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* Annex 1
  Patent application
  2011/B(Ch)/EN/1-12

* Annex 2
  Communication
  2011/B(Ch)/EN/13-14

* Annex 3
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  2011/B(Ch)/EN/15-16

* Annex 4
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* Annex 5
  Letter from the applicant
  2011/B(Ch)/EN/21
Compositions and their uses in medicine

[0001] The present application concerns new compounds that are very useful in the treatment of peptic ulcers, also known as stomach ulcers. The application is also directed to the uses of these compounds and to a method of their production. The application also describes compositions in which these compounds are used.

[0002] Between 10 and 15 percent of the world's population suffer from peptic ulcers, more commonly known as stomach ulcers. A peptic ulcer is a lesion that occurs primarily in the mucous membrane of the stomach or duodenum (the upper segment of the small intestine); it is produced when external factors reduce the ability of the mucosal lining to resist the acidic effects of gastric juice (a mixture of digestive enzymes and hydrochloric acid). Until recently the factors responsible for peptic ulcers remained unclear; a stressful lifestyle and an unhealthy diet were commonly blamed.

[0003] Treatment of peptic ulcers has seen tremendous progress since the 1970’s. Previously, bed rest and ingestion of alkaline compounds (for example calcium salts, magnesia and carbonates) comprised the standard treatment.

[0004] Nowadays proton pump inhibitors are used. They cure almost 100% of the cases within four weeks of treatment by preventing acid from being generated in the stomach.

[0005] It was realised recently that the bacteria *Helicobacter pylori* adversely influence peptic ulcer complaints. Treatment has been improved by combining the proton pump inhibitor with antibiotics to kill the bacteria.
[0006] Even though the current drugs for treating peptic ulcers give reasonable results, there is still room for improvement. We have now come up with a new class of compounds that is very useful in the treatment of peptic ulcers. The compounds can be used on their own, mixed with each other or mixed with, for example, antibiotics.

[0007] The new compounds have the following general formula (Formula 1).

![Formula 1]

(FORMULA 1)

The general structure has been given the non-official name belliake. So, if for example, X is NH and R is dodecyl and Y is phenyl, the compound will be called nitrogen-3-phenyl-4-dodecyl-belliake, in which dodecyl is an alkyl group with 12 carbon atoms. The substituents Y and R have a strong influence on the properties, although all compounds falling within this general formula exhibit activity for the treatment of peptic ulcers. Also X can be varied, which also influences the activity. The substituents R and Y can be independently chosen from alkyl groups, aryl groups and hydroxyalkyl groups. The alkyl chain of the alkyl group and the hydroxyalkyl group can have 3 to 20 carbon atoms, preferably 3 to 6 carbon atoms. The aryl groups may be chosen from phenyl, i.e. -C₆H₅; tolyl, i.e. -C₆H₄CH₃ and xylyl, i.e. -C₆H₃(CH₃)₂. The alkyl groups may be chosen from methyl, i.e. -CH₃; propyl, i.e. -C₃H₇; hexyl, i.e. -C₆H₁₃; octyl, i.e. -C₈H₁₇ and dodecyl, i.e. -C₁₂H₂₅. X is chosen from NH, S and O.
[0008] The compounds of the present invention are produced by reaction of compounds A and B at a temperature of -78 to 0ºC in the presence of a base having a pKa 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 (THF) and dimethyl formamide. Compound A is commercially available for example from Zetar Inc. The synthesis of compound B is described in the literature (see H. Plieninger and I. Nogradi, Chem. Ber. 88, 1964 (1955)).

[0009] The product of the reaction, compound C, is then oxidised with an oxidising agent selected from t-butyl hydroperoxide, peracetic acid, m-chloroperbenzoic acid and pyridinium chlorochromate. As a solvent dichloromethane, chloroform or toluene can be used. Typical reaction temperatures are 0 to 30ºC.

With different combinations of X and the groups R and Y, the properties of the compounds can be tailored. Z is a leaving group chosen from Br, I, tosylate and mesylate. This becomes clear from the examples that are given below. It is preferred that group R is an alkyl group of 3 to 20, preferably of 3 to 6 carbon atoms. For group Y, very good results are obtained if this group is an aryl group.
[0010] Dependent on the activity of the compounds *per se* other components may be added to the composition to make a complete treatment of peptic ulcers possible. In case the proton pump inhibition is not sufficient, a further proton pump inhibitor may be added. Such proton pump inhibitors are well-known in the art. An antibiotic may be added when the activity for removing *Helicobacter pylori* is needed. These antibiotics are also known and are readily available to the person skilled in the art.

[0011] As with most medication, side-effects are often present. For the belliae compounds these side effects are mainly headache and dizziness. However, by careful selection of the groups R and Y, these side-effects can be minimised. Especially compounds in which R and Y are alkyl groups have minimal side effects.

[0012] The compounds are, of course, not used as such but as tablets. Methods known in the art are used to make such tablets, for example by mixing the ingredients and then pressing them in a tablet press. The ingredients comprise, together with the active agent or agents, a binder, lubricants, disintegrants (to ensure that the tablet breaks up in the digestive tract) and sweeteners or flavours. All these are well-known to the person skilled in tablet production.

[0013] In order to optimise the effectiveness for peptic ulcer treatment, it may be necessary to add a proton pump inhibitor and/or one or more antibiotics. As proton pump inhibitor any known inhibitor in the art can be used, for example rabeprazole. Also the antibiotic that is useful to use with the compounds of the present invention is not limited, as long as it is active against *Helicobacter pylori*. Examples of suitable antibiotics are amoxicillin, clarithromycin and metronidazole. Antibiotics can be used alone or in mixtures. If any of these components are added, they are added in the same tablet as the compound of the invention.
Examples:

[0014] In the following examples several compounds of the Formula 1 have been synthesised. X, Y and R have been varied in order to study the variations in activities of these compounds.

![Formula 1]

The procedure described above was used to synthesise these compounds. For all compounds the same procedure was used. This is shown in the following preparation example:

**PREPARATION EXAMPLE**

Preparation of 2-[4-pentyloxy-5-phenyl-pyrid-2-yl]-methylthiobenzimidazole, hereinafter referred to as “desoxy-nitrogen-3-phenyl-4-pentyl-belliake”

15 g (0.1 mol) of 1H-benzimidazole-2-thiol (Formula A1) (obtained from Zetar Inc.)

![Formula A1]

was dissolved in dry THF (200 ml) at 0°C under nitrogen. n-Butyl lithium 0.1 mol (50 ml of 2M solution) in THF was added dropwise with stirring.
42.5 g (0.1 mol) of 2-Tosyloxymethyl-4-pentyloxy-5-phenylpyridine (Formula B1) (obtained from Zetar Inc.) dissolved in THF (100 ml) was added dropwise with stirring. After stirring for an hour the mixture was poured into water (500 ml) and extracted with ethyl acetate (3 x 2500 ml). The ethyl acetate extracts were dried over magnesium sulphate. The ethyl acetate was evaporated and the solid residue recrystallised from ethyl acetate/hexane (60/40) to yield 2-[4-pentyloxy-5-phenyl-pyrid-2-yl]-methylthiobenzimidazole or “desoxy-nitrogen-3-phenyl-4-pentyl-belliake” (Formula C1).

20.3 g as colourless plates; melting point 146-147°C.

Elemental analysis: Calculated: C 71.4%, H 6.2%, N 10.4%, S 7.9%
Found: C 71.3%, H 6.2%, N 10.5%, S 8.0%

Preparation of nitrogen-3-phenyl-4-pentyl-belliake

To a solution of 20.2 g (0.05 mol) of “desoxy-nitrogen-3-phenyl-4-pentyl-belliake” (Formula C1) in chloroform (200 ml) at 0°C was added dropwise a solution of 9.5 g (0.055 mol) m-chloroperbenzoic acid dissolved in chloroform.
After stirring for 30 minutes the solution was washed with saturated sodium bicarbonate solution (100 ml), dried over magnesium sulphate and concentrated.

The residue was recrystallised from acetone/isopropyl ether to give "nitrogen-3-phenyl-4-pentyl-belliake" (Formula 1a).

![Formula 1a](image)

18.9 g as pale yellow needles; melting point 170-171°C.

Elemental analysis:
- Calculated: C 68.7%, H 6.0%, N 10.0%, S 7.6%
- Found: C 68.9%, H 5.9%, N 10.0%, S 7.6%

[0015] In order to test the activity, the compounds were formed into tablets. The activities given in the tables are expressed in the well-known proton pump inhibition factor (ppif) and the pylori decrease factor (pdf), the decrease of the bacteria *Helicobacter pylori*. Both factors were devised by Sir Rennie Gaviscon, they are widely accepted in the field and are described in Journal of Microbiology and Biotechnology 2, 106-114, (1978). Both factors are dimensionless and vary from zero to 100, with 100 being complete proton pump inhibition and *H. pylori* elimination respectively.
Examples 1 to 17:

[0016] In examples 1 to 11 a large number of compounds in which the group X is NH are synthesised. These compounds are tested for their efficiency in the treatment of peptic ulcers.

Table 1: Nitrogen-belliakes tested for proton pump inhibition and *Helicobacter pylori* decrease

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>Proton pump inhibition factor (ppif)</th>
<th>Pylori decrease factor (pdf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>example 1</td>
<td>NH</td>
<td>methyl</td>
<td>propyl</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>example 2</td>
<td>NH</td>
<td>methyl</td>
<td>phenyl</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>example 3</td>
<td>NH</td>
<td>octyl</td>
<td>dodecyl</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>example 4</td>
<td>NH</td>
<td>octyl</td>
<td>phenyl</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>example 5</td>
<td>NH</td>
<td>phenyl</td>
<td>propyl</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>example 6</td>
<td>NH</td>
<td>phenyl</td>
<td>dodecyl</td>
<td>89</td>
<td>18</td>
</tr>
<tr>
<td>example 7</td>
<td>NH</td>
<td>phenyl</td>
<td>phenyl</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>example 8</td>
<td>NH</td>
<td>xylyl</td>
<td>propyl</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>example 9</td>
<td>NH</td>
<td>xylyl</td>
<td>dodecyl</td>
<td>85</td>
<td>20</td>
</tr>
<tr>
<td>example 10</td>
<td>NH</td>
<td>toyl</td>
<td>propyl</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>example 11</td>
<td>NH</td>
<td>toyl</td>
<td>hexyl</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

[0017] As can be seen, some of the belliakes are excellent proton pump inhibitors, whereas others are very good in decreasing the amount of *H. pylori*. Some of the belliakes have good activity in both.

[0018] Similar, but less extensive tests, were also performed for belliakes in which the group X is O and S. The results of these experiments are given in tables 2 and 3.
Table 2: Oxygen-belliakes tested for proton-pump inhibition and *Helicobacter pylori* decrease

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>Proton pump inhibition factor (ppif)</th>
<th>Pylori decrease factor (pdf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>example 12</td>
<td>O</td>
<td>methyl</td>
<td>propyl</td>
<td>15</td>
<td>69</td>
</tr>
<tr>
<td>example 13</td>
<td>O</td>
<td>octyl</td>
<td>dodecyl</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>example 14</td>
<td>O</td>
<td>phenyl</td>
<td>propyl</td>
<td>79</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 3: Sulphur-belliakes tested for proton pump inhibition and *Helicobacter pylori* decrease

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>Proton pump inhibition factor (ppif)</th>
<th>Pylori decrease factor (pdf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>example 15</td>
<td>S</td>
<td>methyl</td>
<td>propyl</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>example 16</td>
<td>S</td>
<td>octyl</td>
<td>dodecyl</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>example 17</td>
<td>S</td>
<td>phenyl</td>
<td>propyl</td>
<td>88</td>
<td>76</td>
</tr>
</tbody>
</table>
Example 18:

[0019] In the following example, compositions are tested that contain combinations of belliake and an antibiotic in order to optimise the properties. As antibiotics amoxicillin and/or metronidazole are used. As compound according to the invention nitrogen-3-phenyl-4-dodecyl-belliake is used. This compound has been chosen because it has the highest proton pump inhibition factor. Varying amounts of antibiotics are used. The ratio of these antibiotics is also varied.

Table 4: Compositions of nitrogen-3-phenyl-4-dodecyl-belliake (NPDB) with different amounts of amoxicillin and/or metronidazole.

<table>
<thead>
<tr>
<th></th>
<th>NPDB (wt.%)</th>
<th>amoxicillin (wt.%)</th>
<th>metronidazole (wt.%)</th>
<th>ppif</th>
<th>pdf</th>
</tr>
</thead>
<tbody>
<tr>
<td>composition A</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>composition B</td>
<td>50</td>
<td>0</td>
<td>50</td>
<td>88</td>
<td>67</td>
</tr>
<tr>
<td>composition C</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>composition D</td>
<td>33.3</td>
<td>33.3</td>
<td>33.3</td>
<td>77</td>
<td>90</td>
</tr>
</tbody>
</table>

[0020] From this table it is apparent that by mixing NPDB and one or two antibiotics, compositions with good proton pump inhibition and *Helicobacter pylori* decrease can be obtained. The NPDB does not seem to influence the activity of the antibiotics, nor do the antibiotics influence the activity of the NPDB.
Claims

1. Compound of formula (1)

\[
\begin{align*}
\text{in which} & \quad X \text{ is chosen from NH, O and S} \\
& \quad R \text{ is chosen from aryl, alkyl and hydroxyalkyl} \\
& \quad Y \text{ is chosen from aryl, alkyl and hydroxyalkyl.}
\end{align*}
\]

2. Compound according to claim 1 in which the alkyl and hydroxyalkyl-groups have 3 to 20 carbon atoms, preferably 3 to 6 carbon atoms.

3. Compound according to claim 1 in which the aryl group is chosen from phenyl, xylyl and tolyl.

4. Compound according to claim 2 in which both groups R and Y are alkyl.

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

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

7. Composition comprising the compound of claims 1 to 4 and a pharmaceutically acceptable excipient.

8. Tablet comprising the composition of claim 7.
9. Compound of formula (C):

![Chemical Structure]

in which  
X is chosen from NH, O and S  
R is chosen from aryl, alkyl and hydroxyalkyl  
Y is chosen from aryl, alkyl and hydroxyalkyl.

10. Process for making the compound of claim 1 comprising the steps of: (1) reacting compound A with compound B at a temperature of -78 to 0ºC in the presence of a base having a pKa 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; and (2) oxidising compound C with an oxidising agent selected from t-butyl hydroperoxide, peracetic acid, m-chloroperbenzoic acid and pyridinium chlorochromate, using dichloromethane, chloroform or toluene as a solvent, the compounds A, B and C being as defined below:

![Chemical Structures]

and where Z is a leaving group chosen from Br, I, tosylate and mesylate.
Annex 2 (Communication)

1. Document 1 discloses nitrogen-3-phenyl-4-dodecyl-belliaka (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 ulcers is obtained. Claims 1-3 and 5-8 therefore lack novelty over document 1 (Articles 52(1), 54(1) and (2) EPC).

2. Document 2 discloses similar compounds to those disclosed in document 1. X can be O, S or NH. Furthermore, Y and R can independently be alkyl, hydroxyalkyl, nitro, amine, aryl or halogen. The compounds are used in medicine. Specific mention is made of their use as proton pump inhibitor. Claims 1-10 therefore lack novelty over document 2 (Articles 52(1), 54(1) and (2) EPC).

3. *Prima facie* claim 9 seems non-unitary with claims 1 to 8, contrary to Article 82 EPC. Claims 1 to 8 are directed to compounds and compositions having a biological activity (for treating peptic ulcers), whereas the compound of claim 9 does not exhibit such activity. There is, therefore, no general inventive concept linking these two inventions.

4. If the applicant wishes to maintain the application, new claims should be filed which take the above objections into account. Care should be taken to ensure that the new claims comply with the requirements of the EPC in respect of clarity, novelty, inventive step and if necessary unity (Articles 84, 54, 56 and 82 EPC). Care should further be taken that any amendments do not introduce subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).
5. In the letter of reply, the difference between the new claims and the prior art disclosed in the documents 1 and 2 and its significance should be indicated. The technical problem underlying the invention in view of the closest prior art and the solution to this problem should be readily derivable from the statement of the applicant (Rule 42(1)(c) EPC and EPO Guidelines, C-IV, 11.5).

6. In order to facilitate the examination as to whether the new claims contain subject-matter which extends beyond the content of the application as originally filed, the applicant is requested to indicate precisely where in the application documents any amendments proposed find a basis (Article 123(2) EPC and Rule 137(4) EPC).
Peptic ulcers are a very common disease worldwide. A lot of research has been done to find treatments for this disease. It is now certain that in order to treat this disease effectively one needs to prevent acid from being generated by use of a proton pump inhibitor and one needs to eliminate the bacteria *Helicobacter pylori*.

In our laboratories we have synthesised a new compound that we have found to be very useful as a proton pump inhibitor. The compound is a special member of the family of belliake compounds that already have been described in a patent application (document 2). This specific belliake compound, nitrogen-3-phenyl-4-dodecyl-belliake (NPDB), has a much higher proton pump inhibition activity than any of the other compounds from the same family.

This article will show the usefulness of this compound in proton pump inhibition and also in tablets for complete treatment of peptic ulcers. In these tablets the NPDB is mixed with a group of antibiotics. In doing so, a medicine is obtained that can address all symptoms of peptic ulcers.

Tests have been performed in which the NPDB compound is combined with three different antibiotics, separately or in mixtures. The three antibiotics are amoxicillin, clarithromycin and metronidazole: well known for their effectiveness against *Helicobacter pylori*. These tests show that some combinations can treat both symptoms of peptic ulcers very effectively. In these tests the well-known Rennie parameters are used, the ppif (proton pump inhibition factor) and the pdf (pylori decrease factor).
Table 1: Compositions of nitrogen-3-phenyl-4-dodecyl-belliake (NPDB) with different amounts of amoxicillin, clarithromycin and metronidazole.

<table>
<thead>
<tr>
<th></th>
<th>NPDB (wt.%)</th>
<th>AMOX (wt.%)</th>
<th>CLAR (wt.%)</th>
<th>METR (wt.%)</th>
<th>ppif</th>
<th>pdf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixture A</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>Mixture B</td>
<td>50</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>Mixture C</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>88</td>
<td>67</td>
</tr>
<tr>
<td>Mixture D</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>0</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>Mixture E</td>
<td>50</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>Mixture F</td>
<td>50</td>
<td>0</td>
<td>25</td>
<td>25</td>
<td>88</td>
<td>70</td>
</tr>
<tr>
<td>Mixture G</td>
<td>50</td>
<td>16.7</td>
<td>16.7</td>
<td>16.6</td>
<td>90</td>
<td>93</td>
</tr>
</tbody>
</table>

As can be seen from this table, the proton pump inhibition is good in all of the mixtures. The high proton pump inhibition is hardly influenced by the presence of the antibiotics. The presence of several antibiotics has a clear effect on the *Helicobacter pylori* decrease. The most effective product is obtained when all three antibiotics are mixed.

**Conclusions**

We have found that nitrogen-3-phenyl-4-dodecyl-belliake (NPDB) is an extremely useful proton pump inhibitor for use in the treatment of peptic ulcers. When it is mixed with amoxicillin, clarithromycin and metronidazole antibiotics, very good products for treatment of peptic ulcers are obtained.
The present application is concerned with a completely new class of compounds that seems very useful in a large number of applications, mostly medical. These compounds have the following general formula:

![Diagram of a compound]

The variables in these compounds are $X$ and the groups $R$ and $Y$. $X$ can be NH, S or O. The $R$ and $Y$ groups can be the same or different and can be chosen from a large number of substituents: alkyl, hydroxyalkyl, nitro, amine, aryl or halogen. The alkyl and hydroxyalkyl groups should have a length of 3 to 30 carbon atoms, preferably 6 to 10 carbon atoms. They can be either branched or linear. The aryl groups are preferably phenyl, xylyl and tolyl.

Preferred compounds are those where both $R$ and $Y$ are alkyl groups, especially those having 6 to 10 carbon atoms.

We propose to call the general structure of these compounds belliake. This means that if, for example, $X$ is NH and $R$ and $Y$ are phenyl, the compound will be called nitrogen-3,4-diphenyl-belliake.
These compounds can be synthesised using the following process. Compounds A and B are reacted at a temperature of -78 to 0°C in the presence of a base having a pKa 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. Z is a leaving group chosen from Br, I, tosylate and mesylate. The product C of the reaction of A and B is then oxidised with an oxidising agent chosen from hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid and sodium hypochlorite in a solvent. As a solvent, chloroform, benzene, toluene or lower alcohols can be used. The oxidation process can be performed at temperatures from -50 to 25°C. Most of the different possible compounds A and B are commercially available. If not, they can easily be synthesised by the person skilled in the art from available compounds.

The compounds have been tested for several medical applications. The most promising application seems to be that some of these compounds can function as a proton pump inhibitor in the treatment of peptic ulcers. A proton pump inhibitor is a compound that prevents generation of protons and is one of the important treatments for peptic ulcers. The compounds also show promise for the treatment of angina and erectile dysfunction.
Example:

[0007] In order to test these activities the compounds were formed into tablets. Some of the compounds have been tested for their effectiveness as proton pump inhibitors. The ppif (proton pump inhibition factor) was determined for these compounds.

Table 1: Proton pump inhibition of some of the compounds of the present invention.

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>Proton-pump inhibition (ppif)</th>
</tr>
</thead>
<tbody>
<tr>
<td>example 1</td>
<td>NH</td>
<td>hexyl</td>
<td>propyl</td>
<td>45</td>
</tr>
<tr>
<td>example 2</td>
<td>NH</td>
<td>octyl</td>
<td>dodecyl</td>
<td>60</td>
</tr>
<tr>
<td>example 3</td>
<td>NH</td>
<td>octyl</td>
<td>octyl</td>
<td>73</td>
</tr>
<tr>
<td>example 4</td>
<td>NH</td>
<td>dodecyl</td>
<td>dodecyl</td>
<td>65</td>
</tr>
</tbody>
</table>

From table 1 it is apparent that some of the compounds are very useful as proton pump inhibitors.
Claims

1. Compound of formula:

\[ \text{OR} \]

\[ \text{N} \]

\[ \text{S} \]

\[ \text{Y} \]

in which

\( X \) is chosen from NH, O and S

\( R \) is chosen from alkyl, hydroxyalkyl, nitro, amine, aryl or halogen

\( Y \) is chosen from alkyl, hydroxyalkyl, nitro, amine, aryl or halogen.

2. Compound according to claim 1 in which both \( R \) and \( Y \) are alkyl groups having from 3 to 30 carbon atoms.

3. Compound according to claims 1 and 2 for use in medicine.

4. Compound according to claims 1 and 2 used for as a proton pump inhibitor.

5. Compound according to claims 1 and 2 for use in the treatment of angina.

6. Compound according to claims 1 and 2 for use in the treatment of erectile dysfunction.
Dear Mr. Attorney,

Further to our discussion of February 21, 2011 we herewith provide you with comments and instructions relating to the Communication of the EPO, dated 23 August 2010. As you have explained, today is the very last day to respond. Today is our annual company trip to Honolulu, so we cannot be reached for further instructions.

We would like to bring to your attention that the United States Patent Office (USPTO) is about to allow the equivalent application. Before the USPTO, we have limited our claims to Y being aryl having 6 to 8 carbon atoms and R being alkyl having 3 to 6 carbon atoms. We are aware of the fact that there are substantial differences between the US patent system and the European patent system. Nevertheless, we would like you to try to at least obtain protection for that embodiment in Europe as well. We would like to inform you that protection for the subject-matter of claim 9 is also very important to us.

Please use the above to prepare and file a suitable response today. As you are aware, we are not prepared to pay any claim fees upon grant.

Yours sincerely,

R. de Medici,
Ulceron PLC