Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 14 November 2024

Case Number:	T 2035/22 - 3.3.02
Application Number:	16751821.6
Publication Number:	3259253
IPC:	C07D231/18, C07D307/64, C07D311/60, C07D407/12, C07D405/12, C07D403/12, C07D213/71, C07D217/22, C07D249/12, C07D271/12, C07D333/34, C07D277/36, C07D333/62, C07D249/04, C07D417/12, C07D307/82, C07C311/54, C07C311/56, C07D307/18, C07D309/08
Language of the proceedings:	EN

Title of invention:
SULFONYLUREAS AND RELATED COMPOUNDS AND USE OF SAME

Patent Proprietor:
The University of Queensland
The Provost, Fellows, Foundation Scholars, and the other members of Board, of the College of the Holy & Undiv. Trinity of Queen Elizabeth near Dublin

Opponent:
Strawman Limited

Relevant legal provisions:
EPC Art. 56, 83, 83, 123(2)
RPBA 2020 Art. 12(6)

Keyword:
Amendments
Sufficiency of disclosure
Inventive step
Late-filed facts

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 2035/22 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 14 November 2024

Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor 1)	The University of Queensland St Lucia, Queensland 4072 (AU)
Respondent: (Patent Proprietor 2)	The Provost, Fellows, Foundation Scholars, and the other members of Board, of the College of the Holy & Undiv. Trinity of Queen Elizabeth near Dublin College Green Dublin 2 (IE)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 June 2022 concerning maintenance of the European Patent No. 3259253 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter appellant) lies from the decision of the opposition division according to which European patent 3 259 253 in amended form met the requirements of the EPC.

II. The following documents *inter alia* were submitted by the parties in opposition proceedings:

D1 : "On Chemistry", M. Stocks *et al.*, 2007, 214-215
D2 : "Bioisosteres in Medicinical Chemistry", N Brown, 2013, 3-20 and 136-138
D3 : Dalvie *et al.*, Chem. Res. in Toxicol., 2002, Vol. 15, No. 3, 269-299
D4 : St. Jean *et al.*, J. Med. Chem. 2012, 55, 6002-6020
D6 : WO 98/32733 A1
D7 : WO 01/19390 A1
D9 : M Febbraio, Trends in Endocrinology and Metabolism, 2014, Vol. 25, No.6, 312-319
D10: R Coll *et al.*, Nature Medicine, 2015, Vol. 21, No. 3, 248-257
D13: R. Coll *et al.*, PLoS One, 2011, Vol. 6, Issue 12, 1-9
D20: "Technical annex" submitted by patent proprietor
D21: Table 2 of the patent with compound structures shown
D24: M Salla *et al.*, ACS Med. Chem. Lett. 2016, 7, 1034-1038

III. In a communication pursuant to Article 15(1) RPBA, the board provided the preliminary view that the subject-matter of the claims of the main request fulfilled the requirements of Article 123(2) EPC and that the

invention defined in the claims was sufficiently disclosed.

IV. Oral proceedings by videoconference took place as scheduled on 14 November 2024 in the presence of the respondent and in the absence of the appellant, as announced by letter dated 1 October 2024.

V. Requests relevant to the present decision

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

The respondent requested that the patent be maintained in amended form on the basis of the set of claims of the main request, which was identical to the set of claims filed with the reply to the statement of grounds as auxiliary request 17.

The respondent also requested that the argument that there was a Structure-Activity-Relationship (SAR) for NLRP3 inhibition at the filing date, based on the text in D9 concerning the identification of a "novel class of sulfonylurea-containing compounds", not be admitted into appeal proceedings pursuant to Articles 12(4) and (6) RPBA.

VI. For the text of claim 1 of the main request, reference is made to the reasons for the decision set out below.

VII. For the relevant party submissions, reference is made to the reasons for the decision set out below.

Reasons for the Decision

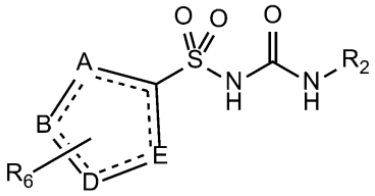
Main request

1. Article 123(2) EPC

1.1 Claim 1

Claim 1 of the main request reads as follows:

*"~~The compound of any one of the preceding claims wherein the compound is a~~ **A** compound of formula (II), or a pharmaceutically acceptable salt~~,~~ **or** solvate ~~or prodrug~~ thereof:*



Formula (II)

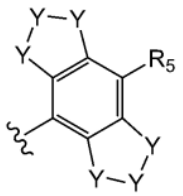
*wherein A, B, D and E are ~~independently~~ selected from **N and** C,~~ N, O, S and Se,~~ but at least one thereof is C **and at least one thereof is N;***
each dashed line may represent a bond;

~~R_2 is as defined in any one of the preceding claims or R_2 may be a fluorescent group;~~

each incidence of R_6 is independently selected from the group consisting of hydrogen, halide, cyano, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_6 cycloalkyl, alkylphenyl, phenyl, benzyl, C_1-C_6 ester, C_2-C_6 alkenyl, C_1-C_6 trifluoroalkyl and C_1-C_6 alkoxy, each of which may be optionally

substituted, as appropriate, ~~*or R_6 may be a fluorescent group*~~ ***wherein any optional substituent is independently selected from the group consisting of C1-10 alkyl; C3-6 cycloalkyl; hydroxyalkyl; C1-10alkoxy; C2- 10 alkenyl; C2-10 alkynyl; C6-C12 aryl; aryloxy; heteroaryl; heterocyclyl; halo; hydroxyl; halogenated alkyl; amino; alkylamino; arylamino; acyl; amido; CN; NO2; N_3; CH_2OH; $CONH_2$; $CONR_{24}R_{25}$; CO_2R_{24}; CH_2OR_{24}; $NHCOR_{24}$; $NHCO_2R_{24}$; C1-3 alkylthio; sulfate; sulfonic acid; sulfonate esters; phosphonic acid; phosphate; phosphonate; mono-, di-, or triphosphate esters; trityl; monomethoxytrityl; $R_{24}SO$; $R_{24}SO_2$; CF_3S; CF_3SO_2; and trialkylsilyl; wherein R_{24} and R_{25} are each independently selected from H or C1-10 alkyl;***

and R_2 is selected from a 2,6-dialkylphenyl, a 2,6-dialkyl-4-halophenyl, a 2,6-dicycloalkylphenyl, a 2,6-dicycloalkyl-4-halophenyl, and:



wherein each incidence of Y is C, which may be optionally substituted as appropriate, wherein any optional substituent is independently selected from the group consisting of C1-10 alkyl; C3-6 cycloalkyl; hydroxyalkyl; C1-10 alkoxy; C2-10 alkenyl; C2-10 alkynyl; C6- C12 aryl; aryloxy; heteroaryl; heterocyclyl; halo; hydroxyl; halogenated alkyl; amino; alkylamino; arylamino; acyl; amido; CN; NO_2; N_3; CH_2OH; $CONH_2$; $CONR_{24}R_{25}$; CO_2R_{24}; CH_2OR_{24}; $NHCOR_{24}$; $NHCO_2R_{24}$; C1-3 alkylthio; sulfate; sulfonic acid; sulfonate esters; phosphonic acid; phosphate; phosphonate; mono-, di-, or triphosphate esters; trityl; monomethoxytrityl; $R_{24}SO$; $R_{24}SO_2$; CF_3S; CF_3SO_2; and trialkylsilyl; wherein

R_{24} and R_{25} are each independently selected from H or C1-10 alkyl; and

R_5 is selected from the group consisting of hydrogen, halo, cyano, amide, sulphonamide, acyl, hydroxyl, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_5cycloalkyl and C_1-C_6 alkoxy, all of which groups may be optionally substituted, as appropriate, with halo, cyano or C_1-C_6 alkoxy" (strike through and bold text denoting deletion and addition respectively compared to claim 17 of the application as filed)

1.2 The appellant's objections in relation to Article 123(2) EPC, submitted with the statement of grounds of appeal, were directed solely to the set of claims found allowable by the opposition division according to the contested decision. These objections were addressed in the board's communication pursuant to Article 15(1) RPBA, and no reply thereto was received from the appellant.

1.3 No objections were submitted by the appellant in relation to the present main request, which is identical to auxiliary request 17 submitted with the reply to the grounds of appeal.

1.4 In the following therefore, the board deals with the appellant's arguments under Article 123(2) EPC insofar as they apply to the present main request by analogy.

1.5 The appellant submitted that the application as filed (PCT publication WO 2016/131098 A1) did not provide basis for claims 1, 14, 15, 17 and 18 of the (then) main request, which therefore contravened Article 123(2) EPC.

1.6 These claims correspond by analogy to claims 1, 12, 13, 15 and 16 of the present main request, respectively. The appellant's objections, insofar as applicable specifically to these claims are hence addressed in the following.

1.7 Claim 1

1.7.1 The appellant argued that compared to claim 17 of the application as filed, the definition of the structure of Formula (II) in claim 1 was *inter alia* amended by

(i) limitation of the scope of R_2 to selected parts of claims 8 and 10 of the application as filed, with deletion of "a fluorescent group",
(ii) limitation of the left-hand ring to an embodiment in which at least one of A, B, D and E is N (i.e. nitrogen),
(iii) deletion of "prodrug", and
(iv) deletion of "fluorescent group" from the definition of R_6.

1.7.2 According to the appellant, these amendments led to a "selective exclusion" of parts of the application as filed, as well as to a combination of features taken from multiple embodiments, those features not being disclosed in combination in the application as filed.

1.7.3 The board disagrees for the reasons provided by the respondent. Firstly, for R_2 (i.e. amendment (i), above), claim 8 of the application as filed defines two options in terms of generic structures, the first of which corresponds to the tricyclic indacene-type structure containing an R_5 group depicted for R_2 in present claim 1. The optional substituents attached to

variable Y, listed in claim 1, find basis in paragraph [0051] of the application as filed.

1.7.4 The definition provided in claim 1 for R_5 is identical to that provided in claim 8 of the application as filed, which therefore serves as basis.

1.7.5 Further options for R_2 according to claim 1 are a 2,6-dialkylphenyl, a 2,6-dialkyl-4-halophenyl, a 2,6-dicycloalkylphenyl and a 2,6-dicycloalkyl-4-halophenyl group. These specific groups find basis in claim 8 of the application as filed, which further defines R_2 as a substituted phenyl ring, and claim 10 dependent thereon, in which the phenyl moieties now specified in claim 1 are listed. These moieties are also disclosed as being preferred in paragraph [0077] of the application as filed.

1.7.6 Therefore, as stated by the respondent, the definition of R_2 has been limited to the structures of claim 8 of the application as filed. The second structure depicted in claim 1 has been limited to the most preferred options chosen from dependent claim 10. This represents a shrinking of the generic definition for R_2 to a group of moieties representing the most preferred moieties according to the application as filed and does not add subject-matter.

1.7.7 Secondly, in relation to the left hand ring in formula (II) of claim 1 (amendment (ii), above), compared to claim 17 of the application as filed, claim 1 of the main request was limited to specify that at least one of A, B, D and E is N. The respondent submitted paragraph [0086] of the application as filed as basis for the amendment. This paragraph reads as follows:

"*In one preferred embodiment of the compound of formula (II), at least one of A, B, D and E is N (i.e. nitrogen)*"

1.7.8 The appellant argued that this paragraph did not serve as appropriate basis because it related to a single embodiment amongst many other embodiments defining the left hand ring (paragraphs [0087] - [0092] of the application as filed). Consequently, a selection from a further list (i.e. in addition to a selection from the possibilities for R_2) was required to arrive at the subject-matter of claim 1.

1.7.9 The board disagrees. The embodiment in paragraph [0086] is stated as being preferred. This indication acts as a pointer towards this narrower definition for the left-hand ring.

1.7.10 In relation to the combination of the definition for R_2 and the left-hand ring of formula (II) in claim 1, as stated by the respondent, no specific definition for R_2 in combination with the definition of the left-hand ring in formula (II) has been singled out from the application as filed. Rather, a shrinking of a generic group of compounds defined by a Markush formula has taken place to focus on the preferred embodiments set out in the application as filed. This does not result in a singling out of any particular combination of meanings not disclosed in the application as filed, and hence, does not add subject-matter.

1.7.11 Finally, the board agrees with the respondent that the deletion of the terms deemed unclear in examination, namely "prodrug" and "fluorescent group" (amendments (iii) and (iv), above), merely involves a shrinking of the list of generically disclosed compounds in the

application as filed, and does not contravene Article 123(2) EPC.

1.8 Claim 12

1.8.1 The appellant argued that claim 12 of the main request contravened Article 123(2) EPC because it included a limited number of specific alternative structures for the left hand ring in formula (II) of claim 1 chosen from the structures depicted in claim 9 of the application as filed, in combination with a limited number of specific alternative structures for R_2 chosen from the structures also depicted in claim 9 of the application as filed.

1.8.2 The board disagrees. As stated by the respondent, the limitations in present claim 12 compared to claim 9 of the application as filed merely conform to the amendments made to claim 1 compared to claim 17 of the application as filed. Therefore, structures from claim 9 of the application as filed are included in present claim 12 of the main request only to the extent that they meet the limited definitions provided for R_2 and the left-hand ring of formula (II) of claim 1. Hence, claim 12 does not contravene Article 123(2) EPC.

1.9 Claim 13

1.9.1 The appellant argued that present claim 13 required a combination of the definition of R_2 from claim 11 of the application as filed with the choice of R_2 being the ring disclosed in paragraph [0079] of the application as filed. This combination was not disclosed in the application as filed.

1.9.2 The board disagrees. Present claim 13 recites the definitions of R_2 from claim 11 of the application as filed (which listed specific moieties falling under the scope of claim 10 as filed) and from paragraph [0079] of the application as filed in a single claim. This limitation represents a shrinking of a generic group of definitions for a single variable R_2 and for that reason does not contravene Article 123(2) EPC.

1.10 Claims 15 and 16

According to the appellant, claims 15 and 16 of the application as filed did not provide basis for claims 15 and 16 of the main request.

However, as noted by the respondent, in present claim 15, the variable R_1 (which corresponds to the left-hand ring of the formula (II) of claim 1 of the main request) was merely limited to the specific rings listed in claim 15 of the application as filed which meet the requirement in claim 1 that they comprise a least one N atom, e.g. by the deletion of "furan". Similarly, the structures depicted for R_1 in present claim 16 result from the deletion from claim 16 of the application as filed of structures no longer falling under the definition provided for formula (II) in claim of the main request. Hence, these amendments do not contravene Article 123(2) EPC.

1.11 Further amendments

1.11.1 As set out above, the foregoing objections addressed by the board concern the appellant's arguments under Article 123(2) EPC set out for a different request, namely the set of claims found allowable by the

opposition division, insofar as they apply to the present main request by analogy.

1.11.2 In relation to the additional amendments comprised within the claims of the present main request, basis in the application as filed was provided by the respondent with the reply to the statement of grounds of appeal by reference to (then) auxiliary request 2. (points 7.14 to 7.20, page 36-37). The (then) auxiliary request 2, is identical to the (then) seventeenth auxiliary request (i.e. the present main request), with the exception that in the latter, medical use claims 27 and 28 are deleted. Hence, the basis provided is relevant for the present main request.

1.11.3 Since no specific objections were submitted by the appellant against the present main request, and the board see no reasons not to accept the basis provided by the respondent with the reply to the grounds of appeal, the board concludes that said further amendments also comply with Article 123(2) EPC.

1.12 It follows that the subject-matter of the claims of the main request meets the requirements of Article 123(2) EPC.

2. Sufficiency of disclosure - Article 83 EPC

2.1 Similarly to that set out above in relation to Article 123(2) EPC, the appellant's objections in relation to sufficiency of disclosure, submitted with the statement of grounds of appeal, were directed solely to the set of claims found allowable by the opposition division according to the contested decision. No specific objections were submitted by the appellant in relation to the present main request.

2.2 In the following therefore, the board addresses the appellant's sufficiency of disclosure arguments insofar as they apply to the present main request by analogy. In this regard, the appellant submitted that the invention defined in claims 1, 11 to 13 and 25 to 28 of the set of claims found allowable by the opposition division was not sufficiently disclosed. Claims corresponding to claims 27 and 28 of this request have been deleted from the present main request. The analogous claims of the present main request are therefore claims 1, 9 to 11, 23 and 24.

2.2.1 In relation to claim 1 and claims 9 to 11 of the main request, it was submitted that the skilled chemist would be unable to synthesise many of the claimed compounds without undue burden. The only example provided by the appellant for claim 1 was for a hypothetical compound (in which all six variables Y were O) which no longer falls within the scope of present claim 1 by virtue of the limitation of variable Y to a carbon atom. For claims 9 to 11, the appellant referred for example to the option according to which "R_{16} and R_{17}, together with the atoms to which they are attached, form a cyclopentyl ring", and argued that there was no way that this could be achieved, since such fused five-membered rings would not be saturated (as required by the definition of "cycloalkyl"), due to the shared double bond of the fused phenyl ring. Consequently, the subject-matter of claims 1 and 9 to 11 was insufficiently disclosed.

2.2.2 The board agrees however with the respondent that it would be clear to the skilled person that a saturated cyclopentyl ring could not be formed including two carbon atoms of the fused phenyl ring. It would also be

immediately clear to the skilled person that what is intended in claims 9 to 11 is that R_{16} and R_{17} form a 5-membered ring with $-CH_2-$ groups. The scope of claims 9 to 11 is therefore to be understood in line with this technically reasonable interpretation.

2.2.3 Finally, as noted in the contested decision (point 14.2), the patent (pages 30-64; the same disclosure is found in the application as filed) discloses the synthesis of a large number of compounds falling with the scope of claim 1. No evidence has been provided that any chemically sensible compounds falling within the scope of claim 1 cannot be prepared following the guidance in the application as filed in combination with the common general knowledge of the skilled person. Hence, a lack of sufficient disclosure does not arise in this regard.

2.2.4 In relation to pharmaceutical composition claim 23, as stated by the respondent, there is no evidence that the preparation of the claimed composition would not be within the routine ability of the skilled person, especially in view of the guidance in the patent regarding possible pharmaceutically acceptable carriers (paragraphs [0114] to [0124]). Hence, a lack of sufficient disclosure does not arise in this regard.

2.2.5 Finally the appellant argued in relation to first medical use claim 24 that the application as filed did not sufficiently demonstrate that all claimed compounds would be suitable for a medical application. However, as stated by the respondent, the NLRP3 inhibition assay according to paragraphs [0377] - [0382] of the patent was used to provide IC_{50} values for seven compounds in paragraph [0390] and 32 further compounds were tested for inhibition of IL-1β release in table 2 of the

patent (page 68; these compounds are depicted structurally in D21). All of the compounds tested showed some level of biological activity in NLRP3 inhibition. The appellant did not provide any evidence to demonstrate that it is more likely than not that other compounds within the scope of the claims lack the effect in question, or at least to establish uncertainty regarding that effect. Hence, the appellant's arguments must fail.

2.3 Consequently, the invention defined in the claims of the main request meets the requirements of sufficient disclosure set out in Article 83 EPC.

3. Priority - Article 87 EPC

The validity of the claimed priority was contested before the opposition division (decision point 16). It was concluded that the outcome of the assessment of novelty and inventive step did not depend on the validity of the priority, with the consequence that it did not need to be assessed.

Since this was not challenged by the appellant in appeal proceedings, there is no need to address the validity of the priority in the present case.

4. Inventive step - Article 56 EPC

4.1 According to the patent, the invention relates to compounds and their use in treating diseases or conditions responsive to modulation or inhibition of the activation of the NLRP3 inflammasome (paragraph [0001]). The aberrant activation of the NLRP3 inflammasome is pathogenic in inherited disorders including multiple sclerosis and Alzheimer's disease

(paragraph [0003]). NLRP3 activation ultimately leads to the formation of the active forms of the inflammatory cytokines IL-1β and IL-18 (paragraph [0004]).

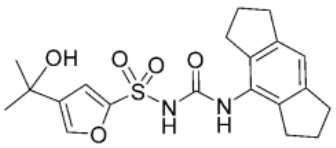
4.2 The appellant's arguments under inventive step were solely directed to the set of claims found allowable by the opposition division. These objections are addressed in the following by analogy to the extent that they still apply to the claims of the present main request.

4.3 Closest prior art

The appellant submitted that D9 represented the closest prior art. This choice was not disputed by the respondent.

Journal article D9 discloses a compound denoted "CRID3", which was was found to inhibit the NLRP3 inflammasome. CRID3 was not only highly specific for the NLRP3 inflammasome, but also extremely potent, with an IC_{50} of approximately 10 nM (D9, page 313, right hand column, second paragraph - page 314, end of bridging paragraph).

CRID3 has the following structure:



4.4 Distinguishing features

4.4.1 As stated by the appellant, the structure of claim 1 is distinguished from CRID3 in the left hand heterocycle,

which according to claim 1 of the main request is also a five-membered ring wherein, however, the ring atoms are selected from N and C, wherein at least one thereof is C and at least one thereof is N. Hence, rather than containing oxygen and carbon atoms as is the case in the five-membered ring of CRID3, the five-membered ring according to claim 1 of the main request contains nitrogen and carbon atoms.

5. Objective technical problem

5.1 According to the respondent, the technical effect of the distinguishing feature over CRID3 was that the claimed compounds are NLRP3 inhibitors having improved pharmacokinetic properties *in vivo*, including higher exposure, a longer half-life and lower clearance.

5.2 In the following, the board assesses whether the effect of NLRP3 inhibition can be acknowledged across the scope of the claim, and if so, whether the above-mentioned pharmacokinetic effects can also be acknowledged.

5.3 The effect of NLRP3 Inhibition

5.3.1 As set out by the respondent, the patent describes an NLRP3 inhibition assay (paragraphs [0377] - [0382]). As explained by the respondent, this assay is also described, for example, in D10 and D13 as being suitable for probing the effect of test compounds on the NLRP3 inflammasome (e.g. D10, page 249, paragraph bridging left and right hand columns; D10, page 256, "Inflammasome activation assays"; D13, page 2, "Results", first paragraph). The assay specifically involves stimulation of the NLRP3 inflammasome, rather than other inflammasomes involved in IL-1β and 1L-18

cytokine production. Hence, the inhibition of the release of these cytokines using the assay described in the patent is indirect evidence of NLRP3 inflammasome inhibition. A number of other inflammasomes besides NLRP3 can produce these cytokines, and anti-IL-1 biologics block the production of such cytokines derived from all sources. Specific inhibition of the NLRP3 inflammasome may therefore generate less generalised immunosuppression compared to anti-IL- biologics (paragraph [0029] of the patent).

5.3.2 The results of the NLRP3 assay in the patent are presented in terms of IC_{50} values for 7 compounds falling within the scope of claim 1 (patent, paragraph [0390]). IC_{50} data for the inhibition of IL-1β release for a further 32 compounds is also presented in table 2. These compounds are depicted structurally in D21.

5.3.3 As noted by the appellant, most of the tested compounds in the patent demonstrate lower NLRP3 inhibition in terms of IC_{50} than CRID3 (table 2, first entry). As stated by the respondent however, in terms of NLRP3 inhibition, the technical effect of NLRP3 inhibition formulated above does not require an improvement in NLRP3 inhibitory activity over that of CRID3, but simply that the claimed compounds are NLRP3 inhibitors. Furthermore, as stated by the respondent, the IC_{50} of a specific compound is not the only factor determining whether that compound makes a suitable drug candidate. Rather, other factors such as toxicity and pharmacokinetic considerations play a role. Therefore, even though the exemplified compounds may show a significantly lower IC_{50} than CRID3, they were still effective inhibitors thereof.

5.3.4 The appellant also argued that in view of the fact that many of the compounds in table 2 of the patent had much lower NLRP3 inhibitory activity compared to CRID3, it was not credible that NLRP3 inflammasome inhibition would be present for all compounds of claim 1. For example, compounds scoring "+" in table 2, having an IC_{50} between 10 and 50 µM, were up to 5,000-fold less active than CRID3. Therefore, in view of the small subset of exemplified compounds, the large structural variation in some of the substituents in claim 1, which allowed for many different possible combinations, was not justified. In the same context, the appellant argued that the 5-membered ring moiety included different regioisomers of the exemplified rings, as well as non-planar non-aromatic rings, while all of the exemplified compounds were aromatic. Hence, the examples could not justify the broad scope of claim 1.

5.3.5 The board disagrees. Claim 1 is limited in the 5-membered ring to those structures having at least one C and at least one N atom. The examples in the patent (paragraph [0390]) and table 2, the structures of which are depicted in D21), comprise both pyrazole and triazole rings in this position, i.e. 5-membered rings with carbon atoms and two or three nitrogen atoms, respectively. Furthermore, as argued by the respondent, the examples demonstrate that despite a large variety in the nature of the substituents on the 5-membered ring (R_6 in claim 1), including methyl, tertiary alkyl (isopropyl), cycloalkyl, fluoroalkyl, aminoalkyl, hydroxyalkyl and heterocycyl, all examples retain a meaningful level of NLRP3 inhibition. Therefore, the examples demonstrate that despite significant variant, NLRP3 inhibition is retained. Consequently, it is credible that NLRP3 inhibition will be retained across the scope of claim 1.

5.3.6 Additionally, the examples demonstrate that despite varying the rings, and in particular implementing a wide variety of substituents on the 5-membered ring, covering a wide range of spatial geometries (e.g. methyl versus cyclopropyl, benzyl, alkylpyrrolidine; see D21), NLRP3 inhibition is retained. Hence, as stated by the respondent, this variety, in the absence of any evidence to the contrary, also renders it credible that also non-aromatic 5-membered rings having a different spatial geometry to aromatic rings, as well as further variety in the substituents around the 5-membered ring will be tolerated, and yield compounds also displaying NLRP3 inhibition.

5.3.7 Similarly, the appellant referred to post-published journal article D24 to illustrate that the scope of claim 1 was not justified. Specifically, D24 demonstrated that metabolism of CRID3 led to hydroxylation of the indacenyl ring of CRID3 (i.e. addition of a single OH group), which had a large effect on NLRP3 inflammasome activity, reducing the IC_{50} from 7.5 nM for CRID3 to 1238 nM for the hydroxylated metabolite (D24, abstract). Since such a minor change in structure had such a large effect, it was not credible that the range of structures covered by the scope of claim 1 would all demonstrate NLRP3 inhibition.

5.3.8 The board again disagrees. As stated by the respondent, the compounds of D24 comprise a furan ring moiety and therefore do not fall under the scope of claim 1. Furthermore, even though the metabolite has a lower activity than CRID3, it still has NLRP3 inhibitory activity. The argument that other substituents than hydroxyl will on the contrary not demonstrate NLRP3

inhibition is merely speculation, not supported by any evidence. Hence, the appellant's argument fails.

5.3.9 In summary, as submitted by the respondent, there is no credible explanation, let alone substantiation, that the effect of NLRP3 inhibition would not be observed across the scope of claim 1. There is no reason to consider that the effect of NLRP3 inhibition is uncertain or unlikely to occur across the entire scope of claim 1. Consequently, the effect of NLRP3 inhibition can be acknowledged, and can be taken into account for formulating the objective technical problem underlying claim 1.

5.4 The effect of improved pharmacokinetic properties

5.4.1 The respondent argued that the examples in the patent and post-published evidence D20 demonstrate that, relative to CRID3, the claimed NLRP3 inhibitors have improved pharmacokinetic properties *in vivo*, including higher exposure, a longer half-life and lower clearance. These effects are referred to collectively as pharmacokinetic effects in the following.

5.4.2 The board agrees. Specifically, as stated by the respondent, table 3 of the patent describes a comparison of a claimed compound (middle structure, MCC7840, see paragraph [0390], first structure) with CRID3 (left hand structure, "MCC950") in terms of plasma concentrations at a 2 hour time point after oral gavage at 20mg/kg (table 3, title). The table demonstrates that MCC7840 according to claim 1 has an increased plasma concentration compared to CRID3 after 2 hours (28231 versus 17490 ng/mL). The data in tables 5 to 8 of the patent also compares the performance of the same compound MCC7890 with CRID3 when given

intravenously or orally to mice, and demonstrates that the claimed compound results in higher Area Under the Curve (AUC) values (indicating higher exposure), increased maximum plasma concentration (C_{max}), extended half life ($T_{1/2}$) and lower clearance (Cl) than CRID3.

5.4.3 The data in the patent is supplemented by that of post-experimental report D20, submitted by the respondent during opposition proceedings. As stated by the respondent, the report describes a comparison of the pharmacokinetic properties of 19 further compounds falling within the scope of claim 1 with those of CRID3 (MCC950, first compound of D20, table 1) and demonstrates that all compounds tested displayed improved pharmacokinetic properties in terms of higher AUC values, a longer half-life, and reduced clearance compared to CRID3 (D20, table 1).

5.4.4 In the same manner as for the effect of NLRP3 inhibition, the appellant argued that the effect of improved pharmacokinetic properties, even if accepted for the exemplified compounds of the patent and D20, could not be extrapolated across the scope of claim 1.

5.4.5 The board disagrees. There is sufficient variation across the examples in D20, in terms of the nature of the 5-membered ring and the substitution pattern, to at least render it credible that the same improvement would be observed across the scope of the claim. Indeed, the fact that improvement is shown despite the variation in the examples serves as an indication that the molecule can tolerate broad structural variation while yielding the same improvement.

5.4.6 The appellant furthermore argued that for a specific technical effect to be acknowledged, the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to originate in the distinguishing feature (heterocycle as claimed versus furan ring in CRID3). For example, the compound MCC7840 in table 3 of the patent differed from CRID3 not only in the conversion of a furan to a pyrazole ring, but also in the removal of a hydroxyl group from the ring side-chain. Hence, the effect demonstrated was not shown to originate in the distinguishing feature.

5.4.7 The board agrees with the appellant's arguments in relation to the specific compound compared with CRID3 in tables 3 and 5 to 8 of the patent, and indeed the data for this compound alone does not justify the acknowledgement of an improvement. However, D20 demonstrates that despite a variety of different substitution patterns on the 5-membered ring, an improvement in pharmacokinetic properties compared to CRID3 is consistently achieved for all compounds. Furthermore and independently, these compounds include a compound comprising a pyrazole ring and the same 5-membered ring substituent as CRID3, namely the final tabulated compound on page 4 of D20, thus representing a direct comparison with CRID3, the only difference being the nature of the 5-membered heterocycle. These results consequently render it credible that the effect of improved pharmacokinetic properties can be achieved across the scope of claim 1.

5.4.8 In a further argument intended to illustrate that the scope of claim 1 was not justified insofar as the effect of improved pharmacokinetic properties was concerned, the appellant noted that claim 1 extended to compounds in which R_6 can be a C_1-C_6 ester moiety,

which, according to the appellant would have poor metabolic stability. It was not credible that such compounds would have improved pharmacokinetic properties compared to CRID3.

5.4.9 The board disagrees for the reasons provided by the respondent. Specifically, there is no evidence that these compounds might be worse than CRID3 in terms of metabolic stability. In particular, the appellant's argument was based on the assumption that metabolism of the molecule would take place on the left hand side of the molecule, i.e. on the 5-membered ring. In contrast, D24 addressed above serves as evidence that CRID3 is metabolised on the indacenyl ring, i.e. on the right hand side of the molecule, and not on the 5-membered ring. Hence, there is no evidence that improved pharmacokinetic properties could not be achieved for compounds for which R_6 is an ester moiety, and the appellant's argument amounts to mere speculation.

5.4.10 In summary, the effects relied on by the respondent, namely that the claimed compounds are NLRP3 inhibitors having improved pharmacokinetic properties *in vivo*, including higher exposure, a longer half-life and lower clearance, are acknowledged across the scope of claim 1.

5.5 The objective technical problem underlying the subject-matter of claim 1 is therefore the provision of compounds that function as NLRP3 inhibitors and display improved pharmacokinetic properties in terms of higher exposure, a longer half-life and lower clearance.

6. Obviousness

6.1 The appellant argued that the claimed subject-matter lacked inventive step in view of D9 in combination with the common general knowledge regarding bioisosterism, known from D1 to D4 to be generally applicable.

6.2 The appellant argued that D1 and D2 disclosed that nitrogen-containing rings were isosteres of furan (point 7.4.1 of D1, table; D2, point 7.5). Furthermore, D3 and D4 taught that the furans were known to be metabolically unstable, and that 5-membered heteroaromatics containing a nitrogen lowered the energy levels, and thus increased the stability of the 5-membered rings. Pyrazole rings (comprised within most of the exemplified compounds of the patent and D20) were known to be particularly stable to metabolism (D3, page 281, right hand column, point 3, first paragraph bridging pages 281 and 282; D4, page 6009, right column, last two paragraph). Therefore, it was common general known that nitrogen-containing 5-membered rings, in particular pyrazoles, were preferred isosteres of furan, and led to increased metabolic stability of the heteroaromatic ring. Hence, the appellant argued, the solution to the above-mentioned problem provided in claim 1, namely the provision of compounds with a nitrogen-containing 5-membered ring, would have been obvious to the skilled person.

6.3 The board disagrees. As stated by the respondent, based on the evidence provided in post-published document D24, addressed above, in which metabolism occurs by hydroxylation on the indacenyl ring system, CRID3 is not metabolised at the furan ring, which is left unaffected. D24 concerns the identification of the metabolites of CRID3 (MCC950; see D3, title). Since it

is post-published, it also indicates that nothing was known about the metabolism of CRID3 before the filing date of the patent. Hence, the skilled person at the filing date of the patent, having no information about the mechanism of metabolism of CRID3, would have no reason to focus on replacement of the furan ring thereof when seeking to influence metabolic processing, and thereby influence the pharmacokinetic properties thereof.

6.4 For the sake of completeness, the board notes that the appellant also submitted an objection under inventive step starting from D9 in combination with D6 and/or D7 (grounds of appeal, point 6.4). These arguments however did not apply in the present situation, namely in the event that the objective technical problem were formulated to include the provision of improved pharmacokinetic properties, and the board notes that neither of D6 and D7 provide any indications in this regard. Hence, there is no need for the board to deal with this objection in the present context.

6.5 Additionally, during oral proceedings, the board granted the respondent's request not to admit the appellant's submission that there was a Structure-Activity-Relationship (SAR) for NLRP3 inhibition at the filing date based on D9. However, for the same reasons as provided for D6 and D7 above, whether D9 disclosed a SAR for NLRP3 inhibition is not relevant to the appellant's arguments in relation to the objective technical problem formulated above. Hence, even if the appellant's submission in this regard had been admitted into the appeal proceedings, it would not have been relevant to the board's conclusion under inventive step. Consequently, there is no need for the board to address the reasons for the non-admittance thereof.

6.6 Consequently, the subject-matter of claim 1 of the main request involves an inventive step. The same conclusion applies by analogy to dependent claims 2-22, claim 23 directed to a pharmaceutical composition comprising a compound of claims 1 to 22, and claim 24 directed to the compound of claims 1 to 22 for use in medicine.

7. The set of claims of the main request is consequently allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the claims according to the main request originally filed as auxiliary request 17 with the statement of grounds of appeal and a description and figures to be adapted thereto where applicable.

The Registrar: The Chairman:

U. Bultmann M. O. Müller

Decision electronically authenticated