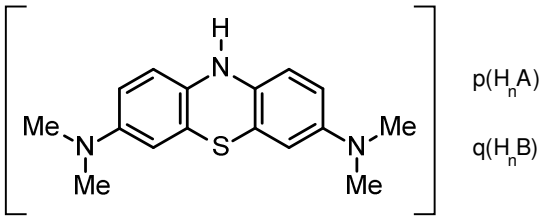
Claims

1 Use of a therapeutic methylthioninium (MT)-containing compound in the preparation of a medicament for the therapeutic treatment of Alzheimer's disease or Mild Cognitive Impairment in a subject,

wherein said MT-containing compound is to be administered to said subject,

wherein the MT-containing compound is an LMTX compound of the following formula:



wherein each of H_nA and H_nB (where present) are protic acids which may be the same or different,

and wherein p = 1 or 2; q = 0 or 1; n = 1 or 2; $(p + q) \times n = 2$,

or a hydrate or solvate thereof,

wherein said subject is selected from the following groups:

(i) a subject who has not historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters; or

(ii) a subject who has historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters, but ceased that treatment at least 3, 4, 5, 6, 7, or 8 weeks prior to treatment with the LMTX compound;

wherein said therapeutic treatment with LMTX is maintained for treatment timeframe without co-administration with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters

followed by;

treatment with LMTX with co-administration of a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters.

wherein the treatment timeframe prior to co-administration of the therapeutic compound with the neurotransmission modifying compound is at least 2 months.

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2. The use as claimed in claim 1 wherein said therapeutic treatment with LMTX comprises a total daily dose of between 2 and 100 mg of MT to the subject per day, optionally split into 2 or more doses.

3 The use as claimed in claim 2 wherein the total daily dose of MT is from 10 - 60 mg or from 20 – 40 mg.

4 The use as claimed in claim 3 wherein the total daily dose is from around any of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mg to around any of 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 mg.

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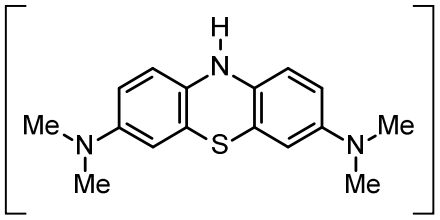
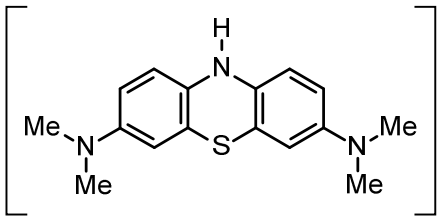
5 The use as claimed in any one of claims 1 to 4 wherein

(a) the LTMX compound has the following formula, where HA and HB are different mono-protic acids:



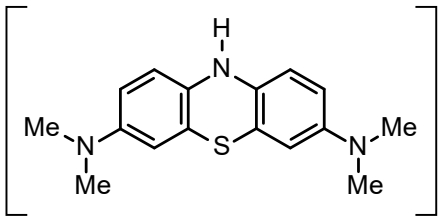
or

(b) the LTMX compound has the following formula:

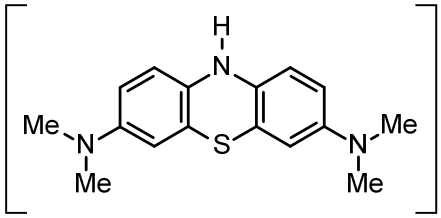


wherein each of H_nX is a protic acid, or.

(c) the LTMX compound has the following formula and H_2A is a di-protic acid:



6 The use as claimed in claim 5 wherein the LTMX compound has the following formula and is a bis-monoprotic acid:

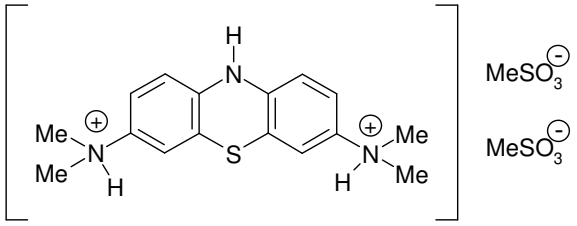


7 The use as claimed in any one of claims 1 to 6 wherein the or each protic acid is an inorganic acid, which is optionally a hydrohalide acid such as HCl; HBr or which is optionally HNO_3; or H_2SO_4.

8 The use as claimed in any one of claims 1 to 6 wherein the or each protic acid is an organic acid.

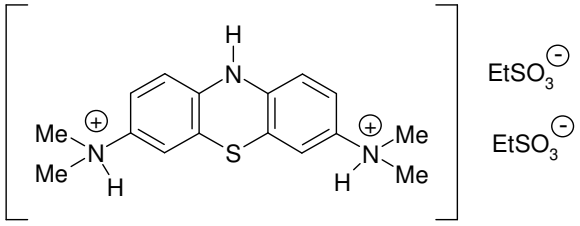
9 The use as claimed in claim 8 wherein the or each protic acid is selected from H_2CO_3; CH_3COOH; methanesulfonic acid, 1,2-ethanedisulfonic acid, ethanesulfonic acid, naphthalenedisulfonic acid, p-toluenesulfonic acid.

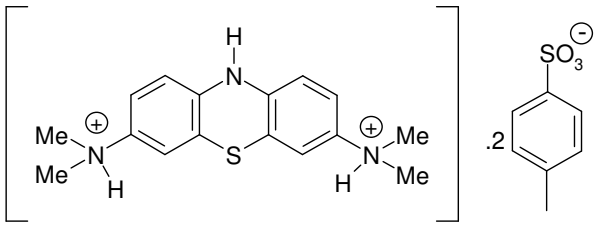
10 The use as claimed in claim 9 wherein the LTMX compound is LMTM:

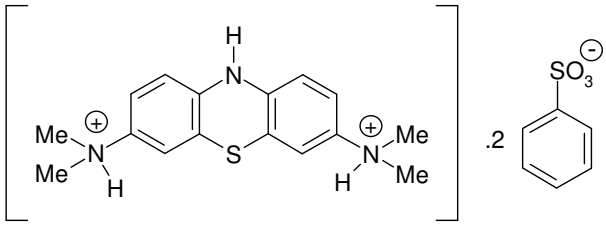


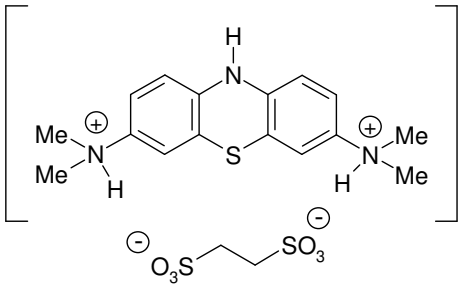
11 The use as claimed in claim 10 wherein said therapeutic treatment with LMTX comprises a total daily dose of LMTM of around 34 to 67, 34 to 100, 34 to 134, or 34 to 167 mg/day optionally wherein the dose of LMTM is about 34, 67, or 100 mg/once per day.

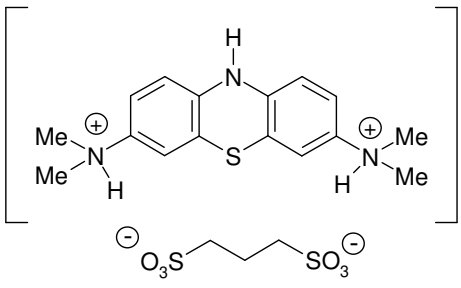
12 The use as claimed in any one of claims 1 to 4 wherein the LTMX compound is selected from the list consisting of:

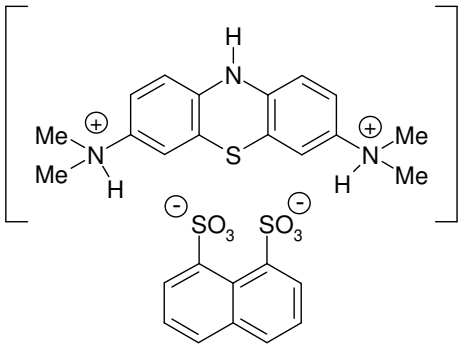












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13 The use as claimed in any one of claims 1 to 12 wherein the LTMX compound is provided as a pharmaceutical composition comprising the LMTX compound and a pharmaceutically acceptable carrier or diluent in the form of a dosage unit, which is optionally a tablet or capsule.

14 The use as claimed in claim 13 wherein the amount of MT in the unit is about 4, 5, 6, 7, 8, 9, 10, 20, or 30 to about 40, 50 or 60 mg.

15 The use as claimed in claim 13 wherein the dosage unit comprises about 34 to 67 mg, 34 to 100, 34 to 134, or 34 to 167 LMTM.

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16 Use of a therapeutic compound which does not contain methylthioninium (MT) in the preparation of a medicament for the therapeutic treatment of Alzheimer's disease or Mild Cognitive Impairment in a subject,

wherein said therapeutic compound which does not contain MT is to be administered to said subject,

wherein said subject is selected from the following groups:

(i) a subject who has not historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters; or

(ii) a subject who has historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters, but ceased that treatment at least 3, 4, 5, 6, 7, or 8 weeks prior to treatment with the LMTX compound;

wherein said therapeutic treatment with said therapeutic compound is maintained for a treatment timeframe without co-administration of a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters

optionally followed by;

treatment with said therapeutic compound with co-administration with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters.

wherein the treatment timeframe prior to co-administration of the therapeutic compound with the neurotransmission modifying compound is at least 2 months.

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17 Use of a therapeutic compound which does not contain methylthioninium (MT) in the preparation of a medicament for use in a method for assessing the efficacy of the compound which does not contain methylthioninium (MT) which is putatively therapeutic for Alzheimer's disease or Mild Cognitive Impairment in a subject, the method comprising the steps of:

(a) selecting a subject group which consists only of:

(i) subjects who have not historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters; and
(ii) subjects who have historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters, but ceased that treatment at least 3, 4, 5, 6, 7, or 8 weeks prior to said assessment;
(b) stratifying the subject groups into at least 2 sub-groups according to a baseline indicator of likely disease progression,
(c) treating members of each subject group with the non-MT-containing compound for a treatment timeframe,
(d) deriving psychometric and optionally physiological outcome measures for each treated patient group,
(e) comparing the outcomes at (d) with a comparator arm of said sub-groups which is optionally a placebo or minimal efficacy comparator arm,
(f) using the comparison in (e) to derive an efficacy measure for the non-MT-containing compound.

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18 The use as claimed in claim 16 or claim 17 wherein said non-MT-containing therapeutic compound or putatively therapeutic compound is disease modifying or putatively disease modifying for Alzheimer's disease or Mild Cognitive Impairment.

19 The use as claimed in claim 18 said non-MT-containing compound is selected from the list consisting of:
a drug affecting Aβ, optionally a BACE inhibitor; an immunotherapeutic targeting Aβ, an α-secretase inhibitor or modulator, a γ-secretase activator, an Aβ aggregation inhibitor which is optionally a metal chelator, optionally PBT2;
a Tau-aggregation inhibitor, optionally daunorubicin, Congo red, an anthraquinone, a benzothiazole, a cyanin dye, a phenylthiazolyl-hydrazide, an N-phenylamine, rhodanine, a polyphenol, a porphyrin, a quinoxaline, an aminthienopyridazine, oleocanthal, curcumin;
a microtubule stabiliser, optionally epithilone D, dictyostatin; TPI-287;
a kinase inhibitor to prevent the phosphorylation of tau, optionally Tideglusib, sodium selenate, LiCl;
an acetylation inhibitor for lowering levels of tau protein, optionally salsalate;
a deglycosylation inhibitor, optionally MK8719;
a phosphodiesterase 4 inhibitor, optionally BPN14770;
a tau immunotherapeutic, optionally AADvac1, ACI-35, RG7345;
a ciliary neurotrophic factor-based peptide;
Dimebon;
an miRNA inhibitor, optionally targeting miR-132, miR-134, miR-124, or miR-138.

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20 The use as claimed in claim 16 or claim 17 wherein said non-MT-containing compound is a symptomatic treatment for Alzheimer's disease or Mild Cognitive Impairment, which is optionally a psychostimulant.

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21 The use as claimed in any one of the preceding claims wherein the treatment timeframe prior to any co-administration of the therapeutic compound with the neurotransmission modifying compound is at least 6 months.

22 The use as claimed in any one of the preceding claims wherein the treatment prior to any co-administration of the therapeutic compound with the neurotransmission modifying compound is a monotherapy.

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23 The use as claimed in any one of the preceding claims wherein the subjects who have historically received treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters, have ceased that treatment at least 6 weeks prior to said treatment or assessment.

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24 Use of a therapeutic compound in the preparation of a medicament for the therapeutic treatment of Alzheimer's disease or Mild Cognitive Impairment in a subject,
wherein said therapeutic compound is to be administered to said subject,
wherein prior to said therapeutic treatment said subject is receiving treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters;
wherein said therapeutic treatment with said therapeutic compound is maintained for a first treatment timeframe with co-administration of the neurotransmission modifying compound during which treatment timeframe the dosage of said neurotransmission modifying compound is reduced to zero, followed by
treatment with said therapeutic compound without co-administration with a neurotransmission modifying compound for a second treatment timeframe,
wherein the first treatment timeframe is between 2 weeks and 8 weeks.
wherein the second treatment timeframe is at least 3 months, more preferably at least 6 months or at least 12 months.

25 The use as claimed in claim 24 where the reduction in dosage to zero is substantially linear over the first time frame.

26 The use as claimed in claim 24 or claim 25 wherein the therapeutic treatment is with an LMTX compound and optionally dosage as defined in any one of claims 2 to 15.

27 The use as claimed in claim 24 or claim 25 wherein the therapeutic treatment is with a non-MT-containing therapeutic compound as defined in any one of claims 19 to 20.

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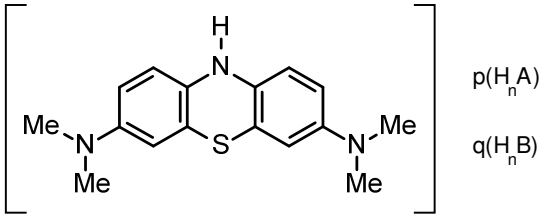
28 Use of a therapeutic methylthioninium (MT)-containing compound in the preparation of a medicament for the therapeutic treatment of Alzheimer's disease or Mild Cognitive Impairment in a subject,

which subject has been selected as being non–responsive to treatment with a neurotransmission modifying compound which is a modifier of the activity of acetylcholine or glutamate neurotransmitters,

wherein said MT containing compound is to be administered to said subject,

wherein the MT-containing compound is an LMTX compound of the following formula:



wherein each of H_nA and H_nB (where present) are protic acids which may be the same or different,

and wherein p = 1 or 2; q = 0 or 1; n = 1 or 2; $(p + q) \times n = 2$,

or a hydrate or solvate thereof,

followed by treatment with said neurotransmission modifying compound.

29 The use as claimed in claim 28, wherein the Alzheimer's disease is mild Alzheimer's disease.

30 The use as claimed in claim 28 or claim 29 wherein said therapeutic treatment with LMTX is maintained for treatment timeframe with co-administration with the neurotransmission modifying compound,

followed by;

treatment with the neurotransmission modifying compound without the LMTX,

wherein optionally the treatment timeframe with co-administration is at least 2 months.

31 The use as claimed in any one of claims 28 to 30 wherein the therapeutic treatment is with an LMTX compound and optionally dosage as defined in any one of claims 2 to 15.

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32 The use as claimed in any one of the preceding claims, wherein the neurotransmission modifying compound is an acetylcholinesterase inhibitor.

33 The use as claimed in any one of claims 1 to 32, wherein the neurotransmission modifying compound is selected from donepezil; rivastigmine; and galantamine.

34 The use as claimed in any one of claims 1 to 32, wherein the neurotransmission modifying compound is an N-methyl-D-aspartate receptor (NMDA) receptor antagonist.

35 The use as claimed in any one of claims 1 to 31 or claim 34, wherein the neurotransmission modifying compound is memantine.