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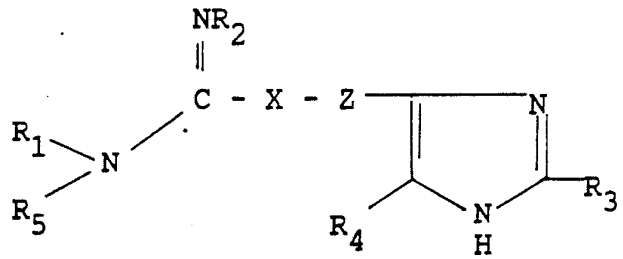
(54) Title: IMIDAZOLE-DERIVATIVES HAVING AGONISTIC OR ANTAGONISTIC ACTIVITY ON THE HISTAMINE H_3-RECEPTOR



(a)

(57) Abstract

The invention relates to imidazole-derivatives of general formula (a). The invention in particular relates to derivatives having agonistic or antagonistic activity on the histamine H_3-receptor. The novel imidazole-derivatives are isothio urea-, guanidine- and amidine-derivatives. The invention further relates to pharmaceutical compositions comprising the novel imidazole-derivatives as well as to methods for preparing the derivatives and for preparing pharmaceutical compositions having antagonistic and agonistic activity on the histamine H_3-receptor.

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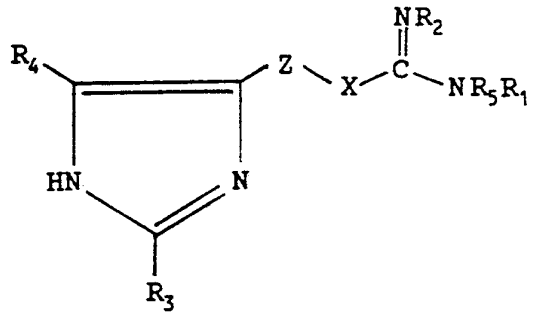
Imidazole-derivatives having agonistic or antagonistic activity on the histamine H_3-receptor.

The invention relates to novel imidazole-derivatives. The invention in particular relates to novel imidazole-derivatives having agonistic or antagonistic activity on the histamine H_3-receptor. More in particular it relates to isothiourea-, guanidine- and amidine-derivatives. The invention further relates to the synthesis of such compounds, a pharmaceutical composition comprising such compounds or pharmacological acceptable salts thereof, the use of the compounds as agents having biological activity, as agents with agonistic or antagonistic activity on the histamine H_3-receptor or for preparing a pharmaceutical composition.

In addition to the already longer known histamine H_1- and H_2-receptors there is also a third type histamine-receptor present in the human body, the so-called H_3-receptor. De H_3-receptor is a presynaptic receptor, i.e. it is located on a cell releasing histamine and stimulation of the receptor leads to inhibition of the histamine-release. Furthermore stimulation of the H_3-receptor influences also the release of other neurotransmitters, such as e.g. serotonine and acetylcholine. H_3-receptors are located in the central and peripheral nervous system, the lung tissue, the intestine and probably also in the spleen, the skin and the gastro-intestinal tract. A number of compounds having an effect on H_3-receptors has already been described. For a review see Schwartz et al., Agents and Actions 30, 1/2 (1990) p. 13-23.

Chemical compounds can stimulate or inhibit the histamine H_3-receptor (Timmerman, J. Med. Chem. 33, p. 4-11 (1990)). Now a group of new imidazole-derivatives showing an agonistic or antagonistic activity on the histamine H_3-receptors has been found.

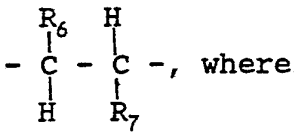
These derivatives are represented by the general formula:



(I)

wherein:

Z is a group of the formula $(CH_2)_m$, wherein m = 1-5 or a group of the formula:

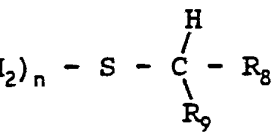


wherein R_6 = (C_1-C_3)alkyl
R_7 = (C_1-C_3)alkyl;

wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or CH_2;

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or aryl alkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, sub-

stituted naphthyl, pyridyl or substituted pyridyl; or pharmacological acceptable salts thereof.

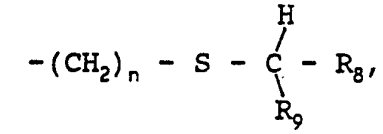
Of these compounds the imidazole-derivatives of formula I wherein:

A) when Z is a group of the formula $(CH_2)_m$, wherein m = 1-5, and

1) when X is S,

R_1 represents (C_1-C_3)alkyl- or aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, when m = 1 or 5, or (C_2-C_3)alkyl- or aryl(C_2-C_{10})alkyl-, wherein aryl may optionally be substituted, when m = 2, 3 or 4;

aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



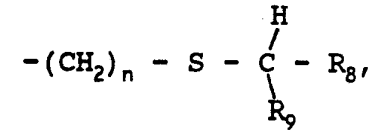
wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 represents hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; and

R_3, R_4 and R_5 represent hydrogen; or

2) when X is NH,

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen or (C_1-C_{10})alkyl-;

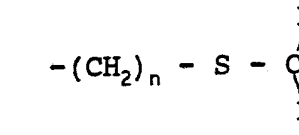
R_2 represents hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may be optionally substi-

tuted; and

R_3, R_4 and R_5 represent hydrogen; or

3) when X is CH_2,

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



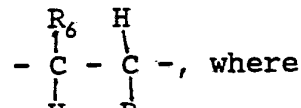
wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

B) when Z is a group of the formula :

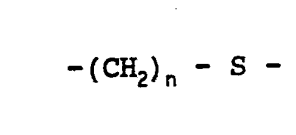


wherein R_6 = (C_1-C_3)alkyl
R_7 = (C_1-C_3)alkyl;

wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or CH_2;

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



wherein n = 1 - 4, R_8 is aryl, aryl(C_1-C_{10})alkyl-,

(C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl, are novel derivatives.

Agonistic activity is in particular shown by compounds of formula I, wherein R_1, R_2, R_3, R_4 and R_5 are hydrogen, m is 2, and X is S or NH. The compound S-[2-(4-imidazolyl)ethyl]isothiourea shows a strong agonistic activity and is therefore preferred as the active ingredient in a pharmaceutical composition having histamine H_3-agonistic activity.

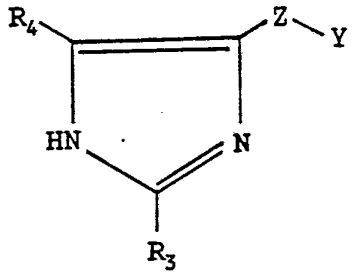
Antagonistic activity is in particular shown by compounds of formula I, wherein R_3, R_4 and R_5 are hydrogen; m is 2 or 3, R_1 is a group of the formula $-(CH_2)_nR_{10}$, wherein R_{10} is aryl or substituted aryl, $n \geq 1$ and X is S or NH. Preferred compounds are S-[2-(imidazol-4-yl) ethyl]-N-(2-phenylethyl)-isothiourea, N-benzyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(2-phenylethyl)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylethyl-)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylbutyl)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea, N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea and S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea.

Other compounds showing strong antagonistic activity are compounds of formula I, wherein R_3, R_4 and R_5 are hydrogen, m is 1, 2 or 3; and R_1 is a group of the formula

$$-(CH_2)_r-S-\underset{R_{11}}{\overset{|}{C}}-\phi,$$

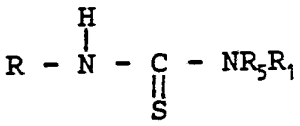
wherein ϕ is aryl, r is 1, 2 or 3; and R_{11} is hydrogen, (C_1-C_{10})alkyl- or aryl. A preferred compound is N-[2-(benzylthio)ethyl]-S-[3-(imidazol-4-yl)propyl]isothiourea.

Compounds of formula I can in general be synthesized in a for analogous compounds known manner. Favourable methods for synthesizing consist in condensation of a imidazole-compound of the general formula:



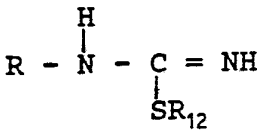
(II)

wherein Y represents Br, OH, or O-alkyl, with a thiourea-derivative having the general formula:



(III)

or condensation of a imidazole of formula II wherein Y represents NH_2, with a isothiourea-derivative having the general formula:



(IV)

wherein in the formulas III and IV R represents hydrogen, (C_1-C_{10})alkyl-, aryl(C_1-C_{10})alkyl- or aryl, and R_{12} represents (C_1-C_{10})alkyl. As solvents polair solvents are used such as ethanol or propanol. The condensations are carried out at temperatures between roomtemperature and the boiling point of the solvents for between 30 minutes and 10 hours. Reactions take place in acid environment, e.g. hydrobromic acid, or in neutral environment. The obtained product can be processed in the usual way. If desired it is further possible to convert the obtained compounds of formula I in other compounds of formula I.

The following examples illustrate the synthesis of compounds of the present invention but are never intended to limit the scope thereof.

EXAMPLE 1

Synthesis of N-benzyl-S-[2-(imidazol-4-yl)ethyl]isothiourea dipicrate (VUF 9028).

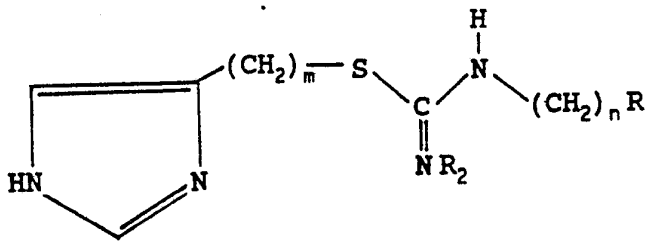
3.5 gram (13.7 mmol) 4(5)-(2-bromoethyl)imidazole.HBr and 2.3 gram N-benzylthiourea were refluxed for 60 hours in 30 ml ethanol. The ethanol was evaporated and the product was purified by means of columnchromatography, using methanol/ethylacetate as eluent.

Subsequently the solvent was evaporated and the residue dissolved in methanol whereto 10 gram picric acid in methanol was added. After addition of water an oil was formed, which after stirring with water became solid. The solid matter with melting point 166.9-169.8°C was subsequently filtrated. The NMR-results of this compound are given in table 1.

EXAMPLE 2

Synthesis of S-[3-(4(5)-imidazolyl)alkyl]-N-(2-(substituted)-arylalkyl)isothiourea-derivatives.

Analogous to the preparation method of VUF 9028 from example 1 a number of compounds were synthesized with the formula:



The meaning of n, m and R, the solvent of the condensation reaction and the melting points of the compounds are given in the table below. The NMR-results are given in table 1.

Compound	R_2	R	n	m	melt.point	salt	solvent
VUF 8397	H	C_6H_5	0	2	174-176°C	2HBr	2-prop.
VUF 9029	H	C_6H_5	2	2	177-185°C	2HBr	eth.
VUF 9030	H	C_6H_5	3	2	152-155°C	dipicr.	eth.
VUF 9031	H	C_6H_5	4	2	136-139°C	2HBr	eth.
VUF 9051	CH_3	C_6H_5	2	2	152-156°C	2HBr	eth.
VUF 9107	H	C_6H_5	1	3	155-160°C	2HBr	eth.
VUF 9151	H	C_6H_5	2	3	178-183°C	2HBr	eth.
VUF 9152	H	C_6H_5	3	3	177-184°C	2HBr	eth.
VUF 9153	H	$4\text{-}ClC_6H_4$	1	3	200-205°C	2HBr	eth.
VUF 9163	H	$c\text{-}C_6H_{11}$	1	3	137-153°C	dipicr.	eth.
VUF 4571	H	C_6H_5	4	3	112-134°C	dipicr.	eth.
VUF 4586	H	$4\text{-}IC_6H_4$*	2	3	188-190°C	2HBr	2-prop.

* Radioactively labeled compound, e.g. for use as a tracer-molecule

EXAMPLE 3

Synthesis of N-[2-(imidazol-4-yl)ethyl]-N'-phenyl guanidine dipicrate (VUF 9006).

Step 1:

Synthesis of S-ethyl-N-phenylisothiourea.

4 gram N-phenylisothiourea (33 mmol) and 5 ml ethylbromide were refluxed for 10 hours in ethanol. Again 5 ml ethylbromide was added. The reaction course was followed by thin layer chromatography (ethylacetate/petroleumether 3:7). Subsequently the solvent was evaporated and the residu crystallised from ethanol/ethylacetate.

Step 2:

15 mmol histamine.2HCl was added to 30 mmol sodiumethanolate in ethanol (prepared by dissolving 30 mmol sodium in ethanol). Subsequently it was refluxed for one half hour, after which the mixture was cooled in ice and the formed NaCl was

filtrated.

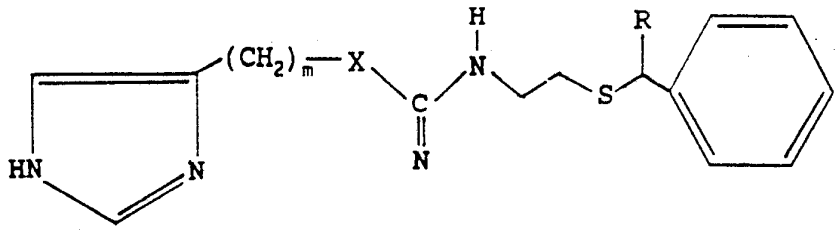
To the filtrate 15 mmol S-ethyl-N-phenylisothiourea was added. Next the reation mixture was refluxed for 35 hours (control with thin layer chromatography (ethylacetate/petroleumether 1:1, saturated with ammonia)). Subsequently the solvent was evaporated and the residue dissolved in methanol. 35 mmol picric acid were added. The product was seperated by the addition of water and was subsequently crystallised from methanol/water. The melting point was 235-238°C.

Analogous to the synthesis of VUF 9006 N-[2-(imidazol-4-yl)ethyl]-N'-phenyl-ethylguanidine dipicrate (VUF 9007; meltingpoint 196-198°C) was prepared. The NMR-resluts are given in table 1.

EXAMPLE 4

Synthesis of N-[2-(arylalkylthio)alkyl]-S-[3-(imidazol-4-yl)alkyl]isothiourea- and -guanidine-derivatives.

Analogous to example 1 compounds were synthesized having the formula:



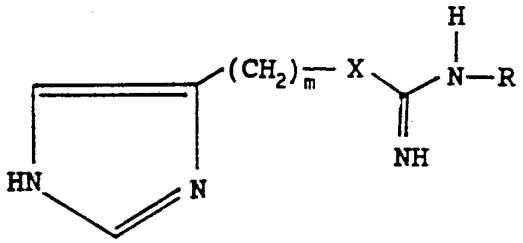
The meaning of the symbols m, X and R, the solvent of the condensation reaction and the melting points of the compounds are given in the table below. The NMR-results are given in table 1.

Compounds	m	X	R	melting point	salt	solvent
VUF 8404	2	S	H	233-235°C	2HBr	2-prop.
VUF 8405	3	NH	H	145-148°C	dipicr.	ethanol
VUF 8409	2	S	C_6H_5	106-109°C	dipicr.	ethanol
VUF 8414	3	S	H	126-133°C	dipicr.	ethanol

EXAMPLE 5

Synthesis of N-alkyl-S-[2-(4-imidazolyl)alkyl]isothiourea- and -guanidine-derivatives.

Analogous to example 1 compounds were synthesized having the formula:



The meaning of the symbols m, X and R, the solvent of the condensation reaction and the melting points of the compounds are given in the table below. The NMR-results are given in table 1.

Compound	m	X	R	melting point	salt	solvant
VUF 8325	2	S	H	210-212°C	2HBr	eth.
VUF 83100	2	NH	H	222-223°C	2HCl	eth.
VUF 8621	2	S	CH_3	180-181°C	2HBr	water

TABLE 1. NMR-results of the compounds mentioned in the description.

COMPOUNDS			
AGONISTS			
VUF8325			
3.06 ppm	triplet	J = 7.0 Hz	2H
3.56 ppm	triplet	J = 7.0 Hz	2H
7.61 ppm	singlet		1H
9.01-9.27 ppm	multiplet		5H
VUF8621			
2.93 ppm	singlet		3H
3.07 ppm	triplet	J = 6.8 Hz	2H
3.59 ppm	triplet	J = 6.8 Hz	2H
7.60 ppm	singlet		1H
9.11 ppm	doublet	J = 1.3 Hz	1H
ANTAGONISTS			
VUF9028			
3.06 ppm	triplet	J = 6.9	2H
3.54 ppm	triplet	J = 6.9	2H
4.58 ppm	singlet		2H
7.29-7.49 ppm	multiplet		6H
7.52 ppm	singlet		4H
8.62 ppm	singlet		1H
9.08 ppm	doublet	J = 1.3 Hz	1H
VUF9029			
2.90 ppm	triplet	J = 7.5 Hz	2H
3.00 ppm	triplet	J = 7.0 Hz	2H
3.50-3.69 ppm	multiplet		4H
7.21-7.35 ppm	multiplet		5H
7.58 ppm	singlet		1H
9.16 ppm	doublet	J = 1.3 Hz	1H
VUF9030			
1.86 ppm	quintet	J = 7.4 Hz	2H
2.62 ppm	triplet	J = 7.4 Hz	2H
3.05 ppm	triplet	J = 6.9 Hz	2H
3.24-3.38 ppm	multiplet		2H
3.51 ppm	triplet	J = 6.9 Hz	2H
7.16-7.39 ppm	multiplet		5H
7.53 ppm	singlet		1H
8.61 ppm	singlet		4H
9.06 ppm	doublet	J = 1.3 Hz	1H
VUF9031			
1.45-1.71 ppm	multiplet		4H
2.60 ppm	triplet		2H
3.05 ppm	triplet	J = 6.8 Hz	2H
3.30-3.45 ppm	multiplet		2H
3.60 ppm	triplet	J = 6.8 Hz	2H
7.13-7.46 ppm	multiplet		5H
7.60 ppm	singlet		1H
9.13 ppm	doublet	J = 1.4 Hz	1H
VUF9051			
2.80-3.06 ppm	multiplet		4H
3.50-3.68 ppm	multiplet		4H
7.18-7.40 ppm	multiplet		5H
7.57 ppm	singlet		1H
9.09 ppm	singlet		1H

SUBSTITUTE SHEET

VUF9006			
2.90 ppm	triplet	J = 6.3 Hz	2H
3.51 ppm	triplet	J = 6.3 Hz	2H
7.14-7.50 ppm	multiplet		5H
7.69-7.86 ppm	multiplet		2H
8.59 ppm	singlet		4H
8.97 ppm	singlet		1H
VUF9007			
2.74-2.92 ppm	multiplet		4H
3.32-3.51 ppm	multiplet		4H
7.18-7.50 ppm	multiplet		6H
8.63 ppm	singlet		4H
9.05 ppm	doublet		1H
VUF8404			
2.66 ppm	triplet	J = 6.3 Hz	2H
3.06 ppm	triplet	J = 6.3 Hz	2H
3.40-3.72 ppm	multiplet		4H
3.81 ppm	singlet		2H
7.28 ppm	singlet		5H
7.58 ppm	singlet		1H
9.07 ppm	doublet	J = 0.8 Hz	1H
VUF8405			
1.64 ppm	quintet	J = 7.2 Hz	2H
2.38-2.84 ppm	multiplet		4H
3.06-3.56 ppm	multiplet		4H
3.80 ppm	singlet		2H
7.26-7.44 ppm	multiplet		6H
8.60 ppm	singlet		4H
9.02 ppm	singlet		1H
VUF8409			
2.56 ppm	triplet	J = 6.8 Hz	2H
3.03 ppm	triplet	J = 6.8 Hz	2H
3.26-3.70 ppm	multiplet		4H
5.40 ppm	singlet		1H
7.10-7.56 ppm	multiplet		11H
8.60 ppm	singlet		4H
9.02 ppm	singlet		1H
VUF8414			
1.94 ppm	quintet	J = 6.8 Hz	2H
2.60-2.94 ppm	multiplet		4H
3.20 ppm	triplet	J = 6.8 Hz	2H
3.30-3.68 ppm	multiplet		2H
3.78 ppm	singlet		2H
7.28-7.42 ppm	multiplet		6H
8.60 ppm	singlet		4H
9.00 ppm	doublet	J = 1.0 Hz	1H
VUF9107			
1.86-2.05 ppm	multiplet		2H
2.76 ppm	triplet	J = 7.5 Hz	2H
3.20-3.51 ppm	multiplet		7H
4.60 ppm	singlet		2H
7.26-7.52 ppm	multiplet		6H
9.01 ppm	doublet	J = 1.3 Hz	1H
VUF9151			
1.81-1.98 ppm	multiplet		2H
2.73 ppm	triplet	J = 7.5 Hz	2H

2.89 ppm	triplet	J = 7.0 Hz	2H
3.22 ppm	triplet	J = 7.0 Hz	2H
3.34 ppm	singlet		6H
3.52-3.68 ppm	multiplet		2H
7.20-7.40 ppm	multiplet		5H
7.48 ppm	singlet		1H
9.02 ppm	doublet	J = 1.3 Hz	1H
VUF9152			
1.78-2.06 ppm	multiplet		4H
2.64 ppm	triplet	J = 7.6 Hz	2H
2.77 ppm	triplet	J = 7.3 Hz	2H
3.19-3.50 ppm	multiplet		10H
7.18-7.40 ppm	multiplet		5H
7.49 ppm	singlet		1H
9.01 ppm	doublet	J = 1.3H	1H
VUF9153			
1.86-2.06 ppm	multiplet		2H
2.77 ppm	triplet	J = 7.2 Hz	2H
3.22-3.49 ppm	multiplet		6H
4.60 ppm	singlet		2H
7.32-7.58 ppm	multiplet		6H
9.04 ppm	doublet	J = 1.3H	1H
VUF9163			
0.80-1.77 ppm	multiplet		11H
1.86-2.03 ppm	multiplet		2H
2.74 ppm	triplet	J = 7.0 Hz	2H
3.08-3.25 ppm	multiplet		4H
3.35 ppm	singlet		10H
7.46 ppm	singlet		1H
8.49 ppm	singlet		4H
8.98 ppm	doublet	J = 1.3H	1H
VUF4571			
1.47-1.70 ppm	multiplet		4H
1.84-2.03 ppm	multiplet		2H
2.42-2.66 ppm	multiplet		50H
2.74 ppm	triplet	J = 7.2 Hz	2H
3.19 ppm	triplet	J = 7.2 Hz	2H
3.26-3.38 ppm	multiplet		2H
3.46 ppm	multiplet		10H
7.11-7.35 ppm	multiplet		5H
7.47 ppm	singlet		1H
8.59 ppm	singlet		4H
VUF4586			
1.89 ppm	multiplet		2H
2.74 ppm	triplet	J = 7.2 Hz	2H
2.83 ppm	triplet	J = 7.0 Hz	2H
3.24 ppm	multiplet		2H
3.57 ppm	multiplet	J = 7.2 Hz	2H
7.05-7.20 ppm	multiplet		2H
7.60-7.75 ppm	multiplet		2H
7.50 ppm	singlet		1H
9.03 ppm	singlet		1H

Pharmacological experiments

The agonistics and antagonistics activities on the H_3-receptor of the various compounds were determined compared to histamine. The testmethods used therefor are described in Van der Werf et al., Agents and Actions 20, 3/4 (1987) p. 239-243 and Menkveld et al., European Journal of Pharmacology, 186 (1990) p. 343-347.

The results of the experiments are given in the tables below. pD_2 is the negative logarithm of the concentration of the testcompound at which 50% agonistic activity was measured. pA_2 is the negative logarithm of the concentration of the testcompound at which the concentration of the agonist had to be doubled to obtain the same effect as obtained when the antagonist was absent.

Pharmaceutical compositions, comprising compounds of formula I as defined in claim 19 as the active ingredient for therapeutically influencing the human and animal histaminergic system have the form of powders, suspensions, solutions, sprays, emulsions, unguents or creams and can be used for local application, intranasal, rectal, vaginal and also for oral or parenteral (intravenous, intradermal, intramuscular, intrathecal etc.) administration. Such compositions can be prepared by combining (i.e. by mixing, dissolving etc.) of the active compound of formula I in the form of a free acid or salt with farmaceutically acceptable excipients with neutral character (such as aquous or non-aquous solvents, stabilizers, emulsifiers, detergents, additives), and further if neccesary colouring agents and flavouring agents. The concentration of the active ingredient in a farmaceutical composition can vary between 0.1% and 100%, depending on the nature of the influence and the method of administration. The dose of the active ingredient that is administered can further be varied between 0.1 mg and 100 mg per kg bodyweight.

TABLE 2. Antagonistic activity

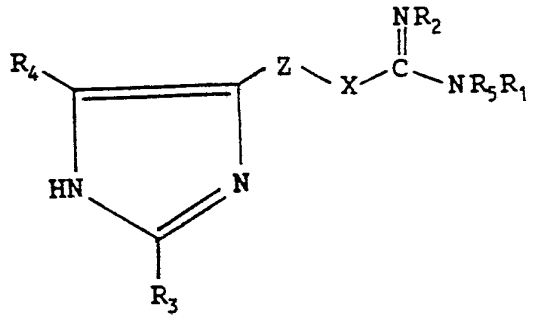
Compound	pA_2	testmethod
VUF 8397	7.0	ratcortex
VUF 9028	7.8	ileum guinea pig
VUF 9029	8.0	ileum guinea pig
VUF 9030	7.6	ileum guinea pig
VUF 9031	7.7	ileum guinea pig
VUF 9051	7.8	ileum guinea pig
VUF 9006	5.8	ileum guinea pig
VUF 9007	6.3	ileum guinea pig
VUF 8404	7.4	ileum guinea pig
VUF 8405	7.9	ileum guinea pig
VUF 8409	6.6	ileum guinea pig
VUF 8414	8.6	ileum guinea pig
VUF 9107	8.8	ileum guinea pig
VUF 9151	8.8	ileum guinea pig
VUF 9152	8.3	ileum guinea pig
VUF 9153	9.9	ileum guinea pig
VUF 9163	8.8	ileum guinea pig
VUF 4571	8.4	ileum guinea pig
VUF 4586	9.2	ileum guinea pig

TABLE 3. Agonistic activity

Compound	pD_2	testmethod
VUF 8325	9.3	ratcortex
VUF 8325	8.1	ileum guinea pig
VUF 83100	7.4	ratcortex
VUF 8621	7.3	ileum guinea pig

C L A I M S

1. Imidazole-derivatives of the general formula:



(I)

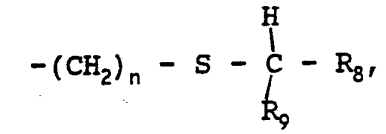
wherein:

A) when Z is a group of the formula $(CH_2)_m$, wherein m = 1-5, and

1) when X is S,

R_1 represents (C_1-C_3)alkyl- or aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, when m = 1 or 5, or (C_2-C_3)alkyl- or aryl(C_2-C_{10})alkyl-, wherein aryl may optionally be substituted,when m = 2, 3 or 4;

aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



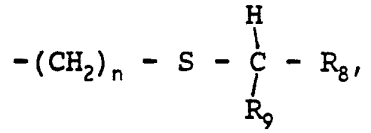
wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 represents hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; and

R_3, R_4 and R_5 represent hydrogen; or

2) when X is NH,

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



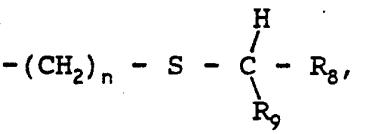
wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen or (C_1-C_{10})alkyl-;

R_2 represents hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may be optionally substituted; and

R_3, R_4 and R_5 represent hydrogen; or

3) when X is CH_2,

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



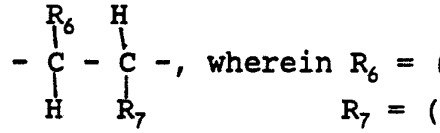
wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

B) when Z is a group of the formula :



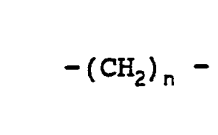
wherein R_6 = (C_1-C_3)alkyl

R_7 = (C_1-C_3)alkyl;

wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or CH_2;

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



wherein n = 1 - 4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl.

2. Imidazole-derivatives according to claim 1, having the formula I, wherein R_3, R_4 and R_5 are hydrogen; m is 2; R_1 is a group of the formula $(CH_2)_nR_{10}$ wherein R_{10} is a substituted or non-substituted arylgroup, $n \geq 1$; and X is S or NH.

3. Imidazole-derivatives according to claim 2, characterized in that R_2 is hydrogen; m is 2; and X is S.

4. Imidazole-derivatives according to claim 3, characterized in that the derivative is S-[2-(imidazol-4-yl) ethyl]-N-(2-phenylethyl)isothiourea.

5. Imidazole-derivatives according to claim 2, characterized in that R_2 is hydrogen; m is 3; and X is S.

6. Imidazole-derivatives according to claim 5, characterized in that the derivative is N-benzyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea.

7. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(2-phenylethyl)isothiourea.

8. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylpropyl)isothiourea.

9. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-phenylbutyl)isothiourea.

10. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea.

11. Imidazole-derivatives according to claim 5, characterized in that the derivative is N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea.

12. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea.

13. Imidazole-derivatives according to claim 1, having the formula I, wherein R_3, R_4 and R_5 are hydrogenatoms; m is 1, 2 or 3; R_1 is a group of the formula

$$-(CH_2)_r-S-\underset{R_{11}}{\overset{|}{C}}-\phi,$$

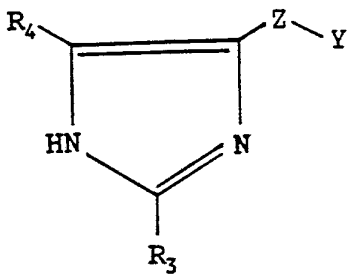
wherein ϕ is an arylgroup, r is 1, 2 or 3 and R_{11} is hydrogen, (C_1-C_{10})alkyl- or aryl.

14. Imidazole-derivatives according to claim 13, characterized in that m is 3, r is 2, R_{11} is hydrogen and X is S or NH.

15. Imidazole-derivatives according to claim 14, characterized in that the derivative is N-[2-(benzylthio)-ethyl]-S-[3-(imidazol-4-yl)propyl]isothiourea.

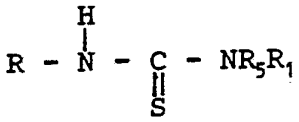
16. Method for preparing imidazole-derivatives, characterized in that compounds of formula I are being synthesized in a for analogous compounds known manner.

17. Method for preparing imidazole-derivatives, characterized in that compounds of formula I are prepared by condensation of an imidazole-derivative of the general formula:



(II)

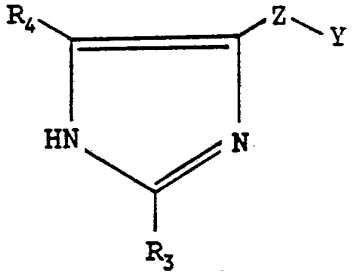
wherein Y represents Br, OH, or O-alkyl; and a thioureade-rivative of the general formula:



(III)

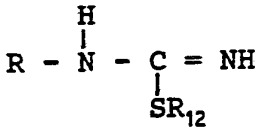
wherein R represents hydrogen, (C_1-C_{10})alkyl, aryl(C_1-C_{10})alkyl- or aryl, and R_{12} represents (C_1-C_10)alkyl-.

18. Method for preparing imidazole-derivatives according to claim 17, characterized in that compounds of formula I are being prepared by condensation of an imidazo-le-derivative of the general formula:



(II)

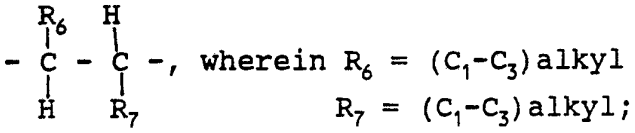
wherein Y represents NH_2; and a thioureaderivative of the general formula



(IV)

19. Pharmaceutical composition having antagonistic or agonistic activity on the histamine H_3-receptor, characte-rized in that it comprises as an active ingredient a com-pound of formula I, wherein :

Z is a group of the formula $(CH_2)_m$, wherein m = 1-5 or a group of the formula:

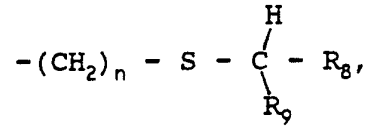


wherein R_6 = (C_1-C_3)alkyl, R_7 = (C_1-C_3)alkyl;

wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or CH_2;

R_1 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_{10})alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl-, or a group of the formula:



wherein n = 1-4, R_8 is aryl, aryl(C_1-C_{10})alkyl-, (C_5-C_7)cycloalkyl- or (C_5-C_7)cycloalkyl(C_1-C_{10})alkyl- and R_9 is hydrogen, (C_1-C_{10})alkyl- or aryl;

R_2 and R_5 represent hydrogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

R_3 represents hydrogen, (C_1-C_3)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R_4 represents hydrogen, amino-, nitro-, cyano-, halogen, (C_1-C_3)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl; or pharmacological acceptable salts thereof.

20. Pharmaceutical composition according to claim 19, characterized in that it comprises as the active ingredient a compound of formula I or pharmacological acceptable salts thereof, wherein R_1, R_2, R_3, R_4 and R_5 are hydrogen-atoms; m is 2; and X is S or NH.

21. Pharmaceutical composition according to claim 20, characterized in that it comprises as the active ingredient S-[2-(4-imidazolyl)ethyl]isothiourea or a pharmacological acceptable salt thereof.

22. Pharmaceutical composition according to claim

19, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein R_3, R_4 and R_5 are hydrogenatoms; m is 2; R_1 is a group of the formula $(CH_2)_nR_{10}$, wherein R_{10} is a substituted or non-substituted aryl, $n \geq 1$ and X is S or NH.

23. Pharmaceutical composition according to claim 22, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein R_2 is hydrogen; m is 2; and X is S.

24. Pharmaceutical composition according to claim 23, characterized in that it comprises as the active ingredient S-[2-(imidazol-4-yl)ethyl]-N-(2-phenylethyl)isothiourea or a pharmacological acceptable salt thereof.

25. Pharmaceutical composition according to claim 23, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein R_2 is hydrogen; m is 3; and X is S.

26. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative is N-benzyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmacological acceptable salt thereof.

27. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(2-phenylethyl)isothiourea or a pharmacological acceptable salt thereof.

28. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylpropyl)isothiourea or a pharmacological acceptable salt thereof.

29. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingre-

dient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-phenylbutyl)isothiourea or a pharmacological acceptable salt thereof.

30. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea or a pharmacological acceptable salt thereof.

31. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmacological acceptable salt thereof.

32. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea or a pharmacological acceptable salt thereof.

33. Pharmaceutical composition according to claim 19, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein R_3, R_4 and R_5 are hydrogen; m is 1-3; R_1 a group is of the formula $-(CH_2)_r-S-\underset{R_{11}}{\overset{|}{C}}-\phi$ wherein ϕ is aryl, r is 1, 2 or 3 and R_{11} is hydrogen, (C_1-C_{10})alkyl- or aryl.

34. Pharmaceutical composition according to claim 33, characterized in that m is 3, r is 2, R_{11} is hydrogen and X is S or NH.

35. Pharmaceutical composition according to claim 34, characterized in that it comprises as the active ingredient N-[2-(benzylthio)ethyl]-S-[3-(imidazole-4-yl)propyl]-isothiourea or a pharmacological acceptable salt thereof.

36. Use of compounds of formula I as defined in claim 1 as an agent having biological activity.

37. Use of compounds of formula I as defined in claim 19 as an agent having agonistic or antagonistic acti-

vity on the histamine H_3-receptor.

38. Use of a compound of the formula I as defined in claim 19 for preparing a farmaceutical composition having agonistic or antagonistic activity on the histamine H_3-receptor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 92/00041

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D233/64; A61K31/415; C07D233/94; C07D233/95
C07D233/90; C07D233/68; C07D401/04; C07D401/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	DE,A,2 052 692 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 6 May 1971 see the whole document ---	1-9, 16-17, 19-29, 36-38
X	WO,A,8 707 891 (CEDONA PHARMACEUTICALS B.V.) 30 December 1987 see page 2 see page 4; example XII see page 6, line 25 - line 31 --- -/--	1,13-14, 18-19, 33-34, 36-37

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 JUNE 1992	30.07.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DE BUYSER I.A.F.

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Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 129 033 (POLAROID CORPORATION) 27 December 1984 see page 13 - page 15 see page 36; example IV see page 37; example VI see page 38; example VIII see page 40; examples X,XI	1
A	EP,A,0 041 359 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 9 December 1981	
A	DE,A,2 433 625 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 30 January 1975	
A	FR,A,2 311 536 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 17 December 1976	
A	US,A,4 262 125 (AMERICAN HOME PRODUCTS CORPORATION) 14 April 1981	
A	EP,A,0 177 808 (KANTO ISHI PHARMACEUTICAL CO.,LTD) 16 April 1986	
A	EP,A,0 262 448 (HEUMANN PHARMA GMBH & CO) 6 April 1988	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. NL 9200041 SA 57446

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/06/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2052692	06-05-71	BE-A- 758145	28-04-71
		CA-A- 953725	27-08-74
		CA-A- 987592	20-04-76
		FR-A,B 2070177	10-09-71
		GB-A- 1296544	15-11-72
		SE-B- 390303	13-12-76
		US-A- 3818097	18-06-74
WO-A-8707891	30-12-87	NL-A- 8601585	18-01-88
		AU-B- 604727	03-01-91
		AU-A- 7589387	12-01-88
		DE-A- 3772202	19-09-91
		EP-A,B 0302896	15-02-89
		JP-T- 1502981	12-10-89
		US-A- 5010095	23-04-91
EP-A-0129033	27-12-84	US-A- 4503139	05-03-85
		AU-B- 574359	07-07-88
		AU-A- 2777084	22-11-84
		CA-A- 1227489	29-09-87
		DE-A- 3473062	01-09-88
		JP-A- 59225168	18-12-84
		US-A- 4847383	11-07-89
EP-A-0041359	09-12-81	AT-T- 10277	15-11-84
		AU-A- 7102681	10-12-81
		JP-A- 57024387	08-02-82
DE-A-2433625	30-01-75	GB-A- 1431589	07-04-76
		AT-B- 346855	27-11-78
		AU-A- 6984574	11-12-75
		BE-A- 816850	27-12-74
		CA-A- 1049524	27-02-79
		CH-A- 601252	30-06-78
		FR-A,B 2274298	09-01-76
		JP-C- 1200542	05-04-84
		JP-A- 50032174	28-03-75
		JP-B- 58030314	28-06-83
		LU-A- 70507	28-11-74
		NL-A- 7408942	15-01-75