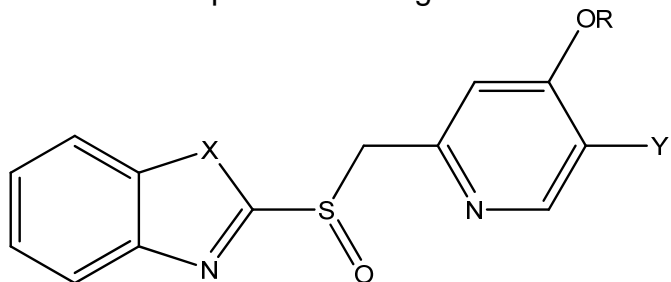


Examiners' Report Paper B 2011 (Chemistry)

Introduction

The paper relates to new compounds for the treatment of peptic ulcers. The application describes compounds of the general formula:



These compounds are very good in treating problems with peptic ulcers. From the examples it is clear that several of the compounds are useful as proton pump inhibitor and active against *Helicobacter pylori* at the same time. The efficacy for these is determined by the choice of groups R and Y in the molecule.

The official communication from the examining division cites two prior art documents. Document 1 is considered prejudicial to the novelty of claims 1-3, 5-8, whereas document 2 is considered prejudicial to the novelty of all claims.

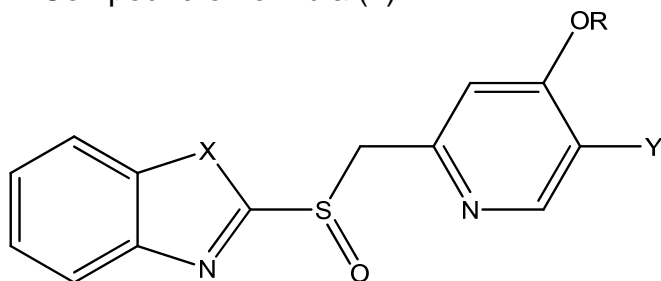
Document 1 discloses nitrogen-3-phenyl-4-dodecyl-belliake (NPDB) the same compound that is used in example 6 of the present application. NPDB is said to be a proton pump inhibitor. When mixed with antibiotics a complete product for the treatment of peptic ulcer disease is obtained.

Document 2 discloses compounds similar to the compound disclosed in document 1. X can be oxygen, sulphur or nitrogen. Furthermore, Y and R can each be alkyl, hydroxyalkyl, nitro, amine, aryl or hydrogen. Preferred compounds are those where both R and Y are alkyl groups, especially those having 6 to 10 carbon atoms. The compounds can be used for several medical applications: proton pump inhibition, angina and erectile dysfunction. The official communication further raised an objection with respect to the unity of claim 9, directed to an intermediate product of the process.

Finally, the paper included a letter from the client in which he indicates that the United States Patent Office is about to allow a set of claims in which Y is aryl having 6 to 8 carbon atoms and R is alkyl having 3 to 6 carbon atoms. The letter further indicated that protection for at least this embodiment was also sought in Europe. Finally it was mentioned that the subject-matter of claim 9 is also very important to the client.

Claims (35 marks):

1. Compound of formula (1)



in which X is chosen from NH, O, and S

R is an alkyl group having 3-6 carbon atoms

Y is an aryl group.

2. Compound according to claim 1 for use in medicine.

3. Compound according to claim 1 for use in the treatment of peptic ulcers.

25 marks were available for claims 1 to 3 together. If only a compound claim was maintained, a maximum of 15 marks were available. If only a first medical use claim was presented, a maximum of 15 marks were available. Finally, if only a second medical use claim was available, a maximum of only 10 marks were available.

Claim 1 as proposed in the client's letter contravenes Article 123(2) EPC. There is no basis for the aryl group having 6 to 8 carbon atoms. Even though the aryl groups specifically mentioned in the application as filed have 6, 7 or 8 carbon atoms (phenyl, tolyl and xylyl), this does not, of course, form a basis for a range. Candidates who kept the range of 6 to 8 carbon atoms for the aryl group lost 10 marks. Most candidates spotted this problem under Article 123(2) EPC.

Candidates who, on the other hand, limited the aryl to phenyl, xylyl and tolyl lost 5 marks, since this was too limiting. A few candidates limited the heterogroup X to one of the groups, ie NH, S or O. Candidates who did this lost 8 marks. Unity and clarity problems could in total lead to a loss of 5 marks.

Maintaining claims 3, 7, 8, and 10 was expected, but did not give any marks.

Candidates who maintained in the main application a claim to an intermediate product (claim 9, now claim 6) having the same X, Y and R as independent claim 1, received 10 marks. Candidates who proposed such a claim for a divisional application received 2 marks. Quite a few candidates deleted claim 9 to the intermediate product. In doing so they acted against the wishes of the client who clearly indicated that that claim was very important to him. Furthermore, candidates are expected to be familiar with the fundamental principles of

unity. The case of unity for intermediate products is discussed in the Guidelines C-III, candidates are expected to be aware of this.

Claims lacking novelty over the cited prior art could not attract any marks.

Candidates who had other claims that had problems in view of novelty, inventive step and/or Article 123(2) EPC could not attract full marks.

Many candidates came up with a reasonable set of claims, covering all the claims mentioned above.

A set of claims that does not fulfil the requirements of Rule 43(2) EPC cannot attract full marks, especially if one of these claims, for example, lacks novelty.

Arguments:**Basis (12 marks):**

Claim 1 is based on claims 1 and 2 as originally filed. From claim 1 Y is chosen to be aryl and R is chosen to be alkyl having 3 to 6 carbon atoms. Paragraph [0009] provides basis for the combination of R and Y groups since this paragraph shows that it is preferred that R is alkyl and Y is aryl. No marks were available for arguing the basis for claim 1 only based on paragraph [0007].

The claim suggested in the client's letter was limited to Y being an aryl group having 6 to 8 carbon atoms. As mentioned above, there is no basis for this claim. Candidates who kept the range of 6 to 8 carbon atoms for the aryl group could only get a maximum of 7 marks for their argumentation of the basis.

Claims 5 and 6 (1st and 2nd medical use claims) are now claims 2 and 3. Claims 7 to 10 are now claims 4 to 7.

Novelty (18 marks):

Document 1 discloses nitrogen, 2-phenyl, 3-dodecyl-belliake (NPDB), the same compound that is used in example 6 of the present application. NPDB is said to be a proton pump inhibitor, the same as in the present application. The compound is also mixed with up to three antibiotics, the same as mentioned in the application. When mixed with antibiotics a complete product for the treatment of peptic ulcer disease is obtained.

In claim 1 R is an alkyl group of 3 to 6 carbon atoms, whereas in D1 the group R has 12 carbon atoms (dodecyl). Claim 1 is, therefore, novel over D1.

Document 2 discloses similar compounds. X can be oxygen, sulphur or nitrogen. Furthermore, Y and R can each be alkyl, hydroxyalkyl, nitro, amine, aryl or hydrogen. Preferred compounds are those where both R and Y are alkyl groups, especially those having 6 to 10 carbon atoms. The compounds can be used for several medical applications: proton pump inhibition, angina and erectile dysfunction. The examples of document 2 do not disclose a combination of alkyl group and aryl group. All the examples disclose R and Y to be both alkyl, which is also mentioned to be the preferred embodiment in claim 2.

Present claim 1 is novel over document 2, because claim 1 provides a novel selection over this document. Looking at the general disclosure of claim 1, one would have to select for R an alkyl group of 3 to 6 carbon atoms and for Y an aryl group. These two choices provide a novel selection (see Guidelines C-IV, 9.8(i)(a)). Claim 1 is, therefore, also novel over document 2.

Summaries of D1 and D2 could give 3 marks each. Arguments for novelty over D1 could give 3 marks. Arguing novelty over D2 can give up to 7 marks, with 4 of those marks being reserved for the selection argumentation. In this case, the argument needs to be the selection from two lists. A reference to the Guidelines was not considered essential, as long as the arguments were there.

For arguments concerning the novelty of the remaining claims 2 marks were available.

Inventive step (30 marks):

Full marks are reserved for arguments correctly applying the problem-solution approach. A full reasoning for each step of the problem-solution approach is expected. It is important not to forget to justify why a particular document is selected as the closest prior art. It is also important to use the examples provided in the application to demonstrate that a technical effect is obtained and thus that the technical problem is solved.

Document 1 is considered to be the closest prior art, because it also discloses a product that can treat all aspects of peptic ulcer disease. As mentioned above, this document discloses nitrogen-3-phenyl-4-dodecyl-belliacke (NPDB). When mixed with antibiotics a complete product for the treatment of peptic ulcer disease is obtained. Justification of the choice of the closest prior art can give up to 7 marks. Document 2 could also be chosen as closest prior art. Full marks could also be obtained for this as long as the justification was properly argued.

The difference between claim 1 and document 1 lies in the fact that in claim 1 R is an alkyl group of 3 to 6 carbon atoms, whereas in D1 the group R has 12 carbon atoms (dodecyl).

The technical effect arising from this difference can clearly be seen from the examples of the present application. In fact, direct comparison with document 1 is possible because example 6 of the application shows the ppif and pdf for nitrogen-3-phenyl-4-dodecyl-belliacke (NPDB), the compound disclosed in D1.

Direct comparison can be made between example 5 and example 6, the only difference being the R group, propyl in example 5 and dodecyl in example 6. From the table it is clear that when the group R is propyl there is much more activity for pylori decrease, 79 when compared with 18 for when R is dodecyl. This large improvement in pylori decrease is achieved while maintaining a high proton pump inhibition. The ppif is 85 in example 5, whereas this is only slightly higher in example 6 with 89.

The technical effect is, therefore, that the presently claimed compound is able to achieve simultaneous proton pump inhibition and pylori decrease. In fact, the belliacke of example 5 achieves very similar peptic ulcer treatment to the compositions of document 1 where antibiotics have been added.

The objective problem can, therefore, be defined as the provision of a single component ulcer treatment. Definition of the problem using the steps above can give up to 10 marks. Of these 10 marks, 3 marks are reserved for showing that the problem has been solved.

There is no indication in document 1 that the groups Y and R could be varied. So based on document 1 only there is no indication that replacing an alkyl group of 12 carbon atoms with an alkyl group of 3 to 6 atoms could have such an effect.

The person skilled in the art will also not find any indication to the solution in document 2. Even though D2 shows that groups Y and R can be varied, the document does not give an

indication that variation of these groups could improve the pylori decrease. As a matter of fact, document 2 does not even investigate pylori decrease. The subject-matter of claim 1 therefore, also involves an inventive step.

It is credible that the effect is obtained over the whole range claimed. Examples 8 and 10 show that with varying aryl group the same effect is obtained, whereas examples 14 and 17 show that the same effects are obtained when nitrogen is replaced by oxygen or sulphur, respectively. Arguing why the subject-matter of claim 1 involves an inventive step can give up to 10 marks.

Other claims are patentable due to the patentability of claim 1. Mentioning this can give 3 marks.

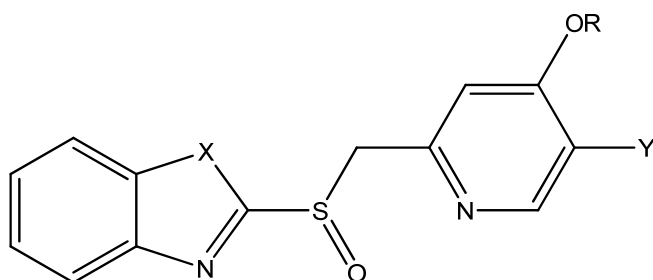
If a candidate had group R in claim 1 limited to alkyl *and hydroxyalkyl* groups having 3 to 6 atoms, arguments are expected why a hydroxyalkyl group solves the same problem as the alkyl group. Candidates who did have *hydroxyalkyl* in their claim, but did not provide separate arguments, lost 2 marks.

Unity (5 marks)

The candidates are expected to argue that the intermediate product of claim 9 is unitary with the other claims. This is clear from the Guidelines C-III, 7.3, in which the aspects of unity for intermediate products are explained. Up to 5 marks were available for this argument. A reference to the Guidelines was not considered essential, as long as the arguments were there.

Claims:

1. Compound of formula (1)



in which X is chosen from NH, O, and S

R is an alkyl group having 3-6 carbon atoms

Y is an aryl group.

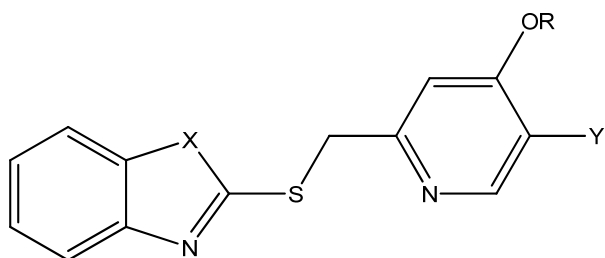
2. Compound according to claim 1 for use in medicine.

3. Compound according to claim 1 for use in the treatment of peptic ulcers.

4. Composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

5. Tablet comprising the composition of claim 4.

6. Compound of formula (c):



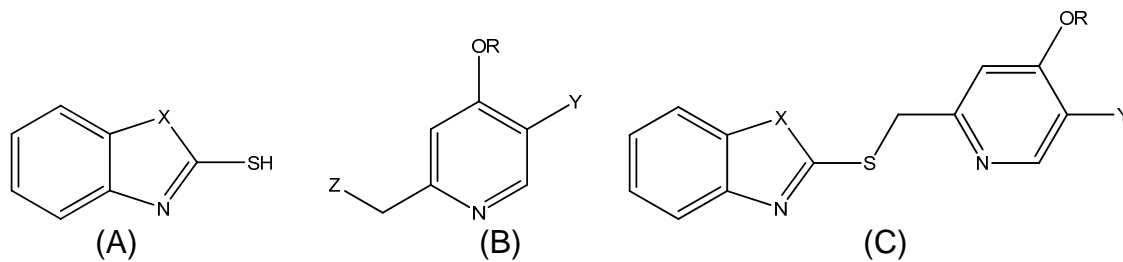
in which X is chosen from NH, O, and S

R is an alkyl group having 3-6 carbon atoms

Y is an aryl group.

7. Process for making the compound of claim 1 comprising the steps of reacting compound A with compound B at a temperature of -78 to 0°C in a solvent in the presence of a base having a pK_a of greater than 13 such as n-butyl lithium, potassium t-butoxide, lithium diisopropylamide, lithium diethylamide and sodium hydride in a solvent selected from

ethoxyethane, tetrahydrofuran and dimethyl formamide, forming compound C, compound A being oxidised with an oxidising agent selected from t-butyl hydroperoxide, peracetic acid, pyridinium chlorochromate and using dichloromethane, chloroform or toluene as a solvent, the compounds A, B and C being as defined below



EXAMINATION COMMITTEE I

Candidate No.

Paper B (Chemistry) 2011 - Marking Sheet

Category		Maximum possible	Marks awarded	
			Marker	Marker
Claims	Compound / medical uses	25		
	Intermediate compound	10		
Arguments	Amendments	12		
	Novelty	18		
	Inventive Step	30		
	Unity	5		
Total		100		

Examination Committee I agrees on marks and recommends the following grade to the Examination Board:

PASS
(50-100)

COMPENSABLE FAIL
(45-49)

FAIL
(0-44)

30 June 2011

Chairman of Examination Committee I