**Patents Act 1977** **Opinion Number** **09/16 &10/16**

## OPINION UNDER SECTION 74A

| | |
|---|---|
| Patent | EP (UK) 0736030 – opinion 09/16 |
| SPC | SPC/GB06/007 – opinion 10/16 |
| Proprietor(s) | Merck Sharp & Dohme Corp. |
| Exclusive Licensee | |
| Requester | Kilburn & Strode |
| Observer(s) | Merck Sharp & Dohme Corp. |
| Date Opinion issued | 31 May 2016 |

## The request

1. The comptroller has been requested by Kilburn and Strode (the Requester) to issue an opinion as to whether EP (UK) 0736030 (the patent) is valid having regard to inventive step. This patent is also the subject of SPC/GB06/007 (the SPC). The patent and the SPC are considered in the opinions 09/16 and 10/16 respectively, but are presented here together. Opinion 09/16 will consider the inventiveness of the patent whereas opinion 10/16 the validity of the SPC. Article 4 of the SPC regulation[1] provides that the scope of an SPC is defined having regard to the scope of the patent therefore, as the validity of the SPC is reliant on the validity of the basic patent, if I find that the patent is invalid to the extent that it would no longer protect the product protected by the SPC, I will have also found the SPC invalid. The request relies on the following documents:

D1 EP 0539938 published 05.05.1993

D2 Antimicrobial Agents and Chemotherapy, vol. 37(10), 1993, Hostetler et al, "Discrepancies in bioassay and chromatography determinations explained by metabolism of itraconazole to hydroxyitraconazole : studies of interpatient variations in concentrations", pages 2224-2227

D3 EP 0228125 published 08.07.1987

[1] Regulation EC No 469/2009

D4 EP0283992 published 28.09.1988

D5 Spizey et al ed. Antivirals, antimycotics experimental infections, Proceedings of the 13th International Congress of Chemotherapy, TOM 6, 1983, Verlag H Egemann pages 40-33 to 40-39

D6 Brandis et al ed Lehrbuch der Medizinischen Mikrobiologie, 1988,. Gustav Fischer Verlag page 534

D7 Graybill, Systemic azole antifungal drugs – into the 1990s, in Ryley ed. Chemotherapy of fungal diseases,1990, Springer, (Handbook of experimental pharmacology vol.96 Chapter 19)

D8 Ryley et al, Other compounds in development, in Ryley ed. Chemotherapy of fungal diseases, 1990, Springer (Handbook of experimental pharmacology vol.96 Chapter 22)

D9 Rinaldi, Biology and pathogenicity of Candida species, in Bodey ed. Candidasis, Raven Press 1993, pages 1-8

D10 Excerpt from approval package for itraconazole filed before the US Food and Drug Administration 1992

## Observations

2. Observations were received from the patent holder (hereafter referred to as the observer) who disputed whether the opinion should be issued and argued that the patent was inventive, observations in reply were also received from the Requester.

3. The observer provided the following documents:

D11 Prosecution file history for EP0736030

D12 Journal of clinical microbiology, vol. 31, 1993, Bart-Delabesse et al, “Candida Albicans genotyping in studies with patients with AIDS developing resistance to fluconazole”, pages 2933-7

D13 Nature reviews drug discovery, vol 6, 2007, Kauffman et al, “Posaconazole”, pages 183-184

D14 Clinical pharmacology, vol 10, 1991, Kowalsky et al “Drug reviews Fluconazole: A new antifungal agent”, pages 179-194

D15 Drugs of Today, vol. 26(8), 1990, Fromtling, “Fluconazole (Diflucan RTM): A new antifungal triazole” pages 547-556

D16 Drugs, vol. 37, 1989, Grant et al, “Itraconazole A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses”, pages 310-344

D17 Journal of medicinal chemistry, vol. 27, 1984, Heeres et al, “Antimycotic Azoles.

7. Synthesis and antifungal properties of a series of novel triazol-3-ones", pages 894-900.

D18 Anitmicrobial agents and chemotherapy, vol. 32(10), 1988, Boelaert et al, "Itraconazole pharmacokinetics in patients with renal dysfunction", pages 1595-1597

D19 Anitmicrobial agents and chemotherapy, vol. 32(9), 1988, Hardin et al, "Pharmacokinetics of itraconazole following oral administration to normal volunteers", pages 1310-1313

D20 Annals of internal medicine, vol.112, 1990, Tucker et al, "Itraconazole therapy for chronic coccidioidal meningitis", pages 108-112

D21 Reviews of infectious diseases, vol. 9, 1987, van Cauteren et al, "Itraconazole:pharmacologic studies in animals and Humans", pages S43-S46

D22 Anitmicrobial agents and chemotherapy, vol. 34(3), 1990, Hector, "Evaluation of Bay R 3783 in rodent models of superficial and systemic candidiasis, meningeal cryptococcosis, and pulmonary aspergillosis", pages 448-454

D23 Journal of antimicrobial chemotherapy, vol. 26, 1990, Wright et al, "the pharmacokinetics of BAY R3783 and its efficacy in the treatment of experimental cryptococcal meningitis", pages 387-397

D24 Anitmicrobial agents and chemotherapy, vol. 35(4), 1991, Brummer et al, SCH 39304 in the treatment of acute or established murine pulmonary blastomycosis", pages 788-790

D25 Anitmicrobial agents and chemotherapy, vol.36(1), 1992, Cacciapuoti et al, "Comparison of SCH 39304, fluconazole, and ketoconazole for treatment of systemic infections in mice", pages 64-67

D26 Journal of Medical and Veterinary Mycology, vol.28, 1990, Schaude et al, "Preclinical antimycotic activity of SDZ 89-485: a new orally and topically effective triazole" pages 445-454

D27 Journal of Medical and Veterinary Mycology, vol.28, 1990, Ryder, "Biochemical mode of action and enantiomeric selectivity of SDZ 89-485, a new triazole antimycotic", pages 385-394

D28 Obach Pharmacologically active drug metabolites:impact on drug discovery in Pharmacology Reviews 2013 pages 578-640

D29 Phytochemistry, vol.28(12), 1989, Weidenboerner et al, "Antifungal activity of isoflavonoids against storage fungi of the genus aspergillus", pages 3317-3319

D30 Clincial pharmacokinetics, vol.14, 1988, Dameshmend et al, "Clinical pharmacokinetics of ketoconazole", pages 13-34

D31 Mycoses, vol 32(1), 1989, Heykants et al, "The clinical pharmacokinetics of itraconazole: an overview", pages 67-87

D32 Abstracts of the 1991 interscience conference on antimicrobial agents and chemotherapy, 1991 Fu et al, “Comparative in vitro antifungal activity of saperconazole (SAP) and hydroxyl-saperconazole (HO-SAP) abstract 217

D33 Antimicrobial agents and chemotherapy, vol. 10, 1976, Lindmark et al, “Antitrichomonad action, mutagenicity and reduction of metronidazole and other nitroimidazoles”, pages 476-482

D34 Sexually transmitted diseases, vol.7(4), 1980, Ralph et al, “Relative susceptibilities of gardnerella vaginalis (haemophilius vaginalis) neisseria gonorrhoeae, and bacteroides fragilis to metronidazole and its two major metabolites” pages 157-160

D35 The journal of infectious diseases, vol132(5), 1975, Ralph et al, “Bioassay of metronidazole with either anaerobic or aerobic incubation”, pages 587-591

D36 The journal of investigative dermatology, vol.45(2), 1965, Stone et al, “Comparison of thiabendazole and 5-hydroxy-thiabendazole (for antihelmintic effect)” pages 132-133

## Allowance of the Request

4. Rule 94 (1)(b) states that the comptroller shall not issue an opinion if the question upon which the opinion is sought appears to him to have been sufficiently considered in any relevant proceedings. The document D1 above was cited as the closest prior art by the EPO examiner in their consideration of obviousness, as such there is a *prima facie* reason to refuse to issue an opinion. However the question of inventive step raised by the EPO examiner was whether or not the invention represents a non-obvious selection of the prior art as regards D1 alone. The request on the other hand raises two question of obviousness:

    i) Is the invention obvious to the person skilled in the art on considering D1 when viewed in combination with D2 and/or D10?; and

    ii) Is the invention obvious to the person skilled in the art on considering D1 when viewed in combination with D3-D5

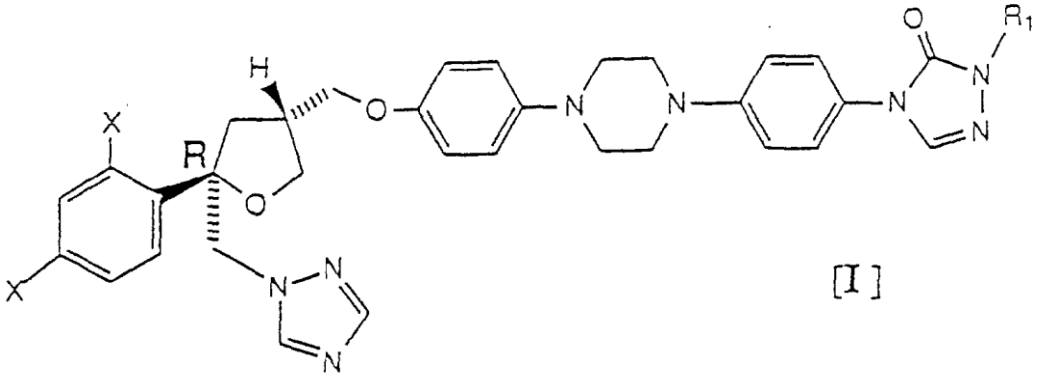
    None of the documents D2-D10 were cited by the EPO examiner, and as such I do not consider these questions of obviousness have been sufficiently considered, and as such I will address both of these questions in this opinion.

5. I do not doubt that the EPO examiner considered whether or not the claimed compounds posses a hitherto unknown technical contribution shared by all the compounds of the claims as compared to D1 and whether or not that technical contribution is shared by substantially all the compounds covered by the compounds of the claims, both requirements having been raised in the international preliminary examination report dated 12.3.96 and in a report dated 28.9.98 leading to the provision of the data with the attorney’s letter of 9.4.99 to show the technical effect of the compounds of the invention as compared to D1. I do not consider the documents

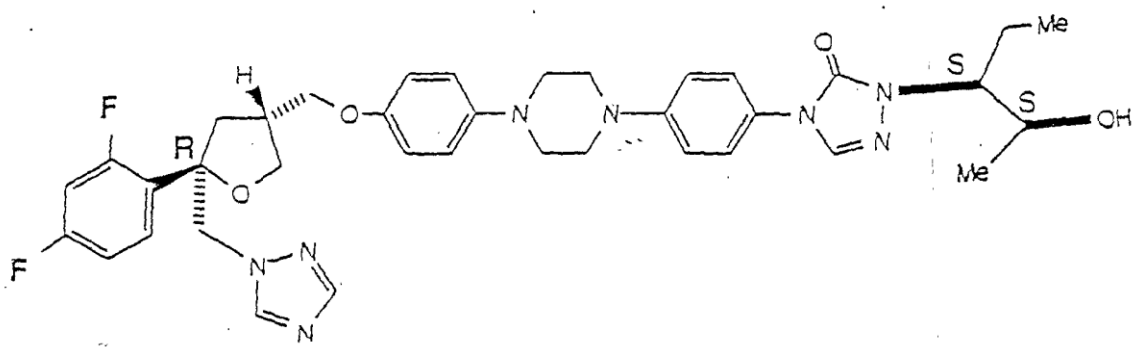
provided by the observer change the question of selection based on D1. Therefore I consider the issue of selection as compared to the prior art has already been sufficiently covered.

## The patent

6. The patent EP (UK) 0736030 B1 is titled “Tetrahydrofuran antifungals” it had a filing date of 20.12.1994, was granted on 29.8.2001. No opposition was filed within the time limit and the patent expired on 19.12.2014. The “product” as that term is used in the SPC regulation[2], is nonetheless protected by SPC/GB/06/007 until 19.12.2019. The patent at claim 1 protects compounds of formula I




wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl; $R_1$ is a straight or branched chain ($C_4$ to $C_5$) alkyl group substituted by one hydroxyl moiety. Within the scope of claim 1 is claim 6 which specifically protects the product of SPC/GB06/007 – now known by the international non-proprietary name - posaconazole.



The claims also concern certain esters of the $R_1$ group and methods of preparing certain compounds. The patent also refers to the closely related compounds of D1.

## Inventive step

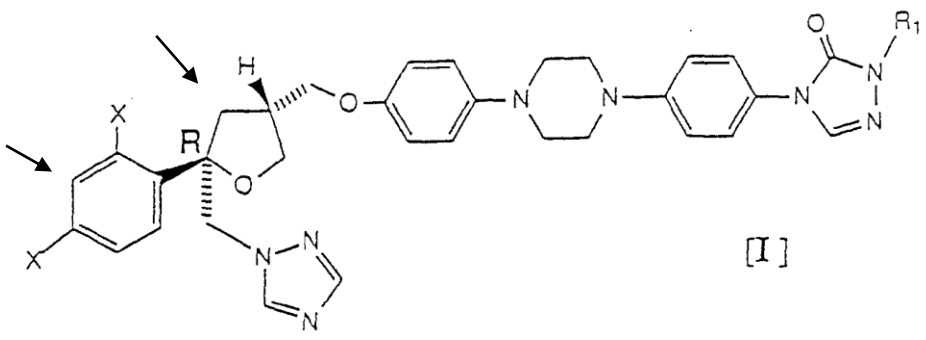
7. To determine whether or not an invention defined in a particular claim is inventive over the prior art, I will rely on the principles established in Pozzoli SPA v BDMO SA [2007] EWCA Civ 588, in which the well known Windsurfing steps were reformulated:

[2] Article 1(b) Regulation EC No 469/2009

*(1)(a) Identify the notional "person skilled in the art";*
*(1)(b) Identify the relevant common general knowledge of that person;*
*(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*
*(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;*
*(4) Viewed without any knowledge of the alleged invention as claimed, determine whether those differences constitute steps which would have been obvious to the person skilled in the art.*

8. **The skilled person in the art and their common general knowledge** - The requester and observer have considered the related steps 1a and 1b together. I propose to do the same. I consider the skilled person is a medicinal chemist familiar with antimycotic agents such as azoles, their preparation, formulation and use in the treatment of fungal infections. The skilled person would be aware of the development of the most important antimycotics of the last 4 decades such as ketoconazole, itraconazole, saperconazole and the development of the compounds IIa-IIc of D1. The requester underlines the importance of structural modifications as having potential effects on biological activity and use in treatment of infections such as *candida* infections, whereas the observer also considers the skilled person is mindful of the need for additional broad spectrum antimycotics with improved efficacy to counteract resistance of fungal infections to existing drugs. All-in-all I consider all of the above characterising features define the skilled person and their common general knowledge.

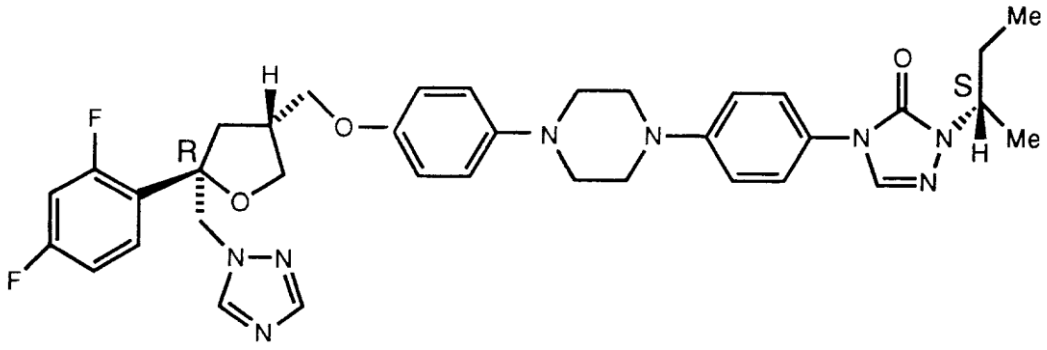
9. In identifying the inventive concept of the present invention the requester concludes that "the problem of providing broad spectrum antifungal agents was known in the art and has been solved e.g., by the provision of the compounds of D1" and as such the inventive concept, at best, can be considered a provision of alternative compounds to the antimycotic agents of the prior art". The observer on the other hand relies on evidence presented to the EPO to demonstrate "that the compounds of the invention have superior *in vitro* and *in vivo* properties against a range of systemic fungal infections when compared to the closest structural analogues of the prior art..." I consider my starting point should be identification of the core of the invention. To this end referring to the broadest claim, claim 1, I consider the core of this claim to be the provision of a straight or branched $C_4$ to $C_5$ alkyl group substituted by one hydroxyl moiety at the $R_1$ position of formula I



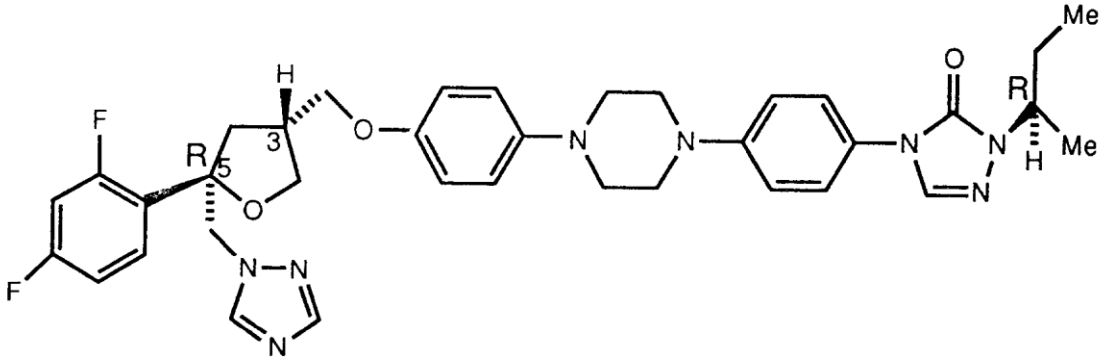

[I]

The arrows show (from left to right) the phenyl and tetrahydrofuran moieties (these, along with $R_1$ are considered in table 1 below).

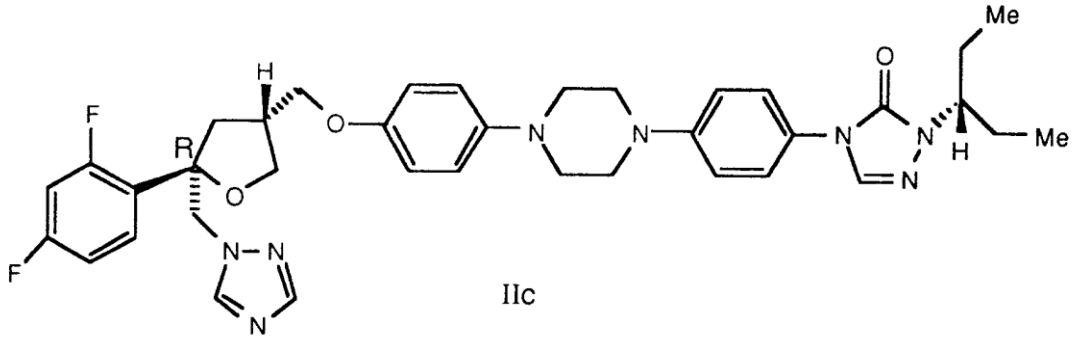
10. **The state of the art and differences between the state of the art and the inventive concept** – from D1 the skilled person would be aware of IIa-IIc, which I reproduce below.




IIa

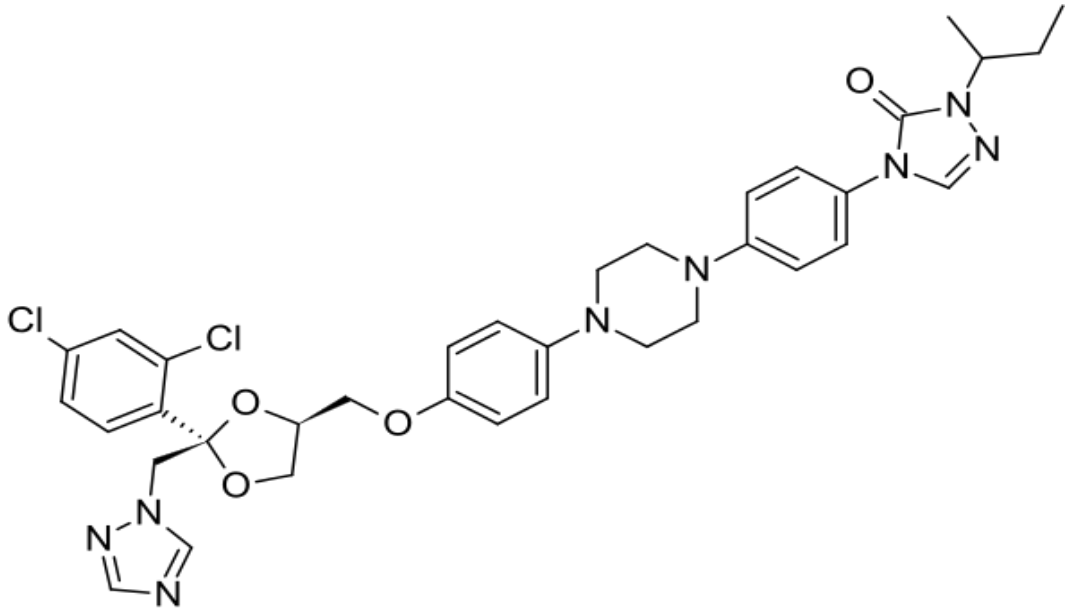



IIb




IIc

D2 cited in the request indicates further related compounds itraconazole (1-methyl-prop-2-yl substituent in the $R_1$ position) and hydroxyitraconazole (1-methyl-prop-2-ol substituent in the $R_1$ position), for comparison I reproduce the structural formula of itraconazole for comparison.




Itraconazole (IZ)[3]

D2 and D10 teach that the metabolites of itraconazole (IZ) include hydroxyitraconazole (HIZ), hydroxyitraconazole has a 1-methylprop-2-ol group at the R1 position as compared to the 1-methylprop-2-yl R1 group in itraconazole.

Other closely related compounds include saperconazole and its hydroxy analogue hydroxysaperconazole. Saperconazole (like IZ) shows a (1-methyl-prop-2-yl) substituent in the $R_1$ position; hydroxy-saperconazole (shown in D3 as compound123), like HIZ, has a (1-methyl-prop-2-ol) substituent in the $R_1$ position, but both have different substituents on the phenyl moiety. I provide this information and the nature of the structural differences between the prior art compounds and the invention (at its broadest) in table 1:

Table 1-Summary of the differences between the prior art and the invention of claim 1

| Compound | Phenyl substituents | Dioxolan / tetrahydrofuran | $R_1$ | Differences with claim 1 |
|---|---|---|---|---|
| itraconazole | 2Cl | Dioxolan | 1-methylprop-2-yl | Replace dioxolan with THF and monohydroxylation of $R_1$ |
| hydroxyitraconazole | 2Cl | Dioxolan | 1-methylprop-2-ol | Replace dioxolan with THF |
| saperconazole | 2F | Dioxolan | 1-methylprop-2-yl | Replace dioxolan with THF and |

[3] Figure By Fuse809 (talk) - Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=30123319

| | | | | |
|---|---|---|---|---|
| | | | | monohydroxylation of $R_1$ |
| hydroxysaperconazole | 2F | Dioxolan | 1-methylprop-2-ol | Replace dioxolan with THF |
| D1 compound IIa<br><br>D1 compound IIb | 2F | Tetrahydrofuran (THF) | IIa: 2R-(1-methylprop-2-yl)<br><br>IIb: 2S-(1-methylprop-2-yl) | Monohydroxylation of $R_1$<br><br>Monohydroxylation of $R_1$ |
| D1 compound IIc | 2F | tetrahydrofuran | Pentan-3-yl | Monohydroxylation of $R_1$ |
| Claim 1 of the patent | 2F or 2Cl | tetrahydrofuran | $C_4$-$C_5$ monohydroxy | - |

It is apparent that IZ and saperconazole share the same $R_1$ group and HIZ and hydroxysaperconazole also share the same $R_1$ group. Analysis of the differences between the named compounds of the prior art and the invention are provided as context only, they are not additional starting points for the analysis of inventive step. The final 3 rows of the table - analysis of the differences between D1 and the present claims forms the basis of the obviousness argument in the request.

11. D1 not only teaches the compounds IIa-IIc and methods for their preparation but also directs the addressee as to the use of IIa and IIb. These compounds are prepared in Examples 23 and 24 and their use in rodent models of infection is set out in Tables I, II and V. In performing these Examples the inevitable consequence will be the formation of certain metabolites. I am taught by Merrell Dow[4] that such metabolites are an aspect of the prior art. D2 and D10 teach that the metabolism of IZ will result in the formation of HIZ (see paragraph 10). Insofar as IZ is analogous to IIa and IIb, I believe it is highly likely that the metabolism of IIa and IIb will be similar to that of IZ and so result in the conversion of the 1-methylprop-2-yl R group to a 1-methylprop-2-ol group.

12. I consider that because the 1-methylprop-2-ol metabolite of IIa and IIb is an aspect of the prior art, there is no difference between the prior art and the invention of claim 1. Insofar as resolving stereoisomers is within the common general knowledge of the skilled person, claims 2-4 are also not inventive.

13. I will continue by analysing the prior art more fully from the perspective of whether or not it shows that it would be obvious to prepare any compounds of the invention, starting with D1 in combination with D2 or D10, and then D1 in combination with D3 and D5.

14. **Do the differences constitute steps which would have been obvious to the person skilled in the art** – I propose to answer this question by firstly reviewing the teaching of the documents that the requester has offered as showing a lack of inventive step, and the teaching of the documents provided by the observer.

[4] Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd [1996]

15. As I have commented above both D2 and D10 propose HIZ as a metabolite of IZ, as regards its utility as an antifungal, D2 proposes that HIZ is equipotent against selected pathogens [*in vitro*]. D2 also explains that IZ is metabolised to HIZ *in vivo* so that a blood sample taken after dosing with IZ will show an approximate 2:1 ratio of HIZ to IZ and that combined with a greater potency of HIZ as compared to IZ in a bioassay explains the discrepancy of IZ analysis by HPLC (accounting for IZ alone) and by bioassay (accounting for HIZ + IZ). D2 suggests the use of HIZ in therapeutic studies, the importance of a higher minimum inhibitory concentration (MIC) for HIZ as compared to IZ against *candida albicans* although apparent for strains used in bioassays does not lead the author to any clear conclusion regarding use *in vivo*, indeed even in the *in vitro* tests the noted equipotency (as referred to in the abstract) and "similar activity" against other fungi (as referred to in the discussion) does not demonstrate monohydroxylation as clearly beneficial in antifungal therapy. D10 shows toxicological studies of 2 active metabolites of IZ, in order to affirm the safety of IZ, the conclusions at page 55 show HIZ to be no more toxic than IZ and shows a gender and species specific metabolism, no clear conclusion attesting to the advantages of HIZ as compared to IZ is noted and I see no justification for such a conclusion.

16. I have also been asked to consider the inventive step in light of the combination D1, D3-D5. The requester has compared the relative activity of HIZ and IZ in the treatment of vaginal candidosis in a rat animal model as set out in D3 and D5 respectively. In particular attention is drawn to the proposed increase in efficacy for the topical treatment 0.031% vs 0.125%. However I do not find that the skilled person would find it particularly instructive to compare these data in that they relate to different experimental quantities, i.e. comparing the lowest topical dose active at 7 days after the last dose (wherein the doses are given twice daily for 3 days starting with the third day after infection) (table 1 D3) and the concentration necessary to give a cure rate of 35 out of 38 animals (wherein the doses are given twice daily for 3 days starting with the third day after infection) (D5). I do not consider D3 and D5 would provide the skilled person with sufficient data to compare the efficacy of HIZ and IZ because the lowest topical dose of active would be expected to be lower than that capable of providing a "highly effective" cure rate, and there is no data in D5 at the 0.0031% concentration. Therefore I do not consider the skilled person would be motivated to introduce an OH group onto the R1 substituent by a combination of D1 with D3 and D5.

17. The observer proposes that the skilled person would not make structure activity predictions based on compounds so removed from each other. In particular the observer considers that the skilled person would not make such predictions as he would be dissuaded by a prejudice in the art that hydroxylation leads to unpredictable effects on *in vivo* activity, and as such the skilled person would be dissuaded from making the necessary monohydroxylation change to the compounds of D1. I will consider if this is justified in light of the documents offered. As a starting point I consider it is justified that the skilled person would give more weight to teaching on the effect that hydroxylation has on activity of closely related compounds to those of D1, as such many of the D14-D27 become less relevant. As regards D28 this document was published after the priority date of the invention and as such was not available to the skilled person. The observer refers to D29 as teaching that "polar hydroxyl groups may minimise the fungal membrane permeability", however this

statement is made in reference to trihydroxy dihydroxy and monohydroxy isoflavanoids. The skilled person would not find this document to assist them in reaching conclusions about the desirability of a monohydroxylated compound as compared to the corresponding alkyl substituent. D30 refers to inactive ketoconazole aromatic hydroxylation, as such this skilled person will put less weight on this document as compared to documents concerning alkyl hydroxylation. As regards D32 I do not agree with the observer that it shows hydroxysaperconazole is inferior to saperconazole, half of the tests on specific fungal geneses showing similar activity and half lower activity. I consider the most relevant teaching as regards monohydroxylation is D31. D31 refers to animal model studies as showing that HIZ lacks activity as compared to IZ. I must of course resolve what the skilled person would conclude from D31 and D2, as D2 is somewhat contradictory to D31. On balance, I do not find the skilled person would be motivated to monohydroxylate a 1-methylprop-2-yl $R_1$ substituent having viewed the prior art concerning IZ and HIZ.

18. Having considered HIZ and IZ, I should also consider what, if anything, the skilled person would conclude about the relationship between the activity of Saperconazole and hydroxyl-saperconazole. In this regard, I have D32, mentioned above, and D3/D4. I have considered the experimental justification for the enhanced activity. stated by the requestor, i.e., the addition of the hydroxyl group to saperconazole in D3 and D4 and consider the skilled person would find these tests directly comparable and that they show the OH group in hydroxysaperconazole confers enhanced activity as compared to saperconazole *in vivo*. However D32 does not clearly show the hydroxyl analogue to be a better or worse antifungal, at least *in vitro*, and for *c.albicans* (the species used in D3 and D4), in particular, the hydroxyl analogue and the parent compound show the same activity. On balance, I consider the skilled person would give more weight to the data from D3/D4 as compared to D32, not least because it relates to *in vivo* activity.

19. On balance considering the prior art as regards the hydroxyl analogues of itraconazole and saperconazole, that whereas *in vitro* studies show somewhat mixed results there is motivation provided by some *in vivo* studies (particularly those concering saperconazole and its hydroxy analogue) to monohydroxylate a 1-methylprop-2-yl $R_1$ substituent to provide a 1-methylprop-2-ol $R_1$ group .

20. The observer has proposed that there are additional barriers in the mind of the skilled person that render the present claims inventive, I paraphrase these below:

    i) the prior art disclosed many other compounds equally or more promising than the compounds disclosed in D1 as a starting point, see item (iv) (i) page 11 of the observations.

    ii) There are many potential sites for monhydroxylation in the compounds of D1, the skilled person would not be taught which to choose, see the observations at the foot of page 14.

    iii) The skilled person would be dissuaded by hydroxylation in that this would introduce a new chiral centre, resulting in a need to control stereochemistry in the drug and so complicate synthesis and regulatory approval (see the observations at the paragraph bridging pages 14 and 15).

Taking i) and ii) together, I consider Laddie J's comments in Brugger[5] (below) demonstrate that merely being faced with a large number of options does not render an obvious route any less obvious.

> "If a particular route is an obvious one to try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well. If a number of obvious routes exist it is more or less inevitable that a skilled worker will try some before others….There is no rule of law or logic which says that only the option which is likely to be tried first or second is to be treated as obvious for the purpose of patent legislation."

Furthermore and of specific relevance to the present questions of obviousness, I consider point ii) is not relevant because the 1-methylprop-2-ol $R_1$ group is well known in the prior art (see paragraph 17 above) and is incorporated into a well known structure found in D1. Accordingly, I do not find points i) and ii) should dissuade me from a conclusion of obviousness.

As regards point iii), the skilled person would consider resolution of the stereoisomers formed by the introduction of another chiral carbon a routine step and would not be dissuaded from preparing and testing the resulting compounds.

21. I make one more observation as regards the obviousness of the hydroxylation of $R_1$ in the compounds of D1. I consider that the skilled person on consulting the methods of D1 and D3, D4 would be able to prepare the hydroxyl derivatives of IIa and IIb without inventive skill. Accordingly I consider the invention of claim 1 is obvious.

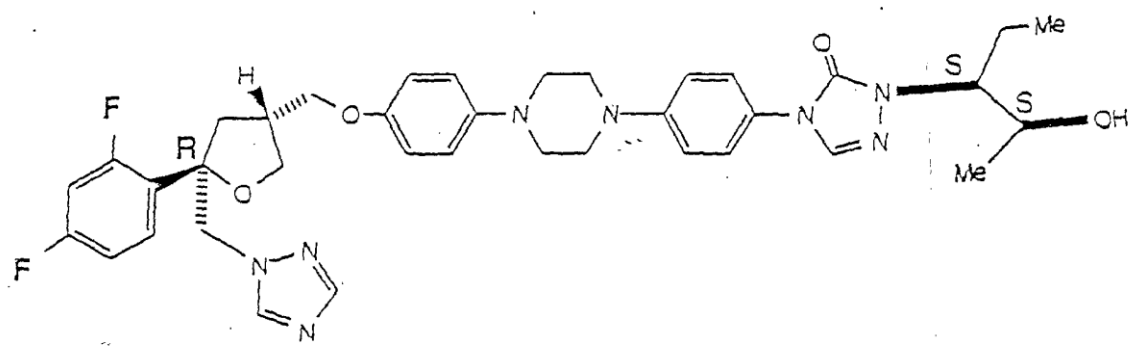
## The invention of claim 6 of the patent

22. I have been asked in the observations in reply to give particular consideration to the invention of claim 6. I consider that claim 6 protects the product of SPC/GB06/007 so in order to give full consideration to the validity of SPC/GB06/007 it is correct that I consider the inventiveness of this claim using the windsurfing Pozzoli test (see paragraph 7 above) and thereby determine the validity of the SPC.

23. For the purposes of Claim 6, I consider that the person skilled in the art and their common general knowledge are suitably defined in paragraph 8 above.

The compound of claim 6 of the patent is shown below

[5] Brugger and Others v medic-Aid Ltd [1996] RPC 635




the inventive concept is the provision of a (2S, 3S)-2-hydroxypentan-3-yl R1 substituent with the aim of finding a new broad spectrum antifungal for use in therapy.

24. The state of the art as regards claim 6 I have summarized in the following table 2

Table 2 - summary of the differences between the prior art and the invention of claim 6

| Compound | Phenyl substituents | Dioxolan / tetrahydrofuran | $R_1$ | Differences with claim 6 |
|---|---|---|---|---|
| itraconazole | 2Cl | Dioxolan | 1-methylprop-2-yl | Replace dioxolan with THF; replace C4 with C5; replace 2Cl with 2F and monohydroxylation of $R_1$ |
| hydroxyitraconazole | 2Cl | Dioxolan | 1-methylprop-2-ol | Replace dioxolan with THF; replace C4 with C5 and ; replace 2Cl with 2F |
| saperconazole | 2F | Dioxolan | 1-methylprop-2-yl | Replace dioxolan with THF; replace C4 with C5 and monohydroxylation of $R_1$ |
| hydroxysaperconazole | 2F | Dioxolan | 1-methylprop-2-ol | Replace dioxolan with THF; replace C4 with C5 |
| D1 compound IIa<br><br>D1 compound IIb | 2F | Tetrahydrofuran (THF) | IIa: 2R-(1-methylprop-2-yl)<br><br>IIb: 2S-(1-methylprop-2-yl) | replace C4 with C5 and monohydroxylation of $R_1$<br><br>replace C4 with C5 and monohydroxylation |

| | | | | |
|---|---|---|---|---|
| | | | | of $R_1$ |
| D1 compound IIc | 2F | tetrahydrofuran | Pentan-3-yl | Monohydroxylation of $R_1$ |
| Claim 6 of the patent | 2F | tetrahydrofuran | (2S, 3S)-2-hydroxypentan-3-yl | - |

Analysis of the differences between the named compounds of the prior art and the invention is provided as context only, they are not additional starting points for the analysis of inventive step. The final 3 rows of the table - analysis of the differences between D1 and the present claims - forms the basis of the obviousness argument in the request.

25. Starting from D1 the differences between the prior art and the invention of claim 6 require the skilled person to replace the pentan-3-yl substituent with a (2S, 3S)-2-hydroxypentan-3-yl $R_1$ substituent. To make such a change requires the skilled person to appreciate that hydroxylation of the $R_1$ substituent is obvious to try in that there is sufficient likelihood of success to warrant a trial.

26. I have reviewed the prior art as regards claim 6, whereas there is an indication in D1 that IIc is “more preferred” (page 15 line 54) than IIa or IIb, there is no indication that it is preferred owing to better activity or for some other reason such as ease of preparation. Taking this statement at face value I do not consider the skilled person would consider it to particularly single out IIc for further study. Even if the skilled person were to consider IIc as a source for further derivatisation I do not consider the skilled person would be motivated to prepare the (2S, 3S)-2-hydroxypentan-3-yl derivative, there being no indication in the prior art provided of the desirability of this group or indeed any hydroxypentanyl group. Therefore I consider that claim 6 is inventive.

27. Having considered claims 1 and 6 I will now turn to the remaining claims. In light of the conclusion that it would be obvious to prepare the 1-methylprop-2-ol substituent of $R_1$ I consider claims 2, 3 and 4 to be obvious (as I found in paragraph 11-12 by argument relating to metabolites and confirmed in paragraph 21). Furthermore I consider claims 20-22 are within the common general knowledge of the skilled person.

28. Having further regard to paragraph 11-12 I also consider that Merrell Dow teaches that claims 1-4 are not novel, in finding that compounds falling within the scope of these claims are the inevitable consequence of performing examples 23 and 24 of D1.

## Conclusion

29. Taking account of all of the above, it is my opinion that claims 6-19 are inventive, and claims 1-4 are not novel or inventive.

30. Insofar as claim 6 is inventive, I find Article 4 of the SPC regulation provides that the SPC is based on a valid claim and as such I consider SPC/GB06/007 is valid.

## Application for review

31. Under section 74B and rule 98, the proprietor may, within three months of the date of issue of this opinion, apply to the comptroller for a review of the opinion.

Dr J.P. Bellia

Examiner

---

**NOTE**

*This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Office.*