NOVEL MEDICAL USE

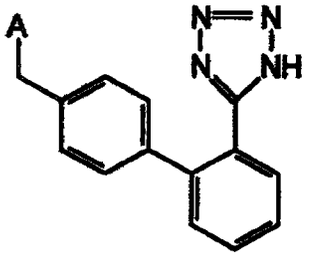
Field of the invention

The present invention is related to the use of angiotensin II type 1 receptor antagonists for the prophylaxis and/or treatment of dyspeptic symptoms and to the manufacture of pharmaceutical preparations with effects on dyspeptic symptoms.

Background of the invention

Angiotensin II type 1 receptor antagonists for which the present invention has found a new medical use are known in the art. However, nothing has been reported or is generally known concerning the pharmacological and/or therapeutic properties of these compounds with respect to effects on dyspeptic symptoms.

In connection with the present invention an angiotensin II type 1 receptor antagonist of the general formula I is employed:



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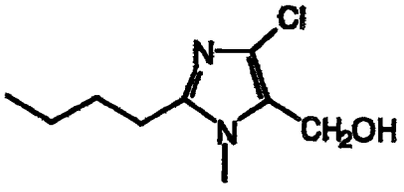

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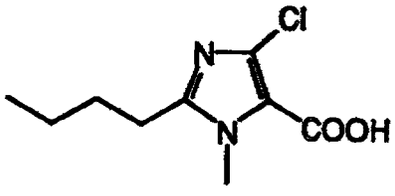

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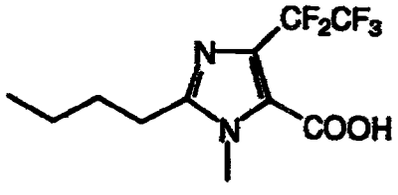

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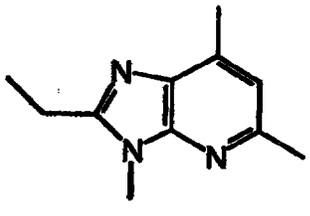

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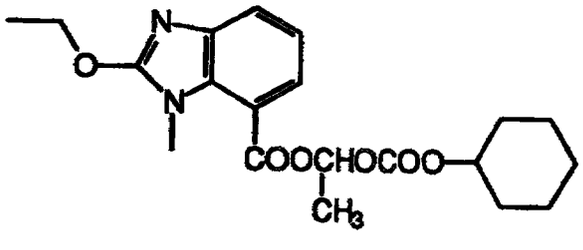

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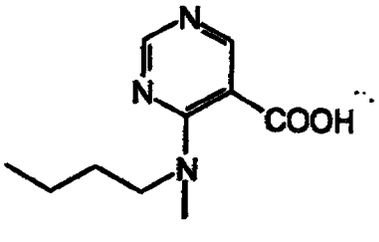

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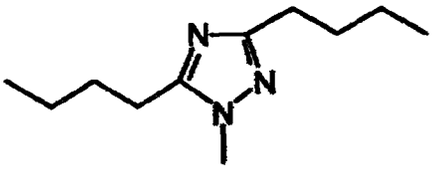

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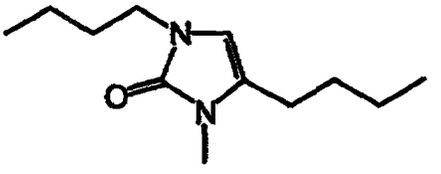

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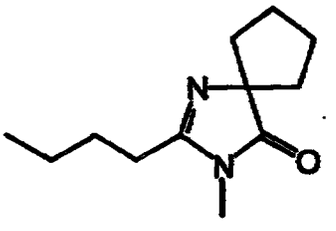

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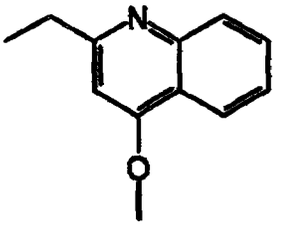

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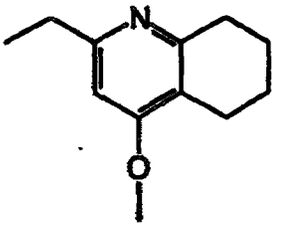

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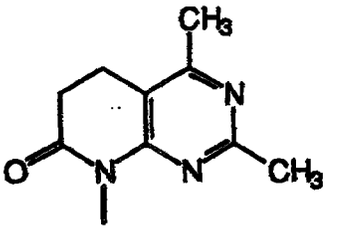

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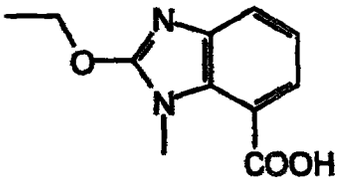

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The compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer; they may be used in neutral form or in the form of a salt, preferably a physiologically acceptable salt such as sodium, potassium, ammonium, calcium or magnesium. Where applicable the compounds listed above can be used in hydrolysable ester form.

The compound of the formula I wherein A is the I:1 moiety has the generic name losartan and is known from European patent no 253 310.

The compound of the formula I wherein A is the I:5 moiety has the generic name candesartan cilexetil, code no TCV-116 and is known from EP-459 136.

The compound of the formula I wherein A is the I:9 moiety is known from under the generic name irbesartan.

The compound of the formula I wherein A is the I:13 moiety has the generic name candesartan and is known from EP-459 136.

Functional disorders of the gastrointestinal tract are common and accounts for a very large number of medical consultations. On an annual basis approximately 30% of a western population experience such dyspeptic symptoms varying from mild indigestion to severe pain. The symptomatology may be due to an organic disease (for example peptic ulcer disease) or, more commonly, be without any known origin (i.e. absence of organic pathology in the upper gut as evidenced by various diagnostic procedures). In clinical

routine the latter symptom-syndrome is commonly called "non-ulcer dyspepsia", "functional dyspepsia", "non organic dyspepsia" etc. Treatment of dyspepsia of unknown origin involves a variety of pharmacological principles (i.e. neutralization of gastric acidity, drugs affecting the motility of the gut wall etc.) some of which having doubtful efficacy and sometimes with severe side effects.

Dyspepsia due to peptic ulcers can be cured by intake of antacids and inhibitors of gastric acid secretion. Ulcer-like dyspeptic symptoms without mucosal pathology, are usually also sensitive to a similar treatment. This subpopulation of dyspeptic symptoms (acid related dyspepsia) is thus defined by the symptom-relief in association with intake of neutralizing agents or inhibition of gastric acid production by use of proton pump inhibitors or histamine type2-receptor antagonists. However the former principle is shortlasting and neutralizing drugs must thus be administered repeatedly during the day. The latter drugs have disadvantages of being expensive and exert a great impact on gut physiology as the antacid gastric conditions increase the risk for intestinal and/or systemic infections. Prokinetic drugs (such as cisapride a o) or anticholinergic compounds are other pharmaceutical principles that are utilized for dyspeptic symptoms, usually with variable effect and high frequency of side effects. It follows that available drug regimens for treating dyspeptic symptoms are impaired by serious disadvantages.

Compounds that interfere with the renin-angiotensin system (RAS) are well-known in the art and are used to treat cardiovascular diseases, particularly arterial hypertension and cardiac failure. Principally, the RAS can be interfered with by inhibition of the enzymes synthesizing angiotensins or by blocking receptors at the effector sites. Available today are renin-antagonists, inhibitors of the angiotensin converting enzyme (ACE) and angiotensinII-receptor (AII-receptor) antagonists. In addition to cardiovascular effects, some of these compounds have been claimed to excert effects on unspecified "gastrointestinal disorders".

Disclosure of the invention

The exact mechanisms behind acid related complaints form the upper gastrointestinal tract are today unknown. A prerequisite is however that luminal acid get access to the superficial mucosal cells. This is not the case during normal conditions, as a continous transport of fluid and bicarbonate provides a neutral compartment at the mucosal surface. This important acid neutralizing process is governed by a complex network of different regulatory mechanisms.

The invention describes a new method to treat dyspeptic symptoms by modulating the gastroduodenal mucosal surface-neutralizating capacity, by pharmacological interference with RAS.

Renin-angiotensin system (RAS):

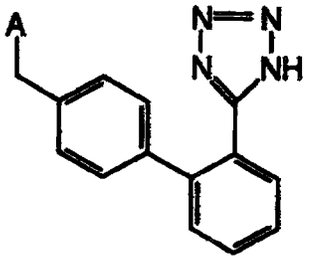
It is known that RAS, in concert with the sympathetic nervous system decreases the gastroduodenal acid neutralizating capacity. As will be clear form above, several different methods can be used in order to interfere with RAS.

It has now surprisingly been found that pharmacological blockade of specific AII type 1 receptors with angiotensin II type receptor antagonists, reversed the inhibitory effects of AII to enhancement of gastroduodenal acid neutralizing capacity. Thus, elevated plasma AII concentrations in presence of angiotensin II type 1 receptor blockade strengthens surface neutralizating capacity, in turn eliminating one prerequisite for the induction of symptoms by luminal acid.

The present application discloses that administration of specific AII type 1 receptor blockers, via an improved gastroduodenal mucosal acid neutralizating capacity, are useful in order to treat dyspeptic symptoms.

The present invention thus relates to a new method of treating dyspepsia by pharmacological interference with the renin-angiotensin system using known compounds of the general formula I above.

Thus, it has now unexpectedly been found that compounds of the general formula I



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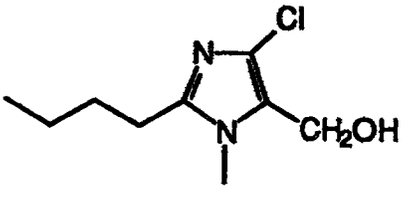

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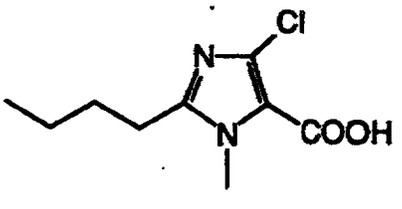

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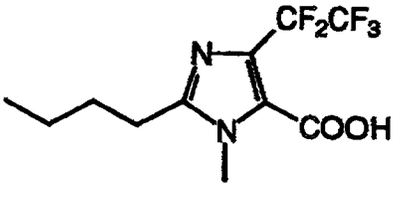

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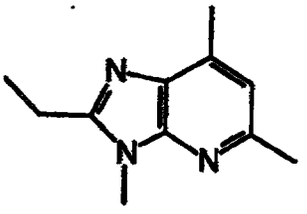

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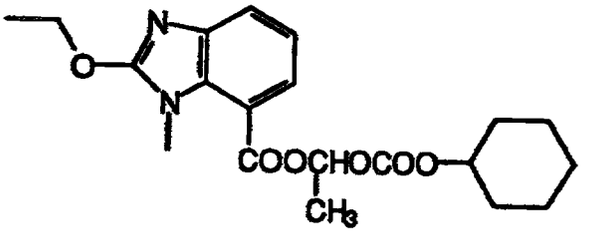

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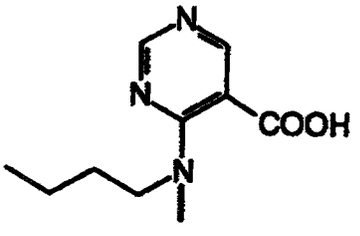

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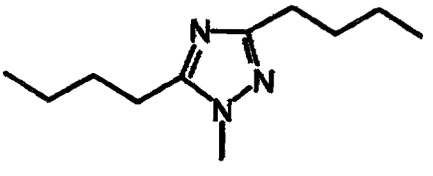

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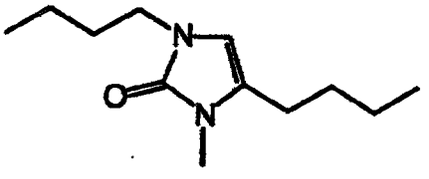

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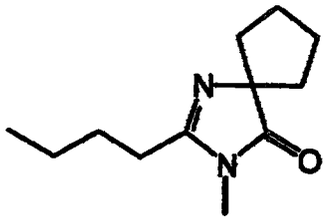

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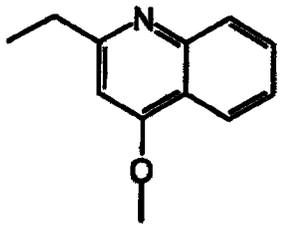

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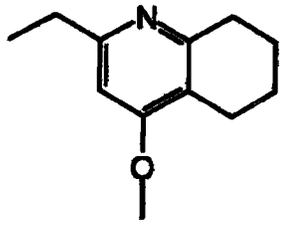

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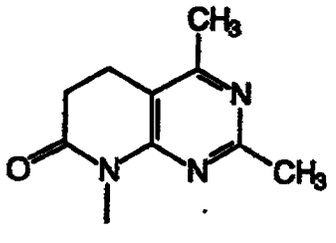

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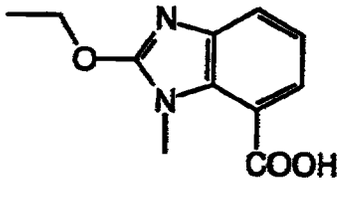

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or a physiologically acceptable salt and/or a stereochemical isomer thereof are effective in the prophylaxis and/or treatment of dyspeptic symptoms.

While the effects on gastroduodenal acid neutralizating capacity have been established in animals by the intravenous route, it is believed that the effect is a systemic effect which is not dependent on what mode of administration that is used, and accordingly the effect will be seen also with other routes of administration such as rectal or oral administration.

The dose of a compound according to formula I to be administered at prophylaxis and/or treatment of dyspeptic symptoms will vary depending on factors such as the severity of the disease and the status of the patient. The dosage range at oral, rectal as well as intravenous administration will be in the interval from 1 to 500 mg per day.

The preferred mode of the invention is the use of a compound of the formula I wherein A is I:1 (Losartan) or I:5 (T CV-116).

Scientific tests

In order to study the gastroduodenal acid neutralizating capacity, the following experiments were performed in anesthetized rats. Intravenous administration of AII in the untreated animals was followed by a slightly decreased ability to neutralize acid. In animals pretreated with the AII-receptor blocker Losartan, an enhanced acid neutralizating capacity was found in response to the same dose AII.

Table 1

Duodenal mucosal acid-neutralizing capacity in anesthetized rats before and during intravenous administration of AII.

	Untreated animals (μEq/h x cm)	Losartan-treated animals (μEq/h x cm)
Baseline	12 ±1,5	13±1,2
During AII-infusion	10±3	22±2,3 *

Data are given as means ±SEM, n=6 + 6. Significant inter-group difference (students t-test, unpaired samples) is indicated by an asterisk. Intravenous administration of AII results in an impaired acid neutralizing capacity in untreated animals. In animals, which are pretreated with the angiotensin II receptor blocking agent losartan, the same dosis of a AII significantly increases the acid neutralizing capacity of the duodenal mucosa.

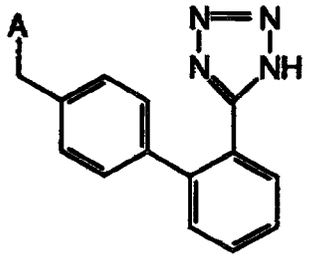
Pharmaceutical preparations

Conventional pharmaceutical preparations can be used. The pharmaceutical preparations are preferentially in the form of injection solutions, but it is also possible to use other kinds of preparation, such as oral solutions, or suspensions, tablets or capsules. Alternative routes of administrations are sublingual tablets or solutions and rectal solutions, suspensionsor or rectiols.

The pharmaceutical preparation contains between 1 mg and 500 mg of active substance, preferably 10 to 250 mg.

Claims

1. The use of a compound of the general formula I



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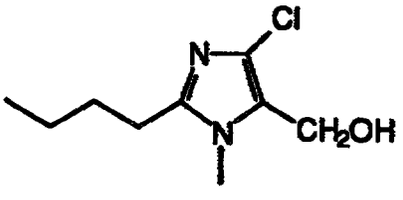

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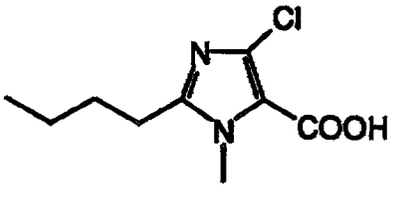

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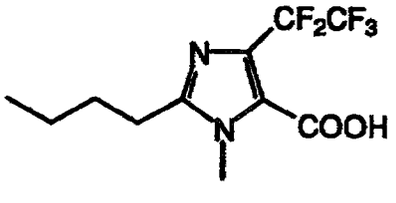

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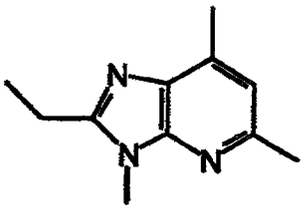

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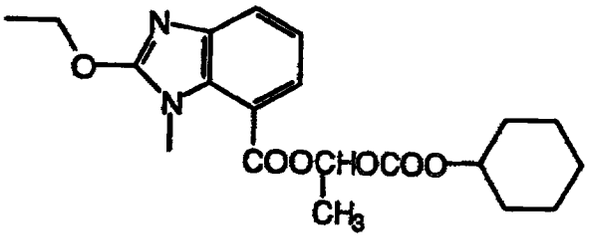

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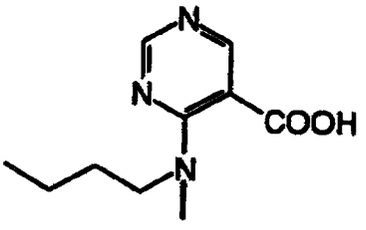

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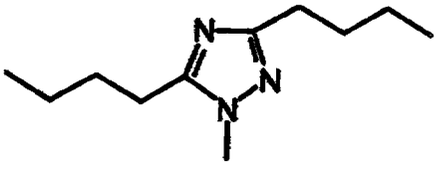

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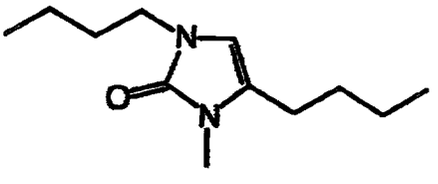

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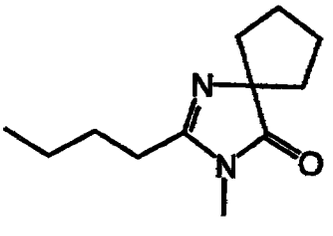

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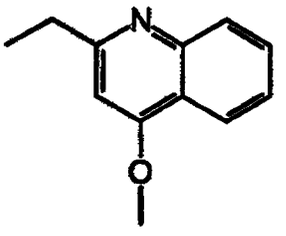

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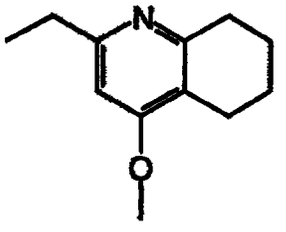

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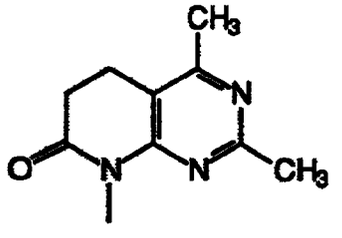

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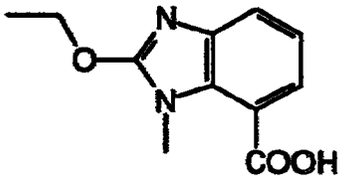

I:13

or a physiologically acceptable salt and/or a stereochemical isomer thereof for the manufacture of a medicament with effect on dyspeptic symptoms.

2. The use according to claim 1 of a compound of the formula I wherein A is I:1.

3. The use according to claim 1 of a compound of the formula I wherein A is I:5.

4. A pharmaceutical preparation for use in the propylaxis and/or treatment of dyspeptic symptoms wherein the active ingredient is a compound as defined in claim 1.

5. A pharmaceutical preparation according to claim 4 in dosage unit form.

6. A pharmaceutical preparation according to claims 4-5 comprising the active ingredients in association with a pharmaceutically acceptable carrier.

7. A pharmaceutical preparation according to claims 4-6 comprising as active ingredients a compound of the formula I wherein A is I:1.

8. A pharmaceutical preparation according to claims 4-6 comprising as active ingredients a compound of the formula I wherein A is I:5.

9. A method for the profylaxis and treatment of dyspeptic symptoms in mammals, including man, whereby an effective amount of a compound as defined in claim 1 is administered to a host in need of such profylaxis and treatment.

10. A method according to claim 9 characterized by the adminstration of a compound of the formula I wherein A is I:1 or I:5.