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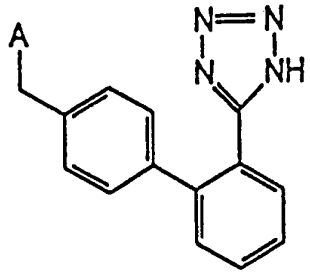
(54) Title: NEW PHARMACOLOGICAL USE OF AII-RECEPTOR ANTAGONISTS

(57) Abstract

A method for the prophylaxis and treatment of MOF using certain angiotensin II type 1 receptor antagonists of general formula (I) and a pharmaceutical preparation comprising these compounds.



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NEW PHARMACOLOGICAL USE OF AII-RECEPTOR ANTAGONISTS

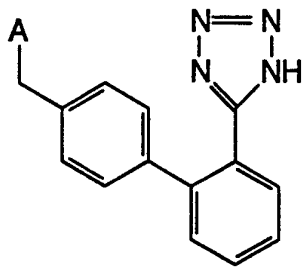
Field of the invention

The present invention is related to the use of angiotensin II type 1 receptor antagonists for the prophylaxis and/or treatment of multiple system organ failure (MOF) and to the manufacture of pharmaceutical preparations with effects on MOF.

Background of the invention

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

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



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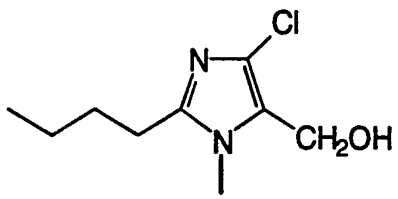
wherein A is



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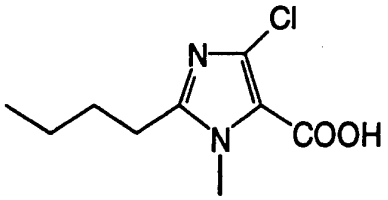

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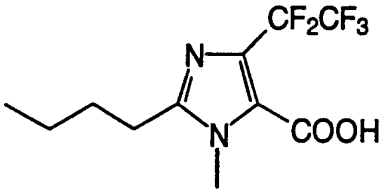

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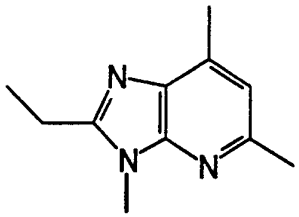

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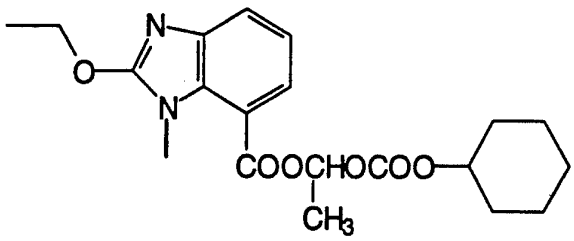

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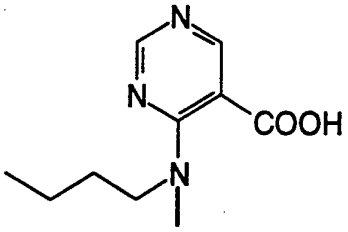

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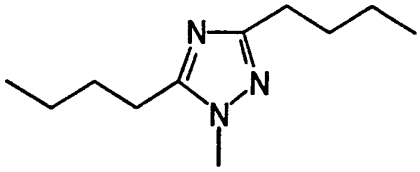

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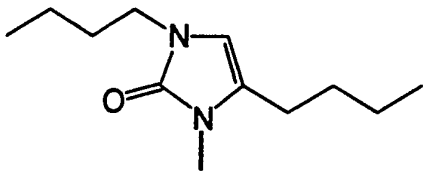

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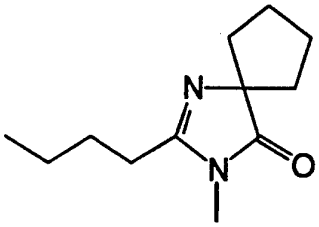

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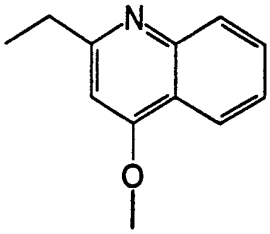

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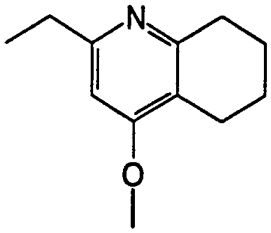

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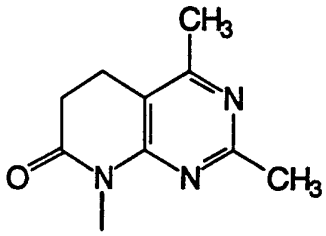

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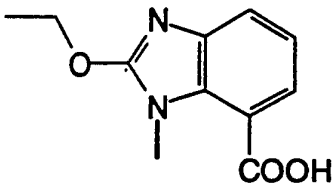

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The compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer; they may be used in neutral form or in the form of a salt, preferably a physiologically acceptable salt such as sodium, potassium, ammonium, calcium 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 European patent no 459 136.

The compound of the formula I wherein A is the I:9 moiety is known 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 European patent no 459 136.

Hemorrhage and/or trauma elicits a vasoconstrictive response that preferentially reduces blood flow to mesenteric organs. If severe, hemorrhage may propagate to circulatory shock, a condition in which oxygen delivery becomes insufficient to maintain tissue integrity and function. Manifestations of circulatory shock in mesenteric organs include collapse of the gut permeability barrier, enabeling gut pathogens to cross the intestinal mucosa and eventually spread to systemic compartments via lymphatics and blood vessels. The barrier dysfunction with microbial translocation, together the initially compromised systemic circulation, leads to functional failure of various organ systems (e.g. kidneys, heart, lungs, hemostasis). Such a sequential development of devastating sequele is defined as multiple system organ failure (MOF).

The treatment of MOF is very costly and results in long term treatments at intensive care units. Therapeutic efforts in MOF treatment today are aimed at life sustaining treatments, such as antibiotics, blood volume expansion and respiration assistance. However, a therapeutical approach in order to maintain mesenteric blood flow and oxygen delivery is not available today.

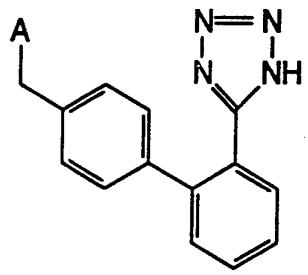
Reduction of mesenteric blood flow in the critically ill patient is mainly mediated by activation of the renin-angiotensin system with elevated plasma angiotensin II (AII) levels. Administration of compounds which blocks the formation of AII (i.e. angiotensin converting enzyme inhibitors, (ACE-inhibitors) have been shown to improve mesenteric oxygenation during severe shock.

The use of ACE inhibitors for treatment of severe shock is, however hampered by the fact that they act as nonspecific enzyme inhibitors and result in the accumulation of several vasoactive peptides e.g. (bradykinin, subst. P, endogenous opoids). This consequence may lead to an instable blood pressure regulation as well as increased risk for allergic manifestations and upper airway irritation.

It will be appreciated therefore that there is need for alternative and improved methods for the prophylaxis and/or treatment of multiple system organ failure.

Disclosure of the invention

It has unexpectedly been found that known compounds of the general formula



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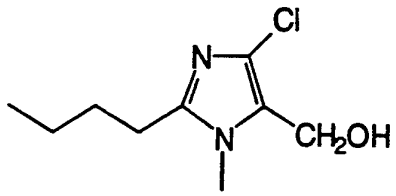

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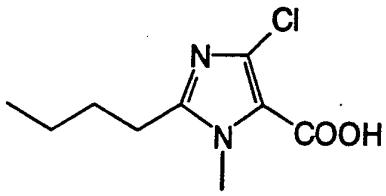

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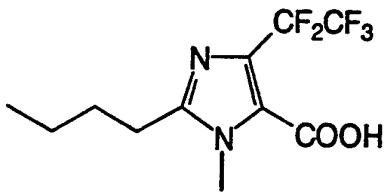

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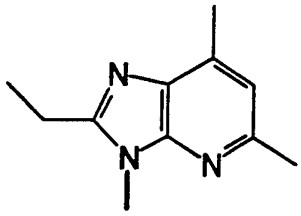

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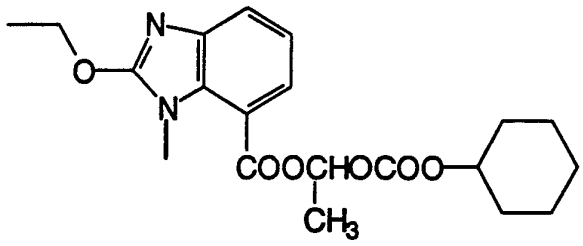

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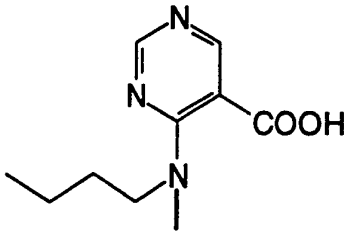

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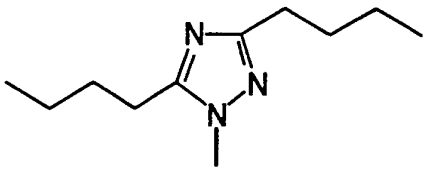

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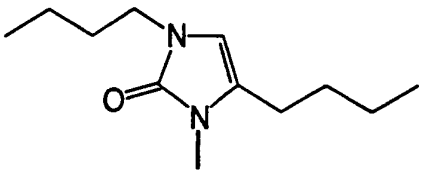

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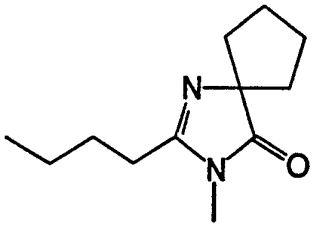

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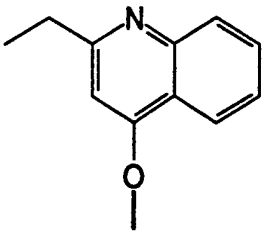

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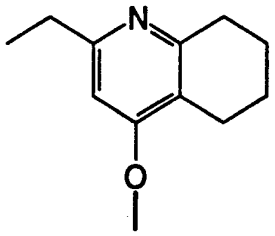

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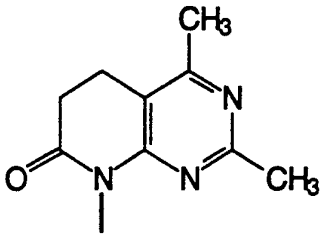

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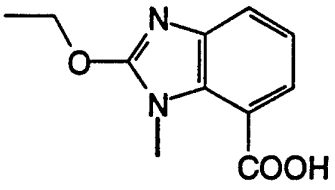

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or a physiologically acceptable salt and/or a stereochemical isomer thereof are effective in the prophylaxis and/or treatment of multiple system organ failure (MOF).

It has been found that pharmacological specific blockade of AII type 1 receptors with a compound according to formula I has a surprisingly good effect on gastro-intestinal tissue oxygenation during conditions comparable to the situation in the critically ill patient. In addition, during conditions with elevated plasma AII concentrations, such a specific blockade of AII type 1 receptors was shown to reinforce the mucosal barrier function in the upper gastrointestinal tract.

The present invention is based on our surprising finding that administration of specific AII type 1 receptor antagonists, which have the effect of maintained oxygen delivery and positive stimulation of the gastrointestinal mucosal barrier, are useful for the prophylaxis and/or treatment of multiple system organ failure.

The compounds of the formula I can be administered orally, rectally or parenterally in neutral form or in the form of a salt. While the effects on splanchnic oxygenation and barrier function have been established in animals by the intravenous route, it is believed that the effect is a systemic effect which is not dependent on the mode of administration which is used, and accordingly the effects 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 for prophylaxis and/or treatment of multiple system organ failure 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 range 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 (TCV-116).

Scientific tests

Animal experiments have been performed during conditions comparable to the situation in the critically ill patient as described in Åneman et al 1995; Anesth. Analg. No 80, p 135-142. Gastrointestinal oxygenation was studied in anestethized pigs during an acute bleeding (40% of estimated blood volume). In an untreated group of animals (n=6) a profund decrease in mesenteric oxygenation was observed following 40% hemorrhage. In the losartan treated animal (n=5) no decrease in mesenteric oxygen delivery was seen following a 40% hemorrhage.

The ability to neutralize acid is an important component of the gastrointestinal mucosal barrier functions, particularly in the upper gut but also in lower parts. The following experiments were performed in the anesthetized rat duodenum. Intravenous administrations of AII were followed by a decreased ability to neutralize luminal acid in the untreated animals (n=6). This inhibition was, surprisingly, reversed to an enhanced acid

neutralisating capacity in response to the same dose AII after pretreatment with the AII-receptor blocker losartan (n=6).

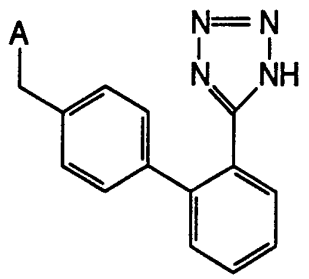
Pharmaceutical preparations

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



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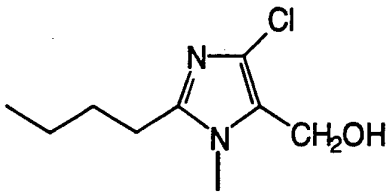
wherein A is



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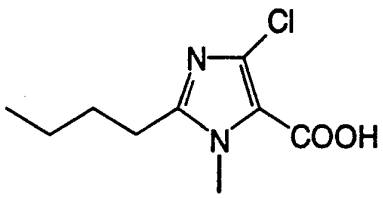

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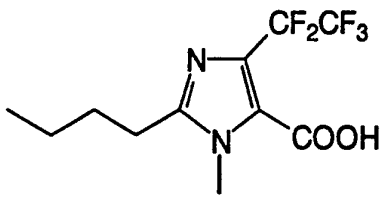

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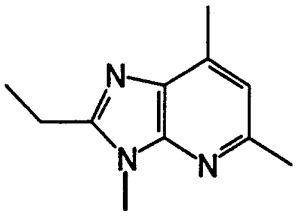

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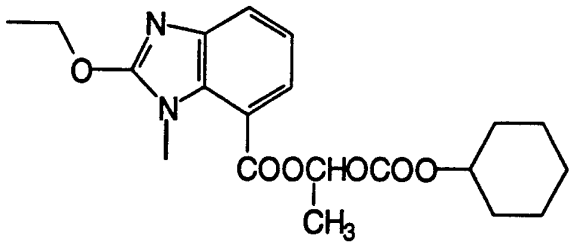

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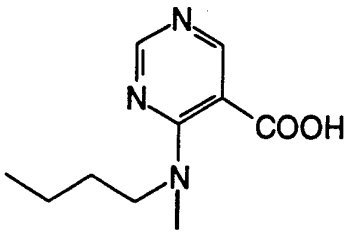

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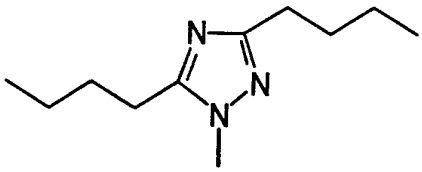

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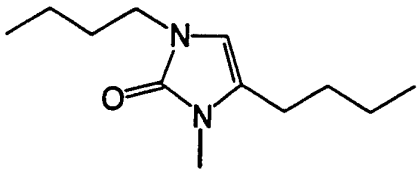

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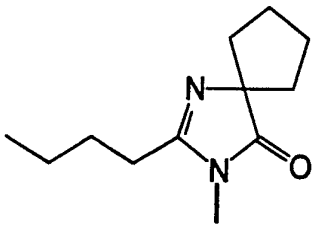
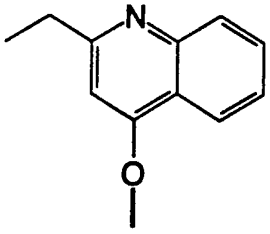
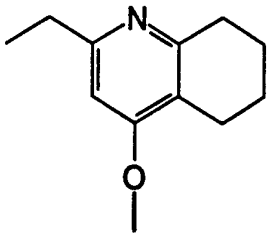


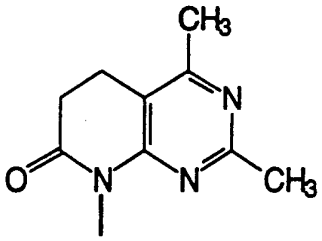
I:9



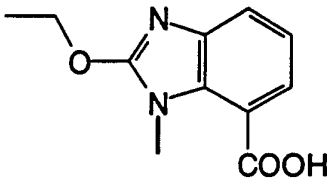
I:10



I:11



I:12



I:13

or a physiologically acceptable salt and/or a stereochemical isomer thereof for the manufacture of a medicament with effect on multiple system organ failure.

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

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

4. A pharmaceutical preparation for use in the propylaxis and/or treatment of multiple system organ failure 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 the I:1 moiety.

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

9. A method for the profylaxis and treatment of multiple system organ failure 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 the I:1 or I:5 moieties.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00602

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/415, A61K 31/395, A61K 31/425, A61K 31/505, A61K 31/47
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5155118 A (DAVID J. CARINI ET AL), 13 October 1992 (13.10.92)	4-7
A	--	1-3
X	EP 0459136 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 4 December 1991 (04.12.91)	8
A	-- --------	1-3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 1996	26 -08- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00602

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-10
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/96

International application No.
PCT/SE 96/00602

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5155118	13/10/92	AT-T- 113276	15/11/94
		AU-B- 599396	19/07/90
		AU-A- 7559687	21/01/88
		CA-A- 1334092	24/01/95
		DE-D,T- 3750687	23/02/95
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		PL-B- 168958	31/05/96