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**Datasheet for the decision
of 31 May 2011**

Case Number: T 2038/07 - 3.3.01

Application Number: 03710903.0

Publication Number: 1472245

IPC: C07D 413/04

Language of the proceedings: EN

Title of invention:

Heteroaryl compounds useful as inhibitors of GSK-3

Applicant:

VERTEX PHARMACEUTICALS INCORPORATED

Opponent:

-

Headword:

GSK-3 Inhibitors/VERTEX

Relevant legal provisions:

EPC Art. 123(2), 82, 53(c)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Remittal of main request after amendment"

Decisions cited:

-

Catchword:

-



Case Number: T 2038/07 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 31 May 2011

Appellant:

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Representative:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 2 August 2007
refusing European patent application
No. 03710903.0 pursuant to Article 97(1) EPC
1973.

Composition of the Board:

Chairman: P. Ranguis
Members: L. Seymour
D. S. Rogers

Summary of Facts and Submissions

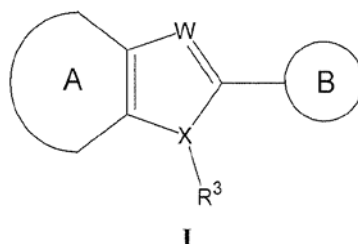
- I. This appeal lies from the decision of the examining division refusing the European patent application No. 03 710 903.0, based on international application WO 03/066629, under Article 97(1) EPC 1973.
- II. The following documents have been cited *inter alia* during the examination and appeal proceedings:
- (1) EP-A-0 406 734
 - (2) US-A-6 130 333
 - (15) WO 03/035065
- III. The decision under appeal was based on the main and sole request submitted to the examining division under cover of a letter dated 21 June 2007.
- The examining division considered that the subject-matter of this request did not comply with the requirements of Article 82 EPC since the structural element shared by the alternatives claimed was already known from documents (2) and (15), for compounds having the same pharmaceutical properties as those claimed.
- Moreover, the examining division considered that claim 10 embraced subject-matter falling within the exclusion under Article 52(4) EPC 1973, since the expression "biological sample" also covered animal and human bodies.
- IV. The appellant (applicant) lodged an appeal against this decision, and filed a new main request with the statement of grounds of appeal.

- V. In a communication by the board dated 24 September 2010, an additional objection of lack of unity based on document (1) was raised. In response, the appellant filed a main request to replace the claims on file.
- VI. In a communication sent as annex to the summons to oral proceedings, the board acknowledged that the reasons for refusal had been removed. However, the claims were found to suffer from several further formal deficiencies.
- VII. Oral proceedings took place on 31 May 2011.

During the oral proceedings, the appellant filed a main request to replace that previously on file.

Independent claim 1 of the main request reads as follows (emphasis added):

"1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein: Ring A is an optionally substituted 5-7 membered, partially unsaturated or fully unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ring A is optionally fused to an optionally substituted saturated, partially unsaturated or fully unsaturated 5-8 member ring having 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein said Ring A is optionally

substituted with halogen, $-\text{NO}_2$, $-\text{R}^\circ$, $-\text{OR}^\circ$, $\text{CO}_2\text{R}^\circ$, or $\text{N}(\text{R}^\circ)_2$, wherein each R° is independently selected from hydrogen and optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having 0-4 hetero atoms independently selected from nitrogen, oxygen or sulfur, phenyl (Ph), $-\text{O}(\text{Ph})$, or $-\text{CH}_2(\text{Ph})-\text{CH}_2(\text{Ph})$, and wherein each optional substituent on the aliphatic group of R° is independently selected from NH_2 , $\text{NH}(\text{C}_{1-4}$ aliphatic), $\text{N}(\text{C}_{1-4}$ aliphatic) $_2$, halogen, C_{1-4} aliphatic, OH, $\text{O}-(\text{C}_{1-4}$ aliphatic), NO_2 , CN, CO_2H , $\text{CO}_2(\text{C}_{1-4}$ aliphatic), $-\text{O}(\text{halo}-\text{C}_{1-4}$ aliphatic), or halo C_{1-4} aliphatic;

Ring B is an optionally substituted 5-6 membered ring selected from pyrazine, or furazanyl, wherein said ring has a first substituent, $-\text{N}(\text{R}^1)_2$, in the position adjacent to the point of attachment, and is optionally substituted by up to two additional substituents, and wherein the optional substituents of ring B are on the unsaturated carbon atom and are selected from halogen, $-\text{R}^\circ$, $-\text{OR}^\circ$, $-\text{SR}^\circ$, 1,2-methylene-dioxy, 1,2-ethylenedioxy, acyloxy, phenyl (Ph), Ph substituted with R° , $-\text{O}(\text{Ph})$ substituted with R° , $-\text{CH}_2(\text{Ph})$, $-\text{CH}_2(\text{Ph})$ substituted with R° , $-\text{CH}_2\text{CH}_2(\text{Ph})$, $-\text{CH}_2\text{CH}_2(\text{Ph})$ substituted with R° , $-\text{NO}_2$, $-\text{CN}$, $-\text{N}(\text{R}^\circ)_2$, $-\text{NR}^\circ\text{C}(\text{O})\text{R}^\circ$, $-\text{NR}^\circ\text{C}(\text{O})\text{N}(\text{R}^\circ)_2$, $-\text{NR}^\circ\text{CO}_2\text{R}^\circ$, $-\text{NR}^\circ\text{NR}^\circ\text{C}(\text{O})\text{R}^\circ$, $-\text{NR}^\circ\text{NR}^\circ\text{C}(\text{O})\text{N}(\text{R}^\circ)_2$, $-\text{NR}^\circ\text{NR}^\circ\text{CO}_2\text{R}^\circ$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\circ$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\circ$, $-\text{CO}_2\text{R}^\circ$, $-\text{C}(\text{O})\text{R}^\circ$, $-\text{C}(\text{O})\text{N}(\text{R}^\circ)_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^\circ)_2$, $-\text{S}(\text{O})_2\text{R}^\circ$, $-\text{SO}_2\text{N}(\text{R}^\circ)_2$, $-\text{S}(\text{O})\text{R}^\circ$, $-\text{NR}^\circ\text{SO}_2\text{N}(\text{R}^\circ)_2$, $-\text{NR}^\circ\text{SO}_2\text{R}^\circ$, $-\text{C}(=\text{S})\text{N}(\text{R}^\circ)_2$, $-\text{C}(=\text{NH})-\text{N}(\text{R}^\circ)_2$, or $-(\text{CH}_2)\text{NHC}(\text{O})\text{R}^\circ$,

wherein y is 0 to 4;

W is selected from nitrogen or CR^4 and X is selected from nitrogen or CH, wherein at least one of W and X is nitrogen;

R^1 is selected from R or R^2 ;

R² is selected from -SO₂R, -SO₂N(R)₂, -CN, -C(O)R, -CO₂R, or -CON(R)₂;

R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or: two R groups on the same nitrogen are taken together with the nitrogen bound thereto to form a 3-7 membered heterocyclic or heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein the optional substituents of R are on the unsaturated carbon atom of an aryl or heteroaryl group, or on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring and are selected from R^o, OR^o, and N(R^o)₂;

R³ is selected from T-CN or L-R;

T is a valence bond or a C₁₋₆ alkylidene chain;

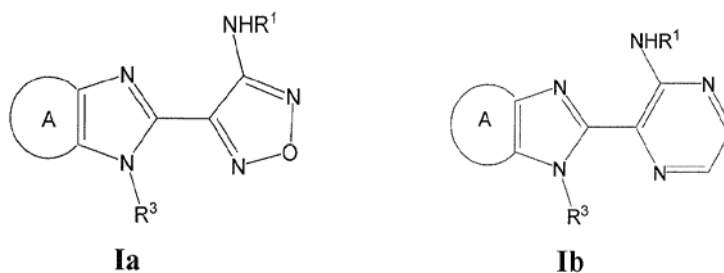
L is a valence bond or a C₁₋₄ alkylidene chain, wherein up to two methylene units of L are optionally, and independently, replaced by -O-, -S-, -NR-, -NRC(O)-, -NRC(O)NR-, -OC(O)NR-, -C(O)-, -CO₂-, -NRCO₂-, -C(O)NR-, -SO₂NR-, -NRSO₂-, or -NRSO₂NR-; and

R⁴ is selected from L-R, -halo, T-NO₂, T-CN

for use in treating or lessening the severity of a disease, disorder, or condition selected from allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, or baldness."

Independent claim 10 of the main request relates to "a method of inhibiting GSK-3 or Lck kinase in a biological sample selected from the group consisting of cell cultures or extracts thereof; biopsied material obtained from mammals or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof, which method comprises contacting said biological sample with, a compound of formula I ...".

Independent claim 11 of the main request relates to compounds of the following formulae Ia and Ib, wherein specific compounds have been disclaimed:



VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted in the following version:

Claims 1-21 of the main request filed during the oral proceedings before the board.

IX. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.
2. *Amendments (Article 123(2) EPC)*

The claims of the main request are based on the claims as originally filed, whereby claim 9 as originally filed has been deleted.

Claim 1 of the main request has been redrafted as a purpose-related product claim in accordance with Article 54(5) EPC 2000 (cf. Special edition No. 1 of OJ EPO 2007, 196-198: Article 1, No. 3). In addition, the meanings of ring B have been restricted based on paragraph [0035] of the application as originally filed. Moreover, the optional substituents at ring A have been defined in accordance with paragraph [0037] of the application as originally filed, in combination with the definitions of R^o given in paragraph [0026]. The definitions introduced for the optional substituents at ring B and substituent R are derived from paragraphs [0026] and [0027] of the application as originally filed. Analogous amendments have been introduced in claims 10 and 11 of the main request.

In claim 10 of the main request, the term "biological sample" has been defined according to paragraph [0074] of the application as originally filed.

In claim 11 of the main request, disclaimed compounds that do not fall within the scope of formulae Ia or Ib have been deleted, namely, compounds I-71, I-73, I-74 and I-75 (not furazan or pyrazine derivatives), and

compounds I-1, I-4, I-8, I-15, I-16, I-19, I-20, I-22, I-61, I-66, I-70 and I-72 (R° may not be halogen or -CN).

A number of the compounds listed in dependent claim 14 as originally filed have been deleted, including compound I-93, which is now separately claimed in dependent claim 6.

In view of the above, the board is satisfied that the subject-matter of the main request meets the requirements of Article 123(2) EPC.

3. *Unity (Article 82 EPC)*

Claim 1 of the main request refers to a compound of formula I for use in treating specific medical indications, which are associated with the inhibition of GSK-3 and Lck kinases (cf. e.g. application as originally filed, paragraphs [0014] and [0015]). Claim 10 relates to a method of inhibiting GSK-3 or Lck kinases in biological samples using a compound of formula I. In claim 11, compounds *per se* are claimed in the form of more restricted Markush formulae Ia and Ib.

Formulae I, Ia and Ib have the common structural feature that a fused nitrogen-containing ring is attached at position 2 to a heteroaromatic "ring B" having two nitrogen atoms (pyrazine or furazanyl); in addition, "ring B" bears an amino substituent at the position adjacent to the point of attachment to the fused ring ($-N(R^1)_2$ or $-NHR^1$).

None of the prior art documents within the meaning of Article 54(2) EPC cited in the International Search Report discloses said common structural element, together with the claimed therapeutic or pharmacological properties. This combination of features can therefore be considered as constituting a special technical feature in the sense of Rule 44(1) EPC (Rule 30(1) EPC 1973). The board notes in this context that an objection of lack of unity cannot be based on document (15), since this was published after the filing date of the present application (cf. point III above).

Consequently, the subject-matter of the present main request is considered to meet the requirement of unity of invention within the meaning of Article 82 EPC.

4. *Article 53(c) EPC 2000 (Article 52(4) EPC 1973)*

The present application is now to be considered under the provisions of Article 53(c) EPC 2000, rather than under Article 52(4) EPC 1973 (cf. Special edition No. 1 of OJ EPO 2007, 196-198: Article 1, No. 1).

In view of the fact that the term "biological sample" is now specifically defined in claim 10 so as not to include the human or animal body, the method claimed can no longer be said to embrace subject-matter excluded from patentability under Article 53(c) EPC 2000.

5. It follows from the considerations outlined above under points 3 and 4 that the main request overcomes the two grounds for refusal of the application (cf. point III above). However, examination has not yet been completed

as regards further requirements of the EPC, in particular those of novelty and inventive step. For this purpose, the case is remitted to the examining division for further prosecution (Article 111(1) EPC).

In its further prosecution of the application in suit, the examining division should not only take into consideration the numerous documents cited in the International Search Report, but also the additional documents cited in the European Search Report issued for application No. 10 180 554.7, which was filed on 28 September 2010 as a divisional application to the present application and published as EP-A-2 322 521.

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 Chairman:

T. Buschek

P. Ranguis