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Datasheet for the decision of 15 October 2020

Case Number: T 0373/18 - 3.3.01

Application Number: 10775209.9

Publication Number: 2434895

IPC: A61K31/495, A61K31/519

Language of the proceedings: EN

Title of invention:
ORGANIC COMPOUNDS

Applicant:
Intra-Cellular Therapies, Inc.

Headword:
Phosphordiesterase 1B inhibitors in the treatment of psychotic symptoms/INTRA-CELLULAR THERAPIES

Relevant legal provisions:
EPC Art. 54, 83
RPBA Art. 12(4)

Keyword:
Novelty - main request (no)
Sufficiency of disclosure for further medical use - auxiliary requests (no)
Main request A, first and second auxiliary request A - not admitted

Decisions cited:
T 0609/02, T 1067/08, T 0745/10, T 1025/10

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0373/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 15 October 2020

Appellant: (Applicant)	Intra-Cellular Therapies, Inc. 430 East 29th Street, Suite 900 New York, NY 10016 (US)
Representative:	Chapman, Paul Gilmour Marks & Clerk LLP 40 Torphichen Street Edinburgh EH3 8JB (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 29 August 2017 refusing European patent application No. 10775209.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	G. Seufert
	E. Mille

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division refusing the European patent application 10775209.9.

II. The current decision refers to the following documents:

P1 WO 2009/075784

IRS1 US 2003/0211040

D3 J. Horacek *et al.*, CNS Drugs, January 2006, vol. 20, no. 5, pages 389 to 409

D4 Lundbeck poster session: "429.2 / UU83 - The phosphodiesterase 1 inhibitor LU AF64386 increases cGMP and cAMP in the brain and exerts procognitive effects in the rat", Society of Neuroscience Meeting, 13 November 2017

D5 Lundbeck poster session: "344 – Discovery of the brain penetrant phosphodiesterase 1 (PDE1) inhibitor LU AF64386", 253rd American Chemical Society National Meeting, 4 April 2017

D6 D. C. Javitt, Am. J. Psychiatry, 1991, vol. 148, no. 10, pages 1301 to 1308, PubMed abstract PMID 1654756

D9 A. Mouri *et al.*, Neurochem. Int., 2007, vol. 51, no. 2-4, pages 173 to 184, PubMed abstract, PMID 17669558

D11 G. L. Synder, K. E. Vanover, Current Pharmaceutical Design, 2014, vol. 20, pages 5093 to 5103

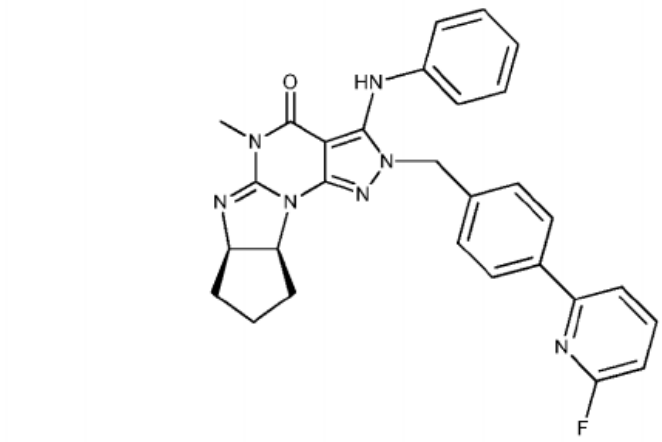
III. The decision under appeal was based on a set of claims according to a main request and sets of claims according to first to tenth auxiliary requests.

The examining division held that auxiliary requests 1, 6 and 9 contravened Article 123(2) EPC, that the priority was invalid for the claimed compound, and that the subject-matter of claims 1 to 3 and 5 to 7 of the main request and auxiliary requests 1, 5, 6, 8 and 9 lacked novelty over the disclosure of document P1. The subject-matter of claims 1 to 8 of all requests was regarded as insufficiently disclosed if a "negative expectation of success" (i.e. failure to treat the claimed disorders or symptoms of the claimed disorders) had to be assumed or obvious in view of document P1. The examining division observed that the application failed to provide for the claimed compound any evidence for PDE1 inhibition let alone for a therapeutic effect in the claimed disorders.

IV. With the statement of grounds of appeal, the appellant filed a new main request A and new first and second auxiliary requests A and resubmitted the main request and the third, fourth and seventh auxiliary requests on which the decision under appeal was based as the main request and the first to third auxiliary requests. It also filed documents D4 to D6.

Claim 1 of the main request reads as follows:

"*1. A PDE 1 inhibitor for use in a method of treatment for psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, or mania, wherein the PDE 1 inhibitor is:*



in free or salt form, including its enantiomers, diastereoisomers and racemates."

Claim 1 of the first auxiliary request differs from claim 1 of the main request in that the use in a method of treatment is for "*psychotic symptoms selected from hallucinations, paranoid or bizarre delusions and disorganized speech and thinking in schizophrenia, in schizoaffective disorder, in schizophreniform disorder, in delusional disorder, or in mania*".

Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request in that the features "*in psychosis*" and "*in psychotic disorder*" have been added to the disorders in which the psychotic symptoms are treated.

Claim 1 of the third auxiliary request differs from claim 1 of the second auxiliary request in that the feature "*in psychotic disorder*" has been deleted from the disorders in which the psychotic symptoms are treated.

Claim 1 of main request A reads as follows:

"*1. A PDE 1 inhibitor in free or salt form for use in a method of treatment of psychosis in schizophrenia, in*

schizoaffective disorder, in schizophreniform disorder, in psychotic disorder, in delusional disorder, in mania, or in bipolar disorder."

Claim 1 of the first auxiliary request A differs from claim 1 of main request A in that the use in a method of treatment is "*for psychotic symptoms selected from hallucinations, paranoid or bizarre delusions and disorganized speech and thinking in schizophrenia, in schizoaffective disorder, in schizophreniform disorder, in psychotic disorder, in delusional disorder, in mania, or in bipolar disorder*".

Claim 1 of the second auxiliary request A differs from claim 1 of main request A in that the use in a method of treatment is limited to "*psychosis, in schizophrenia*".

V. The board issued summons to oral proceedings. By communication dated 3 August 2020, the board informed the appellant that the oral proceedings scheduled for 15 October 2020 would take place by videoconference, to which the appellant had agreed.

VI. In a communication pursuant to Article 15(1) RPBA 2020, the board expressed its preliminary opinion on the issues of priority, novelty, sufficiency of disclosure and inventive step. As regards novelty of the subject-matter of claim 1 of the main request, the board indicated certain issues that required discussion and expressed the opinion that in addition to the objections raised in the decision under appeal, document P1 was novelty-destroying for this claim for the treatment of schizophrenia. It also indicated that the admission of main request A and first and second auxiliary requests A might be an issue for discussion.

The board also introduced several documents, including document D9, into the appeal proceedings.

VII. The arguments of the appellant, as far as they concern the decisive issues of this decision, can be summarised as follows:

- Admission of main request A, first auxiliary request A and second auxiliary request A

A divisional application had been filed. It would therefore be most expeditious if the board considered the newly filed requests. The subject-matter of claim 1 of the new requests had been searched completely. The therapeutic aspect had not changed, and the search had covered the area of claimed activity. This was apparent from the fact that document ISR1 had been found.

During the examination proceedings, the appellant had tried to come to an allowable set of claims. In view of the examining division's arguments in total, in particular as regards the priority issue, the filing of new main and auxiliary requests A was considered appropriate.

- Novelty

The subject-matter of claim 1 of the main request was novel over the disclosure of document P1. Depression and bipolar illness referred to in this document were different from psychotic disorder. As regards the board's preliminary opinion on novelty, the appellant had no further comments.

- Sufficiency of disclosure

The subject-matter of claim 1 of the first auxiliary request was sufficiently disclosed. The claimed compound could be manufactured and was suitable for the treatment of the claimed psychotic symptoms (see application paragraph [0003] bridging pages 3 and 4 of the application).

At the time the invention was made, the prevailing train of thought was that positive symptoms, such as hallucination, delusion or paranoia, were the result of over-expression of dopamine. The appellant also counted disorganised speech and thinking among the positive symptoms - a view not always shared in the prior art. Antipsychotics such as haloperidol primarily acted by suppressing dopamine signalling, even to the point of causing catalepsy and Parkinson's-like symptoms. This was the opposite effect to that discussed in paragraph [0002] on page 3 of the application, according to which many dopaminergic medications for Parkinson's disease, for example dopamine agonist or dopamine precursors, might cause hallucination. It was entirely contrary to the prevailing knowledge that the use of PDE1 inhibitors, which increased dopamine D1 signalling, would be effective in the treatment of positive symptoms.

The "negative expectation of success" referred to in the decision under appeal did nevertheless not apply to the application. Both the present application and P1 contained technical teaching about the relationship between PDE1 inhibition and potentiation of dopamine D1 agonism and similarly inhibition of dopamine D2 receptor signalling pathways (see paragraph [0005] on page 2 of the application and paragraph [0005] of P1). The application, however, contained additional technical teaching that was not found in P1, namely

that contrary to antipsychotics, which primarily had antagonistic activity at the dopamine D2 receptor, PDE1 inhibitors primarily acted to enhance signalling at the dopamine D1 receptor (see paragraph [0004] on page 4 of the application). In other words, PDE1 inhibitors agonised a different receptor to that which antipsychotic had been understood to antagonise. The application therefore presented a credible technical reason why the invoked negative expectation of success did not apply and why the claimed compound was suitable to treat the claimed psychotic symptoms.

Furthermore, documents D4 and D5 were submitted as evidence that the claimed compound was suitable for the treatment of the claimed psychotic symptoms. As described in D4, phencyclidine was administered to rats followed by the administration of the PDE1 inhibitor Lu AF64386, which attenuated the effects of phencyclidine. It was well known that phencyclidine induced psychosis that manifested in both positive and negative schizophrenic symptoms (see D6). The administration of phencyclidine to rats would therefore have evoked positive schizophrenic symptoms, and the tests carried out in D4 showed that a compound that like the claimed compound functioned as a PDE1 inhibitor had an attenuating effect. The tests in D4 may have been related to cognitive functions. However, the skilled person would have known that phencyclidine treated rats were a model for schizophrenia and would have placed the observed attenuation in a broader context, in particular as positive symptoms were otherwise difficult to observe.

Document D11 was further evidence that the claimed compound could be used to treat the claimed psychotic symptoms. This document taught (second paragraph of

page 5093) that there was now considerable evidence that glutamate neurotransmission, mediated through NMDA-type receptors, was deficient in schizophrenic patients and that hypoactivity in cortical dopamine and glutamate pathways was a key feature of the schizophrenic brain. The PDE1 inhibitor ITI-007, which increased NMDA receptor activity, was effective in preclinical studies for antipsychotic activity and would have been expected to contribute positively to the treatment of psychosis.

Furthermore, it was known in the art (see ISR1) that PDE1 inhibitor regulated a variety of signalling pathways. It was therefore not so clear cut that PDE1 inhibitors were unsuitable for the treatment of the claimed psychotic symptoms because they enhanced the dopamine D1 signalling pathway.

The same arguments applied to second and third auxiliary request.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 5 of main request A or, alternatively, claims 1 to 5 of first and second auxiliary requests A filed with the statements of grounds of appeal and, subsidiarily, on the basis of claims 1 to 8 of the main request as identified in the examining division's decision or, alternatively, claims 1 to 8 of the first to third auxiliary requests, corresponding respectively to the third, fourth and seventh auxiliary requests as identified in the examining division's decision.

IX. The oral proceedings took place by videoconference on 15 October 2020. At the end, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of main request A and first and second auxiliary requests A into the appeal proceedings

2.1 Pursuant to Article 12(4) RPBA 2007, applicable under the provision of Article 25(3) RBPA 2020, the board has the discretionary power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first-instance proceedings. This includes requests which were withdrawn or abandoned. When exercising its discretion, the board has to consider the specific circumstances of the case bearing in mind that the purpose of an appeal is to offer the losing party the possibility to challenge the decision of the examining division on its merits; not to conduct the case anew or provide the appellant with an opportunity to recast the claims as its sees fit. While new submissions are not precluded, their admission is restricted.

2.2 The board notes that claim 1 of main request A is similar to claim 1 of the main request and the first auxiliary request, on the basis of which the examination proceedings had started. In its first communication dated 3 April 2014, the examining division agreed with the lack of unity objection raised in the supplementary European search report and the European search opinion and informed the applicant that the examination could only cover the first invention. In response, the appellant replaced all previously filed requests with a revised set of claims restricted

to subject-matter according to the first invention, for which a search had been carried out. No arguments against the correctness of the examining division's objection of lack of unity were provided.

2.3 By filing main request A at the appeal stage, the appellant reverts to claims which are not restricted to the first invention and therefore contain unsearched subject-matter and which are similar to those it had deliberately chosen to replace. Admitting this request into the proceedings would compel the board to decide on subject-matter that had been present before the examining division but for which no reasoned decision had been given. This is not in line with the main purpose of the appeal proceedings, which is to review what has been decided; not to review what has not been decided (see T 1525/10, point 2.3 of the Reasons). In the board's judgement, the applicant cannot simply replace requests to avoid a negative decision by the examining division and then reinstate these or similar requests at the appeal stage to shift its case at liberty from the examining division to the board of appeal. According to the case law of the boards of appeal, this would jeopardise the proper distribution of functions between the departments of first instance and the boards of appeal (see T 1067/08, point 7.2 of the Reasons, T 745/10, point 3.5 of the Reasons).

Moreover, since a decision to grant a patent could not be made for claims containing unsearched subject-matter, admission of main request A would have compelled the board to remit the case to the examining division, which would clearly be contrary to procedural economy.

2.4 The board is also not convinced that the filing of main request A is a reaction to the examining division's reasoning in the decision under appeal, as argued by the appellant. All key issues of the decision, including the partial invalidity of the priority, had been communicated to the appellant before the oral proceedings took place, and a decision was taken by the examining division. No new issues were discussed in the decision under appeal.

2.5 For the reasons set out above, the board made use of its discretionary power pursuant to Article 12(4) RPBA 2007 and decided not to admit main request A into the appeal proceedings. For the same reasons, the first and second auxiliary requests A were not admitted.

Main request

3. Novelty

3.1 Claim 1 of the main request is a second medical use claim drafted in the form of a purpose-related compound claim pursuant to Article 54(5) EPC. It is directed to a specific PDE1 inhibitor for use in a method of treatment for psychosis, schizophrenia and other disorders (see point IV above).

In the board's view, the person skilled in the art would have understood the term "treatment of a disorder" as referring to the treatment or amelioration of anyone of the symptoms of a disorder in a patient. The same understanding is reflected in paragraph [0059] of the application.

3.2 In the communication sent pursuant to Article 15(1) RPBA 2020, the board was of the preliminary opinion

that the subject-matter of claim 1 is anticipated by the disclosure of document P1. The appellant did not respond in writing to the issues raised in the board's communication. Nor did it provide any comments regarding novelty of the subject-matter of claim 1 of the main request at the oral proceedings before the board. The board therefore has no reason to deviate from its preliminary opinion.

3.3 Document P1 discloses compounds, including the compound currently claimed (see claim 11, page 13, and example 14), and their use as PDE1 inhibitors in the treatment of, *inter alia*, cognitive impairment in schizophrenia (see paragraphs [0001] and [0019]). As claim 1 of the main request is not limited to the treatment of specific symptoms of the claimed disorders and encompasses the treatment of cognitive impairment in schizophrenia, the subject-matter of claim 1 of the main request lacks novelty over the disclosure of document P1, at least for the treatment of schizophrenia. For this reason alone, the board concludes that the main request is not allowable for non-compliance with Article 54 EPC.

First auxiliary request

4. Sufficiency of disclosure

4.1 Claim 1 of the first auxiliary request differs from claim 1 of the main request in that the medical use is for treating psychotic symptoms selected from hallucinations, paranoid or bizarre delusion and disorganised speech and thinking in schizophrenia and other disorders. Attaining the claimed therapeutic effect is a functional technical feature of a claim directed to a second medical use, regardless of whether

such a claim is drafted in Swiss-type form or as a purpose-limited compound claim pursuant to Article 54(5) EPC. As a consequence, under Article 83 EPC, unless this would have already been known to the person skilled in the art at the relevant date, the application must disclose the suitability of the compound to be used for the claimed therapeutic application (see T 609/02, point 9 of the Reasons).

4.2 It is common ground that the application does not contain any experimental evidence that shows that the compounds disclosed therein, let alone the specific compound currently claimed, are suitable for the treatment of any of the claimed psychotic symptoms. The "Examples" of the application simply describe an assay which can be used for measuring PDE1B inhibition.

4.3 Documents D4 and D5 on which the appellant relied in this context do not support the treatment of the claimed psychotic symptoms either. The board notes that both documents are post-published. This may raise the question of whether they can be considered for sufficiency of disclosure (see T 609/02, point 9 of the Reasons). However, since these documents do not support the treatment of any of the claimed symptoms, this question can be left undecided.

Document D4 discloses results of studies, which investigated the effect of the PDE1 inhibitor Lu AF64386 on cognitive functions in phencyclidine treated rats. A similar link between PDE1 inhibition and cognition is mentioned in D5.

The board does not dispute that phencyclidine induces a psychomimetic state that closely resembles schizophrenia-like psychosis. Phencyclidine causes

positive symptoms (e.g. hallucination or delusion), negative symptoms (e.g. deficits in social function) and cognitive dysfunction (see abstract D9), and phencyclidine treated rats can be used as a model to investigate the suitability of a compound in the treatment of those symptoms by carrying out appropriate tests. The tests carried out in D4 were designed to examine the effect of PDE1 inhibition on cognitive impairment, and the attenuation to which the appellant referred in its statement of grounds of appeal has been observed in tests for memory and cognition. D4 may be suitable evidence in support of the statement in paragraph [0002] on page 3 of the application suggesting that PDE1 inhibitors may help to improve cognitive impairment in schizophrenic patients. However, no conclusion as regards the treatment of positive symptoms, such as hallucination or delusion, can be drawn from either D4 or D5.

The appellant's argument that the attenuation observed in D4 in tests relating to memory and cognitive function could be extrapolated to positive or negative symptoms does not convince the board in the absence of any evidence supporting the appellant's assumption. It is also inconsistent with the assertion that it is surprising that PDE1 inhibitors, suitable for the treatment of cognitive dysfunction, are useful in the treatment of the claimed psychotic symptoms (see paragraph [0003] bridging pages 3 and 4 of the application).

4.4 At the oral proceedings before the board, the appellant also relied on post-published document D11 as further evidence that the claimed PDE1 inhibitor was suitable for the treatment of the claimed psychotic symptoms (see point VII above).

The board is not convinced. The compound to which the appellant referred in this context, i.e. ITI-007 (see D11, page 5093, second paragraph, penultimate sentence), is not a PDE1 inhibitor according to the invention. This was clarified at the oral proceedings before the board. Thus, it cannot be used as evidence that the claimed PDE1 inhibitor is suitable for the treatment of the claimed psychotic symptoms.

4.5 The board agrees with the appellant that experimental evidence is not always necessary to establish that a claimed therapeutic application or effect is attained. Common general knowledge or convincing technical reasons may also be relied on. However, contrary to the appellant's view, the board holds that in the case at hand the application does not provide convincing technical reasons on the basis of which the person skilled in the art would have concluded that the claimed PDE1 inhibitor would be suitable for the treatment of the claimed symptoms. The common general knowledge would not have been helpful either. The reasons for this are as follows.

4.5.1 The board accepts the appellant's argument that it was the prevailing train of thought at the relevant date of the application that positive symptoms of schizophrenia, such as hallucination and delusion, which may also occur in the other claimed disorders, are the result of dopamine over-expression. Antipsychotics which are known to ameliorate positive symptoms and are the mainstay of treatment of schizophrenic patients act to suppress dopamine signalling by blocking D2 receptors in the brain (see, for example, document D3, page 391, left-hand column, third line from the bottom, to right-hand column,

line 3, page 393, right-hand column, section 3.1.1; D11, page 5093, left-hand column, first paragraph). This is also acknowledged in paragraph [0002] on page 3 and paragraph [0004] on page 4 of the application.

4.5.2 In contrast, according to the application, the PDE1 inhibitors of the invention primarily act to enhance signalling at the dopamine D1 receptor (see paragraph [0004] on page 4), i.e. they act as dopamine D1 receptor agonist. This is an entirely different working principle compared to that on which the efficacy of antipsychotics is based. As also explained in the application, enhancing dopamine D1 signalling may exacerbate psychotic symptoms, similar to dopaminergic medications for Parkinson's disease, for example, dopamine agonists, which can cause hallucination (see paragraph [0004] on page 4).

4.5.3 In these circumstances, where the application goes against the prevailing technical knowledge and where the activity of the compounds in fact speaks against the treatment of positive symptoms, such as hallucination, it is of the utmost importance for sufficiency of disclosure that the application provides some kind of experimental evidence which shows that PDE1 inhibitors are suitable for the treatment of the claimed symptoms. A simple verbal statement (see paragraph [0003] bridging pages 3 and 4 of the application) that it has surprisingly been found that PDE1 inhibitors are useful for the treatment of conditions characterised by psychotic symptoms, such as hallucinations, paranoid or bizarre delusions or disorganised speech and thinking, is not enough. The board also notes that at the oral proceedings before the board, the appellant was unable to identify a single document on record which at the relevant date of

the application supported an established relationship between enhanced dopamine D1 signalling and the treatment of positive symptoms of schizophrenia. As already explained in point 4.5.2 above, the opposite was likely to occur, i.e. what the examining division called the "negative expectation of success".

4.6 The appellant further argued that the situation was not as simple as presented in the application and that according to prior art documents such as ISR1, PDE1 inhibitors were potential modulators of other receptors signalling pathways.

However, in these circumstances, it would have been even more important that the application provided more than a simple verbal statement as evidence that PDE1 inhibitors are in fact suitable for the treatment of positive symptoms. It is mere speculation whether or not the modulation of other receptor signalling pathways has any attenuating effect on the psychotic symptoms or counteracts the exacerbating effects the enhanced dopamine D1 signalling is believed to have on the claimed psychotic symptoms.

The application mentions in the background information that PDE1 inhibitor may not only potentiate the effect of a dopamine D1 agonist but also inhibit dopamine D2 receptor signalling pathways (see paragraph [0005] on page 2). However, this cannot detract from the fact that, according to the application, PDE1 inhibitors mainly act to enhance dopamine D1 receptor signalling, which is believed to exacerbate positive symptoms and cause hallucination.

4.7 For the aforementioned reasons, the board concludes that the subject-matter of the main request does not

comply with Article 83 EPC and is therefore not allowable.

Second to third auxiliary requests

5. Sufficiency of disclosure

The subject-matter of claim 1 of the second and third auxiliary request differs from claim 1 of the first auxiliary request in that the treatment of the same psychotic symptoms is extended to additional disorders (see point IV above). This does not change the board's reasoning as set out in point 4 above. Hence, the same observations and conclusion under Article 83 EPC apply *mutatis mutandis* to the subject-matter of claim 1 of the second and third auxiliary request. Therefore, these requests are not allowable either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated