EP Attorney Letter Head

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European Patent Office (Munich)
80298 Munich
Germany

Our Reference
PA/EP/2040

European Patent Application No: 16761162.3
Applicant: UNICHEM LABORATORIES LIMITED

We are writing in response to the communication pursuant to Rules 70(2) and 70a(2) EPC, dated 06.07.18.

At the outset it is confirmed that it is desired to proceed further with the subject European patent application.

In view of the objections raised in the opinion accompanying the European Search Report, we submit amended claims 1-15 as a basis for further examination. The amended claims are enclosed as a highlighted version of the claims previously on file and as a clean copy. We respectfully ask to at this point defer any amendments to the description.

I. Amendments to the Claims

Instant claim 1 corresponds to previous claim 1, amended solely to address formal issues.

New claim 2 is added to recite that the acid as used in claim 1(a) is selected from the group consisting of formic acid, acetic acid, benzoic acid, p-toluenesulphonic acid, methanesulphonic acid, phosphoric acid, pyrrophosphoric acid, polyphosphoric acid and sulphuric acid. Basis for this claim can be found in previous claim 6 and on page 10 of the application as filed.

New claim 3, referring to claim 1, is added to recite that the acid salt of piperazine is a phosphate salt. Basis for this claim can be found in previous claim 7 and throughout the application as filed.

New claim 4 is added to recite that the organic solvent as used in claim 1(e) is selected from the group consisting of water, acetone, DMF, DMSO, actonitrile, dimethyl acetamide, methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, tert-butanol and mixture(s) thereof. Basis for this claim can be found in previous claim 8 and on page 11, last paragraph of the application as filed.

Instant claim 5 corresponds to previous claim 2, amended to add the structure of formula (7) and formula (6). Basis for this amendment can be found in original claim 1 and on page 10 of the application as filed. Previous claim 2 (instant claim 5) is also amended to address formal issues.

New claim 6 is added to recite that the acid as used in claim 5(a) is selected from the group consisting of formic acid, acetic acid, benzoic acid, p-toluenesulphonic acid, methanesulphonic acid, phosphoric acid, pyrrophosphoric acid, polyphosphoric acid and sulphuric acid. Basis for this claim can be found in previous claim 6 and on page 10 of the application as filed.

New claim 7, referring to claim 5, is added to recite that the acid salt of piperazine is a phosphate salt. Basis for this claim can be found in previous claim 7 and throughout the application as filed.

New claim 8, referring to claim 5, is added to recite that the base is selected from the group consisting of triethylamine, tributylamine, N,N-diisopropylethylamine, sodium hydroxide, lithium hydroxide, potassium hydroxide, cesium hydroxide, Lithium carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, barium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, calcium bicarbonate and aqueous solution thereof. Basis for this claim can be found in previous claim 9 and on page 11, third paragraph of the application as filed.

Instant claim 9 corresponds to previous claim 3, amended to add the structure of formula (7) and formula (6). Basis for this amendment can be found in original claim 1 and on page 10

of the application as filed. Previous claim 3 (instant claim 9) is also amended to address formal issues.

New claim 10, referring to claim 9, is added to recite that the base is selected from the group consisting of triethylamine, tributylamine, N,N-diisopropylethylamine, sodium hydroxide, lithium hydroxide, potassium hydroxide, cesium hydroxide, Lithium carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, barium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, calcium bicarbonate and aqueous solution thereof. Basis for this claim can be found in previous claim 9 and on page 11, third paragraph of the application as filed.

Instant claim 11 corresponds to previous claim 4, amended to add the structure of formulas (1), (6), (3) and (7). Basis for this amendment can be found in original claim 1 and on page 10 of the application as filed. Previous claim 4 (instant claim 11) is also amended to address formal issues.

New claim 12, referring to claim 11, is added to recite that the organic solvent is selected from the group consisting of water, acetone, DMF, DMSO, actonitrile, dimethyl acetamide, methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, tert-butanol and mixture(s) thereof. Basis for this claim can be found in previous claim 8 and on page 11, last paragraph of the application as filed.

Instant claim 13 corresponds to previous claim 5, amended to add the structure of formulas (1), (6), (3) and (7). Basis for this amendment can be found in original claim 1 and on page 10 of the application as filed. Previous claim 5 (instant claim 13) is also amended to address formal issues.

Previous claim 6 is cancelled.

Instant claim 14 corresponds to previous claim 7, amended to correct its dependency and to address formal issues.

Instant claim 15 corresponds to previous claim 8, amended to correct its dependency and to address formal issues. The term “aliphatic alcohols such as” is also removed from previous claim 8.

Previous claim 9 is cancelled.

Previous claim 10 is cancelled without prejudice or disclaimer.

The dependencies and the numbering of the claims have been revised in order to be consistent with the amendments made.

As none of the above amendments comprise subject matter extending beyond the application as originally filed, they should be allowable within the meaning of Article 123(2) EPC.

II. Comments Regarding the Objections Raised in the European Search Opinion

Article 123(2) EPC:

In Item 1, the Examiner has acknowledged that the amendments as filed with our previous letter of June 20, 2017 meet the requirements of Article 123(2) EPC.

Clarity:

With regard to Item 2 of the communication, concerning the presence of multiple independent claims of the same category, i.e., present independent claims 1, 5, 9 and 13, we would like to point out that these claims each claim a partial steps of an overall process (instant claim 11) to obtain the Ranolazine compound of formula (1) when starting from 2,6-dimethyl aniline as a starting material. They are hence processes to obtain a plurality of interrelated products in the sense of R. 43 (2) (a) EPC, cf. Guidelines, Nov 2017, F.IV.3.2.(i), where "*intermediate(s) and final chemical product*" are given as example of interrelated products in the sense of R. 43 (2) (a) EPC. As such, the claims constitute alternative solutions to a particular problem, i.e., the provision of these intermediates, in the sense of R. 43 (2) (c) EPC, cf. Guidelines, F.IV.3.2.(iii), where "*two or more processes for the manufacture of such [i.e. interrelated, ed.] compounds*" are given as example of alternative solutions to a particular problem in the sense of R. 43 (2) (c) EPC.

Novelty:

The Applicant is pleased to note that the Examiner has acknowledged under Item 5 of the communication that the subject-matter of previous claims 1 to 9 is novel over the prior art of record.

With this response, previous claim 10 has been cancelled and thus the novelty objection raised against this claim no longer applies.

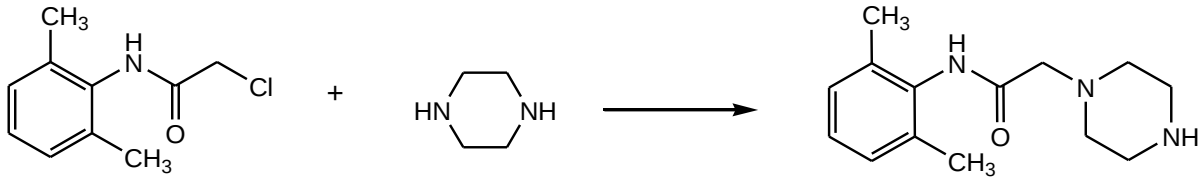
Inventive Step:

In Item 6, the Examiner stated that previous claims 1 to 9 do not meet the requirements of inventive step in light of the disclosure of document D4 in combination with the teaching of documents D1-D3. Applicant respectfully disagrees.

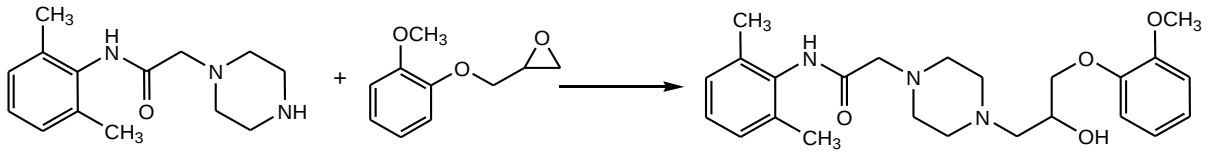
The Examiner identifies D4 as the closest prior art as D4 also discloses the synthesis of ranolazine through intermediates of present formula 6, 7 and 3.

D4 discloses in a process for preparation of ranolazine, the following reactions:

Step c): reaction of [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride with piperazine in a solvent to yield N-(2,6-dimethylphenyl)-1-piperazine acetamide (see, D4, Para [0064]):



Step d): reaction of N-(2,6-dimethylphenyl)-1-piperazine acetamide with 1-(2-methoxyphenoxy)-2,3-epoxypropane to yield ranolazine (see, D4, Para [0065]):



D4 in Example 20 describes synthesis of N-(2,6-dimethylphenyl)-1-piperazine acetamide by reaction of [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride with piperazine in methanol.

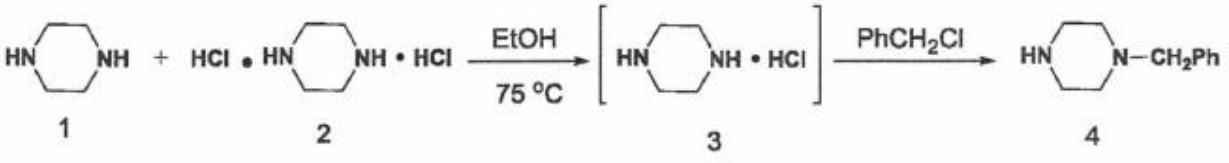
The closest prior art D4 reacts [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride (present formula 6) with piperazine to obtain N-(2,6-dimethylphenyl)-1-piperazine acetamide (present formula 7). Differing from the teachings of D4, the process recited in present independent claims 1, 5, 9, 11 and 13 requires that [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride be reacted with an acid salt of piperazine to form N-(2,6-dimethylphenyl)-1-piperazine acetamide. D4 does not disclose or suggest reacting [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride with an acid salt of piperazine to yield N-(2,6-dimethylphenyl)-1-piperazine acetamide, as required by Applicant's independent claims 1, 5, 9, 11 and 13. The Examiner cites documents D1-D3 to fill in the gap, arguing that masking of one nitrogen in piperazine by salt formation in order to achieve a more selective monoalkylation is a well known method in the art regarding the chemistry of piperaine. According to the Examiner, the skilled person starting from example 20 of D4 would have considered the general strategy as exercised in D1-D3 in order to modify the process of D4. Applicant respectfully disagrees.

It is submitted that the skilled person has no incentive to modify the process disclosed in D4. In D4, the reaction of [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride (present formula 6) with piperazine to yield N-(2,6-dimethylphenyl)-1-piperazine acetamide (present formula 7) is performed in one step, while Applicant's conversion of formula (6) to formula (7) is performed in two steps. In the first step, as claimed, Applicant reacts piperazine with an acid to yield an acid salt of piperazine and then, in subsequent step, reacts the acid salt of piperazine with formula (6) to obtain formula (7). There is no mention anywhere in D4 that including an additional reaction step of converting the piperazine to its acid salt would be beneficial. In fact, a skilled person would not have been motivated to convert a one-step process (such as the one disclosed in D4) into a two-step process in order to increase yield because usually a higher number of steps correlates to lower yields, especially in light of the low skill in chemical arts. Because no incentive or motivation exists to modify this step, it cannot be said to be obvious to modify the process of D4.

D1 discloses a process for the N-monoalkylation of piperazine, which comprises reacting a monopiperazinium salt with an alkylating agent containing up to 6 carbon atoms or an

aralkylating agent. D1 does not teach or suggest any compound of Formula 6 or Formula 7, or any method of synthesizing a compound of Formula 6 or Formula 7, or any method of synthesizing Ranolazine compound of formula (1) using any of Formula 6 or Formula 7 as an intermediate. D1 relates to compounds having different chemical structures as compared to the present invention, and there is no indication in D1 that the same reaction can be applied to compound of formula 6.

D2 discloses synthesis of N-benzyl piperazine. In D2, monobenzylation is achieved by treating anhydrous piperazine with piperazine dihydrochloride salt (2) to form an unstable piperazine monohydrochloride (3) which is then treated with benzyl chloride to yield N-benzyl piperazine (see, D2, Scheme 1).



Scheme 1

In D2, piperazine is reacted with piperazine dihydrochloride salt (2) to obtain monoacid salt of piperazine. Differing from the teachings of D2, the process recited in the independent claims requires that piperaine be reacted with an acid to yield a monoacid salt of piperazine. Thus, D2 discloses a completely different process than the process claimed in the present application. Also, the monoalkylated piperazine (**4**) formed according to the process of D2 always needs further purification, as described by the use of flash column chromatography in the experimental section (see, D2, page 471, under "Synthesis of N-benzyl piperazine (4) "). To the contrary, the use of monoacid salt of piperazine allows the Applicant to use the monoalkylated piperazine product (i.e. formula 7) in the subsequent step without purification. Clearly, the process disclosed in D2 is quite different than the claimed process and does not yield the same result. Moreover, D2 does not teach or suggest any compound of Formula 6 or Formula 7, or any method of synthesizing a compound of Formula 6 or Formula 7, or any method of synthesizing Ranolazine compound of formula (1) using any of Formula 6 or Formula 7 as an intermediate.

In D3, reaction of amide with piperazine is carried out in presence of aqueous HCl in order to minimize dialkylation of the piperazine moiety. D3 does not teach or suggest any compound of Formula 6 or Formula 7, or any method of synthesizing a compound of Formula 6 or

Formula 7, or any method of synthesizing Ranolazine compound of formula (1) using any of Formula 6 or Formula 7 as an intermediate. D3 relates to compounds having different chemical structures as compared to the present invention, and there is no indication in D3 that the same reaction can be applied to compound of formula 6. In addition, the monoalkylated product formed according to the method of D3 always needs further purification, as described by the use of column chromatography in the detailed examples (page 3343, preparation 5.1.13 and 5.1.14). In contrast, the Applicant's monoalkylation reaction with acid salt of piperazine results in a purity of the monoalkylated product (i.e. formula 7) that allows it to be used in subsequent steps without additional purification (see for example 7). It has been further mentioned on page 3335 of D3 that the monoalkylation yield varies in the range of 38-94%, thus clearly mentioning that depending upon the alkylation moiety used, the yield varies and will need to be optimized accordingly. D3 does not guarantee high yield of monoalkylation using acid salt of piperazine. On the other hand, the present application clearly demonstrates that in the case of monoalkylated product prepared in one step or carrying out all steps in one pot (examples 4 to 8) by use of piperazine phosphate salt, the yield is 80% with purity in the range of 98-99%.

Therefore, no incentive can be derived from documents D1-D3 for modifying the process of D1 in the manner as claimed.

Thus, the cited documents D1-D3 involve completely different compounds and processes--which are contrary to applicant's invention and cannot be combined in any reasonable fashion with the closest prior art document D4 to render obvious the claimed invention.

Furthermore, none of the documents D1 to D4, alone or in combination, describe the unexpected results achieved by the claimed process. The Examiner in Item 6.2 of the communication acknowledges that the claimed process imparts improved yield. Moreover, as described in the present application, Applicant's use of acid salt of piperazine minimizes or eliminates the formation of impurities (11), (12) and (13). See for example, paragraph bridging pages 15 and 16. Therefore, Applicant's reaction of [(2,6-dimethylphenyl)aminocarbonylmethyl]-chloride (formula 6) with an acid salt of piperazine results not only in a high yield but also in a purity of the product (i.e. formula 7) that allows it to be used in subsequent steps without additional purification. These unexpected and superior results weight heavily in favour of finding the claimed processes inventive.

In view of the foregoing, Applicant respectfully submits that instant independent claims 1, 5, 9, 11 and 13 are inventive and as such, instant claims 1, 5, 9, 11 and 13 are patentable over the prior art of record. Further, dependent claims 2-4, 6-8, 10, 12 and 14-15 are similarly patentable not only by virtue of their dependency from patentable independent claims, but also by virtue of the additional features of the invention they define.

In light of the arguments presented above, Applicant kindly requests that the inventive step objection be withdrawn.

III. REQUEST:

Based on the above submissions and enclosed amended claims, Applicant respectfully requests allowance of the claims and a speedy grant of the patent.

Nonetheless, should the Examiner have further issues, a Communication under Art 94(3) is requested. In order to avoid direct rejection of the present application, oral proceedings under Art 116 EPC are requested.

Sincerely yours,

Enclosures:
Marked up copy of Amended claims
Clean copy of amended claims