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Datasheet for the decision of 10 May 2017

Case Number: T 0883/16 - 3.3.01

Application Number: 08735211.8

Publication Number: 2137192

IPC: C07D491/10, A61K31/4355, A61P25/00

Language of the proceedings: EN

Title of invention:
Derivatives of galantamine as pro-drugs for the treatment of human brain diseases

Patent Proprietor:
Neurodyn Life Sciences Inc.

Opponent:
Synaptech Inc.

Headword:
Galantamine pro-drug/Neurodyn

Relevant legal provisions:
EPC Art. 54, 56
RPBA Art. 13(1)

Keyword:
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 0883/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 10 May 2017

Appellant: (Opponent)	Synaptech Inc. 126 Via Palacio Palm Beach Gardens, FL 33418 (US)
Representative:	Richards, John Ladas & Parry LLP Temple Chambers 3-7 Temple Avenue London EC4Y 0DA (GB)
Respondent: (Patent Proprietor)	Neurodyn Life Sciences Inc. Suite 508 NRC-INH 550 University Ave., Charlottetown, P.E.I., C1A 4P3 (CA)
Representative:	Hertin und Partner Rechts- und Patentanwälte PartG mbB Kurfürstendamm 54/55 10707 Berlin (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 February 2016 rejecting the opposition filed against European patent No. 2137192 pursuant to Article 101(2) EPC.**

Composition of the Board:

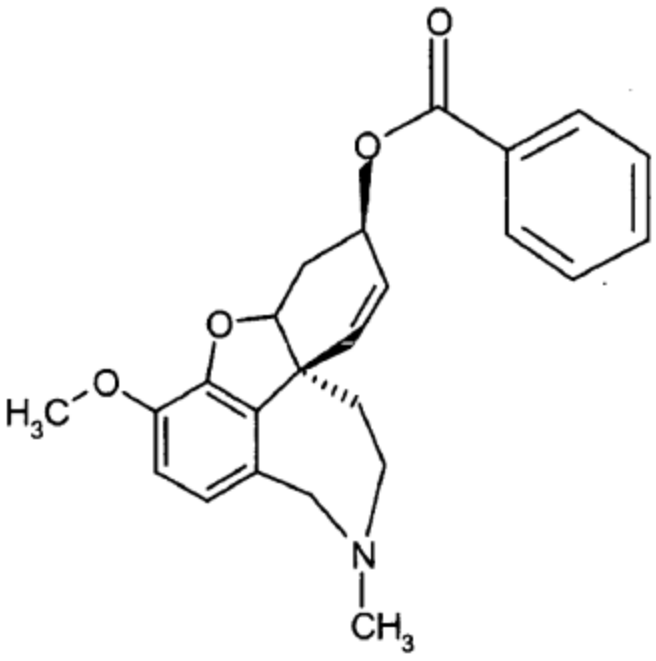
Chairman	A. Lindner
Members:	M. Pregetter
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 2 137 192 is based on European patent application No. 08735211.8, filed as an international application published as WO2009/127218.

II. The independent claims of the patent as granted read as follows:

"1. Galantamine pro-drug according to the following formula



[GLN 1062]

for use as a medicament in the treatment of a neurodegenerative or psychiatric or neurological disease associated with a cholinergic deficit, wherein the disease is selected from Alzheimer's and Parkinson's disease, other types of dementia, schizophrenia, epilepsy, oxygen and nutrient deficiencies in the brain after hypoxia, anoxia,

asphyxia, cardiac arrest, various types of poisoning, anesthesia, particularly neuroleptic anesthesia, autism, postoperative delirium and/or subsyndronal postoperative delirium, subsequences of the abuse of alcohol and drugs, addictive alcohol and nicotine craving, and subsequences of radiotherapy."

"2. Pharmaceutical composition comprising a galantamine pro-drug according to GLN 1062 for use as a medicament in the treatment of a neurodegenerative or psychiatric or neurological disease associated with a cholinergic deficit according to claim 1."

III. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(1) Han et al., Bioorganic & Medicinal Chemistry Letters, 1991, vol. 1, no. 11, page 579

(2) WO 00/30446

(3) EP 1 777 222

(4) Han et al., Eur J Med Chem, 1992, page 673

(7) Baakman et al., CHDR Pharmacokinetics, safety and pharmacodynamics of Memogain®, a new prodrug of galantamine, in healthy subjects

(12) Declaration of Professor Alfred Maelicke

(13) Hart et al., CHDR Safety, pharmacokinetics and pharmacodynamics of Memogain® in healthy male volunteers

(22) Brodaty et al., Dementia and Geriatric Cognitive Disorders, 2005, vol. 20, page 120

(23) Fonck et al., The Journal of Neuroscience, 2003, vol. 23, no. 7, page 2582

(24) Kewitz et al., Alzheimer Disease: Therapeutic Strategies, 1994, page 140

(25) Haroutunian et al., Life Sciences, 1985, vol. 37, page 945

(26) Aronson et al., Drugs Aging, 2009, vol. 26, no. 3, page 231

(29) Baakman et al., Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2016, page 1

(30) US2009253654

(31) Baakman supplementary material

(32) Abstract P4-265; published in Alzheimer's and Dementia, 2012, page S799

(33) WO2014/016430

(34) Leonard et al., International Journal of Pharmaceutics, 2007, vol. 335, 138-146

(35) Maelicke, J Mol Neuroscience, 2009

(36) Bickel et al., Neuropharmacology, 1991, vol. 30, page 447

(37) Wilcock et al., Int J Geriat Psychiatry, 1993, page 781

(38) Kewitz et al., Alzheimer Disease: Therapeutic Strategies, edited by E Giacobini and R Becker, 1994

(39) Wilcock et al., BMJ, 2000, vol. 321, page 1

(40) Raskind et al., Neurology, 2000, vol. 54, page 2261

(41) Wilkinson et al., Int J Geriat Psychiatry, 2001, vol. 16, page 852

IV. The present appeal lies from the decision of the opposition division to reject the opposition (Article 101(2) EPC).

The opposition division held that the patent as granted met the requirements of Article 83 EPC. Novelty of the claimed subject-matter was acknowledged, *inter alia,* in view of document (2). Concerning inventive step, document (3) was considered to represent the closest prior art. The technical problem was formulated in relation to the blood-brain barrier passing properties of Gln-1062. The brain-to-blood concentration ratio was discussed in relation to the data of the patent in suit and of various other documents. Inventive step was acknowledged.

V. The opponent (appellant) lodged an appeal against the decision of the opposition division and on the basis of filed evidence requested acceleration of the appeal proceedings. Lack of novelty and lack of inventive step (Article 100(a) and Articles 54 and 56 EPC,

respectively) were further pursued.

VI. The board decided to grant accelerated processing by giving the appeal priority. Oral proceedings were held before the board on 10 May 2017.

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant argued that documents (29) to (41) were filed merely to clarify some arguments and to provide a more detailed analysis of data that had already been under discussion.

With respect to novelty the appellant invoked document (2). Document (2) disclosed benzoyl esters of galantamine for the treatment of Alzheimer's disease. Starting from claim 8, selection from a single list - benzoyl being specifically mentioned in claim 8 - led to the subject-matter of claim 1 of the patent in suit.

The appellant considered compound 26 of document (3), which is galantamine nicotinate, to be extremely close to the subject-matter of claim 1 of the patent in suit. Any effects invoked were only shown for intranasal administration. Although the appellant did not dispute the blood-brain transfer of Gln-1062 and its inactivity, it questioned, with reference to example 15 of the patent in suit, whether a significant cleavage of Gln-1062 in the brain took place. Also, the results of the tests relating to the reduction of side-effects were at best mixed, see documents (7) and (29). In the absence of any evidence supporting an improvement, the skilled person would routinely test for further compounds and when doing so would substitute the nicotinate group by a benzoate group. The subject-

matter of the patent in suit was not inventive.

VIII. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Documents (29) to (41) should not be admitted into the proceedings. A party should present its case when filing the grounds of appeal. Documents (29) to (41) were filed only two months before the date of oral proceedings. They were filed in connection with a substantial change in the line of argument. Based on these documents the appellant cast doubt on the data disclosed in the patent in suit, for the first time ever. Their filing could therefore lead to a lengthy discussion of complex data. These documents should have been filed within the opposition period.

On the question of novelty the respondent referred to point 14.2 of the contested decision. In document (2) several selections were necessary in order to arrive at Gln-1062, the compound claimed in the patent in suit. In document (2), claim 8, the first selection required choosing the core structure from galantamine or lycoramine, followed by a second selection from an unlimited list also comprising some generic groups. Other passages in document (2) required many more selections, e.g. when looking at page 2 of the description, first paragraph after heading "Detailed Description of the Invention", sentence starting with "The most suitable compounds", or at page 5, first full paragraph. Furthermore, the respondent stressed that document (2) contained no enabling disclosure for benzoyl galantamine.

With respect to the issue of inventive step, the respondent started from document (3) as the closest prior art. It considered the difference to lie in the structure of the compound under consideration. While the patent in suit defined a galantamine derivative in the form of Gln-1062, which had a phenyl group attached via an ester group to galantamine (galantamine benzoate), document (3) disclosed, *inter alia*, a pyridine group attached via an ester group (galantamine nicotinate). Gln-1062 had many technical effects associated directly with its structure. Due to its structure it acted as a pro-drug, cf. example 14 and figure 1 of the patent in suit. Also, due to its structure the distribution of said compound led to an enrichment in the brain, as could be seen in the blood-to-brain ratio. The patent in suit, in figures 4a and 4b, clearly demonstrated that Gln-1062 was cleaved to galantamine. In figure 5, upon intraperitoneal administration, a very strong reduction of side-effects could be seen, when compared to galantamine. The high efficacy in the T-maze test could be judged on the basis of figure 6. The objective technical problem to be solved was thus to provide a galantamine pro-drug having low activity, good transport to the brain, cleavage in the brain, reduced side-effects and enhanced cognitive properties. There were no pointers in the prior art that would have led a skilled person towards Gln-1062 in expectation of these properties.

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed. Documents (22) to (26) and (29) to (41) filed by the

appellant should not be admitted into the proceedings.

X. At the oral proceedings the board indicated that it would take a decision on the admission of documents (22) to (26) if and when a party referred to such a document. No such reference was made. Moreover, the appellant confirmed, after discussion of inventive step starting from document (3), that there were no further arguments concerning inventive step which had to be considered by the board. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of documents into the appeal proceedings*

The board considers the filing of documents (29) to (41) by the appellant to be in direct reaction to the arguments provided by the respondent in its reply to the statement of grounds of appeal. These documents address in detail some of the points made by the respondent in its reply. Even though quite a number of documents had been filed, the board did not consider their admission unfair to the respondent as they were filed about two months before the oral proceedings. Consequently, these documents are admitted pursuant to Article 13(1) RPBA.

As to documents (22) to (26), no party had referred to them at the oral proceedings and the board did not consider them relevant in order to decide the present case. Hence, no decision as to their admission into the appeal proceedings was required.

3. *Novelty*

Claim 1 of the patent in suit is directed to a specific compound, Gln-1062, for use in certain therapeutic applications. Claim 2 relates to a composition comprising Gln-1062 for the same use.

Novelty has been contested in view of document (2), whose claim 8 has been invoked. Claim 8 of document (2) defines a composition comprising an acetylcholinesterase inhibitor selected from the group consisting of analogs of galantamine and lycoramine, wherein the hydroxy group of galantamine or lycoramine is replaced by a member of a list including specific and generic substituents. One of the substituents is the benzoyloxy group. Two selections are involved in order to arrive at Gln-1062. Galantamine has to be selected over lycoramine, followed by a second selection from the list of substituents. The board thus comes to the conclusion that Gln-1062 cannot be directly and unambiguously derived from the disclosure of claim 8 of document (2).

Further passages have been identified by the parties, page 2, passage starting with "The most suitable compounds", and page 5, first full paragraph. These two passages involve at least one further selection in addition to the selection of galantamine over lycoramine, namely the selection of the group of galantamine to be substituted and/or whether a further group is to be substituted as well.

Since the structure of Gln-1062 cannot be directly derived from the disclosure of document (2), it is not necessary to consider the issue of enablement.

The subject-matter of the claims of the patent in suit is novel (Articles 52(1) and 54 EPC).

4. Inventive step

4.1 The subject-matter of the contested patent relates to a specific galantamine derivative in the form of Gln-1062 for use as a medicament in the treatment of a neurodegenerative or psychiatric or neurological disease associated with a cholinergic deficit (paragraph [0001]). Gln-1062 is identified as a pro-drug which effectively passes the blood-brain barrier and thereafter is cleaved by endogenous enzymes. The relatively higher drug concentration in the brain will result in higher efficacy at a given dose and in fewer or less significant side-effects of treatment (paragraph [0013]).

4.2 In appeal proceedings both parties based their argumentation on document (3) as the closest prior art.

Document (3) relates to compounds that act as cholinesterase inhibitors and have an enhanced blood-brain barrier permeability. The compounds either interact as such with their target molecules or act as pro-drugs. The compounds are derived from galantamine, narwedine and lycoramine (paragraph [0001]). The compounds are defined by a Markush formula in claim 1, galantamine itself being disclaimed. The Markush formula of claim 1 allows for a great variety of substituents in various positions. Also, the central ring system is variable and can contain single and/or double bonds. In table 4 forty compounds that fall within said Markush formula and the claimed subject-matter are exemplified. The appellant has pointed to one of these compounds, compound 26. The compounds of

table 4 vary considerably, both in the central ring system and in the various substituents in different positions. Compound 26 differs from Gln-1062 in that the substituent at the hydroxy position of galantamine is a nicotinate and not a benzoate group. Compound 26 is listed in document (3) as having a calculated logP value of 2.62; logP values of the other compounds of table 4 have also been calculated. Apart from the calculated logP values, no data is contained in document 3. There is no information as to which compounds act as such and which compounds are considered to be pro-drugs (see paragraphs [0054] and [0062]).

Documents (1) and (2) are farther removed from the subject-matter of the contested patent. Document (1) speculates that no hydrolysis of its compounds takes place (page 579, last paragraph). Therefore a skilled person would not consider the compounds disclosed in document (1) for use as pro-drugs. Document (2) focuses on dosage formulations and does not mention a possible cleavage of its compounds (claim 1, summary of the invention).

Consequently, the board also considers document (3) to represent the closest prior art.

4.3 The difference between the subject-matter claimed in the contested patent and the closest prior art, document (3), lies in the structure of the compound claimed, i.e. Gln-1062.

4.4 Several effects have been associated with the structure of Gln-1062: pro-drug status, brain-to-blood concentration ratio, lower levels of side-effects and efficacy in treatment of brain diseases.

The respondent has formulated the technical problem as the provision of a galantamine pro-drug having low activity in its pro-drug state, good transport to the brain, cleavage in the brain, reduced side-effects and enhanced cognitive properties. The appellant seems to see the technical problem as the provision of an alternative galantamine derivative.

The effects invoked by the respondent are assessed in the following:

4.4.1 Transport to the brain, activity of Gln-1062

The appellant has acknowledged the good transport to the brain and the inactivity of Gln-1062 when measuring inhibition of brain cholinesterases. The board sees these effects confirmed by the data presented in table 1 and in example 14 in connection with figure 1 of the contested patent.

4.4.2 Cleavage of Gln-1062 to galantamine

Example 15 of the contested patent, which is set up to show the cleavage of Gln-1062 in the brain, contains no data. Example 17 and its results presented in figures 4a and 4b show that, after intravenous bolus injection of Gln-1062 in the tail vein of male SAM mice, almost immediately (first point of measurement 0.05 hours after injection) a high concentration of Gln-1062 can be observed in the brain, which decreases rapidly (figure 4a). With a certain delay, galantamine (resulting from cleavage of Gln-1062) can be detected in the brain as well. Reference is made to figure 5b of document (30), which has been acknowledged by both parties to be a better reproduction of figure 4b of the

contested patent than the one reproduced in the B1 publication of the contested patent. Example 17 provides no indication of where in the organism the cleavage takes place. It does however point to the conclusion that Gln-1062 is cleaved and that more galantamine, resulting from said cleavage, is found in the brain than in the blood.

4.4.3 Reduced side-effects

Example 18 of the contested patent relates to gastro-intestinal side-effects in ferrets. After intraperitoneal administration, administered galantamine leads to higher cumulative side-effects (81% behavioural index at 20 mg/kg) than Gln-1062 (34% behavioural index at 40 mg/kg and 62% at 80 mg/kg) (see figure 5). Thus the data as presented in the contested patent shows a reduction of side-effects.

The appellant has invoked post-published evidence to show that subsequent data throws doubt on this result. This later data is shown in documents (7), (13) and (29), which all relate to the same phase I clinical study. In the following the board will refer to document (29), which discloses in table 1 the data underlying the respective figures 1 of documents (7) and (13). Also, table 1 of document (29) has been partly reproduced in letters by both the proprietor, now respondent, and the appellant. The data of document (29) is derived from the treatment of healthy subjects, Gln-1062 being administered intranasally at doses of 5.5, 11, 22, 33 and 44 mg, galantamine being given orally at a dose of 16 mg (see abstract). A dose of 22 mg Gln-1062 provides the molar equivalent of active agent to a dose of 16 mg galantamine (see respondent's letter dated 26 April 2017, page 8). The overall

frequency of side-effects is reduced for a dose of 22 mg Gln-1062 compared to a dose of 16 mg galantamine. It is however questionable whether the data on which documents (7), (13) and (29) are based allows a difference to be established between the side-effects of Gln-1062 and of galantamine, since the mode of administration of the two compounds is different. Therefore, the post-published evidence cannot be taken into account.

4.4.4 Enhanced cognitive properties

The data concerning the cognitive properties is presented in the patent in suit, example 19, as performance recovery in a scopolamine-induced amnesia T-Maze test. After intraperitoneal administration of the drug, the mice having received Gln-1062 show a faster performance recovery compared to mice having received galantamine (example 19, figure 6). The appellant has questioned these results. According to the appellant, the same data points are depicted in various publications for experiments carried out under different conditions.

4.5 However, none of the tests of the patent in suit shows a comparison with compound 26. Consequently, no improvement over the closest prior art has been shown.

The technical problem can thus be seen as the provision of an alternative effective and safe drug for use in the treatment of certain diseases associated with a cholinergic deficit.

The board considers that the problem has been solved. By comparing Gln-1062 to galantamine, by providing evidence for the cleavage of Gln-1062 and by showing

that the administration of Gln-1062 leads to positive results in the T-Maze test, the respondent has shown that said diseases can be safely treated by administration of Gln-1062.

4.6 It remains to be established whether the solution to the problem, i.e. the use of Gln-1062, is obvious to the skilled person. Document (3) does not focus on any particular substitution, e.g. specific substituents at the hydroxy position of galantamine. Document (3) stresses the importance of the logP values of its compounds and mentions parameters such as total polar surface area, the existence of ionisable groups and the affinity of binding to biological membranes (see paragraphs [0004] and [0005]). Of these parameters detailed information linked to some chemical structures is provided only for the logP values. It can be seen from comparing the logP values of various compounds in table 4 that small variations in the central ring system, in the position of the substitution and/or in the substituents lead to relatively large changes in the calculated logP values. There is no teaching in document (3) that links certain structures (central ring system, various substituents and/or substitution site) to certain, advantageous, logP values. There is consequently no guidance in document (3) that would lead a skilled person, when starting from compound 26, to an alternative compound having a benzoate substituent, while expecting to have the same properties. Consequently, Gln-1062 is considered to represent a non-obvious alternative in view of document (3) on which the appellant's line of argument concerning a lack of inventive step was based.

The subject-matter of claims 1 and 2 involves an inventive step (Articles 52(1) and 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated