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Datasheet for the decision of 16 November 2010

Case Number: T 1824/08 - 3.3.01

Application Number: 04758869.4

Publication Number: 1611119

IPC: C07D 311/22

Language of the proceedings: EN

Title of invention:
PI-3 kinase inhibitor prodrugs

Patentee:
Semafore Pharmaceuticals, Inc., et al

Opponent:
-

Headword:
Benzo(thio) pyran derivatives/SEMAFORE

Relevant legal provisions:
EPC Art. 111(1), 109(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Fresh case - incorrect compound claims before examining division replaced by product by process claims - Examining Division should have allowed interlocutory revision"

Decisions cited:
T 0139/87

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1824/08 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 16 November 2010

Appellant: Semafore Pharmaceuticals, Inc.
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Indianapolis, IN 46268 (US)

Representative: Greaves, Carol Pauline
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 18 January 2008 refusing European patent application No. 04758869.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: P. Ranguis
Members: G. Seufert
R. Menapace

Summary of Facts and Submissions

I. The Appellant lodged an appeal on 11 March 2008 against the decision of the Examining Division dated 18 January 2008 refusing European patent application No. 04758869.4 and filed a written statement on 22 May 2008 setting out the grounds of appeal.

II. The decision under appeal was based on the set of claims filed with letter of 11 September 2007 as the sole request. The Examining Division, relying *inter alia* on the documents

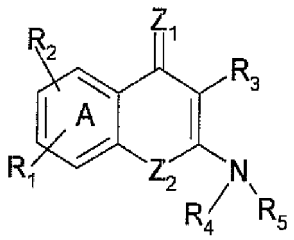
(1) WO 03/024949
(8) C. G. Wermuth et al., The Practice of Medicinal Chemistry 1996, Academic Press, London (GB),

held that the subject-matter of the claims was not inventive in view of document (1) in combination with the general knowledge of the person skilled in the art as reflected by document (8).

III. With the statement of grounds of appeal the Appellant provided an amended main request and an auxiliary request replacing the set of claims underlying the decision under appeal. With letter of 4 June 2008 a corrected page 1 was filed for both requests.

The main request consists of 28 claims, independent claim 1 reading as follows:

"1. A compound which is obtainable by a process comprising reacting Compound 2



Compound 2

wherein,

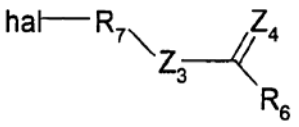
Z_1 and Z_2 are S or O;

R_1 and R_2 independently are H, optionally substituted aliphatic, optionally substituted aryl, hydroxyl, halogen, alkoxy, heterocycle, cyano, amino, or, are taken together to form an optionally substituted cycloaliphatic or optionally substituted aryl;

R_3 represents H, optionally substituted aliphatic or optionally substituted aryl;

R_4 and R_5 independently are H, optionally substituted aliphatic, optionally substituted aryl, heterocycle, aryloxy, carboxy, or, are taken together to form an optionally substituted heterocycle or optionally substituted heteroaryl;

with a halomethyl ester of formula



where hal is a halogen atom, R_7 is $-CH_2-$, $-CH(CH_3)$, $-CH(Ph)$, $C(CH_3)(COOH)$ or $CH(CH(CH_3)_2$, Z_3 and Z_4 are O and R_6 represents H, optionally substituted aliphatic, optionally substituted aryl, alkoxy, carboxy, amino heterocycle, aryloxy, any of which are optionally substituted with either a targeting agent to form a

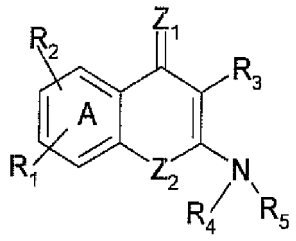
group R_6-T, or second functional group which can covalently bond to a targeting agent,

and thereafter if required, covalently linking any second functional groups present to a targeting group to form a group R_6-T."

Independent claims 18, 23 and 28 refer to the compound according to claim 1 for use as a medicament, the use of compound according to claim 1 for the manufacture of a medicament for treating certain diseases and a method of purifying a compound according to claim 1 comprising adding a composition comprising said compound to a solution, wherein said solution comprises at least 0.1% by (v/v) of an acid; adding the solution of (a) comprising said compound to a chromatography system optionally HPLC; and isolating said compound.

The auxiliary request consists of 27 claims, independent claim 1 reading as follows:

"1. A compound which is obtainable by a process comprising reacting Compound 2

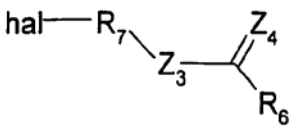


Compound 2

wherein,
Z_1 and Z_2 are S or O;

R_1 and R_2 independently are H; optionally substituted aliphatic wherein the aliphatic group is selected from C_{1-24} unbranched or branched saturated or unsaturated hydrocarbon or C_{3-12} non-aromatic cyclic hydrocarbon; optionally substituted aryl; hydroxyl; halogen; C_{1-24}alkoxy; benzyloxy, C_{3-12}heterocycle; cyano; amino; or, are taken together to form an optionally substituted C_{3-l2}cycloaliphatic or optionally substituted aryl;
R_3 represents H; optionally substituted aliphatic wherein the aliphatic group is selected from C_{1-24} unbranched or branched saturated or unsaturated hydrocarbon or C_{3-12} non-aromatic cyclic hydrocarbon; or optionally substituted aryl;
R_4 and R_5 independently are H, optionally substituted C_{1-12}aliphatic, optionally substituted aryl, C_{3-12}heterocycle, aryloxy, carboxy, or, are taken together to form an optionally substituted C_{3-12}heterocycle or optionally substituted heteroaryl;

with a halomethyl ester of formula



where hal is a halogen atom, R_7 is $-CH_2-$, $-CH(CH_3)$, $-CH(Ph)$, $-C(CH_3)(COOH)$ or $CH(CH(CH_3)_2$, Z_3 and Z_4 are O and
R_6 represents H, optionally substituted aliphatic wherein the aliphatic group is selected from C_{1-24} unbranched or branched saturated or unsaturated hydrocarbon or C_{3-12} non-aromatic cyclic hydrocarbon, optionally substituted aryl, alkoxy, carboxy, amino

C_{3-12}heterocycle, aryloxy, any of which are optionally substituted with either a targeting agent to form a group R_6-T, or second functional group which can covalently bond to a targeting agent,
wherein the targeting agent is selected from a carbohydrate, vitamin, peptide or peptidomimetic, protein, nucleoside, nucleotide, nucleic acid, liposome, lipid, bone-seeking agent, cartilage-seeking agent, diazepine, glucose, galactose, mannose or mannose-6-phosphate thereto;

and thereafter if required, covalently linking any second functional groups present to a targeting group to form a group R_6-T;

and wherein optional substitutents for any group R_1, R_2, R_3, R_4, R_5 and R_6 are one or more groups selected from aromatic groups, C_{1-24}alkyl, C_{2-24}alkenyl, C_{2-24}alkynyl, aryl, C_{1-24}alkoxy, halo, aryloxy, carbonyl, acryl, cyano, amino, nitro, phosphonic acids, phosphonic acids, phosphinic acids, phosphate esters, phosphinidenes, phosphinos, phosphinyls, phosphinylidenes, phosphos, phosphonos, phosphoranyls, phosphoranylidenes, phosphorosos, sulfhydryls, sulfenos, sulfinos, sulfinyl, sulfos, sulfonyl, thios, thioxos, hydroxyl, C_{l-24}alkylcarbonyloxy,arylcarbonyloxy, C_{l-24}alkoxycarbonyloxy,aryloxycarbonyloxy, C_{1-24}alkylcarbonyl,arylcarbonyl, C_{1-24}alkoxycarbonyl, aminocarbonyl, C_{1-24}alkylaminocarbonyl, di(C_{1-24})alkylaminocarbonyl, C_{1-24}alkylthiocarbonyl, acylamino, amidino, imino, C_{1-24}alkylthio, arylthio, thiocarboxylate, C_{1-24}alkylsulfinyl, trifluoromethyl, azido, C_{3-12}heterocyclyl, C_{1-14}alkylaryl, heteroaryl,

semicarbazido, thiosemicarbazido, maleimido, oximino, imidate, C_{3-12}cycloalkyl, C_{3-l2}cycloalkylcarbonyl, di(C_{1-24})alkylamino, arylC_{3-12}cycloalkyl, arylcarbonyl, arylC_{l-24}alkylcarbonyl, arylC_{3-12}cycloalkylcarbonyl, arylphosphinyl, arylC_{1-24}alkylphosphinyl, arylC_{3-12}cycloalkylphosphinyl, arylphosphonyl, arylC_{1-24}alkylphosphonyl, arylC_{3-12}-cycloalkylphosphonyl, arylsulfonyl, aryl(C_{1-24})alkylsulfonyl, arylC_{1-24}cycloalkylsulfonyl."

Independent claims 17, 22 and 27 refer to the compound according to claim 1 for use as a medicament, the use of compound according to claim 1 for the manufacture of a medicament for treating certain diseases and a method of purifying a compound according to claim 1 comprising adding a composition comprising said compound to a solution, wherein said solution comprises at least 0.1% by (v/v) of an acid; adding the solution of (a) comprising said compound to a chromatography system optionally HPLC; and isolating said compound.

IV. In a communication dated 15 February 2010 accompanying the summons to oral proceedings the Board expressed its preliminary opinion on the appeal. In particular, the Board pointed out that the transformation of the product claims into product by process claims appeared to raise an issue under Article 123(2) EPC. The Board furthermore indicated its intention to remit the case to the department of first instance, since the Appellant's recent realisation that the products obtained in the application were the O-alkylated instead of the N-alkylated products had created an entirely new situation to the extent that it was not

even apparent whether O-alkylated products formed part of the searched subject-matter.

V. In reply to the Board's communication the Appellant requested postponement of the oral proceedings, emphasising that it had only this single opportunity to address the new issue raised by the Board and that in order to address this issue fully it would have to "undertake detailed investigation, potentially involving further experimental work".

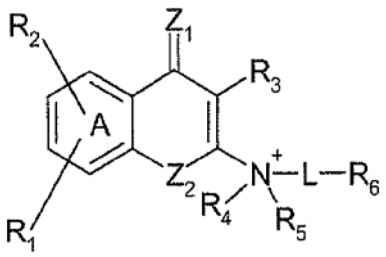
VI. The Board informed the Appellant that it was prepared to remit the case to the first instance in order to give the Appellant, if it so wished, a fair chance to defend its whole case before two instances. In response, in a letter dated 12 March 2010, the Appellant requested the remittal to the department of first instance for further prosecution on the basis of the main and auxiliary claim requests at present on file. Subject to the grant of the request for remittal it withdrew its request for oral proceedings.

VII. By communication dated 19 March 2010 the oral proceedings were cancelled.

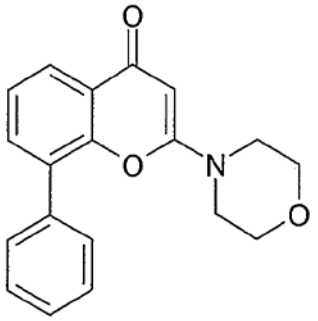
Reasons for the Decision

1. The appeal is admissible.

2. In the decision under appeal the sole ground for refusing the application was lack of inventive step of the claimed **N-alkylated** compounds of the following formula:



In particular, the Examining Division held that the N-alkylated benzo(thio)pyranones or benzo(thio)pyranthiones according to the formula of claim 1 were obvious in view of document (1), which disclosed a benzopyranone compound (**LY294002**) of the following formula



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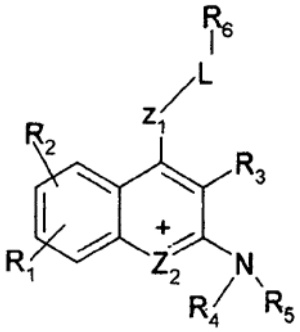
and document (8) which referred to the designing of prodrugs and bioprecursors. According to the Examining Division, document (8) gave a clear hint to the skilled person to use soft quaternary ammonium salts, i.e. N-alkylated compounds, which can be easily cleaved in the body, in order to solve the underlying technical problem of providing "pro-compounds" having improved pharmacokinetik and pharmacodynamic properties.

3. The amended main and auxiliary requests filed with the statement setting out the grounds of appeal are no longer directed to N-alkylated benzo(thio)pyranones or benzo(thio)pyranthiones. Claim 1 of both requests

refers instead to a compound obtainable by the reaction of a benzo(thio)pyranone or benzo(thio)pyranthione compound with a halomethylester. The reason for changing the form of the claims was the Appellant's recent finding that the compounds it had prepared using this method **starting from LY294002 or a LY294002 derivative** (emphasis added by the Board) corresponded in fact to "**O- or S-alkylated**" compounds illustrated by the following formula



and that N-alkylated compounds were not obtained.

4. The Appellant's realisation that an incorrect formula had been used to define the compounds it had prepared and its attempt to remedy this deficiency by characterising the obtained compounds by their process of production have altered the case in such a way that the reasons for the decision based on the obviousness of the **N-alkylated** compounds are no longer relevant. Compounds wherein the C=O or the C=S group of the benzo(thio)pyranone or benzo(thio)pyranthione had been alkylated were never considered by the Examining Division. It is not even apparent to the Board whether or not these compounds were properly covered by the search. One is therefore faced with a fresh case concerning subject-matter which was not considered before by the Examining Division and which may not have been properly searched. In these circumstances, the

Board judges it appropriate to exercise its power under Article 111(1) EPC and remit the case to the Examining Division for further prosecution.

5. In its preliminary opinion, the Board raised the question whether or not the product by process claims are, in the absence of any reaction conditions, in compliance with Article 123(2) EPC. This issue was never addressed by the Examining Division, which did not rectify its decision, although it could and, therefore, should have done so (T 139/87, O.J. EPO, 1990, 68). Furthermore, the Board appreciates that in order to address fully the question whether or not and in what form a product by process claim in the present case may be considered allowable, further investigations into the scientific literature and further experimental work by the Appellant appear to be necessary. Depending on these results, further substantive examination may be required, and this is normally the task of the Examining Division. The Board further notes that the outcome of a further search, which might turn out to be necessary, may well influence the answer to this question.

6. In these circumstances and in order to give the Appellant a fair chance to defend its whole case before two instances, the Board considers it appropriate to allow the Appellant's request for remittal of the case to the Examining Division without deciding on the issue of Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution.

The Registrar: The President:

M. Schalow P. Ranguis