Commissioner's Decision #1242
Décision du Commissaire #1242

TOPIC: B20; ;B22; C00
SUJET: B20; B22; C00

Application No: 2,152,792
Demande No: 2,152,792

COMMISSIONER'S DECISION SUMMARY

C.D. 1242 ....Application No. 2,152,792 (B20; B22; C00)

Several claims of the application rejected in view of a copending application.

The application discloses novel compounds useful as antiinflammatories for the treatment of arthritis, the improvement over previous medicines being that they cause less stomach irritation. Several claims were rejected under the provisions of Paragraph 28.2(1)(d) of the Patent Act in view of a copending application. The Board recommended that the rejection of the claims directed to groups of compounds be reversed, that the rejection of claims directed to specific compounds be upheld and that the application be returned to the examiner for further prosecution, a recommendation which was accepted by the Commissioner of Patents.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,152,792 having been rejected under Subsection 30(4) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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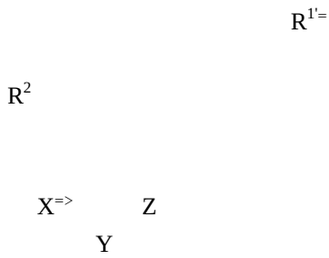
This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application number 2,152,792 which was filed on January 14, 1994. The Applicant is G.D Searle & Co. and the Monsanto Company, assignee of inventors Stephen R. Bertenshaw, Paul W. Collins, Thomas D.Penning, David B. Reitz, Roland S. Rogers and John J. Talley and the application is entitled "NOVEL 3,4-DIARYL THIOPHENES AND ANALOGS THEREOF HAVING USE AS ANTIINFLAMMATORY AGENTS@. The Examiner in charge issued a Final Action on March 18, 1999 refusing certain claims on the grounds that they did not comply with Paragraph 28.2(1)(d) of the *Patent Act* in that before the claim date the subject matter was disclosed in United States patent application numbers 08/082,196 and 08/179,467 to Merck Frosst Canada Inc., said applications being named as priority documents in Merck Frosst Canada Inc.=s copending Canadian application number 2,176,974 filed on June 9, 1994 (hereinafter called the Merck application). The Applicant replied on April 13, 1999 contesting the rejection, submitting new claims 197 to 204 and requesting both a review by the Commissioner of Patents and a hearing before the Board. A hearing was subsequently held on May 12, 1999 at which the Applicant was represented by Mr. I. Fincham, Mr. A. Zahl, Mr. R. Hughes, Mr. Bulock, the Applicant=s American agent, Dr. A. Fallis, a Chemistry Professor at the University of Ottawa and Dr. J. Talley one of the named inventors, the Patent Office was represented by Ms. E. Zurakowska, the Examiner in charge of the application, Ms. S. Arpin and Mr. D. Cillis and the Board consisted of Mr. P. Davies, Dr. M. Howarth and Mr. M. Wilson.

The application, as filed, discloses compounds having the formula

where Y is selected from S, O, and NR^1; R^1 is selected from hydrogen or C_{1-6} alkyl, X is selected from various substituents selected from hydrogen, halo, cyano, hydroxy, etc.; and R^2 and R^3 are independently selected from aryl or heteroaryl groups which can themselves be substituted. The compounds selectively inhibit the enzyme cyclooxygenase II (COX-II) over cyclooxygenase I (COX-I) and are useful as antiinflammatory agents having a reduced capacity to cause stomach irritation. The present claims of the application are limited to those compounds where Y is O and at least one of the groups R^2 and R^3 are independently selected from C_{6-12} aryl or heteroaryl and at least one of R^2 and R^3 is substituted with C_{1-10} alkylsulfonyl or sulfamyl.

The Examiner has rejected claims directed towards a sub-group of the subject matter currently being claimed, this being the 3,4- diaryl furanones. It is the Examiner=s position that the Merck application has an earlier claim date for these furanones. Accordingly, the Examiner has rejected claims 12, 17 to 26, 39 to 46, 53, 54, 66, 71 to 80, 90, 93 to 100, 107 to 114, 126, 131 to 140, 152 to 159, 166 to 170, 181, 185 to 187 and 194. Claims 12 and 39, which include these furanones, are representative of the rejected claims and are as follows:

> 12. A compound of claim 11 selected from compounds and their pharmaceutically acceptable salts of the group consisting of 3-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2(5H)-furanone; and 3-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)furan.
>
> 39. A compound of Formula I^{11}

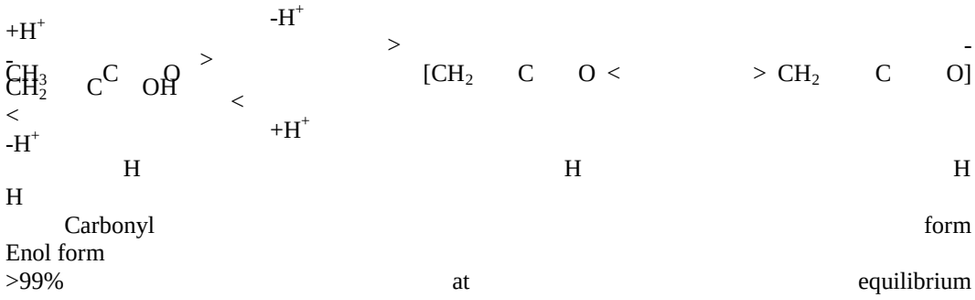


or a pharmaceutically acceptable salt thereof, wherein $X^{=>}$-Y-Z is selected from the group consisting of:
(a) -$CR^{35}(R^{35'})$-O-C(O)-,
(b) -C(O)-O-$CR^{35}(R^{35'})$-;
with side b having a double bond and sides a and c being a single bond;
(c) =CH-O-CH=;
with sides a and c having double bonds and side b being a single bond;
$R^{1'=}$ is selected from the group consisting of
(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,
R^2 is selected from the group consisting of
(a) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
- (1) hydrogen,
- (2) halo,
- (3) C_{1-6} alkoxy,
- (4) C_{1-6} alkylthio, and
- (5) C_{1-6} alkyl,

(b) mono-, di-, or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additionally N atoms, or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, including fluoro, chloro, bromo, and iodo,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy.
(5) C_{1-6} alkylthio; and
R^{35} and $R^{35'}$ are each hydrogen.

There is a preliminary issue to be decided relating to the question of tautomerism. The applicant, in response to the Final Action, filed several affidavits and declarations which describe tautomerism and its applicability to the present application. Tautomerism is defined in the excerpt from the textbook AOrganic Chemistry@ by Cram and Hammond attached as exhibit B to the affidavit of Dr. Fallis dated February 26, 1999 in the following terms:

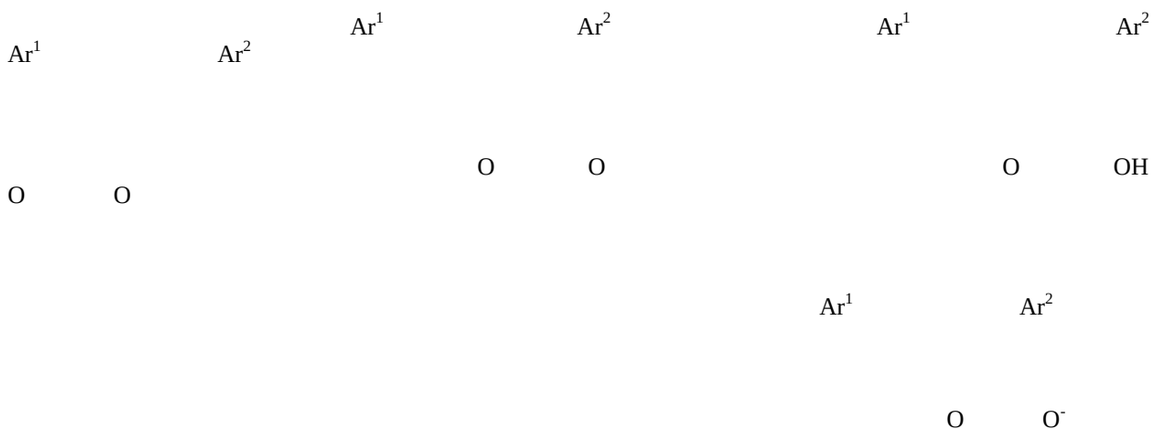
> The term *tautomerism* designates the structural ambiguity which arises from certain rapid and reversible rearrangements that occur in organic molecules. Most frequently, the term is applied to the migration of a proton between two or more basic and conjugated sites in an organic molecule. In a sense, *tautomeric shifts* of protons are internal acid-base reactions, and the various structural isomers that result from such migrations are known as *tautomers*. When a proton is completely removed from two tautomers, the same resonating anion is produced, as is illustrated in the conversion of both the *carbonyl* and *enol* forms of acetaldehyde into the same enolate anion.



< 1% at equilibrium

Tautomerism in acetaldehyde

In similar fashion this concept applies to the furanol/furanone systems which are the subject of the instant Final Action and which were illustrated in the Corey affidavit of January 12, 1999 as follows:



The Board is of the opinion that the use of the structural formulae as shown above, is a way of representing on paper the actual chemical entity being referred to. A chemist could choose, in the first instance, to represent the molecule as either the keto or enol structure without stating (or deciding) in which form the molecule actually existed. Further research, after synthesising and isolating the furanol/furanone would elicit which tautomer, and under what conditions, is the predominant form.

The question before the Board is therefore whether or not the subject matter claimed in the rejected claims was disclosed in Applicant=s priority application, United States application number 08/004,822 filed on January 15, 1993 (a certified copy of which was supplied by the Applicant), so that the Applicant under the provisions of Paragraph 28.2(1)(d) of the *Patent Act* is entitled to claim the said subject matter. In order to do this it is necessary to determine whether the furanones have been disclosed in the Applicant=s application as filed and then to examine the priority application to see whether the Applicant is entitled to an earlier claim date.

The application as filed states in the opening paragraph that the invention relates to 3, 4- diaryl substituted thiophene, furan and pyrrole derivatives which are selected effective and safe compounds having antiinflammatory and/or analgesic activity without erosion of the stomach. The mode of action of these compounds is discussed in relation to their ability to inhibit the enzyme COX-II over the enzyme COX-I. Under the heading ADescription of the Invention@ the Applicant sets out the class of compounds of the invention as Formula I, wherein R^2 and R^3 may be aryl, Y may be oxygen, sulphur or nitrogen corresponding to the 3, 4- diaryl substituted thiophenes, furans and pyrroles. There is also a definition of the moiety X and under Aa)@ appears the value Ahydroxy@ which when Y is oxygen would correspond to a 3, 4-diaryl substituted furanol. A preferred class of compounds is set out on page 9 of the application with a more preferred class of compound on the bottom of page 9. This narrower class also includes the furanols; i.e. Y can be oxygen and X can be hydroxyl (or hydroxy). On pages 11 to 17 there appears a list or a family of specific compounds of particular interest within Formula I but there is no mention of any hydroxy substituted furan (i.e. any furanol). On page 28 of the description the Applicant provides AGeneral Synthetic Procedures@ for synthesizing the compounds of the invention followed by the experimental section or examples which provide a description of the compounds actually synthesized and form the basis upon which the invention is predicated.

These examples describe the synthesis of 14 thiophene derivatives, but example 12 is directed towards the synthesis of a 3,4- diaryl furan. In step 5 of this example there is shown a specific 3, 4- diaryl furanone which was further processed in step 6 to the corresponding

3,4- diaryl furan. Finally the description sets out the biological evaluation of the chemical entities that had been synthesized and the table on page 70-71, for example, shows the assay of the COX-I and COX-II activity for the 14 thiophenes and the specific furan exemplified.

The Examiner raised two issues with respect to the description provided by the Applicant. Firstly she sought to distinguish between the two tautomeric forms i.e. the furanones and the furanols. Secondly, she argued that the utility disclosed was for the furan, the furanone being disclosed as a mere intermediate. As to the tautomers, the Board notes that the furan derivative of Example 12 is named as a furanone whereas the general description employed in the application refers to hydroxy substituted furans; i.e. furanols. The Board accepts this apparent ambiguity on the basis, as stated above, that a chemist would fully understand the tautomeric relationship between the enol and keto form and that this is merely an example of this dichotomy. On the question of utility the Board agrees with the submission of counsel for the Applicant who referred to the Supreme Court decision in *Monsanto v Commissioner of Patents* (1972) 42 C.P.R. (2d) 161 at 176 arguing that it stood for the premise that the Board could not reject the claims in the absence of evidence that Applicant had not made a Asound prediction@ of utility with respect to the furanones. The Board is of the opinion that when the totality of the description in the application as filed is considered not only is there a disclosure of a specific 3,4- diaryl furanone, but also there is a general disclosure of the furanols and a general indication that they have the utility of the invention. The Board therefore believes that the furanones as a sub group and the specific 3,4-diaryl furanone can be given a claim date corresponding to the filing date of the application in Canada.

The Board turns next to Applicant=s priority document. This priority document relates to 3,4-diaryl substituted thiophene, furan and or pyrrole derivatives which are disclosed to have antiinflammatory and/or analgesic activity without erosion of the stomach. On pages 2 to 3 of the U. S. application under the ASummary of the Invention@ there is a general formula (I=) wherein Y may be sulphur, oxygen or nitrogen corresponding to the thiophenes, furans and pyrroles. The substituent X embraces several moieties, and there is a lack of clarity as to whether Ahydroxy@ can be a value for X in its own right as opposed to a substituent of another value of X, a point brought up in a previous Examiner=s report, and it is only after repeated analysis that the Board concludes that Ahydroxy@ can in fact be a value for X.

It is the Applicant=s position that, since the definition given for X in the priority document on pages 2 to 3 includes Ahydroxy@, this is sufficient disclosure to give a claim date all of the claims to the furanones. The Board cannot accept this proposition. In the Board=s opinion there are two aspects to the invention disclosed, firstly there is the broad concept that a class of compounds embracing thiophenes, furans and pyrroles with a multiplicity of substituents (including hydroxy) generally have pharmacological activity as antiinflammatory agents, and secondly, the narrower concept that certain specific compounds have been specifically disclosed to have such pharmacological activity. In assessing what has been disclosed in the earlier priority document a distinction can be drawn between these two concepts.

In examining the Applicant=s priority document the Board accepts, based on the principle

enunciated in *Monsanto* supra, that the Applicant is making a Asound prediction@ with respect to the broad class of chemical entities that they possess an utility as antiinflammatory agents. Accordingly on this basis the Board believes that the Applicant=s broad claims directed towards the substituted 3,4- diaryl thiophenes, furans and pyrroles are entitled to the claim date of the priority document; i.e. January 15, 1993.

The Board however comes to an opposite conclusion with respect to the specific furanones claimed by the Applicant. Claim 12, for example, is directed towards a specific furanone viz 3-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2(5H)-furanone and its pharmaceutically acceptable salts. The Applicant=s priority document does not disclose an invention with respect to this specific compound. In the Board=s opinion the Asound prediction@ theory does not aid the Applicant because the priority document makes no reference whatsoever to such a furanone.

This is consistent with the principle enunciated in the *Monsanto* decision relied upon by the Applicant. In the *Monsanto* decision one claim under rejection referred to some 126 species which had been specifically referred to the disclosure of the application. Thus there was a specific reference to the specific compounds which were being specifically claimed. The Applicant=s priority document does not do this with respect to the specific furanones claimed by the Applicant.

Accordingly the Board finds that the claim date that can be accorded the specific furanones is the filing date of Applicant=s Canadian application; i.e. January 14, 1994, while the claim date that can be given the claims directed towards the broad inventive concept covering substituted thiophenes, furans and pyrroles is the filing date of Applicant=s priority application, January 15, 1993.

As to the Merck application, it is only necessary to look at the first of its priority applications; i.e. the certified copy of U.S. patent application 08/082,196 filed on June 24, 1993. In Examples 9, 10 and 12, the synthesis of three 3,4- diaryl substituted furanones which includes the specific furanone which is the subject of Applicant=s claim 12 is described. Their utility in inhibiting COX-2 in preference to COX-1 is demonstrated in the table bridging pages 45 and 46. The Board has no difficulty therefore in finding that the Merck application has an earlier claim date for the 3-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2(5H)-furanone and its pharmaceutically acceptable salts.

Since the claim date given to Merck is earlier than the claim date given to the Applicant for these specific furanones the Applicant is not by law entitled to claim these compounds. Accordingly the Board recommends to the Commissioner that the rejection of claims 12, 66, 126 and 181 be upheld but that the rejection of the remaining claims be reversed. In view of the Board=s recommendation that the rejection of Applicant=s broad claims be reversed the Board sees no reason why claims 197 to 204 should not be entered into the application since these claims all also similar broad claims.

In conclusion the Board recommends that the rejection of claims 12, 66, 126 and 181 be upheld but that the rejection of claims 17 to 26, 39 to 46, 53, 54, 71 to 80, 90, 93 to 100, 107 to 114, 131 to 140, 152 to 159, 166 to 170, 185 to 187 and 194 be reversed.

P.J. Davies	M. Howarth	M. Wilson
Chairman	Member	Member

I concur with the recommendations of the Board that the Examiner=s rejection of claims 12, 66, 126 and 181 be upheld and that the rejection of claims 17 to 26, 39 to 46, 53, 54, 71 to 80, 90, 93 to 100, 107 to 114, 131 to 140, 152 to 159, 166 to 170, 185 to 187 and 194 be reversed and therefore refuse to grant a patent on the application as long as it contains claims 12, 66, 126 and 181.

P. Trépanier
Acting Commissioner of Patents

Dated at Hull, Quebec,
this 12th day of August, 1999