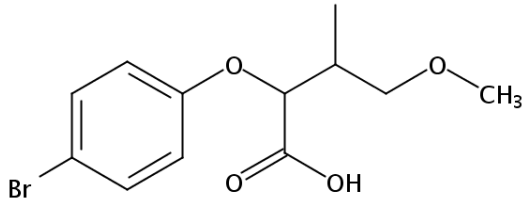
Formula (XXII)



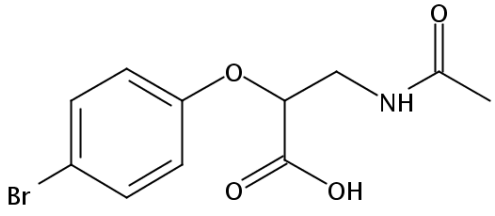
Formula (XXVII)



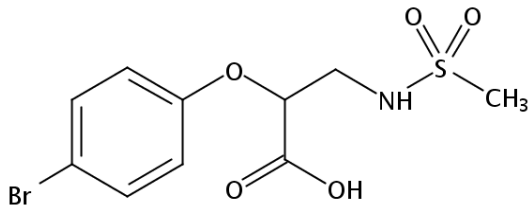
Formula (XX)



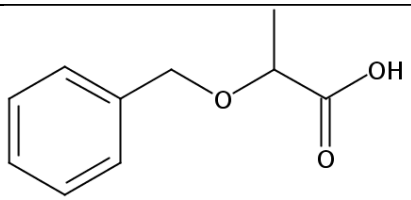
Formula (XXVIII)



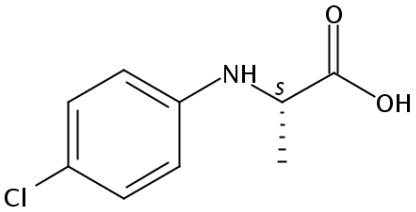
Formula (XXIII)



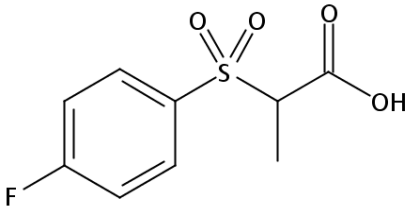
Formula (XXIV)



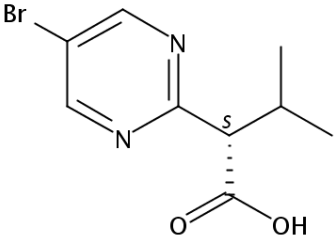
Formula (LIII)



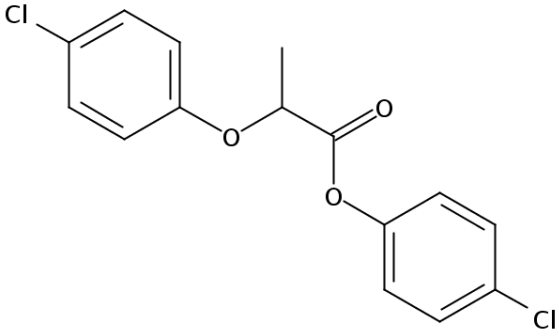
Formula (LII)



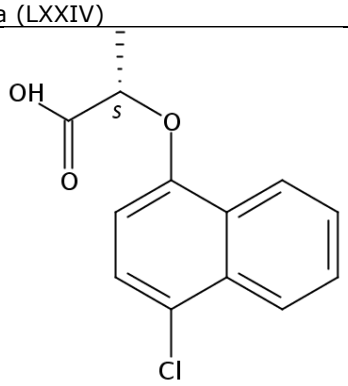
Formula (XXXIII)



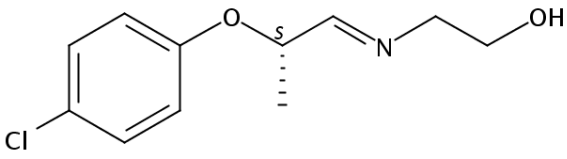
Formula (LXXIV)



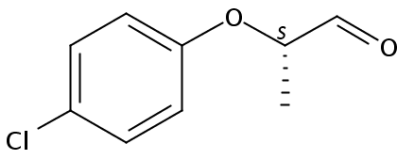
Formula (LXXVI)



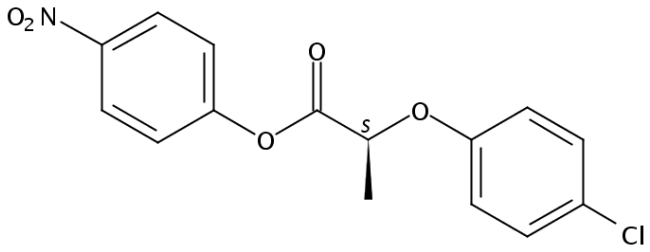
Formula (XLVI)



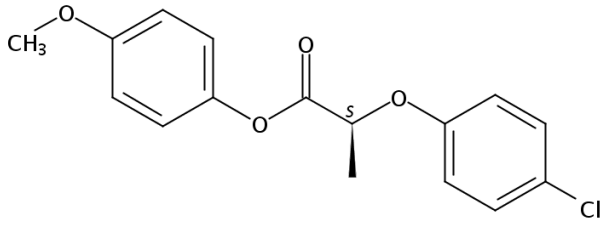
Formula (LXXV)



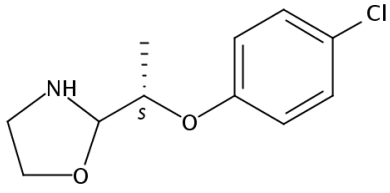
Formula (LXXVII)



Formula (LXXVIII)



Formula (LXXIX)



Formula (LXXX)

33. The compound according to claim 32, wherein the compound is selected from the group consisting of formulas (XXI), (XXII), (XXVII), (XX), (XXVIII), (XXIII), (XXIV), (LIII), (LII), and (XXXIII).

34. The compound according to any one of claims 32 to 33, wherein the compound is selected from the group consisting of formulas (XXI) and (XXII).