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Datasheet for the decision of 22 April 2009

Case Number: W 0017/08 - 3.3.01

Application Number: PCT/GB 2007/050118

Publication Number: WO 2007/105015

IPC: C07J 63/00

Language of the proceedings: EN

Title of invention:
Derivatives of 18-β-Glycyrrhetinic acid

Applicant:
YORK PHARMA PLC

Opponent:
-

Headword:
Glycyrrhetinic acid/YORK

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13.2, 40.1, 40.2

Relevant legal provisions (EPC 1973):
EPC Art. 154(3)

Keyword:
"Lack of unity "a posteriori" (yes) - absence of a common technical feature distinguishing the claimed Markush groupings over the prior art"
"Refund of the protest fee (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0017/08 - 3.3.01

International Application No. PCT/GB 2007/050118

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 22 April 2009

Applicant:
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Decision under appeal:
Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 30 August 2007 .

Composition of the Board:

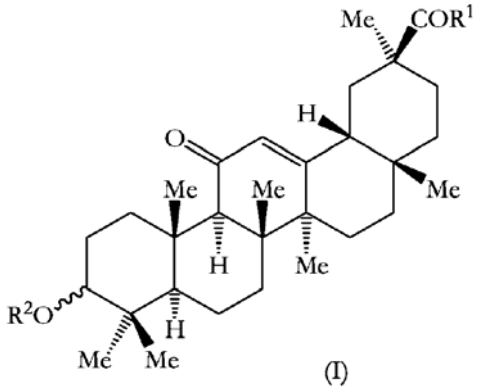
Chairman: P. Ranguis
Members: C. M. Radke
T. Bokor

Summary of Facts and Submissions

I. International patent application PCT/GB2007/050 118 was filed on 09 March 2007 with 102 claims.

Independent claim 1 reads as follows:

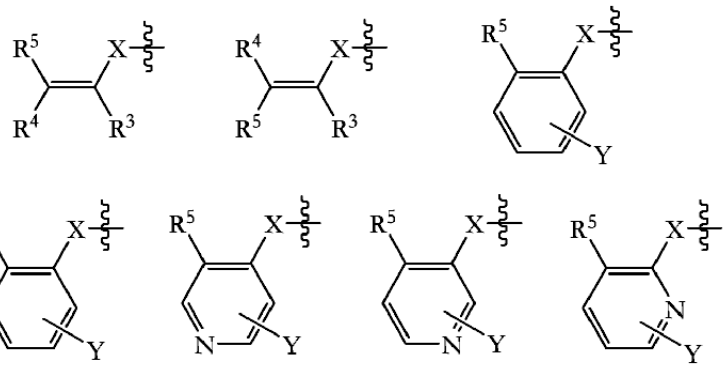
1. A compound having the formula I:

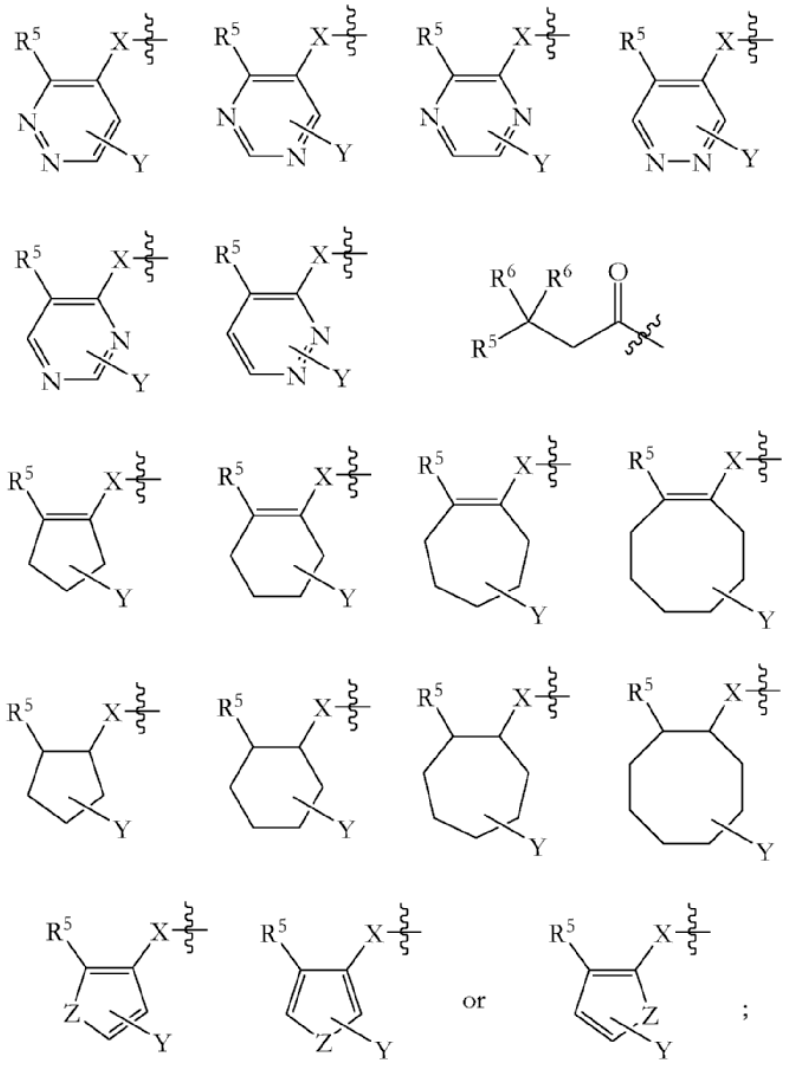


(I)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is $-OR^a$ or $-N(R^a)_2$;
R^a is hydrogen, or a substituted or unsubstituted, straight-chained or branched alkyl, alkenyl or alkynyl group which contains 1, 2, 3, 4, 5 or 6 carbon atoms and optionally includes 1, 2 or 3 heteroatoms N, O or S in its carbon skeleton;

R^2 is





R^3 and R^4 are independently hydrogen, or an unsubstituted, straight-chained or branched alkyl group which contains 1, 2, 3 or 4 carbon atoms;

R^5 is -OH, $-CO_2H$, $-CO_2R^6$, $-SO_3H$, or $-PO_3H_2$;

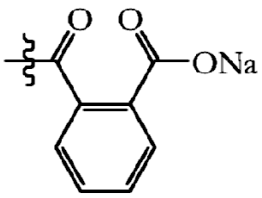
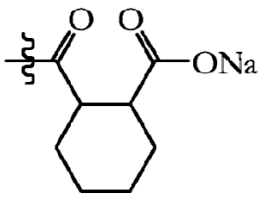
R^6 is an unsubstituted, straight-chained or branched alkyl group which contains 1, 2, 3 or 4 carbon atoms;

X is -CO- or $-CH_2-$;

Y is -H, -F, -Cl, -Br, -I, -Me, or -OMe; and

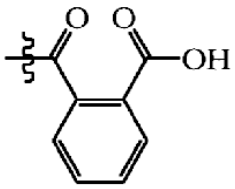
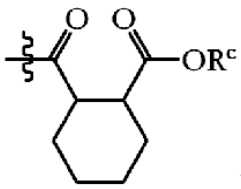
Z is -NH-, -O-, or -S-;

provided that: when R^1 is -ONa, R^2 is not

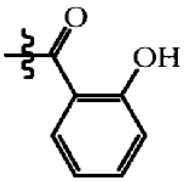
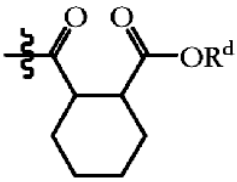
; and

when R^1 is -OMe, R^2 is not

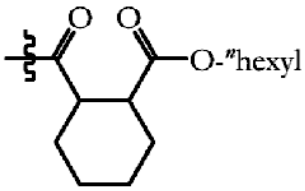
where R^c is H or Me; and

when R^1 is -OH, R^2 is not

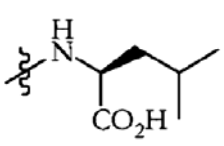
where R^d is H or "hexyl; and

when R^1 is -O-"hexyl, R^2 is not

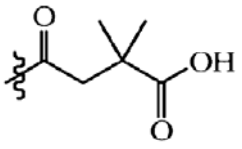


; and

when R^1 is -OH or



, R^2 is not



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II. On 30 August 2007 the European Patent Office (EPO), acting as the International Searching Authority (ISA) invited the Applicant pursuant to Article 17(3)(a) PCT and Rule 40.1 PCT to pay nine additional search fees.

III. In this invitation to pay the additional fees, the ISA considered that the application in suit comprised ten different inventions, namely the

Invention 1 (Claims 1-11, 17, 18, 22-102 (in part), and claims 12 and 16 (in full)):
Compounds of formula (I) where R^2 is selected from groups of the formulae $(R^4)(R^5)C=C(R^3)-C(O)-$ and $(R^4)(R^5)C=C(R^3)-CH_2-$, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 2 (Claims 1-11, 17-102 (in part), and claim 13 (in full)):
Compounds of formula (I) where R^2 is selected from groups of the formulae $[o-(R^5),(Y)-Ph]-C(O)-$ and $[o-(R^5),(Y)-Ph]-CH_2-$, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 3 (Claims 1-11, 17-21, 23-51, 53, 54, 56-59, 61, 63-73, 75, 76, 78-81, 83, 85-102 (in part)):
Compounds of formula (I) where R^2 is selected from groups of the formulae $[o-(R^5),(Y)-pyridyl]-C(O)-$ and $[o-(R^5),(Y)-pyridyl]-CH_2-$, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 4 (Claims 1-10, 17-102 (in part)):
Compounds of formula (I) where R^2 is selected from groups of the formulae $[o-(R^5),(Y)-heterocyclyl]-C(O)-$ and $[o-(R^5),(Y)-heterocyclyl]-CH_2-$, wherein the heterocyclyl group is a six membered aromatic ring with two nitrogen atoms as heteroatoms therein,

pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 5 (Claims 1-10, 17, 19-21, 23-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formula $(R^5)(R^6)_2C-CH_2-C(O)-$, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 6 (Claims 1-11, 17-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formulae $(R^5)(Y)$-cycloalkenyl-C(O)- and $(R^5)(Y)$-cycloalkenyl-CH_2-, wherein the cycloalkenyl group has 5 to 8 carbon atoms in the ring, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 7 (Claims 1-10, 14, 15, 17-21, 23-51, 53, 54, 56-59, 61, 63-73, 75, 76, 78-81, 83, 85-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formulae $(R^5)(Y)$-cyclopentyl-C(O)- and $(R^5)(Y)$-cyclopentyl-CH_2-, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 8 (Claims 1-10, 14, 15, 17-21, 23-59, 61-81, 84-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formulae $(R^5)(Y)$-cyclohexyl-C(O)- and $(R^5)(Y)$-cyclohexyl-CH_2-, pharmaceutical compositions

containing the same, medical uses thereof and processes for preparing the same.

Invention 9 (Claims 1-10, 14, 15, 17-21, 23-51, 53, 54, 56-59, 61, 63-73, 75, 76, 78-81, 83, 85-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formulae $(R^5)(Y)$-cycloalkyl-C(O)- and $(R^5)(Y)$-cycloalkyl-CH_2-, wherein the cycloalkyl group is either a cycloheptyl or a cyclooctyl group, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

Invention 10 (Claims 1-11, 17-21, 23-51, 53, 54, 56-59, 61, 63-73, 75, 76, 78-81, 83, 85-102 (in part)): Compounds of formula (I) where R^2 is selected from groups of the formulae [o-(R^5),(Y)-heterocyclyl]-C(O)- and [o-(R^5),(Y)-heterocyclyl]-CH_2-, wherein the heterocyclyl group is a five membered ring with two double bonds and one heteroatom Z (N, O or S) in the ring, pharmaceutical compositions containing the same, medical uses thereof and processes for preparing the same.

IV. In this context, the ISA considered the following document to be most relevant when assessing unity of invention:

(D8) D. J. Dargan and J. H. Subak-Sharpe, Journal of General Virology, vol. 66, no. 8 (1985), 1771-1784.

This document disclosed the cicloxolone sodium (CCX), namely the compound of formula (I) according to present claim 1, wherein R^1 means -ONa and R^2 is a 2-

sodiumcarboxy-cyclohexylcarbonyl-group (see figure 1 on page 1772). CCX is specifically excluded from the scope of the claims by the first disclaimer in claim 1.

Thus the common chemical structure of the compounds claimed in present claim 1, namely the olean-12-ene-30-oic acid, 11-one structure with a substituent of the formula $-O-R^2$ in position 3, cannot be seen as a common or corresponding technical feature in the sense of Rule 13.2 PCT.

Moreover, document (D8) discloses that CCX possesses a good anti-viral activity and is cytotoxic to cell replication which is an indication of anti-cancer activity (see page 1781, the first and second paragraphs under the heading "DISCUSSION"). Hence the multiple medical uses cited in present claims 51-59 - which include the use against carcinoma and against virus infections - can also not be seen as a common or corresponding technical feature in the sense of Rule 13.2 PCT.

The fact that CCX corresponds to a compound of formula (I) of present claim 1 where R^2 is a 2-sodiumcarboxy-**cyclohexyl**-carbonyl-group has the effect that the three **Inventions 7** (in which R^2 contains a cyclopentyl ring), **8** (in which R^2 contains a cyclohexyl ring) **and 9** (in which R^2 contains a cycloheptyl or cyclooctyl ring) lack unity of invention with each other.

V. With a letter dated 27 September 2007, the Applicant authorised the ISA to charge his account with nine additional search fees under protest.

In this letter it argued that the number of ten inventions was excessive, at least because the following groups of inventions shared a structural feature forming a novel and inventive concept in view of document (D8):

(a) **Inventions 1 and 6**, sharing the unsaturation immediately adjacent to the group X; and

(b) **Inventions 2, 3, 4 and 10** having the same aromatic or heteroaromatic structure adjacent to the group X.

The Applicant concluded that the present application related to a maximum of six inventions and requested that at least four of the nine additional search fees be refunded.

VI. In a notification pursuant to Article 40.2 (e) PCT dated 07 February 2008, replaced by an amended version dated 12 March 2008 denoting the correct protest fee, as indicated in the telephone protocol of the same day, the review panel of the ISA held that the invitation to pay the nine additional search fees was justified and invited the Applicant to pay the protest fee.

The review panel argued that **Inventions 1 and 6** lacked unity of invention because the more restrained cyclic group present in the radical R^2 of **Invention 6** differed considerably in structure from the less restrained linear group of **Invention 1** when compared with the disclosure of document (D8).

The radical R^2 in **Invention 2** has a phenyl group directly attached to the radical X whereas the corresponding group

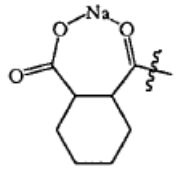
- in **Invention 3** is a pyridyl ring,
- in **Invention 4** is six membered heteroaromatic ring with two nitrogen atoms in the ring;
- in **Invention 10** is a five membered heteroaromatic ring with a nitrogen, an oxygen or a sulphur atom as the only heteroatom in the ring.

The review panel considered these ring structures to be structurally sufficiently diverse from one another such as to constitute separate inventions lacking unity of invention with each other if seen in comparison with the compound CCX disclosed in document (D8), where the group corresponding to the radical R^2 in formula (I) of present claim 1 contained a six membered carbocyclic ring.

VII. With the telecopy dated 07 March 2008 and the respective confirmation copy which was received by the ISA on 18 March 2008, the Applicant authorised the ISA to charge his account with the protest fee.

In this letter the Applicant considered the three-dimensional structure of the $-O-R^2$ group of the claimed compounds to play a vital role in their biological activity because this part of the compounds was believed to bind to certain enzymes such as retinol dehydrogenase.

In CCX the radical R^2 formed a puckered seven membered ring of the structure



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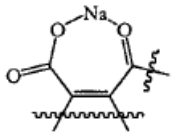
whereas those of the **Inventions 1, 2, 3, 4, 6 and 10** with X= -C(O)- had a flat seven membered ring of the formula



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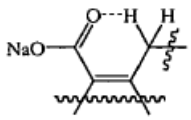
and those with X= $-CH_2-$ had a flat six membered ring structure of the formula



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Moreover, the **Inventions 1 and 6** contained an unsaturated structure adjacent to the group X which is entirely different from the structure of the cyclohexyl group present in CCX disclosed in document (D8). Hence, he argued, the subject-matter of these **Inventions** was novel and inventive in view of the disclosure of document (D8).

He concluded that the **Inventions 1 and 6** on the one hand and **Inventions 2, 3, 4 and 10** on the other, or even **Inventions 1, 2, 3, 4, 6 and 10** as a group met the requirement of unity of invention, so that the present application related to a maximum of six or five inventions.

VIII. The Applicant requested that four or five of the additional search fees and the protest fee be refunded.

Reasons for the Decision

1. The protest is admissible.

2. The present application was filed on 9 March 2007, i. e. before the date of entry into force of the EPC 2000. Due to this fact, the Board is competent to decide on a protest of the Applicant against an additional search fee charged by the EPO as the ISA, and hence has to decide whether or not any the additionally paid search fees may be reimbursed (see Article 154 (3) EPC 1973 in conjunction with the decision of the Administrative Council of 28 June 2001, the transitional provisions set out in Article 3 of the decision of the President of the EPO dated 24 June 2007 and the chapter II of the Notice of the EPO of the same date (see OJ EPO, Spec. Ed. 3, 2007, 140 and 142) and Rule 40.2 PCT).

3. According to Rule 13.2 PCT the requirement of unity of invention of a group of inventions is fulfilled "... only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

4. Claim 1 of the present application gives several alternative formulae as meanings for the radical R^2, i. e. it defines the radical R^2 by a "Markush group". The PCT International Search and Preliminary Examination Guidelines state that the members of a "Markush group" are considered to have the same or

corresponding special technical features as defined in Rule 13.2 PCT if the alternatives are of a similar nature. This applies "... where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, that is, a significant structural element is shared by all the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains."

In this context

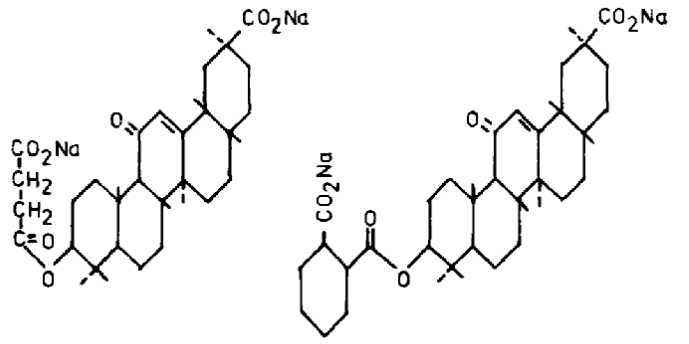
- "the words "significant structural element is shared by all the alternatives" refer to cases where the compounds share a common chemical structure which ... in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity.";
- "the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention.".

(see the PCT International Search and Preliminary Examination Guidelines as in force from 25 March 2004, chapter 10.17).

5. Neither the ISA nor the Applicant considered the compounds of any two or more of the **Inventions 1 to 10** to belong to a "recognized class of chemical compounds" in the sense of the requirement (B)(2) cited under point 4 above. Their argumentation was restricted to the assessment whether or not any two or more of the **Inventions 1 to 10** met the requirements (A) and (B)(1) mentioned above.

6. The ISA has based its objection that the **Inventions 1 to 10** mentioned above lacked unity of invention, on document (D8) of the prior art, hence *a posteriori*.

This document reports on clinical trials for the treatment of herpes simplex virus infections with carbenoxolone sodium (CBX) and cicloxolone sodium (CCX), namely those of the following formulae:



(see the abstract and Figure 1 on page 1772).

In view of this disclosure the ISA essentially held that any one of the **Inventions 1 to 10** did not share a "significant structural element" with any other of

these **Inventions** due to the difference in chemical structure of the meanings of the radicals R^2 (see point IV above).

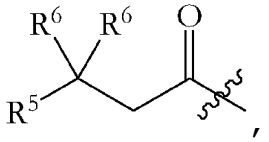
In contrast to this, the Applicant argued that **Inventions 1 and 6** and **Inventions 2, 3, 4 and 10** or even all the **Inventions 1 to 4, 6 and 10** shared a "significant structural element" which conferred to these groups or this group of **Inventions** unity.

Based on these arguments, the Board has to assess whether or not one or more of the additionally paid search fees are to be refunded.

7. **Inventions 5, 7, 8 and 9**

7.1 The Applicant did **not** argue that the **Inventions 5, 7, 8 and 9** fulfilled the requirement of unity of invention with respect to the remaining **Inventions 1 to 10**.

7.2 In **Invention 5**, R^2 means



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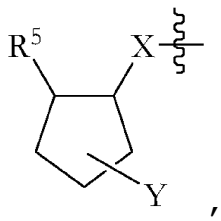
in **Invention 7**



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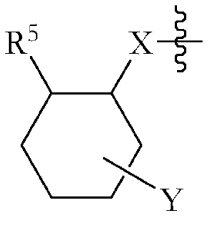
in **Invention 8**



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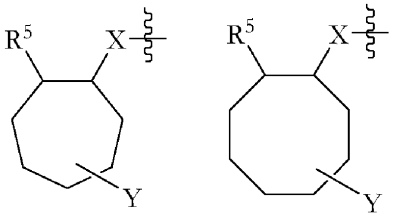
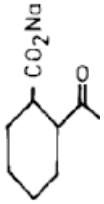
and in **Invention 9** a radical of one of the following formulae



(see point II and III above).

7.3 Document (D8) discloses the compound CCX, namely one of the formula (I) of present claim 1 where R^2 means



, although CCX is expressly excluded from this claim (see point 5 above).

In present claim 1, X may mean -CO- and R^5 may be $-CO_2Na$ (see the expression "or a pharmaceutically acceptable salt thereof" in the line directly under formula (I)).

Hence, the structure of the compounds of **Invention 8** differs from CCX in the meaning of the radicals X and R^5, whereas the compounds of **Inventions 7 and 9** differ from CCX in that the ring size of the cycloalkyl group is smaller (**Invention 7**) or larger (**Invention 9**).

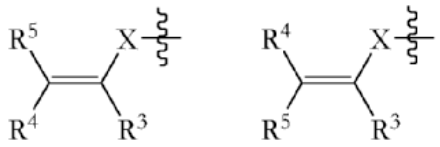
Consequently, the ISA was right in its argument why any of the **Inventions 7, 8 and 9** does not share a "significant structural element" with any of the other **Inventions 1 to 10**.

7.4 Nor do the compounds of **Invention 5** share such an element in view of document (D8) with any of the **Inventions 1 to 4 and 6 to 10** in which R^2 is required to have olefinic unsaturation or to be cyclic.

7.5 For these reasons, the arguments of the ISA lead indeed to the conclusion that each of the **Inventions 5, 7, 8 and 9** lacks unity of invention with respect to the remaining **Inventions 1 to 10**.

8. **Inventions 1 and 6**

8.1 **Invention 1** relates to compounds of formula (I) according to present claim 1 where R^2 means a radical of one of the formulae



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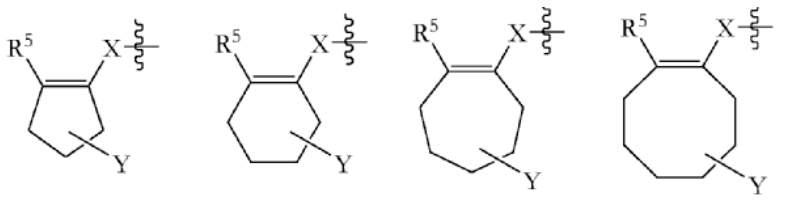
whereas in **Invention 6**, R^2 means a radical of one of the formulae



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8.2 The ISA considered the chemical structures of the meanings of the radical R^2 for **Invention 1** to be so different from those for **Invention 6** that these two

Inventions lacked unity, especially because the cycloalkene rings in the compounds of **Invention 6** were more constrained than the respective alkene structures of **Invention 1**.

8.3 In fact all the compounds of **Inventions 1 and 6** are constrained in that the olefinic carbon-carbon double bond hinders rotation around its axis. Compared to that hindered rotation, the constraint caused by the ring structure in **Invention 6** is minimal because the carbon atoms which are not vicinal to the double bond may swing.

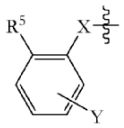
Hence, the argument of the ISA that lead to its conclusion that **Inventions 1 and 6** lack unity of invention is not persuasive. For this reason, one of the additionally paid search fees is to be refunded.

8.4 This olefinic carbon-carbon double bond distinguishes **Inventions 1 and 6** from any of the other **Inventions 2-5 and 7-10.** The Board cannot follow the argument of the Applicant that **Inventions 1 to 4, 6 and 10** share a flat seven or six membered ring (see the second and third formulae under point VII above). Such a flat ring is not a common structural element of these inventions; there is no reason to believe that such a ring, if it is formed at all when X means $-CH_2-$ and R^5 means -OH, is flat. Therefore, **Inventions 1 and 6** lack unity of invention with respect to the remaining **Inventions 2-5 and 7-10.**

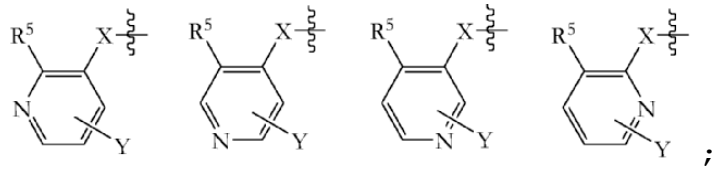
9. **Inventions 2, 3, 4 and 10**

9.1 These **Inventions** relate to compounds of formula (I) according to present claim 1 where R^2 means

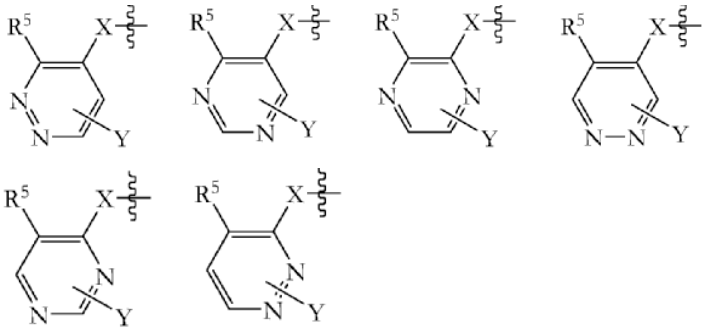
for **Invention 2** a radical of the formula


;

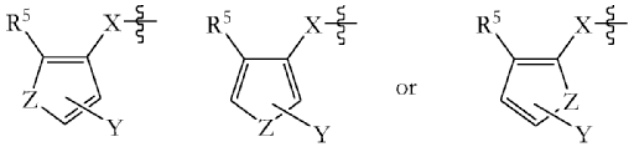
for **Invention 3** a radical of one of the formulae


;

for **Invention 4** a radical of one of the formulae



for **Invention 10** a radical of one of the formulae


.

9.2 The ISA held that **Inventions 2, 3, 4 and 10** shared with document (D8) the problem to be solved and the basic structure of formula (I), while these **Inventions** differed so much in chemical structure of the radical R^2 (namely did not share a "significant structural element") that they lacked unity. The Applicant argued that the **Inventions** shared the same aromatic or heteroaromatic structure adjacent to the group X and

were novel and inventive in view of the disclosure of document (D8) (see point V(b) above).

9.3 First of all, the chemical structure of the radical R^2 for **Inventions 2, 3, 4 and 10** differs by the absence, presence and number of heteroatoms in the ring as well as by the ring size (see point 9.1 above). Due to the higher electronegativities of the heteroatoms as compared to that of the carbon atom, the radicals R^2 for **Inventions 2, 3, 4 and 10** differ considerably in electron density of the (hetero)aromatic ring and in their dipole moment.

As the ISA pointed out, all the compounds of these **Inventions** are to have a certain pharmaceutical activity. As far as they do so, they meet the requirement (A) mentioned under point 4 above. The Applicant stated that the three-dimensional structure of the $-OR^2$ group played "a vital role in the biological activity of the claimed derivatives, because it is this part of the derivatives which is believed to bind to enzymes such as retinol dehydrogenase." (see the penultimate paragraph on page 3 of the Applicant's letter dated 07 March 2008). If the $-OR^2$ group is the site at which the enzyme is to bind, then also the electronic structure (such as the dipole moment) of this group may play a vital role. Moreover, it is to be noted that the present application does not contain test results for compounds of **Inventions 3 and 10** so that the pharmaceutical effect of the compounds of these two **Inventions** is not proven. Hence, the mere fact that the compounds of **Inventions 2, 3, 4 and 10** differ from those disclosed in document (D8) in that the $-OR^2$ groups all contain an aromatic or a

heteroaromatic ring adjacent to the group X is not sufficient to consider this structural element to be "significant", namely to "be essential to the common property or activity" (see point 4 above).

Therefore, each of the **Inventions 2, 3, 4 and 10** lacks unity of invention with respect to the remaining **Inventions.**

10. For these reasons, the arguments provided by the ISA lead to the conclusion that the present application contains at least **nine** inventions lacking unity of invention, namely **Inventions 1 and 6 combined** and each of the **Inventions 2 to 5 and 7 to 10.** This justifies the payment of eight additional search fees. As the Applicant paid nine additional search fees under protest, one search fee is to be refunded.

11. Request to refund the protest fee

According to Rule 40.2(e) PCT, the "protest fee shall be refunded to the applicant where the review body ... finds that the protest was entirely justified."

In the framework of this protest, the Applicant requested that four or five search fees be refunded (see point VIII above). The Board has decided to refund only one search fee and thus does not find the protest to be **entirely** justified (see point 10 above). Therefore, the requirement for refunding the protest fee is not met.

Order

For these reasons it is decided that:

1. One additional search fee is refunded.

2. The request to refund the protest fee is refused.

The Registrar | The Chairman:

C. Eickhoff | P. Ranguis