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].

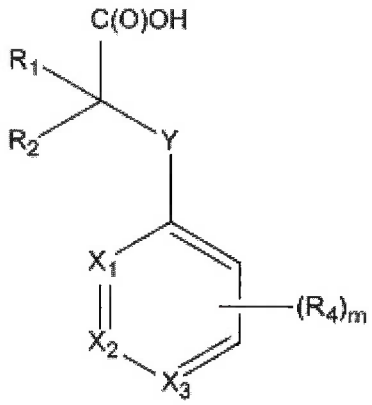
Summary

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;

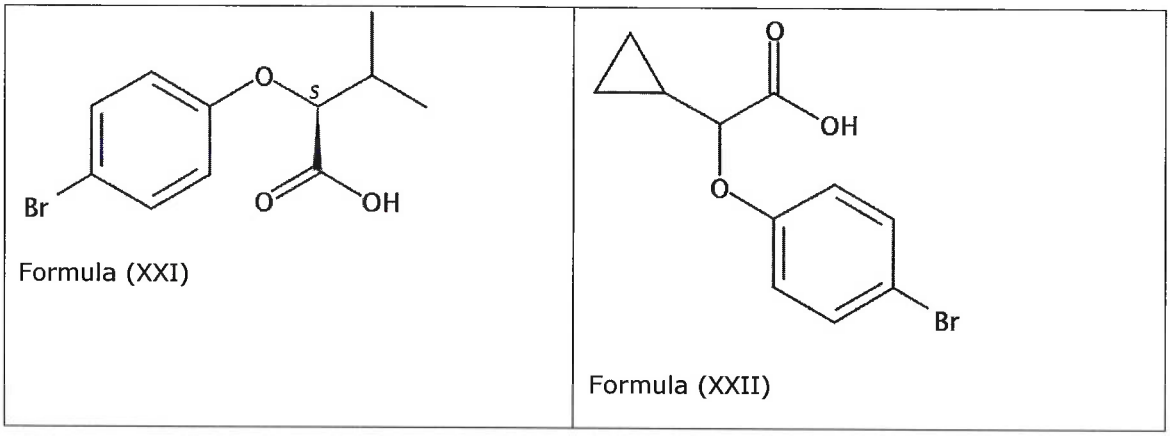
in the manufacture of a medicament for treating, ameliorating and/or preventing a neuromuscular disorder, and/or reversing and/or ameliorating a neuromuscular blockade after surgery,

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), reversal diabetic polyneuropathy, Guillain-Barré

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

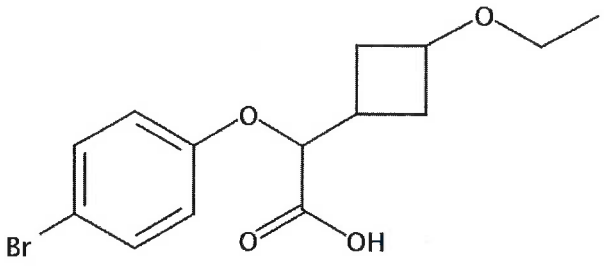
In another aspect, the present disclosure provides use of a composition as defined herein in the manufacture of a medicament for recovery of neuromuscular transmission.

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):

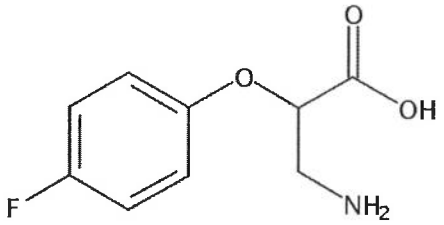


Formula (XXI)

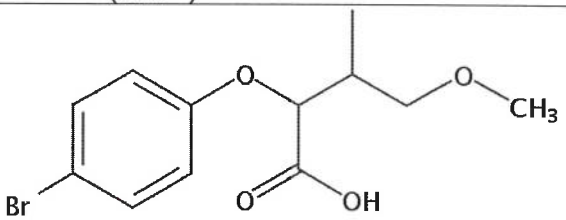
Formula (XXII)



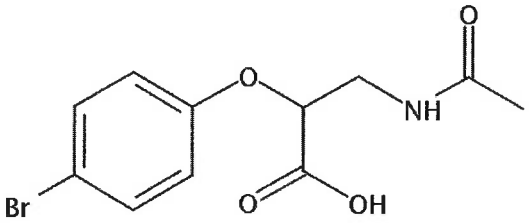
Formula (XXVII)



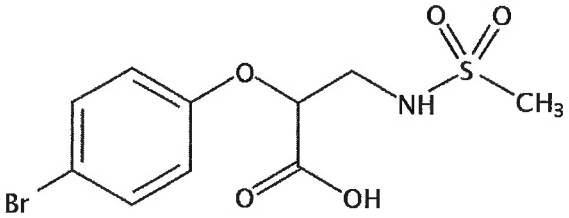
Formula (XX)



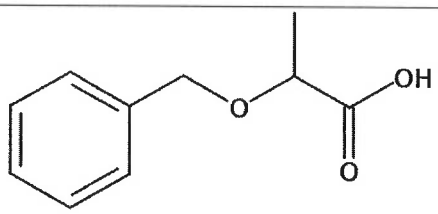
Formula (XXVIII)



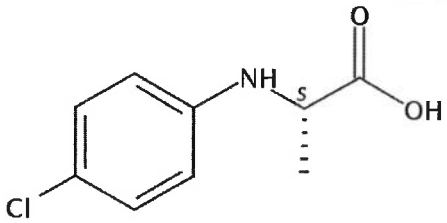
Formula (XXIII)



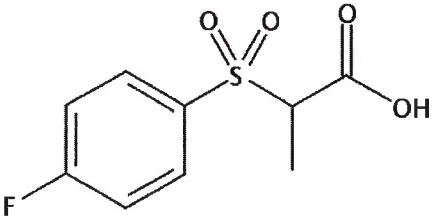
Formula (XXIV)



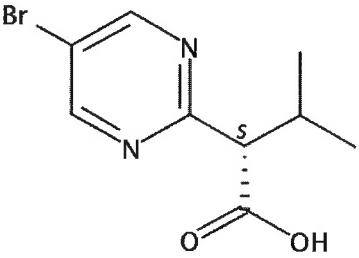
Formula (LIII)



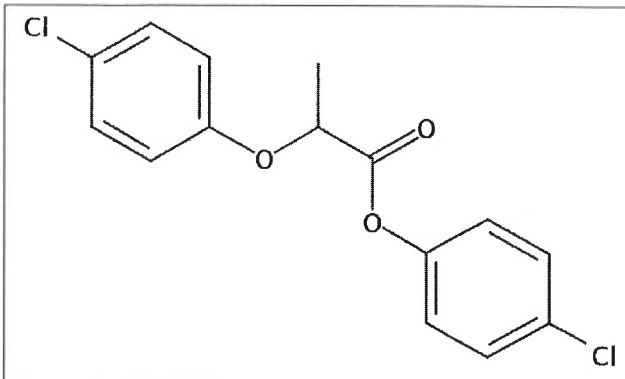
Formula (LII)



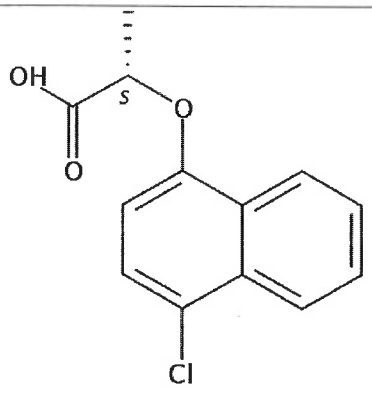
Formula (XXXIII)



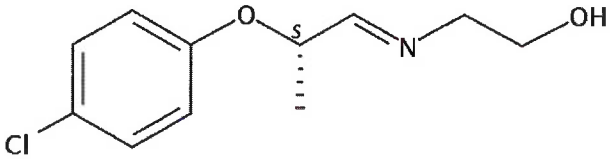
Formula (LXXIV)



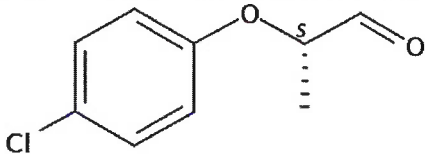
Formula (LXXVI)



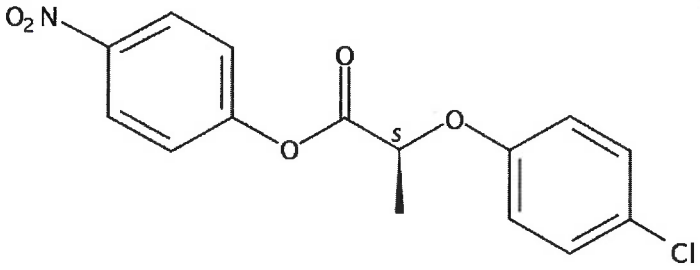
Formula (XLVI)



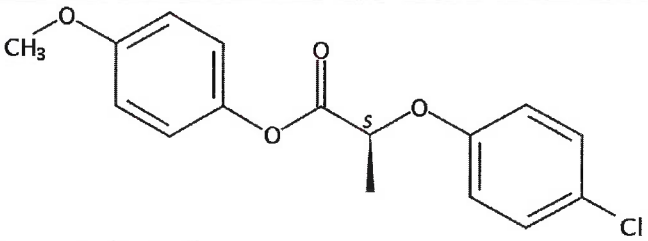
Formula (LXXV)



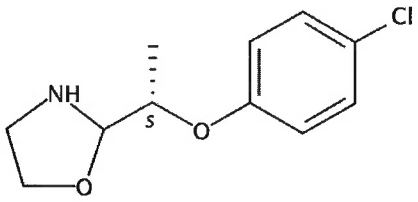
Formula (LXXVII)



Formula (LXXVIII)

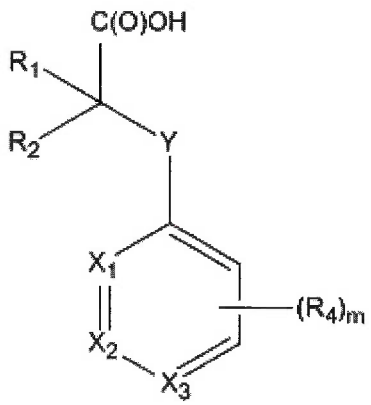


Formula (LXXIX)



Formula (LXXX)

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



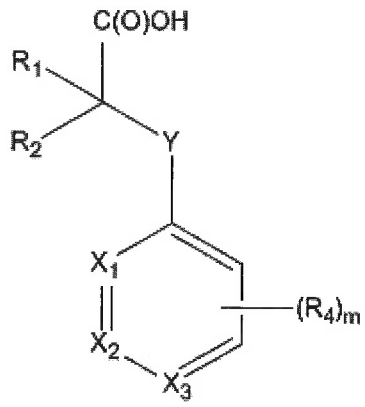
Formula (II)

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

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), reversal 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.

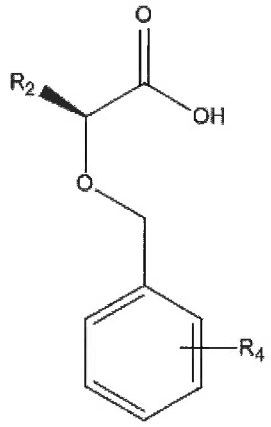
5. The use according to any of the preceding claims, wherein R_1 is H and R_2 is selected from the group consisting of H, -CH_3, -$CH(CH_3)_2$ and cyclopropyl.

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):



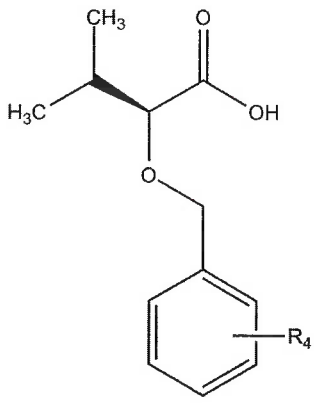
Formula (V)

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):

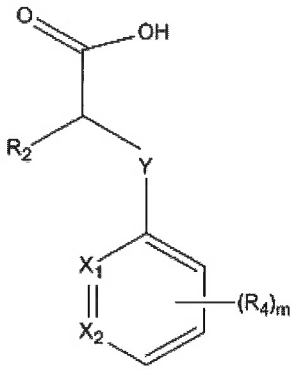


Formula (VI)

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):



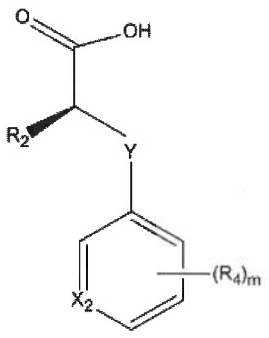
Formula (VII)

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;

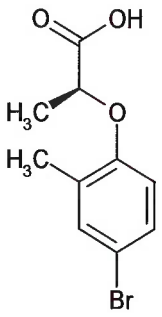
- R_4 is selected from the group consisting of H, halo, cyano, -CHO, C_{1-4}-alk(en)yl, halo-C_{1-4}-alk(en)yl, -O- C_{1-4}-alk(en)yl;
- R_9, R_{10}, R_{11} are independently selected from H or C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl;
- R_{12} is selected from C_{1-4}-alk(en/yn)yl and C_{3-6}-cycloalk(en)yl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

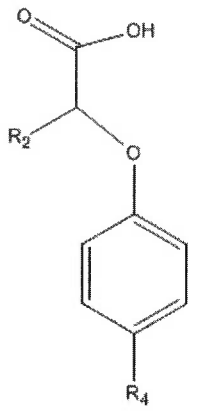
16. The use according to any one of claims 13 to 15, wherein R_4 is selected from the group consisting of H, $-CH_3$ and halogen.

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



Formula (IX)

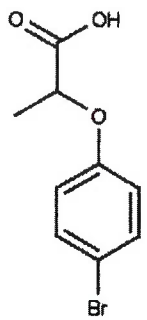
18. The use according to claim 1, wherein the compound of Formula (VII) is further defined by Formula (X):



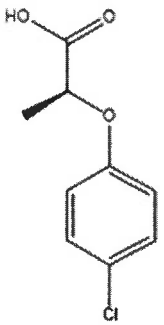
Formula (X)

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.

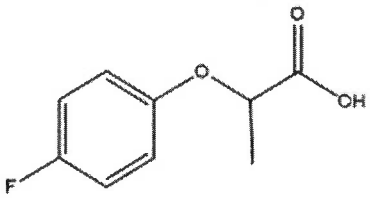
19. The use according to claim 1, wherein the compound of Formula (VII) is further defined by any one of Formulas (XI) to (XXVIII):



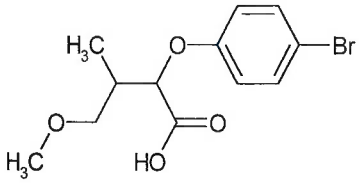
Formula (XI)



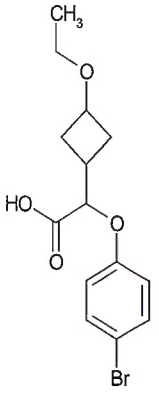
Formula (XII)



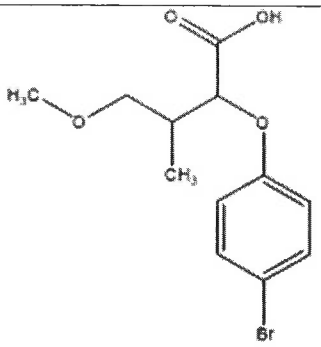
Formula (XIII)



Formula (XXVI)

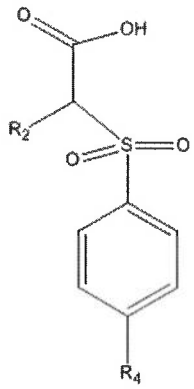


Formula (XXVII)



Formula (XXVIII)

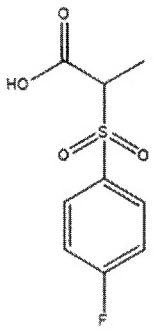
20. The use according to claim 1, wherein the compound of Formula (VII) is further defined by Formula (XXXII):



Formula (XXXII)

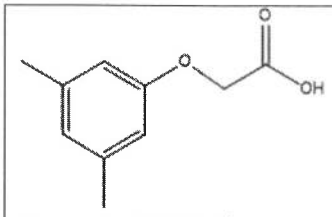
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof; wherein R_2 is selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2-CH_2-CH_3$ and $-CH_2-NH_2$ and R_4 is selected from the group consisting of H, Br, Cl, F and I.

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

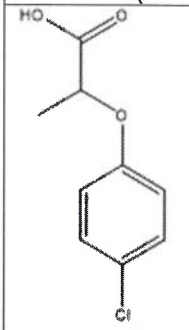


Formula (XXXIII)

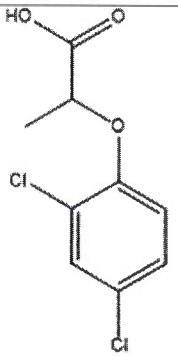
22. The use according to claim 1, wherein the compound of Formula (II) is further defined by any one of Formulas (XXXVI) to (LIX)



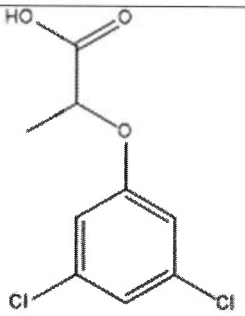
Formula (XXXVI)



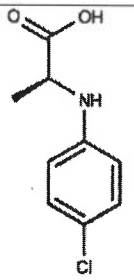
Formula (XXXIX)



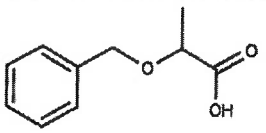
Formula (XLII)



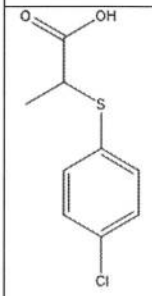
Formula (XLIII)



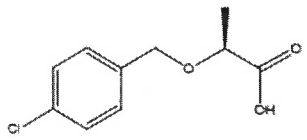
Formula (LII)



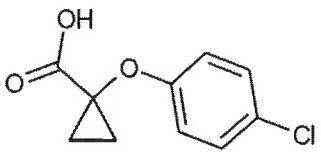
Formula (LIII)



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 reversal 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.

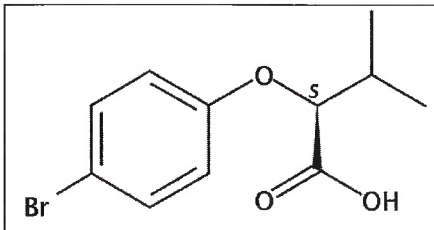
29. The use according to claim 28, wherein said acetylcholine esterase inhibitor is selected from the group consisting of Delta9-tetrahydrocannabinol, carbamates, physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, rivastigmine, phenanthrene derivatives, galantamine, caffeine – noncompetitive,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

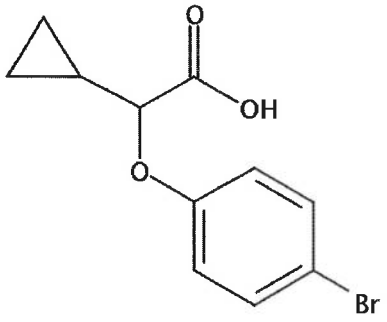
fragments conjugated to said compound, thus generating a moiety-conjugated compound.

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.

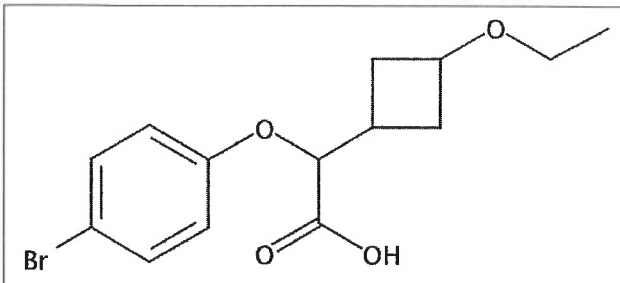
32. A compound selected from the group consisting of formulas (XXI), (XXII), (XXVII), (XX), (XXVIII), (XXIII), (XXIV), (LIII), (LII), (XXXIII), (XLVI), (LXXIV), (LXXV), (LXXVI), (LXXVII), (LXXVIII), (LXXIX), and (LXXX):



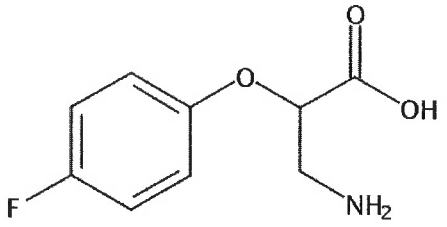
Formula (XXI)



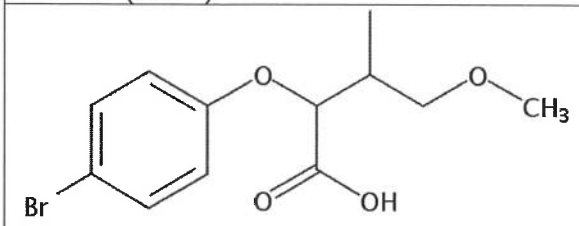
Formula (XXII)



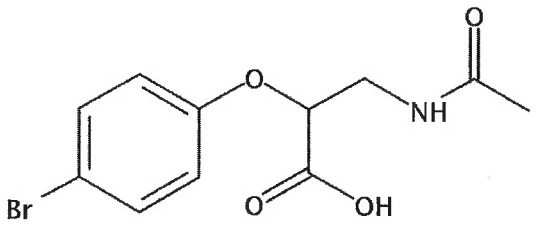
Formula (XXVII)



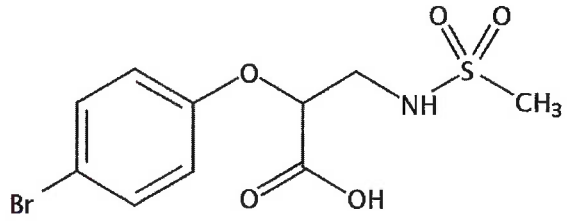
Formula (XX)



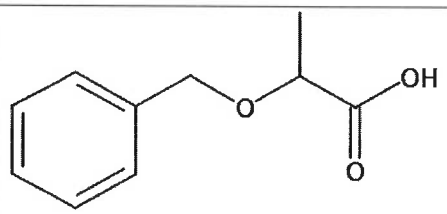
Formula (XXVIII)



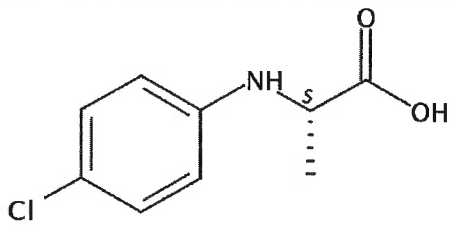
Formula (XXIII)



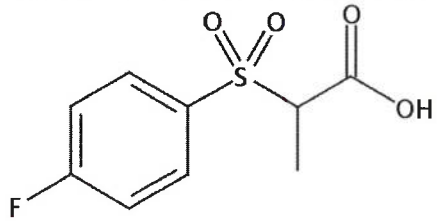
Formula (XXIV)



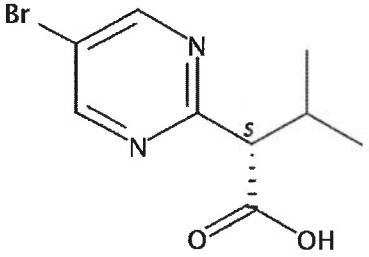
Formula (LIII)



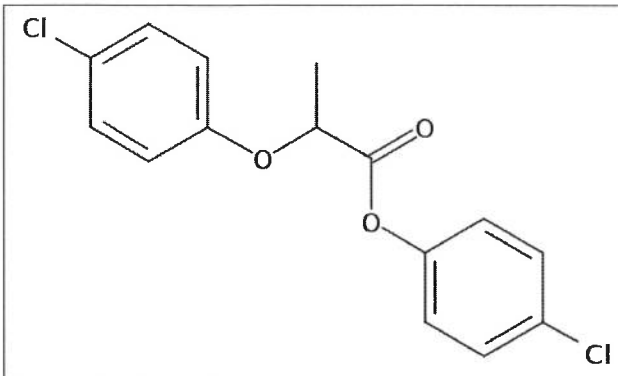
Formula (LII)



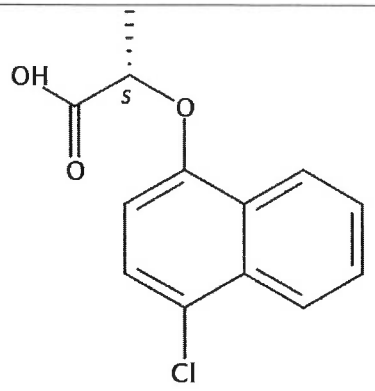
Formula (XXXIII)



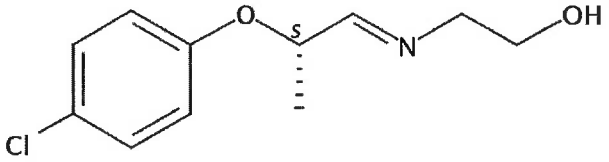
Formula (LXXIV)



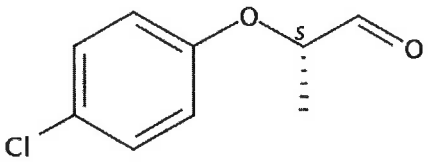
Formula (LXXVI)



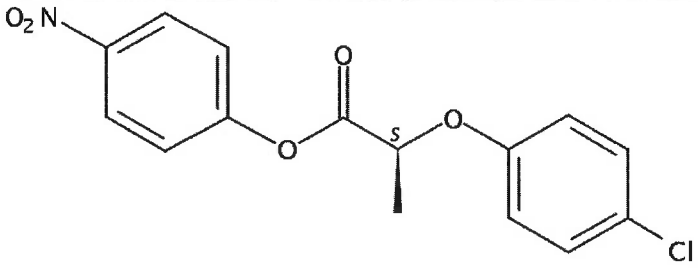
Formula (XLVI)



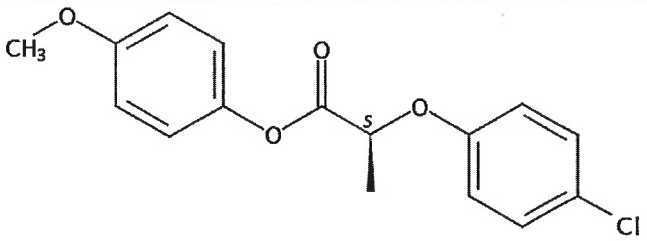
Formula (LXXV)



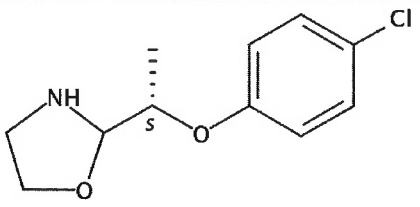
Formula (LXXVII)



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).