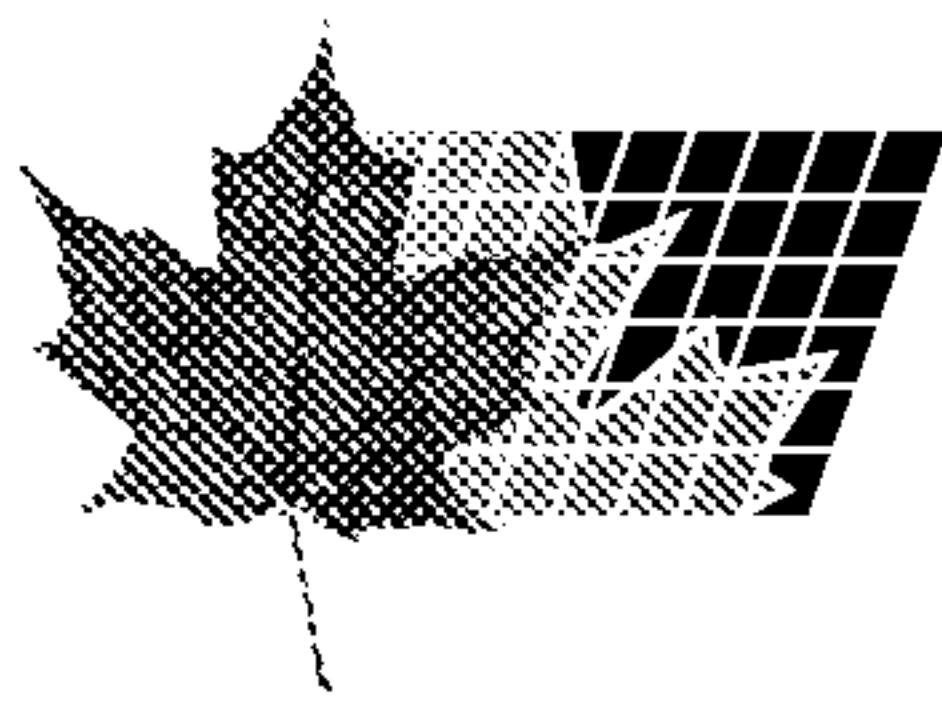




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(54) **MALEATE DE 5-(2-ETHYL-2H-TETRAZOLE-5-YL)-1-METHYLE-1,2,3,6-TETRAHYDROPYRIDINE**

(54) **5-(2-ETHYL-2H-TETRAZOL-5-Y1)-1-METHYL-1,2,3,6-TETRAHYDROPYRIDINE MALEATE**

(57) La présente invention concerne un sel d'addition d'acide maléique de 5-(2-éthyl-2H-tétrazol-5-yl)-1-méthyl-1,2,3,6-tétrahydropyridine, des compositions pharmaceutiques contenant ledit sel d'addition d'acide ainsi que leur utilisation dans le traitement de troubles provoqués par un dysfonctionnement du système de l'acétylcholine (AcCh) ou du système muscarinique.

(57) The present invention relates to a maleate acid addition salt of 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, pharmaceutical compositions containing the acid addition salt and the use thereof for the treatment of disorders caused by a malfunction of the acetylcholine (AcCh) or muscarinic system.

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(21) International Application Number: PCT/DK98/00294 (22) International Filing Date: 1 July 1998 (01.07.98) (30) Priority Data: 0781/97 1 July 1997 (01.07.97) DK (71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottliavej 9, DK-2500 Valby-Copenhagen (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): BECH SOMMER, Michael [DK/DK]; Aldershvilevej 23 A, DK-2880 Bagsværd (DK). NIELSEN, Ole [DK/DK]; Nystedvej 19, DK-2500 Valby-Copenhagen (DK). (74) Common Representative: H. LUNDBECK A/S; Petersen, John, Meidahl, Ottliavej 9, DK-2500 Valby-Copenhagen (DK).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: 5-(2-ETHYL-2H-TETRAZOL-5-Y1)-1-METHYL-1,2,3,6-TETRAHYDROPYRIDINE MALEATE (57) Abstract The present invention relates to a maleate acid addition salt of 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, pharmaceutical compositions containing the acid addition salt and the use thereof for the treatment of disorders caused by a malfunction of the acetylcholine (AcCh) or muscarinic system.		

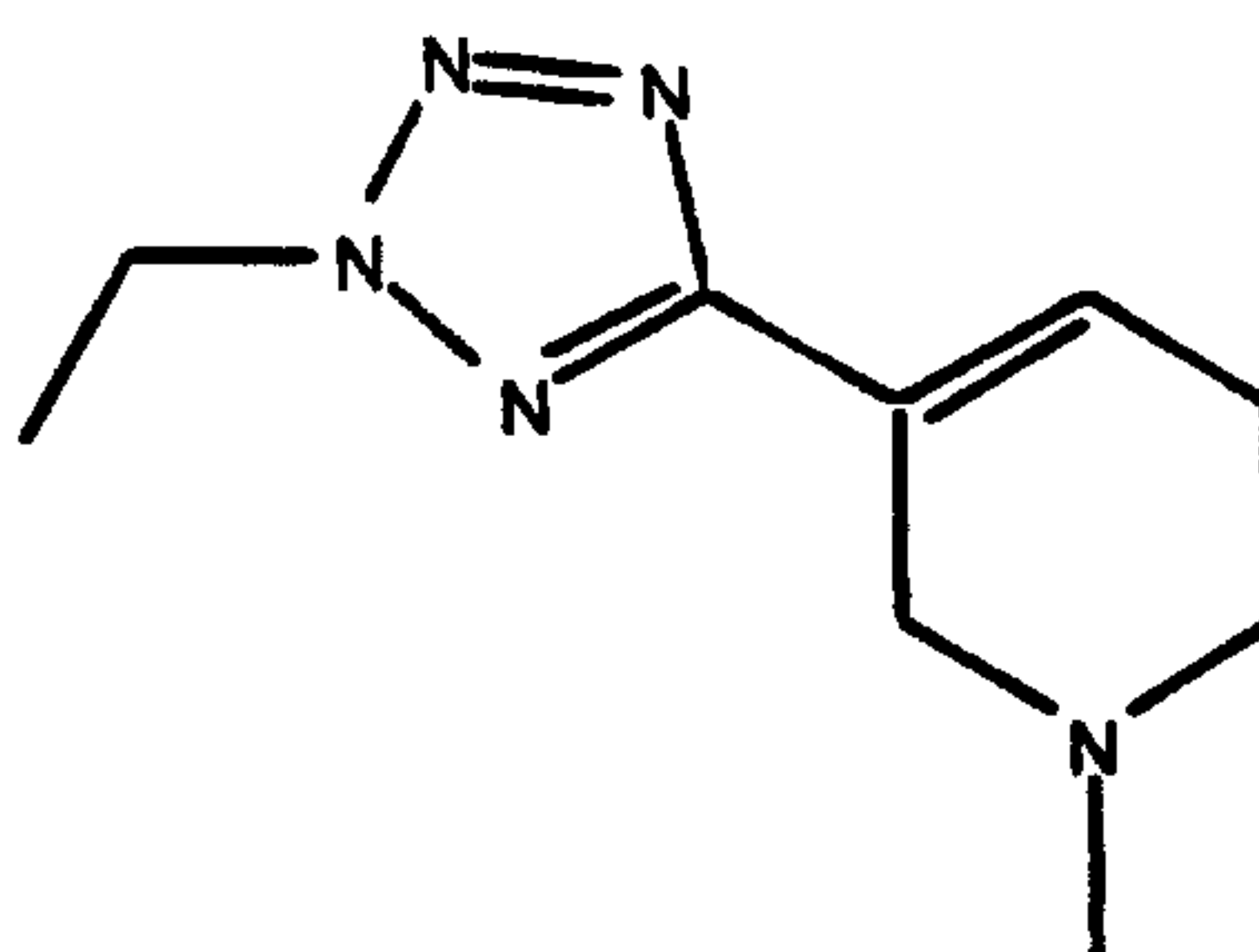
5-(2-Ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine maleate

The present invention relates to a maleic acid addition salt of 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, pharmaceutical compositions containing the acid addition salt and the use thereof for the treatment of diseases or disorders caused by a malfunction of the cholinergic or muscarinic system.

Background of the Invention

US patent No. 4,866,077 discloses a series of piperidine and tetrahydropyridine compounds substituted in position 5 with a 1,2,3-triazole or a tetrazole group. These compounds have high affinity to central AcCh receptors, including muscarinic M1 receptors, and are considered useful for the treatment of disorders involving malfunction of the cholinergic system, e.g. Alzheimer's disease, senile dementia, and impaired learning or memory function.

The structure-activity relationship of these compounds has been described by Moltzen et al., in *Med. Chem.* **1994**, 37, 4085-4099. The compound, 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine having the formula



which is the subject of the present invention, has been reported to be a partial agonist at muscarinic M1 receptors and an antagonist at muscarinic M2 and M3 receptors (*Subtypes of Muscarinic Receptors, The sixth International Symposium*, Nov. 9-12, **1994**, Fort Lauderdale). Ligands at muscarinic receptors with this pharmacological profile are considered of particular interest for the treatment of Alzheimer's disease.

Further, it has been demonstrated that 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine may be useful for the treatment of traumatic brain injury (TBI) and psychosis or other schizophreniform diseases (WO97/17074 and co-pending PCT application claiming priority from DK 620/97).

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TBI may be caused by various physical and neurological conditions or diseases such as conditions associated with trauma to the brain or spinal cord e.g. caused by physical forces acting on the skull or spinal column, ischaemia, stroke, arrested breathing, cardiac arrest, cerebral thrombosis or embolism, neurological problems
10 caused by AIDS, cerebral hemorrhage, encephalomyelitis, hydrocephalus, post-operative events, cerebral infections, concussions, or elevated intracranial pressure.

Psychosis means to include all forms of psychoses such as organic psychoses, drug induced psychoses, Alzheimer related psychoses, and psychoses or related
15 conditions associated with other mental disorders, such as paranoid personality disorder, ect.

The terms schizophrenia and schizophreniform diseases include all types of such disorders, e.g. catatonic, disorganised, paranoid, undifferential and residual schizo-
20 phrenia, and all conditions associated with such diseases, including the positive and negative symptoms thereof.

Unfortunately, the 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine free base is a liquid and as such not suitable for the production of solid pharmaceu-
25 tical preparations, such as tablets or capsules. As oral administration a solid entity is the preferred and most convenient method for the administration of a pharmaceutical, a solid form of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, suitably a pharmaceutically acceptable salt thereof, which can be mixed with various adjuvants or diluents and formed into tablets or filled in cap-
30 sules, is highly desirable.

The oxalic acid addition salt of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetra-

hydropyridine is specifically disclosed in US patent No. 4,866,077. However, while oxalic acid addition salts may be particularly useful for crystallization and purification purposes, they are not suitable for the preparation of pharmaceuticals due to the toxicity of oxalic acid.

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A pharmaceutically acceptable salt of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, the tartrate, has been described in Moltzen et al., *J. Med. Chem.* **1994**, 37, 4085-4099. Unfortunately, the tartrate is difficult to precipitate and recrystallize in large scale productions. Accordingly, the tartrate salt is not suitable
10 for commercial production of solid pharmaceutical preparations.

Surprisingly, it has now been found that precipitation and recrystallization of the corresponding maleic acid addition salt proceed smoothly even in large scale.

15 The Invention

It is the object of the present invention to provide a solid pharmaceutically acceptable form of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine suitable for large scale production of solid pharmaceutical entities, e.g. tablets or capsules.

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According to the present invention the maleic acid addition salt of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine and pharmaceutical compositions comprising said acid addition salt have been provided.

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The maleic acid addition salt according to the invention may be obtained by treatment of 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine or a salt derivative thereof with maleic acid in an inert solvent, followed by precipitation, isolation and optionally recrystallization by known methods and if desired followed by micronisation of the crystalline product by wet or dry milling or another convenient
30 process, or preparation of particles from a solvent-emulsification process.

Precipitation of the maleate salt is carried out in an inert aprotic solvent, preferably tetrahydrofuran (THF).

The maleate acid addition salt of the invention may be administered in any suitable way e.g. orally or parenterally, and the compounds may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the maleate of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tableting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in an amount from about 10 $\mu\text{g/day/kg}$ to 15 mg/day/kg body weight, preferably 25 $\mu\text{g/day/kg}$ to 10 mg/day/kg and most preferred 4-5- mg/kg/day body weight. Accordingly, a suitable daily dose is 500 μg to 1000 mg/day , preferably 1.0 to 500 mg/day and most preferred 300-400 mg/day .

The maleate acid addition salt according to the invention is readily soluble in water, alcohol and other polar solvents and may, if desired, be used for the preparation of solutions for injection.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the vehicle, preferably sterile water, adjusting the solution to the desired volume, sterilization of the solution, and filling in suitable am-

poules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, ect.

The invention will be illustrated in the following examples. The examples may not
5 be construed as limiting.

The 5-(2-ethyl-2*H*-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, oxalate starting material can be prepared as described in US patent No. 4,866,077.

Example 1**5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, maleate**

5 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, oxalate (5.6 kg) was suspended in demineralized water (22 L). Ethyl acetate (17 L) was added, and a cooled solution (15-20 °C) of potassium hydroxide (2.8 kg) in demineralized water (12.5 L) was added with stirring and cooling. pH was adjusted to 10 by adding aqueous potassium hydroxide. The aqueous layer was further extracted with ethyl
10 acetate (2 x 11 L). The combined organic extracts were dried with sodium sulphate (3.8 kg) and evaporated in vacuo until a pot temperature of 75-80 °C was reached. The residue was dissolved in tetrahydrofuran (11 L), and a solution of maleic acid (2.4 kg) in tetrahydrofuran (11 L) was added with stirring. The solution was cooled to approximately 15 °C and stirred for a minimum of 1 hour.

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The precipitate was isolated on a nutche filter, and washed with tetrahydrofuran (2 x 2 L). The wet filtercake was recrystallized once from tetrahydrofuran (13 L). The recrystallized material was isolated on a nutche filter, washed with tetrahydrofuran (5 L), and finally dried in vacuo at 65 °C overnight. Yield 5.0. kg (83%) mono-
20 maleate. M.p. 116 °C.

Example 2**5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, maleate**

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Liberation of the free base: A nitrogen purged reactor was charged with 62-64 kg 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, oxalate, water, and toluene. The mixture was stirred and cooled to below 10 °C while adding potassium hydroxide pellets dissolved in water until pH > 12 was achieved. The layers were
30 separated, the aqueous layer re-extracted with toluene and subsequently discarded.

The combined organic phases were washed with water. Toluene was distilled off in vacuo at a temperature of not more than 50 °C.

Precipitation: The residue was re-dissolved by adding THF and maleic acid (26.5-
5 27.5 kg) while heating to reflux. The temperature of the reaction mixture was adjusted to approx. 50 °C. The solution was left with slow agitation and voluntary cooling for crystallization⁽¹⁾. The slurry was cooled to below 20 °C and isolated. The product was washed with tetrahydrofuran and dried in vacuo yielding 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, mono-maleate.

10 Recrystallisation: A reactor was charged with 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, maleate, and tetrahydrofuran. The solution was heated to reflux and then allowed to crystallize ⁽¹⁾. The product was isolated, washed several times with THF, and dried in vacuo.

15 ⁽¹⁾ If necessary, the solution may be seeded with 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine, maleate from a previous batch.

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Claims:

1. A maleic acid addition salt of 2-ethyl-5-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)-2*H*-tetrazole.
2. The maleic acid addition salt according to claim 1 which is the mono-maleic acid addition salt.
3. A pharmaceutical composition comprising a maleic acid addition salt according to claims 1 to 2 together with at least one pharmaceutically acceptable carrier or diluent.
4. A method for the treatment of a disorder or disease caused by malfunction of the acetylcholine (AcCh) or muscarinic system, comprising administering a therapeutically effective amount of a maleic acid addition salt according to claims 1 to 2 to a subject suffering from such a disorder.
5. The method according to claim 3 wherein Alzheimer's disease, traumatic brain injury, or psychotic disorders are treated.
6. The use of a maleic acid addition salt according to claims 1 to 2 for the preparation of a pharmaceutical composition for the treatment of a disorder or disease caused by malfunction of the acetylcholine (AcCh) or muscarinic system.
7. The use according to claim 5 wherein the disease or disorder is Alzheimer's disease, traumatic brain injury, or psychotic disorders.
8. A method for the preparation of maleic acid addition salt according to claims 1 to 2 characterized in that the acid addition salt is precipitated from a solution of 2-ethyl-5-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)-2*H*-tetrazole, THF and maleic acid.