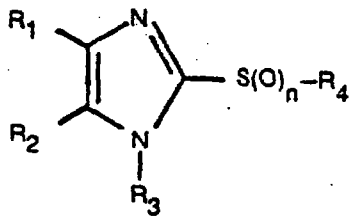
CIBA-GEIGY AG
Basel, Switzerland Case: 4-11666/+

Novel mercaptoimidazole derivatives, process for their preparation, mercaptoimidazole derivatives for the treatment of inflammatory disorders, and pharmaceutical products containing them

The present invention relates to substituted 2-mercaptoimidazoles of the formula



(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino,

alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur atom and from 6-membered heteroaryl radicals having one nitrogen atom, or radicals R_3 are different from hydrogen, when R_4 denote (sic) a lower alkyl radical which is substituted in the 2-, 3- or 4-position by a hydroxyl group, and with the further proviso that, in compounds of the formula I in which n represents 1 or 2, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur or oxygen atom or from 6-membered heteroaryl radicals having one nitrogen atom, when R_4 represents a lower alkyl which is substituted by one..... (sic) two hydroxyl groups, a lower alkoxy group or by phenyl which is optionally ....(sic) as indicated, or unsubstituted lower alkynyl and to pharmaceutically utilisable salts, especially pharmaceutically utilisable acid addition salts thereof.

In the foregoing and subsequent text, "lower" organic radicals and compounds are to be understood as meaning compounds having up to and including 7, especially up to and including 4, carbon atoms.

5-membered heteroaryl radicals having one oxygen or sulfur atom, one sulfur and one nitrogen atom, or at least two nitrogen atoms, or 6-membered heteroaryl radicals having at least one nitrogen atom are bonded via a C atom. Particular examples which may be mentioned are furyl, for example 2-furyl, thienyl, for example 2-thienyl, thiazolyl, for example 1,3-thiazol-2-yl or -4-yl, imidazolyl, for example imidazol-2-yl or -4-yl, triazolyl, for example 1H- or 2H-1,2,3-triazol-4-yl or -5-yl or 1H- or 2H-1,2,4-triazol-3-yl or -5-yl, tetrazolyl, for example 1H-tetrazol-5-yl, pyridyl, for example 2-, 3- or 4-pyridyl, pyrimidinyl, for example 2- or 4-pyrimidinyl, or triazinyl, for example 1,3,5-triazin-2-yl or 1,2,4-triazin-3-yl.

Examples which may be mentioned of lower alkylamino, di-lower-alkylamino and alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, are, in addition to methylamino and ethylamino, especially dimethylamino, diethylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino and N'-lower-alkyl-, for example N'-methyl-, piperazino.

Examples of lower alkyl, lower alkenyl and lower alkynyl which are optionally substituted by phenyl are lower alkyl having 1 to 4 C atoms, phenyl-lower-alkyl, such as 1- or 2-phenyl-lower-alkyl having 7 to 10 C atoms, for example benzyl or 2-phenylethyl, lower alkenyl having 2 to 4 C atoms, for example vinyl, allyl or methallyl, phenyl-lower-alkenyl having 8 to 10 C atoms, for example styryl, lower alkynyl having 2 to 4 C atoms, for example ethynyl or propargyl, or phenyl-lower-alkynyl having 8 to 10 C atoms, for example phenylethynyl.

Lower alkyl which is substituted in a position higher than the α-position by hydroxyl (hydroxy-lower-alkyl) is, for example, mono- or dihydroxy-lower-alkyl, has, in particular, 2 to 4 C atoms, and is, for example, 2-hydroxyethyl, 2- or 3-hydroxypropyl or 2,3-dihydroxypropyl.

Lower alkyl which is substituted in a position higher than the α-position of which (sic) lower alkoxy (lower

alkoxy-lower-alkyl) has, for example, 1 to 4 C atom in each, and is, for example, 2-methoxyethyl, 2-ethoxyethyl or 2- or 3-methoxypropyl.

Lower alkyl which is substituted in a position higher than the α-position by lower alkylthio (lower alkylthio-lower-alkyl) and has 1 to 7 C atoms, is, for example, 2-methylthioethyl.

Lower alkyl which is substituted in a position higher than the α-position by phenoxy or phenylthio which is optionally substituted as indicated, and has 1 to 7 C atoms in the alkyl moiety is, for example, 2-phenoxyethyl or 2-phenylthioethyl.

Examples of lower alkyl having 1 to 7 C atoms are methyl, ethyl, propyl, isopropyl or n-, iso-, sec- or tert.-butyl or, secondarily, one of isomeric pentyl, hexyl or heptyl groups.

Examples of lower alkoxy having 1 to 7 C atoms are methoxy, ethoxy, propoxy, isopropoxy, n-, sec-, iso- or tert.-butoxy or, secondarily, one of the isomeric pentyloxy, hexyloxy or heptyloxy groups.

Lower alkenyl and lower alkynyl have, for example, 2 to 4 C atoms; examples of lower alkenyl are vinyl, allyl or methallyl, while lower alkynyl especially denotes ethynyl or propargyl.

Halogen is preferably halogen of atomic number up to and including 35, such as fluorine, chlorine or bromine.

Salts of compounds of the formula I are especially pharmaceutically utilisable acid addition salts with strong acids, such as mineral acid, for example salts with hydrogen halide acids, especially hydrochloric or hydrobromic acid, i.e. hydrohalides, especially hydrochlorides and hydrobromides, or sulfuric acid salts, i.e. bisulfates and sulfates.

The invention especially relates to substituted 2-mercaptoimidazoles of the formula I in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom, or at least two nitrogen

atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 5-aza (sic) , 3-oxa or 3-thia-alkylene-amino, each having 5 or 6 ring members, and/or trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl or hydroxy-lower-alkyl, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0 and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted or (sic) in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur atom and from 6-membered heteroaryl radicals having one nitrogen atom, or radicals R_3 are different from hydrogen, when R_4 denotes a lower alkyl radical which is substituted in the 2-, 3- or 4-position by a hydroxyl group, and to pharmaceutically utilisable salts, especially pharmaceutically utilisable acid addition salts thereof.

The compounds of the formula I have valuable pharmacological properties. In particular, they exhibit pronounced

antiinflammatory and/or antinociceptive activity and an ...(sic) effect on prostaglandin synthesis. Thus, they prove to have excellent activity in the kaolin paw oedema of the rat, according to Helv. Physiol. Acta 25, 156 (1967), in the dose range from about 50 to 200 mg/kg orally, and on the writhing syndrome induced by phenyl-p-benzoquinone in the mouse, according to J. Pharmacol. exp. Therap. 125, 237 (1959), in the dose range from about 100 mg/kg orally.

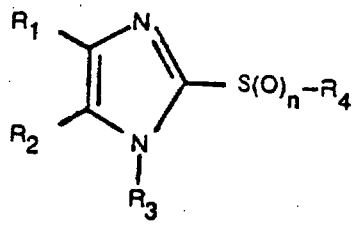
Furthermore, in the concentration range from about 10 to 30 ml/l, they inhibit the in vitro synthesis of prostaglandins from arachidonic acid, detected in the test design according to Prostaglandins 7, 123 (1974).

Mercaptoimidazole derivatives having antiinflammatory activity have already been disclosed in German Patent A-2,635,876, their 2-mercapto group being substituted by lower alkyl which is optionally substituted in a certain manner or by certain lower alkenyl groups, and their 4- and 5-position being substituted by optionally substituted phenyl groups. In addition, 2-polyhalogeno-lower-alkylthioimidazoles having an antiinflammatory effect have been disclosed in German Patent A-2,805,167, their 4- and 5-position being substituted by at least one thienyl, pyridyl or furyl group and, optionally, additionally by optionally substituted phenyl. Mercaptoimidazoles of less closely related structure were, furthermore, previously known from US Patent A-2,981,739, US Patent A-3,714,179 and French Patent A-2,194,433. Furthermore, reference may be made to the non-prior-published European Patent Applications Nos. 353,5545 and 13732 which likewise partly belong to the state of the art.

Compounds of the formula I are distinguished from mercaptoimidazole derivatives disclosed in German Patent A-2,805,167 by a more favourable therapeutic index.

For this reason, the compounds of the formula I are excellently suitable as active compounds in pharmaceutical products for the treatment of inflammatory disorders, especially chronic rheumatic inflammations, such as chronic arthritis.

Accordingly, the invention likewise ...(sic) compounds of the formula



(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom or at least two nitrogen atoms, or 5-membered heteroaryl group which has at least 2 nitrogen atoms, ...(sic) or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino,

lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that, in compounds of the formula I in which n represents 1 or 2, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur or oxygen atom or from 6-membered heteroaryl radicals having one nitrogen atom, when R_4 represents a lower alkyl which is substituted by one or two hydroxyl groups, a lower alkoxy group or by phenyl which is optionally substituted as indicated, or unsubstituted lower alkynyl and to their pharmaceutically utilisable salts for use in a process for the therapeutic treatment of the human or animal body, to their pharmaceutical products containing them, and to their use of (sic) medicament or for the preparation of medicaments by non-chemical means.

The invention primarily relates to those of the compounds which were defined in the introduction and in which, in the formula I, at least one of the radicals R_1 and R_2 denotes furyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or triazinyl, it being possible for ring carbon atoms of the said radicals R_1 and R_2 to be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, amino, lower alkylamino, and/or alkylene- or 3-aza-, 3-oxa- or 3-thio(sic)-alkyleneamino, each having 5 or 6 ring members, ring nitrogen atoms of pyrimidinyl, triazinyl or pyridyl radicals as well as by oxy, and a radical R_1 or R_2 which is different from this represents phenyl which can be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, R_3 denotes hydrogen or lower alkyl, n represents 0, 1 or ... (sic), and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is optionally substituted by lower alkyl, lower alkoxy, halogen of atomic number

up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and has not more than 7 C atoms, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is optionally substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and has not more than 7 C atoms, and to their, preferably pharmaceutically utilisable, acid addition salts and to pharmaceutical products containing these compounds and to their use.

The invention especially relates to compounds of the formula I in which one of the radicals R_1 and R_2 denotes an optionally substituted pyridyl group and the other denotes an optionally substituted phenyl or pyridyl group, R_3 represents hydrogen or lower alkyl having 1 to 4 C atoms, such as methyl, n represents 0, and R_4 denotes lower alkyl which is optionally substituted by phenyl or, in a position higher than the α-position, by hydroxyl, lower alkoxy or lower alkylthio having 1 to 4 C atoms, phenoxy or phenylthio, and has 1 to 7 C atoms, or denotes a lower alkenyl or lower alkynyl radical which is optionally substituted by phenyl and has 2 to 4 C atoms, it being possible for pyridyl, phenyl, phenoxy or phenylthio groups to be substituted by lower alkyl having 1 to 4 C atoms, such as methyl, lower alkoxy having 1 to 4 C atoms, such as methoxy or ethoxy, halogen of atomic number up to and including 35, such as chlorine, nitro, amino or N,N-di-lower-alkylamino, each having 1 to 4 C atoms, such as dimethylamino, and to their salts, and to pharmaceutical products containing these compounds and to their use.

The invention preferably relates to compounds of the formula I in which one of the radicals R_1 or R_2 denotes pyridyl and the other denotes phenyl, it being possible for these radicals, independently of one another, to be substituted

by lower alkyl having 1 to 4 C atoms, such as methyl, lower alkoxy having 1 to 4 C atoms, such as methoxy or ethoxy, halogen of atomic number up to and including 35, such as chlorine, and/or N,N-di-lower-alkylamino, each having 1 to 4 C atoms, such as dimethylamino, but being preferably unsubstituted, R_3 denotes hydrogen or lower alkyl having 1 to 4 C atoms, such as methyl, n represents 0, and R_4 denotes lower alkyl having 1 to 4 C atoms, such as methyl, ethyl, propyl, isopropyl or butyl, lower alkenyl having 2 to 4 C atoms, such as allyl, phenyl-lower-alkyl which is optionally substituted by lower alkyl having 1 to 4 C atoms, such as methyl, lower alkoxy having 1 to 4 C atoms, such as methoxy or ethoxy, and/or halogen of atomic number up to and including 35, such as chlorine, and has 1 to 4 C atoms in the alkyl moiety, mono- or dihydroxy-lower-alkyl which carries hydroxyl group(s) in a position higher than the α-position and has 1 to 4 C atoms, such as 2-hydroxyethyl, lower alkoxy- or lower alkylthio-lower-alkyl which carries the alkoxy or alkylthio group in a position higher than the α-position and each has 1 to 4 C atoms in the alkyl moieties, such as 2-methoxyethyl or 2-methylthioethyl, and to their acid addition salts, and to pharmaceutical products containing these compounds and to their use.

The invention especially relates to compounds of the formula I in which one of the radicals R_1 and R_2 denotes unsubstituted pyridyl, such as 3-pyridyl, or thienyl, such as 2-thienyl, and the other denotes phenyl which is unsubstituted or substituted by lower alkyl having 1 to 4 C atoms, such as methyl, lower alkoxy having 1 to 4 C atoms, such as methoxy and/or halogen of atomic number up to and including 35, such as chlorine or, especially, fluorine, R_3 denotes hydrogen or, secondarily, lower alkyl having 1 to 4 C atoms, such as methyl, n represents 0, 1 or 2, and R_4 represents lower alkyl having 1 to 4 C atoms, such as ethyl, and to their salts, and to pharmaceutical products containing these compounds and to their use.

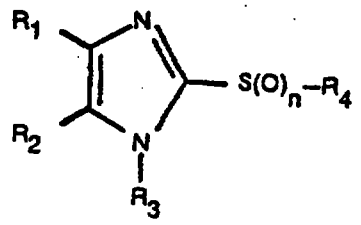
The invention particularly relates to compounds of

the formula I in which one of the radicals R_1 and R_2 denotes unsubstituted pyridyl, such as 3-pyridyl, and the other denotes phenyl which is unsubstituted or, secondarily, substituted by lower alkyl having 1 to 4 C atoms, for example methyl, lower alkoxy having 1 to 4 C atoms, for example methoxy, or halogen, for example chlorine or bromine, R_3 represents hydrogen or lower alkyl having 1 to 4 C atoms, for example methyl or ethyl, n represents 0 and R_4 denotes hydrogen, lower alkyl having 1 to 4 C atoms, for example methyl or ethyl or hydroxy-lower-alkyl which carries the hydroxyl group in a position higher than the α-position and has 2 to 4 C atoms, for example 2-hydroxyethyl, and to their acid addition salts, and to pharmaceutical products containing these compounds and to their use.

The invention relates above all to compounds of the formula I in which one of the radicals R_1 and R_2 denotes pyridyl, such as 3-pyridyl, and the other denotes phenyl, R_3 is hydrogen, n represents 0 or 1, and R_4 denotes lower alkyl having 1 to 4 C atoms, such as ethyl, and to their acid addition salts, and to pharmaceutical products containing these compounds and to their use.

The invention relates in particular to the compounds of the formula I mentioned in the Examples and to their acid addition salts.

The invention also relates to a process for the preparation of compounds of the formula



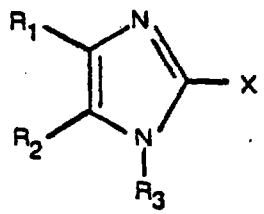
(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen

atom or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl and of their acid addition salts.

The compounds of the formula I and their salts can be prepared by methods known per se, for example by

a) reacting together compounds of the formulae



(II) and Y-R_4 (III)

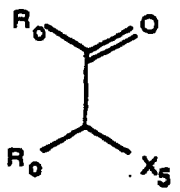
... (sic) in the form of mercapto and the other denotes a radical which is replaceable by etherified mercapto, with the proviso that, in compounds of the formula (II) in which X is mercapto which is optionally in the form of a salt, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radical (sic) having one sulfur atom or 6-membered heteroaryl radical (sic) having one nitrogen atom, or radicals R_3 are different from hydrogen, when in compounds of the formula (III) Y represents reactive esterified hydroxyl and R_4 represents a lower alkyl radical which is substituted once by hydroxyl in the 2-, 3- or 4-position or

b) reacting together compounds of the formulae II and III, in which one of the radicals X and Y is a group of the formula $-S(O)_n-Y_1$, in which Y_1 is a reactive esterified hydroxyl group or, if n represents 0, is an etherified mercapto group or, if n represents 1 or 2, is an etherified hydroxyl group, and the other represents a metal radical Y_2, or

c) reacting a compound of the formula II, in which X represents the mercapto group, with a lower alkene which is optionally substituted as indicated for R_4 and

d) reacting a compound of the formula II, in which X denotes a sulfinic or sulfonic acid group in the form of a salt, with a compound of the formula III, in which Y denotes a reactive esterified hydroxyl group, or,

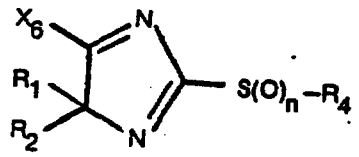
e) reacting a compound of the formula



(VI)

in which one of the radicals R_o represents a group R_1 and the other represents a group R_2, and X_5 denotes a reactively (sic) esterified hydroxyl group, or an acid addition salt thereof, with an $N-R_3-S-R_4$-isothiourea, or

f) rearranging a compound of the formula



(VII)

in which X_6 is lower alkylthio which is optionally substituted by phenyl which in turn can be substituted as R_1 and R_2, or an acid addition salt thereof, and, if desired, oxidising the thio group in a compound of the formula I, obtained according to process variants a) to f), in which n represents 0, and R_1, R_2, R_3 and R_4 have the above meanings, with the proviso that in compounds of the formula (I) obtained according to process variant a) by a reaction of compounds of the formulae (II) and (III), in which X is mercapto which is optionally in the form of a salt, and Y is reactive esterified hydroxyl, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur or oxygen atom or 6-membered heteroaryl radicals having one nitrogen atom, when R_4 represents a lower alkyl radical which is substituted by one or two hydroxyl groups or one lower alkoxy group or by phenyl which is optionally substitued as indicated, or unsubstituted lower alkynyl radical, to the sulfinyl or sulfonyl group, and/or in compounds, obtained according to one of the process variant (sic) a) to f), in which R_1 and/or R_2 has at least one nitrogen atom $\geqslant$ N carrying out N-oxidation of the latter, or oxidising the sulfinyl or sulfonyl group in compounds obtained according to one of the process variant (sic) b) or f), in which n represents 1 or 2, to the thio group, and/or ... (sic) compounds, obtained according to process variant a) to f), in which R_1 and R_2 have an N-oxidised nitrogen atom reducing the latter to a group $\geqslant$ N, N-lower-alkylating a compound of the formula I obtained according to the process, in which R_3 represents hydrogen, in compounds of the formula I obtained according to the process optionally introducing additional C-substituents ... (sic) radicals R_1, R_2 and/or phenyl, phenoxy or phenylthio groups as constituent of R4, and/or converting

a free compound obtained according to the process into an acid addition salts (sic), or converting an acid addition salt obtained according to the process into the free compound or into another salt.

Mercapto or sulfinic acid groups in the form of a salt are, for example, mercapto or sulfinic acid groups in the form of alkali metal or ammonium salts, for example as sodium, potassium or ammonium salt.

Examples of radicals X and Y which are replaceable by etherified mercapto are halogen atoms, for example chlorine, bromine or iodine, radicals X which are replaceable by the group $-SR_4$ are, furthermore, sulfonyl groups, especially sulfonyl groups derived from organic sulfonic acids, for example methane-, ethane-, benzene-, p-bromobenzene- or p-toluenesulfonyl. Radicals Y which are replaceable by $1-R_3-4-R_1-5-R_2$-imidazol-2-ylthio are, furthermore, other reactively (sic)esterified hydroxyl groups as halogen (sic), such as hydroxyl groups esterified with sulfuric acid or with an organic sulfonic acid, for example with methane-, ethane-, benzene-, p-bromobenzene- or p-toluenesulfonic acid.

Examples of reactively (sic) esterified hydroxyl groups Y and Y_1 are halogen atoms, such as chlorine, bromine or iodine, or sulfonyloxy groups, preferably sulfonyloxy groups of the formula $-SO_2-R_4$ in groups Y of the formula $-S(O)_n-Y_1$ in which n represents 2. Etherified mercapto groups Y_1 are in groups X of the formula $-S(O)_n-Y_1$ in which n represents 0, for example $1-R_3-4-R_1-5-R_2$-imidazol-2-ylthio radicals and in groups Y of the formula $S(O)_n-Y_1$ in which n represents 0, for example those of the formula $-SR_4$. Etherified hydroxyl is, for example, hydroxyl which is etherified with an aromatic alcohol, such as an optionally substituted phenol, in groups of the formula $-S(O)_n-Y_1$, in which n represents 1, also lower alkoxy. Examples of metal radicals Y_2 are those of the formulae $-M^I$, $-M^{II}/2$ or $-M^{II}$-Hal, in which M^I denotes an alkali metal atom, for example lithium or sodium, and M^{II} denotes an alkaline earth metal atom, for example magnesium, cadmium (sic) or zinc (sic).

The reaction according to process variants a) - d) can be carried out in the customary manner, in particular in the manner known from the literature for analogous reactions, where necessary in the presence of a catalytic agent, for the reaction of mercapto compounds of the formula II with alkenes of phenylalkenes, for example of acidic agents, such as Lewis acids, for example of iron-II salts or boron trifluoride, of peroxides, for example of di-tert.-butyl peroxide, or under the action of UV light, for example of the wavelength from about 200 to 350 um (sic). The said reactions are preferably carried out in a solvent, starting from compounds of the formulae II and III, in which one of the radicals X and Y is a metal radical and the other is a group of the formula $-S(O)_n-Y_1$, and in the reaction of mercapto compounds of the formula II with alkenes or phenylalkenes of the formula III, for example in ether, tetrahydrofuran or dioxane, or in the reaction of mercaptans or mercaptides or sulfonic acid salts of the formula II with reactive esters, for example halides, of the formula III, for example in an alcohol, for example in methanol, ethanol, ethylene glycol or ethylene glycol monomethyl ether, in each case advantageously under an atmosphere of inert gas, for example under nitrogen, and, if necessary, at elevated temperature, for example at the boiling point.

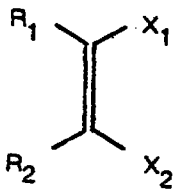
A preferred embodiment of the abovementioned process variant a) or d) comprises, for example, reaction of a 2-mercapto- or 2-sulfoimidazole derivative of the formula II, which is optionally in the form of one of the said salts, in a lower alkanol, for example in methanol or ethanol, with an ester of hydrochloric, hydrobromic or hydriodic or sulfuric acid, of the formula II.

In a preferred embodiment of process variant b), for example a compound of the formula II, in which X denotes a metal radical Y_2, preferably lithium, and R_3 is preferably different from hydrogen, is reacted, for example in an open-chain or cyclic aliphatic ether, for example in diethyl ether, tert.-butyl methyl ether, tetrahydrofuran or dioxane,

with a compound of the formula III, in which Y denotes a group of the formula $-S-S-R_4$, halogen-$S-R_4$ or $-S(O)_2-O-S(O)_2-R_4$.

Some of the starting materials are known. New starting materials can be prepared by methods known per se.

The compounds of the formula II mentioned as starting materials, in which X denotes mercapto, i.e. $1-R_3-4-R_1-5-R_2$-2-mercapto-imidazoles or $1-R_3-4-R_1-5-R_2$-imidazolinethiones, in which R_1, R_2 and R_3 have the meanings indicated in the introduction under formula I, can be prepared by, for example, carrying out intramolecular cyclisation of a compound of the formula



(IV),

in which X_1 denotes a group of the formula $-NH-C(=S)-NHR_3$ and X_2 denotes hydroxyl, or X_2 denotes a group of the formula $-NR_3-C(=S)-NH_2$ and X_1 denotes hydroxyl, or of a tautomer thereof which is optionally in a ketalised form.

Preferred tautomers of compounds of the formula IV are the ketones which are tautomeric to enols corresponding to the formula IV. These ketones can be ketalised with lower alkanols or lower alkanediols, for example with methanol, ethanol or ethylene glycol or 1,3-propylene glycol.

The intramolecular cyclisation can be carried out in a customary manner, in particular in the manner described in the literature for analogous reactions, for example in a solvent, such as water, or an alcohol, for example in water, ethanol, butanol, ethylene glycol or ethylene glycol monomethyl ether, if necessary in the presence of an acidic condensing agent, such as a mineral acid, for example of hydrochloric acid and/or at elevated temperature, for example at the boiling point.

The starting materials of the formula lv in turn can

be obtained by methods known per se, it being advantageous to prepare them in situ and to cyclise them without isolation. For this purpose, it is preferable to start from a compound of the formula R_1-CO-CH(NHR_3)-R_2 (Iva), or from an acid addition salt thereof, and to react this with thiocyanic acid or a metal thiocyanate. The intermediate formed in this reaction is a compound of the formula IV which undergoes cyclisation according to the invention. It is particularly advantageous to react a hydrohalide, for example the hydrochloride, of a compound of the formula Iva with an alkali metal thiocyanate or ammonium thiocyanate, for example with sodium thiocyanate or potassium thiocyanate, in aqueous solution, where necessary with heating to 60 to 100°C.

One variant of this process comprises reaction, in an analogous manner, of a compound of the formula R_1-CH(NH_2)-CO-R_2 (Ivb), or of an acid addition salt thereof, with an isothiocyanate of the formula R_3-N=C=S (Ivc).

The starting materials of the formula IV can furthermore be prepared by reaction of a compound of the formula R_0-CO-CHOH-R_0 (Ivd), or of a compound of the formula R_0-CO-CH(Halogen)-R_0 (Ivf) obtainable by α-halogenation of a compound of the formula R_0-CO-CH_2-R_0 (Ive), for example with bromine in acetic acid, in which one of the groups R_0 represents the radical R_1 and the other represents the radical R_2, in a customary manner with a thiourea compound of the formula R_3NH-CS-NH_2 (Ivg) or with a compound generating this in situ, for example with an R_3-ammonium thiocyanate. At elevated temperatures, for example at 100-250°, the compound of the formula IV, which is initially formed in this reaction, cyclises in the manner according to the invention. In this way it is possible to obtain, where R_1 and R_2 are different and R_3 does not represent hydrogen and according to the reactivities of the individual component of the formula Ivc and/or the reaction conditions, both or only one of the possible isomers, i.e. a 1-R_3-4-R_1-5-R_2-2(3H)-imidazoline-2-thione and-or a 1-R_3-4-R_2-5-R_1-2(3H)-imidazoline-2-thione, which can optionally be separated in a customary

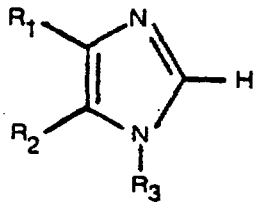
manner, for example by fractional crystallisation or by chromatography.

The starting materials in formula IVa in turn can be prepared in a manner known per se, for example by oximation of a compound of the formula R_1-CO-CH_2-R_2, conversion, with toluenesulfonyl chloride in pyridine, of the oxime into the oxime ester, subjecting the latter to the Neber oxy-aminoketone rearrangement and, if desired, introducing a radical R_3 into the resulting compound of the formula R_1-CO-CH(NH_2)-R_2, for example by reaction with a lower alkyl bromide or iodide.

Starting materials of the formula Ivb can be prepared in an analogous manner, starting from a compound of the formula R_1-CH_2-CO-R_2.

Starting materials of the formula Ivd, in which R_1 and R_2 denote the same radicals R_0, can furthermore be prepared by self-condensation, for example brought about by potassium cyanide in ethanol/water or tetrabutylammonium cyanide in water, of an aldehyde of the formula R_0-CHO (Ivh).

The compounds of the formula II, in which X is mercapto, can furthermore be obtained by heating a corresponding imidazole derivative of the formula



(V)

which is unsubstituted in the 2-position, in tetramethylene sulfone, with sulfur to about 150-250°C, for example to about 200°C.

Starting materials of the formula II, in which X denotes a metal radical Y_2, are preferably prepared in situ, for example by reaction of a compound of the formula V with an organometallic compound of the formula R-Y2 (VI), in which R is an aliphatic radical, preferably lower alkyl, for example with butyllithium or methyl or butyl magnesium bromide. From the organomagnesium compounds thus obtainable it

is then possible to obtain, by reaction with zinc chloride or cadmium dichloride, compounds of the formula II in which Y_2 is a group Zn-halogen or Cd-halogen.

The starting materials of the formula V can in turn be prepared by heating of a compound of the formula R_0-CO-CH(halogen)-R_0 (Ivf), in which one of the radicals R_0 represents a group R_1 and the other represents a group R_2, with formamide, preferably at the boiling point. The compounds of the formula Ivf can in turn be obtained by reaction of a compound of the formula R_1-CH=O or R_2CH=O (Va) in the presence of a di-lower-alkylamine hydrochloride, for example of dimethylamine hydrochloride, with an alkali metal cyanide, treatment of the resulting 2-R_1- or 2-R_2-di-lower-alkylaminoacetonitrile (Vb) with sodium hydride in dimethylformamide and then with a compound of the formula R_2- or R_1-CH_2-halogen (Vc), hydrolysis of the condensation product by heating for several hours in a mixture of concentrated hydrochloric acid and chloroform, and halogenation of the resulting compound of the formula R_0-CO-CH_2-R_0 (Ive), for example using bromine in acetic acid or copper-II bromide in ethyl acetate.

Starting materials of the formula II in which X denotes an optionally esterified or anhydridised sulfo group, such as sulfo, lower alkoxy- or phenoxysulfonyl, or a sulfonyloxysulfonyl group, can be obtained by, for example, oxidation of the mercapto group in a compound of the formula II, in which X is mercapto, to the sulfo group, and, if desired, halogenation of the latter, for example with phosphorus pentachloride, and conversion of the halogenosulfonyl group into esterified sulfo using an alcohol, for example lower alkanol or phenol, or anhydridisation in a customary manner, for example by reaction with a sulfonic acid salt. It is also possible to prepare sulfinic esters of the formula II analogously, the oxidation of the mercaptan being stopped at the sulfinic acid stage. Compounds of the formula II in which X is a group -S-S-R_4 can be obtained by mild oxidation of mercaptans of the formula II, for example using iron-III

chloride or atmospheric oxygen.

In process variant e), it is also possible for the compound of the formula VI, in which R_1 and/or R_2 represents a basic group, to be in the form of an acid addition salt.

The reaction according to process variant b) is carried out in a customary manner, preferably by liberation in situ of the N-R_3-S-R_4-isothiourea and, where appropriate, the compound of the formula VII, for example by the action of a base, such as an alkali metal hydroxide or carbonate, for example of sodium hydroxide or carbonate or potassium hydroxide or carbonate, or a nitrogen base, for example of ammonia, of a tri-lower-alkylamine, such as triethylamine or N,N-diisopropylethylamine or pyridine, from an N-R_3-S-R_4-isothiuronium salt, such as alkosulfate or halide, for example bromide or chloride, and from a compound of the formula VI which is optionally in the form of a salt, three equivalents of bases being necessary when starting from starting materials of the formula VI which are in the form of salts, otherwise two equivalents being necessary, advantageously in a solvent, such as a lower alkanol, for example in methanol, ethanol, butanol or amyl alcohol, where necessary at elevated temperature, for example at the boiling point.

The starting materials of the formula VI can be prepared by methods known per se, for example by reaction of a compound of the formula R_1-CH=O or R_2-CH=O (Va) in the presence of a di-lower-alkylamine hydrochloride, for example of dimethylamine hydrochloride, with an alkali metal cyanide, treatment of the resulting 2-R_1- or 2-R_2-di-lower-alkylaminoacetonitrile (Vb) with sodium hydride in dimethylformamide, and then with a compound of the formula R_2- or R_1-CH_2-halogen (Vc), hydrolysis of the condensation product by heating for several hours in a mixture of concentrated hydrochloric acid and chloroform, and halogenation of the resulting compound of the formula R_0-CO-CH_2-R_0 (Ive), for example using bromine in acetic acid or copper-II bromide in ethyl acetate.

The rearrangement according to process variant f) can be carried out in a customary manner, where necessary in the presence of a catalyst, such as a Lewis acid, for example of aluminium trichloride, and advantageously in a solvent, for example in benzene, toluene, N,N-dimethylaniline, anisole, tetralin, chlorobenzene, pyridine or decalin.

The starting materials of the formula VII can be prepared in a manner known per se, for example by first reacting a compound of the formula R_1-CO-CO-R_2 (VIIa) with thiourea, conversion of the resulting S-R_1-5-R_2-2-thiohydantoin with phosphorus pentasulfide into the corresponding 5-R_1-5-R_2-di-thiohydantoin, and further reaction of the latter with a lower alkyl halide which is optionally substituted as indicated for X_6.

Introduction, conversion or elimination of substituents in resulting compounds of the formula I is possible within the scope of the definition given.

Thus, for example, it is possible to introduced (sic) an organic radical R_3 in place of a hydrogen atom R_3 by reaction with an agent introducing the radical R_3. Examples of such agents are reactive esters, such as esters of hydrohalic acids, for example esters of hydrochloric, hydrobromic or hydroiodic acid, organic sulfonic esters, for example methane-, ethane-, benzene-, p-bromobenzene- or p-toluenesulfonic esters, or sulfuric esters of appropriate lower alkanols R_3OH. The reaction with these agents is carried out in a customary manner, for example in the presence of a basic condensing agent, such as an alkali metal hydroxide or carbonate, for example sodium hydroxide or potassium hydroxide or sodium carbonate or potassium carbonate, an alcoholate, for example alkali metal lower alkanolate, such as sodium methanolate, as well as of sodium hydride, advantageously in an inert solvent, for example in dimethylformamide or N-methylpyrrolidone.

Furthermore, in compounds of the formula I, it is possible to carry out N-oxidation (sic) of radicals -S(O)n-R_4, in which n represents 0, to give the corresponding

sulfinyl or sulfonyl radicals, in which n represents 1 or 2, of radicals $-S(O)_n-R_4$, in which n represents 1, to give the corresponding sulfonyl radicals, in which n denotes 2, and/or of heteroaryl radicals R_1 and/or R_2 having at least one free ring nitrogen atom $\gg N$, such as pyridyl radicals. The oxidation is preferably carried out by the action of a suitable oxidising agent, advantageously in a solvent which is inert towards the latter, where necessary while cooling or heating, for example in the temperature range from about -30°C to +100°C, preferably at about 0° to 60°C, in a closed vessel and/or under inert gas, such as nitrogen. Examples of suitable oxidising agents are peroxy compounds, such as hydrogen peroxide, organic hydroperoxides, for example tert.-butyl hydroperoxide, organic peracids, such as aromatic or aliphatic percarboxylic acids, for example m-chloroperoxybenzoic acid, peroxyacetic acid or permonophthalic acid, oxidising heavy metal compounds, such as chromium-VI or manganese-IV or manganese-VII compounds, for example chromium trioxide, chromic acid, manganese dioxide or potassium permanganate, oxidising inorganic oxygen acids, such as oxygen acids of nitrogen, the halogens or chalcogens, or their anhydrides or salts, for example nitric acid, dinitrogen tetroxide, selenium dioxide or sodium metaperiodate, furthermore ozone. Examples of suitable solvents are halogenated hydrocarbons, such as halogenoalkanes, for example carbon tetrachloride, chloroform or methylene chloride, or carboxylic acids, such as alkanoic acids, for example acetic acid, or their anhydrides.

In a preferred embodiment of this oxidation process, it is possible, for example, to oxidise thioethers of the formula I, in which n represents 0, and/or one of the radicals R_1 and/or R_2 has an unsubstituted ring nitrogen atom $\gg N$, by reaction with an organic peracid, for example with m-chloroperbenzoic acid, in a halogenoalkane, for example in chloroform, to give the corresponding sulfinyl or sulfonyl compounds, in which n represents 1 or 2, and, where appropriate, to oxidise on the nitrogen atom $\gg N$.

In another preferred embodiment, it is possible to oxidise thioethers of the formula I, in which n represents 0, by treatment with sodium metaperiodate, preferably in a halogenoalkane, for example in carbon tetrachloride or chloroform, selectively to the corresponding sulfonxides (sic), in which n represents 1, or to oxidise the latter with hydrogen peroxide in acetic acid to give sulfones, in which n represents 2.

Conversely, in compounds of the formula I, in which n represents 1 or 2 and/or heteroaryl radicals R_1 and/or R_2 are N-oxidised, it is possible to reduce the group $-S(O)-R_4$ or $-S(O)_2-R_4$ to the corresponding group $S(O)_0-R_4$ and/or N-oxidised ring nitrogens $\gg N-O$ to $\gg N$. The reduction is carried out by treatment with customary reducing agents, for example with nascent or catalytically activated hydrogen, such as iron or zinc and acid, such as hydrochloric acid, and with hydrogen in the presence of Raney nickel, advantageously in an inert solvent, such as a lower alkanol or with light metal hydrides or di-light-metal hydrides, for example with alkali metal aluminium hydrides or alkali metal borohydrides, for example with sodium borohydride or lithium aluminium hydride, advantageously in an inert solvent, such as an ether, for example diethyl ether or tetrahydrofuran, or, for the selective reduction of groups N-O, with a phosphorus-III compound, such as a phosphine, for example triphenylphosphine or tri-n-butylphosphine, or a phosphorous ester, such as tri-lower-alkyl phosphite, for example with trimethyl or triethyl phosphite.

Furthermore, it is possible, where appropriate, to introduce additional C-substituents into the radicals R_1 and R_2 and into phenyl, phenoxy and phenylthio groups as constituents of R_4. Thus, it is possible to halogenate in a customary manner, for example by reaction with chlorine or bromine in the presence of iron or using N-chlorosuccinimide. Furthermore, it is possible in a customary manner to carry out lower alkylation, for example by reaction with a lower alkyl halide, lower alkanol or lower alkene in the presence

of aluminium trichloride. In addition, it is possible to carry out nitration in a customary manner, for example using nitric acid/sulfuric acid.

In addition, nitro groups can be reduced in a customary manner, such as with nascent hydrogen, for example with iron/hydrochloric acid, to amino.

Lower alkylation of amino groups is furthermore possible in a customary manner by reaction with a lower alkylating agent, such as one of those mentioned, in the presence of a basic condensing agent.

Furthermore, resulting free compounds can be converted in a manner known per se into acid addition salts, for example by reaction of a solution of the free compound, in a suitable solvent or mixture of solvents, with one of the abovementioned acids or with a solution thereof, or with a suitable anion exchanger.

It is possible to convert resulting acid addition salts into the free compounds in a manner known per se, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or bicarbonate, or ammonia, or with a suitable anion exchanger.

It is possible to convert resulting acid addition salts into other acid addition salts in a manner known per se, for example by treatment with an anion exchanger or by treatment of a salt of an inorganic acid with a suitable metal salt, such as a sodium, barium or silver ...(sic) of an acid in a suitable solvent in which an inorganic salt which is being formed is insoluble and thus separates out of the reaction mixture.

The compounds, including their salts, can also be obtained in the form of the hydrates or can entrap the solvent used for the crystallisation.

As a consequence of the close relation between the new compounds in the free form and in the form of their salt, in the preceding and following text where appropriate the free compounds or their salts are to be understood as also meaning, in accordance with the sense and purpose, the

corresponding salts or free compounds respectively.

The invention relates to onto (sic) those embodiments of the process in which a start is made with a compound obtainable as an intermediate at any desired stage of the process, and the remaining process steps are carried out, or where a starting material is formed under the reaction conditions, or in the form of a derivative thereof, where appropriate a salt, is used. (sic)

In the process of the present invention, the starting materials which are preferably used are those which lead to the compounds which have been described in the introduction as particularly valuable.

The pharmaceutical products according to the invention, which contain compounds of the formula I or II or pharmaceutically utilisable salts thereof, are those which are for enteral, such as oral or rectal, and parenteral administration, and for topical administration to warm-blooded animal(s), which contain the pharmacological active compound alone or together with a pharmaceutically utilisable vehicle. The dosage of the active compound depends on the species of warm-blooded animal, the age and the individual condition, and on the mode of aministration. In the normal case the approximate daily dose for oral administration to a warm-blooded animal weighing about 75 kg is estimated to be about 30-300 mg, advantageously divided into several equal part-doses.

The new pharmaceutical products contain, for example, from about 10% to about 80%, preferably from about 20% to about 60%, of the active compound. Examples of pharmaceutical products according to the invention for enteral or parenteral administration are those in the form of dose units, such as coated tablets, tablets, capsules or suppositories, also ampoules. These are prepared in a manner known per se, for example using conventional mixing, granulating, grading, dissolving of freeze-drying processes. Thus, pharmaceutical products for oral administration can be obtained by combination of the active compound with solid vehicles, where

appropriate granulation of a resulting mixture, and ... (sic) of the mixture or granules, when desired or necessary, after addition of suitable auxiliaries, to give tablets or cores of coated tablets.

Particularly suitable vehicles are fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose products and/or calcium phosphate, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch mucilage, using, for example, maize starch wheat starch, rice starch or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrants, such as the abovementioned starches, also carboxylmethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are primarily flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/polyethylene glycol. Cores of coated tablets are provided with suitable coatings, which are, where appropriate, resistant to gastric juice, use being made of, inter alia, concentrated sugar solutions which contain, where appropriate, gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or mixtures of solvents or, for the preparation of coatings resistant to gastric juice, solutions of suitable cellulose products, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. It is possible to add to the tablets or coatings for coated tablets colorants or pigments, for example for the identification or labelling of different doses of active compound.

Further pharmaceutical products which can be administered orally are hard capsules made of gelatin, and soft closed capsules made of gelatin and a softening agent, such as glycerol or sorbitol. The hard capsules can contain the active compound in the form of granules, for example mixed with fillers, such as lactose, binders, such as starches, and/or ... (sic) agents, such as talc or magnesium stearate,

and, where appropriate, stabilisers. In soft capsules, the active compound is preferably in suitable fluids, such as fatty oils.(sic) Paraffin oil or liquid polyethylene glycols, dissolved or suspended, it also being possible to add stabilisers.

Examples of suitable pharmaceutical products for rectal administration are suppositories which such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, bases which are suitable, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. (sic) It is also possible to use gelatin rectal capsules which contain a combination of the active compound with a base; examples of suitable base materials are liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Primarily suitable for parenteral administration are aqueous solutions of an active compound in a water-soluble form, for example a water-soluble salt, also suspensions of the active compound, such as appropriate oily suspensions for injection, use being made of suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyloeate (sic) or triglycerides, or aqueous suspensions for injection which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, where appropriate, stabilisers as well.

Pharmaceutical products which are suitable for topical ... (sic) are primarily creams, ointments, pastes, foams, tinctures and solutions, which contain from 0.5 to about 20% of the active compound.

Creams are oil-in-water emulsions which have more than 50% water. The oily base which is primarily used is fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, lanolin or beeswax, and/or hydrocarbons, for example vaseline (petrolatum) or parffin (sic) oil. Suitable emulsifiers are

surface-active substances having predominantly hydrophilic properties, such as appropriate non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid esters or polyoxyethylene-sorbitan fatty acid esters (Tweens), as well as polyoxyethylene fatty alcohol ethers or fatty acid esters, or appropriate ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, for example sodium lauryl sulfate, sodium cetyl sulfate or sodium stearyl sulfate, which are customarily used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additions to the water phase are, inter alia, agents which reduce the drying out of the cream, for example polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, as well as preservatives, perfumes etc.

Ointments are water-in-oil emulsions which contain up to 70%, but preferably from about 20% to about 50%, of water or aqueous phases. Primarily suitable as the fatty phase are hydrocarbons, for example vaseline, paraffin oil and/or hard paraffins, which contain, to improve the water-binding capacity, preferably suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool alcohols, or lanolin. Emulsifiers are appropriate lipophilic substances, such as sorbitan fatty acid esters (spans), for example sorbitan oleate and/or sorbitan isostearate. Additions to the water phase are, inter alia, fumectants, such as polyalcohols, for example glycerol, propylene gylcol (sic), sorbitol and/or polethylene (sic) glycol, and preservatives, perfumes etc.

Fatty ointments are anhydrous and contain as the base, in particular, hydrocarbons, for example paraffin, vaseline and/or liquid paraffins, also natural or partially synthetic fat, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated arachis or castor oil, as well as fatty acid partial esters of glycerol, for example glycerol monostearate and distearate, as well as, for example, the fatty alcohols, emulsifiers and/

or additives, which increase the capacity to absorb water and which were mentioned in connection with the ointments.

Pastes are creams or ointments with discharge-absorbing powder constituents, such as metal oxides, for example titanium oxide or zinc oxide, also talc and/or aluminium silicates, which have the task of binding moisture or discharge which is present.

Foams are administered from pressurised containers and are liquid oil-in-water emulsions in the form of aerosols, use being made of halogenated hydrocarbons, such as chlorofluoro-lower-alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, as propellants. The oily phase used is, inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. Emulsifiers which are used are, inter alia, mixtures of those which have predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens) and those which have predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). To these are added the customary additives, such as preservatives, etc.

Tinctures and solutions usually have an aqueous-ethanolic base to which are added, inter alia, polyalcohols, for example glycerol, gycols (sic) and/or polyethylene glycol, as humectants to reduce evaporation, and superfatting substances, such as fatty acid esters with lower polyethylene glycols, i.e. lipophilic substances which are soluble in the aqueous mixture, as a replacement for the fatty substances removed from the skin with the ethanol, and, if necessary, other auxiliaries and additives.

The pharmaceutical products which can be administered topically are prepared in a manner known per se, for example by dissolving or suspending the active compound in the base or in a portion thereof, if necessary. When the active compound is processed as a solution, the latter is, as a rule, dissolved in one of the two phases from (sic) the

emulsification; when processed as a suspension, it is mixed with a portion of the base after the emulsification, and then added to the rest of the formulation.

The present invention also relates to the use of the compounds of the formulae I and II and of the salts of these types of compounds having salt-forming properties, preferably for the treatment of inflammations, primarily of inflammatory chronic rheumatic disorders, especially of chronic arthritis.

The Examples which follow illustrate the invention which is described above; however, they are not intended to restrict its extent in any way. Temperatures ... (sic) indicated in degrees Celsius.

Example 1

0.8 g of sodium are dissolved in 200 ml of ethanol. 8 g of 2-mercapto-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole are added to the solution, and the mixture is heated to reflux. After a clear solution has been produced, 2.3 ml of 2-chloroethanol are added dropwise, and the reaction mixture is heated to reflux for 16 hours. The solvent is evaporated off at (sic) vacuum, and the residue is partitioned between water and ethyl acetate. The organic phases are washed with water and saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue obtained is crystalline 2-(2-hydroxyethylthio)-5(4)-phenyl-4(5)-(3-pyridyl)-imidazole which, after recrystallisation from ethyl acetate/petroleum ether, melts at 128-130°C.

The starting material can be prepared, for example, as follows.

10.8 g of benzyl 3-pyridyl ketone are stirred together with 40 ml of pyridine and a solution of 8 g of hydroxylamine hydrochloride in 15 ml of pyridine at 100° for 6 hours. The reaction mixture is poured onto ice/water and the mixture is then stirred for 15 minutes. The crystals which have separated out are filtered off with suction, washed with water and dried under high vacuum. Benzyl 3-pyridyl ... (sic) oxime of melting point 122-126° is obtained.

A solution of 7.7 g of p-toluenesulfonyl chloride in

15 ml of pyridine is added dropwise within 5 minutes to a stirred solution, at -10°, of 8.5 g of benzyl 3-pyridyl ketone oxime in 20 ml of pyridine. The ... (sic) mixture is stored in a refrigerator for 24 hours and is then poured onto ice/water. After some stirring and trituration, the oil which has separated out solidifies to give crystals. These are filtered off with suction, washed with water and dried under high vacuum. The p-toluenesulfonic ester of benzyl 3-pyridyl ketone oxime is obtained and is used in the next stage without further purification.

11.6 g of crude p-toluenesulfonic ester of benzyl 3-pyridyl ketone oxime are suspended in 90 ml of absolute ethanol. Then, while stirring at 0°, the solution of 3.7 g of potassium tert.-butylate in 30 ml of absolute ethanol is added dropwise. The reaction mixture is stirred at 0° for 2 hours. The suspension is filtered with suction, and the filtrate, which contains the desired α-amino-benzyl 3-pyridyl ketone, is immediately reacted further in the next stage.

3.6 g of sodium thiocyanate are dissolved in 60 ml of ethanol, and 4.5 ml of concentrated hydrochloric acid are added. The suspension is filtered with suction, and the filtrate is heated to reflux together with the alcoholic solution of α-amino-benzyl 3-pyridyl ketone for 18 hours. After the reaction mixture has cooled, the crude 2-mercapto-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole can be filtered off with suction. The filtrate contains further product. The crude product is recrystallised from dimethylformamide/water and then melts at 290-300°.

Example 2

5 g of 2-mercapto-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole are dissolved in 50 ml of methanol and 10 ml of 2N sodium hydroxide solution. 2.85 g of methyl iodide are added dropwise, the mixture is stirred at room temperature for 2 hours, 50 ml of water are added, and the mixture is filtered with suction and the residue is washed with water. Crude 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole is obtained, which when recrystallised from a mixture of

isopropanol and petroleum ether (8:5 parts by volume) melts at 193-194°.

Example 3

8 g of 2-mercapto-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole are dissolved in 40 ml of methanol and 16 ml of 2N sodium hydroxide solution. 4.55 g of methyl iodide are added dropwise to the solution. The mixture is then stirred at room temperature for 2 hours, 40 ml of water are added, and the mixture is filtered with suction and the residue is washed with water. A mixture of 1-methyl-2-methylthio-4-phenyl-5-(3-pyridyl)-imidazole and 1-methyl-2-methylthio-5-phenyl-4-(3-pyridyl)-imidazole is obtained. This can be separated into the components by chromatography. Thus, on a silica gel column, first one component of melting point 141-143° is eluted with chloroform and then the other component of melting point 125-127° is eluted with chloroform/ethyl acetate (8:2 parts by volume).

Example 4

The following can also be prepared in a manner analogous to that described in Examples 1-3:

2-(2-hydroxyethylthio)-1-methyl-4-phenyl-5-(3-pyridyl)-imidazole,

2-(2-hydroxyethylthio)-1-methyl-5-phenyl-4-(3-pyridyl)-imidazole,

2-(2-methoxyethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole,

2-(2-methoxyethylthio)-1-methyl-4-phenyl-5-(3-pyridyl)-imidazole,

2-(2-methoxyethylthio)-1-methyl-5-phenyl-4-(3-pyridyl)-imidazole,

2-(2-methylthioethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole,

1-methyl-2-(2-methylthioethylthio)-4-phenyl-5-(3-pyridyl)-imidazole,

1-methyl-2-(2-methylthioethylthio)-5-phenyl-4-(3-pyridyl)-imidazole,

2-ethylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole,

2-propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole,

2-isopropyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, 2-methylthio-4,5-bis-(2-thienyl)-imidazole and 2-ethylthio-4,5-bis-(2-thienyl)-imidazole.

Example 5

In a manner analogous to that described in Example 2, it is possible to prepare, in each case starting from 7.6 g of 2-mercapto-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, the 2-ethyl-thio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, melting point 196-198° (from isopropanol/petroleum ether), 2-propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, melting point 143-144° (from isopropanol/petroleum ether) and 2-isopropylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, melting point 182-184° (from isopropanol/petroleum ether).

Example 6

A solution of 6.3 g of 85% pure m-chloroperbenzoic acid in 70 ml of chloroform is added dropwise to a stirred suspension of 8 g of 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole in 400 ml of chloroform. The resulting solution is allowed to stand overnight and then is washed successively with sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness. The residue is recrystallised twice from isopropanol/petroleum ether. The 2-methanesulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole of melting point 166-169° is obtained.

In an analogous manner, starting from 2-ethylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, the 2-ethanesulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole of melting point 162-164° is obtained.

Example 7

8 ml of acetic acid and 0.38 ml of 30% strength hydrogen peroxide are added to 1.0 g of 2-ethanesulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, and the mixture is stirred at 70° overnight. It is allowed to cool, neutralised with sodium hydroxide solution and filtered with suction. The 2-ethanesulfonyl-4(5)-phenyl-5(4)-[3-(1-oxidopyridinio)]-imidazole of melting point 208-210° is obtained.

Example 8

2.86 g of α-bromobenzyl 3-pyridyl ketone hydrobromide and 1 g of S-methylisothiuronium bromide are suspended in 30 ml of acetonitrile, 3.1 g of N,N-diisopropyl-ethylamine are added, and the mixture is stirred overnight. The red-orange suspension is filtered and the filtrate is evaporated under reduced pressure. The residue is taken up in chloroform, dried over sodium sulfate, evaporated and recrystallised from chloroform/petroleum ether. The 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole of melting point 193-194° is obtained.

The starting material can be prepared, for example, as follows:

A solution of 17 g of bromine in 150 ml of acetic acid is added dropwise to 20 g of benzyl 3-pyridyl ketone in 200 ml of acetic acid, and the mixture is stirred overnight. The precipitated α-bromobenzyl 3-pyridyl ketone hydrobromide is filtered off and can be used without further purification.

Example 9

It is also possible to prepare the following in a manner analogous to that described in Examples 1 to 8:
2-ethylthio-4(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole,
2-methylthio-4(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole and
2-propylthio-4(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole.

Example 10

Tablets containing 25 mg of active compound, for example 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, can be prepared as follows:

Constituents (for 1,000 tablets):

active compound	25.0 g
lactose	100.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g

magnesium stearate	1.8 g
demineralised water	q.s.

Preparation

All the solid ingredients are first passed through a sieve of mesh size 0.6 mm. Then the active compound, the lactose, the talc, the magnesium stearate and half of the starch are mixed. The other half of the starch is suspended in 40 ml of water, and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting starch mucilage is added to the main quantity, and the mixture is granulated, if necessary with the addition of water. The granules are dried at 35° overnight, passed through a sieve of mesh size 1.2 mm, and compressed to form biconcave tablets of approximate diameter 6 mm.

It is also possible to prepare in an analogous manner tablets each containing 25 mg of another of the compounds of the formula I mentioned in Examples 1 to 4.

Example 11

Chewable tablets containing 30 mg of active compound, for example 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazoline (sic), can be prepared, for example, as follows:

Composition (for 1,000 tablets):

active compound	30.0 g
mannitol	267.0 g
lactose	179.5 g
talc	20.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.0 g
5% strength gelatin solution	q.s.

Preparation

All the solid ingredients are first passed through a sieve of mesh size 0.25 mm. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, passed through a sieve of mesh size 2 mm, dried at 50° and again passed through a sieve of mesh size 1.7 mm. The active compound, the glycine and the saccharin are carefully mixed,

the mannitol, the lactose granules, the stearic acid and the talc are added, and the whole is thoroughly mixed and compressed to form biconcave tablets of approximate diameter 10 mm with a breaking groove on the upper side.

It is also possible to prepare in an analogous manner chewable tablets each containing 30 mg of another of the compounds of the formula I mentioned in Examples 1 to 4.

Example 12

Tablets containing 100 mg of active compound, for example 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole, can be prepared as follows:

Composition (for 1,000 tablets):

active compound	100.0 g
lactose	248.5 g
maize starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	15.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Preparation

The solid ingredients are first passed through a sieve of mesh size 0.6 mm. Then the active compound, lactose, talc magnesium stearate and one half of the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water, and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting mucilage is added to the powdered substances, and the whole is mixed and granulated, if necessary with the addition of water. The granules are dried overnight at 35°, passed through a sieve of mesh size 1.2 mm, and compressed to form biconcave tablets of approximate diameter 10 mm, with a score on the upper side. It is also possible to prepare in an analogous manner tablets containing 100 mg of another compound of the formula I according to Example 1.

Example 13

Furthermore, it is possible to prepare in a manner analogous to that described in Examples 10 to 12, tablets

each containing 25 or 100 mg of chewable tablets containing 30 mg of a compound according to one of Examples 5 to 8.

Example 14

Furthermore, it is possible to prepare in a manner analogous to that described in Examples 1 to 8 the following:

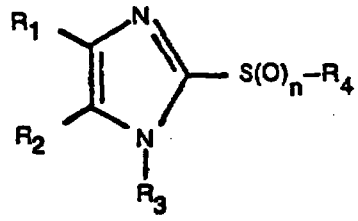
2-ethanesulfinyl-1(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole,

2-ethanesulfonyl-4(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole and

2-ethanesulfonyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole.

Patent claims

1. Compounds of the formula



(I),

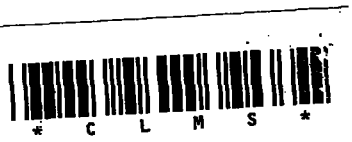
in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom or at least two nitrogen atoms, or a 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa-

or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur atom and from 6-membered heteroaryl radicals having one nitrogen atom, or radicals R_3 are different from hydrogen, when R_4 denotes a lower alkyl radical which is substituted in the 2-, 3- or 4-position by a hydroxyl group, and with the further proviso that, in compounds of the formula I in which n represents 1 or 2, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur or oxygen atom or from 6-membered heteroaryl radicals having one nitrogen atom, when R_4 represents a lower alkyl which is substituted by one or two hydroxyl groups, a lower alkoxy group or by phenyl which is optionally substituted as indicated, or unsubstituted lower alkynyl, where "lower" radicals have up to and including 7 C atoms, and their acid addition salts.

2. Compounds according to claim 1, in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom, or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 5-aza (sic) , 3-oxa or 3-thia-alkylene-amino, each having 5 or 6 ring members, and/or trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl or hydroxy-lower-alkyl, and a radical R_1 or R_2 different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0 and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted

or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur atom and from 6-membered heteroaryl radicals having one nitrogen atom, when R_4 denotes a lower alkyl radical which is substituted in the 2-, 3- or 4-position by a hydroxyl group and their acid addition salts.

3. Compounds according to claim 1, in which at least one of the radicals R_1 and R_2 denotes furyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or triazinyl, it being possible for ring carbon atoms of the said radicals R_1 and R_2 to be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, amino, lower alkylamino, and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, ring nitrogen atoms of pyrimidinyl, triazinyl or pyridyl radicals as well as by oxy, and a radical R_1 or R_2 which is different from this represents phenyl which can be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa-or 3-thia-alkyleneamino, each having 5 or 6 ring members, R_3 denotes hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is optionally substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including



35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is optionally substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members and their acid addition salts.

4. Compounds according to claim 2, in which at least one of the radicals R_1 and R_2 denotes furyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or triazinyl, it being possible for ring carbon atoms of the said radicals R_1 and R_2 to be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, amino, lower alkylamino, and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and a radical R_2 or R_3 (sic) which is different from this represents phenyl which can be substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, R_3 denotes hydrogen or lower alkyl, n represents 0, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is optionally substituted by lower alkyl, lower alkoxy, halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, or denotes ....(sic) lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is optionally substituted by lower alkyl, lower alkoxy,

halogen of atomic number up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and their acid addition salts.

5. Compounds according to claim 2, in which one of the radicals R_1 and R_2 denotes pyridyl and the other denotes phenyl, it being possible for these radicals, independently of one another, to be substituted by lower alkyl having 1 to 4 C atoms, lower alkoxy having 1 to 4 C atoms, halogen of atomic number up to and including 35 and/or N,N-di-lower-alkylamino each having 1 to 4 C atoms, R_3 denotes hydrogen or lower alkyl having 1 to 4 C atoms, n represents 0, and R_4 denotes lower alkyl having 1 to 4 C atoms, lower alkenyl having 2 to 4 C atoms, phenyl-lower-alkyl which has 1 to 4 C atoms in the alkyl moiety and is unsubstituted or substituted by lower alkyl having 1 to 4 C atoms, lower alkoxy having 1 to 4 C atoms and/or halogen of atomic number up to and including 35, mono- the (sic) dihydroxy-lower-alkyl which has 2 to 4 C atoms and carries the hydroxyl group(s) in a position higher than the α-position, and lower alkoxy or lower alkylthio-lower-alkyl which has 1 to 4 C atoms in the alkoxy or alkylthio moiety and 2 to 4 C atoms in the alkyl moiety and carries the alkoxy or alkylthio group in a position higher than the α-position, and their acid addition salts.

6. Compounds according to claim 1, in which one of the radicals R_1 and R_2 denotes unsubstituted pyridyl or thienyl and the other denotes phenyl which is unsubstituted or substituted by lower alkyl having 1 to 4 C atoms, lower alkoxy having 1 to 4 C atoms and/or halogen of atomic number up to and including 35, R_3 denotes hydrogen or lower alkyl having 1 to 4 C atoms, n represents 0, 1 or 2, and R_4 denotes lower alkyl having 1 to 4 C atoms, and their acid addition salts.

7. Compounds according to claim 2, in which one of the radicals R_1 and R_2 denotes unsubstituted pyridyl and the other denotes phenyl which is unsubstitued or substituted by lower alkyl having 1 to 4 C atoms, lower alkoxy having 1 to

4 C atoms or halogen, R_3 represents hydrogen or lower alkyl having 1 to 4 C atoms, n represents 0, and R_4 denotes lower alkyl having 1 to 4 C atoms or hydroxy-lower-alkyl which has 2 to 4 C atoms and carries the hydroxyl group in a position higher than the α-position, and their acid addition salts.

8. Compounds according to claim 1, in which one of the radicals R_1 and R_2 denotes pyridyl and the other denotes phenyl, R_3 is hydrogen, n represents 0 or 1, and R_4 denotes lower alkyl having 1 to 4 C atoms, and their acid addition salts.

9. Compounds according to one of claims 1 to 8 as anti-inflammatory and/or antinociceptive agents.

10. 2-ethylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

11. 2-ethylsulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

12. 2-ethylthio-4(5)-(p-fluorophenyl)-5(4)-(2-thienyl)-imidazole.

13. 2-(2-hydroxyethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

14. 2-methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

15. 2-(2-methylthioethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

16. 2-(2-methoxyethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

17. 2-propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

18. 2-isopropylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

19. 2-ethanesulfonyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

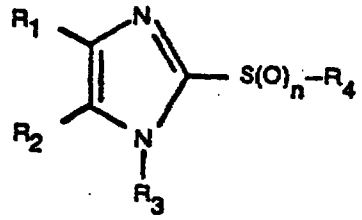
20. 2-ethanesulfinyl-4(5)-(p-fluorophenyl)-(2-thienyl)-imidazole or an acid addition salt thereof.

21. 2-ethanesulfonyl-4(5)-(p-fluorophenyl)-(2-thienyl)-imidazole or an acid addition salt thereof.

22. 2-ethylthio-4,5-bis-(2-thienyl)-imidazole or an acid

22. 2-ethylthio-4,5-bis-(2-thienyl)-imidazole or an acid addition salt thereof.

23. Compounds of the formula

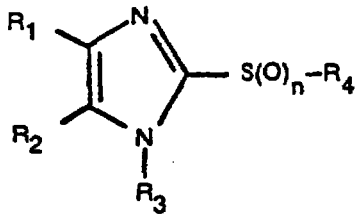


(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-

alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, with the proviso that, in compounds of the formula I in which n....., where 'lower' radicals have up to and including 7 C atoms, and their pharmaceutically utilisable acid addition salts for the treatment of inflammatory disorders.

24. Compounds of the formula



(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom, or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza, 3-oxa or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower-alkyl, hydroxy-lower-alkyl, and a radical R_1 or R_2 different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alky-leneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0 and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower

alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio or a phenoxy or phenylthio group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, where "lower" radical (sic) have up to and ... (sic) 7 C atoms, and their pharmaceutically utilisable acid addition salts for the treatment of inflammatory disorders.

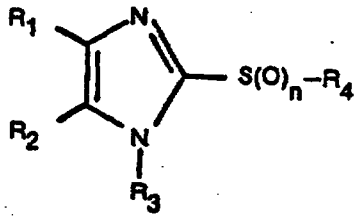
25. Compounds according to one of claims 2, 4, 5, 7, 10, 13-18 and 22 for the treatment of inflammatory disorders.

26. Compounds according to one of claims 1, 3, 6, 8, 9 and 19-21 for the treatment of inflammatory disorders.

27. Pharmaceutical products containing a compound according to one of claims 2, 4, 5, 7, 10, 13-18, 22, 24 and 25 together with customary pharmaceutical auxiliaries.

28. Pharmaceutical products containing a compound according to one of claims 1, 3, 6, 8, 9, 19-21, 23 and 26 together with customary pharmaceutical auxiliaries.

29. Process for the preparation of compounds of the formula

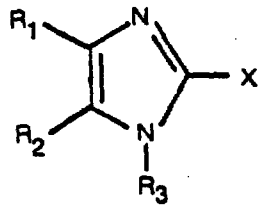


(I),

in which at least one of the radicals R_1 and R_2 denotes a monocyclic 5-membered heteroaryl group which has one oxygen or sulfur atom, one sulfur and one nitrogen atom or at least two nitrogen atoms, or 6-membered heteroaryl group which has at least one nitrogen atom, which is bonded via a C atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkylene- or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, and/or trifluoromethyl and/or is N-substituted by lower alkyl, lower

alkoxy-lower-alkyl, hydroxy-lower-alkyl or oxy, and a radical R_1 or R_2 which is different from this denotes a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, R_3 represents hydrogen or lower alkyl, n represents 0, 1 or 2, and R_4 denotes a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring members, nitro and/or trifluoromethyl, or denotes a lower alkyl radical which is substituted in a position higher than the α-position by hydroxyl, lower alkoxy, lower alkylthio, or a phenoxy or phenylthio group which is unsubstituted or substi-tuted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower-alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each having 5 or 6 ring mem-bers, nitro and/or trifluoromethyl, and of their acid addition salts, where "lower" radicals have up to and including 7 C atoms, which comprises

a) reacting together compounds of the formulae

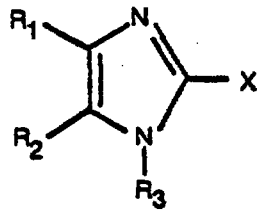


(II) and Y-R_4 (III)

in which one of the radicals X and Y denotes mercapto which is optionally in the form of a salt and the other denotes a radical which is replaceable by etherified mercapto, with the proviso that, in compounds of the formula (II) in which X is mercapto which is optionally in the form of a salt, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radical (sic) having one sulfur atom or 6-membered

heteroaryl radical (sic) having one nitrogen atom, or radicals R_3 are different from hydrogen, when in compounds of the formula (III) Y represents reactive esterified hydroxyl and R_4 represents a lower alkyl radical which is substituted once by hydroxyl in the 2-, 3- or 4-position or

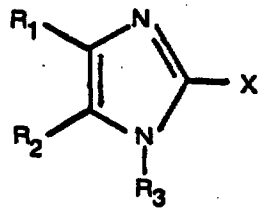
b) reacting together compounds of the formulae



(II) und Y—R_4 (III),

in which one of the radicals X and Y is a group of the formula $-S(O)_n-Y_1$, in which Y_1 is a reactive esterified hydroxyl group or, if n represents 0, is an etherified mercapto group or, if n represents 1 or 2, is an etherified hydroxyl group, and the other represents a metal radical Y_2, or

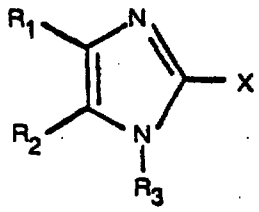
c) reacting a compound of the formula



(II),

in which X represents the mercapto group, with a lower alkene which is optionally substituted as indicated for R_4 and

d) reacting a compound of the formula

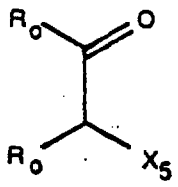


(II)

in which X denotes a sulfinic or sulfonic acid group in the form of a salt, with a compound of the formula

in which Y denotes a reactive esterified hydroxyl group, or,

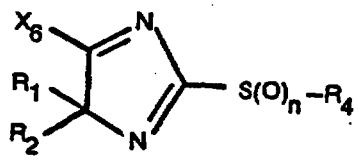
e) reacting a compound of the formula



(VI)

in which one of the radicals R_o represents a group R_1 and the other represents a group R_2, and X_5 denotes a reactively (sic) esterified hydroxyl group, or an acid addition salt thereof, with an N-R_3-S-R_4-isothiourea, or

f) rearranging a compound of the formula



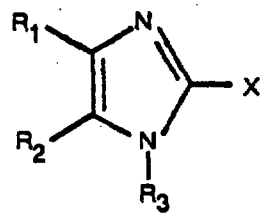
(VII)

in which X_6 is lower alkylthio which is optionally substituted by phenyl which in turn can be substituted as R_1 and R_2, or an acid addition salt thereof, and, if desired, oxidising the thio group in a compound of the formula I, obtained according to process variants a) to f), in which n represents 0, and R_1, R_2, R_3 and R_4 have the above meanings, with the proviso that, in compounds of the formula (I) obtained according to process variant a) by reaction of compounds of the formulae (II) and (III), in which X is mercapto, which is optionally in the form of a salt, and Y is reactive esterified hydroxyl, heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals having one sulfur or oxygen atom or 6-membered heteroaryl radicals having one nitrogen atom, when R_4 represents a lower alkyl radical which is substituted by one or two hydroxyl groups or one lower alkoxy group or by phenyl which is optionally substitued as indicated, or unsubstituted lower alkynyl radical, to the sulfinyl or sulfonyl group, and/or in compounds

obtained according to one of the process variant (sic) a) to f), in which R_1 and/or R_2 has at least one nitrogen atom >N carrying out N-oxidation of the latter, or oxidising the sulfinyl or sulfonyl group in compounds obtained according to one of the process variant (sic) b) or f), in which n represents 1 or 2, to the thio group, and/or ... (sic) compounds obtained according to process variant a) to f), in which R_1 and R_2 have a N-oxidised nitrogen atom reducing the latter to a group >N, N-lower-alkylating a compound of the formula I obtained according to the process, in which R_3 represents hydrogen, in compounds of the formula I obtained according to the process optionally introducing additional C-substituents in radicals R_1, R_2 and/or phenyl, phenoxy or phenylthio groups as constituent of R_4, and/or converting a free compound obtained according to the process into an acid addition salt, or converting an acid addition salt obtained according to the process into the free compound or into another salt.

30. Process according to claim 29 for the preparation of compounds of the formula (I), in which R_1, R_2, R_3 and R_4 have the meanings indicated in claim 29, but heteroaryl radicals R_1 and/or R_2 are not N-substituted by oxy, and n represents 0, and their acid addition salts, which comprises

a) reacting together compounds of the formulae

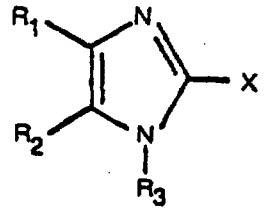


(II) and Y-R_4 (III)

in which one of the radicals X and Y denotes mercapto which is optionally in the form of a salt and the other denotes a radical which is replaceable by etherified mercapto, with the proviso that, in compounds of the formula (II) in which X is mercapto which is optionally in the form of a salt, heteroaryl radicals R_1 and/or R_2 are different from 5-membered

heteroaryl radical (sic) having one sulfur atom or 6-membered heteroaryl radical (sic) having one nitrogen atom, or radicals R_3 are different from hydrogen, when in compounds of the formula (III) Y represents reactive esterified hydroxyl and R_4 represents a lower alkyl radical which is substituted once by hydroxyl in the 2-, 3- or 4-position or

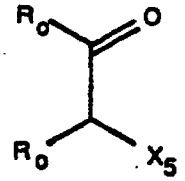
c) reacting a compound of the formula



(II),

in which X represents the mercapto group, with a lower alkene which is optionally substituted as indicated for R_4 and

e) reacting a compound of the formula



(VI)

in which the radical R_0 in the α-position to the oxo group denotes a radical R_1, and the other radical R_0 denotes a radical R_2, and X_5 denotes a reactive esterified hydroxyl group, with an N-R_3-S-R_4-isothiuronium salt and, if desired, N-lower-alkylating a compound of the formula I, in which R_3 represents hydrogen, obtainable according to the process, introducing optional additional C-substituents in radicals R_1, R_2 and/or phenyl, phenoxy or phenylthio groups as constituent of R_4 in compounds of the formula I obtainable according to the process, and/or converting a free compound obtained according to the process into an acid addition salt or converting an acid addition salt obtained according to the process into the free compound.

31. The compounds obtained according to the process of claim 29 or 30.

32. Compounds according to one of claims 1-26 as anti-inflammatory agent.

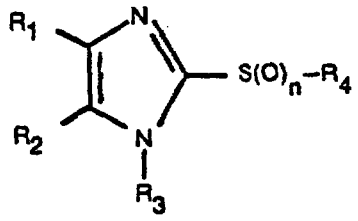
33. Use of compounds according to one of claims 1-26 for the preparation of medicaments by non-chemical routes.

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Patentansprüche (as printed)

1. Verbindungen der Formel



(I),

worin mindestens einer der Reste R_1 und R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern und/oder Trifluormethyl C-substituierte und/oder durch Niederalkyl, Niederalkoxyniederalkyl, Hydroxyniederalkyl oder Oxy N-substituierte monocyclische, über ein C-Atom gebundene, ein Sauerstoff- oder Schwefelatom, ein Schwefel- und ein Stickstoffatom oder mindestens 2 Stickstoffatome aufweisende 5-gliedrige oder mindestens ein Stickstoffatom aufweisende 6-gliedrige Heteroarylgruppe und ein davon verschiedener Rest R_1 oder R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenylgruppe bedeutet, R_3 Wasserstoff oder Niederalkyl darstellt, n für 0, 1 oder 2 steht und R_4 einen unsubstituierten oder durch unsubstituiertes oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino, bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer Stellung als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio, eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, mit der Massgabe, dass Heteroarylreste R_1 und/oder R_2 von ein Schwefelatom aufweisenden 5-gliedrigen und ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylresten oder Reste R_3 von Wasserstoff verschieden sind, wenn R_4 in 2-, 3- oder 4-Stellung durch eine Hydroxygruppe substituiertes Niederalkyl bedeutet, und mit der weiteren Massgabe, dass in Verbindungen der Formel I, worin n für 1 oder 2 steht, Heteroarylreste R_1 und/oder R_2 von ein Schwefel- oder Sauerstoffatom aufweisenden 5-gliedrigen und ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylresten verschieden sind, wenn R_4 durch ein oder zwei Hydroxygruppen, eine Niederalkoxygruppe oder durch gegebenenfalls wie angegeben substituiertes Phenyl substituiertes Niederalkyl oder unsubstituiertes Niederalkinyl darstellt, wobei "niedere" Reste bis und mit 7 C-Atome aufweisen, und ihre Säureadditionssalze.

2. Verbindungen gemäß Anspruch 1 worin mindestens einer der Reste R_1 und R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylen- bzw. 5-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern und/oder Trifluormethyl C-substituierte und/oder durch Niederalkyl, Niederalkoxyniederalkyl oder Hydroxyniederalkyl N-substituierte monocyclische, über ein C-Atom gebundene, ein Sauerstoff- oder Schwefelatom, ein Schwefel- und ein Stickstoffatom oder mindestens 2 Stickstoffatome aufweisende 5-gliedrige oder mindestens ein Stickstoffatom aufweisende 6-gliedrige Heteroarylgruppe und ein davon verschiedener Rest R_1 oder R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenyl-

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gruppe bedeutet. R_3 Wasserstoff oder Niederalkyl darstellt, n für 0 steht und R_4 einen unsubstituierten oder durch unsubstituiertes oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino, bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer Stellung als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio, eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, mit der Massgabe, dass Heteroarylreste R_1 und/oder R_2 von ein Schwefelatom aufweisenden 5-gliedrigen und ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylresten verschieden sind, wenn R_4 in 2-, 3- oder 4-Stellung durch eine Hydroxygruppe substituiertes Niederalkyl bedeuten, und ihre Säureadditionssalze.

3. Verbindungen gemäss Anspruch 1, worin mindestens einer der Reste R_1 und R_2 Furyl, Thienyl, Thiazolyl, Imidazolyl, Triazolyl, Tetrazolyl, Pyridyl, Pyrimidinyl oder Triazinyl bedeutet, wobei Ringkohlenstoffatome der genannten Reste R_1 und R_2 durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Ringstickstoffatome von Pyrimidinyl-, Triazinyl- oder Pyridylresten ferner durch Oxy substituiert sein können, und ein davon verschiedener Rest R_1 oder R_2 Phenyl darstellt, welches durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituiert sein kann, R_3 Wasserstoff oder Niederalkyl bedeutet, n für 0, 1 oder 2 steht, und R_4 einen unsubstituierten oder durch gegebenenfalls durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio oder eine gegebenenfalls durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgleidern substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, und ihre Säureadditionssalze.

4. Verbindungen gemäss Anspruch 2, worin mindestens einer der Reste R_1 und R_2 Furyl, Thienyl, Thiazolyl, Imidazolyl, Triazolyl, Tetrazolyl, Pyridyl, Pyrimidinyl oder Triazinyl bedeutet, wobei Ringkohlenstoffatome der genannten Reste R_1 und R_2, durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituiert sein können, und ein davon verschiedener Rest R_2 oder R_1 Phenyl darstellt, welches durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino, und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituiert sein kann, R_3 Wasserstoff oder Niederalkyl bedeutet, n für 0 steht, und R_4 einen substituierten oder durch gegenbenenfalls durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder in höherer als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio oder eine gegebenenfalls durch Niederalkyl, Niederalkoxy, Halogen mit und bis Atomnummer 35, Trifluormethyl, Nitro, Amino, Niederalkylamino und/oder Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, und ihre Säureadditionssalze.

5. Verbindungen gemäss Anspruch 2, worin einer der Reste R_1 und R_2 Pyridyl und der andere Phenyl bedeutet, wobei diese Reste unabhängig voneinander durch Niederalkyl mit 1 bis 4 C-Atomen, Niederalkoxy mit 1 bis 4 C-Atomen, Halogen bis und mit Atomnummer 35 und/oder N,N-Diniederalkylamino mit jeweils 1 bis 4 C-Atomen substituiert sein können, R_3 Wasserstoff oder Niederalkyl mit 1 bis 4 C-Atomen bedeutet, n für 0 steht, und R_4 Niederalkyl mit 1 bis 4 C-Atomen, Niederalkenyl mit 2 bis 4 C-Atomen, unsubstituiertes oder durch Niederalkyl mit 1 bis 4 C-Atomen, Niederalkoxy mit 1 bis 4 C-Atomen und/oder Halogen mit Atomnummer bis und mit 35 substituiertes Phenylniederalkyl mit 1 bis 4 C-Atomen im Alkylteil, die Hydroxygruppe(n) in höherer als der α-Stellung tragendes Mono- der Dihydroxyniederalkyl mit 2 bis 4 C-Atomen, die Alkoxy- oder Alkylthiogruppe in einer höheren als der α-Stellung tragendes Niederalkoxy- oder Niederalkylthioniederalkyl mit 1 bis 4 C-Atomen im Alkoxy bzw. Alkylthioteil und 2 bis 4 C-Atomen im Alkylteil bedeutet, und ihre Säureadditionssalze.

6. Verbindungen gemäss Anspruch 1, worin einer der Reste R_1 und R_2 unsubstituiertes Pyridyl oder Thienyl und der andere unsubstituiertes oder durch Niederalkyl mit 1 bis 4 C-Atomen, Niederalkoxy mit 1 bis 4 C-Atomen und/oder Halogen mit Atomnummer bis und mit 35 substituiertes Phenyl bedeutet, R_3 Wasserstoff oder Niederalkyl mit 1 bis 4 C-Atomen bedeutet, n für 0, 1 oder 2 steht, und R_4 Niederalkyl mit 1 bis 4 C-Atomen bedeutet, und ihre Säureadditionssalze.

7. Verbindungen gemäss Anspruch 2, worin einer der Reste R_1 und R_2 unsubstituiertes Pyridyl und der andere unsubstituiertes oder durch Niederalkyl mit 1 bis 4 C-Atomen, Niederalkoxy mit 1 bis 4 C-

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Atomen oder Halogen, substituiertes Phenyl bedeutet, R_3 Wasserstoff oder Niederalkyl mit 1 bis 4 C-Atomen darstellt, n für 0 steht, und R_4 Niederalkyl mit 1 bis 4 C-Atomen oder die Hydroxygruppe in höherer als der α-Stellung tragendes Hydroxyniederalkyl mit 2 bis 4 C-Atomen bedeutet, und ihre Säureadditionssalze.

8. Verbindungen gemäss Anspruch 1, worin einer der Reste R_1 und R_2 Pyridyl und der andere Phenyl bedeutet, R_3 Wasserstoff ist, n für 0 oder 1 steht, und R_4 Niederalkyl mit 1 bis 4 C-Atomen bedeutet, und ihre Säureadditionssalze.

9. Verbindungen gemäss einem der Ansprüche 1 bis 8 als antiinflammatorica und/oder antinociceptiva.

10. 2-Aethylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

11. 2-Aethansulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

12. 2-Aethylthio-4(5)-(p-fluorphenyl)-5(4)-(2-thienyl)-imidazol.

13. 2-(2-Hydroxyäthylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

14. 2-Methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

15. 2-(2-Methylthioäthylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

16. 2-(2-Methoxyäthylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

17. 2-Propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

18. 2-Isopropylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

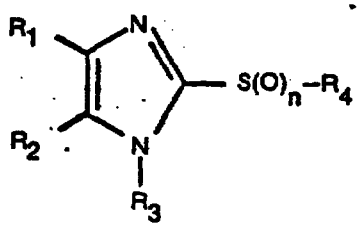
19. 2-Aethansulfonyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol oder ein Säureadditionssalz davon.

20. 2-Aethansulfinyl-4(5)-(p-fluorphenyl)-(2-thienyl)-imidazol oder ein Säureadditionssalz davon.

21. 2-Aethansulfonyl-4(5)-(p-fluorphenyl)-(2-thienyl)-imidazol oder ein Säureadditionssalz davon.

22. 2-Aethylthio-4,5-bis-(2-thienyl)-imidazol oder ein Säureadditionssalz davon.

23. Verbindungen der Formel

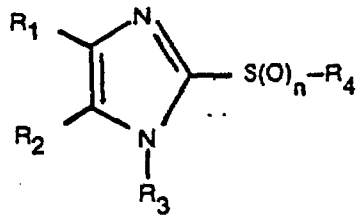


(I),

worin mindestens einer der Reste R_1 und R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern und/oder Trifluormethyl C-substituierte und/oder durch Niederalkyl, Niederalkoxyniederalkyl, Hydroxyniederalkyl oder Oxy N-substituierte monocyclische, über ein C-Atom gebundene, ein Sauerstoff- oder Schwefelatom, ein Schwefel- und ein Stickstoffatom oder mindestens 2 Stickstoffatome aufweisende 5-gliedrige oder mindestens ein Stickstoffatom aufweisende 6-gliedrige Heteroarylgruppe und ein davon verschiedener Rest R_1 oder R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenylgruppe bedeutet, R_3 Wasserstoff oder Niederalkyl darstellt, n für 0, 1 oder 2 steht, und R_4 einen unsubstituierten oder durch unsubstituiertes oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6-Ringgliedern, Nitro und/oder Trifluormethyl substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio, oder eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, mit der Massgabe, dass in Verbindungen der Formel I, worin n für 1 oder 2 steht, Heteroarylreste R_1 und/oder R_2 von ein Schwefel- oder Sauerstoffatom aufweisenden 5-gliedrigen und ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylresten verschieden sind, wenn R_4 einen durch ein oder zwei Hydroxygruppen, eine Niederalkoxygruppe oder durch gegebenenfalls wie angegeben substituiertes Phenyl substituierten Niederalkyl- oder unsubstituierten Niederalkinylrest darstellt, wobei "niedere" Reste bis und mit 7 C-atome aufweisen, und ihre pharmazeutisch verwendbaren Säureadditionssalze zur Behandlung entzündlicher Erkrankungen.

24. Verbindungen der Formel

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(I),

worin mindestens einer der Reste R_1 und R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylen- bzw. 5-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern und/oder Trifluormethyl C-substituierte und/oder durch Niederalkyl, Niederalkoxyniederalkyl oder Hydroxyniederalkyl N-substituierte monocyclische, über ein C-Atom gebundene, ein Sauerstoff- oder Schwefelatom, ein Schwefel- und Stickstoffatom oder mindestens 2 Stickstoffatome aufweisende 5-gliedrige oder mindestens ein Stickstoffatom aufweisende 6-gliedrige Heteroarylgruppe und ein davon verschiedener Rest R_1 oder R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenylgruppe bedeutet, R_3 Wasserstoff oder Niederalkyl darstellt, n für 0 steht und R_4 einen unsubstituierten oder durch unsubstituiertes oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino, bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer Stellung als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio, eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, wobei "niedere" Reste bis und mit 7 C-Atome aufweisen, und ihre pharmazeutisch verwendbaren Säureadditionssalze zur Behandlung entzündlicher Erkrankungen.

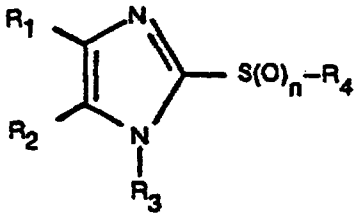
25. Verbindungen gemäss einem der Ansprüche 2, 4, 5, 7, 10, 13—18 und 22 zur Behandlung entzündlicher Erkrankungen.

26. Verbindungen gemäss einem der Ansprüche 1, 3, 6, 8, 9 und 19—21 zur Behandlung entzündlicher Erkrankungen.

27. Pharmazeutische Präparate enthaltend eine Verbindung gemäss einem der Ansprüche 2, 4, 5, 7, 10, 13—18, 22, 24 und 25 zusammen mit üblichen pharmazeutischen Hilfsstoffen.

28. Pharmazeutische Präparate enthaltend eine Verbindung gemäss einem der Ansprüche 1, 3, 6, 8, 9, 19—21, 23 und 26 zusammen mit üblichen pharmazeutischen Hilfsstoffen.

29. Verfahren zur Herstellung von Verbindungen der Formel



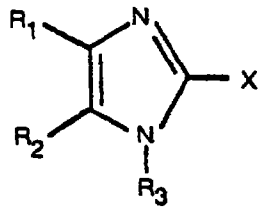
(I),

worin mindestens einer der Reste R_1 und R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylen- bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern und/oder Trifluormethyl C-substituierte und/oder durch Niederalkyl, Niederalkoxyniederalkyl, Hydroxyniederalkyl oder Oxy N-substituierte monocyclische, über ein C-Atom gebundene, ein Sauerstoff- oder Schwefelatom, ein Schwefel- und ein Stickstoffatom oder mindestens 2 Stickstoffatome aufweisende 5-gliedrige oder mindestens ein Stickstoffatom aufweisende 6-gliedrige Heteroarylgruppe und ein davon verschiedener Rest R_1 oder R_2 eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituierte Phenylgruppe bedeutet, R_3 Wasserstoff oder Niederalkyl darstellt, n für 0, 1 oder 2 steht, und R_4 einen unsubstituieren oder durch unsubstituiertes oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Diniederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl substituiertes Phenyl substituierten Niederalkyl-, Niederalkenyl- oder Niederalkinylrest oder einen in höherer als der α-Stellung durch Hydroxy, Niederalkoxy, Niederalkylthio oder eine unsubstituierte oder durch Niederalkyl, Niederalkoxy, Halogen, Amino, Niederalkylamino, Di-

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niederalkylamino, Alkylenamino bzw. 3-Aza-, 3-Oxa- oder 3-Thia-alkylenamino mit jeweils 5 oder 6 Ringgliedern, Nitro und/oder Trifluormethyl, substituierte Phenoxy- oder Phenylthiogruppe substituierten Niederalkylrest bedeutet, und ihrer Säureadditionssalze, wobei "niedere" Reste bis und mit 7 C-Atome aufweisen, dadurch gekennzeichnet, dass man

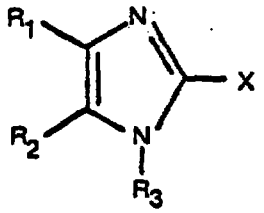
a) Verbindungen der Formel



(II) und Y—R_4 (III),

worin einer der Reste X und Y gegebenenfalls in Salzform vorliegendes Mercapto und der andere einen gegen verätherfes Mercapto austauschbaren Rest bedeutet mit der Massgabe, dass in Verbindungen der Formel (II), worin X gegebenenfalls in Salzform vorliegendes Mercapto ist, Heteroarylreste R_1 und/oder R_2 von ein Schwefelatom aufweisenden 5-gliedrigen und ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylrest oder Reste R_3 von Wasserstoff verschieden sind, wenn in Verbindungen der Formel (III) Y reaktionsfähiges verestertes Hydroxy und R_4 in 2-, 3- oder 4-Stellung durch Hydroxy einfach substituiertes Niederalkyl darstellt, oder

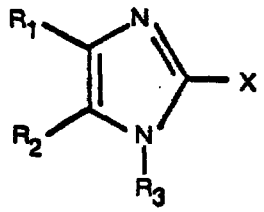
b) Verbindungen der Formeln



(II) und Y—R_4 (III),

worin einer der Reste X und Y eine Gruppe der Formel —$S(O)_n$—Y_1, worin Y_1 eine reaktionsfähige veresterte Hydroxygruppe oder, wenn n für 0 steht, eine verätherte Mercaptogruppe oder, wenn n für 1 oder 2 steht, eine verätherte Hydroxygruppe ist, und der andere ein Metallradikal Y_2 darstellt, miteinander oder

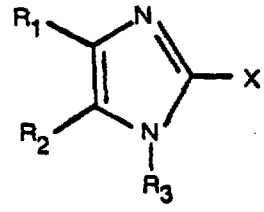
c) eine Verbindung der Formel



(II),

worin X die Mercaptogruppe darstellt, mit einem gegebenenfalls wie für Niederalkyl R_4 angegeben substituierten Niederalken umsetzt, bzw.

d) eine Verbindung der Formel



(II)

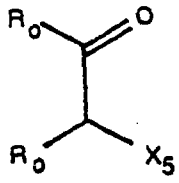
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worin X eine in Salzform vorliegende Sulfin- oder Sulfonsäuregruppe bedeutet, mit einer Verbindung der Formel

$$Y—R_4 \qquad (III),$$

worin Y eine reaktionsfähige veresterte Hydroxygruppe bedeutet, umsetzt, oder

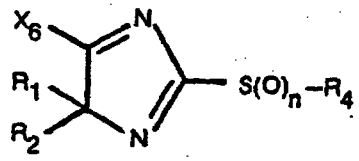
e) eine Verbindung der Formel



(VI)

worin einer der Reste R_0 eine Gruppe R_1 und der andere eine Gruppe R_2 darstellt und X_5 eine reaktionsfähig veresterte Hydroxygruppe bedeutet, oder ein Säureadditionssalz davon, mit einem $N—R_3—S—R_4$-Isothioharnstoff umsetzt oder

f) eine Verbindung der Formel

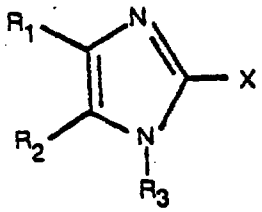


(VII)

worin X_6 gegebenenfalls durch Phenyl, das seinerseits wie R_1 und R_2 substituiert sein kann, substituiertes Niederalkylthio ist, oder ein Säureadditionssalz davon, umlagert und gewünschtenfalls in einer gemäss der Verfahrensvarianten a) bis f) erhaltenen Verbindung der Formel I, worin n für 0 steht, und R_1, R_2, R_3 und R_4 obige Bedeutungen haben, mit der Massgabe, dass in gemäss der Verfahrensvariante a) durch Umsetzung von Verbindungen der Formeln (II) und (III), worin X gegebenenfalls in Salzform vorliegendes Mercapto und Y reaktionsfähiges verestertes Hydroxy ist, erhaltenen Verbindungen der Formel (I) Heteroarylreste R_1 und/oder R_2 von ein Schwefel- oder Sauerstoffatom aufweisenden 5-gliedrigen oder ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylreste verschieden sind, wenn R_4 einen durch ein oder zwei Hydroxygruppen, eine Niederalkoxygruppe substituierten oder durch gegebenenfalls wie angegeben substituiertes Phenyl substituierten Niederalkyl- oder unsubstituierten Niederalkinylrest darstellt, die Thiogruppe zur Sulfinyl- oder Sulfonylgruppe oxidiert und/oder in gemäss einer der Verfahrensvariante a) bis f) erhaltenen Verbindungen, worin R_1 und/oder R_2 mindestens ein Stickstoffatom >N aufweist, dieses N-oxidiert oder in gemäss einer der Verfahrensvariante b) oder f) erhaltenen Verbindungen, worin n für 1 oder 2 steht, die Sulfinyl- oder Sulfonylgruppe zur Thiogruppe und/oder gemäss der Verfahrensvariante a) bis f) erhaltenen Verbindungen, worin R_1 und R_2 ein N-oxidiertes Stickstoffatom aufweist, dieses zu einer Gruppe >N reduziert, eine verfahrensgemäss erhaltene Verbindung der Formel I, worin R_3 Wasserstoff darstellt, N-niederalkyliert, in verfahrensgemäss erhaltenen Verbindungen der Formel I in Reste R_1, R_2 und/oder Phenyl-, Phenoxy- oder Phenylthiogruppen als Bestandteil von R_4 gegebenenfalls zusätzliche C-Substituenten einführt und/oder eine verfahrensgemäss erhaltene freie Verbindung in ein Säureadditionssalz oder ein verfahrensgemäss erhaltenes Säureadditionssalz in die freie Verbindung oder in ein anderes Salz überführt.

30. Verfahren gemäss Anspruch 29 zur Herstellung von Verbindungen der Formel (I), worin R_1, R_2, R_3 und R_4 die in Anspruch 29 angegebenen Bedeutungen haben, Heteroarylreste R_1 und/oder R_2 jedoch nicht durch Oxy N-substituiert sind, und n für 0 steht, und ihrer Säureadditionssalze, dadurch gekennzeichnet, dass man

a) Verbindungen der Formeln

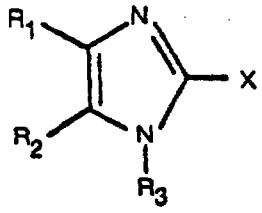


(II) und $Y—R_4$ (III),

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worin einer der Reste X und Y gegebenenfalls in Salzform vorliegendes Mercapto und der andere einen gegen verätherfes Mercapto austauschbarer Rest bedeutet, mit der Massgabe, dass in Verbindungen der Formel (II), worin X gegebenenfalls in Salzform vorliegendes Mercapto ist, Heteroarylreste R_1 und/oder R_2 von ein Schwefelatom aufweisenden 5-gliedrigen oder ein Stickstoffatom aufweisenden 6-gliedrigen Heteroarylrest oder Reste R_3 von Wasserstoff verschieden sind, wenn in Verbindungen der Formel (III) Y reaktionsfähiges verestertes Hydroxy und R_4 einen in 2-, 3- oder 4-Stellung durch Hydroxy einfach substituierten Niederalkylrest darstellt, miteinander umsetzt oder

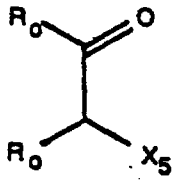
c) eine Verbindung der Formel



(II),

worin X Mercapto darstellt, mit einem gegebenenfalls wie für Niederalkyl R_4 angegeben substituierten Niederalken umsetzt, oder

e) eine Verbindung der Formel



(VI)

worin der zur Oxogruppe α-ständige Rest R_0 einen Rest R_1 und der andere Rest R_0 einen Rest R_2 bedeutet und X_5 eine reaktionsfähige veresterte Hydroxygruppe bedeutet, mit einem N—R_3—S—R_4-Isothiuroniumsalz umsetzt und gewünschtenfalls eine verfahrensgemäss erhältliche Verbindung der Formel I, worin R_3 für Wasserstoff steht, N-niederalkyliert, in verfahrensgemäss erhältlichen Verbindungen der Formel I in Reste R_1, R_2 und/oder Phenyl-, Phenoxy- oder Phenylthiogruppen als Bestandteil von R_4 gegebenenfalls zusätzliche C-Substituenten einführt und/oder eine verfahrensgemäss erhaltene freie Verbindung in ein Säureadditionssalz oder ein verfahrensgemäss erhaltenes Säureadditionssalz in die freie Verbindung überführt.

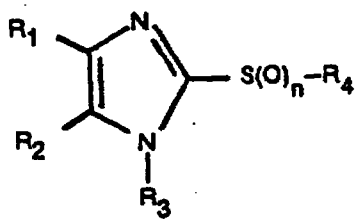
31. Die nach dem Verfahren des Anspruches 29 oder 30 erhaltenen Verbindungen.

32. Verbindungen gemäss einem der Ansprüche 1—26 als entzündungshemmendes Mittel.

33. Verwendung von Verbindungen gemäss einem der Ansprüche 1—26 zur Herstellung von Arzneimitteln auf nichtchemischem Wege.

Claims (as printed)

1. A compound of the formula



(I),

wherein at least one of the radicals R_1 and R_2 is a monocyclic 5-membered heteroaryl group containing one oxygen atom or one sulfur atom, one sulfur atom and one nitrogen atom, or at least two nitrogen atoms, or a monocyclic 6-membered heteroaryl group containing at least one nitrogen atom, which group is linked through a carbon atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each containing 5 or 6 ring members, and/or by trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl or oxy, and a radical R_1 or R_2 different therefrom is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-

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thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, R_3 is hydrogen or lower alkyl, n is 0, 1 or 2, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals containing one sulfur atom and from 6-membered heteroaryl radicals containing one nitrogen atom, or radicals R_3 are different from hydrogen, if R_4 is lower alkyl substituted in the 2-, 3- or 4-position by a hydroxyl group, and with the further proviso that, in a compound of the formula I, in which n is 1 or 2, heteroaryl radicals R_1 and/or R_2 differ from 5-membered heteroaryl radicals containing one sulfur atom or one oxygen atom, and from 6-membered heteroaryl radicals containing one nitrogen atom, if R_4 is lower alkyl substituted by one or two hydroxyl groups, a lower alkoxy group or by phenyl which is unsubstituted or substituted as indicated above, or is unsubstituted lower alkynyl, the radicals qualified by "lower" containing up to and including 7 carbon atoms, or an acid addition salt thereof.

2. A compound according to claim 1, wherein at least one of the radicals R_1 and R_2 is a monocyclic 5-membered heteroaryl group containing one oxygen atom or one sulfur atom, one sulfur atom and one nitrogen atom, or at least two nitrogen atoms, or a monocyclic 6-membered heteroaryl group containing at least one nitrogen atom, which group is linked through a carbon atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, and/or by trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, and a radical R_1 or R_2 different therefrom is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, R_3 is hydrogen or lower alkyl, n is 0, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, with the proviso that heteroaryl radicals R_1 and/or R_2 are different from 5-membered heteroaryl radicals containing one sulfur atom and from 6-membered heteroaryl radicals containing one nitrogen atom, or radicals R_3 are different from hydrogen, if R_4 is lower alkyl substituted in the 2-, 3- or 4-position by a hydroxyl group, or an acid addition salt thereof.

3. A compound according to claim 1, wherein at least one of the radicals R_1 and R_2 is furyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or triazinyl, and the ring carbon atoms of said radicals R_1 and R_2 may be substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, amino, lower alkylamino and/or alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, and the ring nitrogen atoms of pyrimidinyl, triazinyl or pyridyl radicals may also be substituted by oxy, and a radical R_1 or R_2 different therefrom is phenyl which may be substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, R_3 is hydrogen or lower alkyl, n is 0, 1 or 2, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkyleneamino and/or alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or an acid addition salt thereof.

4. A compound according to claim 2, wherein at least one of the radicals R_1 and R_2 is furyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl or triazinyl, and the ring carbon atoms of said radicals R_1 and R_2 may be substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, amino, lower alkylamino and/or alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, and a radical R_1 or R_2 different therefrom is phenyl which may be substituted by lower alkyl, lower alkoxy, halogen having an

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atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, R_3 is hydrogen or lower alkyl, n is 0, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkylamino and/or alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, nitro, amino, lower alkyleneamino and/or alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or an acid addition salt thereof.

5. A compound according to claim 2, in which one of the radicals R_1 and R_2 is pyridyl and the other is phenyl, and these radicals independently of each other may be substituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms, halogen having an atomic number of up to and including 35 and/or N,N-di-lower alkylamino containing 1 to 4 carbon atoms in each alkyl moiety, R_3 is hydrogen or lower alkyl having 1 to 4 C atoms, n is 0 and R_4 is lower alkyl of 1 to 4 carbon atoms, lower alkenyl of 2 to 4 carbon atoms, phenyl-lower alkyl which contains 1 to 4 carbon atoms in the alkyl moiety and is unsubstituted or substituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms and/or halogen having an atomic number of up to and including 35, mono- or dihydroxy-lower alkyl which contains 2 to 4 carbon atoms and carries the hydroxyl group or groups in a position higher than the α-position, or lower alkoxy- or lower alkylthio-lower alkyl, which contains 1 to 4 carbon atoms in the alkoxy or alkylthio moiety and 2 to 4 carbon atoms in the alkyl moiety, and carries the alkoxy or alkylthio group in a position higher than the α-position, or an acid addition salt thereof.

6. A compound according to claim 1, wherein one of the radicals R_1 and R_2 is unsubstituted pyridyl or thienyl and the other is phenyl which is unsubstituted or substituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms and/or halogen having an atomic number of up to and including 35, R_3 is hydrogen or lower alkyl of 1 to 4 carbon atoms, n is 0, 1 or 2, and R_4 is lower alkyl of 1 to 4 carbon atoms, or an acid addition salt thereof.

7. A compound according to claim 2, wherein one of the radicals R_1 and R_2 is unsubstituted pyridyl and the other is phenyl which is unsubstituted or substituted by lower alkyl of 1 to 4 carbon atoms, lower alkoxy of 1 to 4 carbon atoms or halogen, R_3 is hydrogen or lower alkyl of 1 to 4 carbon atoms, n is 0, and R_4 is lower alkyl of 1 to 4 carbon atoms or hydroxy-lower alkyl of 2 to 4 carbon atoms which carries the hydroxyl group in a position higher than the α-position, or an acid addition salt thereof.

8. A compound according to claim 1, wherein one of the radicals R_1 and R_2 is pyridyl and the other is phenyl, R_3 is hydrogen, n is 0 or 1, and R_4 is lower alkyl of 1 to 4 carbon atoms, or an acid addition salt thereof.

9. A compound according to any one of claims 1 to 8 as antiinflammatory or antinociceptive agent.

10. 2-Ethylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

11. 2-Ethanesulfinyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

12. 2-Ethylthio-4(5)-(p-fluorophenyl-5(4)-(2-thienyl)-imidazole or an acid addition salt thereof.

13. 2-(2-Hydroxyethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

14. 2-Methylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

15. 2-(2-Methylthioethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

16. 2-(2-Methoxyethylthio)-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

17. 2-Propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

18. 2-Isopropylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

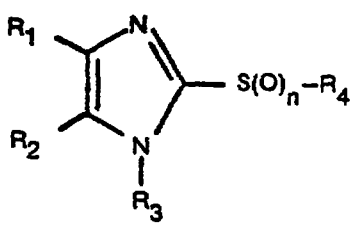
19. 2-Ethanesulfonyl-4(5)-phenyl-5(4)-(3-pyridyl)-imidazole or an acid addition salt thereof.

20. 2-Ethanesulfinyl-4(5)-(p-fluorophenyl)-(2-thienyl)-imidazole or an acid addition salt thereof.

21. 2-Ethanesulfonyl-4(5)-(p-fluorophenyl)-(2-thienyl)-imidazole or an acid addition salt thereof.

22. 2-Ethylthio-4(5)-bis-(2-thienyl)-imidazole or an acid addition salt thereof.

23. A compound of the formula



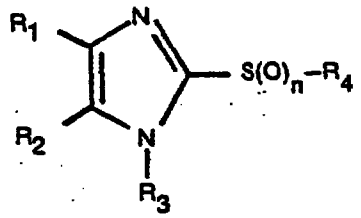
(I),

wherein at least one of the radicals R_1 and R_2 is a monocyclic 5-membered heteroaryl group containing

* C L M S *

one oxygen atom or one sulfur atom, one sulfur atom and one nitrogen atom, or at least two nitrogen atoms, or a monocyclic 6-membered heteroaryl group containing at least one nitrogen atom, which group is linked through a carbon atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, and/or by trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl or oxy, and a radical R_1 or R_2 different therefrom is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, R_3 is hydrogen or lower alkyl, n is 0, 1 or 2, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, with the proviso that, in a compound of the formula I, in which n is 1 or 2, heteroaryl radicals R_1 and/or R_2 differ from 5-membered heteroaryl radicals containing one sulfur atom or one oxygen atom, and from 6-membered heteroaryl radicals containing one nitrogen atom, if R_4 is lower alkyl substituted by one or two hydroxyl groups, by a lower alkoxy group or by phenyl which is unsubstituted or substituted as indicated above, or is an unsubstituted lower alkynyl radical, the radicals qualified by "lower" containing up to and including 7 carbon atoms, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of inflammatory conditions.

24. A compound of the formula



(I)

wherein at least one of the radicals R_1 and R_2 is a monocyclic 5-membered heteroaryl group containing one oxygen atom or one sulfur atom, one sulfur atom and one nitrogen atom, or at least two nitrogen atoms, or a monocyclic 6-membered heteroaryl group containing at least one nitrogen atom, which group is linked through a carbon atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, and/or by trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, and a radical R_1 or R_2 different therefrom is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, R_3 is hydrogen or lower alkyl, n is 0, 1 or 2, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, the radicals qualified by "lower" containing up to and including 7 carbon atoms, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of inflammatory conditions.

25. A compound according to any one of claims 2, 4, 5, 7, 10, 13—18 and 22, for the treatment of inflammatory conditions.

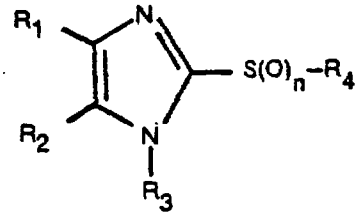
26. A compound according to any one of claims 1, 3, 6, 8, 9 and 19—21, for the treatment of inflammatory conditions.

27. A pharmaceutical preparation containing a compound according to any one of claims 2, 4, 5, 7, 10, 13—18, 22 and 25, together with conventional pharmaceutical excipients.

28. A pharmaceutical preparation containing a compound according to any one of claims 1, 3, 6, 8, 9, 19—21, 23 and 26, together with conventional pharmaceutical excipients.

29. A process for the production of a compound of the formula

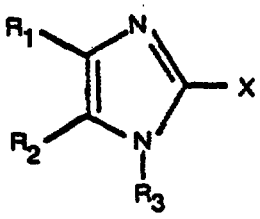
(112)



(I),

wherein at least one of the radicals R_1 and R_2 is a monocyclic 5-membered heteroaryl group containing one oxygen atom or one sulfur atom, one sulfur atom and one nitrogen atom, or at least two nitrogen atoms, or a monocyclic 6-membered heteroaryl group containing at least one nitrogen atom, which group is linked through a carbon atom and is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thia-alkyleneamino, each containing 5 or 6 ring members, and/or by trifluoromethyl, and/or is N-substituted by lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl and a radical R_1 or R_2 different therefrom is a phenyl group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, R_3 is hydrogen or lower alkyl, n is 0, and R_4 is a lower alkyl, lower alkenyl or lower alkynyl radical which is unsubstituted or substituted by phenyl which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, or is a lower alkyl radical which is substituted in a position higher than the α-position by hydroxy, lower alkoxy, lower alkylthio, or by a phenoxy or phenylthio group which is itself unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, amino, lower alkylamino, di-lower alkylamino, alkyleneamino or 3-aza-, 3-oxa- or 3-thiaalkyleneamino, each containing 5 or 6 ring members, or by nitro and/or trifluoromethyl, the radicals qualified by "lower" containing up to and including 7 carbon atoms, or an acid addition salt thereof, which process comprises

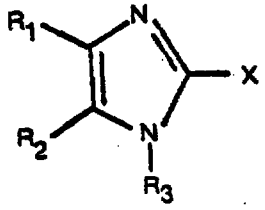
a) reacting compounds of the formulae



(II) and Y—R_4 (III),

wherein one of the radicals X and Y is mercapto which may be in salt form and the other is a radical which is replaceable by etherified mercapto, with the proviso that, in compounds of the formula (III), in which X is mercapto which may be in salt form, heteroaryl radicals R_1 and/or R_2 differ from 5-membered heteroaryl radicals containing a sulfur atom and from 6-membered heteroaryl radicals containing a nitrogen atom, or radicals R_3 differ from hydrogen, if in compounds of the formula (III) Y is reactive esterified hydroxy and R_4 is lower alkyl monosubstituted in the 2-, 3- or 4-position by hydroxy, with one another, or

b) reacting compounds of the formulae

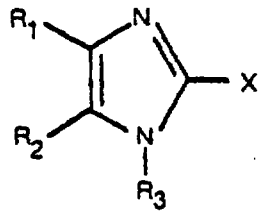


(II) and Y—R_4 (III),

wherein one of the radicals X and Y is a group of the formula —$S(O)_n$—Y_1, wherein Y_1 is a reactive esterified hydroxyl group or, if n is 0, an etherified mercapto group, or if n is 1 or 2, an etherified hydroxyl group, and the other is a metal radical Y_2, with one another, or

c) reacting a compound of the formula

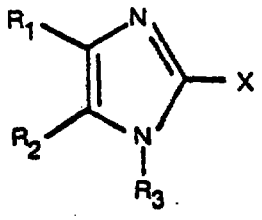
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(III),

wherein X is the mercapto group, with a lower alkene which is unsubstituted or substituted as indicated for lower alkyl R_4, or

d) reacting a compound of the formula



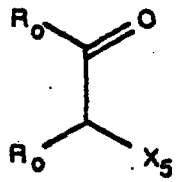
(II),

wherein X is a sulfinic or sulfonic acid group in salt form, with a compound of the formula

$$Y—R_4 \qquad \text{(III)},$$

wherein Y is a reactive esterified hydroxyl group, or

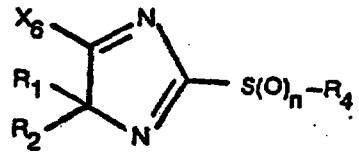
e) reacting a compound of the formula



(VI)

wherein one of the radicals R_o is a group R_1 and the other is a group R_2 and X_5 is a reactive esterified hydroxyl group, or an acid addition salt thereof, with a N—R_3—S—R_4 isothiourea, or

f) rearranging a compound of the formula



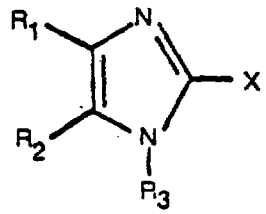
(VII)

wherein X_6 is lower alkylthio which is unsubstituted or substituted by phenyl which may itself be substituted as for R_1 and R_2, or an acid addition salt thereof, and, if desired, in a compound of the formula I obtained by one of process variants a) to f) and in which n is 0, and R_1, R_2, R_3 and R_4 are as defined above, with the proviso that, in compounds of the formula I obtained by process variant a) by reacting compounds of the formulae (II) and (II), in which X is mercapto which may be in salt form and Y is reactive esterified hydroxy, heteroaryl radicals R_1 and/or R_2 differ from 5-membered heteroaryl radicals containing a sulfur atom or an oxygen atom, or from 6-membered heteroaryl radicals containing a nitrogen atom, if R_4 is a lower alkyl radical which is substituted by one or two hydroxyl groups, a lower alkoxy group or by phenyl which is unsubstituted or substituted as indicated, or is an unsubstituted lower alkynyl radical, oxidising the thio group to the sulfinyl or sulfonyl group, and/or in a compound obtained by one of process variants a) to f), wherein R_1 and/or R_2 contain at least one nitrogen atom $\geqslant$N, N-oxidising said nitrogen atom, or in a compound obtained by one of process variants b) or f), in which n is 1 or 2, reducing the sulfinyl or sulfonyl group to the thio group, and/or in a compound obtained by one of process variants a) to f), in which R_1 and R_2 contain a N-oxidised nitrogen atom, reducing said nitrogen atom to a group $\geqslant$N, N-lower alkylating a compound of the formula I, in which R_3 is hydrogen, or in a compound of the formula I optionally introducing additional C-substituents into radicals R_1, R_2 and/or into phenyl, phenoxy or phenylthio groups as constituents of R_4, and/or converting a free compound into an acid addition salt or an acid addition salt into the free compound or into another salt.

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30. A process according to claim 29 for the production of a compound of the formula (I), in which R_1, R_2, R_3 and R_4 are as defined in claim 29, but heteroaryl radicals R_1 and/or R_2 are not N-substituted by oxy, and n is 0, or an acid addition salt thereof, which process comprises

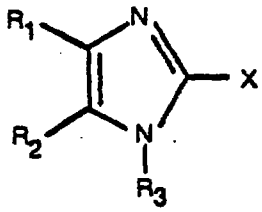
a) reacting compounds of the formulae



(II) and Y—R_4 (III),

wherein one of the radicals X and Y is mercapto which may be in salt form and the other is a radical which is replaceable by etherified mercapto, with the proviso that, in compounds of the formula (II), in which X is mercapto which may be in salt form, heteroaryl radicals R_1 and/or R_2 differ from 5-membered heteroaryl radicals containing a sulfur atom, and from 6-membered heteroaryl radicals containing a nitrogen atom, or radicals R_3 are different from hydrogen, if in compounds of the formula (III) Y is reactive esterified hydroxy and R_4 is lower alkyl mono-substituted in the 2-, 3- or 4-position by hydroxy, with one another, or

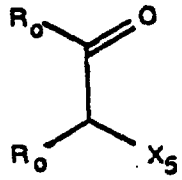
c) reacting a compound of the formula



(II),

wherein X is the mercapto group, with a lower alkene which is unsubstituted or substituted as indicated for lower alkyl R_4, or

e) reacting a compound of the formula



(VI)

wherein the radical R_o α-oriented to the oxo group is a radical R_1 and the other radical R_o is a radical R_2 and X_5 is a reactive esterified hydroxyl group, with a N—R_3—S—R_4 isothiuronium salt and, if desired, N-lower alkylating a compound of the formula I in which R_3 is hydrogen, in compounds of the formula I optionally introducing additional C-substituents into radicals R_1, R_2 and/or into phenyl, phenoxy or phenylthio groups as constituents of R_4, and/or converting a free compound into an acid addition salt or an acid addition salt into the free compound.

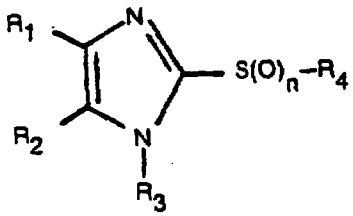
31. A compound obtained by the process as claimed in either of claim 29 or claim 30.

32. A compound as claimed in any one of claims 1 to 26 as antiinflammatory agent.

33. Use of a compound as claimed in any one of claims 1 to 26 for the preparation of medicaments by a non-chemical route.

Revendications (as printed)

1. Composés de formule



(I),

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dans laquelle l'un au moins des symboles R_1 et R_2 représente un groupe hétéroaryle monocyclique relié par l'intermédiaire d'un atome de carbone, à 5 chaînons contenant un atome d'oxygène ou de soufre, un atome de soufre et un atome d'azote ou au moins deux atomes d'azote ou à 6 chaînons contenant au moins un atome d'azote, non substitué ou substitué sur le carbone par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques et/ou trifluorométhyle, et/ou substitué à l'azote par des groupes alkyles inférieurs, (alcoxy inférieur)-alkyles inférieurs, hydroxyalkyles inférieurs ou oxy, et un symbole R_1 ou R_2 différent du précédent représente un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou chaînons cycliques, nitro et/ou tri-fluorométhyle, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0,1 ou 2 et R_4 représente un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur non substitué ou substitué par un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, ou un groupe alkyle inférieur substitué en position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs, un groupe phénoxy ou phénylthio non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, étant spécifié que les groupes hétéroaryles R_1 et/ou R_2 diffèrent de groupes hétéroaryles à chaînons portant un atome de soufre et de groupes hétéroaryles à chaînons portant un atome d'azote, ou les restes R_3 diffèrent de l'hydrogène lorsque R_4 représente ungroupe alkyle inférieur substitué par un groupe hydroxy en position 2, 3 ou 4, et étant en outre spécifié que dans les composés de formule I dans laquelle n est égal à 1 ou 2, les groupes hétéroaryles R_1 et/ou R_2 diffèrent de groupes hétéroaryles à 5 chaînons portant un atome de soufre ou d'oxygène et de groupes hétéroaryles à 6 chaînons contenant un atome d'azote lorsque R_4 représente un groupe alkyle inférieur substitué par un ou deux groupes hydroxy, un groupe alcoxy inférieur, ou par un groupe phényle éventuellement substitué comme indiqué ci-dessus, ou un groupe alcynyle inférieur non substitué, les restes "inférieurs" contenant jusqu'à 7 atomes de carbone inclus, et leurs sels formés par addition avec des acides.

2. Composés selon la revendication 1, dans lesquels l'un au moins des symboles R_1 et R_2 représente un groupe hétéroaryle monocyclique, relié par l'intermédiaire d'un atome de carbone, à 5 chaînons contenant un atome d'oxygène ou de soufre, un atome de soufre et un atome d'azote ou au moins deux atomes d'azote, ou à 6 chaînons contenant au moins un atome d'azote, non substitué ou substitué sur le carbone par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène- ou 5-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques et/ou trifluorométhyle, et/ou substitué sur l'azote par des groupes alkyles inférieurs, (alcoxy inférieur)-alkyles inférieurs ou hydroxyalkyles inférieurs, et un reste R_1 ou R_2 différent du précédent est un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à O et R_4 représente un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur non substitué ou substitué par un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, ou bien un groupe alkyle inférieur substitué en position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs, un groupe phénoxy ou phénylthio non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylèneamino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, étant spécifié que les groupes hétéroaryles R_1 et R_2 diffèrent de groupes hétéroaryles à 5 chaînons contenant un atome de soufre et de groupes hétéroaryles à 6 chaînons contenant un atome d'azote lorsque R_4 représente un groupe alkyle inférieur substitué par un groupe hydroxy en position 2, 3 ou 4, et leurs sels formés par addition avec des acides.

3. Composés selon la revendication 1, dans lesquels l'un au moins des symboles R_1 et R_2 représente un groupe furyle, thiényle, thiazolyle, imidazolyle, triazolyle, tétrazolyle, pyridyle, pyrimidinyle ou triazinyle, les atomes de carbone cycliques des restes R_1 et R_2 en question pouvant être substitués par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35, des groupes trifluorométhyle, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, les atomes d'azote cycliques des restes pyrimidinyle, triazinyle ou pyridyle pouvant en outre porter un substituant oxy, et un symbole R_1 ou R_2 différent du précédent représente un groupe phényle qui peut être substitué par des groupes

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alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques. R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0, 1 ou 2 et R_4 représente un groupe alkyle inférieur, alcényle inférieur, ou alcynyle inférieur non substitué ou substitué par un groupe phényle éventuellement substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs, et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, ou un groupe alkyle inférieur substitué dans une position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs ou un groupe phénoxy ou phénylthio éventuellement substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, et leurs sels formés par addition avec des acides.

4. Composés selon la revendication 2, dans lesquels l'un au moins des symboles R_1 et R_2 représente un groupe furyle, thiényle, thiazolyle, imidazolyle, triazolyle, tétrazolyle, pyridyle, pyrimidinyle ou triazinyle, les atomes de carbone cycliques des restes R_1 et R_2 en question pouvant être substitués par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35, des groupes trifluorométhyle, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, et un symbole R_2 ou R_3 différent du précédent représente un groupe phényle qui peut être substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35 inclus, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0 et R_4 représente un groupe alkyle inférieur, alcényle inférieur, ou alcynyle inférieur non substitué ou substitué par un groupe phényle éventuellement substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35 inclus, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, ou un groupe alkyle inférieur substitué dans une position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs ou un groupe phénoxy ou phénylthio éventuellement substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes de nombre atomique allant jusqu'à 35 inclus, des groupes trifluorométhyle, nitro, amino, alkylamino inférieurs et/ou alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, et leurs sels formés par addition avec des acides.

5. Composés selon la revendication 2, dans lesquels l'un des symboles R_1 et R_2 représente un groupe pyridyle et l'autre un groupe phényle, ces groupes pouvant être substitués indépendamment l'un de l'autre par des groupes alkyles inférieurs en C1—C4, alcoxy inférieurs en C1—C4, des halogènes de nombre atomique allant jusqu'à 35 inclus et/ou des groupes N,N-di-(alkyle inférieur)-amino contenant chacun 1 à 4 atomes de carbone, R_3 représente l'hydrogène ou un groupe alkyle inférieur en C1—C4, n est égal à 0 et R_4 représente un groupe alkyle inférieur en C1—C4, alcényle inférieur en C2—C4, phénylalkyle inférieur contenant de 1 à 4 atomes de carbone dans la partie alkyle, non substitué ou substitué par des groupes alkyles inférieurs en C1—C4, alcoxy inférieurs en C1—C4 et/ou des halogènes de nombre atomique allant jusqu'à 35 inclus, mono- ou di-hydroxyalkyles inférieurs en C2—C4 portant le ou les groupes hydroxy en position supérieure à la position alpha, (alcoxy inférieur)- ou (alkylthio inférieur)-alkyles inférieurs contenant 1 à 4 atomes de carbone dans la partie alcoxy ou alkylthio et 2 à 4 atomes de carbone dans la partie alkyle, portant le groupe alcoxy ou alkylthio dans une position supérieure à la position alpha, et leurs sels formés par addition avec des acides.

6. Composés selon la revendication 1, dans lesquels l'un des symboles R_1 et R_2 représente un groupe pyridyle ou thiényle non substitué et l'autre un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs en C1—C4, alcoxy inférieurs en C1—C4 et/ou des halogènes de nombre atomique allant jusqu'à 35 inclus, R_3 représente l'hydrogène ou un groupe alkyle inférieur en C1—C4, n est égal à 0, 1 ou 2 et R_4 représente un groupe alkyle inférieur en C1—C4, et leurs sels formés par addition avec des acides.

7. Composés selon la revendication 2, dans lesquels l'un des symboles R_1 et R_2 représente un groupe pyridyle non substitué et l'autre un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs en C1—C4, alcoxy inférieurs en C1—C4 ou des halogènes, R_3 représente l'hydrogène ou un groupe alkyle inférieur en C1—C4, n est égal à 0 et R_4 représente un groupe alkyle inférieur en C1—C4 ou un groupe hydroxy-alkyle inférieur en C2—C4 portant le groupe hydroxy dans une position supérieure à la position alpha, et leurs sels formés par addition avec des acides.

8. Composés selon la revendication 1, dans lesquels l'un des symboles R_1 et R_2 représente un groupe pyridyle et l'autre un groupe phénule, R_3 représente l'hydrogène, n est égal à 0 ou 1 et R_4 représente un groupe alkyle inférieur en C1—C4, et leurs sels formés par addition avec des acides.

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9. Composés selon l'une des revendications 1 à 8, en tant qu'agents anti-inflammatoires et/ou anti-nociceptifs.

10. Le 2-éthylthio-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

11. Le 2-éthane-sulfinyl-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

12. Le 2-éthylthio-4(5)-(p-fluorophényl)-5(4)-(2-thiényl)-imidazole.

13. Le 2-(2-hydroxyéthylthio)-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

14. Le 2-méthylthio-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

15. Le 2-(2-méthylthioéthylthio)-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

16. Le 2-(2-méthoxyéthylthio)-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

17. Le 2-propylthio-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

18. Le 2-isopropylthio-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

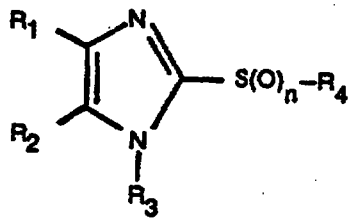
19. Le 2-éthane-sulfonyl-4(5)-phényl-5(4)-(3-pyridyl)-imidazole ou un sel de ce composé formé par addition avec un acide.

20. Le 2-éthane-sulfinyl-4(5)-(p-fluorophényl)-(2-thiényl)-imidazole ou un sel de ce composé formé par addition avec un acide.

21. Le 2-éthane-sulfonyl-4(5)-(p-fluorophényl)-(2-thiényl)-imidazole ou un sel de ce composé formé par addition avec un acide.

22. Le 2-éthylthio-4,5-bis-(2-thiényl)-imidazole ou un sel de ce composé formé par addition avec un acide.

23. Composés de formule



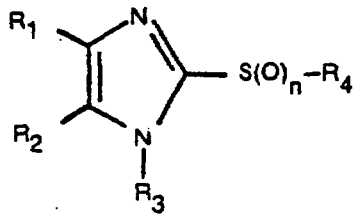
(I),

dans laquelle l'un au moins des symboles R_1 et R_2 représente un groupe hétéroaryle monocyclique, relié par l'intermédiaire d'un atome de carbone, à 5 chaînons contenant un atome d'oxygène ou de soufre, un atome de soufre et un atome d'azote ou au moins deux atomes d'azote, ou à 6 chaînons contenant un atome d'azote, non substitué ou substitué sur le carbone par des groupes alkyles inférieurs, alcoxy inférieurs, des atomes d'halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques et/ou trifluorométhyle et/ou substitué à l'azote par des groupes alkyles inférieurs, (alcoxy inférieur)-alkyles inférieurs, hydroxyalkyles inférieurs ou oxy, et un symbole R_1 ou R_2 différent du précédent représente un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0, 1 ou 2 et R_4 représente un groupe alkyle inférieur, alcényle inférieur, ou alcynyle inférieur non substitué ou substitué par un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, ou un groupe alkyle inférieur substitué dans une position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs ou un groupe phénoxy ou phénylthio non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkyl-amino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, étant spécifié que dans les composés de formule I dans laquelle n est égal à 1 ou 2, les groupes hétéroaryles R_1 et/ou R_2 diffèrent de groupes hétéroaryles à 6 chaînons portant un atome de soufre ou d'oxygène et de groupes hétéroaryles à 6 chaînons portant un atome d'azote lorsque R_4 représente un groupe alkyle inférieur substitué par un ou deux groupes hydroxy, un groupe alcoxy inférieur ou un groupe phényle éventuellement substitué comme indiqué ci-dessus, ou

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un groupe alcynyle inférieur non substitué, l'expression "inférieur" s'appliquant à des restes contenant jusqu'à 7 atomes de carbone inclus, et leurs sels formés par addition avec des acides acceptables pour l'usage pharmaceutique, pour le traitement des maladies inflammatoires.

24. Composés de formule



(I),

dans laquelle l'un an moins des symboles R_1 et R_2 représente un groupe hétéroaryle monocyclique, relié par l'intermédiaire d'un atome de carbone, à 5 chaînons contenant un atome d'oxygène ou de soufre, un atome de soufre et un atome d'azote, ou au moins deux atomes d'azote, ou à 6 chaînons contenant au moins un atome d'azote, non substitué ou substitué sur le carbone par des groupes alkyles inférieur, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène- ou 5-aza, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques et/ou trifluorométhyle, et/ou substitué à l'azote par des groupes alkyles inférieurs, (alcoxy inférieur)-alkyles inférieurs ou hydroxyalkyles inférieurs, et un symbole R_1 ou R_2 différent du précédent représente un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0 et R_4 représente un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur non substitué ou substitué par un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, ou un groupe alkyle inférieur substitué dans une position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs, un groupe phénoxy ou phénylthio non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, l'expression "inférieur" s'appliquant à des restes contenant jusqu'à 7 atomes de carbone inclus, et leurs sels formés par addition avec des acides acceptables pour l'usage pharmaceutique, pour le traitement des maladies inflammatoires.

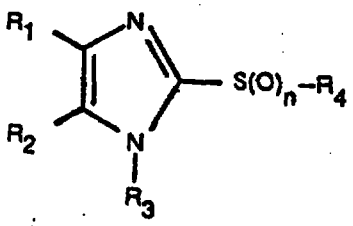
25. Composés selon l'une des revendications 2, 4, 5, 7, 10, 13 à 18 et 22 pour le traitement des maladies inflammatoires.

26. Composés selon l'une des revendications 1, 3, 6, 8, 9 et 19 à 21, pour le traitement des maladies inflammatoires.

27. Compositions pharmaceutiques contenant un composé selon l'une des revendications 2, 4, 5, 7, 10, 13 à 18, 22, 24 et 25 avec des produits auxiliaires pharmaceutiques usuels.

28. Compositions pharmaceutiques contenant un composé selon l'une des revendications 1, 3, 6, 8, 9, 19 à 21, 23 et 26 avec des produits auxiliaires pharmaceutiques usuels.

29. Procédé de préparation de composés de formule



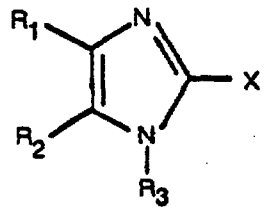
(I),

dans laquelle l'un au moins des symboles R_1 et R_2 représente un groupe hétéroaryle monocyclique, relié par l'intermédiaire d'un atome de carbone, à 5 chaînons contenant un atome d'oxygène ou de soufre, un atome de soufre et un atome d'azote ou au moins deux atomes d'azote, ou à 6 chaînons contenant au moins un atome d'azote, non substitué ou substitué sur le carbone par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groups amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène- ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques et/ou trifluorométhyle et/ou substitué à l'azote par des groupes alkyles inférieurs, (alcoxy inférieur)-alkyles inférieurs, hydroxyalkyles inférieurs ou oxy, et un symbole R_1 ou R_2 différent

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du précédent représente un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, R_3 représente l'hydrogène ou un groupe alkyle inférieur, n est égal à 0, 1 ou 2 et R_4 représente un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur non substitué ou substitué par un groupe phényle non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, ou un groupe alkyle inférieur substitué dans une position supérieure à la position alpha par des groupes hydroxy, alcoxy inférieurs, alkylthio inférieurs ou un groupe phénoxy ou phénylthio non substitué ou substitué par des groupes alkyles inférieurs, alcoxy inférieurs, des halogènes, des groupes amino, alkylamino inférieurs, di-(alkyle inférieur)-amino, alkylène-amino ou 3-aza-, 3-oxa- ou 3-thia-alkylène-amino contenant chacun 5 ou 6 chaînons cycliques, nitro et/ou trifluorométhyle, et leurs sels formés par addition avec des acides, l'expression "inférieur" s appliquant à des restes qui contiennent jusqu'à 7 atomes de carbone inclus, caractérisé en ce que:

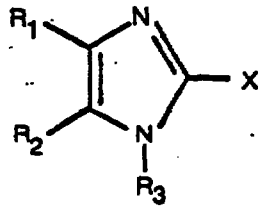
a) on fait réagir entre eux des composés de formules



(II) et $Y—R_4$ (III),

dans lesquelles l'un des symboles X et Y est un groupe mercapto éventuellement à l'état de sel et l'autre un reste échangeable contre un groupe mercapto éthérifié, étant spécifié que dans les composés de formule II dans laquelle X représente un groupe mercapto éventuellement à l'état de sel, les groupes hétéroaryles R_1 et/ou R_2 diffèrent d'un groupe hétéroaryle à 5 chaînons contenant un atome de soufre et d'un groupe hétéroaryle à 6 chaînons contenant un atome d'azote ou bien les restes R_3 diffèrent de l'hydrogène lorsque, dans les composés de formule III, Y représente un groupe hydroxy estérifié réactif et R_4 un groupe alkyle inférieur monosubstitué par un groupe hydroxy en position 2, 3 ou 4, ou bien

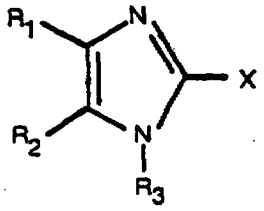
b) on fait réagir entre eux des composés de formules



(II) et $Y—R_4$ (III),

dans lesquelles l'un des symboles X et Y représente un groupe de formule $—S(O)_nY_1$ dans laquelle Y_1 représente un groupe hydroxy estérifié réactif ou bien, lorsque n est égal à 0, un groupe mercapto éthérifié ou bien, lorsque n est égal à 1 ou 2, un groupe hydroxy éthérifié, et l'autre représente un radical métallique Y_2, ou bien

c) on fait réagir un composé de formule

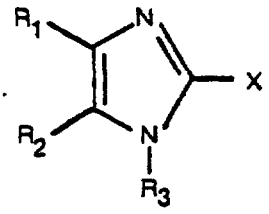


(II),

dans laquelle X représente le groupe mercapto, avec un alcène inférieur éventuellement substitué comme indiqué pour le groupe alkyle inférieur R_4, ou bien

d) on fait réagir un composé de formule

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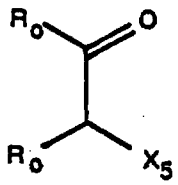
(II),

dans laquelle X représente un groupe acide sulfinique ou acide sulfonique à l'état de sel, avec un composé de formule

$$Y—R_4 \qquad \text{(III)},$$

dans laquelle Y représente un groupe hydroxy estérifié réactif, ou bien

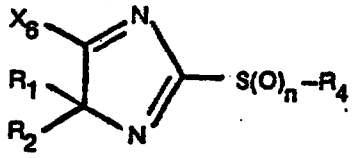
e) on fait réagir un composé de formule



(VI)

dans laquelle l'un des symboles R_o représente un groupe R_1 et l'autre un groupe R_2 et X_5 représente un groupe hydroxy estérifié réactif, ou un sel d'un tel composé formé par addition avec un acide, avec une N—R_3—S—R_4—isothiourée, ou bien

f) on transpose un composé de formule



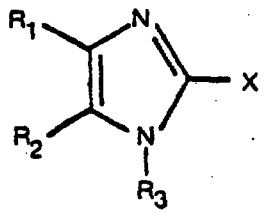
(VII)

dans laquelle X_6 est un groupe alkylthio inférieur éventuellement substitué par un groupe phényle qui peut lui-même être substitué comme R_1 et R_2, ou un sel d'un tel composé formé par addition avec un acide, et si on le désire, dans un composé de formule I dans laquelle n est égal à 0 et R_1, R_2, R_3 et R_4 ont les significations indiquées ci-dessus, obtenu selon les variantes opératoires a) à f), étant spécifié que dans les composés de formule I obtenus selon la variante opératoire a) par réaction des composés de formules II et III dans lesquelles X représente un groupe mercapto éventuellement à l'état de sel et Y un groupe hydroxy estérifié réactif, les groupes hétéroaryles, R_1 et/ou R_2 diffèrent de groupes hétéroaryles à 5 chaînons portant un atome de soufre ou d'oxygène ou de groupes hétéroaryles à 6 chaînons portant un atome d'azote lorsque R_4 représente un groupe alkyle inférieur substitué par un ou deux groupes hydroxy, un groupe alcoxy inférieur, ou par un groupe phényle éventuellement substitué comme indiqué ci-dessus, ou un groupe alcynyle inférieur non substitué, on oxyde le groupe thio en groupe sulfinyle ou sulfonyle et/ou dans les composés obtenus selon l'une des variantes opératoires a) à f), dans lesquels R_1 et/ou R_2 porte au moins un atome d'azote >N, on oxyde à l'azote, ou dans des composés obtenus selon l'une des variantes opératoires b) ou f) et dans lesquels n est égal à 1 ou 2, on réduit le groupe sulfinyle ou sulfonyle en groupe thio et/ou dans les composés obtenus selon les variations opératoires a) à f) et dans lesquels R_1 et R_2 contiennent un atome d'azote oxydé, on réduit cet atome d'azote en un groupe >N, on alkyle à l'azote par un groupe alkyle inférieur un composé de formule I obtenu conformément à l'invention dans lequel R_3 représente l'hydrogène, dans les composés de formule I obtenus conformément à l'invention, dans les restes R_1, R_2 et/ou les groupes phényle, phénoxy ou phénylthio constituants de R_4, on introduit éventuellement des substituants additionnels sur le carbone et/ou on convertit un composé obtenu conformément à l'invention à l'état libre en un sel formé par addition avec un acide ou un sel d'acide obtenu conformément à l'invention en le composé libre ou en un autre sel.

30. Procédé selon la revendication 29, pour la préparation des composés de formule I dans laquelle R_1, R_2, R_3 et R_4 ont les significations indiquées dans la revendication 29, les groupes hétéroaryles R_1 et/ou R_2 ne portant pas toutefois de substituant oxy à l'azote, et n est égal à 0, et de leurs sels formés par addition avec des acides, caractérisé en ce que:

a) on fait réagir entre eux des composés de formules

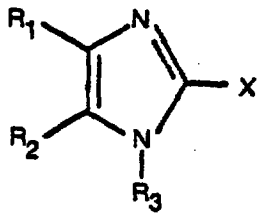
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(II) et $Y—R_4$ (III),

dans lesquelles l'un des symboles X et Y représente un groupe mercapto éventuellement à l'état de sels et l'autre un reste échangeable contre un groupe mercapto éthérifié, étant spécifié que dans les composés de formule II dans laquelle X représente un groupe mercapto éventuellement à l'état de sel, les groupes hétéroaryles R_1 et/ou R_2 diffèrent d'un groupe hétéroaryle à 5 chaînons contenant un atome de soufre ou d'un groupe hétéroaryle à 6 chaînons portant un atome d'azote ou bien les restes R_3 diffèrent de l'hydrogène lorsque, dans les composés de formule III, Y représente un groupe hydroxy estérifié réactif et R_4 un groupe alkyle inférieur monosubstitué par un groupe hydroxy en position 2, 3 ou 4, ou bien

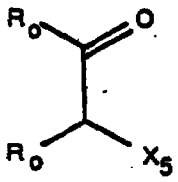
c) on fait réagir un composé de formule



(II),

dans laquelle X représente un groupe mercapto, avec un alcène inférieur éventuellement substitué comme indiqué pour le groupe alkyle inférieur R_4, ou bien

e) on fait réagir un composé de formule



(VI)

dans laquelle le reste R_0 en position alpha du groupe oxo est un reste R_1 et l'autre reste R_0 est un reste R_2, et X_5 représente un groupe hydroxy estérifié réactif, avec un sel de $N—R_3—S—R_4$-isothiuronium et si on le désire on alkyle à l'azote par un groupe alkyle inférieur un composé de formule I obtenu conformément à l'invention et dans lequel R_3 représente l'hydrogène, dans les composés de formule I obtenus conformément à l'invention, dans les restes R_1, R_2 et/ou les groupes phényle, phénoxy ou phénylthio constituants de R_4, on introduit éventuellement des substituants additionnels au carbone, et/ou on convertit un composé obtenu conformément à l'invention à l'état libre en un sel formé par addition avec un acide ou un sel d'acide obtenu conformément à l'invention en le composé libre.

31. Les composés obtenus par le procédé de la revendication 29 ou 30.

32. Composés selon l'une des revendications 1 à 26 en tant qu'agents anti-inflammatoires.

33. Utilisation des composés selon l'une des revendications 1 à 26 pour la préparation de médicaments par voie non chimique.