(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 January 2014 (30.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/016430 A1

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61K 31/55* (2006.01)

(21) International Application Number:
PCT/EP2013/065880

(22) International Filing Date:
29 July 2013 (29.07.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/676,348 27 July 2012 (27.07.2012) US
12178187.6 27 July 2012 (27.07.2012) EP

(71) Applicant: **NEURODYN LIFE SCIENCES INC.** [CA/CA]; Suite 508 NRC-INH, 550 University Ave, C1A 4P3 Charlottetown (CA).

(72) Inventor: **MAELICKE, Alfred**; Hinter der Hecke 1, 55268 Nieder-Olm (DE).

(74) Agent: **BOECKH, Tobias**; HERTIN Anwaltssozietät, Kurfürstendamm 54/55, 10707 Berlin (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

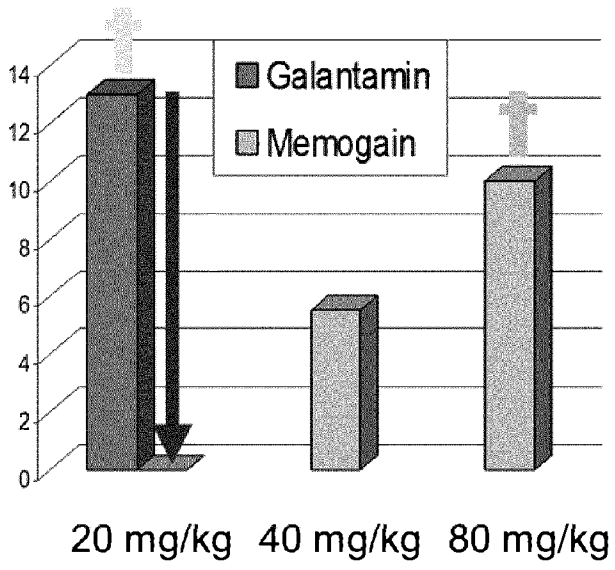
Published:

— *with international search report (Art. 21(3))*

(54) Title: ENHANCED BRAIN BIOAVAILABILITY OF GALANTAMINE BY SELECTED FORMULATIONS AND TRANSMUCOSAL ADMINISTRATION OF LIPOPHILIC PRODRUGS

(57) Abstract: The invention relates to selected administration routes for CNS (central nervous system) therapeutics and highly soluble salts, solutions, emulsions or powder formulations thereof, having optimal brain delivery due to the mode of administration and the chemical nature of the compounds of the invention.

Fig. 10



WO 2014/016430 A1

ENHANCED BRAIN BIOAVAILABILITY OF GALANTAMINE BY SELECTED FORMULATIONS AND TRANSMUCOSAL ADMINISTRATION OF LIPOPHILIC PRODRUGS

DESCRIPTION

The invention relates to selected administration routes for CNS (central nervous system) therapeutics and highly soluble salts, solutions, emulsions or powder formulations thereof, having optimal brain delivery due to the mode of administration and the chemical nature of the compounds of the invention. The therapeutic compounds of the present invention relate to lipophilic pro-drugs of pharmacologically active compounds that - as prodrugs - are inactive in regard to their major targets in the CNS, in particular cholinesterases and/or nicotinic acetylcholine receptors. Via cleavage by endogenous enzymes, the pharmacologically active parent drugs are produced and act as allosterically potentiating ligands (APL) on nicotinic acetylcholine receptors (nAChR), and/or as reversible inhibitors of acetylcholinesterases (AChE) and other cholinesterases (ChE). To maximize transport through the blood-brain barrier (BBB) and in order to protect the prodrugs of the invention from cleavage by endogenous esterases before crossing the BBB to their site(s) of action, the pro-drugs are designed to be highly lipophilic (logP > 2.5) and are delivered via transmucosal absorption pathways in the oral or nasal cavity.

BACKGROUND OF THE INVENTION

Currently, the first line of drug treatment for Alzheimer's disease (AD) is the use of cholinesterase inhibitors, such as donepezil, rivastigmine and galantamine. Among these, galantamine has been shown to have a distinct second mode of action, i.e. allosterical sensitisation of nicotinic acetylcholine receptors (Maelicke A; Albuquerque E X (1996) New appoaches to drug therapy in Alzheimer's dementia. Drug Discovery Today 1, 53-59). Galantamine enhances the probability of channel opening induced by submaximal concentrations of acetylcholine (ACh), or choline (Ch), or other nAChR agonists. Because progression of AD is associated by an increasing loss of nAChR, the APL-enhanced activity of nicotinic receptors is a suitable symptomatic and possibly also disease-modifying treatment for AD and other forms of dementia (Storch A et al. (1995). Physostigmine, galantamine and codeine act as noncompetitive nicotinic agonists on clonal rat pheochromocytoma cells. Eur J Biochem 290: 207-219; Kihara T et al. (2004) Galantamine modulates nicotinic receptors and blocks Aß-enhanced glutamate toxicity. Biochem Biophys Res Commun 325: 976-982; Akata K et al. (2011) Galantamine-induced amyloid-clearance mediated via stimulation of microglial nicotinic acetylcholine receptors. J Biol Chem 286; Maelicke A (2006) Allosteric sensitisation

of brain nicotinic receptors as a treatment strategy in Alzheimer's dementia. In: Therapeutic Strategies in Dementia (Eds: Ritchie CW, Ames DJ, Masters CL, Cummings J), Clinical Publishing, Oxford, 2006; 153-172)).

In contrast to rivastigmine and donepezil, galantamine does not significantly enrich in the human brain in comparison to blood plasma. This is because galantamine, being a plant alkaloid rather than a rationally designed drug, is much less lipophilic than the other two cholinesterase inhibitors used as drugs in AD and hence exhibits in steady-state only a rather low brain-to-blood concentration ratio (BBCR < 2).

To enhance the lipophilicity of CNS drugs and their passage through the blood-brain barrier, hydrophobic side chains have been appended to the basic alkaloid structures, as described in EP1 940 817 B1 and WO 2009/127218 A1. The attached groups were selected in order to increase the BBRC to larger than 5.

Similar to other cholinesterase inhibitors, galantamine has a clinically significant level of mechanism-based gastro-intestinal (GI) side effects, including nausea, vomiting and diarrhea (Loy C et al., Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database of Systematic Reviews 2006, Issue 1). To accommodate patients to these side effects, cholinesterase inhibitors usually are initially administered at a low (non-efficacious) dose, with the dose being carefully up-titrated to an efficacious one, within a period of months. Moreover, the maintenance dose often is adjusted to what the patients experience as an acceptable level of GI side effects, making it likely that most, if not all, patients never achieve treatment with the most effective dose. Accordingly, cholinesterase inhibitors are generally perceived as of only low effectiveness and as associated with unpleasant side effects. In light of the prior art regarding the administration of galantamine, it becomes apparent that the potential therapeutic efficacy of galantamine has never been able to be applied in human subjects to its full extent due to the poor brain-to-blood concentration ratio and significant peripheral side effects arising from poor brain delivery.

Because galantamine is known to affect motor and evacuative function of intestinal tissue (Turiiski VI et al. (2004), *in vivo* and *in vitro* study of the influence of the anticholinesterase drug galantamine on motor and evacuative functions of rat gastrointestinal tract. Eur J Pharmacol 498, 233–239), a reduction in GI side effects of galantamine was attempted by intranasal rather than oral administration of the drug (Leonard AK et al. (2007), *In vitro* formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response *in vivo*. Int J Pharmaceut 335: 138-146).

Because of the limited volume of spray that can be applied in one spray event to each nostril, the intranasal route of administration requires highly soluble drug product formulations. This was only in part achieved for galantamine by replacing in the hydrobromide of the drug the bromide ion by lactate or gluconate. This change in salt form did not significantly improve transport through the BBB of galantamine, as it is the rather hydrophilic and polar galantamine base that is resorbed at the nasal epithelium and then transported across the blood-brain barrier. Because of these physicochemical limitations, galantamine and its tertiary and quarternary nitrogen salts exhibit brain-to-blood concentration ratios below 2, meaning that such drugs must be administered in rather large quantities in order to achieve significant drug levels in the target organ brain. Sufficiently effective doses in the brain of such hydrophilic drugs are therefore achieved at the expense of considerable levels of peripheral side effects, in particular gastro-intestinal side effects. It can be concluded that salt formulations of galantamine have not provided a satisfactory solution for enhancing the brain drug distribution via the BBB.

As described previously (WO2009/127218 A1), the relatively hydrophilic parent drugs of interest can be reformulated by chemical conversion to lipophilic ester pro-drugs. Alcoholic OH groups have been used for attaching aliphatic, aromatic or heteroaromatic carboxylic acids to the parent drug thereby (i) partially or fully inactivating them pharmacologically, and (ii) significantly enhancing their lipophilicity and BBB penetration.

Although ester formation is a commonly employed approach to increase the lipophilicity of polar molecules having limited BBB penetration, the abundance of nonspecific esterases in brain and peripheral tissues limits the effectiveness of this approach in enhancing brain/plasma concentration ratios of drugs. To maximize brain drug levels by the pro-drug approach, the kinetics of absorption, BBB penetration and bioconversion of pro-drug to drug in the target organ brain have to be sufficiently fast in order to successfully compete with elimination from brain of the less lipophilic drug after its generation. There remain therefore significant hurdles in the development of strategies, methods and/or medicinal agents that allow or exhibit reliable penetration of the BBB and are cleaved in the target organ (brain), in order to provide an enhanced amount of active substance in the brain without leading to cleavage in other organs or tissues of the body, which leads in many cases to substantial side-effects during treatment.

The possibility of intranasal administration of galantamine derivatives is disclosed in US 2009/0253654 A1. No mention is made of enhanced delivery to the brain or of means of avoiding in vivo enzymatic cleavage by endogenous esterases of the ester prodrug compounds post-administration. The salts and concentrations of the compounds disclosed in US 2009/0253654 A1 represent arbitrary disclosures without regard to the in vivo properties of

the compounds. Neither specific salts nor transmucosal administration routes are disclosed with respect to GLN 1062.

WO2009/127218 A1 and Maelicke et al (J Mol Neurosci, 2010, 40:135-137) disclose GLN 1062 as such and its administration in the treatment of brain disorders with cognitive deficit. No mention is made of particular modes of administration or of particular salts. These earlier disclosures are based on intravenous administration of the compounds disclosed therein. Such bolus injections permit very fast distribution from blood to other organs, including the brain, and hence reduce the probability of enzymatic cleavage prior to reaching the BBB and distribution to the brain. Intravenous administration is however not acceptable for daily patient self-administration. More easily administered but equally effective alternatives are required.

Leonard AK et al. (2007, Int J Pharmaceut 335: 138-146) discloses intranasal administration of the lactate salt of galantamine. No particular effect is prescribed to the use of the lactate salt. The polar galantamine base is resorbed at the nasal epithelium and then transported across the blood-brain barrier, but only poorly, according to its limited propensity for brain drug distribution via the BBB. US 2004/0254146 discloses various salts of galantamine including lactate and gluconate salts and their administration in Alzheimer's disease. Neither US 2004/0254146 nor Leonard AK et al. is relevant for administration of salts of GLN 1062, which - due to its prodrug properties - represents the solution to an entirely different technical problem when compared to galantamine.

SUMMARY OF THE INVENTION

Transmucosal routes of delivery for the compounds described herein in the oral and nasal cavity have been examined as non-invasive routes of pro-drug administration best suited to achieve enhanced levels of drug in the brain. For systemic drug delivery, transmucosal routes are enhanced by prodrug salt formulations that accommodate to the structure and environment of the particular absorption area.

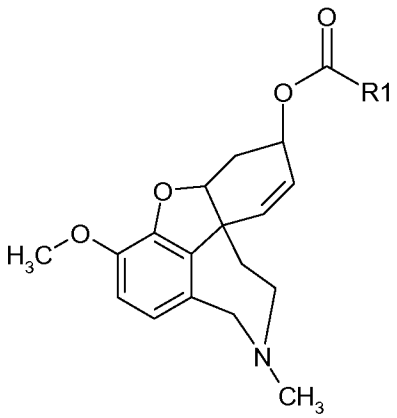
The advantageous transport properties of the pro-drugs discussed herein can be achieved when the pro-drugs are administered by intravenous injections, but less well, or only to a very small extent, when they are administered orally as tablets. This is because the pro-drugs are esters that have now been found to be instable in acidic environment (such as exists in the stomach) and are also cleaved enzymatically in many tissues, including in the intestines and in the liver (first-pass effect). In light of these findings and the problems of the administration methods of the prior art, and in order to take advantage of the nature of the pro-drugs in the treatment of CNS diseases, the invention makes use of administration routes that avoid the gastro-intestinal tract and the first-pass effect. These routes provide brain delivery about as

efficiently as intravenous injection, which due to significant medical risk is normally not suited for reliable self-administration. The invention provides special pharmaceutical formulations to be used for the selected routes of administration that optimize rapid resorption and uptake of prodrug into the brain.

In light of the prior art the technical problem underlying the present invention is to provide alternative or improved means for enhanced bioavailability of the CNS therapeutics described herein, thereby providing effective treatment of brain diseases associated with cognitive impairment.

This problem is solved by the features of the independent claims. Preferred embodiments of the present invention are provided by the dependent claims.

Therefore, an object of the invention is to provide a chemical substance according to Formula I for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein said treatment comprises transmucosal administration, selected from intranasal, sublingual or buccal administration, of a therapeutically effective amount of said substance,



Formula I

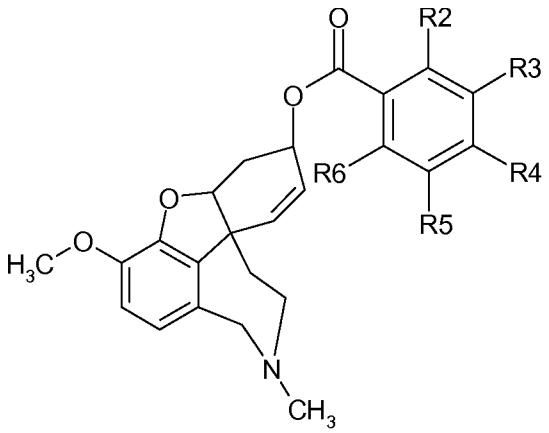
wherein

R1 = aromatic or heteroaromatic 5- or 6-membered ring, such as optionally substituted benzene, naphthaline, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole; or straight or branched chained aliphatic residues, such as CH(C2H5)CH3, CH2-C(CH3)3, cyclopropane or preferably an aliphatic residue comprising more than 5 C atoms, more preferably 6 C atoms, or more than 10 C atoms, such as a fatty acid residue.

The invention relates therefore primarily to the use of, or a method of treatment comprising administration of, the chemical substance as described herein for the treatment of brain disease associated with cognitive impairment by administering a therapeutically effective

amount of said chemical substance by a transmucosal route selected from intranasal, buccal and/or sublingual administration.

In a preferred embodiment the chemical substance of the present invention is characterised in that the substance is selected from Formula II,



Formula II

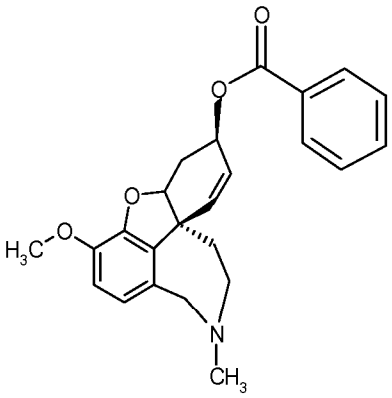
wherein

R2-R6 comprise of any substituent selected from H, halogen, optionally substituted C_1-C_3 alkyl or cyclopropyl, OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl, N-dialkyl, optionally substituted aryl or heteroaryl, whereby neighbouring substitutents can cooperate to form an additional ring.

The optional substitution of the substituents described in Formula I and II relates to substitution with an alkyl, OH, halogen, NH_2, alkyl-NH_2 or NO2 group, or other substituent described with regard to those compounds provided Table 2.

Compounds according to Formula I or II with aromatic or heteroaromatic 5- or 6-member rings at the R1 position of Formula I are preferred; examples of such compounds are found in Table 2, namely GLN-1062, GLN-1081, GLN-1082, GLN-1083, GLN-1084, GLN-1085, GLN-1086, GLN-1088, GLN-1089, GLN-1090, GLN-1091, GLN-1092, GLN-1093, GLN-1094, GLN-1095, GLN-1096, GLN-1097, GLN-1098, GLN-1099, GLN-1100, GLN-1101, GLN-1102, GLN-1103, GLN-1104, GLN-1105, GLN-1113.

In a particularly preferred embodiment the chemical substance of the present invention is characterised in that the substance is GLN-1062, whereby GLN-1062 is represented by



GLN-1062

The transmucosal administration of the present invention is based on the unexpected realisation that the compounds of the present invention exhibit relatively low stability when administered via oral administration. Cleavage of the ester group occurs in the gut and liver, in addition to other tissues of the body. The transmucosal administration provides an enhanced transport into brain and blood and corresponding enhanced efficacy by avoiding the first pass effect and cleavage of the prodrugs during passage through the gastro-intestinal tract and other organs.

Transmucosal administration of galantamine according to the prior art provides no such enhancement, as galantamine is not susceptible to cleavage by endogenous esterases. The surprising concept of the invention is based on the avoidance of cleavage of the prodrug post-administration but before partition via the BBB, thereby enhancing brain transport and increased relative concentration of the active substance after cleavage, which under conditions of the proposed routes of administration and drug formulations occurs primarily in the brain.

It was entirely surprising that the transmucosal administration of the prodrugs as described herein would lead to further enhancements in brain delivery of the prodrug and ultimately (after cleavage of the prodrug) to an effective dose of galantamine in the brain of subjects.

The invention therefore relates to a chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment as described herein, wherein transmucosal administration provides avoidance and/or reduction of post-administration cleavage of the ester group of said substance by endogenous esterases.

This aspect of the invention represents a novel technical effect not previously disclosed or suggested in the art. The relatively low stability of the ester moiety of Memogain in the gastro-intestinal tract and liver has not been previously described in the art. A skilled person would therefore not have attempted to provide the modes of administration, or the salts as described

herein, in order to improve delivery of the uncleaved compound to the brain. As demonstrated in the examples provide herein, the recognition of post-administration cleavage after oral administration in form of tablets has enabled the provision of the transmucosal administration of the invention, in addition to the salts as described herein.

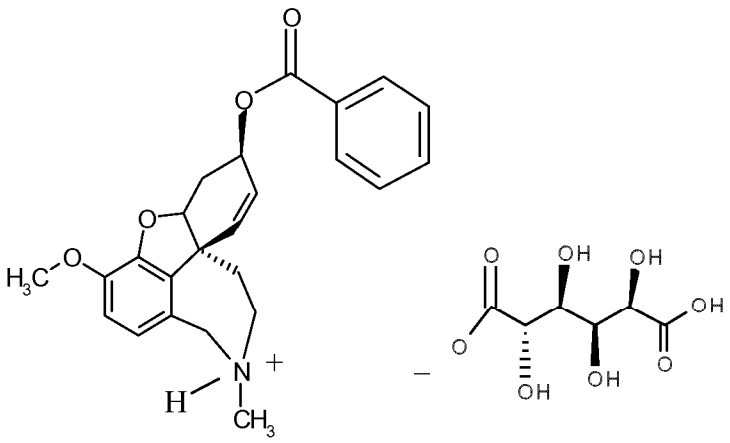
The avoidance of in vivo esterase cleavage – with regard to the significant improvements obtained by transmucosal administration and the enhanced delivery of the salts described herein – enables treatment of patients who previously have avoided treatment with ChE inhibitors due to strong gastro-intestinal side effects associated with orally administered tablets. The improved brain delivery via transmucosal administration, in particular of high concentration aqueous solutions of Memogain salts, permits dosage regimes which were until now simply not possible with either galantamine itself (due to significant side effects) or Memogain (due to in vivo degradation).

Despite showing promising effects, galantamine treatment is associated with low compliance (of approximately 30%) due to strong unwanted side effects, indicating the strong need in the field for more sustainable therapeutic approaches. The administration routes and salts described herein enable treatment regimes with Memogain and its active principle galantamine that have never been achieved before, potentially enabling treatment of severe neurodegenerative disease – in patients who previously were not able to be effectively treated due to unwanted side effects – with the means and methods of the present invention.

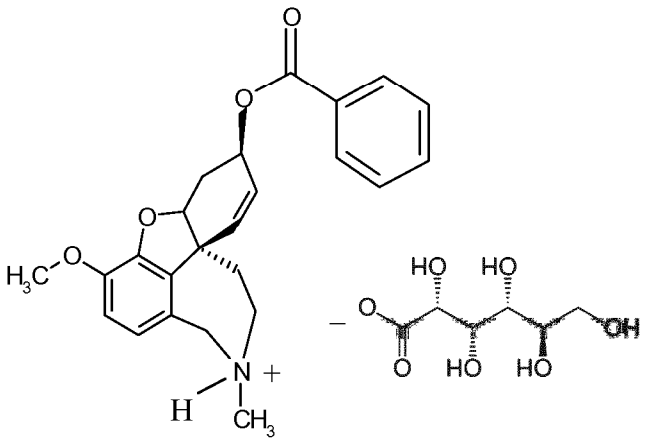
In a preferred embodiment the chemical substance of the present invention is characterised in that the chemical substance is present as a salt, preferably a lactate, gluconate, maleate or saccharate salt.

In a preferred embodiment the salt comprises of stoichiometric and/or non-stoichiometric salts and/or hydrates of the chemical substances according to Formula I, II or III, whereby the salt is preferably described as:
Substance of Formula I, II or III · n HX · m H2O,
whereby n, m = 0 – 5 and n and m can be the same or different, and HX = an acid, selected preferably from lactic acid, gluconic acid, maleic acid or saccharic acid.

The invention also relates to a chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance is the saccharate salt of GLN 1062. The saccharate salt of the present invention enables surprisingly high concentrations of up to 70% in water, providing an improved stable solution for high transmucosal doses of prodrug.



One preferred example of the invention relates to a chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance is the gluconate salt of GLN-1062.



The gluconate salt of GLN 1062 has a high solubility, of 40% and more in water, especially in temperatures of around 25 to 50 degrees C. This high solubility at elevated temperatures can be used to produce high concentration liquid solutions of the gluconate salt of GLN 1062, which is relatively stable and can be administered for some days after creation of the solution.

The invention also relates to a chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance is the maleate salt of GLN 1062.

The invention also relates to a chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance is the lactate salt of GLN 1062.

The salts of the present invention also additionally show the surprising property of improved taste (reduced bitterness), reducing the need for taste masking components in the composition. The salts of the invention also show reduced numbing effects, such are as known for galantamine, when administered transmucosally. Due to their fast and efficient uptake the numbing (analgesic) effect and poor taste are reduced compared to those compositions described in the art.

In one embodiment the chemical substance of the present invention is characterised in that the chemical substance has solubility in water of at least 10%, preferably > 20%, or more preferably >30% weight per volume (w/v).

The enhanced solubility of the salts as described herein represents a surprising and beneficial development. The solubility of the salts described herein enables higher concentrations of the compound to be administered in smaller volumes, thereby further enhancing the direct administration to the brain via transmucosal administration as described herein.

The transmucosal administration in combination with the salts of the prodrugs of the present invention exhibits a synergistic effect. The enhanced solubility allows higher concentrations of chemical substance to be administered, thereby enabling larger amounts of the active substance after cleavage (galantamine) to be active in the brain. The transport of substance (measured either by substance itself in the brain or by galantamine levels in the brain after cleavage of the prodrug) is greater than the expected sum of effects of transmucosal administration, administration of salts and administration of the prodrug when considered individually.

The prodrug properties of the compounds described herein are exploited and enhanced in a synergistic manner by the transmucosal application of their salts. The transmucosal administration of salts of prodrugs (with high solubility) provides a unique combination of administration parameters that enable dosage regimes previously not possible with galantamine, or salts of galantamine.

In one embodiment the present invention is characterised in that the chemical substance is administered at a dosage of from 0.1 to 200 mg, 1 to 100 mg, preferably 2 to 40 mg, preferably from one to three times daily, more preferably twice daily, and even more preferably only once daily.

The dosage regimes as described herein represent novel and surprisingly beneficial developments in comparison to the prior art with respect to effective galantamine treatment. The biological and medical effect of galantamine has never previously been tested with regard to the potential effect generated by administration at high doses. Many patients in need of galantamine treatment have not been able to be treated due to the significant side effects that occur with regular doses of galantamine. In order to obtain meaningful levels of galantamine in the brain of subjects, the prior art teaches high but also highly toxic doses. Because only a small fraction of orally or intranasally administered galantamine drug reaches the brain, the dose required to show an effect during treatment of brain disease is often intolerably high due to the large amount of galantamine in other tissues of the body, thereby causing unwanted side effects.

The dosages of the present invention are enabled by the transmucosal administration of the prodrugs disclosed herein. Due to enhanced brain delivery of the hydrophobic prodrugs, in combination with further enhanced delivery due to transmucosal administration, smaller doses of the prodrug are required in order to achieve the same or greater effect of galantamine in the brain after prodrug cleavage and release of the active compound. It is entirely surprising that also lower doses of the prodrugs of the invention, for example GLN 1062, within the ranges of the invention, lead to more pronounced and/or more potent effect in cognitive recovery compared to oral administration of galantamine.

These dosage regimes are particularly beneficial when administered in the form of salts of the compounds as described herein.

In one embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance or salt thereof is administered intranasally, bucally or sublingually as a 2 to 40% weight per volume (w/v) solution at an amount of 20 to 100 microliters, preferably in a single (intranasal or oral) spray event, one to three times daily.

At these doses effective cognitive recovery is possible in patients with brain diseases with no (or only very minor) observable side effects. It was at the time of the invention unexpected, that through the combination of prodrug (preferably GLN 1062) and transmucosal administration such dosages could lead to an effective galantamine treatment through a dosage regime comprising a relatively small number of administration events of relatively small volumes of active compound (via sprays or administration of oral transmucosal formulations).

In one preferred embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the chemical substance or salt thereof is administered intranasally, bucally or sublingually as a 10% weight per volume (w/v) solution at an amount of 50 microliters, preferably in a single (intranasal or oral) spray event, one to three times daily.

In one embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the brain disease to be treated is Alzheimer's and/or Parkinson's disease, the chemical substance is the gluconate or saccharate salt of GLN 1062, which is administered intranasally, bucally or sublingually as a 2 to 40% weight per volume (w/v) solution at an amount of 20 to 100 microliters, preferably in a single (intranasal or oral) spray event, one to three times daily.

The salt formulations of GLN 1062 show surprisingly high solubility, allowing high doses of GLN 1062 to be applied with ease by the patients themselves in small volumes, providing therapeutically relevant results without the need for much higher doses of the prodrugs or their active parent drug galantamine and without the occurrence of significant side effects.

In one embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the brain disease to be treated is Alzheimer's disease, the chemical substance is the gluconate salt of GLN 1062, which is administered intranasally, bucally or sublingually as a 10% weight per volume (w/v) solution at an amount of 50 microliters, preferably in a single intranasal spray event, twice daily.

In one embodiment the chemical substance of the present invention is characterised in that intranasal application is carried out by administering a therapeutically effective amount of the chemical substance using a suitable metered dose device such as a atomizer, sprayer, pump spray, dropper, squeeze tube, squeeze bottle, pipette, ampule, nasal cannula, metered dose device, nasal spray inhaler, nasal continuous positive air pressure device, and/or breath actuated bi-directional delivery device.

In one embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the sublingual administration is carried out by administering a therapeutically effective amount of the chemical substance under the tongue by placing one or more drops of a solution, or an amount of particulate in the form of freeze-dried powder or emulsion

underneath the tongue and/or by spraying the underside of the tongue with a preselected volume of a liquid composition comprising the chemical substance.

In one embodiment the invention relates to a chemical substance as described herein for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein the buccal administration is carried out by administering a therapeutically effective amount of the chemical substance to the buccal vestibule inside the mouth between the cheek and the gums as a freeze-dried powder or emulsion, or an orally disintegrating or orodispersible tablet (ODT).

In one embodiment the chemical substance of the present invention is characterised in that the subject is a mammal, preferably a human.

In one embodiment the chemical substance of the present invention is characterised in that the brain disease to be treated is selected from Alzheimer's and/or Parkinson's disease, other types of dementia, schizophrenia, epilepsy, stroke, poliomyelitis, neuritis, myopathy, oxygen and nutrient deficiencies in the brain after hypoxia, anoxia, asphyxia, cardiac arrest, chronic fatigue syndrome, various types of poisoning, anaesthesia, particularly neuroleptic anaesthesia, spinal cord disorders, inflammation, particularly central inflammatory disorders, postoperative delirium and/or subsyndronal postoperative delirium, neuropathic pain, abuse of alcohol and drugs, addictive alcohol and nicotine craving, and/or effects of radiotherapy.

In one embodiment the chemical substance of the present invention is characterised in that the distribution of the chemical substance in a patient after administration exhibits a brain-to-blood concentration ratio of more than 5, preferably more than 10, more preferably between 15 and 25.

The invention further relates to the use of the chemical substance as described herein for the treatment of brain disease associated with cognitive impairment by administering a therapeutically effective amount of said chemical substance by a transmucosal route selected from the group consisting of intranasal, buccal and/or sublingual administration.

In another aspect the present invention relates to a pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 of the present invention and preferably one or more pharmaceutically acceptable carriers for use in the treatment of brain diseases associated with cognitive impairment in a mammal, characterised in that the composition is suitable for intranasal, buccal and/or sublingual application. The invention therefore relates to nose drops or under-the-tongue drops in the form of a liquid composition for transmucosal administration via nasal or buccal mucous membranes.

The invention relates to a pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 of the present invention for use as a medicament in the treatment of brain diseases associated with cognitive impairment via transmucosal administration, wherein the composition is an aqueous solution, comprising 2 to 40%, preferably 5 to 15% and more preferably 10% weight per volume (w/v) of the chemical substance.

In one embodiment the invention relates to a pharmaceutical composition, wherein the composition comprises N-ethylpyrrolidone. In a preferred embodiment the invention relates to a pharmaceutical composition, wherein the composition comprises a self-microemulsifying drug delivery (SMEDD) system. Such compositions preferably comprise glyceryl caprylate, polyethyleneglycol, propyleneglycol and/or diethyleneglycolemonoethylether.

The invention also relates to a pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 of the present invention for use as a medicament in the treatment of brain diseases associated with cognitive impairment via transmucosal administration, wherein the composition comprises a sustained release formulation comprising chitosan.

A further embodiment of the invention relates to a pharmaceutical composition comprising a micronized powder formulation of the chemical substance to be administered, preferably with a particle size of 0.01 to 1000 microns, preferably 0.1 to 100 or 1 to 10 microns.

The invention relates to a pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 of the present invention for use as a medicament in the treatment of brain diseases associated with cognitive impairment via transmucosal administration, wherein the composition comprises a sublingual tablet, preferably comprising lactose monohydrate, corn starch, polyvinylpyrrolidone (PVP) and/or magnesium stearate, and optionally with a flavouring agent. Alternatively the composition may comprise a sublingual tablet comprising mannitol, sodium starch glycolate, croscarmellose, ascorbic acid and/or magnesium stearate, optionally with a flavouring agent.

The invention also relates to a pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 of the present invention for use as a medicament in the treatment of brain diseases associated with cognitive impairment via transmucosal administration, wherein the composition comprises a multi-layered tablet with digestive acid resistant coating, such as comprising eudragit.

In a preferred embodiment the pharmaceutical composition of the invention comprises the substance to be administered at 2 to 40 % weight per weight (w/w), preferably 10 to 30%, or

more preferably 5, 10, 20 or 30 % weight per weight (w/w) in a composition in the form of a self-microemulsifying drug delivery (SMEDD) system, sustained release formulation comprising chitosan, micronized powder formulation or sublingual or buccal tablet.

In a particularly preferred embodiment, the CNS therapeutic is the established anti-dementive drug galantamine, the pro-drug is the benzoic ester of galantamine (galantamine benzoate, GLN 1062, otherwise mentioned as "Memogain"), and the salt forms used for intranasal delivery are preferably the lactate, gluconate, maleate or saccharate salts of said benzoylester of GLN 1062. GLN 1062 is also known as (4a*S*,6*R*,8a*S*)- 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-Benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, 6-benzoate. For example, the gluconate salt of Memogain is also known as the galantamine benzoate gluconate.

The invention also relates therefore to a method of treatment for brain disease associated with cognitive impairment by administering a therapeutically effective amount of the above described chemical substances by a transmucosal route selected from the group consisting of intranasal, buccal and/or sublingual administration. The method of treatment of the present invention may also be further defined by embodiments of the invention provided herein with respect to the administration regime, the substance itself and/or other administration parameters.

DETAILED DESCRIPTION OF THE INVENTION

A detailed description of the present invention encompasses the following developments:

(1) In preferred embodiments pro-drugs of galantamine are provided that are significantly more lipophilic than their parent compounds, thereby enhancing their passive transport through the blood-brain barrier (BBB) into the brain.

(2) These pro-drugs are pharmacologically inactive and hence do not produce any significant GI or other side effects, as long as they remain un-cleaved in the particular tissue. After enzymatic cleavage, from each molecule of pro-drug one molecule of parent drug is formed, thereby producing the full pharmacological effect of the drug. If cleavage is preferentially in the brain, due to enhanced distribution into this organ, and the availability of suitable endogenous enzyme(s) therein, a significantly higher concentration of drug at the target sites in the CNS and consequently larger medically beneficial effects are achieved.

(3) Preferential transport to the target organ brain is further optimized in a surprising and beneficial manner by transmucosal routes of administration in the oral or nasal cavity.

(4) High-dose formulations and extended-release formulations of the pro-drugs further optimize the pharmacokinetics of uptake into the brain and maintain drug levels therein for optimal effectiveness of action.

Taken together, these features of the formulations of pro-drugs described herein, foster delivery to the brain of much higher concentrations of drug than can be achieved by oral administration in form of tablets of the unmodified drug. The improved distribution of the drug to the brain dramatically reduces all locally produced side effects in the GI tract, thereby permitting to immediately apply an efficacious dose of the drug to its CNS-located target molecules, e.g. nicotinic receptors and cholinesterases.

As the blood-brain barrier (BBB), located at the level of the brain capillaries, is the major barrier to the passage of drugs from the blood compartment to the brain, initial focus on optimizing penetration of the pro-drugs through the BBB yielded promising results. The brain microvessel endothelial cells forming the BBB have as typical morphological characteristics tight junctions between cells, absence of fenestrations and diminished pinocytotic activity. A variety of enzymes further contributes to the restrictive nature of the BBB. The ability of drugs to cross the BBB mostly depends on their physicochemical properties, such as their lipophilicity. Consequently, the compounds considered in the present disclosure all are pro-drugs with improved lipophilicity, in comparison to their parent compounds.

The BBCR is to be understood as the brain-to-blood concentration ratio after transport equilibrium via the BBB has been achieved.

In general, a LogP value of a galanthamine derivative of approximately 1.3 leads to a BBRC (brain-to-blood concentration ratio) of approximately 2 or somewhat less than 2, a logP value of approx. 2 leads to a BBRC of approx. 5 to 10 and a logP value of approx. 3 leads to a BBRC of approx. 20 or over 20. This is intended as a guideline for comparing logP values with BBB permeability and may vary for some particular compounds. This guideline does not represent a limiting feature of the invention.

Pro-drugs are defined as *per se* therapeutically inactive agents that are predictably transformed in specific locations in the body to active metabolites. In this sense, pro-drugs are inactive precursors of parent drugs that undergo transformation into active agents *in vivo* by enzymatic cleavage or chemical spontaneous process(es) in a predictable fashion. In the pro-drugs discussed here, there exists preferably a covalent ester linkage between the parent drug and the selected transport pro-moiety, and upon cleavage of this ester bond, ideally in the target organ brain, the inactive pro-drug releases the active parent drug at or close to its target sites in the CNS.

Rapid absorption in the oral cavity is best achieved by sublingual administration, as the mucosal thickness in this area is lower than in other buccal areas, in addition to being significantly less keratinized (Shojaei A (1998) Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharmaceut Sci 1: 15-30). Fast dissolving sublingual formulations, such as rapidly degrading tablets or liquid-filled capsules, can additionally help reducing enzymatic degradation of pro-drug in saliva. The nasal cavity also provides a promising starting point for alternative administration regimes, with its large surface area, high vasculature and low enzymatic environment. Intranasal delivery is capable of providing a similarly high level of bioavailability as intravenous administration with the advantages of non-invasiveness, ease of self-administration, patient comfort and patient compliance in comparison to the latter. These advantages may have been known generally by practitioners of the art; however, significant hurdles remain for developing such application routes. For chronic systemic delivery, the problems of epithelial damage and toxicity need to be solved, and that for sufficient bioavailability high concentrations of drug in small volumes of vehicle are provided. This requires first selection of suitable chemical compounds that enable the required formulations and concentrations, in addition to finding appropriate methods for administration and finally developing preferred salts and/or solutions thereof that allow optimal administration of effective substance to the brain.

It was therefore not predictable in light of the prior art, which compounds would provide successful outcomes with regard to alternative administration modes. It can also not be predicted from the prior art, which salts and/or formulations could be generated for the prodrugs of this invention, nor whether these products would provide an effective BBB penetration and cleavage to active substance in the brain.

Suitable pro-drug formulations according to the invention were selected as follows. By way of monitoring the concentrations of the pro-drug in whole brain and blood plasma after intravenous injection of the pro-drug into animals, we determined their basic BBCR.

By additionally monitoring the concentrations of the released parent drug in brain and blood, we determined the rates and effectiveness of conversion from pro-drug to drug. These studies demonstrated that uptake of pro-drug into the brain was very fast indeed, and that the fast uptake strongly favored conversion of pro-drug to drug to take place in the brain. As most of the parent drugs under study are known to act as cholinesterase inhibitors, we reasoned and then proved that the related pro-drugs are cleaved to their active parent drugs by esterases of the butyrylesterase and carboxyesterase type.

We then changed to transmucosal delivery in the oral and nasal cavity and determined in animal models again the kinetics of uptake into the brain, the drug levels achieved therein, and

the pharmacodynamics achieved in comparison to oral delivery of the derivative and parent drug. The administration of the chemical substances described herein via transmucosal routes represents a surprising and unexpected advantage in comparison to previously known methods of oral administration. It was neither disclosed nor suggested in the prior art that certain derivatives of galantamine could be preferentially transported into the brain via transmucosal administration. As described above, previous attempts of intranasal application of galantamine had failed due to poor physicochemical properties. Surprisingly, the transmucosal application of the galantamine derivatives as described herein as preferred chemical substances does enable improved brain-to-blood concentration ratios. This effect is surprising in light of the previous failures of similar administration regimes for galantamine itself.

A goal of the present invention is therefore to present novel CNS therapeutics having optimal brain bioavailability due to being formulated as lipophilic pro-drugs and administered via transmucosal absorption pathways in the oral or nasal cavity

The invention is based on the fundamental understanding that the base compound itself, i.e. galantamine, has to be delivered to the brain by crossing the blood-brain barrier. Due to the fact that galantamine itself has a very low LogP value and therefore is not able to pass the blood brain barrier in sufficiently effective amounts, it is necessary to modify the base compound in a manner which makes the substance more lipophilic in order to more efficiently cross the blood-brain barrier. Once the substance has reached the brain, the modified base compound, preferably a chemical substance (CS) according to formula I or II, is reconverted by enzymatic cleavage of the ester bond on the R1 residue to the effective base compound itself, namely galantamine.

An aim of the invention is to deliver the chemical compound in a way into the brain to make sure that an effective amount of the base compound (after cleavage within the brain following crossing the blood-brain barrier) is available in the brain, in particular in order to ensure higher bioavailability of the later base compound galantamine.

As previously described (Maelicke et al., Memogain is a galantamine Pro-drug having Dramatically Reduced Adverse Effects and Enhanced Efficacy, J Mol Neurosci (2010) 40:135–137) the substance according to formula I is an inactive pro-drug of galantamine having more than 10-fold higher bioavailability in the brain than the same doses of galantamine. Said derivative of galantamine can be obtained by a one-step chemical modification of the parent drug (galantamine). The modification almost completely abolishes the pharmacological activity of galantamine on its two major targets in the human body, nicotinic acetylcholine receptor (nAChR) and acetylcholinesterase (AChE). At the physiologically interesting concentration of 1

µM, Memogain has less than 4% of the esterase inhibition induced by the same concentration of galantamine.

Synthesis, preparation and pharmacokinetic data of the substance according to formula I are previously described in detail in WO 2009/127218 A1 as well as in US 2009/0253654 A1, both are herewith incorporated by reference.

It is preferred to administer the chemical substance of the present invention by a route selected from the group consisting of intranasal, buccal, including sublingual, and/or intravenous administration. This way of administration guarantees a relative short bio-transport from the site of application, namely mouth, nose, tongue, buccal, intravenous, to the brain. Therefore the chance of disintegration of the chemical substance is low and the likelihood of effective transport from the nearby place of application to the blood-brain barrier is high.

In a preferred embodiment, the chemical substance is used as a salt, preferably a quaternary ammonium salt, preferably a lactate, gluconate, maleate or saccharate salt, having a solubility in water of at least 10%, preferentially of more than 20%.

It is intended to use the chemical substance in manner that enables distribution of the chemical substance in a patient after administration at a brain-to-blood concentration ratio of more than 5, preferably more than 10, more preferably between 15 and 25.

In a preferred embodiment, the CNS therapeutics are galantamine and structurally related compounds, the pro-drugs are aliphatic, aromatic and heteroaromatic esters of alcoholic OH-groups being essential for the pharmacological activity of the therapeutics. To be suitable for transmucosal delivery in the oral or nasal cavity, they are formulated as high-concentration aqueous salt solutions, or as emulsions, or as selfmicroemulsifying drug delivery systems (SMEDDs) or as micronized powder formulations. It was surprising, that the pharmaceutically applicable solutions of Memogain salts fulfilled the criteria for appropriate stability, concentration, pH, osmolarity, small and nasal mucosal tolerance in solution for intranasal application, as described in the following table 1.

Table 1.

Acceptance criteria	**Preclinic**	**Phase 1**	**Market**
Desired maximal concentration	25%	25%	10%
Acceptable maximal concentration	20%	10%	5%
pH	4.5 - 7	5 - 6.5	5 - 6.5
Chemical stability	> 3 hours	> 7 days	> 2 years
Stability of solution	> 3 hours	> 7 days	> 2 years
%F in rat	> 80%	n.a.	n.a.

Osmolarity	>250 mosmol/l	>250 mosmol/l	>250 mosmol/l
Smell	not unpleasant	not unpleasant	not unpleasant
Tolerance of nasal mucosa	no significant irritation during 28-day repeat dose study in rat & dog	no irritation in human	no irritation in human over period of administration

The pharmaceutical composition is preferably an aqueous solution, comprising 2 to 20% weight per volume (w/v), preferably 5 to 15% weight per volume (w/v), more preferably 10% weight per volume (w/v) of the chemical substance. To be suitable for transmucosal delivery in the oral or nasal cavity, they are formulated as high-concentration aqueous salt solutions, or as emulsions, or as selfmicroemulsifying drug delivery systems (SMEDDs) or as micronized powder formulations.

The term transmucosal administration relates to the entering of a pharmaceutical agent through, or across, a mucous membrane. The transmucosal routes of administration of the present invention are defined as intranasal, buccal and/or sublingual.

Nasal or intranasal administration relates to any form of application of the prodrug or pharmaceutical composition thereof to the nasal cavity. The nasal cavity is covered by a thin mucosa which is well vascularised. Therefore, a drug molecule can be transferred quickly across the single epithelial cell layer without first-pass hepatic and intestinal metabolism. Intranasal administration is therefore used as an alternative to oral administration of for example tablets and capsules, which lead to extensive degradation in the gut and/or liver.

Buccal administration relates to any form of application that leads to absorption across the buccal mucosa, preferably pertaining to adsorption at the inside of the cheek, the surface of a tooth, or the gum beside the cheek.

Sublingual administration refers to administration under the tongue, whereby the chemical comes in contact with the mucous membrane beneath the tongue and diffuses through it.

Pharmaceutical compositions suitable for buccal and/or sub-lingual administration may comprise additional pharmaceutically acceptable carriers, for example a buccal dosage unit may comprise the active agent to be administered in addition to a polymeric carrier that bioerodes and provides for delivery of the active agent over a predetermined time period, and, preferably, a lubricant, such as magnesium stearate. Additional carrier agents are known to one in the art. This active agent can be physically compounded with materials of some or all of classes of ingredients that function as pH controls, preservative agents, viscosity control

agents, absorption enhancers, stabilizing agents, solvents, and carrier vehicles. Such agents may be present in either solid or liquid forms of the pharmaceutical composition.

A self-microemulsifying drug delivery system (SMEDDS) may be present in said pharmaceutical composition, meaning a drug delivery system that uses a microemulsion achieved by chemical rather than mechanical means. That is, by an intrinsic property of the drug formulation, rather than by special mixing and handling. It employs the familiar effect displayed by anethole in many anise-flavored liquors. Microemulsions have significant potential for use in drug delivery, and SMEDDS (including so-called "U-type" microemulsions) are the best of these systems identified to date. SMEDDS are of particular value in increasing the absorption of lipophilic drugs taken by mouth. SMEDDS in may include in a non-limiting manner include formulations of the drugs anethole trithione, oridonin, curcumin, vinpocetine, tacrolimus, berberine hydrochloride, nobiletin and/or piroxicam.

The salt relates to any salt of the compounds of formulae I - II or of GLN 1062 itself. The term salt preferably refers to compounds comprising a protonated, positively charged N atom in the 7-member ring structure of the base compound.

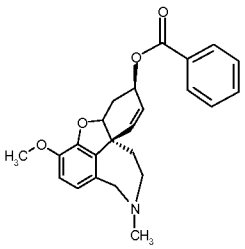
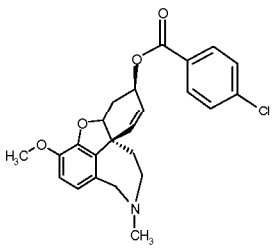
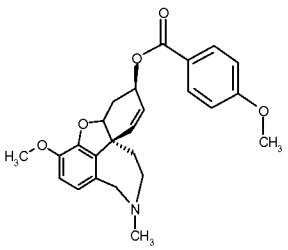
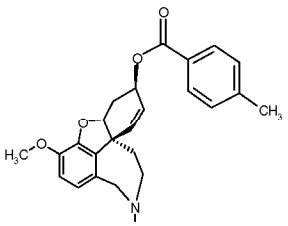
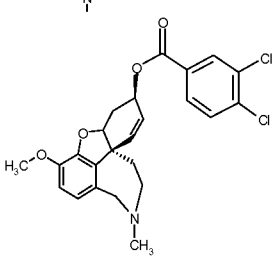
"Administration" or "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of a pharmaceutical, therapeutic, diagnostic agent, compound, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. "Administration" and "treatment" can refer, e.g., to therapeutic, placebo, pharmacokinetic, diagnostic, research, and experimental methods. "Treatment," as it applies to a human, veterinary, or research subject, refers to therapeutic treatment, prophylactic or preventative measures, to research and diagnostic applications.

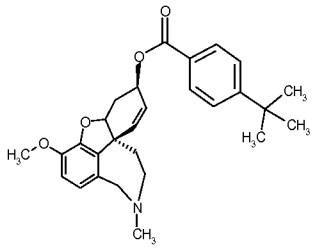
The invention encompasses administration of an effective amount of chemical substance as described herein to a patient in need thereof. "Effective amount" or "therapeutically effective amount" means an amount sufficient to ameliorate a symptom or sign of a disorder or physiological condition or an amount sufficient to permit or facilitate a diagnosis of the disorder or physiological condition. An effective amount for a particular patient or veterinary subject may vary depending on factors such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side effects. An effective amount can be the maximal dose or dosing protocol that avoids significant side effects or toxic effects. The effect will result in an improvement of a diagnostic measure, parameter, or detectable signal by at least 5%, usually by at least 10%, more usually at least 20%, most usually at least 30%, preferably at least 40%, more preferably at least 50%, most preferably at least 60%, ideally at least 70%, more ideally at least 80%, and most ideally at least 90%, where 100% is defined as the diagnostic parameter shown by a normal subject.

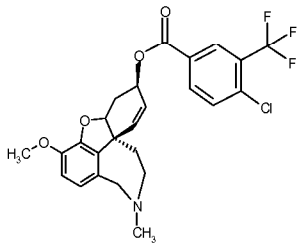
"Effective amount" also relates to an amount of the prodrug substance or pharmaceutical composition thereof, sufficient to allow or facilitate the amelioration and/or diagnosis of a symptom or sign of a disorder, condition, or pathological state.

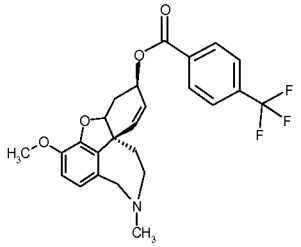
Preferred chemical substances according to the present invention are provided in Table 2.

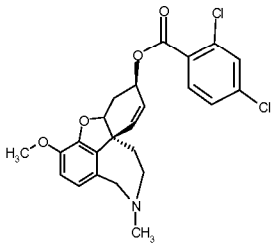
Table 2.

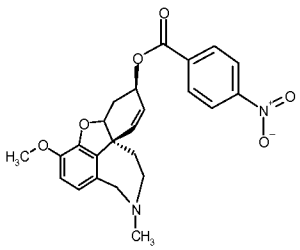
molregno	molstructure	abbrev.
GLN-1062		Bz-Gal
GLN-1081		4-Cl-Bz-Gal
GLN-1082		4-MeO-Bz-Gal
GLN-1083		4-Me-Bz-Gal
GLN-1084		3,4-Cl2-Bz-Gal

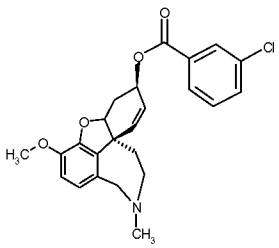
GLN-1085  4-tBu-Bz-Gal

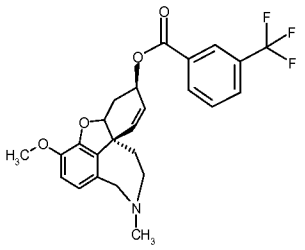
GLN-1086  3-CF3-4-Cl-Bz-Gal

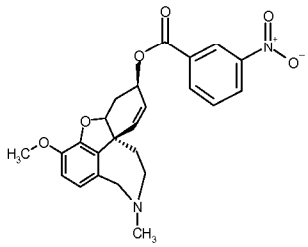
GLN-1088  4-CF3-Bz-Gal

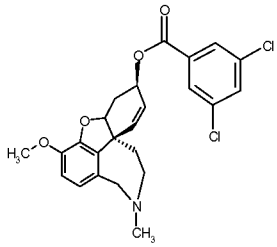
GLN-1089  2,4-Cl2-Bz-Gal

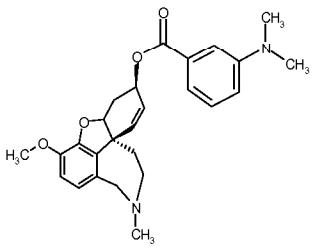
GLN-1090  4-NO2-Bz-Gal

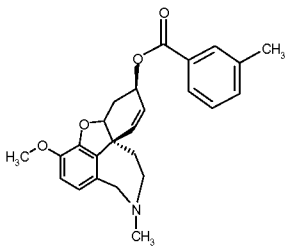
GLN-1091  3-Cl-Bz-Gal

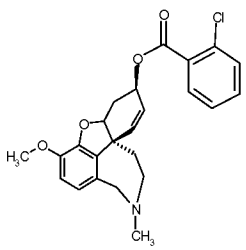
GLN-1092  3-CF3-Bz-Gal

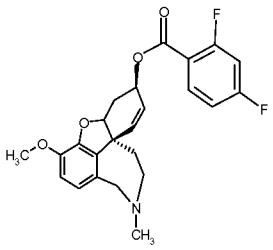
GLN-1093  3-NO2-Bz-Gal

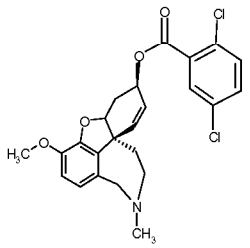
GLN-1094  3,5-Cl2-Bz-Gal

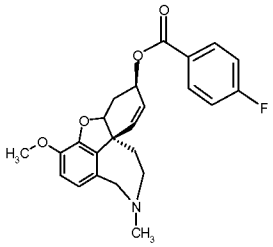
GLN-1095  3-Me2N-Bz-Gal

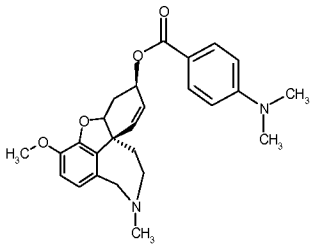
GLN-1096  3-Me-Bz-Gal

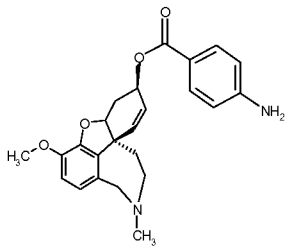
GLN-1097  2-Cl-Bz-Gal

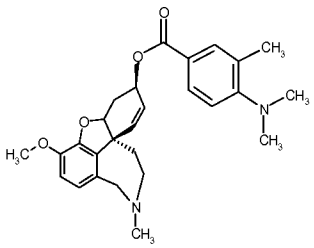
GLN-1098  2,4-F2-Bz-Gal

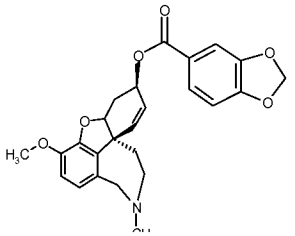
GLN-1099  2,5-Cl2-Bz-Gal

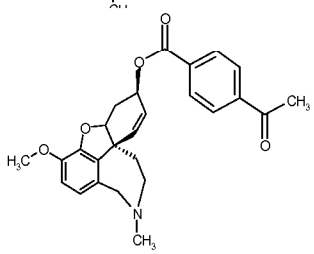
GLN-1100  4-F-Bz-Gal

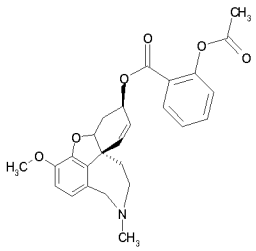
GLN-1101  4-NMe2-Bz-Gal

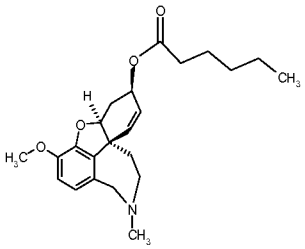
GLN-1102  4-NH2-Bz-Gal

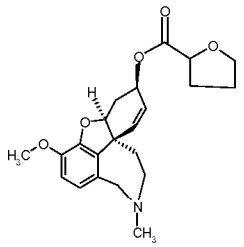
GLN-1103  3-Me-4-NMe2-Bz-Gal

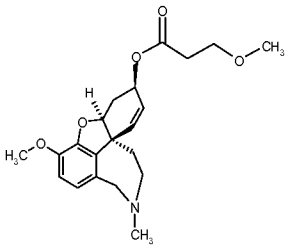
GLN-1104  3,4-OCH2O-Bz-Gal

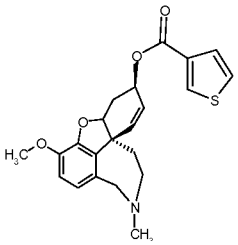
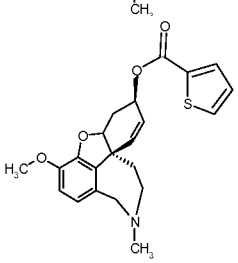
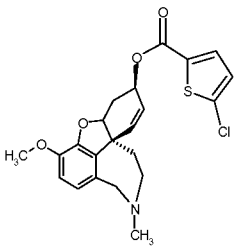
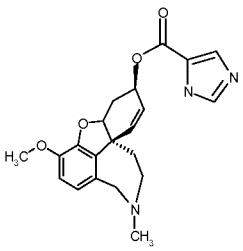
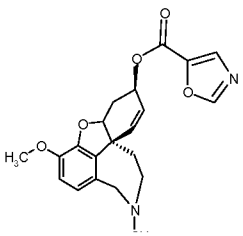
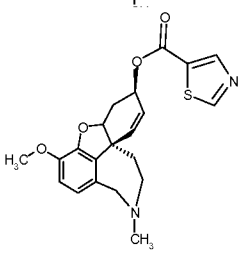
GLN-1105  4-Ac-Bz-Gal

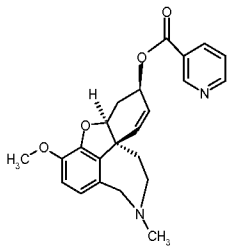
GLN-1113  2-AcO-Bz-Gal

GLN-0993  n-Hex-Gal

GLN-1060 

GLN-1061 

GLN-1106		**3-Th-Bz-Gal**
GLN-1107		**2-Th-Bz-Gal**
GLN-1108		**5-Cl-2-Th-Bz-Gal**
GLN-1109		**5-Im-Bz-Gal**
GLN-1110		**5-OA-Bz-Gal**
GLN-1111		**5-Th-Bz-Gal**

GLN-0926  Nic-Gal

FIGURES

The invention is further described by the figures. These are not intended to limit the scope of the invention.

Fig. 1: Powder diffraction diagram of Memogain gluconate obtained using dioxane.

Fig. 2: Adsorption/desorption isotherm of Memogain gluconate monohydrate.

Fig. 3: Weight loss on heating of Memogain gluconate monohydrate.

Fig. 4: Differential scanning calorimetry (DSC) the wet cake of Memogain gluconate.

Fig. 5: Powder diffraction diagram of Memogain gluconate obtained using ethanol.

Fig. 6: Experimental brain-to-blood concentration ratios for galantamine and several pro-galantamines.

Fig. 7: Intranasal Memogain is more potent than galantamine. Mice were challenged with scopolamine and dosed with increasing concentrations of oral galantamine and intranasal Memogain before performance evaluation in the mouse T-maze model.

Fig. 8: The first-pass effect of Gln-1062 was evaluated after intravenous and intraportal dosing of 3 mg/kg in Wistar rats.

Fig. 9: Intranasal administration of Memogain leads to low amounts of liberated galantamine in plasma.

Fig. 10: Memogain produces fewer gastro-intestinal side effects than galantamine.

Fig. 11: Lower toxicity of Memogain is due to the lower steady-state plasma levels of galantamine resulting from enzymatic cleavage of the pro-drug.

Fig. 12: The pharmacokinetic profiles of Memogain and galantamine in female Wistar rat after intra-nasal application of 5% Memogain salt in 10% NEP in water, 10 µL per nostril, a total of 20 µL containing 1 mg are shown below.

Fig. 13: Mice were injected with 3 mg/kg i.v. of either Memogain or galantamine. The data demonstrate that galantamine does not penetrate the brain well compared to Memogain.

Fig. 14: Intranasal administration of Memogain in a Rat PK study. 5 mg/kg intranasal (i.n.) Memogain dosing was performed under GLP-like conditions.

EXAMPLES

The invention is further described by the following examples. The examples are intended to further describe the invention by way of practical example and do not represent a limiting description of the invention.

Example 1. High-concentration aqueous salt solutions and organic solvent solutions of pro-drugs

For one of the drugs considered herein, galantamine, intranasal formulations were previously developed on the basis of aqueous solutions of highly soluble salts (WO 2005/102275 A1; Leonhard AK et al. (2005) Development of a novel high-concentration galantamine formulation sutable for intranasal delivery. J Pharmaceut Sciences 94: 1736-1746; Leonard AK et al. (2007) In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo. Int J Pharmaceutics 335: 138-146).

While the reported galantamine salt formulations allowed administration of galantamine at similarly high doses as is recommended for oral administration of tablets, intranasal administration did not improve the brain/blood concentration ratio of galantamine, as the physicochemical properties of the drug and hence penetration through the BBB did not change by this approach. In contrast, when the same salt formulations are formed from the pro-drugs disclosed herein, a large increase in lipophilicity (logP) is achieved, concomitantly with much better penetration through the BBB. This can be seen in Figure 1.

The combination of salt formation with prodrug properties, in particularly with regard to GLN 1062, shows a synergistic effect of improved absorption through the mucosal membrane and direct uptake to the brain, thereby enabling enhanced delivery to the site of action.

The blood-brain barrier penetration achieved by the various salts of the invention - in comparison to both the galantamine base compound, but also in comparison to oral administration of the derivatives themselves, - is increased in an unexpected and significant manner.

1.1. Salt of Memogain with acetic acid: (General procedure A):

To the solution of Memogain (502 mg, 1.28mmol in 2 ml 96% ethanol) acetic acid (463 mg, 7.71 mmol) was added and the resultant solution was stirred for some time and left overnight for salt formation resulting in the precipitation of the acetate salt. The yield was improved by addition of diethyl ether and the precipitate was filtered and washed with 96% ethanol. The precipitate was dried in a desiccator at r.t. at 40 mbar for 20h.. Results: colorless solid (Hygroscopic). Yield: 62%, m.p.: 89.3-91.2 °C, HPLC > 95%. Elemental analysis: Calcd. for $C_{24}H_{25}NO_4$ * 1.5 CH_3COOH C:71.24, H: 6.46, N: 3.32 Found C: 71.36, H: 6.17, N: 3.43.

Several other crystal forms containing 1-2 molar equivalents of acetic acid were obtained in a similar manner by changing the relative amounts of Memogain and acid as well as the precipitation method.

1.2. Salt of Memogain with lactic acid: (General procedure B):

To the solution of 2.5 g Memogain (6.4 mmol) in methanol (4 ml) a solution of 95% racemic lactic acid (7.85 mmol) in methanol (2 ml) was added at 40-50°C and stirred for 20 min. The solvent was evaporated and the resulting residue was dried first using a rotavap for 2 hrs at 9 mbar and at 50 – 60°C followed by overnight drying at 40 mbar at r.t. resulting in a solid light yellow foam that was highly hygroscopic. Yield: 98.92%, m.p.: 62.9-64.1°C, Elemental analysis: Calcd. for $C_{24}H_{25}NO_4$ * 1.1 $C_3H_6O_3$ C: 66.84, H: 6.49, N: 2.86. Found: C: 66.69, H: 6.45, N: 2.80 HPLC purity > 97%.

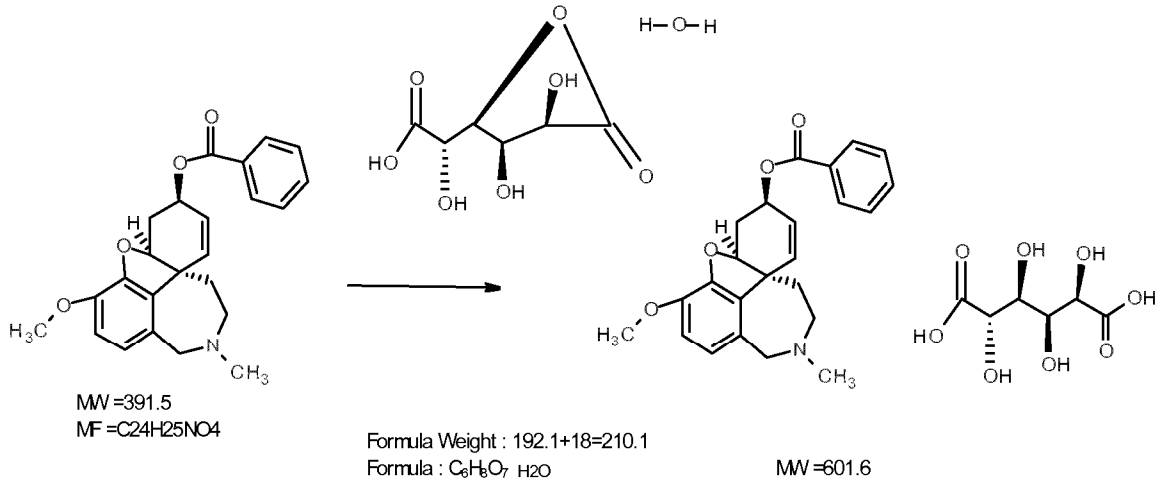
In a similar manner the corresponding salt with (+)-lactic acid was obtained: Calcd. for $C_{24}H_{25}NO_4$ * 1.5 $C_3H_6O_3$ C: 65.01, H: 6.51, N: 2.66. Found: C: 64.91, H: 6.28, N: 2.70.

1.3. Salt of Memogain with citric acid:

Using general procedure B but dry ethanol as solvent the citrate was obtained in 91.0 % yield as sticky solid that turned into a colorless solid after trituration using dry diethyl ether followed by high vacuum evaporation with m.p.: 117.5-119 °C Elemental analysis: Calcd for C: 73.64, H: 6.44, N: 3.58 Found C: 59.61, H: 5.93, N:2.26. HPLC > 97%

1.4. Salt of Memogain with Saccharic acid (General procedure C):

To a solution of Memogain (1120mg) in 96% ethanol (4 ml) was added a solution of saccharolactone (200 - 604 mg) in 96% ethanol (3 ml) at 60°. The hot solution was immediately diluted with ethyl acetate resulting in the formation of a colorless precipitate that was filtered after cooling to 5° for 2 hrs, washed with ethyl acetate and dried at 40 mbar for 20 hrs at r.t. to give a 83.7% yield of the saccharic acid salt as colorless solid with m.p.: 132-134°C and HPLC-purity of > 97%. Elemental analysis: Calcd. for $C_{24}H_{25}NO_4$ * $C_6H_{10}O_8$ C: 59.89, H: 5.86, N: 2.33. Found: C: 60.10, H: 5.61, N: 2.37. The lactone of saccharic acid is hydrolyzed with water present under these conditions resulting in the salt described.



1.5. Salt of Memogain with Gluconic acid:

Following in general procedure C starting from Memogain (150 mg, 0.38 mmol) but using dioxane as solvent and a solution of D-gluconic acid delta-lactone (68.2 mg, 0.38 mmol) in dioxane containg water (13 mg, 0.76 mmol) and stirring at 50-60 °C for 30 min. until a clear solution was obtained followed by addition of dry diethyl ether (10 ml) to the cooled solution resulted in a colorless precipitate that was filtered, washed with diethyl ether and dried to obtain 170 mg (75.6%) of the salt as colorless, crystalline solid. m.p.:159.3-159.4°C HPLC purity > 98% Elemental analysis: Calcd. for $C_{24}H_{25}NO_4$ * 1.5 $C_6H_{12}O_7$ C: 57.80, H: 6.32, N: 2.04. Found: C: 58.22, H: 5.98, N: 2.28. The powder diffraction diagram of this salt is shown in Fig. 1.

From a similar experiment on twice the scale but without adding diethyl ether for precipitation spontaneous crystals were formed on standing at r.t. for 3 days that were filtered, washed with dioxane and dried to obtain 145 mg (32%) of the 1:1 salt as colorless crystals with m.p. 173.3-173.4°C Calcd. for $C_{24}H_{25}NO_4$ * $C_6H_{12}O_7$ C: 61.32, H: 6.35, N: 2.38. Found: C: 61.65, H: 6.27,

N: 2.64. Microtitration of this salt verified the stochiometry calculated from the elemental analysis.

Under similar conditions but prolonged drying other salt-forms containing 0-2 equival. of water in the crystal were obtained. It is known that D-gluconic acid delta-lactone is hydrolyzed to gluconic acid by water.

In an alternative procedure ethanol was used as a solvent. Thus Memogain (9.4 g, 24 mmol) in 96% ethanol) was added to a solution of D-gluconic acid delta-lactone (6416 mg, 36 mmol) in 96% ethanol (10 ml) and heated to 50-60 °C for 30 min. until a clear solution was obtained that was kept at r.t. for 2 days with the formation of a colorless precipitate that was filtered, washed with dry ethanol (2 x 20 ml) and isopropanol (60 lm) and dried at 40 mbar at r.t. for 20 hr to obtain 7.91 g (84.2%) of the product as colorless crystalline solid m.p.: 122-126°C, HPLC purity > 98%. Elemental analysis: Calcd. for $C_{24}H_{25}NO_4$ * $C_6H_{12}O_7$ * H_2O C: 59.50, H: 6.49, N: 2.31. Found: C: 59.60, H: 6.59, N: 2.32.

This salt was used to obtain the adsorption/desorption isotherm of water (Fig.2) as well as the weight loss on heating (Fig. 3). Furthermore by differential scanning calorimetry (DSC) of the wet cake of Memogain gluconate it was determined, that drying takes place between 53 and 87 °C and melting around 123°C (Fig. 4). The powder diffraction diagram of this salt is shown in Fig. 5

^{1H}NMR (200 MHz, D2O): δ7.35-7.46(d,2H), 7.09-6.94 (t,1H), 6.92-6.80 (t,2H),6.59-6.36 (m, 2H), 6.14-6.00(d, 1H), 5.85-5.72(m, 1H), 5.16-5.07(s, 1H), 4.48-4.31(m, 4H), 4.13-3.84(m, 5H), 3.73-3.53(m, 6H), 3.53-3.39 (m, 5H), 2.76-2.58(s, 3H)2.39-2.21(d, 1H), 2.06-1.69(m, 3H)
^{13C}NMR (50 MHz, D2O): δ178.39 (s, 1C), 167.03 (s.1C), 146.09 (s, 1C), 145.11 (s,1C), 133.09 (s,1C),131.57(s,1C),129.26
(s,1C),128.04(s,1C),123.75(s,1C),123.40(s,1C),119.02(s,1C),118.74(s,1C)118.67(s,1C), 112.05(s,1C), 85.82(s,1C), 73.93(s, 1C), 73.52(s, 1C), 72.46(s, 1C), 71.07(s, 1C), 70.81(s, 1C), 64.23(s, 1C),62.54(s, 1C), 58.51(s, 1C), 55.52(s, 1C), 53.98(s, 1C), 46.50(s, 1C), 40.96(s, 1C)40.82 (s, 1C), 32.07 (s, 1C), 26.83(s, 1C).

Using the general procedures A, B and C the following salts were prepared on a 0.5 to 10 mmol scale in a similar manner and un-optimized yields of 42-91% were obtained. For those salts that were obtained in a crystalline state the melting points are indicated. Salts that showed solubility in water higher than 10% or even 20% were investigated further.

In addition to this list, pharmaceutically acceptable salts as described in table 1 of the book Pharmaceutical Salts, Properties, Selection and Uses, Stahl, P.H. and Wermuth, C.G., eds., VHCA Verlag 2002, can be used.

1.6. Solubility test

10 mg of the corresponding salt and 100 microliters of water were sonicated for 5 min at r.t.. The resulting solution or suspension was centrifuged for 3 min. and filtered using a filter tip. 10 microliters of the filtrate was transferred in a volumetric flask and diluted to 10.0 ml with water to obtain the sample solution. 20 microliters of this sample solution was injected for HPLC and the amount of Memogain quantified using a Merck Chromolith RP18 column and a gradient of 5% to 60% acetonitrile and water, both solvents containing 0.1% formic acid, injection volume: 20 microliters.

The Memogain salts of acetic acid, maleic acid, lactic acid (lactate salt), citric acid, saccharic acid (saccharate salt) and gluconic acid (gluconate salt) all showed solubility at above 10% in water.

The lactate, gluconate, maleate and saccharate salts of Memogain showed solubility above 10% weight per volume (w/v), sometimes forming meta-stable salts at 20% concentration in solution. The gluconate salt showed solubility at 40% weight per volume (w/v) and the saccharate salt at 70% weight per volume (w/v).

Table 3: Additional Memogain Salts

Acid	m.p.(°C)
Ascorbic acid	110-131 (decomp.)
Arabic acid	213 (decomp.)
Adipic acid	
DL-Mandelic acid	
D-Glucoheptono-1,4-lactone	147 (decomp.)
Formic acid	146-147
Fumaric acid	
Galactaric acid	143-144
D-(+)-Galacturonic acid	148-151
Glucuronic acid	145-146
Glycolic acid	97-103

Hydrobromic acid	221-222
Hydroxy citric acid	
Hydrochloric acid	
Isethionic acid	191-195
Maleic acid	
L-(-)-Malic acid	107-108
Malonic acid	
Nicotinic acid	117-118
Phosphoric acid	
Succinic acid	
Sulfuric acid	172-173
L-(+)-Tartaric acid	185-186
D-(-)tartaric acid	212-213
Meso tartaric acid	107-109

Particularly preferred are quaternary nitrogen salts (otherwise termed quaternary ammonium salts) of acetic acid, maleic acid, lactic acid (lactate salt), citric acid, saccharic acid (saccharate salt) and gluconic acid (gluconate salt).

These acids form salts with Memogain and other galantamine pro-drug nitrogen bases having solubility of up to 70% at neutral pH in water. While high-concentration of the gluconate salt in aqueous solution is metastable and is later converted to less soluble stable salt forms, the fully dissolved homogenous solutions can be recovered by warming the aqueous mixtures to > 50 ^{0}C until precipitations have disappeared. These metastable homogenous solutions remain stable for hours and days, provided that precautions are taken to reduce or avoid precipitation seeding. Appropriate documentation of the dissolution procedure to form such metastable (hypercritical) solutions renders these solutions suitable drug product formulations for use by patients and medical personal. A short warming, for example for 5 minutes by hand, before administration allows optimal administration of such metastable solutions.

As sustained release aqueous formulations of the pro-drugs discussed here, we have dissolved in water a powder of the natural biopolymer chitosan, and mixed it with Memogain base or hydrogen salt so as to achieve formulations for intranasal delivery of 5% (w/v) or more (Illium L et al. (2002). Intranasal delivery of morphine. J Pharmacol Exp Therap 301: 391-400). The method of application described in Illium et al is also suitable for use with the chemical substances of the present invention.

Sustained release formulations of Memogain salts comprising chitosan also proved effective when applied in solid form in oral sublingual or buccal administration, and showed unexpectedly fast initial absorption with long release times.

The preferred salts of the present invention represent preferred embodiments that exhibit unexpectedly surprising and advantageous effects in comparison to what was disclosed in the prior art or what could have been expected by a skilled person in light of the prior art. The solubility of the particular preferred salts is unexpectedly good, allowing a higher concentration of medicament in the pharmaceutical composition (i.e. in the form of a solution in a particularly preferred embodiment for intranasal administration, but also buccal or sub-lingual application). This is of great importance in light of the requirements mentioned above for compounds that are suitable for intranasal, sublingual or buccal administration. Due to the limited size of the nasal cavity the required concentration of the active substance in solution is high. This means that salts needed to be found, which could be very soluble and therefore provided at a high concentration. This is surprisingly the case for the salts mentioned herein, preferably for acetic acid (acetate salt), lactic acid (lactate salt), citric acid, saccharic acid (saccharate salt) and gluconic acid (gluconate salt).

Example 2. Emulsions and selfmicroemulsifying drug delivery systems (SMEDDs)

Emulsions and SMEDDs are established means of brain delivery systems (Botner S, Sintov AC (2011) Intranasal delivery of two benzodiazepines, Midazolam and Diazepam, by a microemulsion system. Pharmacol Pharmacie 2:180-188). In the present application they were produced by mixing the pro-drug under investigation, as nitrogen base or as hydrogen salt, with various organic solvents or by mixing with suitable surfactants, oils and co-surfactants (all recognized as safe; GRAS) under stirring and/or ultrasound until a clear solution was achieved. In particular, we avoided using alcohols or other irritant chemicals in the formulations so as to avoid any irritability of the nasal or buccal mucosa. Typical components of such microemulsions were Labrasol, N-ethyl-2-pyrrolidone (NEP), glyceryl oleate, PEG, propylene glycol, Transcutol, and suitable oils, such as palmitate. We achieved drug solubilities of the order of 10% (w/w), or more, with a maximal water solubilization capacity of approx.. 50% (the lower the water content, the higher oil concentrations could be achieved, and the higher the solubility of nitrogen base). The highest solubilities of pro-drug nitrogen bases or salts were obtained at water concentrations around 20% in the microemulsions.

Preferred embodiments of the self-microemulsifying drug delivery (SMEDD) formulation, preferably for Memogain maleate, relate to the following:

Used materials:

Memogain maleate (No. 022563-A-1-1, GALANTOS Pharma GmbH, Germany)
Capmul MCM (Lot: 080726-7, BERENTZ - ABITEC CORP., USA)
(glyceryl caprylate/caprate; Pharm. Eur.)
PEG 300 / 400 (Lot: 1349048-41108320, FLUKA, Vienna, Austria)
(polyethyleneglycol; Pharm. Eur.)
Propyleneglycol (Lot: S44324-108, SIGMA, Vienna, Austria)
(propyleneglycol; Pharm. Eur)
Transcutol (Lot: 18703CE, SIGMA, Vienna, Austria)
(diethyleneglycolemonoethylether; Pharm. Eur.)

Preparation of a 10% Memogain maleate SMEDD formulation (1 L):
As the first step, 100 g of Memogain maleate are weighted into an appropriate steel tank. In the following the solubilizers and fatty oils are added one after each other:
170 ml of Capmul MCM
500 ml PEG 300
220 ml Propyleneglycol
110 ml Transcutol

Finally the SMEDD formulation is treated with ultrasound until the mixture becomes a clear solution.

The Memogain base and salt emulsion and SMEDD formulations demonstrate reduced local irritation of the mucosal surface upon application. Furthermore, the bitter taste of the prodrug is effectively masked through the various lipid and PEG components and no analgesic effect on the transmucosal surface was evident.

Example 3. Micronized powder formulations and nano-suspensions of pro-drug crystals

Other suitable formulations for transmucosal delivery are pro-drug nano-crystals and polymeric micro-particles to which pro-drugs are adsorbed. In both cases, the more lipophilic pro-drug bases were used. The formulations were obtained by co-precipitation of polymer and pro-drug, by pearl milling and homogenization in water, or as nano-suspensions of pro-drugs that are lipid conjugates. Such methods are known to one skilled in the art and could be applied with the chemical substances and methods of administration of the present invention.

The micronized powder compositions of GLN 1062 or salts thereof enable fast absorption and a reduction in the bitter taste of the compound, compared to when applied as an aqueous solution.

Example 4. Memogain-Formulations

Solubility of Memogain

Free Base in Water:	26 µg/ml (66 µM)
Maleate in Water:	7,5 mg/ml (15 mM)
Maleate in 0,9 % NaCl:	0,6 mg/ml (1,5 mM)
Free Base in Cyclodextrin-Vehicle[1)]:	8,9 mg/ml (23 mM)
Maleate in Cyclodextrin-Vehicle[1)]:	21 mg/ml (41 mM)

[1)] 15 % (109 mM) Hydroxypropyl-β-cyclodextrin, 96 mM NaCl

Table 4. Formulations

Name	GEA1
Type	Sublingual Tablet
API	Memogain maleate
API/Tablet	1 mg
Tablet mass	20 mg
Carrier	Lactose monohydrate Ethanol [1)] Corn starch Povidon K30 (polyvinylpyrrolidone (PVP)) Magnesium stearate [1)] removed during production

Name	GEA2
Type	Sublingual Tablet
API	Memogain maleate
API/Tablet	2 mg
Tablet mass	50 mg
Carrier	Mannitol Explotab (sodium starch glycolate) Croscarmellose Ascorbic acid Magnesium stearate Orange flavour

Name	Evonik 1
Type	Multi-layered Pellets (ca. 1 mm) with digestive acid resistant coating
API	Memogain maleate
API-amount	1 %
Pellet core	Cellet 700 (MCC)
API-layer	Memogain maleate and Methocel E5 (HPMC)
Subcoating	Methocel E5 (HPMC)
Coating	Eudragit FS30D, Talc, Triethylcitrate
Layer thickness Eudragit:	Approx. 30 µm bei 15 % Coating; also Pellets with 5 % and 10 % were manufactured.

Name	Evonik 2
Type	Multi-layered Tablets (appr. 9 mg) with digestive acid resistant coating
API	Memogain maleate
API-amount	2 mg
Pellet core	Memogain maleat, Avicel PH 102 (MCC), corn starch, Methocel E5 (HPMC), Magnesium stearate
Subcoating	Methocel E5 (HPMC)
Coating	Eudragit FS30D, Talc, Triethylcitrate
Layer thickness Eudragit:	appr. 90 µm bei 15 % coating; also Pellets with 5 % and 10 % were manufactured.

The sub-lingual tablets and multi-layered formulations of the present invention show surprisingly good adsorption properties, enabling quick uptake and reduced flavour bitterness, in addition to reduced analgesic effects in the mouth of the patient. The fast adsorption of chemical substance enables a reduced risk of swallowing; thereby ensuring the administration occurs transmucosally through the oral mucous membrane, avoiding unwanted degradation of the prodrug.

Example 5. Interaction with carrier substance and Eudragit (Poly(meth)acrylate)

Experiment 1: a small amount (0,1 mg) of Memogain maleate in 1 ml HBSS-Puffer, pH 7,4 was incubated with various carriers at 37 °C 2,5 h. The amount of free (not bound to the particle of the carrier substance) of Memogain was then measured by HPLC. Typical amounts of carrier substance were applied and shown in Table 5.

Table 5.

Nr.	Substance	mg carrier	Non-absorbed Memogain
			(% of control)
control	none	0	100
1	Lactose	10	105
2	MCC	10	100
3	HPMC	1	105
4	Corn starch	5	100
5	Eudragit L100	2	21
6	Eudragit FS30D	1,8	7
7	Talc	2	94
8	Mg Stearate	0,1	101
9	Mg Stearate + Tw20	0,1 plus 0,1 % Tw20	103
10	Aerosil (SiO_2)	1	89
11	Emcompress ($CaHPO_4$)	10	101
12	Explotab	2	99
13	Triethylcitrat	0,2	101

Result: Eudragit L100 and Eudragit FS30D adsorb Memogain.

Experiment 2: a fixed amount of Eudragit (0,5 mg/ml) was incubated with various amounts of Memogainmaleate for 2h in a saline solution (HBSS). The amount of free (not bound to the particle of the carrier substance) of Memogain was then measured by HPLC. In parallel the solubility of the Eudragit amount alone in the salt solution was analysed.

Result: L100 is completely soluble in the provided concentration, FS30D forms a cloudly solution. FS30D binds to Memogain over the entire tested concentration range. As of 0,25 mg/ml Memogain forms a precipitate with L100, which can be re-solubilised by the addition of 6 % Cycldodextrin (HPCD).

Example 6. In vitro studies of permeation behavior, pre-systemic metabolism and stability

Permeation behavior of pro-drug formulations was tested using tissue samples of 3-4 cm^2 freshly excised porcine nasal or buccal mucosa inserted in an Ussing-type chamber displaying a permeation area of 0.64 cm^2 and a volume of 1ml on both sides. The apical side of the

tissue was facing the donor compartment. One ml of pre-warmed (37°C) permeation medium was added to the donor and acceptor chamber. The temperature within the chambers was maintained at 37°C throughout the entire experiment. After a pre-incubation time of 15 min the permeation medium in the donor chamber was substituted by a 1% solution of the pro-drug formulation under investigation. Every 30 min aliquots of 100 µl were withdrawn from the acceptor compartment and immediately replaced by 100 µl of fresh pre-warmed permeation medium over a time period of 180 min. The concentration of compounds in the collected aliquots was determined via HPLC. Corrections were made for previously removed samples. Apparent permeability coefficients (Papp) were calculated. Control samples were withdrawn from the donor compartment after 180 min and analyzed to investigate the stability of the compound in the formulation under investigation.

During the above described permeation experiments, 10 µl aliquots were withdrawn from the donor compartment at time points 0, 60, 120 and 180 min. These aliquots were analyzed by HPLC to determine the degree of pre-systemic metabolism over time.

Using these methods, aqueous solutions of pro-drug salts, and solutions of pro-drug bases in organic solvents, co-solvents and surfactants were tested as to their solubility, their permeation coefficient, and their pre-systemic metabolism and stability. The formulations further studied had solubilities of at least 10% (m/v), and permeation coefficients of pro-drugs of Papp > $1 \cdot 10^{-6}$ cm/s. Within the time periods tested, there was no significant pre-systemic metabolism of pro-drugs in both porcine mucosa preparations.

Example 7. Pharmacokinetics

The pharmacokinetics of pro-drugs and parent drugs after transmucosal delivery in the nasal or buccal cavity were tested in Wistar rats. These data confirmed rapid (within minutes) uptake into blood and brain of the pro-drugs under investigation, bioavailabilites in the brain of pro-drugs similar to those produced by intravenous injections, and much higher BBRC, as compared to oral delivery as tablet of the related parent drug.

Because redistribution of parent drug via BBB to the circulation, after enzymatic production from pro-drug in the brain, is very fast indeed, pharmacokinetic studies do not suffice to exactly determine the momentary concentrations of parent drug in the brain. We therefore used pharmacodynamics studies to determine the effective concentrations of parent drug in suitable experimental conditions, such as the reversal of scopolamine-induced temporary amnesia in the T-maze cognitive paradigm studied in mice. These studies confirmed that several fold higher (up to 20fold) BBRC of parent drug (and related effectiveness in cognitive

enhancement) can be achieved by transmucosal delivery of pro-drug formulations via the nasal or buccal cavity.

Experiments directly comparing potency and reduced GI side effects of Memogain between oral and transmucosal (nasal) administration also demonstrate that intranasally administered Memogain exhibits surprisingly beneficial properties in comparison to orally administered Memogain.

Pharmacokinetc studies were carried out using intranasal and sublingual administration of the Memogain maleate salt.

Intranasal report:

This experimental plan describes the blood and brain pharmacokinetic profiles of the pro-galantamine Memogain maleate and galantamine in female wistar rat following intra-nasal application of the Memogain maleate and galantamine Hydrobromide in various formulations.

a. 5% galantamine in water, 10 µL per nostril, a total of 20 µL containing 1 mg 5%

b. Memogain salt in 10% NEP in water, 10 µL per nostril, a total of 20 µL containing 1 mg

c. 5% Memogain salt in an emulsion, 10 µL per nostril, a total of 20 µL containing 1 mg

d. 20% Memogain salt in an emulsion, 10 µL per nostril, a total of 20 µL containing 4 mg

e. Intravenous administration of Memogain salt at dose rate of 5 mg\kg (previously carried out as control)

Sublingual report:

This experimental plan describes the blood and brain pharmacokinetic profiles of the pro-galantamine Memogain maleate and galantamine in female wistar rat following sub-lingual application of the Memogain maleate and galantamine Hydrobromide in various formulations.

a. 5% galantamine in water, 20 µL under tongue containing 1 mg

b. 5% Memogain salt in 10% NEP in water, 20 µL under tongue containing 1 mg

c. 5% Memogain salt in an emulsion, 20 µL under tongue containing 1 mg

d. 20% Memogain salt in an emulsion, 20 µL under tongue containing 4 mg

e. intravenous administration of Memogain salt at dose rate of 5 mg\kg as control

Both the intranasal and sublingual studies show that beneficial pharmacokinetic (PK) properties were observed with the maleate salt. Similar results are to be expected from the other preferred salts of the invention, when considering the additional experimentation described herein and in light of preliminary studies with nasal or buccal mucosa, which show good uptake across the mucosal membranes of all preferred salts of the invention. The PK data show that Memogain was detected in the brain for extended periods of time, and showed high brain to blood concentration ratios, indicating that very little of the applied prodrug is carried into the blood stream and subsequently degraded. Over time the levels of Memogain in the brain decrease, as levels of galantamine in the brain increase, which indicates cleavage of the prodrug to its active form in the brain of the subject. One example is shown for the intranasal experiment in Figure 12, sample b.

The administration of the Memogain salt intranasally provides a very effective method of directing the prodrug specifically to the brain, where it is processed thereby releasing the active compound galantamine.

Memogain gluconate:

Further tests were performed with Memogain gluconate. It has a much larger BBRC than galantamine (see Figure 6). The pharmacokinetics and brain-to-blood concentration ratios (BBRC) of several galantamine derivatives and their cleavage product galantamine were evaluated after intranasal administration in Swiss albino mice at a dose of 3 mg/kg. After extraction from brain and blood, the drug concentrations were determined by LC/MS/MS. For comparison, the BBRC for the parent drug galantamine was also determined. As demonstrated in the figure, the studied pro-galantamines all display larger BBRCs than galantamine, with a particularly large BBRC for Gln-1062

Memogain gluconate is highly water soluble and has no burning sensation to nose, or any taste or smell. Intranasal dosing can be done with simple spray-pump methods, although also many other methods can be used. As Memogain is a pharmacologically inactive precursor of galantamine and was administered intranasally as gluconate, no GI side effects were observed.

Example 8. Memogain shows improved brain penetration and low blood levels compared to galantamine

Data are shown in Figure 13. Mice were injected with 3 mg/kg i.v. of either Memogain or galantamine. The data demonstrate clearly that galantamine does not distribute into the brain well (BBRC ~ 1:1), whereas Memogain has a much higher BBRC (8:1).

Additional data are shown in Figure 14 for i. n. administration. A Rat PK study was carried out with 5 mg/kg intranasal (i.n.) Memogain dosing performed under GLP-like conditions. The data demonstrate that Memogain has a much higher BBRC (10:1).

Example 9. Intranasal Memogain is more potent than galantamine

To test whether intranasal Memogain is in-vivo a more effective cognition enhancer than galantamine, the following cognition paradigm was applied. Mice were treated with scopolamine to induce acute amnesia and were then tested for performance in a T-maze, in the absence or presence of oral galantamine or intranasal Memogain (Fig. 7). Clearly, Memogain was more effective than galantamine in reversing the acutely induced amnesia. Mice were challenged with Scopolamine i.p. in a T-maze assay to induce disorientation/amnesia (set to 0% performance recovery). Co-application of galantamine (i.p.) or of Memogain® (i.n.) rescues orientation in the T-maze in a dose-dependent manner.

Example 10. First pass effect of Memogain

The first-pass effect of Gln-1062 was evaluated after intravenous and intraportal dosing of 3 mg/kg in Wistar rats (Fig. 8). Gln-1062 was observed to undergo first-pass effect by rapidly decreasing blood concentration levels independently of whether it was administered i.v. or i.n. In contrast, the concentration levels of galantamine liberated from Gln-1062 by enzymatic cleavage did not decrease similarly rapidly. Moreover, higher maximal concentration levels of Gln-1062 were observed in brain and blood following i.v administration as compared to intraportal administration. From these data, the first-pass effect was estimated to be between 35 and 45%.

When Gln-1062 was administered intranasally at the same dose, similarly high maximal concentration levels were observed in the brain as after i.v. administration, indicating that uptake into the brain was as efficient as after i.v. administration and with little impairment by a first-pass effect.

Example 11. Intranasal administration of Memogain leads to low amounts of liberated galantamine in plasma

The study was performed in dogs. A single dose of 4 mg/kg intranasal Memogain was administered and the plasma levels of Memogain and liberated galantamine were determined as a function of time after administration. As Memogain is preferentially partitioned into the brain, only a small fraction of the pro-drug appears in the blood. The levels of galantamine liberated from Memogain are much smaller, as galantamine is rapidly metabolized and

excreted (Fig. 9). This leads to a much reduced likelihood of side effects, considering the small amounts of systemic galantamine present in the blood after i. n. administration.

The data from the dog experiments demonstrate:

- Brain : Blood ratio of Memogain (@120 min post administration) = 9
- Brain : Blood ratio of galantamine (@120 min post administration) = 1 – 1.5
- Memogain in blood t½ = 90 min (conscious animals)
- Galantamine t½ = 6 h (conscious animals)
- Low blood levels of galantamine indicates fewer side effects
- High brain concentrations of Memogain indicate release of galantamine from Memogain mainly in the brain.

Example 12. Memogain produces fewer gastro-intestinal side effects than galantamine

These studies were performed in ferrets that were dosed i.p. with either 20 mg/kg galantamine (maximal tolerated dose), or with 20, 40 and 80 mg/kg Memogain, respectively. At 20mg/kg Memogain, no adverse effects were observed. From the dose dependency of adverse effects, at least 4 times lower toxicity in this animal model was observed for Memogain, as compared to galantamine (Fig. 10).

Similarly, much less adverse effects than observed with galantamine were seen in the Irwin assay, respiratory toxicity studies, both performed in rats, and in a cardiovascular toxicity study in dogs.

Example 13. Memogain is at least 10 times safer than galantamine

This study was performed in dogs, and both drugs were administered as intravenous bolus. The lower toxicity of Memogain is due to the much lower steady-state plasma levels of galantamine resulting from enzymatic cleavage of the pro-drug (Fig. 11).

Medical benefits of galantamine pro-drugs and their formulations for transmucosal delivery to the nasal and buccal cavity:

The key benefits are as follows:

1. Higher bioavailability and higher effectiveness in the target organ

2. Lower levels of peripheral side effects
3. Pharmacokinetics can be adjusted to medical needs (sustained delivery)
4. Dosing not limited by GI adverse effects
5. Faster and stronger onset of medical benefit
6. Up-titration of dose (to enhance compliance) not needed
7. Immediate administration of efficacious doses
8. Improved patient compliance

Higher bioavailability in the brain and higher effectiveness as a cognition enhancer was demonstrated by pharmacodynamics studies using suitable cognition paradigms in animal models of cognitive impairment. Dramatically lowered incidences of gastro-intestinal adverse effects, i.e. retching and emesis, were shown for intranasal delivery of Memogain in comparison to oral administration of identical doses of Memogain or galantamine. . For intranasal delivery of the pro-galantamine Memogain, even at very high doses, GI-related side effects had practically disappeared, as the combined result of better brain penetration of the lipophilic pro-drug and avoidance of the gastro-intestinal tract during drug delivery.

In summary, the oral administration of Memogain and galantamine provide comparable BBB-penetration due to the rapid cleavage of Memogain (to galantamine) post-administration. The Memogain salts provide no noticeable enhanced effect when administered orally at the same concentration.

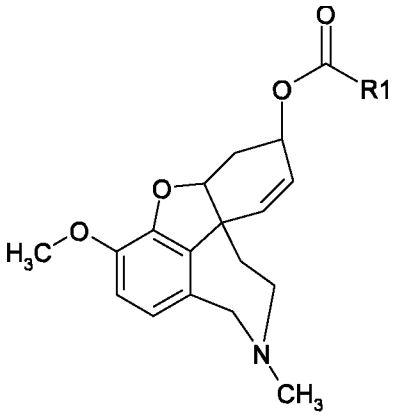
Intravenous administration (i. v.) of Memogain compared to galantamine demonstrates a vastly improved BBB-penetration for Memogain due to its more hydrophobic nature. The i. v. administration of galantamine provides only a very minor (if any) advantage in comparison to oral delivery of galantamine, as the active compound itself is relatively stable when compared to Memogain and is not susceptible to esterase cleavage.

Transmucosal administration (intranasal; i. n.) reveals unexpected enhanced effects with respect to Memogain, and particularly the salts of Memogain. The i. n. administration of the salts of Memogain show further improved BBB-penetration.

Brain penetration of galantamine is not enhanced by i. n. administration of galantamine, as the hydrophilic nature of the molecule prohibits effective penetration regardless of administration route. The i. n. administration of galantamine may avoid some common side effects (Leonard et al (2007)) of galantamine by avoiding administration through the digestive tract. The efficacy as cognition enhancer of the molecule is however not enhanced due to the remaining poor BBRC.

CLAIMS

1. Chemical substance according to Formula I for use as a medicament in the treatment of brain disease associated with cognitive impairment, wherein said treatment comprises transmucosal administration, selected from intranasal, sublingual or buccal administration, of a therapeutically effective amount of said substance,

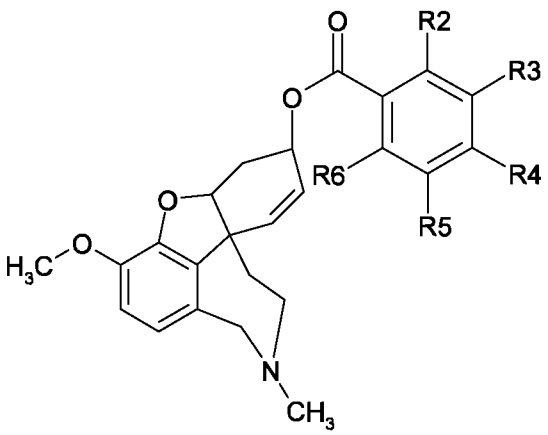


Formula I

wherein

R1 = aromatic or heteroaromatic 5- or 6-membered ring, such as optionally substituted naphthaline, thiophene, pyrrole, imidazole, pyrazole, oxazole, thiazole; or straight or branched chained aliphatic residues, such as CH(C2H5)CH3, CH2-C(CH3)3, cyclopropane or preferably an aliphatic residue comprising more than 5 C atoms, more preferably 6 C atoms or more than 10 C atoms, such as a fatty acid residue.

2. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to claim 1 characterised in that the substance is selected according to Formula II

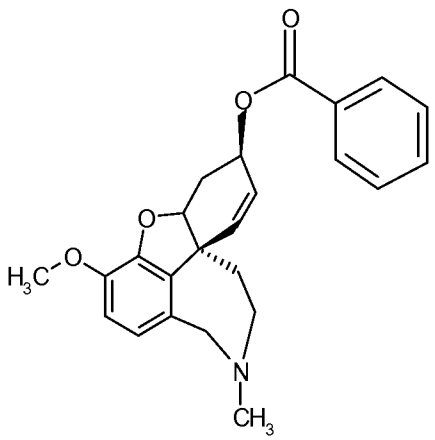


Formula II

wherein

R2-R6 comprise of any substituent selected from H, halogen, optionally substituted C_1-C_3 alkyl or cyclopropyl, OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl, N-dialkyl, optionally substituted aryl or heteroaryl, whereby neighbouring substitutents can cooperate to form an additional ring.

3. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to claim 1 or 2, wherein the substance is GLN-1062



GLN-1062

4. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein transmucosal administration provides avoidance and/or reduction of post-administration cleavage of the ester group of said substance by endogenous esterases.

5. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is present as a salt.

6. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the salt comprises of stoichiometric and/or non-stoichiometric salts and/or hydrates of the chemical substances according to Formula I, II or GLN 1062, whereby the salt is described as:

A compound of Formula I, II or GLN 1062 · n HX · m H2O,

whereby n, m = 0 – 5 and n and m can be the same or different, and HX = an acid, selected preferably from gluconic acid, saccharic acid, maleic acid or lactic acid.

7. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is present as a gluconate salt.

8. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is present as a saccharate salt.

9. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is present as a maleate salt.

10. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is present as a lactate salt.

11. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof has a solubility in water of at least 10% weight per volume (w/v).

12. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof has a solubility in water of at least 20% weight per volume (w/v).

13. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof has a solubility in water of at least 30% weight per volume (w/v).

14. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is the gluconate salt of GLN 1062.

15. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is the saccharate salt of GLN 1062.

16. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is the maleate salt of GLN 1062.

17. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance is the lactate salt of GLN 1062.

18. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof is administered at a dosage of 1 to 100 mg one to three times daily.

19. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof is administered at a dosage of 2 to 40 mg twice daily.

20. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof is administered intranasally as a 2 to 40% weight per volume (w/v) solution at an amount of 20 to 100 microliters in a single intranasal spray event, one to three times daily.

21. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the chemical substance or salt thereof is administered intranasally as a 10% weight per volume (w/v) solution at an amount of 50 microliters in a single intranasal spray event, one to three times daily.

22. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the brain disease to be treated is Alzheimer's and/or Parkinson's disease, the chemical substance is the gluconate or saccharate salt of GLN 1062, which is administered intranasally as a 2 to 40% weight per volume (w/v) solution at an amount of 20 to 100 microliters in a single intranasal spray event, one to three times daily.

23. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the brain disease to be treated is Alzheimer's disease,

the chemical substance is the gluconate or saccharate salt of GLN 1062, which is administered intranasally as a 10% weight per volume (w/v) solution at an amount of 50 microliters in a single intranasal spray event, twice daily.

24. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein intranasal administration is carried out by administering a therapeutically effective amount of the chemical substance using a suitable metered dose device, such as a atomizer, sprayer, pump spray, dropper, squeeze tube, squeeze bottle, pipette, ampule, nasal cannula, metered dose device, nasal spray inhaler, nasal continuous positive air pressure device, and/or breath actuated bi-directional delivery device.

25. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the sublingual administration is carried out by administering a therapeutically effective amount of the chemical substance under the tongue by placing one or more drops of a solution, or an amount of particulate in the form of freeze-dried powder or emulsion underneath the tongue and/or by spraying the underside of the tongue with a preselected volume of a liquid composition comprising the chemical substance.

26. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the buccal administration is carried out by administering a therapeutically effective amount of the chemical substance to the buccal vestibule inside the mouth between the cheek and the gums as a freeze-dried powder or emulsion, or an orally disintegrating or orodispersible tablet (ODT).

27. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the brain disease to be treated is selected from Alzheimer's and/or Parkinson's disease, other types of dementia, schizophrenia, epilepsy, stroke, poliomyelitis, neuritis, myopathy, oxygen and nutrient deficiencies in the brain after hypoxia, anoxia, asphyxia, cardiac arrest, chronic fatigue syndrome, various types of poisoning, anaesthesia, particularly neuroleptic anaesthesia, spinal cord disorders, inflammation, particularly central inflammatory disorders, postoperative delirium and/or subsyndronal postoperative delirium, neuropathic pain, abuse of alcohol and drugs, addictive alcohol and nicotine craving, and/or effects of radiotherapy.

28. Chemical substance for use as a medicament in the treatment of brain disease associated with cognitive impairment according to any one of the preceding claims, wherein the distribution of the chemical substance in a patient after administration exhibits a brain:blood ratio of more than 5, preferably more than 10, more preferably between 15 and 25.

29. Pharmaceutical composition comprising the chemical substance according to Formula I, II or GLN 1062 according to any one of the preceding claims and preferably one or more pharmaceutically acceptable carriers for use as a medicament in the treatment of brain diseases associated with cognitive impairment in a mammal, said treatment comprising transmucosal administration, selected from intranasal, sublingual or buccal administration, characterised in that the composition is suitable for transmucosal application.

30. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to the preceding claim, wherein the composition is an aqueous solution, comprising 2 to 40% weight per volume (w/v) of the substance to be administered.

31. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to the preceding claim, wherein the composition is an aqueous solution, comprising 5 to 15% weight per volume (w/v) of the substance to be administered.

32. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to the preceding claim, wherein the composition is an aqueous solution, comprising 10% weight per volume (w/v) of the substance to be administered.

33. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises N-ethylpyrrolidone.

34. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a self-microemulsifying drug delivery (SMEDD) system.

35. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to the preceding claim,

wherein the composition comprises glyceryl caprylate, polyethyleneglycol, propyleneglycol and/or diethyleneglycolemonoethylether.

36. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a sustained release formulation comprising chitosan.

37. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a micronized powder formulation of the chemical substance to be administered, preferably with a particle size of 0.1 to 100 microns, more preferably 1 to 10 microns.

38. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a sublingual tablet comprising lactose monohydrate, corn starch, polyvinylpyrrolidone (PVP) and/or magnesium stearate, and optionally a flavouring agent.

39. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a sublingual tablet comprising mannitol, sodium starch glycolate, croscarmellose, ascorbic acid and/or magnesium stearate and optionally a flavouring agent.

40. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises a multi-layered tablet with digestive acid resistant coating, such as eudragit.

41. Pharmaceutical composition for use as a medicament in the treatment of brain diseases associated with cognitive impairment according to any one of the preceding claims, wherein the composition comprises the substance to be administered at 2 to 40 % weight per weight (w/w), preferably 10 to 30%, or more preferably 5, 10, 20 or 30 % weight per weight (w/w) in a composition in the form of a self-microemulsifying drug delivery (SMEDD) system, sustained release formulation comprising chitosan, micronized powder formulation or sublingual or buccal tablet.

Fig. 1

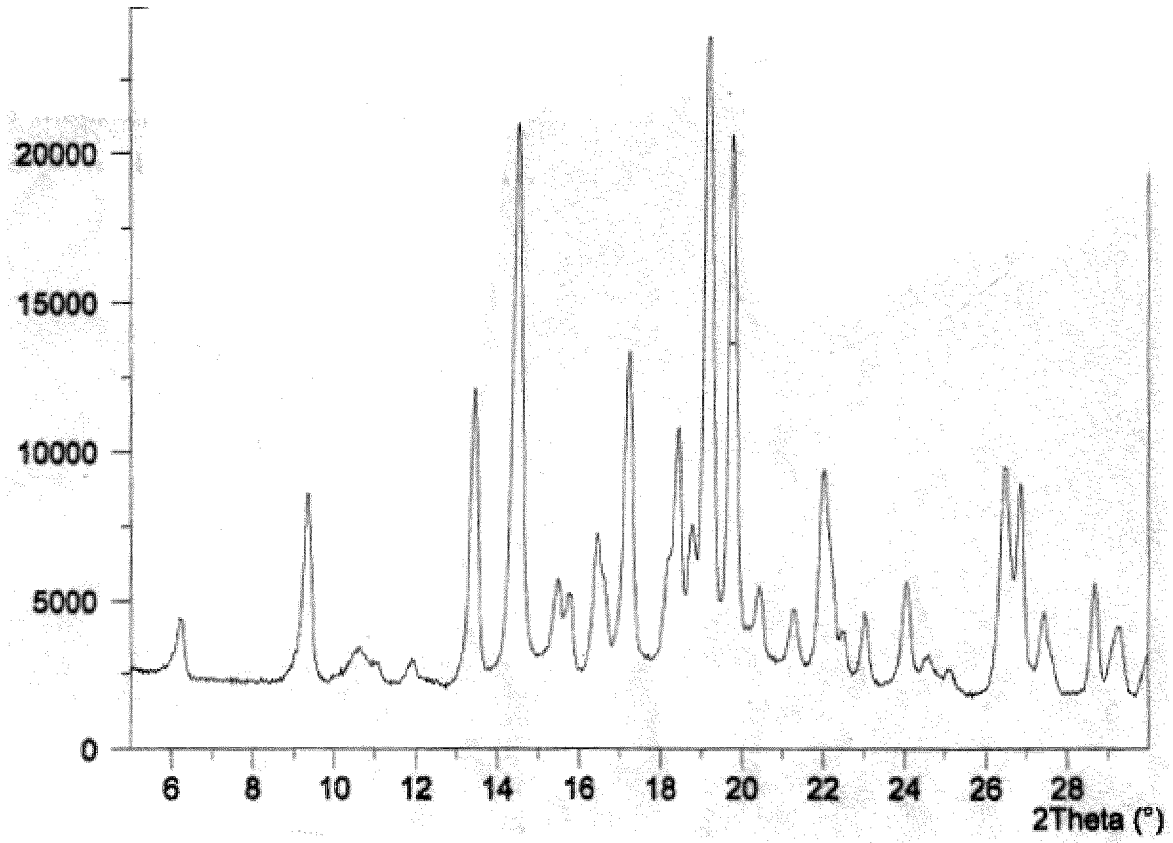


Fig. 2

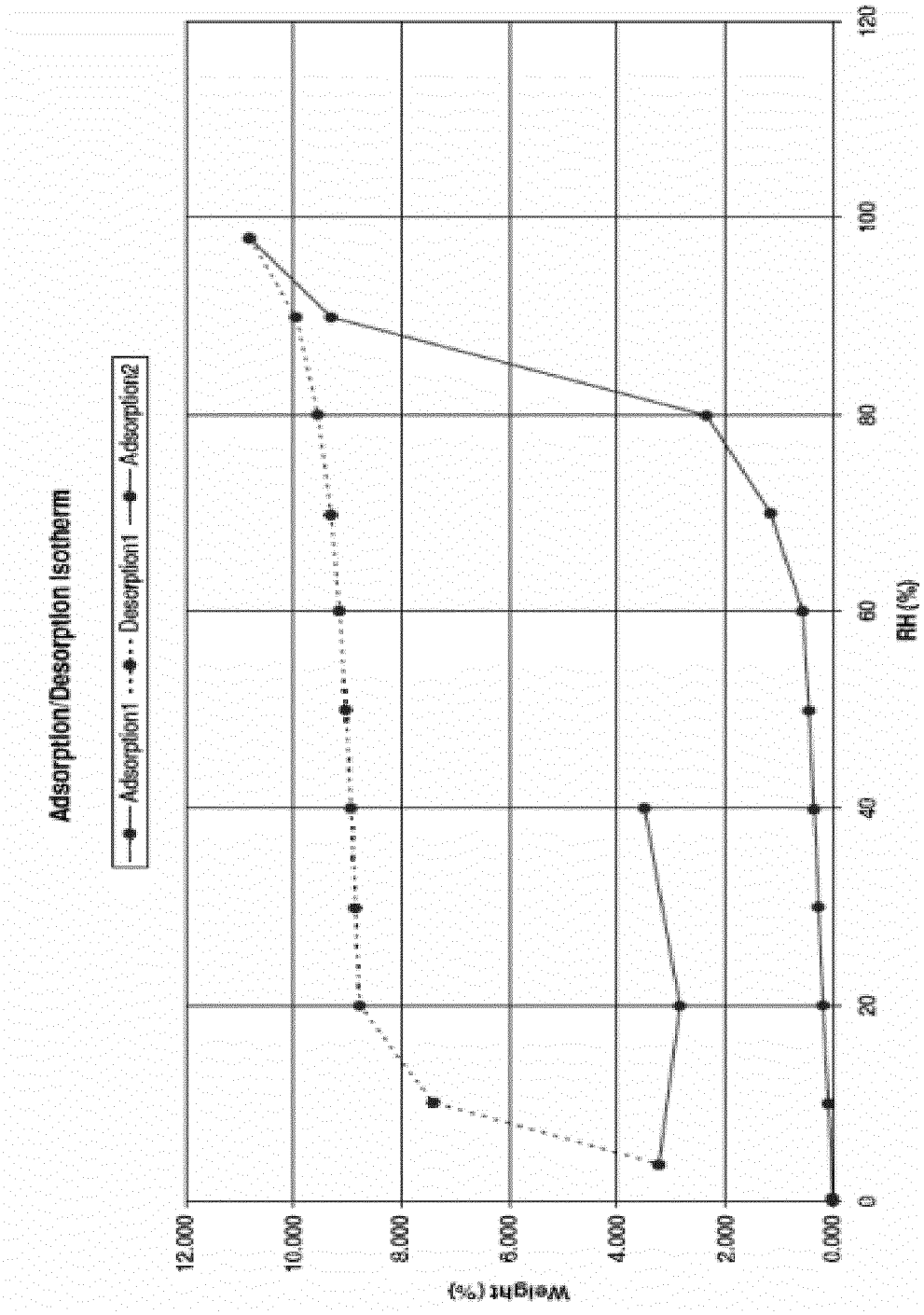

Adsorption/Desorption Isotherm
Adsorption1
Desorption1
Adsorption2
Weight (%)
RH (%)
0.000
2.000
4.000
6.000
8.000
10.000
12.000
0
20
40
60
80
100
120

Fig. 3

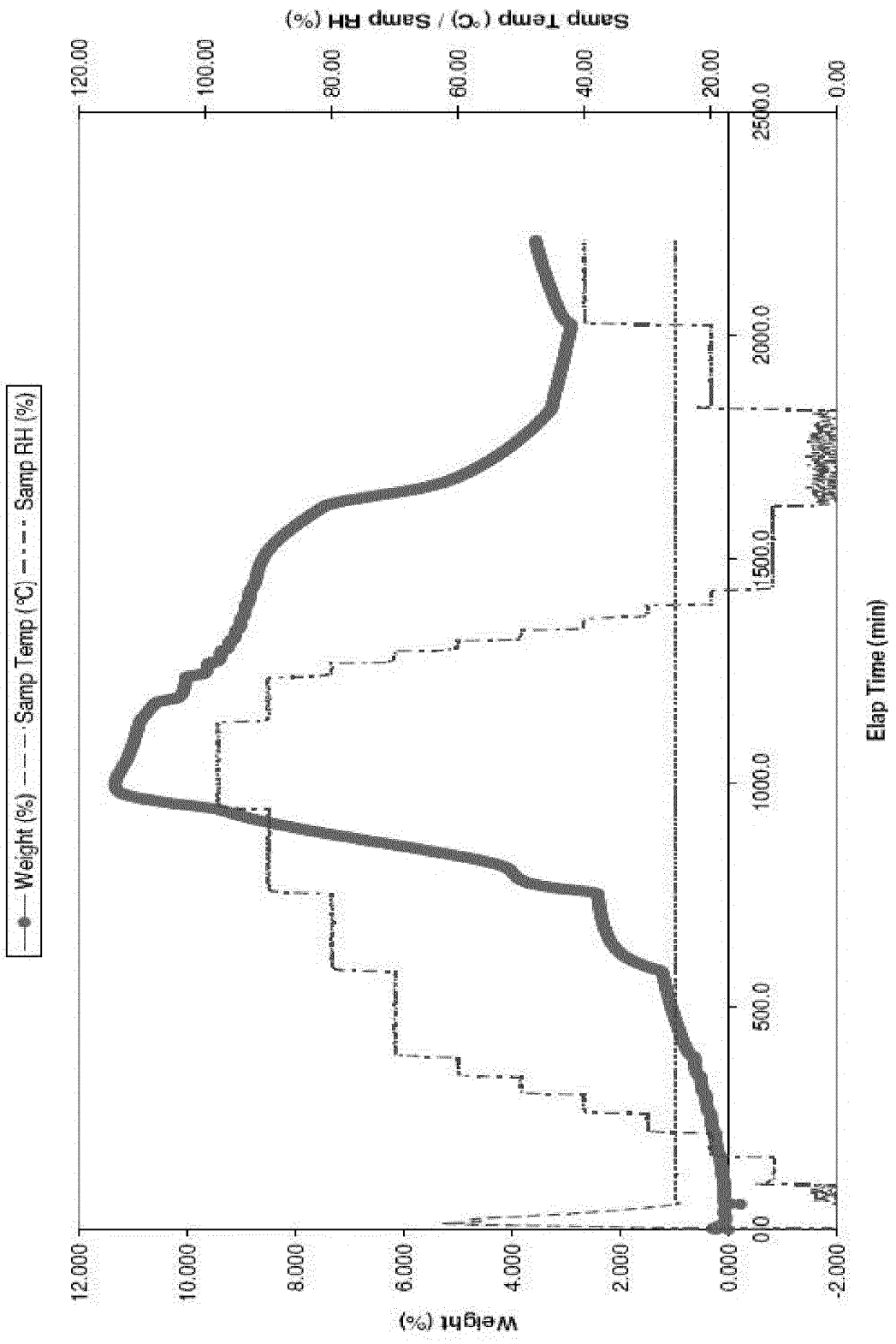

Weight (%)
Samp Temp (°C)
Samp RH (%)
Elap Time (min)
Weight (%)
Samp Temp (°C) / Samp RH (%)
12.000
10.000
8.000
6.000
4.000
2.000
0.000
-2.000
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0.0
500.0
1000.0
1500.0
2000.0
2500.0

Fig. 4

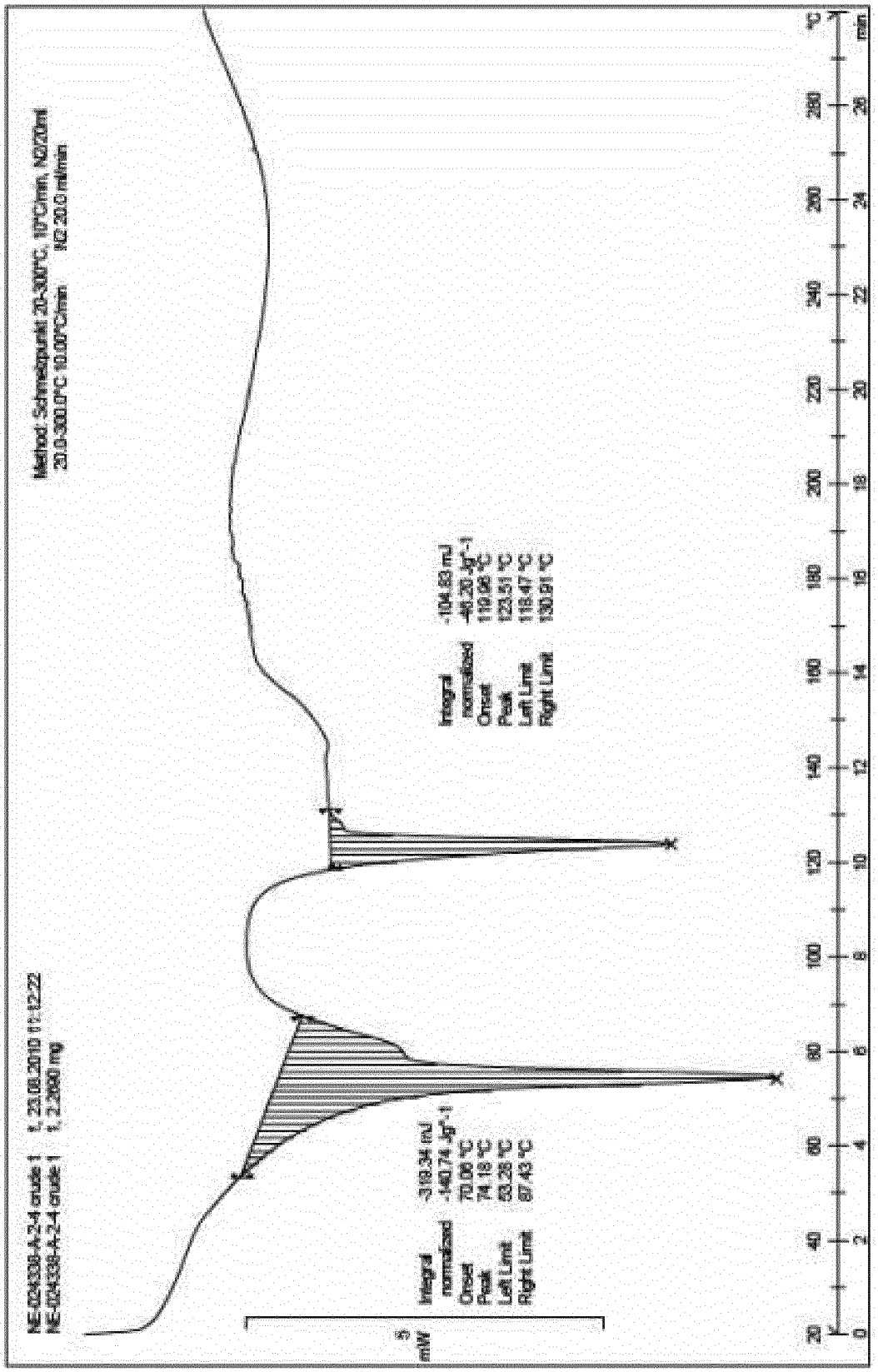

NE-024338-A-2-4 crude 1 t, 23.08.2010 11:12:22
NE-024338-A-2-4 crude 1 t, 2.2000 mg
Method: Schmelzpunkt 20-300°C, 10°C/min, N2/20ml
20.0-300.0°C 10.00°C/min N2 20.0 ml/min
mW
exo
-104.83 mJ
-46.20 Jg-1
Integral
normalized
Onset 119.68 °C
Peak 123.51 °C
Left Limit 118.47 °C
Right Limit 130.91 °C
-318.34 mJ
-140.74 Jg-1
Integral
normalized
Onset 72.06 °C
Peak 74.18 °C
Left Limit 63.28 °C
Right Limit 87.43 °C
°C
min

Fig. 5

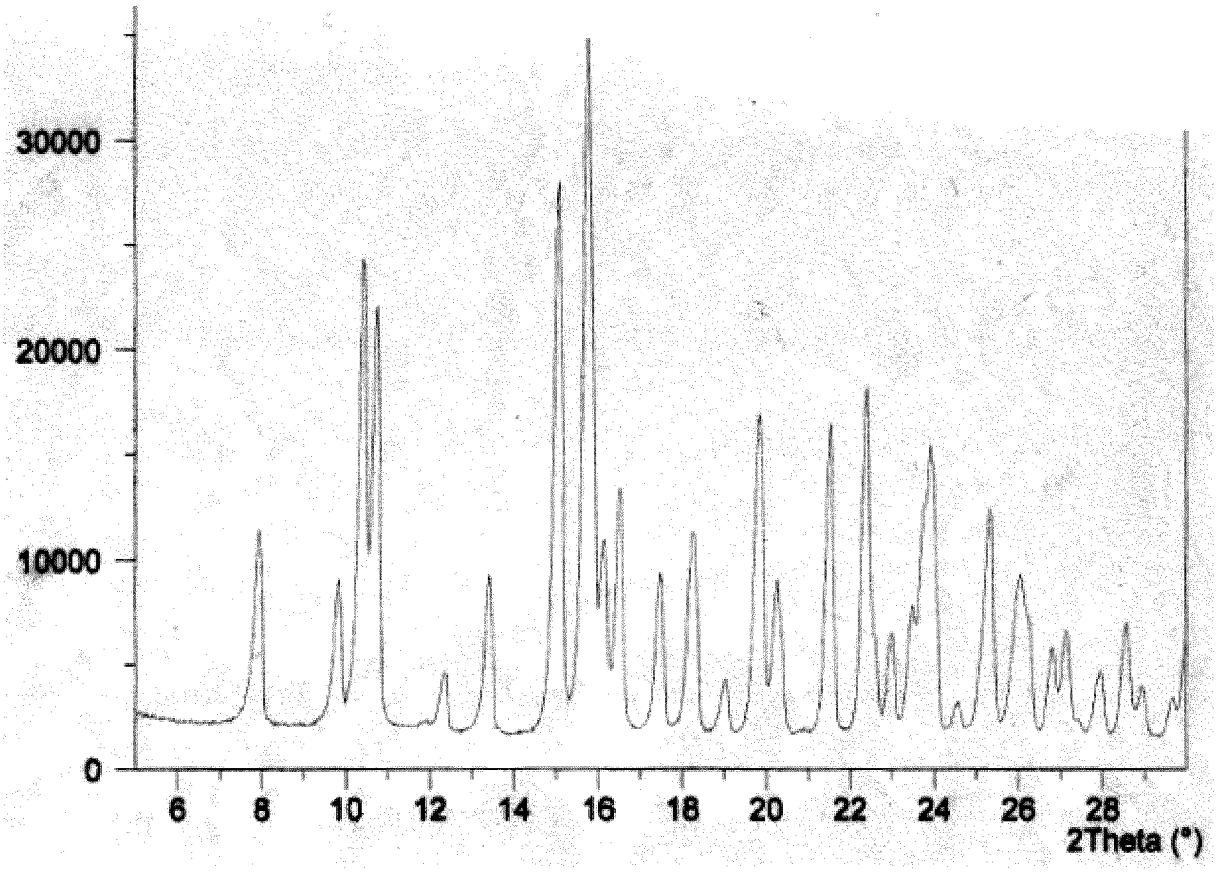


Fig. 6

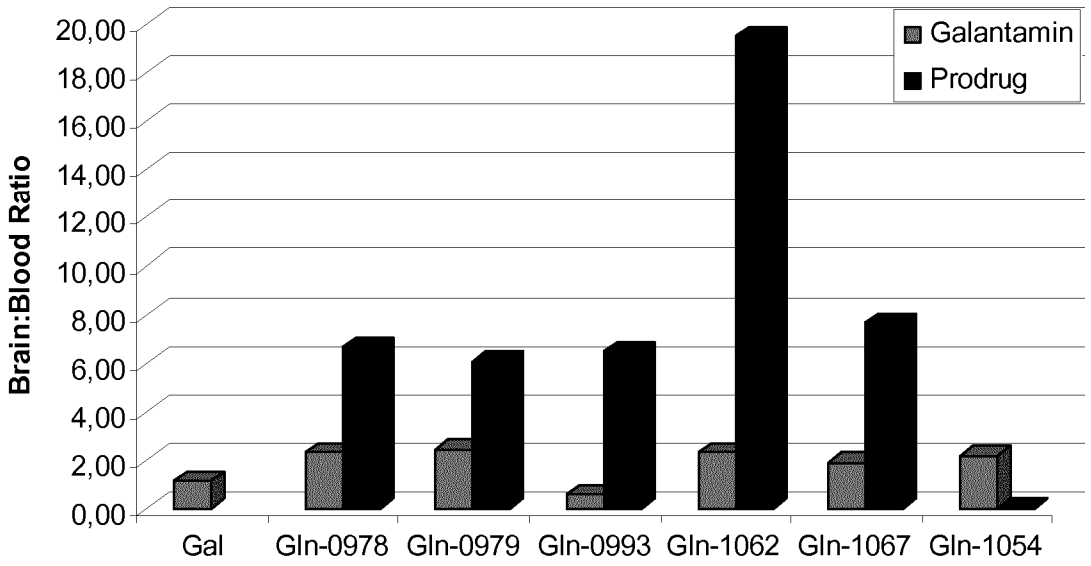

Brain:Blood Ratio
20,00
18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Galantamin
Prodrug
Gal
Gln-0978
Gln-0979
Gln-0993
Gln-1062
Gln-1067
Gln-1054

Fig. 7

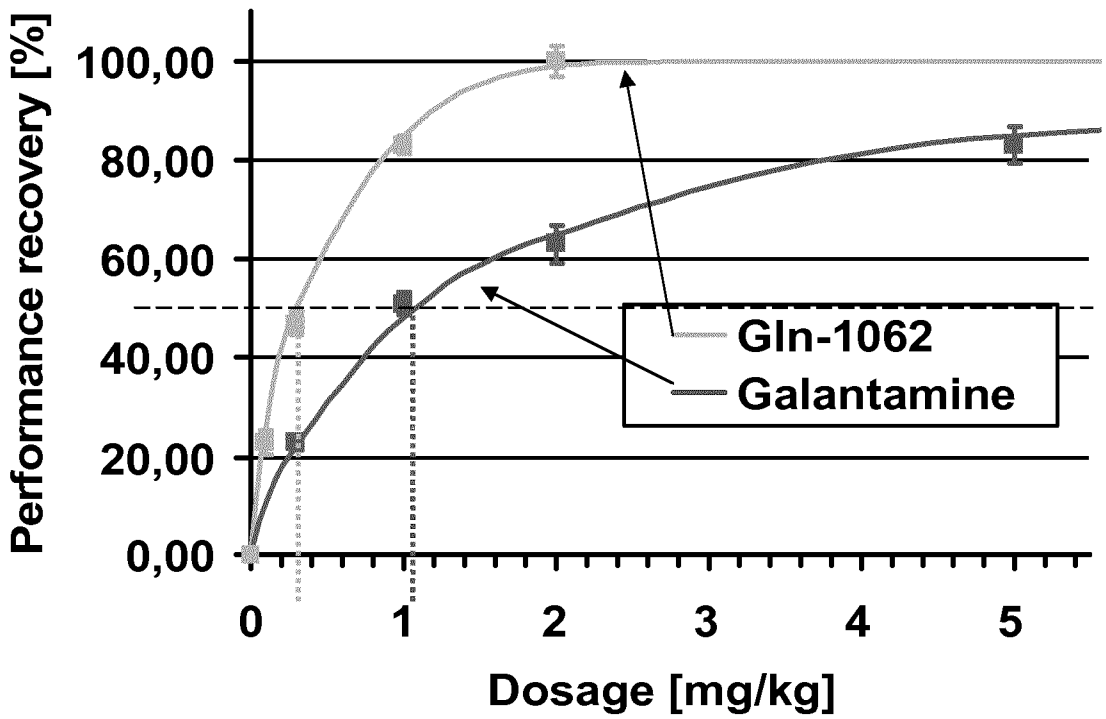

Performance recovery [%]
100,00
80,00
60,00
40,00
20,00
0,00
0
1
2
3
4
5
Dosage [mg/kg]
Gln-1062
Galantamine

Fig. 8

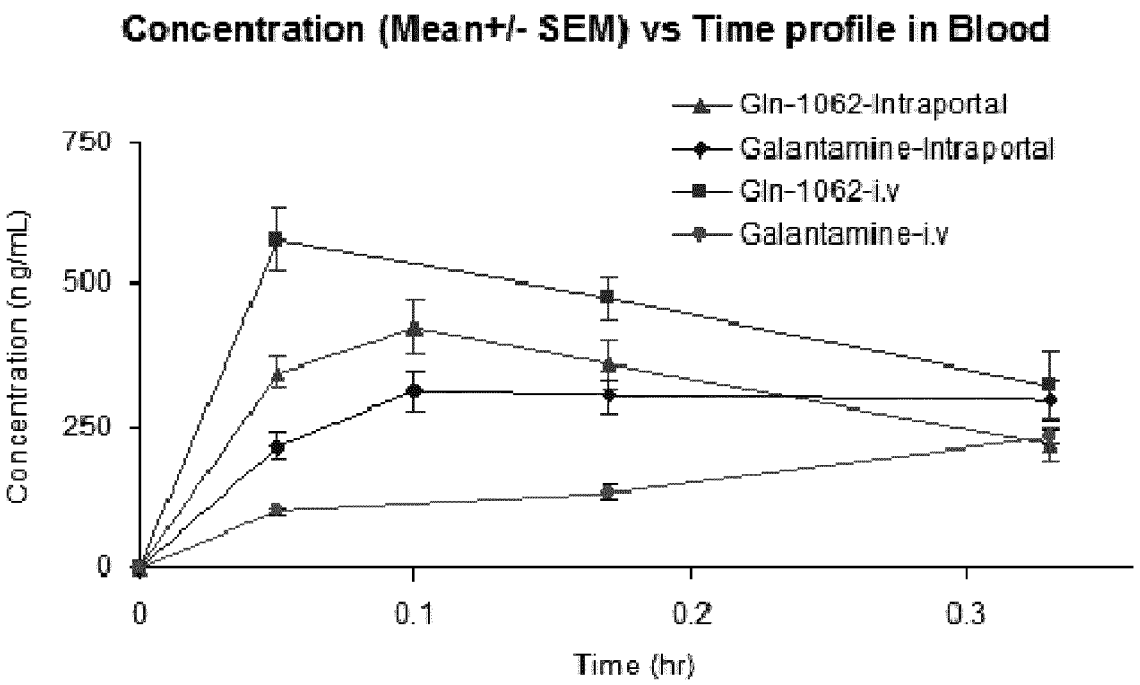

Concentration (Mean+/- SEM) vs Time profile in Blood
Gln-1062-Intraportal
Galantamine-Intraportal
Gln-1062-i.v
Galantamine-i.v
Concentration (ng/mL)
750
500
250
0
0
0.1
0.2
0.3
Time (hr)

Fig. 9

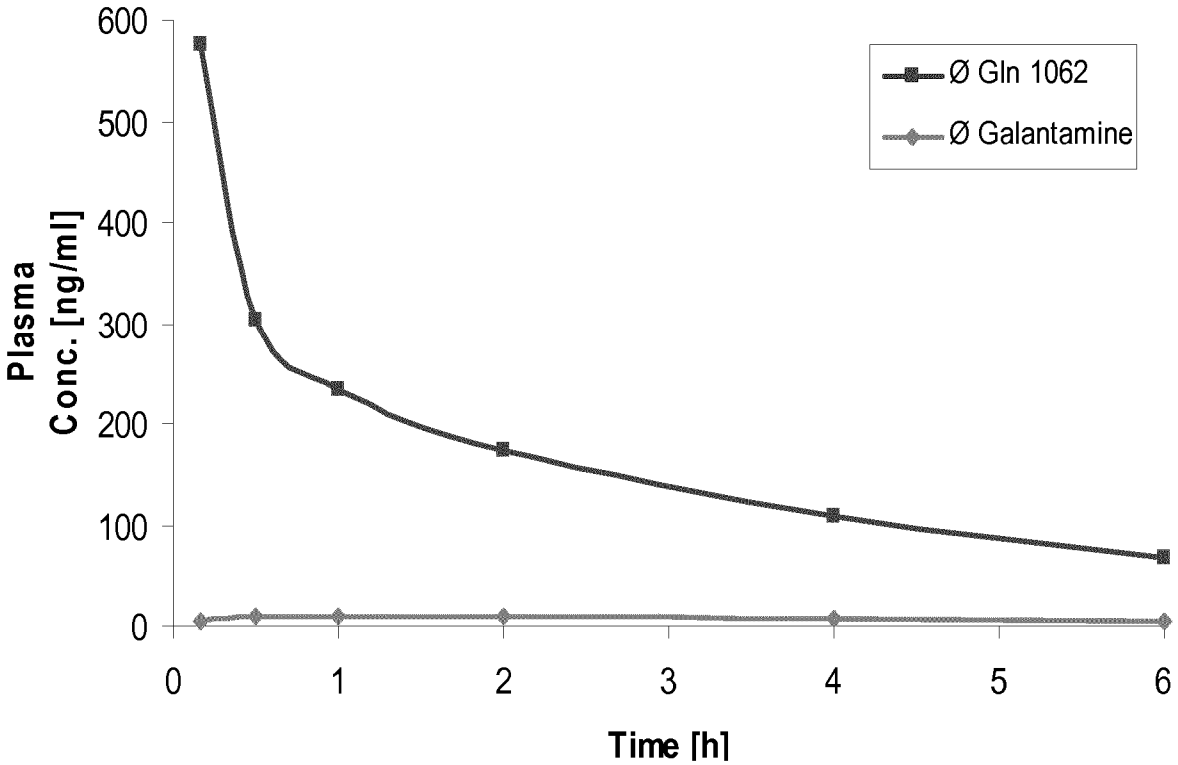

Ø Gln 1062
Ø Galantamine
Plasma Conc. [ng/ml]
600
500
400
300
200
100
0
0
1
2
3
4
5
6
Time [h]

Fig. 10

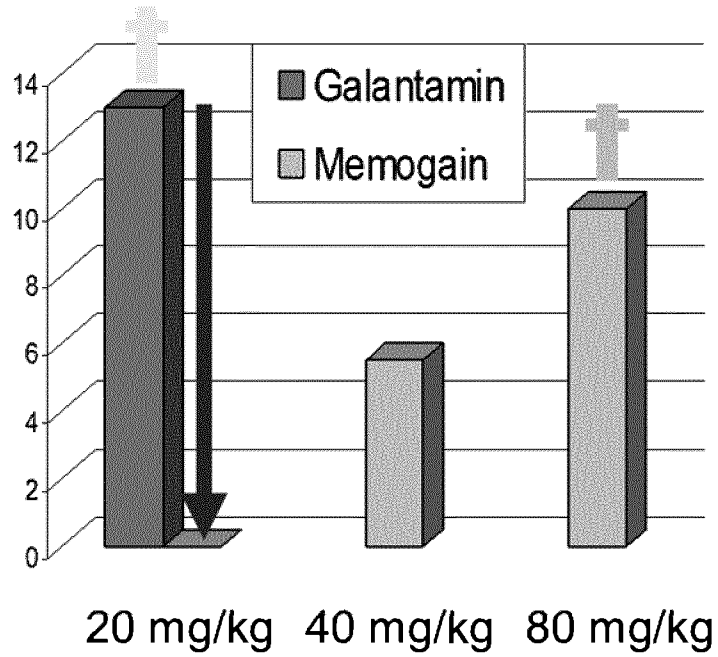

Galantamin
Memogain
14
12
10
8
6
4
2
0
20 mg/kg
40 mg/kg
80 mg/kg

Fig. 11

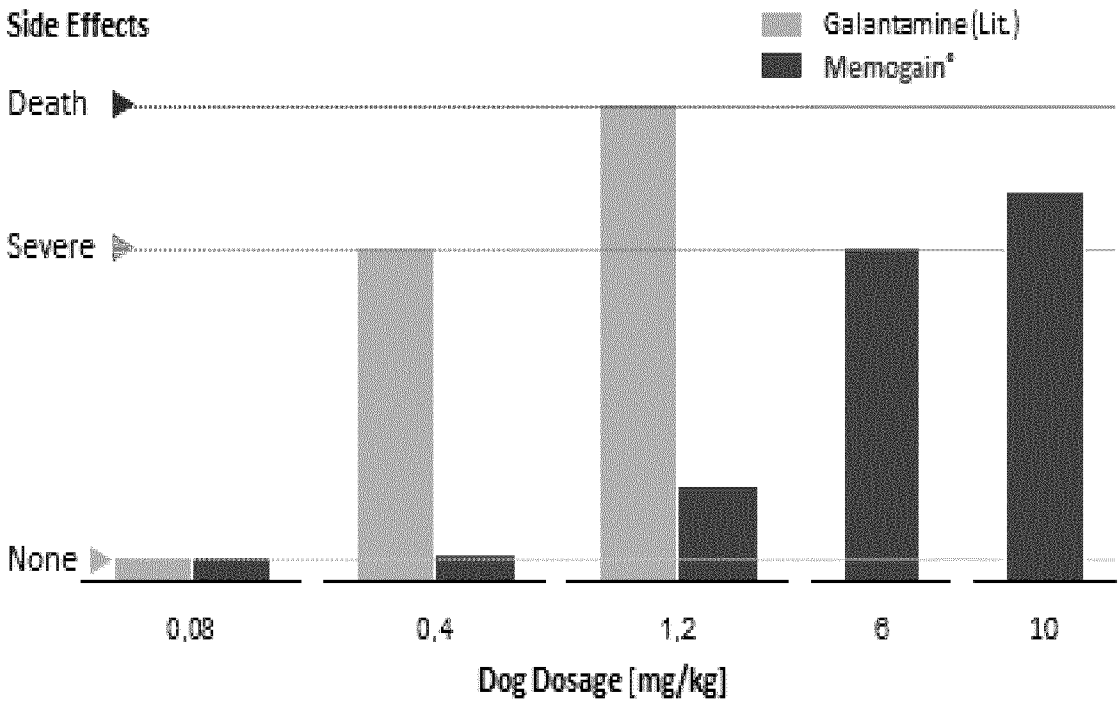

Side Effects
Galantamine (Lit.)
Memogain®
Death
Severe
None
0,08
0,4
1,2
8
10
Dog Dosage [mg/kg]

Fig. 12

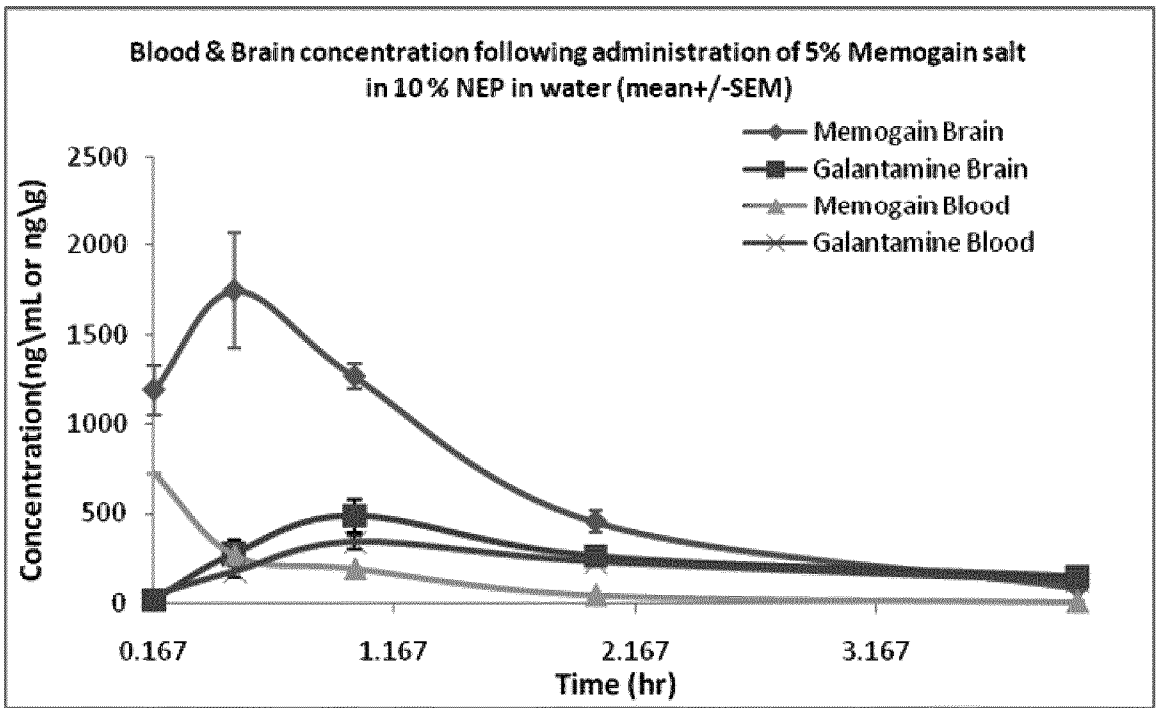

Blood & Brain concentration following administration of 5% Memogain salt in 10 % NEP in water (mean+/-SEM)
Memogain Brain
Galantamine Brain
Memogain Blood
Galantamine Blood
Concentration(ng\mL or ng\g)
2500
2000
1500
1000
500
0
0.167
1.167
2.167
3.167
Time (hr)

Fig. 13

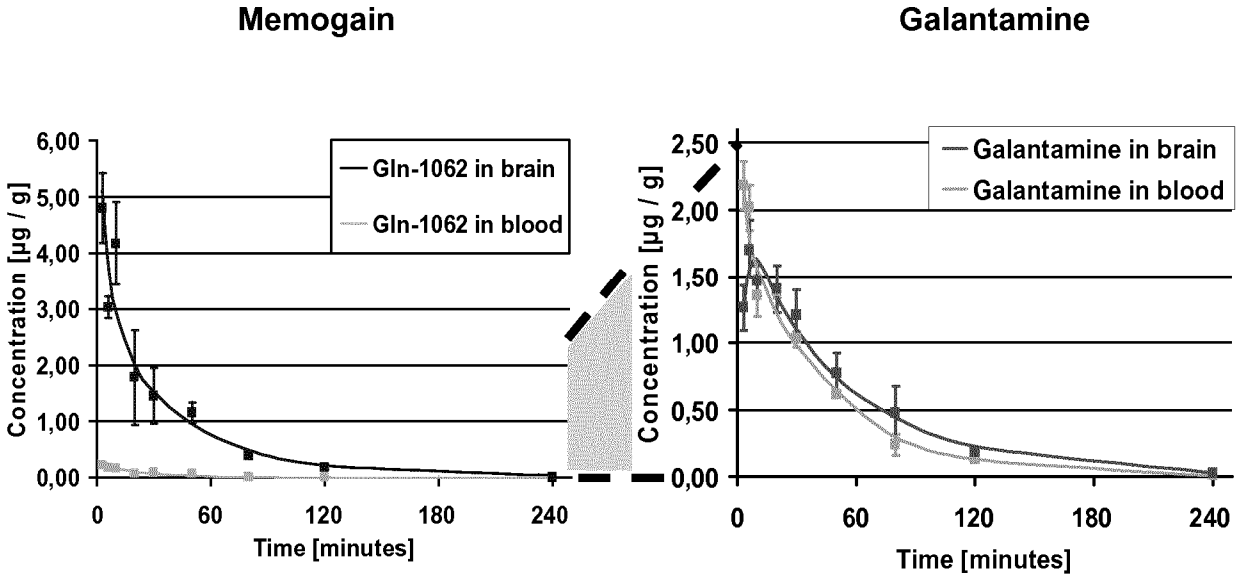
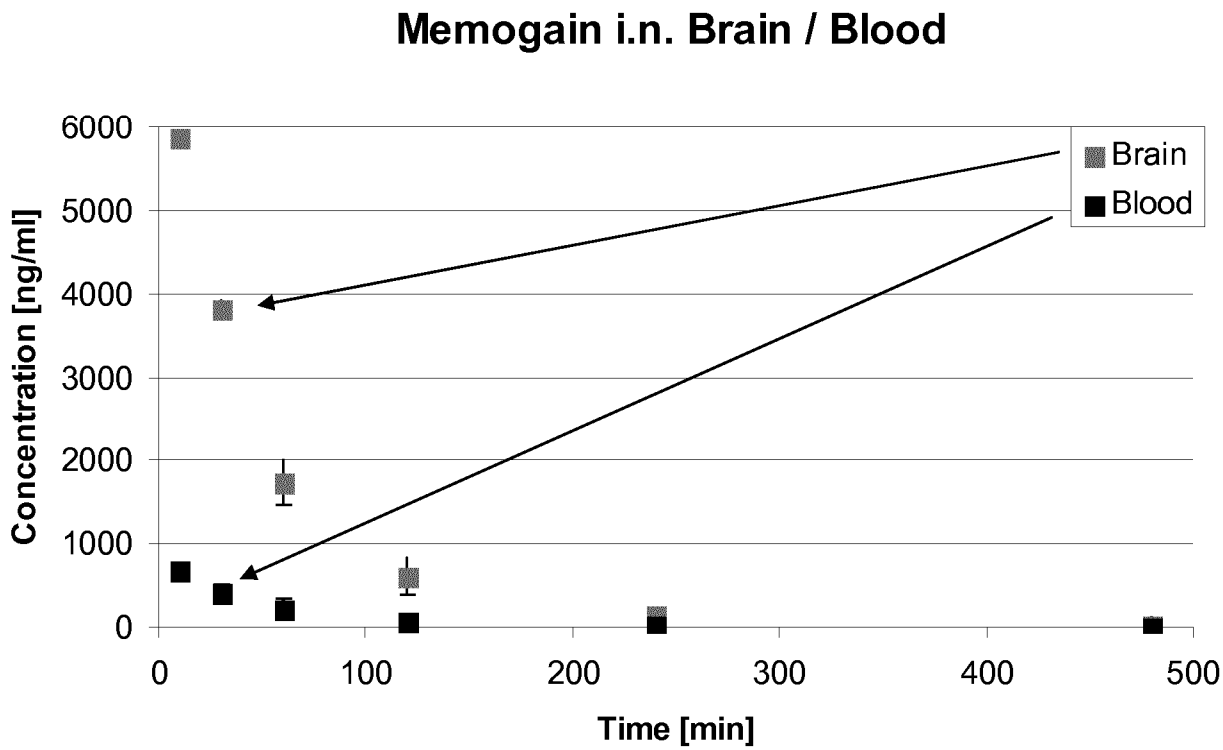

Memogain
Galantamine
Gln-1062 in brain
Gln-1062 in blood
Concentration [µg / g]
6,00
5,00
4,00
3,00
2,00
1,00
0,00
0
60
120
180
240
Time [minutes]
Galantamine in brain
Galantamine in blood
Concentration [µg / g]
2,50
2,00
1,50
1,00
0,50
0,00
0
60
120
180
240
Time [minutes]

Fig. 14


Memogain i.n. Brain / Blood
Concentration [ng/ml]
6000
5000
4000
3000
2000
1000
0
0
100
200
300
400
500
Time [min]
Brain
Blood

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/065880

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065880

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/55
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/253654 A1 (MAELICKE ALFRED [DE]) 8 October 2009 (2009-10-08)	1-41
Y	claims 21 and 22; 0147; 0197 and 0198; 0201; 0194 -----	1-41
Y	WO 2009/127218 A1 (GALANTOS PHARMA GMBH [DE]; MAELICKE ALFRED [DE]) 22 October 2009 (2009-10-22) claims 21 and 22; 0147; 0197 and 0198; 0201; 0194 ----- -/--	1-41

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2013	31/10/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALFRED MAELICKE ET AL: "Memogain is a Galantamine Pro-drug having Dramatically Reduced Adverse Effects and Enhanced Efficacy", JOURNAL OF MOLECULAR NEUROSCIENCE, vol. 40, no. 1-2, 1 January 2010 (2010-01-01), pages 135-137, XP055041228, ISSN: 0895-8696, DOI: 10.1007/s12031-009-9269-5 abstract	1-41
X	KALETTA T ET AL: "Memogain, a novel high potency drug treatment for AD", SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 40, 2010, XP009163806, & 40TH ANNUAL MEETING OF THE SOCIETY-FOR-NEUROSCIENCE; SAN DIEGO, CA, USA; NOVEMBER 13 -17, 2010	1-4, 11-13, 24,27-29
Y	whole document, in particular first 5 lines of abstract	1-41
Y	LEONARD ET AL: "In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 335, no. 1-2, 28 March 2007 (2007-03-28), pages 138-146, XP022003898, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2006.11.013 abstract; p. 139, col. 1, first	1-41
Y	US 2004/254146 A1 (QUAY STEVEN C [US] ET AL) 16 December 2004 (2004-12-16) example 1; 0004; 0006; 0011	1-41
Y	VIVIANA DE CARO ET AL: "Evaluation of galantamine transbuccal absorption by reconstituted human oral epithelium and porcine tissue as buccal mucosa models: Part I", EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 70, no. 3, 1 November 2008 (2008-11-01), pages 869-873, XP055085293, ISSN: 0939-6411, DOI: 10.1016/j.ejpb.2008.06.025 abstract	1-41

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/065880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009253654 A1	08-10-2009	US 2009253654 A1	08-10-2009
		US 2013210808 A1	15-08-2013
WO 2009127218 A1	22-10-2009	CA 2721007 A1	22-10-2009
		CN 102007129 A	06-04-2011
		EP 2137192 A1	30-12-2009
		JP 2011516588 A	26-05-2011
		WO 2009127218 A1	22-10-2009
US 2004254146 A1	16-12-2004	CA 2564353 A1	03-11-2005
		EP 1753397 A2	21-02-2007
		JP 2007534686 A	29-11-2007
		US 2004254146 A1	16-12-2004
		WO 2005102275 A2	03-11-2005

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 24(completely); 1-23, 27-37, 41(partially)

   A substance/composition according to formula I for use as a medicament in the treatment of brain diseases associated with cognitive impairment, wherein said treatment comprises intranasal administration of a therapeutically effective amount of said substance.

   ---

2. claims: 25, 26, 38-40(completely); 1-23, 27-37, 41(partially)

   A substance/composition according to formula I for use as a medicament in the treatment of brain diseases associated with cognitive impairment, wherein said treatment comprises sublingual or buccal administration of a therapeutically effective amount of said substance.

   ---

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104507461 A
(43)申请公布日 2015.04.08

(21)申请号 201380039870.3

(22)申请日 2013.07.29

(30)优先权数据
12178187.6 2012.07.27 EP
61/676,348 2012.07.27 US

(85)PCT国际申请进入国家阶段日
2015.01.27

(86)PCT国际申请的申请数据
PCT/EP2013/065880 2013.07.29

(87)PCT国际申请的公布数据
WO2014/016430 EN 2014.01.30

(71)申请人 神经动力生命科学公司
地址 加拿大夏洛特敦

(72)发明人 阿尔弗雷德·梅里克

(74)专利代理机构 北京银龙知识产权代理有限公司 11243
代理人 钟晶 於毓桢

(51)Int.Cl.
A61K 31/00(2006.01)
A61K 31/55(2006.01)

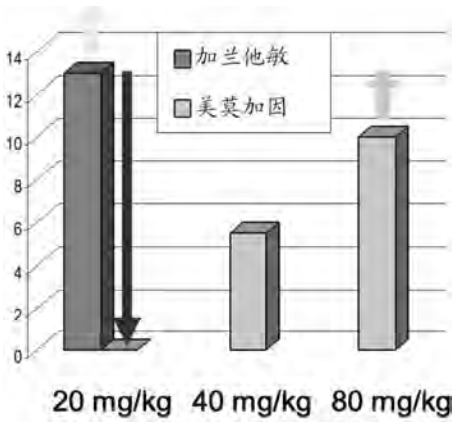
权利要求书5页 说明书35页 附图9页

(54)发明名称

通过亲脂性前体药物的选定制剂和粘膜给药来提高加兰他敏的脑生物利用度

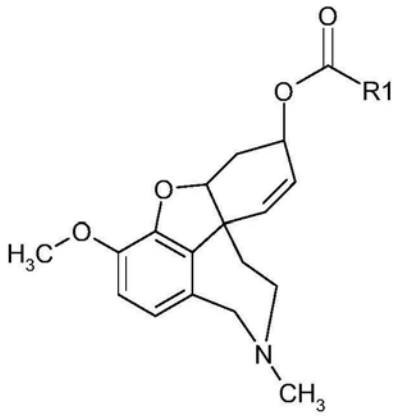
(57)摘要

本发明涉及用于CNS(中枢神经系统)治疗性且高溶解性盐、其溶液、乳剂或粉末制剂的选定给药途径,由于本发明的化合物的给药模式和化学性质,该选定的给药途径具有最佳的脑递送。



CN 104507461 A

1.用作治疗与认知障碍相关的脑疾病的药物的根据式 I 的化学物质，其中，所述治疗包括将治疗有效量的所述物质进行粘膜给药，所述粘膜给药选自鼻内给药、舌下给药或颊内给药，

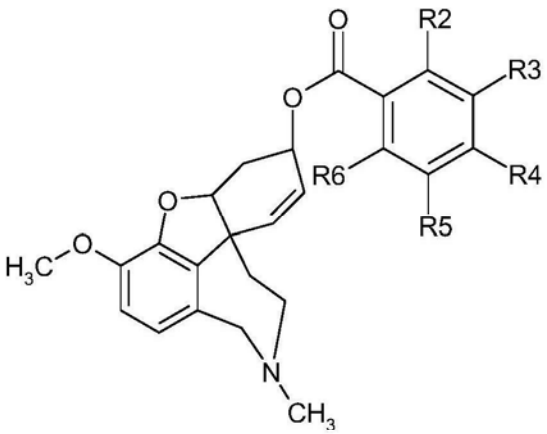


式 I

其中，

R1 ＝芳族或杂芳族的 5 元或 6 元环，诸如可选地取代的萘、噻吩、吡咯、咪唑、吡唑、噁唑、噻唑；或直链或支链的脂肪族残基，诸如 $CH(C_2H_5)CH_3$、CH_2-$C(CH_3)_3$、环丙基，或优选的包括多于 5 个 C 原子、更优选多于 6 个 C 原子或多于 10 个 C 原子的脂肪族残基，诸如脂肪酸残基。

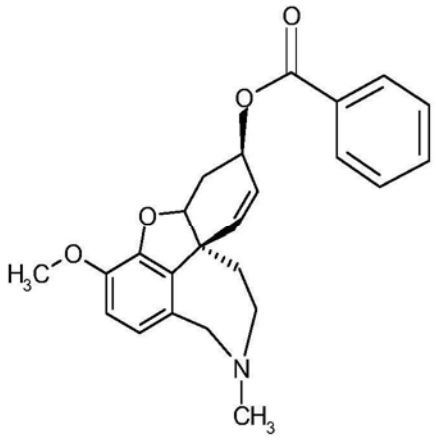
2.根据权利要求 1 所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其特征在于，所述物质选自式 II：



式 II

其中，R2 至 R6 包括从 H、卤素、可选地取代的 C_1-C_3烷基或环丙基、OH、O- 烷基、SH、S- 烷基、NH_2、NH- 烷基、N- 二烷基、可选地取代的芳基或杂芳基中选择的任何取代基，其中，相邻的取代基能够配合而形成额外的环。

3.根据权利要求 1 或 2 所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述物质为 GLN-1062



GLN-1062。

4.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，粘膜给药避免和/或降低由于内源性酯酶而造成的所述化学物质的酯基在给药后裂解。

5.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质以盐的形式存在。

6.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述盐包括根据式I、式II或GLN 1062的化学物质的化学计量的盐和/或非化学计量的盐和/或水合物，其中，所述盐被描述为如下的化合物：

式I、式II或GLN 1062·nHX·mH_2O，

其中，n、m＝0至5，并且n和m相同或不同，并且HX＝酸，所述酸优选地选自葡萄糖酸、糖二酸、马来酸或乳酸。

7.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质以葡萄糖酸盐的形式存在。

8.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质以糖二酸盐的形式存在。

9.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质以马来酸盐的形式存在。

10.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质以乳酸盐的形式存在。

11.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐具有在水中至少10wt％/单位体积(w/v)的溶解度。

12.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐具有在水中至少20wt％/单位体积(w/v)的溶解度。

13.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐具有在水中至少30wt％/单位体积(w/v)的溶解度。

14.根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化

学物质，其中，所述化学物质是 GLN 1062 的葡萄糖酸盐。

15. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质是 GLN 1062 的糖二酸盐。

16. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质是 GLN 1062 的马来酸盐。

17. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质是 GLN 1062 的乳酸盐。

18. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐以 1mg 至 100mg 的剂量每日 1 ～ 3 次地给药。

19. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐以 2mg 至 40mg 的剂量每日 2 次地给药。

20. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐按照 2 至 40wt％ / 单位体积 (w/v) 的溶液的形式以 20 微升至 100 微升的量通过单次鼻内喷雾动作进行鼻内给药，每日 1 ～ 3 次。

21. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述化学物质或所述化学物质的盐按照 10wt％ / 单位体积 (w/v) 的溶液的形式以 50 微升的量通过单次鼻内喷雾动作进行鼻内给药，每日 1 ～ 3 次。

22. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，待治疗的所述脑疾病为阿兹海默氏症和 / 或帕金森氏病，所述化学物质为 GLN 1062 的葡萄糖酸盐或糖二酸盐，其按照 2 至 40wt％ / 单位体积 (w/v) 的溶液的形式以 20 微升至 100 微升的量通过单次鼻内喷雾动作进行鼻内给药，每日 1 ～ 3 次。

23. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，待治疗的所述脑疾病为阿兹海默氏症，所述化学物质为 GLN 1062 的葡萄糖酸盐或糖二酸盐，其按照 10wt％ / 单位体积 (w/v) 的溶液的形式以 50 微升的量通过单次鼻内喷雾动作进行鼻内给药，每日 2 次。

24. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，鼻内给药通过用合适的计量剂量装置将治疗有效量的所述化学物质进行给药来完成，所述合适的计量剂量装置诸如雾化器、喷雾器、喷雾泵、滴管、挤压筒、挤压瓶、移液管、安瓿、鼻腔插管、计量剂量设备、喷鼻吸入器、鼻腔持续正空气压力装置和 / 或呼吸驱动的双向输送装置。

25. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述舌下给药通过如下完成 :将包括所述化学物质的一滴或多滴溶液、或一定量的包括所述化学物质的冷冻干燥粉末形式或乳剂形式的颗粒放置到舌下，和 / 或将预定体积的包括所述化学物质的液体组合物喷雾到舌下，从而在舌下将治疗有效量的所述化学物质进行给药。

26. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，所述颊内给药通过如下完成 :将治疗有效量的所述化学物质以冷冻干燥粉末或乳剂的形式或口腔崩解片或口腔分散片 (ODT) 的形式给药至口中位于脸颊和牙龈之间

的颊前庭。

27. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，待治疗的所述脑疾病选自：阿兹海默氏症和 / 或帕金森氏病，其它类型的痴呆，精神分裂症，癫痫症，中风，脊髓灰质炎，神经炎，肌病，以及低氧、缺氧、窒息、心搏停止后在脑中的氧和营养缺乏，慢性疲劳综合症，各种类型的中毒，麻醉、尤其是神经安定药麻醉，脊髓病症，炎症、尤其是中央炎性疾病，术后谵妄和 / 或亚综合症术后谵妄，神经疼痛，酒精和药物滥用，酒精成瘾和尼古丁成瘾，和 / 或放射疗法效应。

28. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，给药后，所述化学物质在患者体内的分布呈现为脑：血液比大于 5，更优选大于 10，更优选在 15 和 25 之间。

29. 用作治疗哺乳动物中与认知障碍相关的脑疾病的药物的药物组合物，其特征在于，所述药物组合物包括根据前述权利要求中任一项所述的式 I、式 II 或 GLN 1062 的化学物质，以及优选的一种或多种药学可接受的载体，所述治疗包括粘膜给药，所述粘膜给药选自鼻内给药、舌下给药或颊内给药，所述组合物适用于粘膜施用。

30. 根据前述权利要求所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物为包括 2 至 40wt％ / 单位体积 (w/v) 的待给药物质的水溶液。

31. 根据前述权利要求所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物为包括 5 至 15wt％ / 单位体积 (w/v) 的待给药物质的水溶液。

32. 根据前述权利要求所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物为包括 10wt％ / 单位体积 (w/v) 的待给药物质的水溶液。

33. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括 N- 乙基吡咯烷酮。

34. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括自微乳化药物递送 (SMEDD) 系统。

35. 根据前述权利要求所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括辛酸甘油酯、聚乙二醇、丙二醇和 / 或二乙二醇单乙基醚。

36. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括包含壳聚糖的缓释制剂。

37. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括待给药化学物质的微粉化粉末制剂，所述微粉化粉末制剂的粒径优选为 0.1 微米至 100 微米，更优选 1 微米至 10 微米。

38. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括舌下片剂，所述舌下片剂包括乳糖一水合物、玉米淀粉、聚乙烯吡咯烷酮 (PVP) 和 / 或硬脂酸镁，以及可选的调味剂。

39. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述化合物包括舌下片剂，所述舌下片剂包括甘露糖醇、淀粉羟乙酸钠、交联甲羧纤维素、抗坏血酸和 / 或硬脂酸镁，以及可选的调味剂。

40. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包括具有耐消化酸的包衣、诸如丙烯酸树脂的多层片剂。

41. 根据前述权利要求中任一项所述的用作治疗与认知障碍相关的脑疾病的药物的药物组合物，其中，所述组合物包含待给药的物质的方式是待给药的物质在组合物中为 2 至 40wt％ / 单位重量 (w/w)、优选 10 至 30wt％ / 单位重量 (w/w)、或更优选 5、10、20 或 30wt％ / 单位重量 (w/w)，并且所述组合物包含待给药物质的形式为自微乳化药物递送 (SMEDD) 系统的形式、或包含壳聚糖的缓释制剂的形式、或微粉化粉末制剂的形式、或舌下片剂或口腔片剂的形式。

通过亲脂性前体药物的选定制剂和粘膜给药来提高加兰他敏的脑生物利用度

技术领域

[0001] 本发明涉及用于CNS(中枢神经系统)治疗性且高溶解性的盐、其溶液、乳剂或粉末制剂的选定给药途径,由于本发明的化合物的给药模式和化学性质,该选定的给药途径具有最佳的脑递送。本发明的治疗性化合物涉及药理学活性化合物的亲脂性前体药物,其作为前体药物,在CNS中对于它们的主要目标、尤其是胆碱酯酶和/或烟碱型乙酰胆碱受体是无活性的。药理学活性的母体药经由内源性酶裂解而成为并且用作烟碱型乙酰胆碱受体(nAChR)上的变构增效配体(APL),和/或乙酰胆碱酯酶(AChE)和其他胆碱酯酶(ChE)的可逆抑制剂。为了最大限度地穿过血脑屏障(BBB)并且为了防止本发明的前体药物在穿过BBB到达其作用位点之前被内源性酯酶裂解,前体药物被设计为具有高度亲脂性(logP>2.5)并且通过口腔或鼻腔内的粘膜吸收途径递送。

背景技术

[0002] 目前,用于阿兹海默氏症(AD)的首选药物治疗是使用胆碱酯酶抑制剂,诸如多奈哌齐、卡巴拉汀和加兰他敏。其中,加兰他敏已经显示出了具有独特的第二作用模式,即,烟碱型乙酰胆碱受体的变构敏化(Maelicke A;Albuquerque E X(1996),New appoaches to drug therapy in Alzheimer's dementia.Drug Discovery Today 1,53-59)。加兰他敏提高了通过次最大浓度的乙酰胆碱(ACh)或胆碱(Ch)或其它nAChR激动剂诱导通道开放的可能性。由于AD的发展与nAChR的损失增加相关,烟碱受体的APL-增强的活性对于AD和其它形式的痴呆而言是在症状上以及有可能在疾病上的合适的缓解治疗方法(Storch A等人,(1995).Physostigmine,galantamine and codeine act as noncompetitive nicotinic agonists on clonal rat pheochromocytoma cells.Eur J Biochem 290:207-219;Kihara T等人,(2004)Galantamine modulates nicotinic receptors and blocks Aβ-enhanced glutamate toxicity.Biochem Biophys Res Commun 325:976-982;Akata K等人(2011)Galantamine-induced amyloid-clearance mediated via stimulation of microglial nicotinic acetylcholine receptors. J Biol Chem 286;Maelicke A(2006)Allosteric sensitisation of brain nicotinic receptors as a treatment strategy in Alzheimer's dementia.In:Therapeutic Strategies in Dementia(Eds:Ritchie CW,Ames DJ,Masters CL,Cummings J),Clinical Publishing,Oxford,2006;153-172))。

[0003] 与卡巴拉汀和多奈哌齐相反,加兰他敏在人脑中并不如在血浆中那样显著地富集。这是由于加兰他敏是一种植物生物碱而不是理性设计的药物,其与用作AD药物的其它两种胆碱酯酶抑制剂相比具有小得多的亲脂性,因此在稳态时显示相当低的脑-血浓度比(BBCR<2)。

[0004] 如EP1 940 817 B1和WO 2009/127218 A1所记载,为了提高CNS药物的亲脂性并且促进他们穿过血脑屏障,向碱性生物碱结构上附接疏水侧链。选择附接的基团,从而使

BBRC 增大至大于 5。

[0005] 与其它胆碱酯酶抑制剂相似，加兰他敏具有临床显著水平的机制性胃肠 (GI) 副作用，包括恶心、呕吐和腹泻 (Loy C 等人 .,Galantamine for Alzheimer's disease and mild cognitive impairment.Cochrane Database of Systematic Reviews2006,Issue 1)。为了使缓解患者的这些副作用，胆碱酯酶抑制剂最初通常以较低（非有效）剂量给药，随后在几个月的时段中谨慎地将该剂量增加到有效量。此外，维持剂量通常调节为使患者经历的 GI 副作用为可接受水平，使得大部分患者（如果不是全部患者）很可能从未以最有效的剂量治疗。因此，胆碱酯酶抑制剂通常被认为仅具有较低的有效性以及与令人不愉快的副作用相关。根据现有技术中关于加兰他敏的给药，显而易见的是，由于较差的脑 - 血浓度比以及由于较差脑递送带来的显著外周副作用，加兰他敏的潜在治疗疗效从未完全地应用到人受试者中。

[0006] 由于已知加兰他敏影响肠组织的蠕动和清除功能 (Turiiski VI 等人 .(2004),in vivo and in vitro study of the influence of the anticholinesterase drug galantamine on motor and evacuative functions of rat gastrointestinal tract. Eur J Pharmacol 498,233-239)，所以试图通过药物的鼻内给药而不是口服给药来降低加兰他敏的 GI 副作用 (Leonard AK 等人 .(2007),In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo.Int J Pharmaceut 335:138-146)。

[0007] 由于在一次喷雾动作中给药至每个鼻孔的喷雾的体积有限，所以鼻内给药途径需要高溶解性的药品制剂。对于加兰他敏，通过用乳酸根或葡萄糖酸根来替代药物的氢溴酸盐中的溴离子，上述目的仅得以部分实现。盐形式的改变并没有使加兰他敏穿过 BBB 的能力显著地改进，这是由于被鼻的上皮细胞中再吸收并且随后被输送穿过血脑屏障的是相当亲水性且极性的加兰他敏碱。由于这些物理化学方面的局限性，加兰他敏和其叔胺盐和季铵盐呈现出低于 2 的脑 - 血浓度比，这就意味着这种药物必须以相当大的量给药，以在目标器官也就是脑中达到显著药物水平。因此，这种亲水性药物在脑中达到显著有效剂量的代价是在相当大程度的外周副作用，尤其是胃肠副作用。可得出的结论是 :加兰他敏的盐制剂并没有提供用于提高穿过 BBB 的脑药物分布的令人满意的方案。

[0008] 如之前所述 (WO2009/127218 A1)，重要的相对亲水性的母体药物能够通过化学转化再配制成亲脂性酯前体药物。醇类 OH 基团已被用于将脂肪族、芳族或杂芳族羧酸附接至母体药物，从而 (i) 部分或完全地钝化其药理活性，以及 (ii) 显著地增强它们的亲脂性和 BBB 渗透性。

[0009] 尽管通常采用形成酯的方法来增加 BBB 渗透性有限的极性分子的亲脂性，但非特异性酯酶在脑中和外周组织中的丰度限制了该方法在增强药物的脑 / 血浆浓度比方面的有效性。为了通过前体药物方法最大化脑药物水平，在目标器官也就是脑中，吸收动力学、BBB 渗透性以及前体药物向药物的生物转化必须足够快，从而在形成后成功地与来自脑的亲脂性较低药物带来的消除作用进行竞争。因此，研发如下的策略、方法和 / 或药剂仍然存在显著的障碍 :允许或呈现可靠的 BBB 渗透性并且在目标器官（脑）中裂解，从而增加脑中的活性物质的量，但不导致在身体的其它器官或组织中发生裂解，其中，在其它器官或组织中发生裂解在许多情况中会引发治疗期间的大量副作用。

[0010] US 2009/0253654 A1 中公开了加兰他敏衍生物的鼻内给药的可能性。并未提及向脑的递送得到增强，也没有提到通过酯前体药物化合物的内源酯酶来避免体内酶裂解的方法。US 2009/0253654 A1 中公开的化合物的盐和浓度呈现的是任意披露，没有涉及化合物在体内的性质。关于 GLN 1062，没有公开具体的盐或粘膜给药途径。

[0011] WO2009/127218 A1 和 Maelicke 等人 (J Mol Neurosci, 2010, 40:135-137) 公开了 GLN 1062 以及其在治疗带有认知障碍的脑疾病中的给药方式。并未提及给药的具体模式或具体的盐。这些早期的公开是基于本文公开的化合物的静脉给药。这种团注法能够实现从血液非常快速地分布至包括脑的其它器官，并且因此降低了酶在到达 BBB 并在脑中的分布之前裂解的可能性。然而，静脉给药并不适用于日常自我给药的患者。因此，需要更易于给药且同等有效的替代给药方式。

[0012] Leonard AK 等人 (2007, Int J Pharmaceut 335:138-146) 公开了加兰他敏的乳酸盐的鼻内给药。使用乳酸盐并未证实具有特别的效果。极性加兰他敏碱在鼻上皮细胞处被再吸收但随后仅仅是较差地穿过血脑屏障，因为其通过 BBB 的脑内药物分布受限。US 2004/0254146 公开了加兰他敏的各种盐，包括乳酸盐、葡萄糖酸盐，以及它们在阿兹海默氏症中的给药。US 2004/0254146 和 Leonard AK 等均没有涉及 GLN 1062 的盐的给药，其中，由于 GLN 1062 的盐的前体药物性质，表现了对于与加兰他敏相比完全不同的技术问题的解决方案。

发明内容

[0013] 测试表明，作为前体药物的非侵入式途径，本文所述的化合物在口腔和鼻腔中的粘膜递送途径最适于实现脑中药物水平的提高。对于全身型药物递送，通过前体药物盐制剂来增强粘膜途径，该前体药物盐制剂能够适应特定吸收区域的结构和环境。

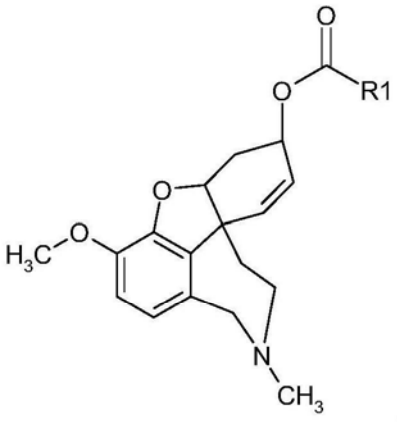
[0014] 当前体药物通过静脉注射给药时，能够实现本文中所讨论的前体药物的有益运输性质，但当其以片剂口服给药时，实现效果不太好，或仅仅实现非常小的程度。这可能是由于前体药物是酯，已经发现该酯在酸性环境中（诸如存在于胃中）不稳定，并且在许多组织中、包括在肠和肝脏中也被酶裂解（首过效应）。鉴于这些发现以及现有技术的给药方法的问题，并且为了在治疗 CNS 疾病中利用前体药物的性质，本发明利用避开胃肠道和首过效应的给药途径。这些途径提供了有效性与静脉注射大约等同的脑递送，而静脉注射由于显著的药物风险通常并不适用于可靠的自身给药。本发明提供了用于选定给药途径的特定药物制剂，其最优化前体药物向脑中的快速再吸收和摄入。

[0015] 根据现有技术，本发明所要解决的技术问题是提供一种用于提高本文所述的 CNS 治疗作用的生物利用度的替代法或改进的方法，从而为与认知障碍相关的脑疾病提供改进的治疗法。

[0016] 通过独立权利要求中的特征解决了该问题。通过从属权利要求提供了本发明的优选的实施方式。

[0017] 因此，本发明的目的是提供一种根据式 I 的化学物质，该化学物质用作治疗与认知障碍相关的脑疾病的药物，其中，所述治疗包括将治疗有效量的所述物质进行粘膜给药，所述粘膜给药选自鼻内给药、舌下给药或颊内给药，

[0018]



式 I

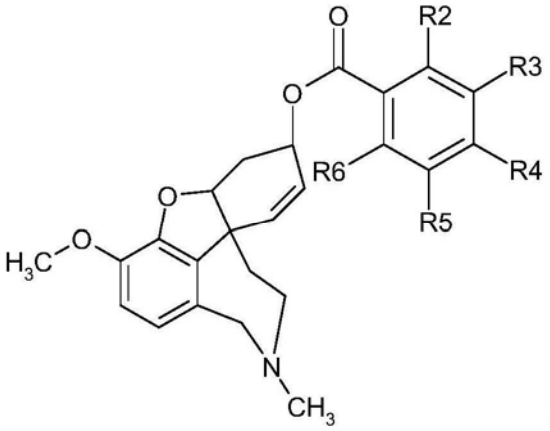
[0019] 其中，

[0020] R1 ＝芳族或杂芳族的 5 元或 6 元环，诸如可选地取代的苯、萘、噻吩、吡咯、咪唑、吡唑、噁唑、噻唑；或直链或支链的脂肪族残基，诸如 $CH(C_2H_5)CH_3$、CH_2-$C(CH_3)_3$、环丙基，或优选包括多于 5 个 C 原子、更优选多于 6 个 C 原子或多于 10 个 C 原子的脂肪族残基，诸如脂肪酸残基。

[0021] 因此，本发明主要涉及：本文所述的化学物质的应用或包括给药在内的治疗方法，从而用于治疗与认知障碍相关的脑疾病，该应用或治疗方法是通过选自鼻内给药、舌下给药或颊内给药的粘膜途径来将治疗有效量的所述化学物质进行给药。

[0022] 在优选的实施方式中，本发明的化学物质的特征在于该物质选自式 II，

[0023]



式 II

[0024] 其中，

[0025] R2 至 R6 包括从 H、卤素、可选地取代的 C_1-C_3烷基或环丙基、OH、O- 烷基、SH、S- 烷基、NH_2、NH- 烷基、N- 二烷基、可选地取代的芳基或杂芳基中选择的任何取代基，其中，相邻的取代基能够配合而形成额外的环。

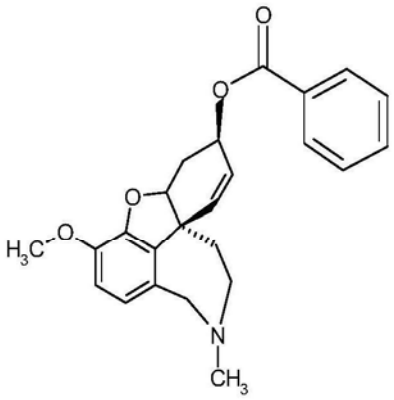
[0026] 式 I 和式 II 中所述的取代基的可选取代涉及被烷基、OH、卤素、NH_2、烷基 -NH_2或 NO_2基、或在表 2 中给出的那些化合物中所对应的其它取代基取代。

[0027] 优选在式 I 的 R1 位置具有芳族或杂芳族的 5 元或 6 元环的根据式 I 或式 II 的化合物，在表 2 中示出了这种化合物的实例，即：GLN-1062、GLN-1081、GLN-1082、GLN-1083、GLN-1084、GLN-1085、GLN-1086、GLN-1088、GLN-1089、GLN-1090、GLN-1091、GLN-1092、GLN-1093、GLN-1094、GLN-1095、GLN-1096、GLN-1097、GLN-1098、GLN-1099、GLN-1100、

GLN-1101、GLN-1102、GLN-1103、GLN-1104、GLN-1105、GLN-1113。

[0028] 在特别优选的实施方式中，本发明的化学物质的特征在于，所述物质为 GLN-1062，其中，GLN-1062 被表示为 ：

[0029]



GLN-1062

[0030] 本发明的粘膜给药是基于这样意想不到的实施 ：当经由口服给药时本发明的化合物呈现出相对低的稳定性。酯基团的裂解不仅发生在身体的其它组织，还发生在肠和肝脏中。粘膜给药避免首过效应以及前体药物在穿过胃肠道和其它器官时的裂解，从而提高了向脑和血液的运输，并相应地提高了疗效。

[0031] 根据现有技术，由于加兰他敏对于内源性酯酶造成的裂解不敏感，所以加兰他敏的粘膜给药并没有实现上述的提高作用。本发明的令人惊奇的理念是基于避免前体药物在给药后且在通过 BBB 从而被分隔前裂解，从而提高了活性物质在裂解后的脑运输和增加的相对浓度，其中，在所提出的给药途径和药物制剂的情况下，裂解主要在脑中发生。

[0032] 完全令人惊奇的是，本文所述的前体药物的粘膜给药会进一步增强前体药物的脑递送并且最终（在前体药物裂解之后）使得受试者脑中存在有效剂量的加兰他敏。

[0033] 因此，如本文所述，本发明涉及一种化学物质，所述化学物质用作治疗与认知障碍相关的脑疾病的药物，其中，通过粘膜给药避免和 / 或降低由于内源性酯酶而造成的所述物质的酯基在给药后裂解。

[0034] 本发明的该方面代表在本领域中之前并未公开或提出的新的技术效果。在本领域中，之前并没有描述美莫加因 (Memogain) 的酯部分在胃肠道和肝脏中的相对较低的稳定性。因此，技术人员不会试图提供本文所述的给药模式、或本文所述的盐来改进未裂解的化合物向脑的递送。正如本文实施例中所证实的，本发明认识到在以片剂形式口服给药之后发生给药后的裂解，在此基础上才提出了本发明的粘膜给药以及本文所述的盐。

[0035] 考虑到通过粘膜给药获得的显著改进以及本文所述的盐的递送增强，避免酯酶在体内裂解使得能够治疗如下这样的患者 ：由于口服给药片剂相关的强烈的胃肠道副作用，这些患者先前避免使用 ChE 抑制剂治疗。通过粘膜给药而改进了脑递送，尤其是美莫加因盐的高浓度水溶液的脑递送，这允许了迄今为止根本不可能的加兰他敏自身（由于显著的副作用）或美莫加因（由于体内降解）的剂量方案。

[0036] 尽管显示出有前景的效果，但是由于加兰他敏强烈的副作用，加兰他敏的治疗与较低的依从性（约 30％）相关，这表明本领域中强烈需要更持续的治疗方法。本文所述的给药途径和盐能够达成之前从未实现的美莫加因及其活性成分加兰他敏的治疗方案，从而

通过本发明的方式和方法可能能够治疗在之前由于不良的副作用而不能得到有效治疗的患有严重神经退行性疾病的患者。

[0037] 在优选的实施方式中，本发明的化学物质的特征在于，该化学物质以盐的形式存在，优选以乳酸盐、葡萄糖酸盐、马来酸盐或糖二酸盐 (saccharate salt) 的形式存在。

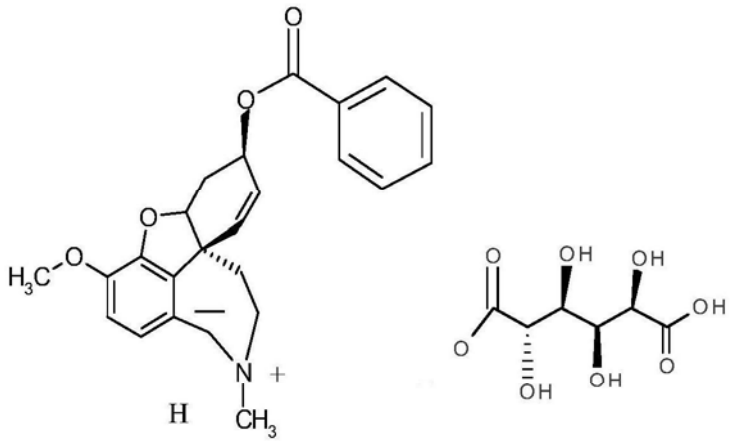
[0038] 在优选的实施方式中，盐包括根据式 I、式 II 或式 III 的化学物质的化学计量的盐和 / 或非化学计量的盐和 / 或水合物，其中，所述盐优选地被描述为如下的物质 ：

[0039] 式 I、式 II 或式 III • nHX • mH_2O，

[0040] 其中，n、m ＝ 0 至 5，并且 n 和 m 相同或不同，并且 HX ＝酸，所述酸优选地选自乳酸、葡萄糖酸、马来酸或糖二酸 (saccharic acid)。

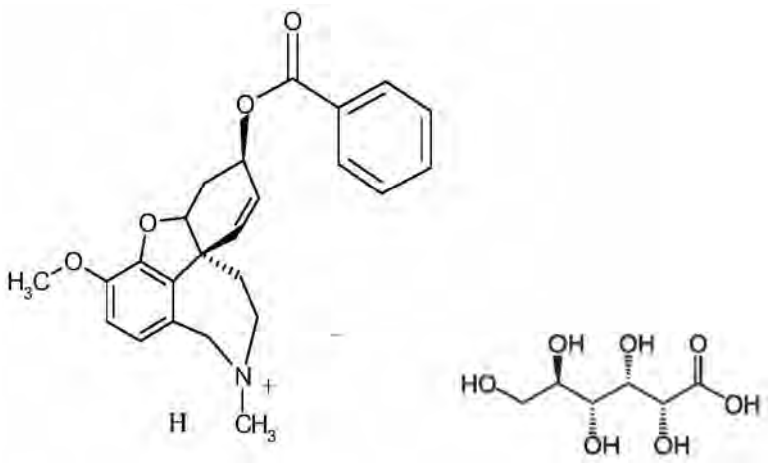
[0041] 本发明还涉及一种化学物质，该化学物质用作治疗与认知障碍相关的脑疾病的药物，其中，该化学物质为 GLN-1062 的糖二酸盐。令人惊奇地，本发明的糖二酸盐实现了在水中高达 70％的高浓度，从而提供了前体药物的高粘膜剂量的更稳定的溶液。

[0042]



[0043] 本发明的一个优选的实施例涉及用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，该化学物质为 GLN-1062 的葡萄糖酸盐。

[0044]



[0045] GLN-1062 的葡萄糖酸盐在水中、尤其是在约 25 摄氏度至 50 摄氏度的温度具有 40％或更高的高溶解度。在升高的温度下的高溶解度可用于制造 GLN1062 的葡萄糖酸盐的高浓度液体溶液，其是相对稳定的并且能够在制造溶液之后的几天中用于给药。

[0046] 本发明还涉及用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，该化

学物质为 GLN 1062 的马来酸盐。

[0047] 本发明还涉及用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，该化学物质为 GLN 1062 的乳酸盐。

[0048] 本发明的盐还额外地显示出如下令人惊奇的性质：改善的口味（减少苦味），从而降低了组合物中对掩味成分的需求。本发明的盐还降低了粘膜给药时已知的加兰他敏的致麻效果。由于其快速且有效地摄取，与本领域中记载的那些组合物相比，其降低了致麻（镇痛）效果和较差的口味。

[0049] 在一个实施方式中，本发明的化学物质的特征在于，该化学物质具有在水中至少 10wt％ / 单位体积、优选 >20wt％ / 单位体积、或更优选 >30wt％ / 单位体积 (w/v) 的溶解度。

[0050] 本文所述的提高的盐的溶解度代表了令人惊奇且有利的发展。本文所述的盐的溶解度使得化合物以较少的体积较高的浓度给药，从而进一步增强通过本文所述的粘膜给药向脑的直接给药。

[0051] 粘膜给药与本发明的前体药物的盐的结合显示出了协同效果。提高的溶解度允许化学物质以较高浓度给药，从而使得在裂解后（加兰他敏）较大量的活性物质在脑中存在活性。物质的运输（通过脑中的所述物质本身或在前体药物裂解之后脑中的加兰他敏水平而测得）优于单独考虑粘膜给药、盐的给药以及前体药物给药的预计效果的总和。

[0052] 通过粘膜施用本文所述的化合物的盐，从而以协同的方式利用且提高了本文所述的化合物的前体药物性质。前体药物的盐（具有高溶解度）的粘膜给药提供了之前不可能的剂量方案的给药参数与加兰他敏或加兰他敏的盐的独特组合。

[0053] 在一个实施方式中，本发明的特征在于化学物质以 0.1mg 至 200mg、1mg 至 100mg、优选 2mg 至 40mg 的剂量优选每日 1 ～ 3 次地给药，更优选每日 2 次地给药，甚至更优选每日 1 次地给药。

[0054] 考虑到有效的加兰他敏治疗，本文所述的剂量方案代表了与现有技术相比新颖且令人惊喜的有益的发展。关于加兰他敏的生物和药学效果，之前从未针对高剂量给药所带来的潜在效果进行测试。由于常规剂量的加兰他敏所带来的显著副作用，许多需要加兰他敏治疗的患者并不能用加兰他敏来治疗。为了在受试者的脑中获得加兰他敏的有效水平，现有技术教导了高剂量但也是高度毒性的剂量。由于口服或鼻内给药的加兰他敏药物仅小部分到达脑中，身体的其它组织中大量存在加兰他敏，因此，在治疗脑疾病期间显示出效果所需的剂量通常是无法忍受的高，进而导致不良的副作用。

[0055] 本发明的剂量能够通过粘膜给药本文所公开的前体药物而实现。由于疏水性前体药物的脑递送提高，并且由于粘膜给药而使递送进一步提高，仅需要较小剂量的前体药物来实现在前体药物裂解和活性化合物的释放之后在脑中加兰他敏的相同或更好的效果。完全令人惊奇的是，与口服给药加兰他敏相比，在本发明的范围内的较低剂量的本发明的前体药物（例如 GLN 1062）带来了在认知恢复方面更显著和 / 或更强有力的效果。

[0056] 当以本文所述的化合物的盐的形式给药时，这些剂量方案是尤其有益的。

[0057] 在一个实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的化学物质，其中，该化学物质或该化学物质的盐按照 2 至 40wt％ / 单位体积 (w/v) 的溶液的形式以 20 微升至 100 微升的量优选地通过单次鼻内喷雾动作每日 1 ～ 3 次地鼻内给药、颊内给

药或舌下给药。

[0058] 在这些剂量下，能够在患有脑疾病的患者中有效地恢复认知，而不带来任何可察觉的副作用（或仅仅非常小的副作用）。在做出本发明时无法预料，通过前体药物（优选GLN 1062）和粘膜给药的组合，这种剂量能够以如下的剂量方案产生有效的加兰他敏治疗效果，剂量方案包括相对少的给药次数和相对小的活性化合物体积（通过喷雾或口服粘膜制剂的给药）。

[0059] 在一个优选的实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的如本文所述的化学物质，其中，所述化学物质或所述化学物质的盐按照10wt％／单位体积(w/v)的溶液的形式以50微升的量优选通过单次（鼻内或口服）喷雾动作每日1～3次地鼻内给药、颊内给药或舌下给药。

[0060] 在一个实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的如本文所述的化学物质，其中，待治疗的脑疾病为阿兹海默氏症和／或帕金森氏病，所述化学物质为GLN 1062的葡萄糖酸盐或糖二酸盐，其按照2至40wt％／单位体积(w/v)的溶液的形式以20微升至100微升的量优选通过单次（鼻内或口服）喷雾动作每日1～3次地鼻内给药。

[0061] GLN 1062的盐制剂显示出令人惊奇的高溶解度，从而患者自己能够轻松地以小体积施加高剂量的GLN 1062，实现了相关治疗效果，却不需要非常高剂量的前体药物或其活性母体药物加兰他敏并且不产生显著副作用。

[0062] 在一个实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的如本文所述的化学物质，其中，待治疗的脑疾病为阿兹海默氏症，所述化学物质为GLN 1062的葡萄糖酸盐，其按照10wt％／单位体积(w/v)的溶液的形式以50微升的量优选通过单次鼻内喷雾动作每日2次地鼻内给药、颊内给药或舌下给药。

[0063] 在一个实施方式中，本发明的化学物质的特征在于，鼻内给药通过用合适的计量剂量装置将治疗有效量的所述化学物质进行给药来完成，所述合适的计量剂量装置诸如雾化器、喷雾器、喷雾泵、滴管、挤压筒、挤压瓶、移液管、安瓿、鼻腔插管、计量剂量设备、喷鼻吸入器、鼻腔持续正空气压力装置和／或呼吸驱动的双向输送装置。

[0064] 在一个实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的如本文所述的化学物质，其中，所述舌下给药通过如下完成：将包括所述化学物质的一滴或多滴溶液、或一定量的包括所述化学物质的冷冻干燥粉末形式或乳剂形式的颗粒放置到舌下，和／或将预定体积的包括所述化学物质的液体组合物喷雾到舌下，从而在舌下将治疗有效量的所述化学物质进行给药。

[0065] 在一个实施方式中，本发明涉及用作治疗与认知障碍相关的脑疾病的药物的如本文所述的化学物质，其中，所述颊内给药通过如下完成：将治疗有效量的所述化学物质以冷冻干燥粉末或乳剂的形式或口腔崩解片或口腔分散片(ODT)的形式给药至口中位于脸颊和牙龈之间的颊前庭。

[0066] 在一个实施方式中，本发明的化学物质的特征在于，受试者是哺乳动物，优选是人。

[0067] 在一个实施方式中，本发明的化学物质的特征在于，待治疗的脑疾病选自阿兹海默氏症和／或帕金森氏病，其它类型的痴呆，精神分裂症，癫痫症，中风，脊髓灰质炎，神经

炎，肌病，以及低氧、缺氧、窒息、心搏停止后在脑中的氧和营养缺乏，慢性疲劳综合症，各种类型的中毒，麻醉、尤其是神经安定药麻醉，脊髓病症，炎症、尤其是中央炎性疾病，术后谵妄和/或亚综合症术后谵妄，神经疼痛，酒精和药物滥用，酒精成瘾和尼古丁成瘾，和/或放射疗法效应。

[0068] 在一个实施方式中，本发明的化学物质的特征在于在给药后，化学物质在患者体内的分布呈现为脑-血浓度比大于5，优选地大于10，更优选在15和25之间。

[0069] 本发明进一步涉及本文所述的化学物质在治疗与认知障碍相关的脑疾病中的应用，其中，通过粘膜途径将治疗有效量的所述化学物质进行给药，所述粘膜途径选自由鼻内给药、颊内给药和/或舌下给药所组成的组。

[0070] 在其它方面，本发明涉及一种用于治疗哺乳动物中与认知障碍相关的脑疾病的药物组合物，其特征在于，该组合物包括根据本发明的式I、式II或GLN1062的化学物质，以及优选的一种或多种药学可接受的载体，所述组合物适用于鼻内给药、颊内给药和/或舌下给药。因此，本发明涉及用于通过鼻腔粘膜和口腔膜进行粘膜给药的液体组合物形式的滴鼻剂或舌下滴液。

[0071] 本发明涉及一种用作治疗与认知障碍相关的脑疾病的药物的通过粘膜给药的药物组合物，其中，该组合物包括根据本发明的式I、式II或GLN 1062的化学物质，其中，该组合物为包括2至40wt％/单位体积、优选5至15wt％/单位体积并且更优选10wt％/单位体积(w/v)的该化学物质的水溶液。

[0072] 在一个实施方式中，本发明涉及一种药物组合物，其中，该组合物包括N-乙基吡咯烷酮。在优选的实施方式中，本发明涉及一种药物组合物，其中，该组合物包括自微乳化药物递送(SMEDD)系统。这种组合物优选地包括辛酸甘油酯、聚乙二醇、丙二醇和/或二乙二醇单乙基醚。

[0073] 本发明还涉及一种用作治疗与认知障碍相关的脑疾病的药物的通过粘膜给药的药物组合物，所述药物组合物包括根据本发明的式I、式II或GLN 1062的化学物质，其中，该组合物包括包含壳聚糖的缓释制剂。

[0074] 本发明的进一步实施方式涉及一种药物组合物，该药物组合物包括待给药的化学物质的微粉化粉末制剂，所述微粉化粉末制剂的粒径优选为0.1微米至100微米，更优选0.1微米至100微米或1微米至10微米。

[0075] 本发明涉及一种用作治疗与认知障碍相关的脑疾病的药物的通过粘膜给药的药物组合物，所述药物组合物包括根据本发明的式I、式II或GLN 1062的化学物质，其中，该组合物包括舌下片剂，所述舌下片剂优选包括乳糖一水合物、玉米淀粉、聚乙烯吡咯烷酮(PVP)和/或硬脂酸镁，以及可选的调味剂。可替代地，该组合物可包括舌下片剂，所述舌下片剂包括甘露糖醇、淀粉羟乙酸钠、交联甲羧纤维素、抗坏血酸和/或硬脂酸镁，以及可选的调味剂。

[0076] 本发明还涉及一种用作治疗与认知障碍相关的脑疾病的药物的通过粘膜给药的药物组合物，该药物组合物包括根据本发明的式I、式II或GLN 1062的化学物质，其中，该组合物包括具有耐消化酸的包衣、诸如包括Eudragit(丙烯酸树脂)的多层片剂。

[0077] 在优选的实施方式中，本发明的药物组合物按照如下方式包括待给药的物资：在组合物中为2至40wt％/单位重量(w/w)、优选10至30wt％/单位重量(w/w)或更优选

5、10、20 或 30wt％ / 单位重量 (w/w)，并且以自微乳化药物递送 (SMEDD) 系统的形式、或包括壳聚糖的缓释制剂的形式、或微粉化粉末制剂的形式、或舌下片剂或口腔片剂的形式。

[0078] 在特别优选的实施方式中，已经建立的 CNS 疗法是抗痴呆药物加兰他敏，前体药物是加兰他敏的苯甲酸酯 (加兰他敏苯甲酸酯，GLN 1062，还被称为“美莫加因”) 以及用于鼻内递送的盐形式优选地为所述 GLN 1062 的苯甲酸酯的乳酸盐、葡萄糖酸盐、马来酸盐或糖二酸盐。GLN 1062 已知为 (4aS,6R,8aS)-4a,5,9,10,11,12- 六氢 -3- 甲氧基 -11- 甲基 -6H- 苯并呋喃 [3a,3,2-ef][2] 苯并氮杂 -6- 醇 ,6- 苯甲酸酯。例如，美莫加因的葡萄糖酸盐已知为加兰他敏苯甲酸酯的葡萄糖酸盐。

[0079] 因此，本发明还涉及一种用于治疗与认知障碍相关的脑疾病的方法，通过粘膜途径来给药治疗有效量的上述化学物质，所述粘膜途径选自由鼻内给药、颊内给药和 / 或舌下给药所组成的组。对于给药方案、物质本身和 / 或其它给药参数，本发明的治疗方法也进一步地通过本文所提供的本发明的实施方式来限定。

具体实施方式

[0080] 本发明的详细描述涵盖了下列进展 ：

[0081] (1) 在优选的实施方式中，提供亲脂性显著优于其母体化合物的加兰他敏的前体药物，从而增加其穿过血脑屏障 (BBB) 而进入脑的被动运输。

[0082] (2) 这些前体药物是无药理学活性的，只要它们保持在特定组织中未裂解，则不产生任何显著的 GI 或其它副作用。在发生酶裂解之后，每分子前体药物形成一分子的母体药物，从而产生该药物的完整药理作用。如果由于在脑中提高的分布以及在其中存在可用的合适的内源性酶，而导致优先在脑中发生裂解，则在 CNS 中的目标位点产生显著较高的药物浓度并且因此产生较大的医药学益处。

[0083] (3) 通过在口腔或鼻腔的粘膜途径的给药，进一步以令人惊奇和有益的方式使得向目标器官也就是脑的有益运输最优化。

[0084] (4) 前体药物的高剂量制剂和缓释制剂进一步使得向脑摄取的药代动力学最优化，并且维持脑中的药物水平以达到作用的最优化效果。

[0085] 综合考虑，本文所述的前体药物制剂的这些特征使得能够与通过口服给药未改性药物的片剂形式相比，向脑递送浓度高得多的药物。药物向脑的分布的改进极大地降低了在 GI 道中所有局部产生的副作用，从而允许将有效剂量的药物立即施用到其位于中枢神经系统 (CNS) 的目标分子中，例如，烟碱受体和胆碱酯酶。

[0086] 由于处于脑毛细血管水平的血脑屏障 (BBB) 是药物从血液分隔区域进入到脑的通路中的主要屏障，所以首先着眼于使前体药物穿过 BBB 的渗透性最优化，产生了可喜的结果。形成 BBB 的脑微血管内皮细胞具有如下的典型形态学特征，即细胞之间紧密连接、缺乏开窗口 (fenestration) 并且胞饮活性减弱。各种酶进一步强化了 BBB 的限制性。药物穿过 BBB 的能力大多取决于其理化性质，例如其亲脂性。因此，在本公开所考虑的这些化合物均为亲脂性与母体化合物相比得到改进的前体药物。

[0087] BBCR 应被理解在穿过 BBB 达到运输平衡后的脑 - 血浓度比。

[0088] 一般来说，当加兰他敏衍生物的 LogP 值为约 1.3，则 BBRC(脑 - 血浓度比) 约为 2 或略小于 2，当 logP 值约为 2，则 BBRC 约 5 至 10，并且当 logP 值约为 3，则 BBRC 约 20 或大

于 20。这可为比较 logP 值与 BBB 渗透性提供参考，并且对于一些特定的化合物可发生变动。这种参考并不提供本发明的限制性特征。

[0089] 前体药物本身被定义为非治疗活性的药剂，其可预见在人体的特定位置转化成活性代谢产物。在这个意义上讲，前体药物是母体药物的非活性前体，前体药物以可预见的方式在体内通过酶裂解或化学自发过程中转变成活性药剂。在本文所讨论的前体药物中，在母体药物和选定的运输前体部分之间优选地存在共价酯键连接，并且该酯键理想地在目标器官也就是脑中裂解，从而在 CNS 中的目标位点处或接近目标位点处，非活性前体药物释放活性母体药物。

[0090] 在口腔内的快速吸收通过舌下给药得以最好地实现，因此在舌下区域中粘膜厚度低于其它颊内区域的粘膜厚度，并且舌下区域角质化程度显著要低 (Shojaei A(1998) Buccal mucosa as a route for systemic drug delivery:a review.J Pharm Pharmaceut Sci 1:15-30)。快速溶解的舌下制剂，诸如迅速降解片或充液胶囊，能够额外地有助于降低前体药物在唾液中的酶降解。鼻腔具有较大的表面积、高度血管化与低酶环境，因此也提供用于另一给药方案的有前景的切入点。鼻内给药能够提供与静脉给药相似高水平的生物利用度，并且与静脉给药相比，具有非侵入性、易于自我给药、患者的舒适度和患者的依从性的优点。本领域的从业者通常知晓这些优点；然而，在开发这样的施用途径中存在显著的障碍。对于慢性系统性递送，需要解决上皮细胞损伤和毒性的问题，并且为了获得充分的生物利用度而在较小量的介质中提供高浓度的药物。这就要求：首先，选择能够获得所需制剂和浓度的合适的化合物，此外，找到适当的给药方法，以及最后，开发其优选的盐和 / 或其溶液从而使有效物质向脑的给药最优化。

[0091] 因此，根据现有技术不可预见的是，哪种化合物能够以替代给药模式提供成功的结果。另外基于现有技术无法预见的是，哪些盐和 / 或制剂可被生产用作本发明的前体药物，也无法预见这些产品是否会提供有效的 BBB 渗透性以及能够在脑中裂解成为活性物质。

[0092] 根据如下所述来选择根据本发明的合适的前体药物制剂。在将前体药物静脉注射到动物中之后，通过监测前体药物在全脑和血浆中的浓度，来确定它们的基础 BBCR。

[0093] 通过额外地监测释放的母体药物在大脑及血液中的浓度，来确定前体药物转化为药物的速率和有效性。这些研究证实了事实上脑对这些前体药物的摄入是非常快的，并且快速摄入强烈有助于在脑中发生的前体药物至药物的转化。在研究中，由于所研究的大多数母体药物都已知作为胆碱酯酶抑制剂，因此推断并随后证明了相关的前体药物通过丁酰酯酶型酯酶和羧基酯酶型酯酶而裂解成其活性母体药物。

[0094] 随后，改为在口腔和鼻腔中的粘膜递送，并且再一次地在动物模型中确定脑摄入的动力学，脑中所达到的药物水平以及所得到的药效，与口服递送衍生物和母体药物进行比较。与之前已知的口服给药方法相比，通过粘膜途径给药本文所述的化学物质显示出了令人惊奇且意想不到的优点。在现有技术中并没有公开或建议加兰他敏的某些衍生物能够通过粘膜给药优先被运输到脑中。如上所述，由于加兰他敏的理化性质较差，先前的加兰他敏的鼻内施用的尝试失败。令人惊奇的是，将本文所述的加兰他敏衍生物作为优选的化学物质进行粘膜施用，确实能够改进脑 - 血浓度比。由于加兰他敏本身的先前的相似给药方案的失败，该结果是令人惊奇的。

[0095] 因此，本发明的目标是提供一种新型 CNS 疗法，由于被配制为亲脂性前体药物并且在口腔或鼻腔中通过粘膜吸收途径给药，该新型 CNS 疗法具有最佳脑生物利用度。

[0096] 本发明基于如下的基本认识，即基础化合物本身（即加兰他敏）必须穿过血脑屏障而被递送到脑。由于加兰他敏本身的 LogP 值非常低，因此不能以足够有效量穿过血脑屏障，所以就必须对基础化合物进行改性以使得物质具有更大的亲脂性从而使其更有效地穿过血脑屏障。一旦该物质到达大脑，改性的基础化合物（优选为根据式 I 或式 II 的化学物质 (CS)）通过 R1 残基上的酯键的酶裂解而被在转化为有效的基础化合物本身，即加兰他敏。

[0097] 本发明的目的在于将化学化合物递送至脑，以确保在脑中能够利用有效量的基础化合物（在穿过血脑屏障后在脑中发生裂解以后），尤其是确保后者基础化合物加兰他敏具有较高的生物利用度。

[0098] 如前文所述 (Maelicke 等人 .,Memogain is a galantamine Pro-drug having Dramatically Reduced Adverse Effects and Enhanced Efficacy,J Mol Neurosci(2010)40:135 - 137)，根据式 I 的物质是加兰他敏的非活性前体药物，其与相同剂量的加兰他敏相比，在脑中具有高出 10 倍的较高生物利用度。所述加兰他敏的衍生物可通过对母体药物（加兰他敏）进行一步化学改性而获得。这种改性几乎完全消除了加兰他敏在人体内两个主要目标 - 烟碱型乙酰胆碱受体 (nAChR) 和乙酰胆碱酯酶 (AChE) 的药理活性。在 1μM 的具有生理学意义的浓度下，美莫加因的酯酶抑制性是相同浓度的加兰他敏诱导的酯酶抑制性的不到 4％。

[0099] 在 WO 2009/127218 A1 和 US 2009/0253654 A1 中已经详细描述了根据式 I 的物质的合成、制备及药代动力学数据，这两篇文献均通过引用而并入本文。

[0100] 优选地，本发明的化学物质通过选自由鼻内给药、颊内给药（包括舌下给药）和 / 或静脉给药所组成的组的途径来给药。这种给药方式确保了从施用位点（即口、鼻、舌、颊、静脉）至脑的生物运输相对较短。因此，化学物质的降解的机率低，并且从施用的相邻位置有效运输至血脑屏障的可能性较高。

[0101] 在优选的实施例中，化学物质以盐的形式存在，优选季铵盐，优选乳酸盐、葡萄糖酸盐、马来酸盐或糖二酸盐，并且在水中具有至少 10％、优选大于 20％的溶解度。

[0102] 计划使用所述化学物质的方式是，使得在给药后化学物质在患者中的分布为，脑 - 血浓度比大于 5、优选大于 10、更优选在 15 和 25 之间。

[0103] 在优选的实施方式中，CNS 疗法是加兰他敏和结构上相关的化合物，前体药物为醇类 OH 基团的脂肪族酯、芳族酯和杂芳族酯，这对于该疗法的药理活性至关重要。为了适用于在口腔或鼻腔中的粘膜递送，它们被配制为高浓度水性盐溶液或乳剂或自微乳化药物递送系统 (SMEDD) 或微粉化粉末制剂。令人惊讶地是，如下表中所示，美莫加因盐的药学可接受的溶液满足用于鼻内施用方案的合适的稳定性、浓度、pH、摩尔渗透压、气味和鼻黏膜耐受性的标准。

[0104] 表 1

[0105]

验收标准	临床前	阶段 1	市场
所需的最大浓度	25%	25%	10%
可接受的最大浓度	20%	10%	5%
pH	4.5-7	5-6.5	5-6.5
化学稳定性	>3 小时	>7 天	>2 年
溶液的稳定性	>3 小时	>7 天	>2 年
大鼠中的%F	>80%	不适用	不适用
摩尔渗透压	>250 mosmol/l	>250 mosmol/l	>250 mosmol/l
气味	没有令人不愉快	没有令人不愉快	没有令人不愉快
鼻粘膜的耐受性	在大鼠和狗中 28 天的重复剂量研究中无显著刺激作用	在人中无刺激	在给药时段中在人中无刺激

[0106] 优选地，该药物组合物是包括 2 至 20wt％ / 单位体积 (w/v)、优选 5 至 15wt％ / 单位体积 (w/v)、更优选 10wt％ / 单位体积 (w/v) 化学物质的水溶液。为了适合于在口腔或鼻腔中的粘膜递送，它们被配制为高浓度水性盐溶液或乳剂或自微乳化药物递送系统 (SMEDD) 或微粉化粉末制剂。

[0107] 术语粘膜给药涉及穿过或跨过粘膜而使得药剂进入。本发明的粘膜给药途径被限定为鼻内、颊内和 / 或舌下。

[0108] 鼻或鼻内给药涉及将前体药物或其药物组合物以任何形式施用至鼻腔。鼻腔内覆盖有薄粘膜，并且良好的血管化。因此，药物分子能够快速地穿过单层上皮细胞而无首过的肝和肠道代谢。因此，鼻内给药被用作口服给药 (其导致在肠道和 / 或肝脏中发生大量降解)、例如片剂和胶囊的替代方法。

[0109] 颊内给药涉及穿过颊内粘膜的任何形式的施用，优选涉及在脸颊的内侧、牙齿的表面或者脸颊旁的牙龈处的吸收。

[0110] 舌下给药涉及给药至舌下，从而化学物质在舌下与粘膜接触并且穿过粘膜扩散。

[0111] 适用于颊内给药和 / 或舌下给药的药物组合物可额外地包括药学上可接受的载体，例如，颊内剂量单元可包括待给药的活性药剂，除此之外还包括聚合物载体，聚合物载体用于在预定时段中生物侵蚀活性药剂并提供活性药剂的递送，以及还优选地包括润滑剂，诸如硬脂酸镁。本领域技术人员知晓其它载体药剂。该活性药剂能够与起到以下作用的一些或全部类型的成分的材料物理地复合 :pH 调节剂、防腐剂、粘度控制剂、吸收增强剂，稳定剂、溶剂和载体介质。这样的药剂可以以固态形式的药物组合物或液体形式的药物组合物存在。

[0112] 自微乳化药物递送系统 (SMEDD) 可存在于所述药物组合物，意味着使用化学方法而不是机械方法获得微乳剂的药物递送系统。也就是说，利用药物制剂的固有性质，而不是通过特定的混合和处理。其采用茴香脑在许多茴香味酒中所显示的相似效果。微乳剂在

药物传递中具有巨大的潜力，SMEDD（包括所谓的“U- 型”乳剂）是迄今为止最好的系统。SMEDD 在增加口服的亲脂性药物的吸收中具有特别的价值。SMEDD 可以非限制性的方式包括以下药物的制剂：茴三硫、冬凌草、姜黄素、长春西汀、他克莫司、盐酸小檗碱、川陈皮素和吡罗昔康。

[0113] 盐涉及式 I、式 II 或 GLN 1062 本身的化合物的任何盐。术语盐优选地涉及在基础化合物的 7 元环结构中包括质子化的带正电荷的 N 原子。

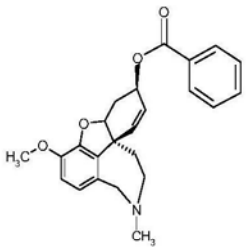
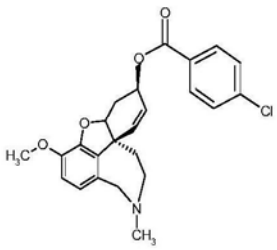
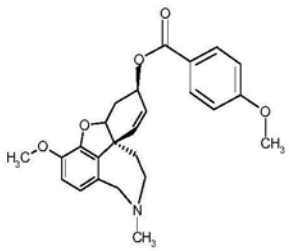
[0114] “给药”或“治疗”是施用于动物、人、实验受试者、细胞、组织、器官或生物流体，因此涉及使药物药剂、治疗药剂、诊断药剂、化合物或组合物与动物、人、受试者、细胞、组织、器官或生物流体接触。“给药”和“治疗”可涉及例如治疗方法、空白对照 (placebo) 法、药动学方法、诊断方法、研究方法和实验方法。因为“治疗”是施用于人、兽或研究受试者，因此涉及治疗性治疗，预先性或预防性措施，涉及研究和诊断施用。

[0115] 本发明涵盖将有效量的本文所述的化学物质给药至需要该化学物质的患者。“有效量”或“治疗有效量”意味着足以减轻病症的症状或病征或者改善生理状况的量，或足以允许或有助于诊断病症或生理状况的量。对于具体的患者或兽受试者，有效量可根据诸如治疗的状况、患者的整体健康、给药的方法途径和剂量以及副作用的严重性等因素而变动。有效量可以是避免显著副作用或毒性作用的最大剂量或剂量方案。该作用将使诊断措施、参数或可探测的信号改进至少 5%，通常至少 10%，更通常至少 20%，最通常至少 30%，优选至少 40%，更优选至少 50%，最优选至少 60%，理想地至少 70%，更理想地至少 80%，最理想地至少 90%，而 100% 被定义为正常受试者的诊断参数。“有效量”还涉及足以允许或有助于减轻和 / 或诊断病症的症状或病征、状况或病理状态的前体物质或其药物组合物的量。

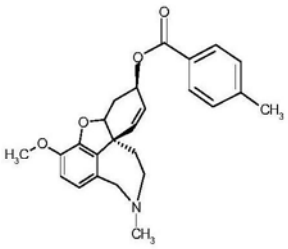
[0116] 表 2 中提供了根据本发明的优选的化学物质。

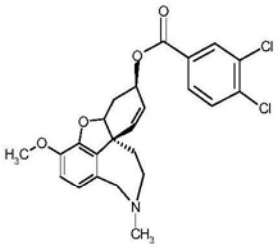
[0117] 表 2.

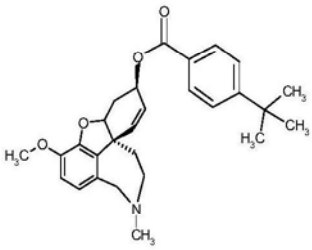
[0118]

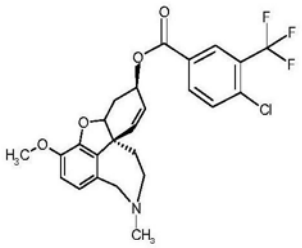
分子编号	分子结构	缩写
GLN-1062		Bz-Gal
GLN-1081		4-Cl-Bz-Gal
GLN-1082		4-MeO-Bz-Gal

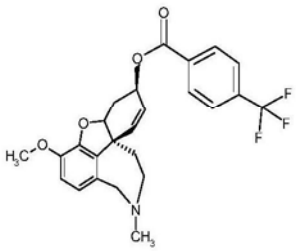
[0119]

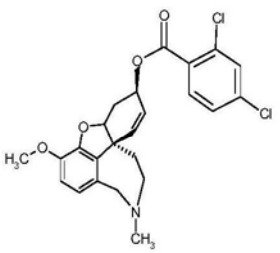
GLN-1083  4-Me-Bz-Gal

GLN-1084  3,4-Cl2-Bz-Gal

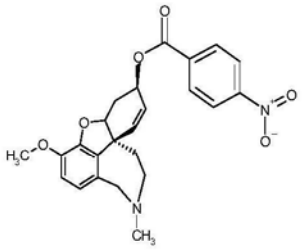
GLN-1085  4-tBu-Bz-Gal

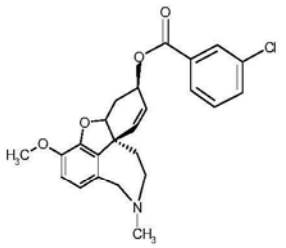
GLN-1086  3-CF3-4-Cl-Bz-Gal

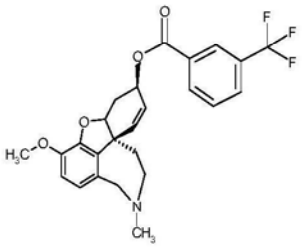
GLN-1088  4-CF3-Bz-Gal

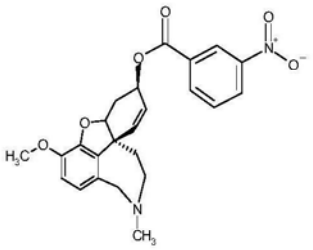
GLN-1089  2,4-Cl2-Bz-Gal

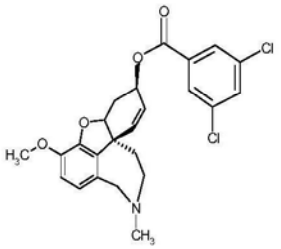
[0120]

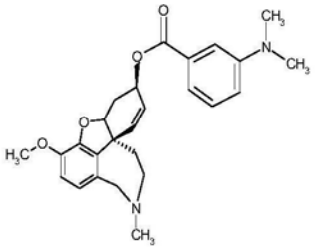
GLN-1090  4-NO2-Bz-Gal

GLN-1091  3-Cl-Bz-Gal

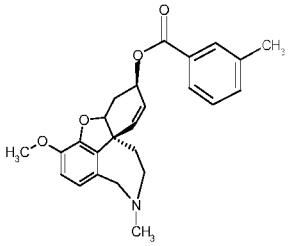
GLN-1092  3-CF3-Bz-Gal

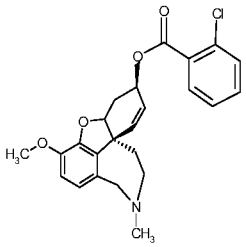
GLN-1093  3-NO2-Bz-Gal

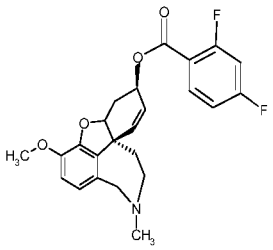
GLN-1094  3,5-Cl2-Bz-Gal

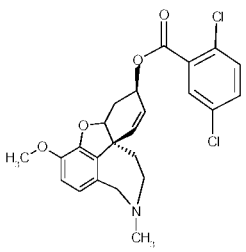
GLN-1095  3-Me2N-Bz-Gal

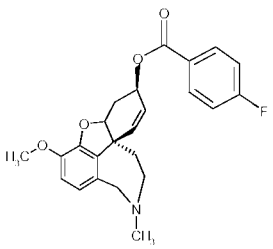
[0121]

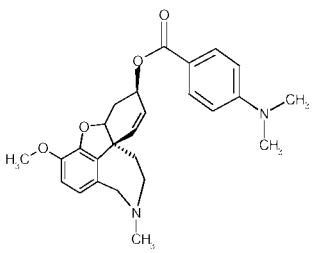
GLN-1096  3-Me-Bz-Gal

GLN-1097  2-Cl-Bz-Gal

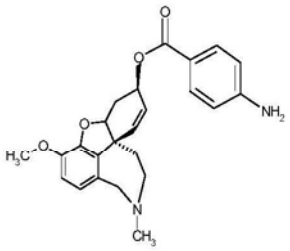
GLN-1098  2,4-F2-Bz-Gal

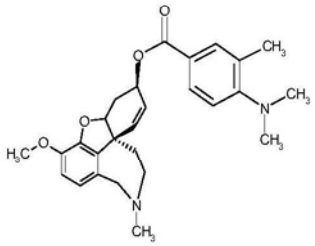
GLN-1099  2,5-Cl2-Bz-Gal

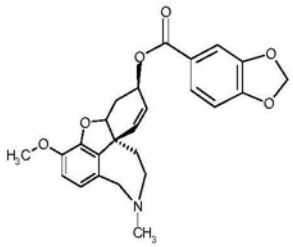
GLN-1100  4-F-Bz-Gal

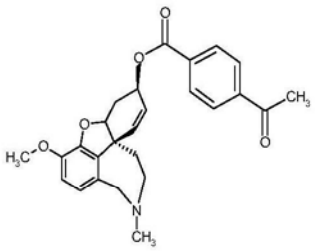
GLN-1101  4-NMe2-Bz-Gal

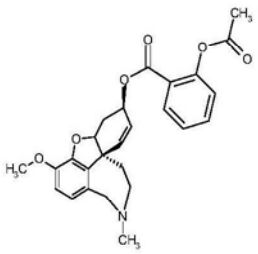
[0122]

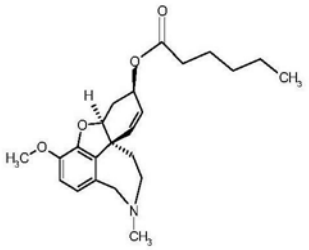
GLN-1102  4-NH2-Bz-Gal

GLN-1103  3-Me-4-NMe2-Bz-Gal

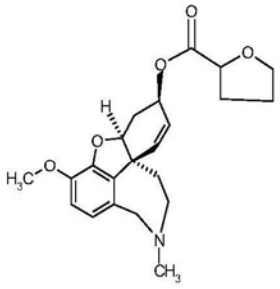
GLN-1104  3,4-OCH2O-Bz-Gal

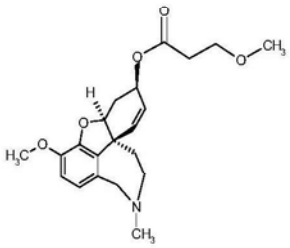
GLN-1105  4-Ac-Bz-Gal

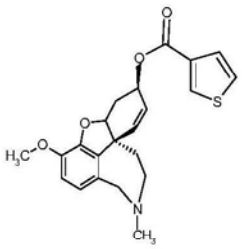
GLN-1113  - 2-AcO-Bz-Gal

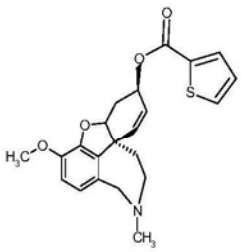
GLN-0993  n-Hex-Gal

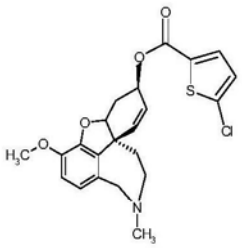
[0123]

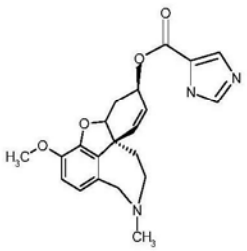
GLN-1060 

GLN-1061 

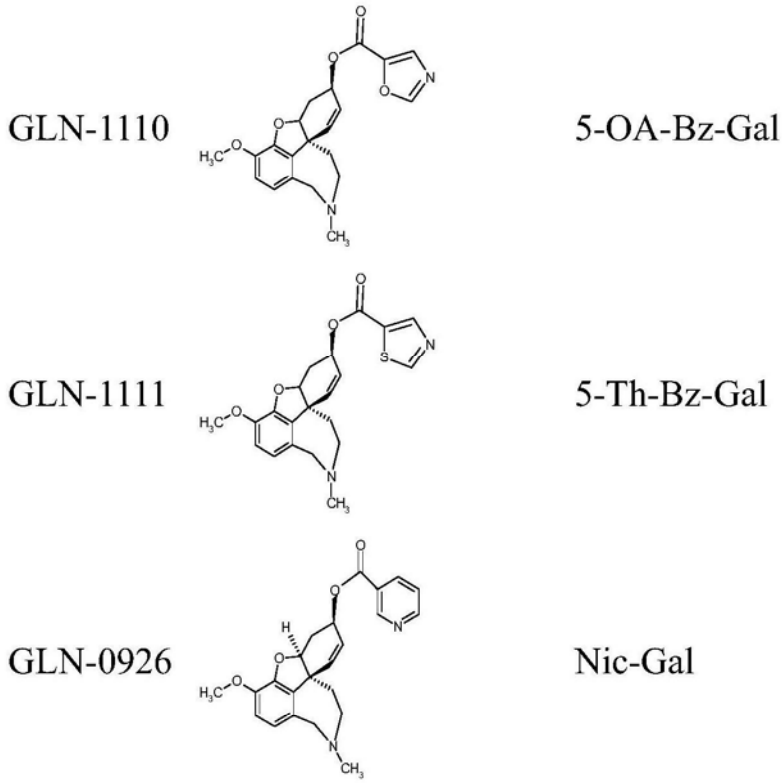
GLN-1106  3-Th-Bz-Gal

GLN-1107  2-Th-Bz-Gal

GLN-1108  5-Cl-2-Th-Bz-Gal

GLN-1109  5-Im-Bz-Gal

[0124]



附图说明

[0125] 通过附图进一步描述本发明。其并不用于限制本发明的范围；

[0126] 图 1 表示利用二噁烷得到的美莫加因葡萄糖酸盐的粉末衍射图；

[0127] 图 2 表示美莫加因葡萄糖酸盐一水合物的吸附 / 解吸等温线；

[0128] 图 3 表示加热美莫加因葡萄糖酸盐一水合物的重量损失；

[0129] 图 4 表示美莫加因葡萄糖酸盐的湿饼的示差扫描量热法结果；

[0130] 图 5 表示利用乙醇得到的美莫加因葡萄糖酸盐的粉末衍射图；

[0131] 图 6 表示加兰他敏和几种前体加兰他敏的实验性脑 - 血浓度比；

[0132] 图 7 与加兰他敏相比，鼻内美莫加因更强有力；用东莨菪碱刺激小鼠并且给予剂量浓度增加的口服加兰他敏和鼻内美莫加因，然而对小鼠 T- 迷宫模型进行性能评估；

[0133] 图 8 表示在威斯塔鼠中静脉和门静脉注射 3mg/kg Gln-1062 并评估首过效应；

[0134] 图 9 表示美莫加因的鼻内给药导致血浆中较低量的游离加兰他敏；

[0135] 图 10 表示与加兰他敏相比，美莫加因产生较小的胃肠副作用；

[0136] 图 11 表示由于前体药物的酶裂解使得加兰他敏的稳态血浆水平较低，因此美莫加因具有较低的毒性；

[0137] 图 12 表示在鼻内施用在 10％ NEP 的水溶液中的 5％的美莫加因盐，每鼻孔 10μL，总共 20μL 且含有 1mg，给出此后雌性威斯塔鼠中的美莫加因和加兰他敏的药代动力学曲线；

[0138] 图 13 表示向小鼠静脉注射 3mg/kg 的美莫加因或加兰他敏；数据证实了与美莫加因相比，加兰他敏确实没有很好地渗透到脑；以及

[0139] 图 14 表示在大鼠 PK 研究中，美莫加因的鼻内给药；在类似 GLP 的条件下，给药

5mg/kg 的鼻内 (i.n.) 美莫加因剂量。

[0140] 实施例

[0141] 通过下列实施例进一步描述本发明。这些实施例旨在以具体实施例的方式进一步描述本发明，但并不用于限制本发明。

[0142] 实施例 1. 前体药物的高浓度水性盐溶液和有机溶液

[0143] 对于本文所讨论的药物之一 - 加兰他敏，之前已基于高溶解性盐的水溶液开发了鼻内制剂 (WO 2005/102275 A1 ;Leonhard AK 等人 .(2005)Development of a novel high-concentration galantamine formulation sutable for intranasal delivery. J Pharmaceut Sciences 94:1736-1746 ;Leonard AK 等人 .(2007)In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo.Int J Pharmaceutics 335:138-146)。

[0144] 尽管所报道的加兰他敏盐制剂允许加兰他敏以与片剂口服给药所建议的剂量相似的剂量给药，但是由于药物的物化性质，鼻内给药并没有改进加兰他敏的脑 / 血浓度比，并且因此通过该方法并没有改变穿过 BBB 的渗透性。与此相反，当由本文的前体药物形成相同的盐制剂时，实现了亲脂性 (logP) 的较大增加，并且伴随有穿过 BBB 的好得多的渗透性。这可从图 1 中看到。

[0145] 盐形式和前体药物性质的组合，尤其是对于 GLN 1062，显示出了通过粘膜的改进吸收和直接被脑摄入的协同效应，从而增强向作用位点的递送。

[0146] 与加兰他敏基础化合物相比，以及与其衍生物的口服给药相比，通过本发明的各种盐以意料不到且显著的方式增加了血脑屏障渗透性。

[0147] 1.1. 美莫加因与乙酸的盐 :(一般方法 A) :

[0148] 将乙酸 (463mg,7.71mmol) 加入到美莫加因 (502mg,1.28mmol 在 2ml 的 96％的乙醇中) 的溶液中，并且将所得到的溶液搅拌一段时间，放置过夜从而形成盐而导致乙酸盐的沉淀。通过加入乙醚来提高产率，并且过滤该沉淀并且用 96％的乙醇进行洗涤。利用干燥器在室温以及 40 毫巴的条件下干燥该沉淀 20h。结果 :无色固体 (易潮解)。产率 :62％，m.p. :89.3℃至 91.2℃，HPLC>95％。元素分析 :计算值为 $C_{24}H_{25}NO_4$*1.5CH_3COOH C:71.24,H:6.46,N:3.32。实际值为 C:71.36,H:6.17,N:3.43。

[0149] 在相似的方式下，通过改变美莫加因和酸的相对量以及沉淀方法，得到含有 1 至 2 摩尔当量的乙酸的几种其它晶体形式。

[0150] 1.2. 美莫加因和与乳酸的盐 :(一般方法 B) :

[0151] 在 40℃至 50℃，将甲醇 (2ml) 中的 95％的外消旋乳酸 (7.85mmol) 加入到在甲醇 (4ml) 中的 2.5g 的美莫加因 (6.4mmol) 的溶液中，并且搅拌 20min。蒸发溶剂，并且首先利用旋转蒸发仪在 9 毫巴以及 50℃至 60℃的条件下将所得到的剩余物干燥 2h，随后在室温和 40 毫巴的条件下过夜干燥从而得到高度易潮解的固体浅黄色泡沫。产率 :98.92％，m.p. :62.9-64.1℃，元素分析 :计算值为 $C_{24}H_{25}NO_4$*1.1$C_3H_6O_3$C:66.84,H:6.49,N:2.86。实际值 :C:66.69,H:6.45,N:2.80。HPLC 纯度 >97％。

[0152] 在相似的方式下，得到的 (+)- 乳酸的相对应的盐 :计算值为 $C_{24}H_{25}NO_4$*1.5$C_3H_6O_3$C:65.01,H:6.51,N:2.66。实际值 :C:64.91,H:6.28,N:2.70。

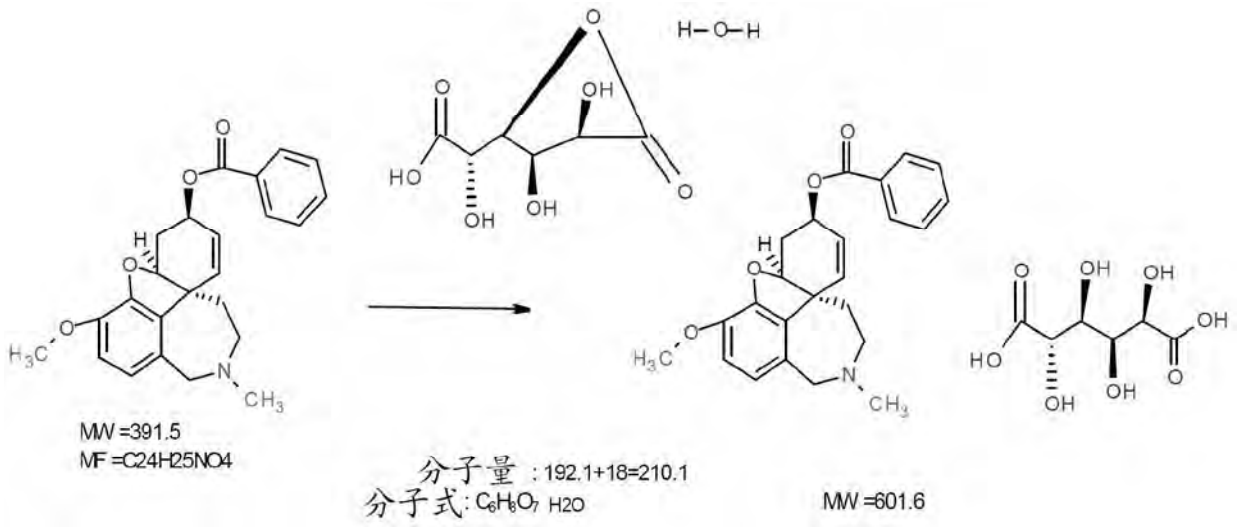
[0153] 1.3. 美莫加因与柠檬酸的盐 :

[0154] 利用一般方法 B，但是利用无水乙醇作为溶剂，来得到产率为 91.0％的粘性固体形式的柠檬酸盐，该柠檬酸盐在利用无水乙醚研磨随后通过高真空蒸发后得到无色固体，其中，m.p. ：117.5-119℃，元素分析：计算值为：C:73.64,H:6.44,N:3.58。实际值：C:59.61,H:5.93,N:2.26。HPLC>97％。

[0155] 1.4. 美莫加因与糖二酸的盐（一般方法 C）：

[0156] 在 60℃，将在 96％乙醇（3ml）中的葡萄糖二酸单内酯（200-604mg）的溶液加入到在 96％乙醇（4ml）中的美莫加因（1120mg）溶液中。立即用乙酸乙酯稀释该热溶液，从而形成无色沉淀物，在 2h 中冷却至 5℃后过滤，并用乙酸乙酯洗涤，且在室温以及 40 毫巴的条件下干燥 20h 以得到产率为 83.7％的无色固体形式的糖二酸盐，其中，m.p. ：132-134℃，HPLC 纯度 >97％。元素分析：计算值：$C_{24}H_{25}NO_4$*$C_6H_{10}O_8$C:59.89,H:5.86,N:2.33。实际值：C:60.10,H:5.61,N:2.37。在上述条件下，糖二酸的内酯在水的存在下发生水解，产生所述的盐。

[0157]



[0158] 1.5. 美莫加因与葡萄糖酸的盐：

[0159] 根据一般方法 C，从美莫加因（150mg，0.38mmol）开始，但是使用二噁烷作为溶剂以及使用 D- 葡萄糖酸 δ - 内酯（68.2mg，0.38mmol）的含水二噁烷（13mg，0.76mmol）溶液，并在 50-60℃搅拌 30min 直至得到澄清的溶液，随后向冷却的溶液中加入无水乙醚（10ml）以产生无色沉淀物，过滤该无色沉淀物并用乙醚洗涤，进行干燥以得到 170mg(75.6％）的无色结晶型固体形式的盐。m.p. :159.3-159.4℃，HPLC 纯度 >98％，元素分析：计算值 $C_{24}H_{25}NO_4$*1.5$C_6H_{12}O_7$C:57.80,H:6.32,N:2.04。实际值：C:58.22,H:5.98,N:2.28。图 1 中示出了该盐的粉末衍射图。

[0160] 以两倍的规模重复相似的实验，但是并不加入乙醚来用于沉淀，而在室温下静置 3 天，从而自发形成晶体，随后进行过滤，用二噁烷进行洗涤，并且随后干燥以得到 145mg(32％）的无色晶体形式的 1:1 的盐，其中，m.p.173.3-173.4℃，计算值 $C_{24}H_{25}NO_4$*$C_6H_{12}O_7$C:61.32,H:6.35,N:2.38。实际值：C:61.65,H:6.27,N:2.64。通过该盐的微量滴定证实了由元素分析计算出的化学计量。

[0161] 在相似的条件下，但是延长干燥时间，得到在晶体中含 0 至 2 等量水的其他盐形式。已知的是，D- 葡萄糖酸 δ - 内酯被水水解为葡萄糖酸。

[0162] 在替代的方法中，使用乙醇作为溶剂。因此，将在96％乙醇中的美莫加因(9.4g，24mmol)加入到在96％乙醇(10ml)中的D-葡萄糖酸δ-内酯(6416mg，36mmol)的溶液中，并且加热至50-60℃并持续30min直至得到澄清的溶液，随后将该溶液在室温下保持2天，以形成无色的沉淀物，对该沉淀物进行过滤，用无水乙醇(2x20ml)和异丙醇(60ml)洗涤，并且在室温以及40毫巴的条件下干燥20h，以得到7.91g(84.2％)的无色结晶固体形式的产物。m.p.:122-126℃，HPLC纯度>98％。元素分析:计算值:$C_{24}H_{25}NO_4*C_6H_{12}O_7*H_2O$ C:59.50,H:6.49,N:2.31。实际值:C:59.60,H:6.59,N:2.32。

[0163] 使用该盐获得水的吸附/解析等温线(图2)以及加热的重量损失(图3)。此外，通过美莫加因葡萄糖酸盐的湿饼的示差扫描量热法(DSC)，确定了在53℃和87℃之间发生干燥，并且在约123℃时熔化(图4)。在图5中示出了该盐的粉末衍射图。

[0164] ^{1H}NMR(200MHz,D2O):δ7.35-7.46(d,2H),7.09-6.94(t,1H),6.92-6.80(t,2H),6.59-6.36(m,2H),6.14-6.00(d,1H),5.85-5.72(m,1H),5.16-5.07(s,1H),4.48-4.31(m,4H),4.13-3.84(m,5H),3.73-3.53(m,6H),3.53-3.39(m,5H),2.76-2.58(s,3H)2.39-2.21(d,1H),2.06-1.69(m,3H)

[0165] ^{13C}NMR(50MHz,D2O):δ178.39(s,1C),167.03(s.1C),146.09(s,1C),145.11(s,1C),133.09(s,1C),131.57(s,1C),129.26(s,1C),128.04(s,1C),123.75(s,1C),123.40(s,1C),119.02(s,1C),118.74(s,1C)118.67(s,1C),112.05(s,1C),85.82(s,1C),73.93(s,1C),73.52(s,1C),72.46(s,1C),71.07(s,1C),70.81(s,1C),64.23(s,1C),62.54(s,1C),58.51(s,1C),55.52(s,1C),53.98(s,1C),46.50(s,1C),40.96(s,1C)40.82(s,1C),32.07(s,1C),26.83(s,1C)。

[0166] 利用一般方法A、B和C，以相似的方法、0.5至10mmol的规模利用制备下列盐，并且得到42-91％的非最佳产率。对于这些以结晶状态获得的盐，给出其熔点。对于在水中显示出高于10％、或甚至高于20％的溶解度的盐进一步进行研究。

[0167] 除了上述列出的内容以外，也可使用在书名为“Pharmaceutical Salts,Properties,Selection and Uses,Stahl,P.H.and Wermuth,C.G.,eds.,VHCA Verlag2002”中的表1中所记载的药学可接受的盐。

[0168] 1.6.溶解度测试

[0169] 在室温下，将10mg的相对应的盐和100微升的水进行超声处理5分钟。将所得到的溶液或悬浮液离心3分钟并且利用过滤嘴进行过滤。将10微升的滤液转移至容量瓶中，并且用水稀释至10.0ml以得到样品溶液。将20微升的该样品溶液注射到HPLC中，并且利用Merck Chromolith RP18柱以及梯度为5％至60％的乙腈和水来定量美莫加因的量，两种溶剂中均含有0.1％的甲酸，注射体积为:20微升。

[0170] 乙酸、马来酸、乳酸(乳酸盐)、柠檬酸、糖二酸(糖二酸盐)以及葡萄糖酸(葡萄糖酸盐)的美莫加因盐在水中均显示出了大于10％的溶解度。

[0171] 美莫加因的乳酸盐、葡萄糖酸盐、马来酸盐或糖二酸盐显示出了大于10wt％/单位体积(w/v)的溶解度，有时在溶液中以20％的浓度形成亚稳态盐。葡萄糖酸盐显示出40wt％/单位体积(w/v)的溶解度，而糖二酸盐显示出70wt％/单位体积(w/v)的溶解度。

[0172] 表3:额外的美莫加因盐

[0173]

酸	m.p.(℃)
柠檬酸	110-131(分解)
阿拉伯酸	213(分解)
己二酸	
DL-扁桃酸	
D-葡庚糖酸-1,4-内酯	147(分解)
甲酸	146-147
反丁烯二酸	
半乳糖酸	143-144
D-(+)-半乳糖醛酸	148-151
葡萄糖醛酸	145-146
羟基乙酸	97-103
氢溴酸	221-222
羟基柠檬酸	
盐酸	
羟基乙磺酸	191-195
马来酸	
L-(-)-苹果酸	107-108
丙二酸	
烟碱酸	117-118
磷酸	
琥珀酸	
硫酸	172-173
L-(+)-酒石酸	185-186

D-(-)-酒石酸	212-213
内消旋酒石酸	107-109

[0174] 尤其优选的是乙酸、马来酸、乳酸（乳酸盐）、柠檬酸、糖二酸（糖二酸盐）和葡萄糖酸（葡萄糖酸盐）的第四氮盐（还被称为季铵盐）。

[0175] 这些酸与在中性 pH 时在水中具有高达 70％溶解度的美莫加因和其它加兰他敏前体药物含氮碱形成盐。尽管在水溶液中高浓度葡萄糖酸盐是亚稳态，并且随后转化成更低溶解性的稳定盐形式，但是通过将水性混合物升温至 >50℃直至沉淀物消失，能够恢复成完全溶解的均一溶液。假若采取降低或避免沉淀出晶种的措施，这些亚稳态均一溶液在数小时和数天内保持稳定。用于形成这种亚稳态（苛刻的）溶液的溶解过程的适当文件材料表明这些溶液是适用于患者和医务人员的合适的药品制剂。在给药前通过短暂加热（例如手动加热 5 分钟）来允许该亚稳态溶液的最优给药。

[0176] 对于本文所述的前体药物的缓释水性制剂，我们将天然生物高分子壳聚糖的粉末溶解在水中，并与美莫加因碱或氢盐混合，从而得到鼻内递送为 5％ (w/v) 或以上的制剂 (lllium L 等人 .(2002).Intranasal delivery of morphine.J Pharmacol Exp Therap 301:391-400)。lllium 等人描述的施用方法也适用于使用本发明的化学物质。

[0177] 包含壳聚糖的美莫加因盐的缓释制剂当以固体形式通过口腔舌下给药或颊内给药时，也被证明有效，并且显示出意想不到的快速初始吸收以及较长的释放时间。

[0178] 与现有技术中所公开的效果相比以及与技术人员基于现有技术所能预料到的效果相比，本发明的优选的盐给出了优选的实施方式，其显示出预料不到的令人惊喜的有利效果。尤其优选的盐的溶解度出乎意料的好，使得在药物组合物能存在较高浓度的药物（即，在用于鼻内给药的尤其优选的实施方式中以溶液的形式存在，另外在颊内施用或舌下施用时也是同样）。鉴于上述所提及的对于适用于鼻内给药、舌下给药或颊内给药的化合物的要求，这是尤其重要的。由于鼻腔的大小有限，溶液中活性物质的所需浓度是较高的。这意味需要发现一种非常易溶从而能提供高浓度的盐。令人惊奇的是，这正是本文所提及的盐的情况，优选乙酸（乙酸盐）、乳酸（乳酸盐）、柠檬酸、糖二酸（糖二酸盐）和葡萄糖酸（葡萄糖酸盐）。

[0179] 实施例 2. 乳剂和自微乳化药物递送 (SMEDD)

[0180] 乳剂和 SMEDD 是既定的脑递送系统的方法 (Botner S,Sintov AC(2011) Intranasal delivery of two benzodiazepines,Midazolam and Diazepam,by a microemulsion system.Pharmacol Pharmacie 2:180-188)。在本申请中，通过如下方式产生 :将所研究的前体药物以氮碱或氢盐的形式与各种有机溶剂混合或在搅拌和 / 或超声下与合适的表面活性剂、油和助表面活性剂（均通过安全认证 ;GRAS) 混合，直至得到澄清的溶液。具体地，避免在制剂中使用醇或或其它刺激性化学品，从而避免对鼻或颊内黏膜的任何刺激性。这种微乳剂的通常成分是聚乙二醇 -8- 甘油辛酸 / 葵酸酯 (Labrasol)、N- 乙基 -2- 吡咯烷酮 (NEP)、油酸甘油酯、PEG、丙二醇、二乙二醇单乙基醚 (Transcutol) 和合适的油，如棕榈酸酯。我们得到了 10％ (w/w) 级别或更高的药物溶解度，最大水溶解容量为约 50％（水分含量越低，可实现的油浓度越高，以及含氮碱的溶解度越高）。在微乳剂中，前体药物含氮碱或盐的最高的溶解度为水中浓度约 20％。

[0181] 自微乳化药物递送 (SMEDD) 制剂的优选的实施方式，优选地对于美莫加因马来酸盐的实施方式，涉及如下内容 ：

[0182] 所使用的材料 ：

[0183] 美莫加因的马来酸盐 (No.022563-A-1-1,GALANTOS Pharma GmbH,德国)

[0184] Capmul MCM(Lot:080726-7,Berentz-Abitec Corp.,美国)

[0185] (甘油辛酸酯 / 癸酸酯 ;Pharm.Eur.)

[0186] PEG 300/400(Lot:1349048-41108320,Fluka,奥地利维也纳)

[0187] (聚乙二醇 ;Pharm.Eur.)

[0188] 丙二醇 (Lot:S44324-108,SIGMA,奥地利维也纳)

[0189] (丙二醇 ;Pharm.Eur)

[0190] 二乙二醇单乙基醚 (Transcutol)(Lot:18703CE,SIGMA,奥地利维也纳)

[0191] (二乙二醇单乙基醚 ;Pharm.Eur.)

[0192] 10％美莫加因马来酸盐的 SMEDD 制剂 (1L) 的制备 ：

[0193] 第一步，将 100g 的美莫加因马来酸盐称重至适当的钢槽中。随后，逐一加入下列增溶剂和脂油 ：

[0194] 170ml 的 Capmul MCM

[0195] 500ml 的 PEG 300

[0196] 220ml 的丙二醇

[0197] 110ml 的二乙二醇单乙基醚

[0198] 最后，用超声处理 SMEDD 制剂直到混合物变得澄清的溶液。

[0199] 美莫加因碱和盐乳剂以及 SMEDD 制剂证实了施用时带来的粘膜表面的局部刺激性降低。此外，通过各种脂质和 PEG 成分有效地掩盖了前体药物的苦味，并且在粘膜表面无明显的镇痛作用。

[0200] 实施例 3. 前体药物晶体的微粉化粉末制剂和纳米悬浮液

[0201] 用于粘膜递送的其它合适的制剂是前体药物纳米晶体和吸附有前体药物的聚合物微粒。在这两种情况下，使用了更具亲脂性的前体药物碱。通过聚合物和前体药物的共沉淀，或通过在水中珍珠铣削和均一化，或制成作为脂质复合物的前体药物的纳米悬浮液，来获得该制剂。这种方法是本领域技术人员所知晓的，并且可应用于本发明的化学物质和给药方法。

[0202] 与以水溶液形式施用相比，GLN 1062 或其盐的微粉化粉末组合物能够更快地吸收并且降低化合物的苦味。

[0203] 实施例 4. 美莫加因 - 制剂

[0204] 美莫加因的溶解度

[0205]

水中的游离碱:	26μg/ml（66μM）
水中的马来酸盐:	7.5mg/ml（15mM）
0.9% NaCl 中的马来酸盐:	0.6mg/ml（1.5mM）
环糊精-介质 [1)] 中的游离碱:	8.9mg/ml（23mM）
环糊精-介质 [1)] 中的马来酸盐:	21mg/ml（41mM）
[1)]15%（109mM）羟丙基-β-环糊精，	96mM NaCl

[0206] 表 4. 制剂

[0207]

名称	GEA1
类型	舌下片剂
API	美莫加因马来酸盐
API/片剂	1mg
片剂重量	20mg

[0208]

载体	乳糖一水合物 乙醇 [1)] 玉米淀粉 Povidon K30（聚乙烯吡咯烷酮（PVP）） 硬脂酸镁 [1)]在生产期间被去除

[0209]

名称	GEA2
类型	舌下片剂
API	美莫加因马来酸盐
API/片剂	2mg
片剂重量	50mg
载体	甘露醇 Explotab（淀粉羟乙酸钠） 交联甲羧纤维素 抗坏血酸硬脂酸镁 橙味调味剂

[0210]

名称	Evonik 1
类型	具有耐消化酸的包衣的多层丸剂（约 1mm）
API	美莫加因马来酸盐
API-量	1%
丸芯	Cellet 700（MCC）
API-层	美莫加因马来酸盐和 Methocel E5（HPMC）
子包衣	Methocel E5（HPMC）
包衣	Eudragit FS30D，滑石粉，柠檬酸三乙酯

[0211]

层厚 Eudragit:	约 30μm bei 15%包衣; 制备具有 5%和 10%的丸剂

[0212]

名称	Evonik 2
类型	具有耐消化酸的包衣的多层片剂（约 9mg）
API	美莫加因马来酸盐
API-量	2mg
丸芯	美莫加因马来酸盐，Avicel PH 102 （MCC），玉米淀粉，Methocel E5（HPMC），硬脂酸镁
子包衣	Methocel E5（HPMC）
包衣	Eudragit FS30D，滑石粉，柠檬酸三乙酯
层厚 Eudragit:	约 90μm bei 15%包衣; 制造具有 5%和 10%的小球

[0213] 本发明的舌下片剂和多层制剂显示出令人惊奇的良好的吸收性能，能够使得快速地摄入并且降低苦涩的味道，此外还能降低患者口中的镇痛效果。化学物质的快速吸收能够降低吞咽的风险；从而确保通过口腔粘膜时发生粘膜给药，避免了前体药物的不良降解。

[0214] 实施例 5. 与载体物质和 Eudragit（聚（甲基）丙烯酸）的相互作用

[0215] 实验 1：将在 1ml HBSS- 缓冲液中、pH 7.4 的少量（0.1 毫克）美莫加因马来酸盐与各种载体在 37℃温育 2.5 小时。随后通过 HPLC 测量游离美莫加因（未结合到载体物质粒子）的量。施用通常量的载体物质，并将施用的量示于表 5。

[0216] 表 5.

[0217]

Nr.	物质	mg 载体	未吸收的美莫加因

[0218]

			（%对照）
对照	无	0	100
1	乳糖	10	105
2	MCC	10	100
3	HPMC	1	105
4	玉米淀粉	5	100

5	Eudragit L100	2	21
6	Eudragit FS30D	1.8	7
7	滑石粉	2	94
8	硬脂酸镁	0.1	101
9	硬脂酸镁 +Tw20	0.1+0.1% Tw20	103
10	微粉硅胶 (SiO_2)	1	89
11	磷酸氢钙 ($CaHPO_4$)	10	101
12	Explotab	2	99
13	柠檬酸三乙酯	0.2	101

[0219] 结果:Eudragit L100 和 Eudragit FS30D 吸附美莫加因。

[0220] 实验 2:将固定量的 Eudragit(0.5 毫克 / 毫升) 与各种量的美莫加因马来酸盐在生理盐水溶液 (HBSS) 中温育 2h。通过 HPLC 测量游离美莫加因 (未结合到载体物质粒子) 的量。并行地分析 Eudragit 量仅在盐溶液中的溶解度。

[0221] 结果:L100 在给定的浓度完全溶解,FS30D 形成絮状溶液。在整个实验的浓度范围内,FS30D 与美莫加因结合。由于 0.25mg/ml 的美莫加因与 L100 形成沉淀物,其通过加入 6%的环糊精 (HPCD) 能够被再溶解。

[0222] 实施例 6. 渗透行为、系统前代谢 (pre-systemic metabolism) 和稳定性的体外研究

[0223] 利用 3-4cm^2新鲜离体猪鼻或颊粘膜的组织样品来测试前体药物制剂的渗透行为,其中该组织样品插入在尤斯室 (Ussing-type chamber) 中,显示出 0.64cm^2的渗透面积且两侧均为 1ml 的体积。组织的顶侧朝向供体房室。将 1 毫升预热 (37℃) 的渗透介质加入到供体和受体腔室。在整个实验中,将腔室内的温度保持在 37℃。经过 15 分钟的预温育时间后,供体腔室中的渗透介质被待研究的前体药物制剂的 1%的溶液所取代。在整个 180 分钟的时段中,每 30 分钟从受体房室中收回 100μl 的等份并用立即用 100μl 新鲜预热的渗透介质取代。通过 HPLC 测定所收集的等份中化合物的浓度。对于先前移除的样品进行校正。计算了表观渗透系数 (Papp)。在 180 分钟之后,从供体腔室中收回对照样品,并对其进行分析以研究化合物在待研究制剂中的稳定性。

[0224] 在上述渗透实验期间,在 0 分钟、60 分钟、120 分钟和 180 分钟的时间点从供体房室中收回 10μL 的等份。通过 HPLC 分析这些等份以确定随着时间的推移的系统前代谢的程度。

[0225] 利用这些方法,对于前体药物盐的水溶液以及前体药物碱在有机溶剂、助溶剂和表面活性剂中的溶液,测定它们的溶解度、它们的渗透系数以及它们的系统前代谢和稳定性。进一步研究的制剂具有至少 10% (m/v) 的溶解度,Papp>1 • 10^{-6}cm/s 的前体药物的渗

透系数。在所测试的时段内，在两个猪粘膜制品中均没有发生前体药物的显著的系统前代谢。

[0226] 实施例 7. 药代动力学

[0227] 测试在鼻腔或口腔中粘膜给药后，在威斯塔鼠中前体药物和母体药物的药代动力学。这些数据证实了待研究的前体药物快速（在数分钟内）摄入至血和脑，前体药物在脑中的生物利用度与通过静脉注射所产生的生物利用度相似，且与以相关母体药物的片剂形式通过口服递送相比，具有高得多的 BBRC。

[0228] 因为在脑中从前体药物酶法产生母体药物之后，母体药物通过 BBB 进入循环而发生再分配事实上是非常快速的，因此药代动力学研究并不足以准确地确定母体药物在脑中的瞬时浓度。因此，我们利用药效学研究在合适的实验条件下确定母体药物的有效浓度，诸如在小鼠的 T- 迷宫认知模式研究中东莨菪碱所诱导的暂时性遗忘症的恢复。这些研究证实了通过鼻腔或口腔来粘膜递送前体药物制剂，能够实现母体药物的高出数倍（达 20 倍）的 BBRC（以及在认知增强中相关的有效性）。

[0229] 通过试验直接比较口服给药美莫加因和粘膜（鼻）给药美莫加因之间效力和降低的 Gl 副作用，也证实了与口服给药美莫加因相比，鼻内给药美莫加因显示出了意想不到的有益特性。

[0230] 利用鼻内给药和舌下给药美莫加因马来酸盐来进行药代动力学研究。

[0231] 鼻内报告：

[0232] 这个实验计划描述了在鼻内施用在各种制剂中的美莫加因马来酸盐和加兰他敏氢溴酸盐后，前体加兰他敏也就是美莫加因马来酸盐和加兰他敏在雌性威斯塔鼠中的血和脑的药代动力学曲线。

[0233] a. 在水中的 5％加兰他敏，每鼻孔 10μL，总量为 20μL，含 1mg 5％加兰他敏。

[0234] b. 在水中 10％ NEP 中的美莫加因盐，每鼻孔 10μL，总量为 20μL，含 1mg。

[0235] c. 在乳剂中的 5％的美莫加因盐，每鼻孔 10μL，总量为 20μL，含 1mg。

[0236] d. 在乳剂中的 20％的美莫加因盐，每鼻孔 10μL，总量为 20μL，含 4mg。

[0237] e. 静脉给药美莫加因盐，剂量率为 5mg/kg（先实施作为对照）。

[0238] 舌下报告：

[0239] 这个实验计划描述了在舌下施用在各种制剂中的美莫加因马来酸盐和加兰他敏氢溴酸盐后，前体加兰他敏也就是美莫加因马来酸盐和加兰他敏在雌性威斯塔鼠中的血和脑的药代动力学曲线。

[0240] a. 在水中的 5％加兰他敏，在舌下施用 20μL，含 1mg。

[0241] b. 在水中 10％ NEP 中的 5％的美莫加因盐，在舌下施用 20μL，含 1mg。

[0242] c. 在乳剂中的 5％的美莫加因盐，在舌下施用 20μL，含 1mg。

[0243] d. 在乳剂中的 20％的美莫加因盐，在舌下施用 20μL，含 4mg。

[0244] e. 静脉给药剂量率为 5mg/kg 的美莫加因盐作为对照。

[0245] 鼻内研究和舌下研究均表明在马来酸盐的情况中观察到了有益的药代动力学 (PK) 特性。当考虑到本文所述的其他实验，并根据鼻内粘膜或口腔粘膜的初步研究时，能够预期到本发明的其它优选的盐也能得到相似的结果，其表明本发明的所有优选的盐穿过粘膜细胞膜的良好摄入。PK 数据显示出在延长的时段中在脑中检测到美莫加因，显示出高

脑 - 血浓度比，表明了所施用的前体药物中只有极少部分进入血流并随后被分解。随着时间的推移美莫加因在脑中的水平会降低，而加兰他敏在脑中的水平增加，这表明前体药物在受试者的脑中裂解成其活性形式。图 12 的样品 b 示出了用于鼻内实验的一个实施例。

[0246] 美莫加因盐的鼻内给药提供了将前体药物特异性引导至脑中的非常有效的方法，其在脑中进行处理从而释放出活性化合物加兰他敏。

[0247] 美莫加因葡萄糖酸盐：

[0248] 对美莫加因葡萄糖酸进行了进一步的测试。与加兰他敏相比，其具有高得多的 BBRC（参见图 6）。在以 3mg/kg 的剂量鼻内给药至瑞士白化小鼠之后，评估几种加兰他敏衍生物和其裂解产物加兰他敏的药代动力学和脑 - 血浓度比 (BBRC)。从脑和血中提取后，采用 LC/MS/MS 测定药物浓度。为了进行比较，还测定了母体药物加兰他敏的 BBRC。如图中所证实的，与加兰他敏相比，所研究的前体加兰他敏均显示较大的 BBRC，Gln-1062 具有尤其高的 BBRC。

[0249] 美莫加因葡萄糖酸盐是高水溶解性的并且对鼻子没有任何的灼烧感，或任何的味道或气味。可通过简单的喷雾泵的方法进行鼻内给药，但也可使用其它的方法。由于美莫加因是加兰他敏的非药学活性前体并且以葡萄糖酸盐的形式经鼻内给药，所以未观察到 Gl 副作用。

[0250] 实施例 8. 与加兰他敏相比，美莫加因显示出改善的脑渗透性和低血水平

[0251] 图 13 示出了该数据。小鼠被静脉 (i.v.) 注射 3mg/kg 的美莫加因或加兰他敏。数据清楚地证实了加兰他敏并没有良好地在脑中分布 (BBRC ～ 1 :1)，而美莫加因具有高得多的 BBRC(8 :1)。

[0252] 图 14 中示出了用于鼻内 (i.n.) 给药的额外的数据。利用在类似 GLP 条件下进行 5mg/kg 鼻内 (i.n.) 美莫加因给药来进行大鼠 PK 研究。数据证实了美莫加因具有高得多的 BBRC(10 :1)。

[0253] 实施例 9. 与加兰他敏相比，鼻内美莫加因更具潜力

[0254] 为了测试鼻内美莫加因在体内是否是比加兰他敏更有效的认知增强剂，采用以下认知范式。小鼠用东莨菪碱处理以诱发急性遗忘症，随后在不进行或进行加兰他敏口服给药或美莫加因鼻内给药的情况下，测试其在 T- 迷宫中的性能（图 7）。明显地，美莫加因在恢复急性诱导遗忘症方面比加兰他敏更有效。在 T- 迷宫分析中，腹腔给药 (i.p.) 东莨菪碱以刺激小鼠，从而诱导定向障碍 / 遗忘症（设置为 0％功能恢复）。加兰他敏（腹腔 i.p.）或 Memogain®（鼻内 i.n.）的共施用以剂量依赖的方式恢复了小鼠在 T- 迷宫中的定向。

[0255] 实施例 10. 美莫加因的首过效应

[0256] 在威斯塔鼠中通过静脉和门静脉以 3mg/kg 的剂量给药后，评估 Gln-1062 的首过效应（图 8）。无论通过静脉 (i.v.) 或鼻内 (i.n.) 给药，都观察到 Gln1062 的首过效应，即血浓度水平迅速降低。与此相反，通过酶裂解而由 Gln-1062 释放的加兰他敏的浓度水平并未同样地迅速降低。此外，与门静脉给药相比，在静脉 (i.v.) 给药后，在脑和血中观察到 Gln-1062 更高的最大浓度。从这些数据可估计首过效应为 35％至 45％之间。

[0257] 当 Gln-1062 以相同剂量鼻内给药时，在脑中观察到与静脉 (i.v.) 给药后相似的高的最大浓度水平，这表明经鼻内给药后向脑中的摄入与静脉 (i.v.) 给药后的有效性相当，并且首过效应仅带来极小损伤。

[0258] 实施例 11. 美莫加因的鼻内给药导致释放到血浆中的加兰他敏的量少

[0259] 该研究用狗进行。鼻内给药单次剂量的 4mg/kg 的美莫加因。并且在给药后测定美莫加因和释放的加兰他敏的血浆水平，作为时间的函数。由于美莫加因优先分配至脑中，因此前体药物仅有一小部分出现在血液中。由于加兰他敏迅速代谢和排泄，所以由美莫加因释放的加兰他敏的水平要低得多（图 9）。考虑到在鼻内（i.n.）给药后，在血中存在的系统性加兰他敏的量少，因此副作用的可能性大大降低。

[0260] 来自狗的实验数据证实：

[0261] - 美莫加因的脑：血比（在给药后 120 分钟）= 9

[0262] - 加兰他敏的脑：血比（在给药后 120 分钟）= 1-1.5

[0263] - 血中的美莫加因 t1/2 = 90min（有意识的动物）

[0264] - 加兰他敏 t1/2 = 6h（有意识的动物）

[0265] - 加兰他敏的较低血水平表明较少的副作用

[0266] - 美莫加因的较高脑浓度表明美莫加因主要在脑中释放出加兰他敏。

[0267] 实施例 12. 与加兰他敏相比，美莫加因产生较少的胃肠道副作用

[0268] 这些研究用雪貂进行，分别用 20mg/kg 的加兰他敏（最大耐受剂量）或用 20mg/kg、40mg/kg 和 80mg/kg 的加兰他敏向雪貂进行腹腔（i.p.）给药。对于 20mg/kg 的美莫加因，未观察到不良效应。根据不良效应的剂量依赖性，观察到在该动物模型中，与加兰他敏相比，美莫加因具有至少低 4 倍的毒性（图 10）。

[0269] 同样，在大鼠中进行的欧文检验（Irwin assay）和呼吸毒性研究中，以及在狗中进行的心血管毒性研究中，观察到比加兰他敏小得多的不良效应。

[0270] 实施例 13. 与加兰他敏相比，美莫加因至少安全 10 倍

[0271] 该项研究用狗进行，通过静脉团注来给药这两种药物。由于前体药物的酶裂解而导致加兰他敏的稳定态血浆水平要低得多，从而美莫加因具有较低的毒性（图 11）。

[0272] 加兰他敏前体药物及其制剂通过鼻腔和口腔的粘膜递送的医学益处：

[0273] 关键的益处如下：

[0274] 1. 在目标器官中较高的生物利用度和较高的有效性

[0275] 2. 较低水平的外周副作用

[0276] 3. 能够根据医学需要调节药代动力学（持续释放）

[0277] 4. 给药不受 GI 不良效应的限制

[0278] 5. 医学益处更快且更强的开始体现

[0279] 6. 不需要剂量的递增剂量（up-titration of dose）（增强了依从性）

[0280] 7. 立即给药至有效剂量

[0281] 8. 改进的患者依从性

[0282] 在认知障碍的动物模型中，利用合适的认知范式，通过药效学研究证实了在脑中较高的生物利用度和作为认知增强剂的较高的有效性。与口服给药相同剂量的美莫加因和加兰他敏相比，鼻内递送美莫加因大大降低了胃肠道不良效应的影响，例如恶心和呕吐。对于鼻内递送前体加兰他敏也就是美莫加因，甚至是以非常高剂量鼻内递送美莫加因，GI 相关的副作用也几乎消失，这是亲脂性前药的较好脑渗透和避免在药物递送期间进入胃肠道的综合结果。

[0283] 总之，美莫加因和加兰他敏的口服给药由于美莫加因在给药后的快速裂解（成为加兰他敏）而产生相当的 BBB 渗透性。当以相同浓度口服给药美莫加因盐时，并没有表现出明显增强的效应。

[0284] 静脉给药 (i.v) 美莫加因证实了，由于美莫加因的疏水性质，美莫加因具有与加兰他敏相比大大改进的 BBB- 渗透性。与口服递送加兰他敏相比，加兰他敏的静脉 (i.v.) 给药仅提供了非常小（如果有的话）的优势，这是由于活性化合物本身与美莫加因相比是相对稳定的且并不易被酯酶裂解。

[0285] 对于美莫加因、尤其是美莫加因的盐，粘膜给药（鼻内 ;i.n.）展现出意想不到的增强的效果。美莫加因的盐的鼻内 (i.n.) 给药进一步显示出改进的 BBB 渗透性。

[0286] 通过鼻内 (i.n.) 给药加兰他敏并不能增强加兰他敏的脑渗透性，这是由于分子的亲水性抑制了有效渗透，而与给药途径无关。加兰他敏的鼻内 (i.n.) 给药通过避免通过消化道的给药而可避免加兰他敏的一些常见的副作用 (Leonard 等人 (2007))。然而，由于 BBRC 仍然较差，所以作为分子认知增强剂的效果并没有被增强。

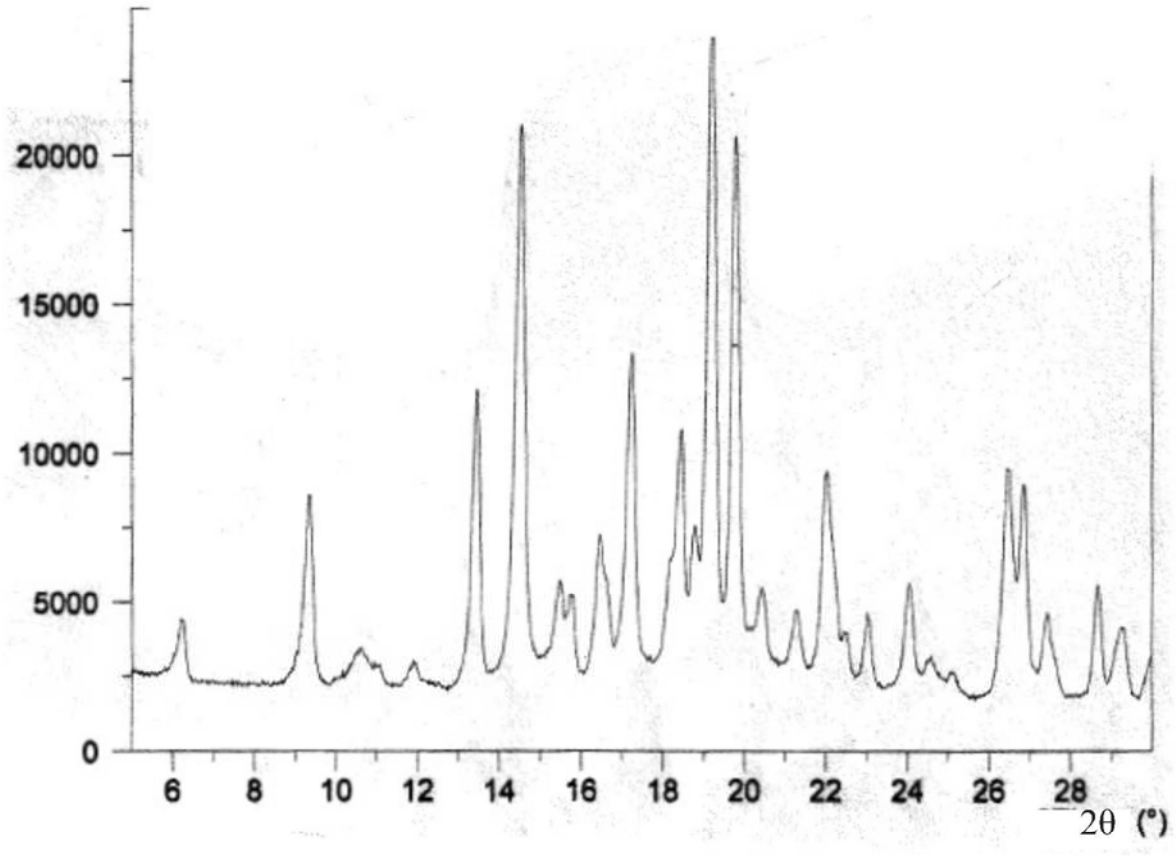


图 1

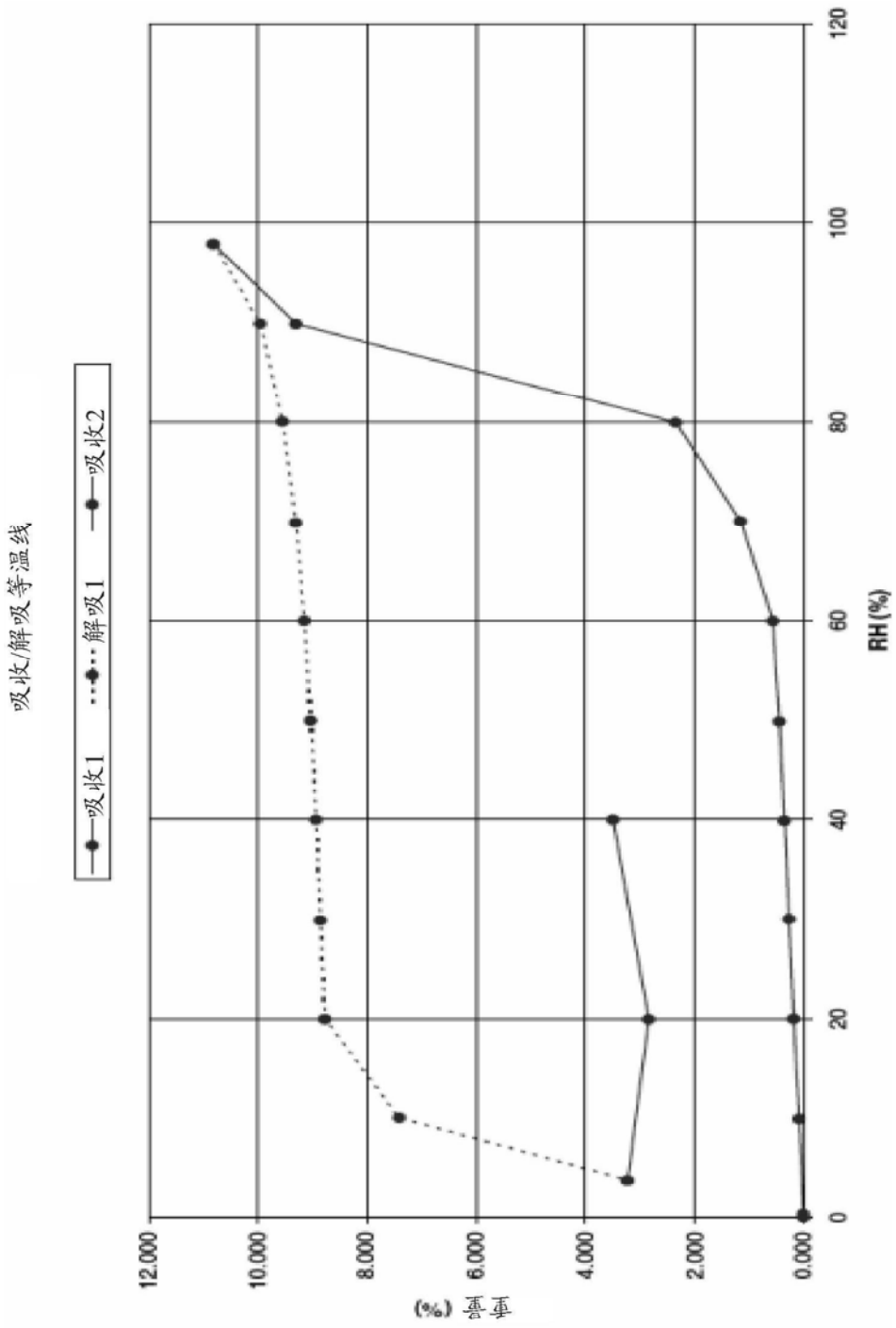

吸收/解吸等温线
吸收1
解吸1
吸收2
重量 (%)
12.000
10.000
8.000
6.000
4.000
2.000
0.000
0
20
40
60
80
100
120
RH (%)

图 2

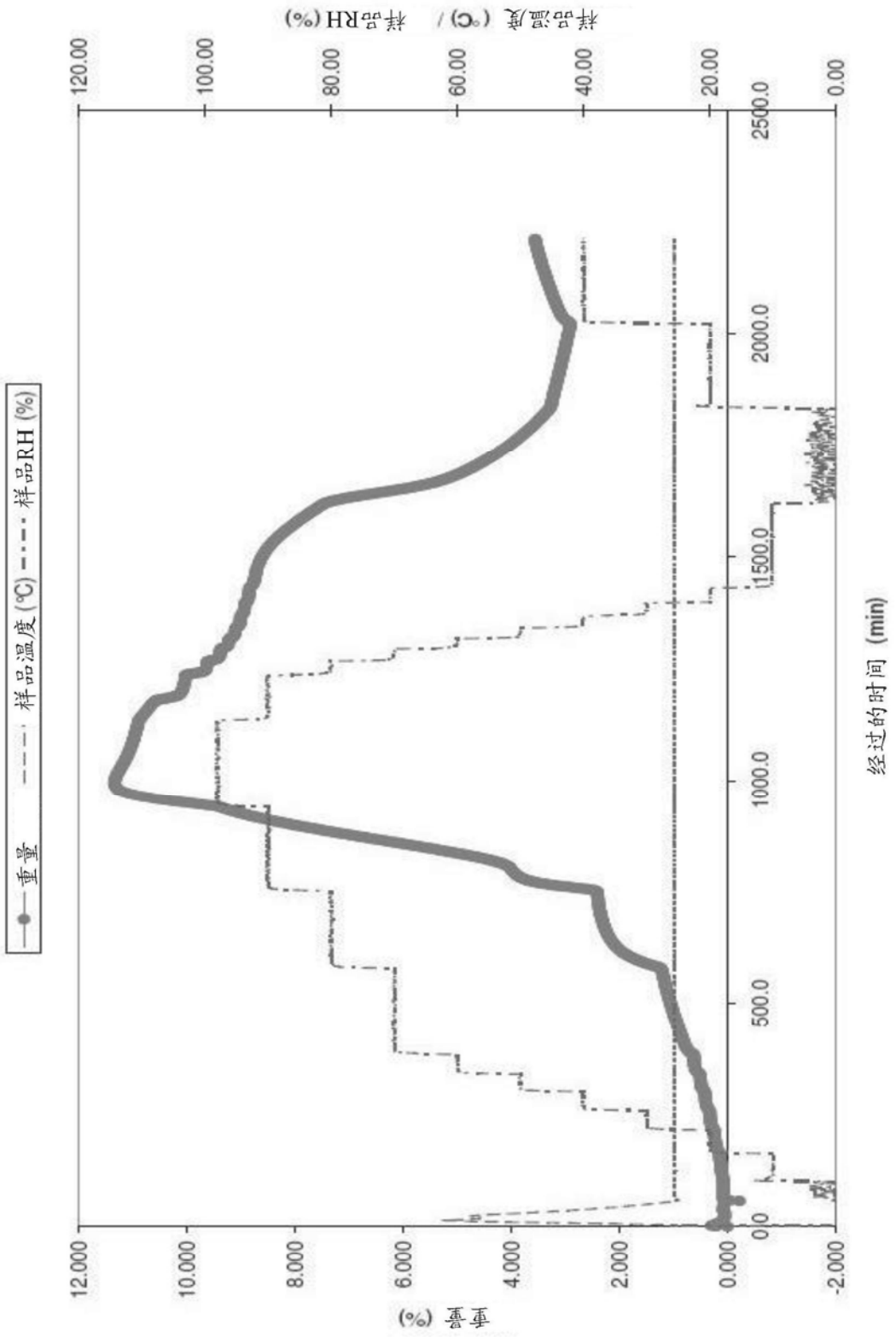

重量
样品温度 (℃)
样品RH (%)
重量 (%)
样品温度 (℃) / 样品RH (%)
经过的时间 (min)
12.000
10.000
8.000
6.000
4.000
2.000
0.000
-2.000
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0.0
500.0
1000.0
1500.0
2000.0
2500.0

图 3

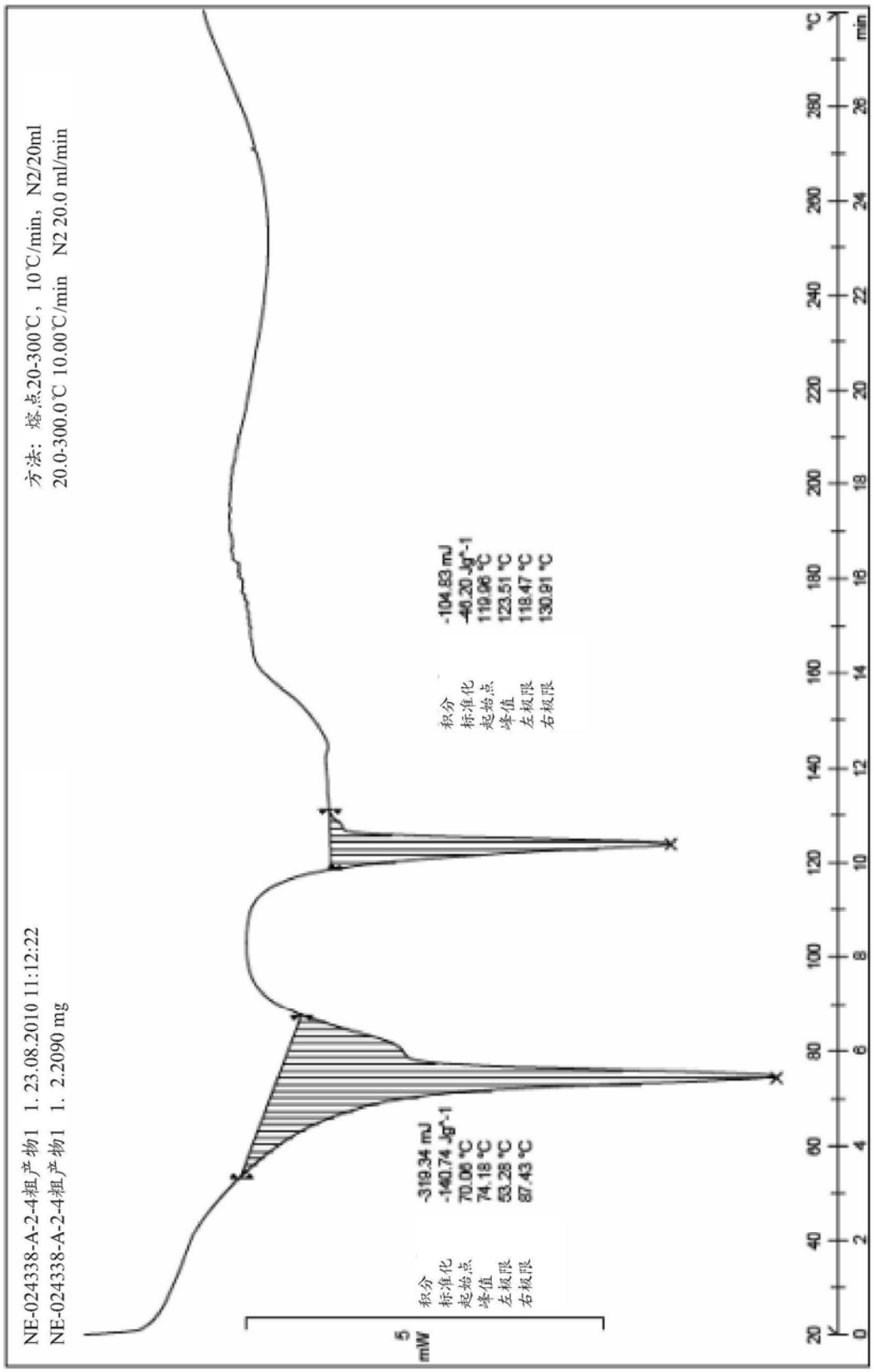

方法：熔点20-300℃，10℃/min，N2/20ml
20.0-300.0℃ 10.00℃/min N2 20.0 ml/min
NE-024338-A-2-4粗产物1 1. 23.08.2010 11:12:22
NE-024338-A-2-4粗产物1 1. 2.2090 mg
5 mW
积分 -318.34 mJ
标准化 -140.74 Jg^-1
起始点 70.06 ℃
峰值 74.18 ℃
左极限 53.28 ℃
右极限 87.43 ℃
积分 -104.83 mJ
标准化 -46.20 Jg^-1
起始点 119.96 ℃
峰值 123.51 ℃
左极限 118.47 ℃
右极限 130.91 ℃
℃
min

图 4

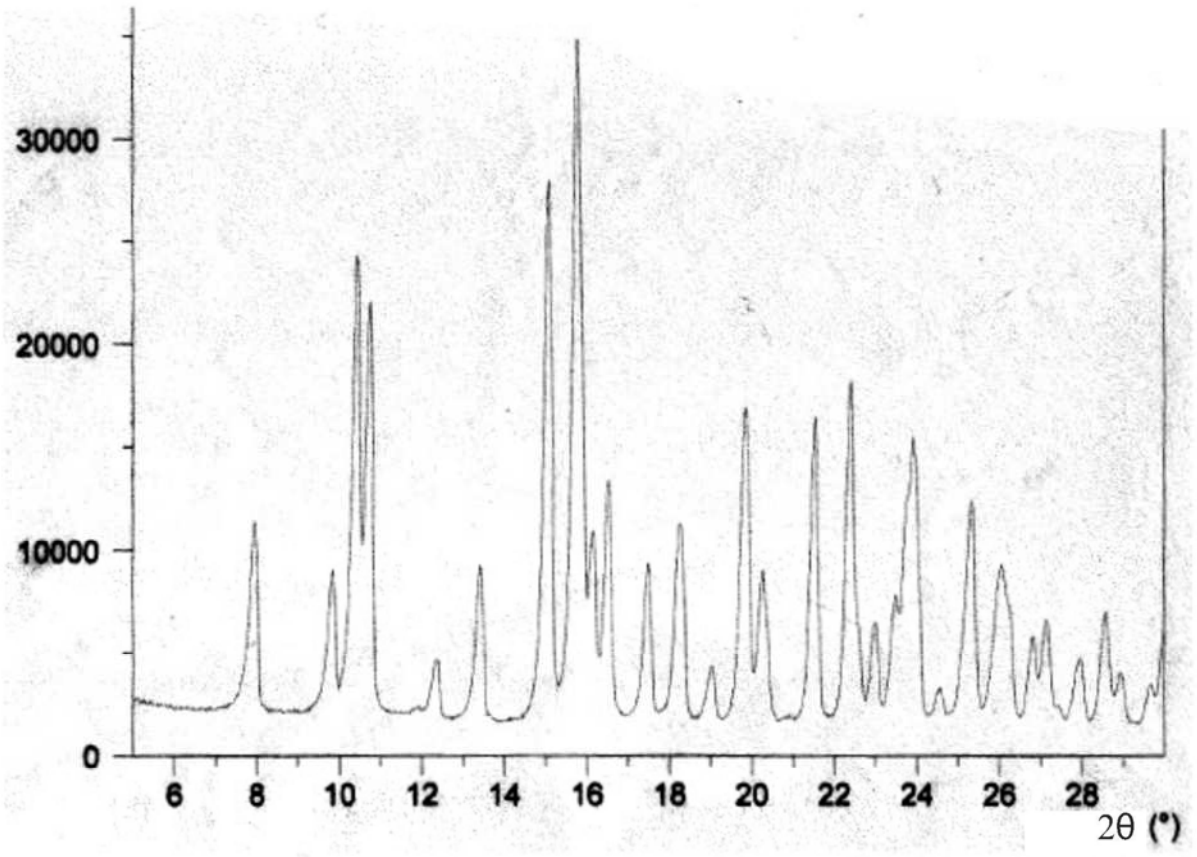

30000
20000
10000
0
6
8
10
12
14
16
18
20
22
24
26
28
2θ (°)

图 5

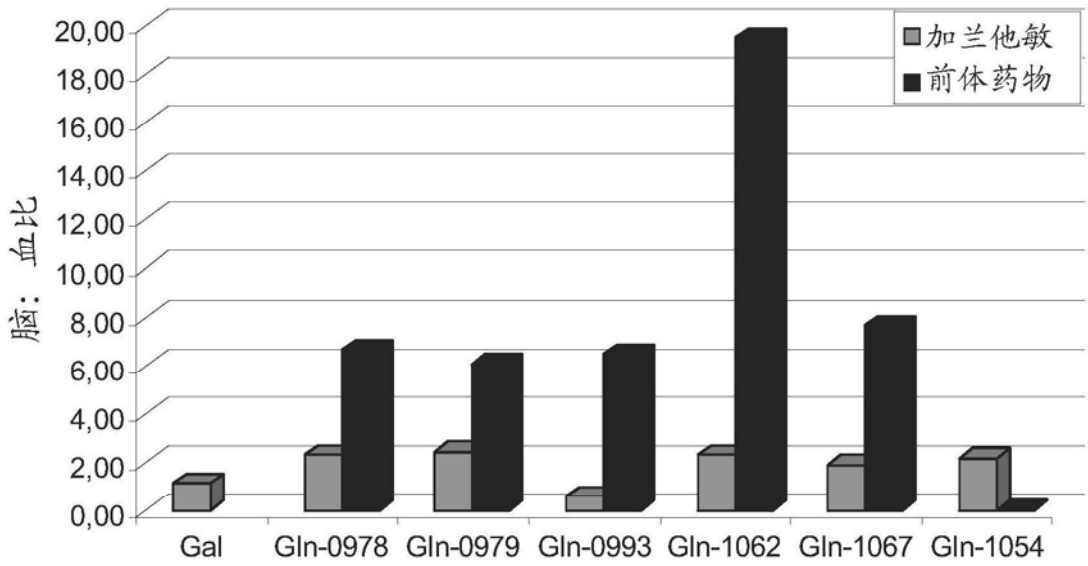

20,00
18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
脑：血比
加兰他敏
前体药物
Gal
Gln-0978
Gln-0979
Gln-0993
Gln-1062
Gln-1067
Gln-1054

图 6

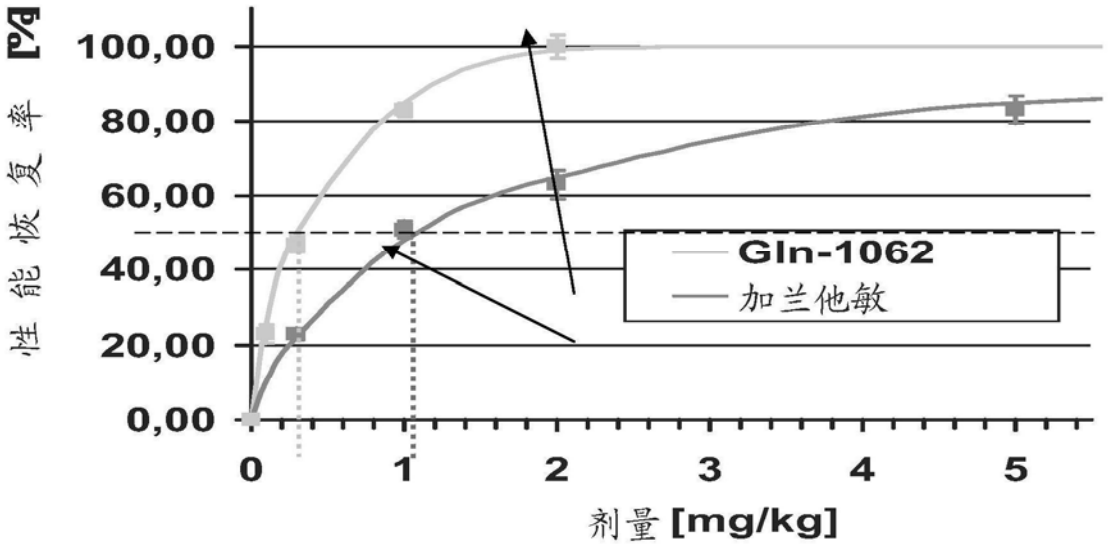

性能恢复率 [%]
100,00
80,00
60,00
40,00
20,00
0,00
0
1
2
3
4
5
剂量 [mg/kg]
Gln-1062
加兰他敏

图 7

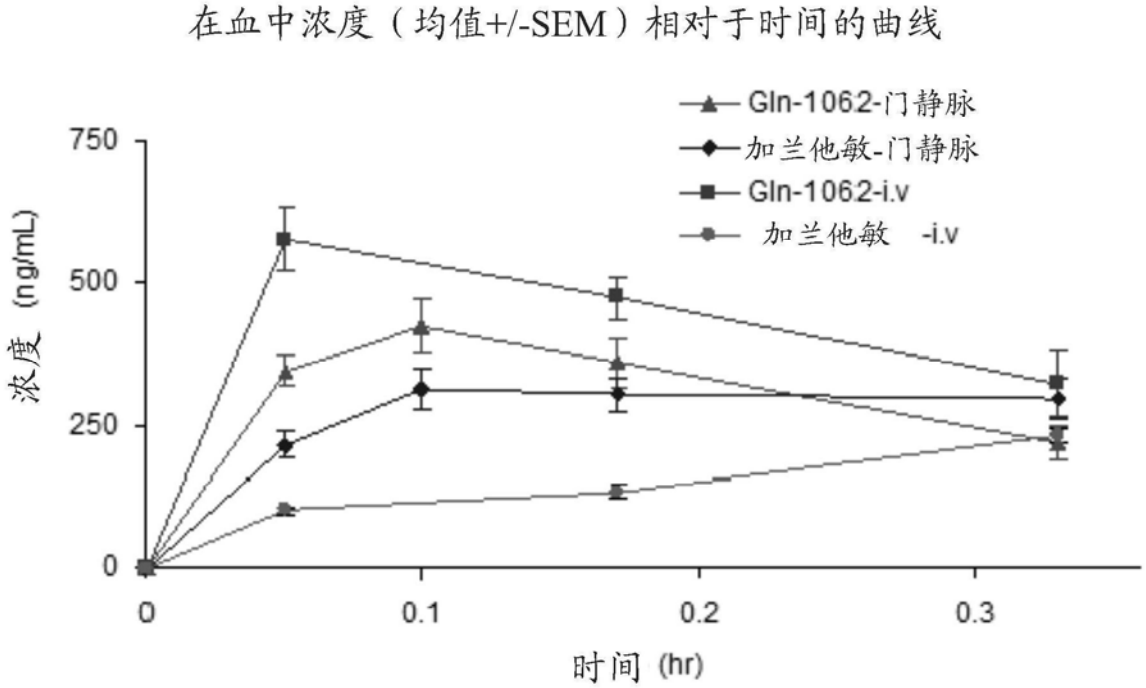

在血中浓度（均值+/-SEM）相对于时间的曲线
Gln-1062-门静脉
加兰他敏-门静脉
Gln-1062-i.v
加兰他敏 -i.v
浓度 (ng/mL)
750
500
250
0
0
0.1
0.2
0.3
时间 (hr)

图 8

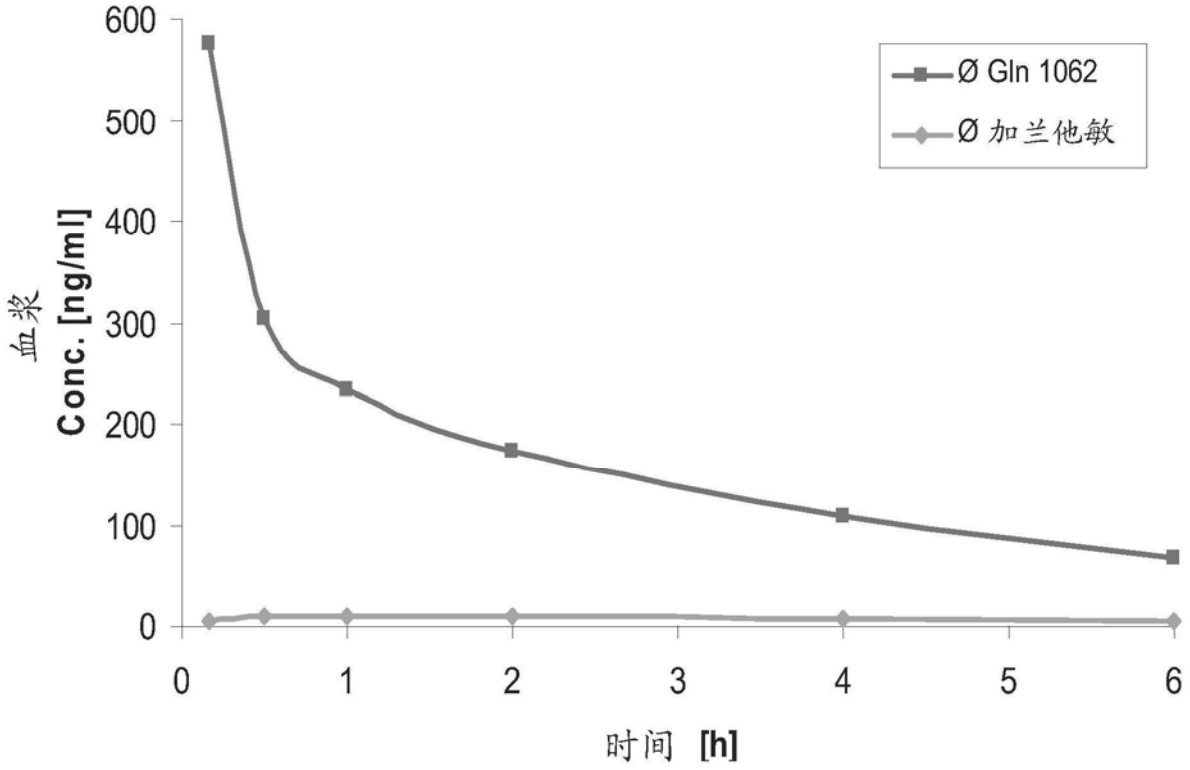

600
500
400
300
200
100
0
血浆
Conc. [ng/ml]
0
1
2
3
4
5
6
时间 [h]
Ø Gln 1062
Ø 加兰他敏

图 9

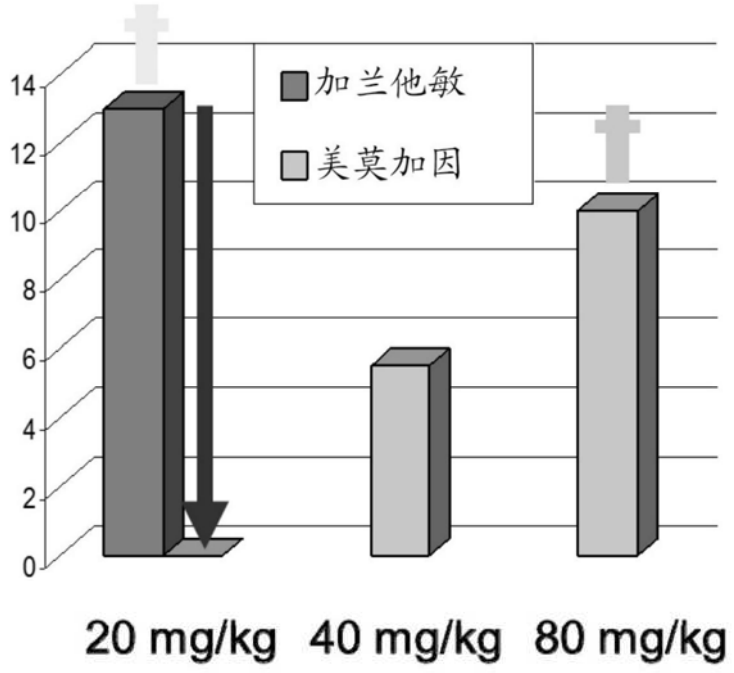

14
12
10
8
6
4
2
0
加兰他敏
美莫加因
20 mg/kg
40 mg/kg
80 mg/kg

图 10

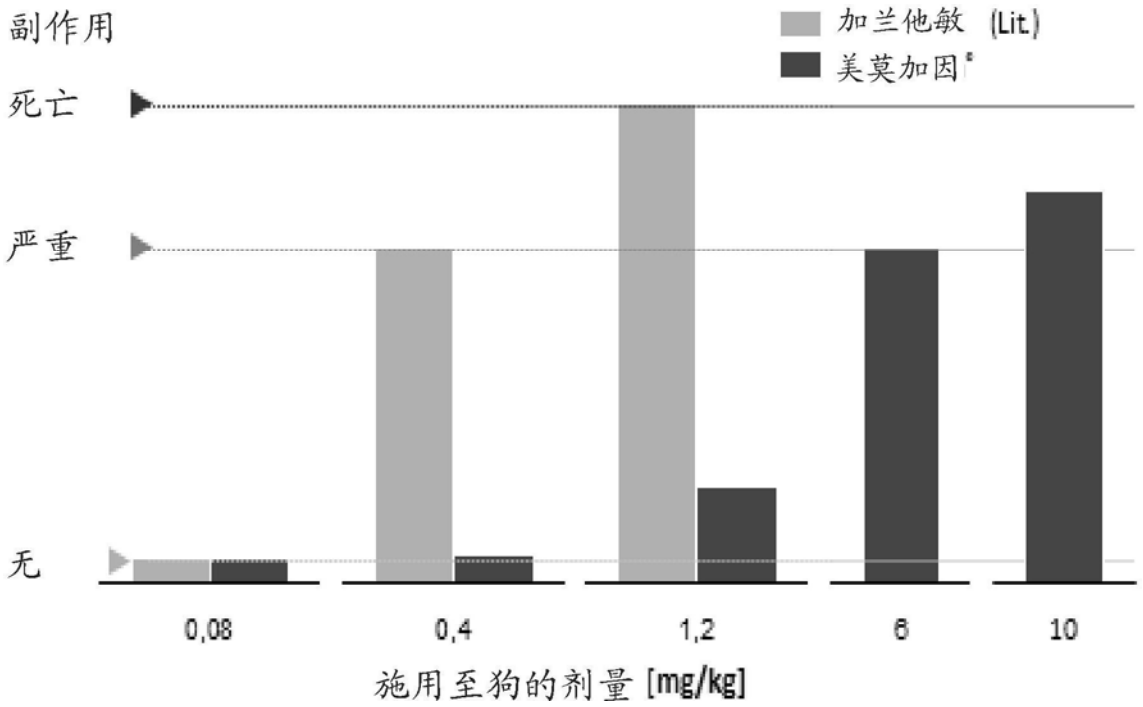

副作用
加兰他敏 (Lit.)
美莫加因
死亡
严重
无
0,08
0,4
1,2
6
10
施用至狗的剂量 [mg/kg]

图 11

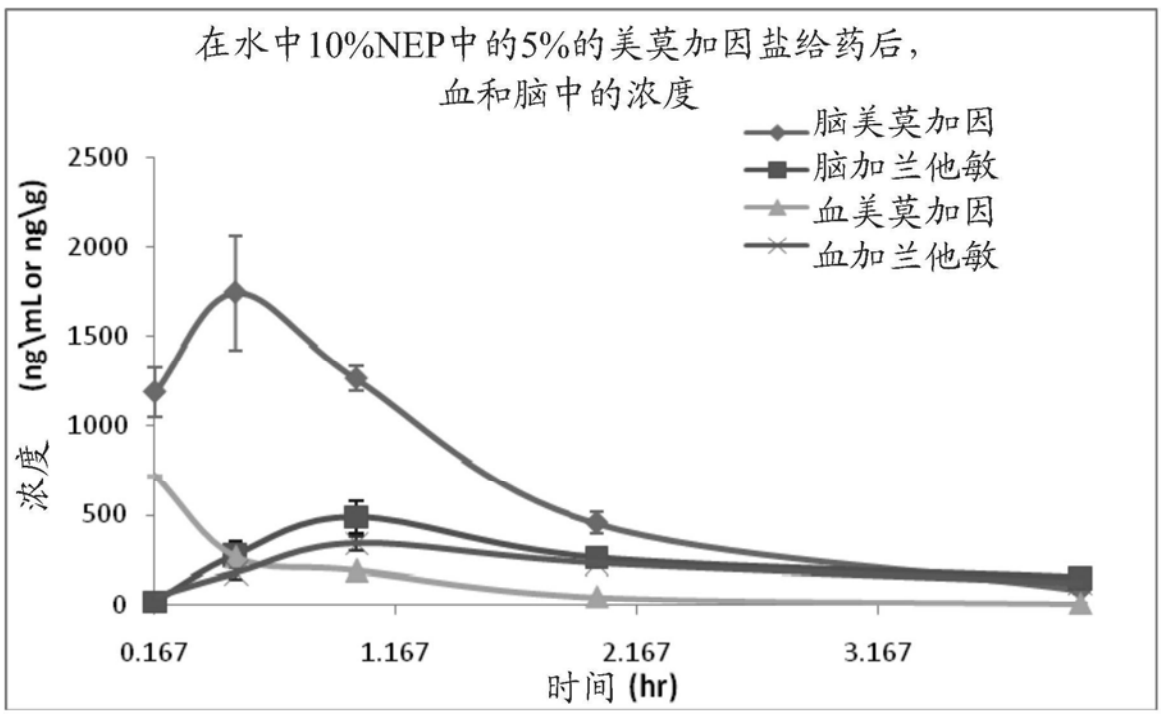

在水中10%NEP中的5%的美莫加因盐给药后，
血和脑中的浓度
脑美莫加因
脑加兰他敏
血美莫加因
血加兰他敏
浓度 (ng\mL or ng\g)
2500
2000
1500
1000
500
0
0.167
1.167
2.167
3.167
时间 (hr)

图 12

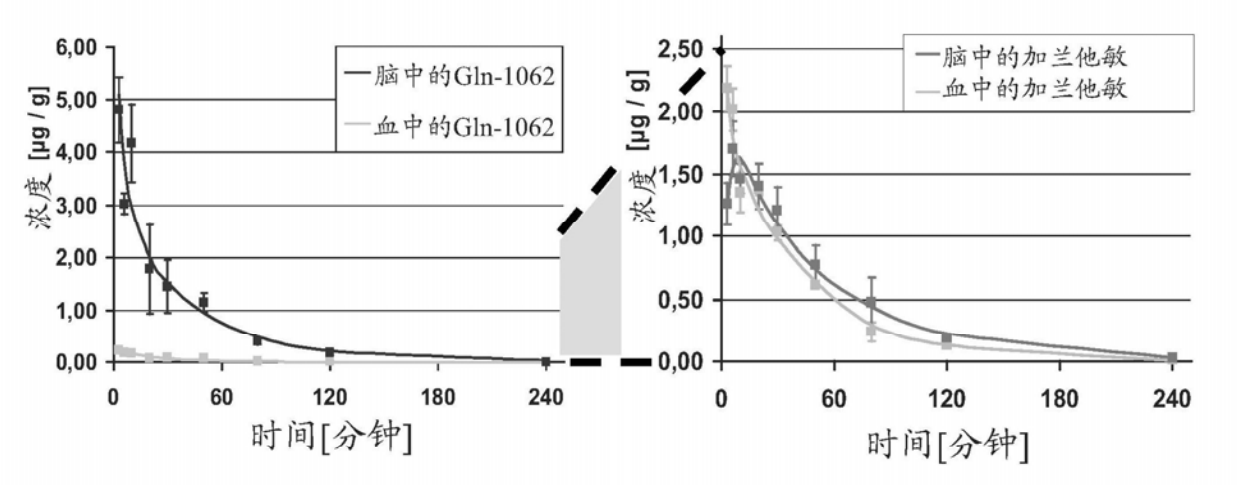

6,00
5,00
4,00
3,00
2,00
1,00
0,00
浓度 [µg / g]
脑中的Gln-1062
血中的Gln-1062
0
60
120
180
240
时间[分钟]
2,50
2,00
1,50
1,00
0,50
0,00
浓度 [µg / g]
脑中的加兰他敏
血中的加兰他敏
0
60
120
180
240
时间[分钟]

图 13

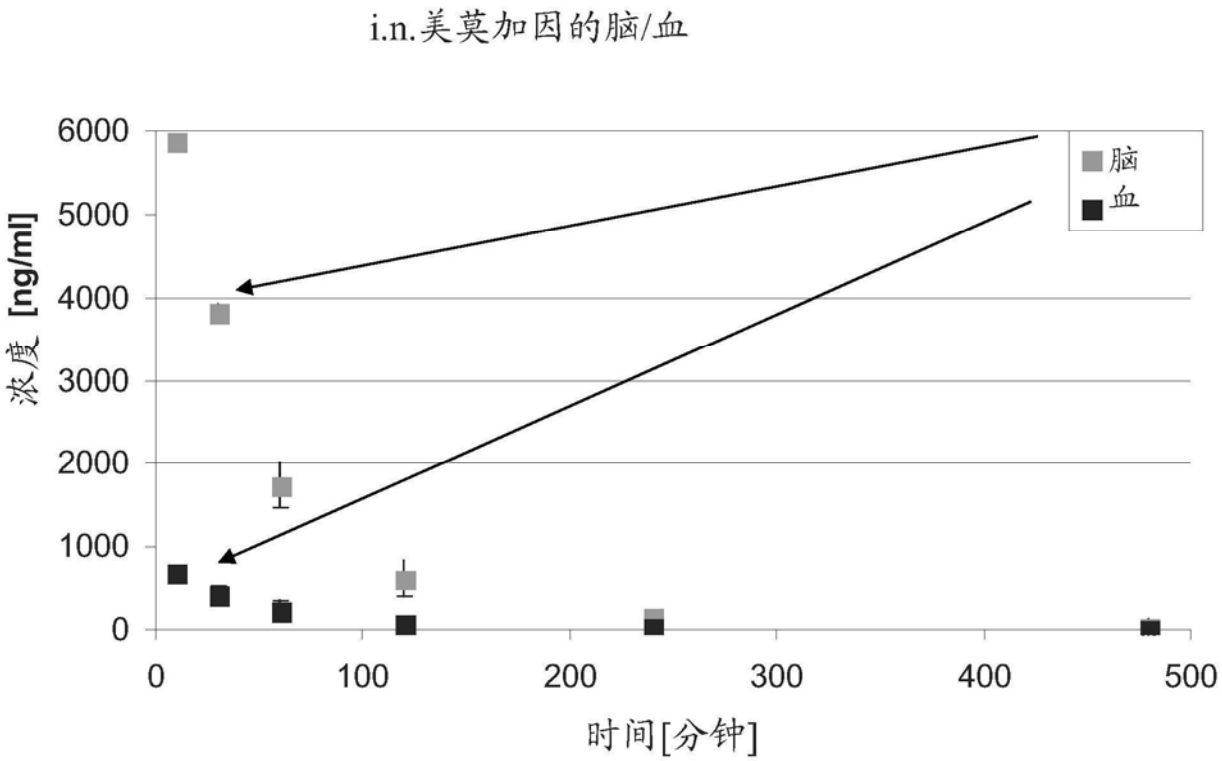

i.n.美莫加因的脑/血
6000
5000
4000
3000
2000
1000
0
浓度 [ng/ml]
脑
血
0
100
200
300
400
500
时间[分钟]

图 14

Abstract

The invention relates to selected administration routes for CNS (central nervous system) therapeutics and highly soluble salts, solutions, emulsions or powder formulations thereof, having optimal brain delivery due to the mode of administration and the chemical nature of the compounds of the invention.