

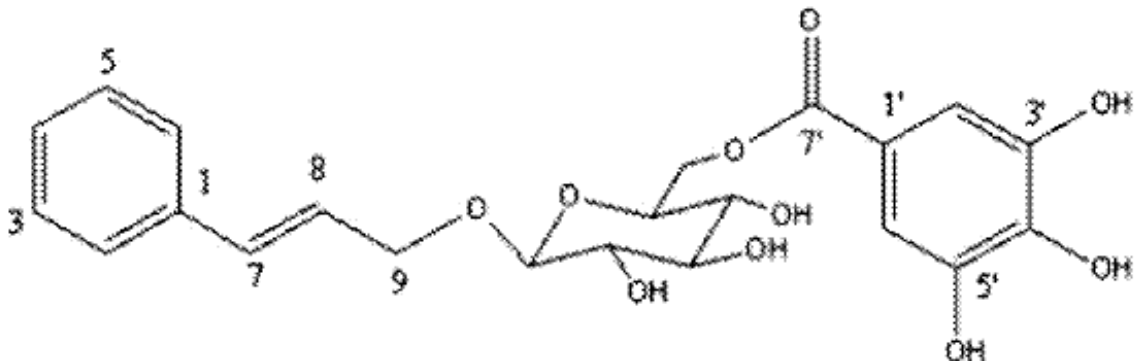
wherein R_{1-11} are independently same or different;

wherein R_1-R_5 are independently selected from hydrogen, hydroxyl, alkoxy, acyl, halogen, alkyl, or aryl;

wherein R_6 is selected from hydrogen, acyl, or alkyl; and

wherein R_7-R_{11} are independently selected from hydrogen, hydroxyl, alkoxy, acyl, halogen, or alkyl."

- 5 It is common ground between the examiner and the applicant that compound, F199-C22, which falls within the scope of this Markush formula, is disclosed in the specification and is a novel compound. This compound is the subject of dependent claim 2:



- 6 The specification describes the isolation of F199-C22 from *Rhodiola rosea*, and also that this compound has some Cdk5 inhibitory activity. The application does not however describe any synthetic preparation or other means by which such a compound can be obtained. Further dependent claims 3-8 relate to the compounds, their medical use or use *in vitro* to inhibit Cdk5 enzyme.
- 7 I consider that there is no need to further construe the scope of the claims currently on file, as these are clear in their meaning as to the scope and the nature of the invention, not merely in the compounds being claimed but also the medical and other uses defined in these claims.

The Relevant Law

- 8 Section 14(3) of the Act requires that:

“The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.”

9 The purpose of S14(3) is to prevent a patentee laying claim to products or processes which the teaching of the patent does not enable the skilled addressee to perform or, in other words, the extent to which the applicant has provided an enabling disclosure for their invention. Insufficiency due to excessive claim breadth arises when the application contains sufficient disclosure for only part of the claim to be worked, but not its entire scope. Showing that the full scope of the claim can be worked is usually done by a combination of general disclosure and particular embodiments. In the case of a single compound, only one example will be needed, as was held in *Generics (UK) Limited & Others v H Lundbeck A/S*¹, since producing a compound for the first time entitles the applicant to a monopoly for that product regardless of others subsequently inventing new methods of producing it.

10 However, if the claim is more complex, for instance being claimed as a generic class, or as a Markush formula, then it is likely that multiple examples will be required. This requirement was established by the judgment of the House of Lords in *Biogen Inc. v Medeva plc*², which held that the entire scope of the claim must be sufficiently disclosed, and also that sufficiency should be decided at the date of filing of the application.

11 The House of Lords at pages 48-49 held that:

“If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms... On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them. Thus if the patent has hit upon a new product which has a beneficial effect but cannot demonstrate that there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not the class, even though some may subsequently turn out to have the same beneficial effect.”

12 This principle in relation to a Markush claim specifically was considered in *Pharmacia Corporation and Others v Merck & Co Inc.*³, at para 56 where it was held:

“Where the claimed invention is to a class of compounds, the same principle applies and, as was made clear by the House of Lords in Biogen, is that the disclosure in the specification must enable the invention to be performed to the full extent of the monopoly claimed. Thus if the invention is a selection of certain compounds, in order to secure an advantage or avoid some disadvantage, not only must the specification contain sufficient information on how to make the compounds, it must also describe the advantage or how to avoid the disadvantage. Further the compounds monopolised by the claim must all have that advantage or avoid the disadvantage. The same principle applies

¹ *Generics (UK) Limited and others v H Lundbeck A/S* [2009] UKHL 12

² *Biogen Inc v Medeva plc* [1997] RPC 1

³ *Pharmacia v Merck* [2002] RPC 775 CA

where the claim is to a class of compounds. To be sufficient, the specification must identify the characteristics of the class and a method of manufacture. Further all the claimed compounds must in substance have the characteristics of the class.”

- 13 Therefore, to satisfy the requirement of S14(3) where a class of products is claimed, it is the class that must be enabled in the relevant sense, not just one member.
- 14 It should also be noted that the concept of the “person skilled in the art” (or team) is construed similarly when considering either sufficiency or inventive step. For the purposes of S14(3) the skilled person has the patent before them and is “*trying to carry out the invention and achieve success ... not searching for a solution in ignorance of it.*” (see *Zipher Ltd v Markem Systems Ltd*⁴, para 366) As such they are seeking to make the patent work, with the common general knowledge that was available at the time the patent was filed, and without facing an undue burden.

The Examiner’s position

- 15 The examiner has consistently maintained throughout the substantive examination that the invention as defined in claim 1 is speculative, unsupported across its full breadth and insufficient due to excessive claim breath.
- 16 He has argued that only one example of a novel compound is provided, namely F199-C22. No principle of general application has been demonstrated by which a skilled person would obtain other compounds possessing the desired technical property of being an inhibitor of Cdk5 activity, across the range of compounds with the core scaffold of the Markush formula represented by claim 1.
- 17 Furthermore, the examiner has also maintained that the application is insufficient because it discloses only one way by which the compound may be obtained, by extraction from a natural source, the plant *Rhodiola rosea*. The application, as filed, provides no alternative synthetic means of producing any compound encompassed by the core scaffold. In his report of 16 February 2017, the examiner set out some illustrative examples of why the single compound disclosed was not sufficient to teach a general class of compounds, such that the range of substitutions possible at particular R groups identified by the Markush formula would not be merely a trivial exercise. The examiner supported his arguments with specific examples of how the range of possible substitutions encompassed by the claimed options at either of R groups R₁-R₅ or also R₈-R₁₀ would each result in numerous potential alternatives. Any one of these examples of R group substitutions as suggested by the examiner would result in the skilled person having to undertake separate extensive research programs, either to develop the synthetic strategy used to produce such compounds or to plausibly determine whether the compounds produced had the desired technical property. Further, if a compound was not an inhibitor of Cdk5 activity, then the application provided no guidance as to how to adapt a compound so this activity was introduced.
- 18 Consequently in the opinion of the examiner, the skilled worker when trying to work the patent would be undertaking an extensive research project requiring inventive

⁴ *Zipher Ltd v Markem Systems* [2009] FSR 1

skill rather than routine trial and error experimentation, not only to produce such compounds by a synthetic route but further to establish that they also had the desired technical advantage of Cdk5 inhibition.

- 19 However, as set out in his report of 1 December 2016, the examiner had considered that the claims could be restricted to the enabled scope of the disclosure in the application, which he identified as the compound F199-C22 as defined in claim 2.

The Applicant's Position

- 20 The applicant has consistently argued that in their opinion the application is sufficient.
- 21 However, in response to the arguments presented by the examiner the applicant has filed amended claims, most recently with their letter of 16 March 2017. Furthermore, in this letter they set out their arguments why these claims were now sufficient, both in respect of the possible R group substitution patterns of the core scaffold and also why the technical property of Cdk5 inhibition was plausible across the range of compounds encompassed by the claims. They have also provided an annex (Annex 1) detailing synthetic information provided by the inventors to show that a synthetic preparation route for compounds of the invention could be established.
- 22 Claim 1 has been amended as set out above so that the possible R group substitutions have been limited. R₁-R₅ are now limited such that they are independently selected from hydrogen, hydroxyl, alkoxy, acyl, halogen, alkyl and aryl. R₆ is limited to be selected from hydrogen, acyl and alkyl, whilst R₇-R₁₁ are limited such that they are independently selected from hydrogen, hydroxyl, alkoxy, acyl, halogen and alkyl. Such amendments, the applicant suggests at page 2 of their letter of 16 March 2017, result "in a claim that covers particularly simple substitution patterns" and this restriction to these substitution patterns thus overcomes the objection to insufficiency.
- 23 Whilst admitting that the application does not disclose a synthetic route to F199-C22 and its derivatives they argue that, as illustrated by Scheme 1 set out in Annex 1, this would be readily taught to the skilled person when reading the specification, which does disclose how to isolate F199-C22 from its natural source. Scheme 1 of Annex 1 they argue illustrates a synthetic route that utilises commercially available precursors and thus the route is easily available to the skilled person. In their scheme the desired compound F199-C22 is identified as consisting of three parts, A, B and C. The proposed scheme demonstrates that F199-C22 can be obtained by first combining Part A with Part C and the product of this reaction is then connected with Part B. This Scheme further references an academic citation by D.T. Khong *et al* in which an analogue of F199-C22 was synthesised by such a route.
- 24 Specifically, in respect of Group R₆ the applicant argues that the proposed reaction of Scheme 1 requires two starting materials. If one of these starting materials is an AcO substituted tetrahydropyran ring as illustrated and which is commercially available, then scheme 1 outlines a route whereby the R₆ group = hydrogen. The alternative options at this point would be either acyl or alkyl, which the skilled person would realise can be easily obtained by esterification or alkylation.

- 25 They further argue that this scheme also allows the skilled person to arrive at the possible R₁-R₅ substituents. In Scheme 1 these R groups are present on the part of the compound represented by Part A. The applicant in Annex 1 provides in Figure 1 a series of alternative modifications of the phenyl ring of Part A of the compound that they allege are routine, to demonstrate that hydroxyl, alkoxy, acyl, halogen, alkyl and aryl substitutions are known. Each of the six examples 1-6 provided is referenced to separate academic publications which set out the individual schemes to generate a different starting material of Part A. By using any one of these initial starting materials, the substitution patterns encompassed by the alternative R₁-R₅ groups are subsequently introduced into the desired F199-C22 derivative.
- 26 The applicant does not set out in their Scheme how the further possible substitutions at groups R₇-R₁₁ which are present on Part B of F199-C22 can be prepared. However, they argue that although no synthetic routes to achieve these substitutions on the phenyl ring of Part B are set out, the desired substitutions can be achieved using analogous synthetic schemes to those set out in Fig. 1 for the phenyl ring alternatives present in Part A of F199-C22.
- 27 The applicant's argument is thus that all the possible substitution patterns defined in claim 1 as amended are covered by different starting materials which form any one of Parts A, B and C of F199-C22 or its derivatives which would be used in synthesis Scheme 1. Consequently, Scheme 1 can be undertaken by a person skilled in the art, without any inventive skill, using such starting materials.
- 28 Further the applicant separately argues that the restriction of the amended claims makes it plausible that the compounds encompassed by claim 1 are Cdk5 inhibitors.
- 29 In support of this they reiterate their assertion that the Cdk5 inhibitory activity is due to the core scaffold structure, and that with the restriction in range of compounds of the amended claims, the Cdk5 inhibitory effect is plausible across this scope. They further argue that this represents a Structure Activity Relationship (SAR), this being a well understood pharmaceutical concept which allows activity to be generalised to structurally similar compounds sharing a molecular core. In support of this argument they refer to the artemisinin and its derivatives dihydroartemesinin, arteether and artemether. All these compounds share the same core scaffold and are highly effective in the treatment of malaria. This example of a SAR they assert thus makes it plausible that Cdk5 inhibitory activity is present across all the compounds of claim 1 and thus the application is also sufficiency in this respect.

Analysis

- 30 As I have set out above, the issue to be decided is whether the application is insufficient due to the breadth of the claims, as termed "Biogen insufficiency". The specification must be sufficient for the invention to be performed without undue burden and that the disclosure in the specification must enable the invention to be performed to the full extent of the monopoly claimed. The House of Lords held in *Biogen* and *Pharmacia* that when a range of compounds is claimed the specification should contain sufficient information on how to make the compounds. Further the compounds monopolized by the claim must all have the advantage or avoid the disadvantage that characterizes the selected range. In addition this requirement of sufficiency must be demonstrated at the date of filing.

- 31 The applicant in their letter of 16 March 2017 has set out in Annex 1 a possible synthetic scheme, Scheme 1, for the production of compounds according to claim 1 of the application, which they consider is rendered plausible by the teachings of the application. They argue this Scheme is also plausible because many of the different starting materials are readily available to the skilled person, either commercially or in the literature as demonstrated by the substituents shown in Figure 1 of Annex 1, even though there is no synthetic pathway disclosed in the application.
- 32 However, Scheme 1 which the applicant proposes is taken from an academic publication of Khong *et al* which was published in 2016. Furthermore, when the proposed different starting materials the applicant refers to in Figure 1 are considered, Example 1 from Jiang *et al* is from an academic publication in 2017, Example 2 from Wang *et al* was published in 2009, Example 3 from Reichi *et al* is from 2015, Example 4 from Thomas *et al* is from 2014, Example 5 from Shi *et al* is from 2016 whilst the final example, Example 6, by Guo *et al* was published in 2015.
- 33 Consequently, whether at the filing date in 2010 or at the earliest priority date of the application in 2009, neither information about Scheme 1 nor any of the proposed starting materials, apart from possibly that of Example 2, would have been available to the skilled person or formed part of their common general knowledge; this information had yet to be part of the state of the art.
- 34 When the skilled person considered the application, they would be aware from its teaching that compounds such as F199-C22 had been obtained and that these had been isolated from a plant species, *Rhodiola rosea*. The application does not teach any information or disclose any specific synthetic steps; this is admitted by the applicant in their letter of 16 March 2017. The application is also silent on those materials that would be required to start from in any synthetic scheme in order to obtain any particular variant of the core scaffold structure with a specific subset of R group substituents, for any of the three parts A, B or C identified by the applicant as forming part of the core scaffold structure. Given that neither Scheme 1 nor many of the starting materials shown in Figure 1 were known, arriving at either the scheme or any of the starting materials would represent the skilled person having to use more than just their common general knowledge to supplement the information contained in the application to arrive at the invention in respect of any of the specific substituent groups R₁-R₅. The skilled person (or team) even if aware of the latest developments in the art, could not have knowledge about a synthetic process that was not available in the prior art, especially one that depended on starting materials that themselves were not disclosed in the art either.
- 35 The applicant admits the skilled person would also then have to undertake a similar approach of alternative synthetic routes using further different starting materials to arrive at the substitution patterns for the R₇-R₁₁ substituents of Part B of the compound. The applicant in Annex 1 provides no such synthetic routes to demonstrate that these would be known to the skilled person from their common general knowledge, but asserts these would be achievable for the skilled person.
- 36 Therefore, in the light of this analysis I consider that the disclosures in the specification are not sufficient to allow the invention as defined in claim 1 on file to be performed without placing an undue burden on the skilled person. The skilled person could not use the disclosures in the specification in combination with their

common general knowledge to supplement the information in the specification to arrive at the claimed invention. As set out above both the proposed scheme that the applicant suggests the skilled person would be able to easily deduce would, in fact, involve the skilled person having to undertake significant research and invention to arrive not only at the scheme but also the starting materials, none of which were known in the prior art or common general knowledge before the priority date of the application.

37 The applicant similar argues that the desired technical property of the compounds claimed, that they inhibit Cdk5 activity, can be considered plausible on the basis of a Structure Activity Relationship (SAR). They argue that the example they provide of Artemisinin in which a range of related compounds with the same structure all have anti-malarial properties shows that this is plausible.

38 However the law as set out in *Biogen* and *Pharmacia* requires that where a Markush formula is claimed, the disclosure in the specification must enable the invention to be performed to the full extent of the monopoly claimed and all the claimed compounds must in substance have the characteristics of the class. The example of Artemisinin, an unrelated compound to those of the current invention, with a different desired technical property, shows that some compounds may well have an SAR. Whilst this may be the case, such SARs are not an inevitable consequence and necessarily predictable for all compounds and their derivatives. As I have noted above the application as filed provides support for only a single compound, F199-C22 having the desired Cdk5 inhibitory effect. As such the application does not contain any evidence to support the assertion that there is clearly an SAR arising from the Core Scaffold Structure provided in the Markush formula. The skilled person would again face an undue burden of experimentation to establish whether the desired technical feature was actually the result of a clear SAR between different compounds and not because of any other SAR from combinations of substituents not identified or characterized in the application.

Conclusion

39 Therefore, having considered the law and the disclosures in the application, it is considered not to be sufficient as required by S14(3) of the Act. The application does not allow the invention claimed to be performed over the whole scope of the invention both in respect of the range of compounds encompassed by the Markush formula and the specific technical property that the compounds claimed can all inhibit Cdk5 activity.

Possible amendments

40 I have carefully considered whether there are any amendments that can be made to the claims that would result in a grantable application to overcome the issue of sufficiency. If the claims were restricted in scope further to the single novel compound F199-C22 disclosed as being isolated from the herbal plant *Rhodiola rosea* and as defined in claim 2, then I consider the application would be sufficient as required by S14(3).

41 I therefore afford the applicant an opportunity to amend. I note that should such amended claims be filed then the application will also require amendment of the

description for clarity and consistency and in respect of the unpatentable methods of treatment. Should the amendments not place the application in order by the extended compliance date of 9 August 2017, the application will be refused for failing to comply with section 18(3).

Appeal

- 42 Any appeal must be lodged within 28 days after the date of this decision.

MRS S E CHALMERS

Deputy Director, acting for the Comptroller