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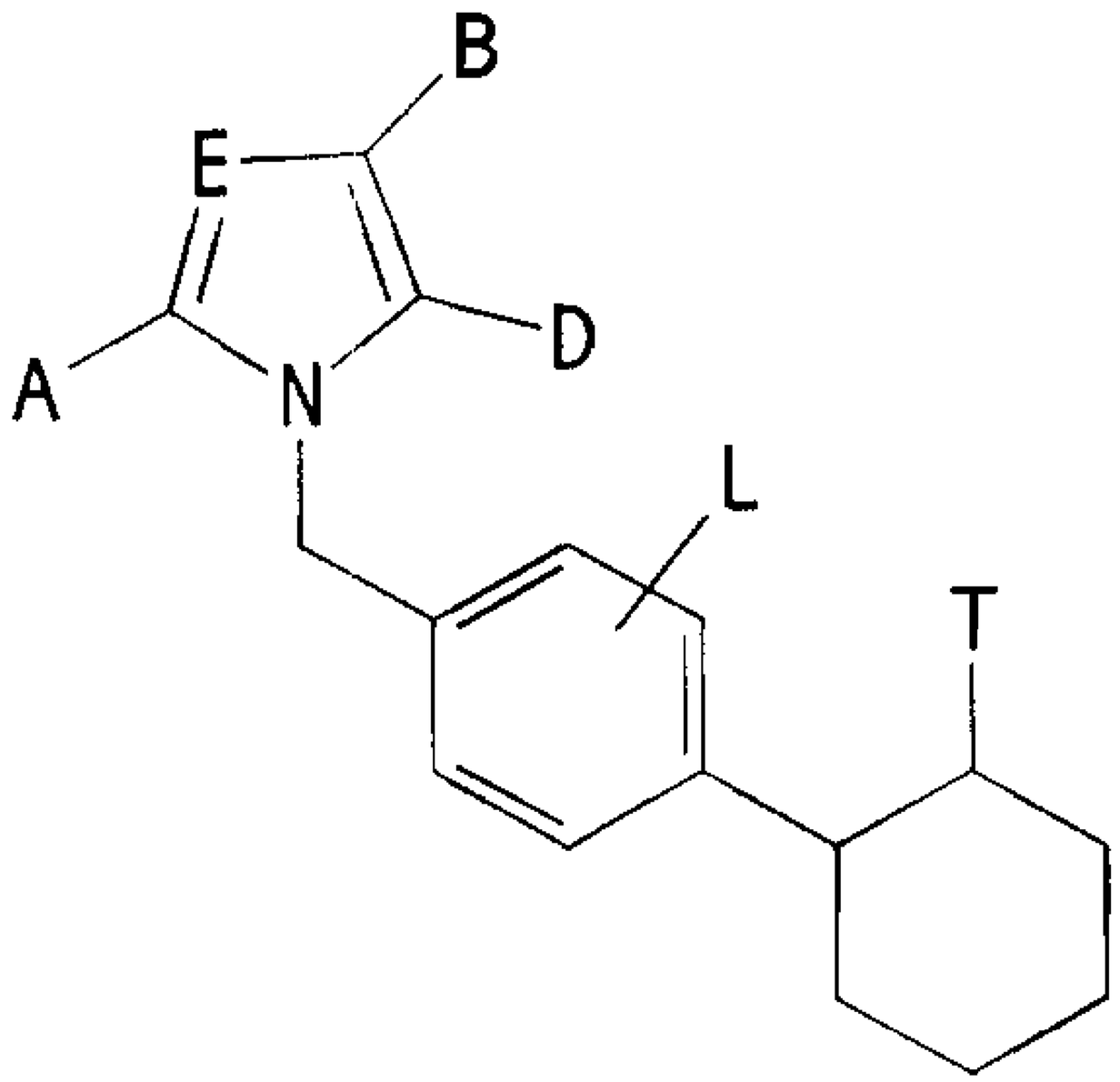
(54) Titre : DERIVES HETEROCYCLIQUEMENT SUBSTITUES DE PHENYL-CYCLOHEXANE-ACIDE CARBOXYLIQUE
(54) Title: HETEROCYCLICALLY SUBSTITUTED PHENYL-CYCLOHEXANE-CARBOXYLIC ACID DERIVATIVES



(I)

(57) Abrégé/Abstract:
Heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivatives are prepared by reacting appropriate heterocyclic compounds with cyclohexanebenzyl halides. The compounds can be employed as active compounds in medicaments for the treatment of arterial hypertension and atherosclerosis. The compounds have the general formula (I) (see formula I) wherein A, B, D, E, L and T are as defined in the description and claims.

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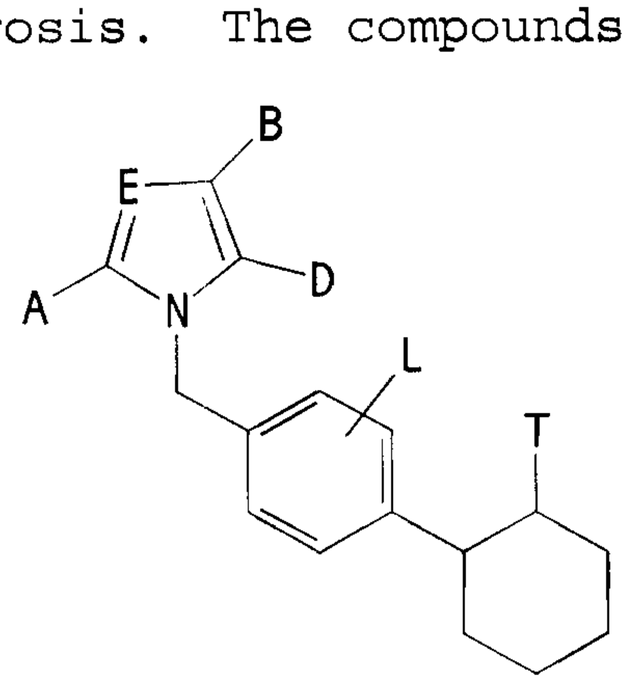
23189-7599

Heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivatives

Abstract

Heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivatives are prepared by reacting appropriate heterocyclic compounds with cyclohexanebenzyl halides. The compounds can be employed as active compounds in medicaments for the treatment of arterial hypertension and atherosclerosis. The compounds have the general formula (I):



(I)

wherein A, B, D, E, L and T are as defined in the description and claims.

The invention relates to heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivatives, a process for their preparation and their use in medicaments, in particular as hypotensive and antiatherosclerotic agents.

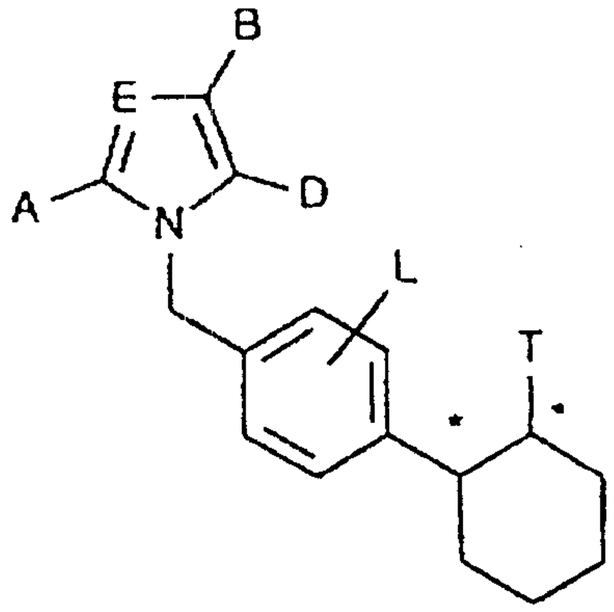
It is known that renin, a proteolytic enzyme, eliminates the decapeptide angiotensin I in vivo from angiotensinogen, and the angiotensin I is in turn degraded in the lungs, the kidneys or other tissues to the hypertensive octapeptide angiotensin II. The various effects of angiotensin II, such as, for example, vascoconstriction, Na^+ retention in the kidney, aldosterone release in the adrenal gland and increase in tone of the sympathetic nervous system act synergistically in the sense of a blood pressure increase.

Moreover, angiotensin II has the property of promoting the growth and the replication of cells such as, for example, cardiac muscle cells and smooth muscle cells, these growing and proliferating at an increased rate in various disease states (for example hypertension, atherosclerosis and cardiac insufficiency).

In addition to the inhibition of renin activity, a possible starting point for intervention in the renin-angiotensin system (RAS) is the inhibition of the activity of angiotensin-converting enzyme (ACE) and the blockade of angiotensin II receptors.

In addition, heterocyclic compounds having angiotensin II-antagonistic action are disclosed in EP 407 102, EP 399 731, EP 399 732, EP 324 377 and EP 253 310.

The present invention relates to heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivatives of the general formula (I)



(I)

in which

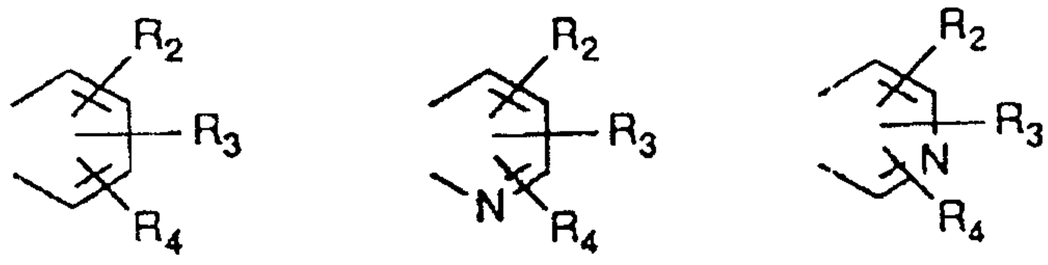
A represents hydrogen or aryl having 6 to 10 carbon atoms, which is optionally substituted by hydroxyl, halogen or trifluoromethyl or by straight-chain or branched alkyl or alkoxy in each case having up to 6 carbon atoms, or
represents straight-chain or branched alkyl or alkenyl in each case having up to 8 carbon atoms, or
represents cycloalkyl having 3 to 8 carbon atoms,

E represents a nitrogen atom or a radical of the formula $-CR^1$,

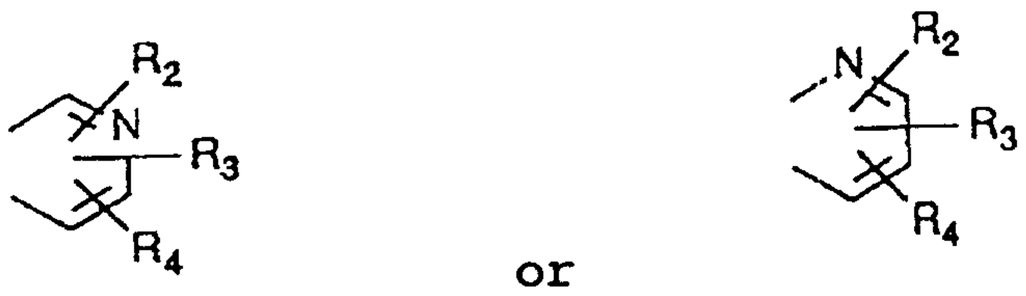
in which

R^1 has the abovementioned meaning of A and is identical to or different from this,

B and D together form a radical of the formula



or

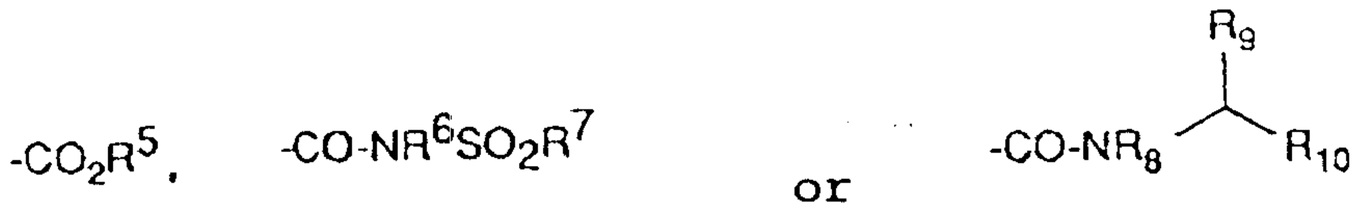


in which

R^2, R^3 and R^4 are identical or different and have the abovementioned meaning of A and are identical to or different from this, or denote halogen,

L represents hydrogen, halogen, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 6 carbon atoms, cyano or carboxyl,

T represents a radical of the formula



in which

R^5 denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, cycloalkyl having 3 to 7 carbon atoms or phenyl,

R^6 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

R^7 denotes trifluoromethyl or straight-chain or branched alkyl having up to 6 carbon atoms, or benzyl or phenyl, each of which is optionally substituted by straight-chain alkyl having up to 6 carbon atoms,

R^9 denotes aryl having 6 to 10 carbon atoms, which is optionally substituted up to 2 times by identical or different substituents from the group consisting of halogen, hydroxyl, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 6 carbon atoms, carboxyl, phenoxy and C_3-C_6-cycloalkoxy,

R^{10} denotes a group of the formula $-CH_2-OR^{11}$,

$-CO_2R^{12}$, $-CO-NR^{13}R^{14}$ or pyridyl,

in which

R^{11} denotes hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms,

R^{12} denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, or phenyl or cycloalkyl having 3 to 6 carbon atoms,

R^{13} and R^{14} are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, or phenyl,

or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl or straight-chain or branched alkyl having up to 4 carbon atoms,

if appropriate in an isomeric form, and their salts.

The compounds of the general formula I according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the new heterocyclically substituted phenyl-cyclohexanecarboxylic acids and -carboxylic acid derivatives can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Those particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

The compounds according to the invention can exist in stereoisomeric forms which behave either as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers or to their respective mixtures. Like the diastereomers, the

racemic forms can be separated in a known manner into the stereoisomerically uniform constituents [cf. E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw Hill, 1962].

Preferred compounds of the general formula (I) are those

in which

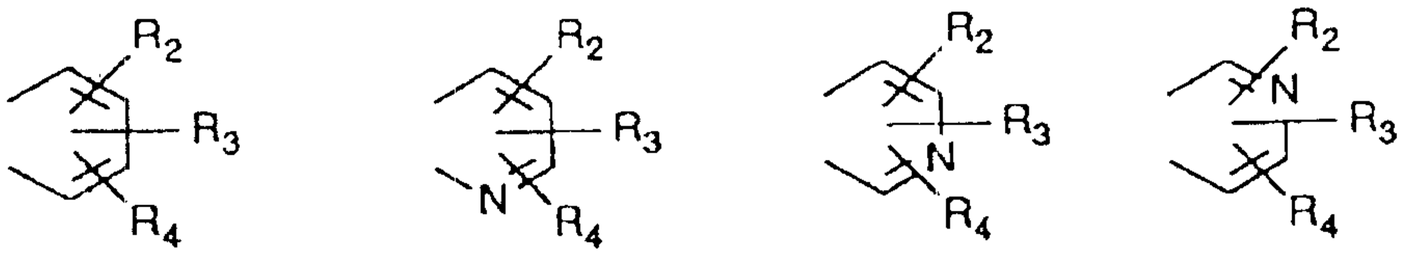
A represents hydrogen or phenyl which is optionally substituted by hydroxyl, fluorine, chlorine, bromine or trifluoromethyl or by straight-chain or branched alkyl or alkoxy in each case having up to 4 carbon atoms, or
represents straight-chain or branched alkyl or alkenyl in each case having up to 6 carbon atoms, or represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl,

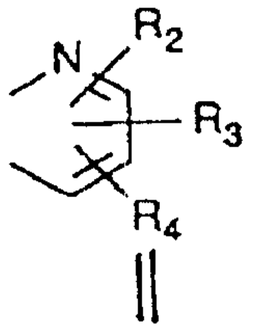
E represents a nitrogen atom or a radical of the formula $-CR^1$,

in which

R^1 has the abovementioned meaning of A and is identical to or different from this,

B and D together form a radical of the formula



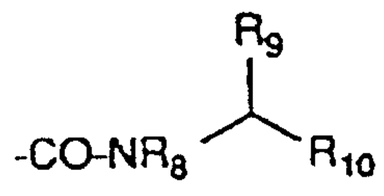


in which

R^2, R^3 and R^4 are identical or different and have the abovementioned meaning of A and are identical to or different from this, or denote fluorine, chlorine or bromine,

L represents hydrogen, fluorine, chlorine, bromine, trifluoromethyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 4 carbon atoms,

T represents a radical of the formula

$-CO_2R^5$, $-CO-NR^6SO_2R^7$ or 

in which

R^5 denotes hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl or phenyl,

R^6 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^7 denotes trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, or benzyl or phenyl, each of which is optionally substituted by straight-chain or branched alkyl having up to 4 carbon atoms,

R^9 denotes phenyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 4 carbon atoms, carboxyl or phenoxy,

R^{10} denotes a group of the formula $-CH_2-OR^{11}$, $-CO_2R^{12}$, $-CO-NR^{13}R^{14}$ or pyridyl,

in which

R^{11} denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

R^{12} denotes hydrogen, straight-chain or

branched alkyl having up to 6 carbon atoms, phenyl, cyclopropyl, cyclopentyl or cyclohexyl,

R^{13} and R^{14} are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl or phenyl,

or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl or methyl,

if appropriate in an isomeric form, and their salts.

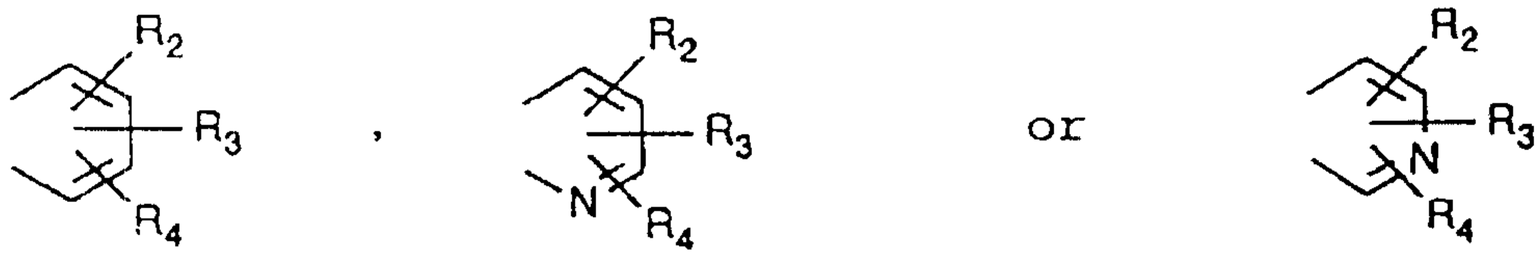
Particularly preferred compounds of the general formula (I) are those

in which

A represents hydrogen or
represents straight-chain or branched alkyl having up to 4 carbon atoms, or
represents phenyl or cyclopropyl, cyclopentyl or cyclohexyl,

E represents a nitrogen atom,

B and D together form a radical of the formula

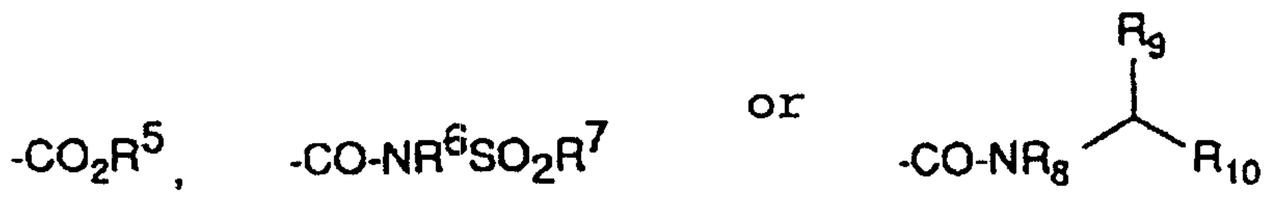


in which

R^2, R^3 and R^4 are identical or different and have the abovementioned meaning of A and are identical to or different from this, or denote fluorine, chlorine or bromine,

L represents hydrogen, fluorine, chlorine, trifluoromethyl or methyl,

T represents a radical of the formula



in which

R^5 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^6 and R^8 are identical or different and denote hydrogen or methyl,

R^7 denotes trifluoromethyl or methyl, ethyl, benzyl, p-tolyl or phenyl,

R^9 denotes phenyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 3 carbon atoms, carboxyl or phenoxy,

R^{10} denotes a group of the formula $-CH_2-OR^{11}$, $-CO_2R^{12}$, $-CO-NR^{13}R^{14}$ or pyridyl,

in which

R^{11} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^{12} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^{13} and R^{14} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl or methyl,

if appropriate in an isomeric form, and their salts.

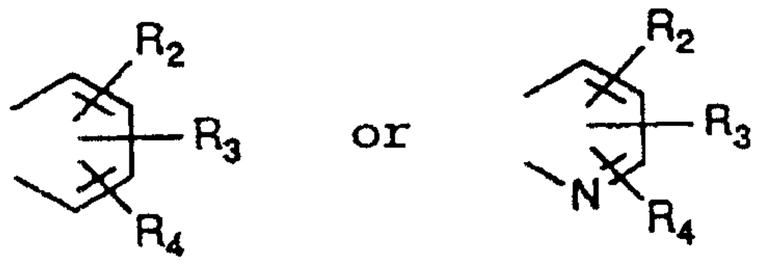
Very particularly preferred compounds of the general formula (I) are those

in which

A represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, or represents phenyl or cyclopropyl,

E represents a nitrogen atom,

B and D together form a radical of the formula



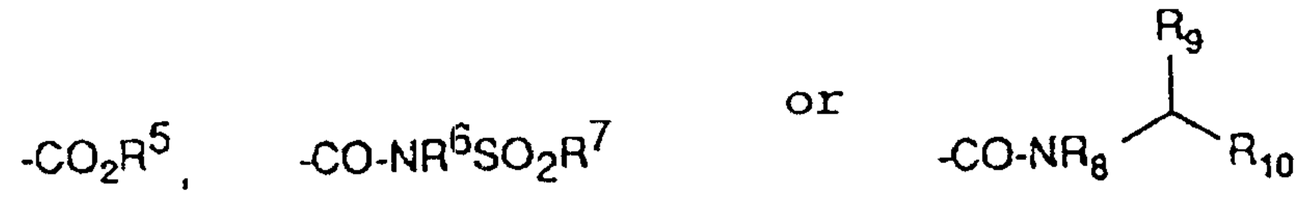
in which

R^2, R^3 and R^4 are identical or different and denote methyl, hydrogen, fluorine, chlorine or

bromine,

L represents hydrogen, fluorine or chlorine,

T represents a radical of the formula



or

in which

R^5 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^6 and R^8 are identical or different and denote hydrogen or methyl,

R^7 denotes trifluoromethyl, methyl or p-tolyl,

R^9 denotes phenyl which can be substituted by fluorine or chlorine,

and

R^{10} denotes a group of the formula $-CH_2-OH$, $-CONH_2$ or pyridyl,

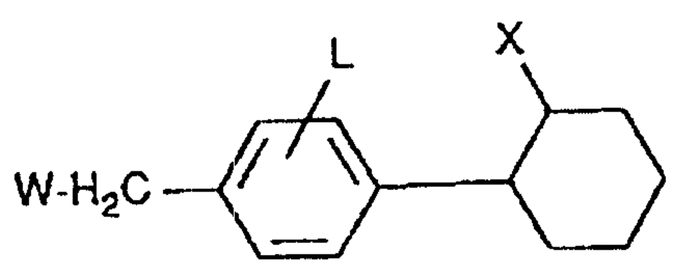
or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl,

if appropriate in an isomeric form, and their salts.

A process for the preparation of the compounds of the general formula (I) according to the invention has additionally been found, characterized in that

compounds of the general formula (II)



(II)

in which

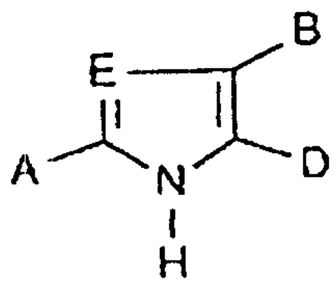
L has the abovementioned meaning,

W represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, preferably bromine

and

X represents C_1-C_6-alkoxycarbonyl or the triphenyl-methyl-tetrazol-1-yl group,

are reacted first with compounds of the general formula (III)

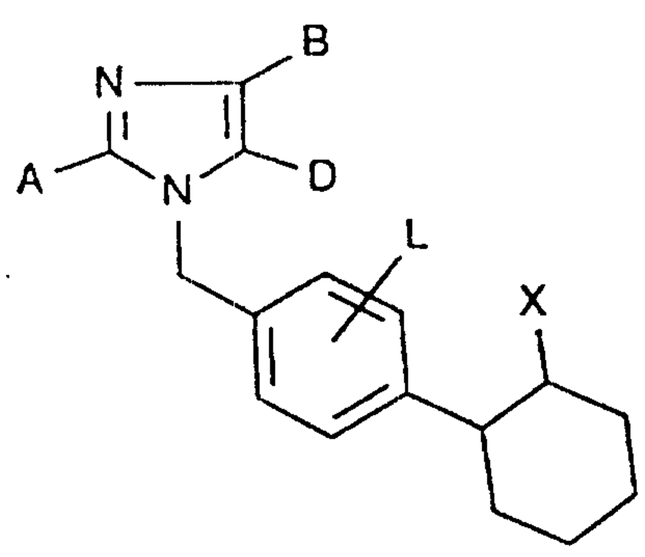


(III)

in which

A, B, D and E have the abovementioned meaning,

in inert solvents, if appropriate in the presence of a base and if appropriate under a protective gas atmosphere, to give compounds of the general formula (IV)



(IV)

in which

A, B, D, L and X have the abovementioned meaning,

and if appropriate starting from the corresponding carboxylic acids, after prior hydrolysis and activation, the products are subsequently amidated in inert solvents with sulphonamides or amines of the general formulae (V) and (Va)

$HNR^6\text{-}SO_2\text{-}R^7$ (V) or (Va)

in which

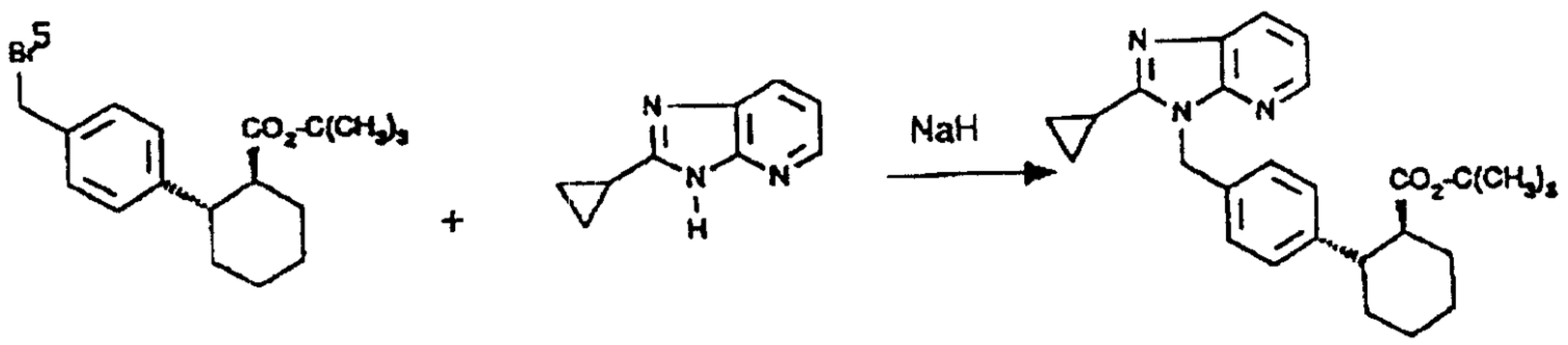
R^6, R^7, R^8, R^9 and R^{10} have the abovementioned meaning,

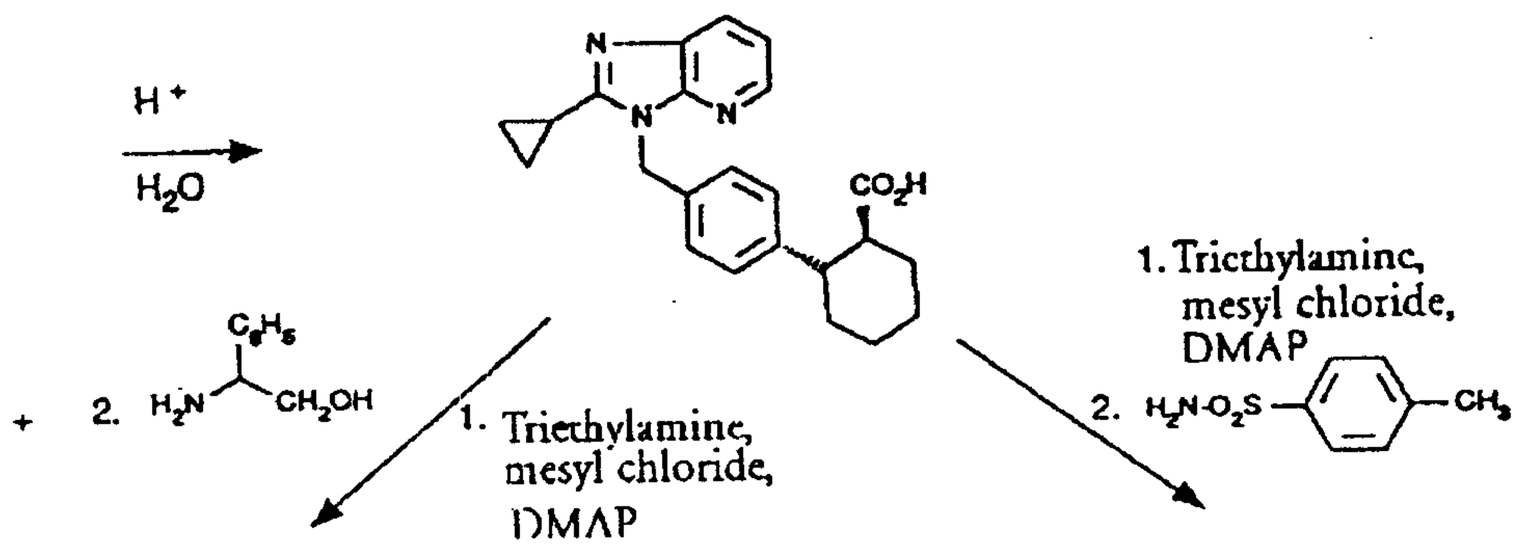
if appropriate in the presence of a base and/or of an auxiliary, for example of a dehydrating agent,

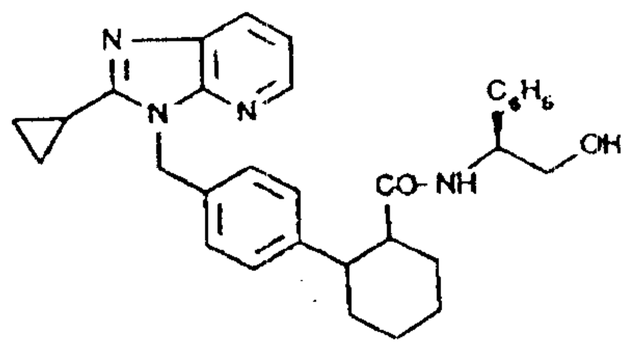
and in the case of the free tetrazoles, if appropriate the triphenylmethyl group is removed by customary methods using acids, preferably using trifluoroacetic acid or hydrochloric acid in dioxane,

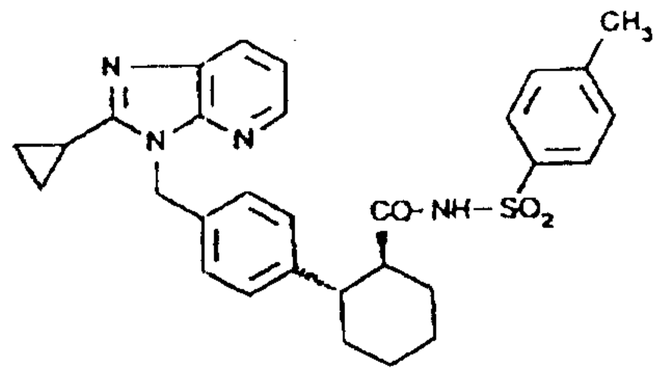
and if appropriate the isomers are separated, and in the case of the preparation of the salts reacted with an appropriate base or acid.

The process according to the invention can be illustrated by way of example by the following reaction scheme:









Suitable solvents for the process are the customary organic solvents which do not change under the reaction conditions. These preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or mineral oil fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Dimethylformamide and tetrahydrofuran are preferred.

Bases which can be employed for the process according to the invention are in general inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkali metal or

alkaline earth metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or potassium tert-butoxide, or organic amines (trialkyl(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, diaminopyridine, methylpiperidine or morpholine. It is also possible to employ as bases alkali metals such as sodium or their hydrides such as sodium hydride. Sodium hydride, potassium carbonate, triethylamine, pyridine and potassium tert-butoxide, DBU or DABCO are preferred.

In general, the base is employed in an amount from 0.05 mol to 10 mol, preferably from 1 mol to 2 mol, relative to 1 mol of the compound of the formula (III).

The process according to the invention is in general carried out in a temperature range from -80°C to +100°C, preferably from -30°C to +60°C.

The process according to the invention is in general carried out at normal pressure. However, it is also possible to carry out the process at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

Suitable bases for the hydrolysis are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, lithium hydroxide, sodium hydroxide,

potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate, or alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide. Lithium hydroxide, sodium hydroxide or potassium hydroxide is particularly preferably employed.

Suitable solvents for the hydrolysis are water or the organic solvents customary for hydrolysis. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol or butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide, or dimethyl sulphoxide. Alcohols such as methanol, ethanol, propanol or isopropanol are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned.

The hydrolysis can also be carried out using aqueous acids such as, for example, trifluoroacetic acid, acetic acid, hydrochloric acid, hydrobromic acid, methanesulphonic acid, sulphuric acid or perchloric acid, preferably using trifluoroacetic acid.

The hydrolysis is in general carried out in a temperature range from 0°C to +100°C, preferably from +20°C to +80°C.

In general, the hydrolysis is carried out at normal pressure. However, it is also possible to work at reduced pressure or at elevated pressure (for example from 0.5 to

5 bar).

When carrying out the hydrolysis, the base is in general employed in an amount from 1 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the ester. Molar amounts of the reactants are particularly preferably used.

When carrying out the reaction, the carboxylates of the compounds according to the invention are formed in the first step as intermediates which can be isolated. The acids according to the invention are obtained by treating the carboxylates with customary inorganic acids. These preferably include acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or trifluoroacetic acid. It has proven advantageous in this case in the preparation of the carboxylic acids to acidify the basic reaction mixture from the hydrolysis in a second step without isolation of the carboxylates. The acids can then be isolated in a customary manner. In the case of the basic heterocycles, the salts of the heterocycles with the inorganic acids can also be obtained by treating the solutions of the carboxylates with the abovementioned acids.

The amidation and the sulphonamidation of the compounds of the general formula (IV) are in general carried out in one of the abovementioned solvents, preferably in tetrahydrofuran or dichloromethane.

The amidation can optionally take place via the activated

stage of the acid halides, which can be prepared from the appropriate acids by reaction with thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide or oxalyl chloride.

The amidation is in general carried out in a temperature range from -20°C to +80°C, preferably from -10°C to +30°C, and at normal pressure.

Suitable bases for this in addition to the abovementioned bases are preferably triethylamine and/or dimethylaminopyridine, DBU or DABCO.

The base is employed in an amount from 0.5 mol to 10 mol, preferably from 1 mol to 5 mol, relative to 1 mol of the compounds of the general formulae (IV) and (V).

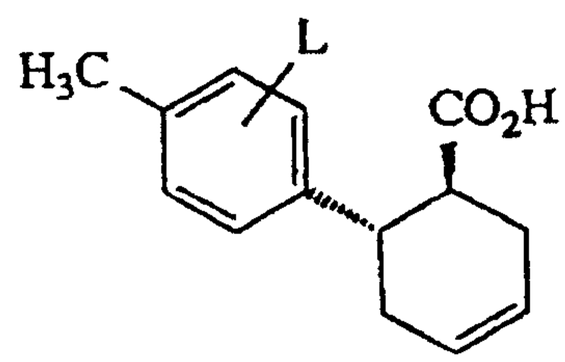
Acid-binding agents which can be employed for the amidation are alkali metal or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, alkali metal or alkaline earth metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, or organic bases such as pyridine, triethylamine or N-methylpiperidine, or bicyclic amidines such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU). Potassium carbonate is preferred.

Suitable dehydrating reagents are carbodiimides such as, for example, diisopropylcarbodiimide, dicyclohexyl-

carbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or carbonyl compounds such as carbonyldiimidazole or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulphonate or propanephosphonic anhydride or isobutyl chloroformate or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate or diphenyl phosphoramidate or methanesulphonyl chloride, if appropriate in the presence of bases such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide.

The acid-binding agents and dehydrating reagents are in general employed in an amount from 0.5 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the corresponding carboxylic acids.

The cyclohexane compounds of the general formula (II) are in the main new and can be prepared by converting compounds of the general formula (VI)



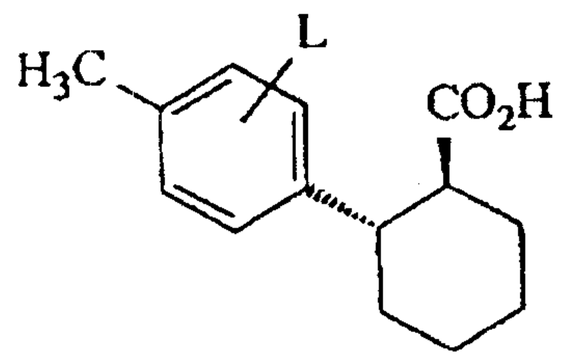
(VI)

in which

L has the abovementioned meaning,

first by hydrogenation with palladium/C in one of the

abovementioned solvents, preferably methanol, in a hydrogen atmosphere into the compounds of the general formula (VII)



(VII)

in which

L has the abovementioned meaning,

in a second step, in the case where T ≠ tetrazole, esterifying by customary methods,

and in the case where T represents the tetrazolyl radical, reacting with chlorosulphonyl isocyanate in dichloromethane to give the corresponding cyano compounds, then introducing the tetrazolyl group using sodium azide/triethylammonium chloride, in the presence of one of the abovementioned bases, preferably N,N-dimethylformamide, under a nitrogen atmosphere, introducing the triphenylmethyl group by further reaction with triphenylmethyl chloride in the presence of one of the abovementioned solvents and bases, preferably dichloromethane and triethylamine,

and in a last step carrying out a bromination of the methylene group, if appropriate in the presence of a

catalyst.

The reduction of the double bond is carried out in a temperature range from 0°C to +40°C, preferably at +20°C and a pressure of 1 bar-10 bar, preferably 1-3 bar.

The esterification is carried out in one of the above-mentioned solvents, preferably toluene and tetrahydrofuran, after the prior activation of the corresponding carboxylic acid which has already been described above, preferably via the carbonyl chlorides, and subsequent reaction with the corresponding alkoxides, in a temperature range from 0°C to +60°C, preferably at +10°C to +35°C and at normal pressure.

The reactions to give the cyano compounds and tetrazolyl compounds are in general carried out at the boiling point of the respective solvent and normal pressure.

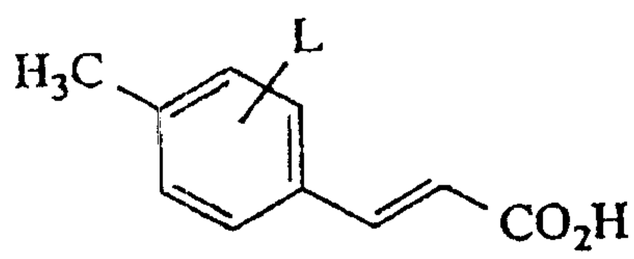
The introduction of the triphenylmethyl group into the tetrazolyl ring is in general carried out at 0°C.

The bromination is in general carried out in a temperature range from +40°C to 100°C, preferably from +60°C to +90°C and at normal pressure. It is carried out in one of the abovementioned solvents, preferably using carbon tetrachloride, and using N-bromosuccinimide.

A suitable starter (catalyst) for the bromination is, for example, azobisisobutyronitrile or dibenzoyl peroxide,

preferably azobisisobutyronitrile, the starter being employed in an amount from 0.01 mol to 0.1 mol, preferably from 0.01 mol to 0.05 mol, relative to 1 mol of the compound of the general formula (VII).

The compounds of the general formula (VI) are also new and can be prepared, for example, by reacting compounds of the general formula (VIII)



(VIII)

in which

L has the abovementioned meaning,

in one of the abovementioned solvents, preferably toluene, with 1,3-butadiene in the presence of hydroquinone, in a temperature range from +180°C to +230°C, preferably at 200°C and a pressure of about 20 bar [cf. Eur. J. Med. Chem. 11, 493 (1976)].

The compounds of the general formula (VIII) are known per se or can be prepared by customary methods.

The compounds of the general formulae (IV) and (VII) are new and can be prepared, for example, by the processes described above.

The compounds of the general formula (III) are likewise known per se or can be prepared by a customary method.

The amines of the general formula (V) are known or can be prepared by known processes.

The compounds of the general formula (I) according to the invention exhibit an unforeseeable, useful spectrum of pharmacological action.

The compounds according to the invention have a specific A II-antagonistic action, since they competitively inhibit the binding of angiotensin II to the receptors. They suppress the vasoconstrictory and aldosterone secretion-stimulating effects of angiotensin II. They moreover inhibit the proliferation of smooth muscle cells.

They can therefore be employed in medicaments for the treatment of arterial hypertension and atherosclerosis. They can moreover be employed for the treatment of coronary heart diseases, cardiac insufficiency, brain function disorders, ischaemic cerebral diseases, peripheral circulatory disorders, functional disorders of the kidney and adrenal gland, bronchospastic diseases and diseases of the respiratory tract having a vascular component, sodium retention and oedemas.

23189-7599

In a composition aspect, the invention provides a pharmaceutical composition for the treatment of arterial hypertension or atherosclerosis, which composition comprises a compound according to the invention, or a pharmaceutically acceptable salt thereof, together with a suitable diluent or carrier.

In a further aspect, the invention provides a process for preparing a pharmaceutical composition for the treatment of arterial hypertension or atherosclerosis, which process comprises admixing a compound according to the invention or a pharmaceutically acceptable salt thereof with a suitable diluent or carrier.

In a use aspect, the invention provides use of a compound according to the invention or a pharmaceutically acceptable salt thereof, or a composition according to the invention for the treatment of arterial hypertension or atherosclerosis.

In a further use aspect, the invention provides use of a compound according to the invention or a pharmaceutically acceptable salt thereof, or a composition according to the invention for preparing a medicament for the treatment of arterial hypertension or a atherosclerosis.

In still a further aspect, the invention provides a commercial package comprising, as active pharmaceutical ingredient, a compound according to the invention or a pharmaceutically acceptable salt thereof, or a composition according to the invention, together with instructions for the use thereof, for the treatment of arterial hypertension or atherosclerosis.

Investigation of the inhibition of the contraction induced by agonists

Rabbits of either sex are stunned by a blow to the back of the head and bled out, or in some cases anaesthetized with Nembutal (about 60-80 mg/kg i.v.) and sacrificed by opening the thorax. The thoracic aorta is removed, freed from adhering connective tissue, divided into ring segments 1.5 mm wide and individually transferred under an initial loading of about 3.5 g to 10 ml organ baths containing Krebs-Henseleit nutrient solution, aerated with 95% O_2/5% CO_2 and temperature-controlled at 37°C, of the following composition: 119 mmol/l of NaCl; 2.5 mmol/l of $CaCl_2 \times 2H_2O$; 1.2 mmol/l of KH_2PO_4; 10 mmol/l of glucose; 4.8 mmol/l of KCl; 1.4 mmol/l of $MgSO_4 \times 7H_2O$ and 25 mmol/l of $NaHCO_3$.

The contractions are determined isometrically by means of Statham UC2 cells via bridge amplifiers (ifd Mülheim or DSM Aalen) and digitalized by means of A/D converters (System 570, Keithley Munich) and assessed. The agonist dose response curves (DRCs) are plotted hourly. With each DRC, 3 or 4 individual concentrations are applied to the baths at a 4 min interval. After the end of the DRC and subsequent washing-out cycles (16 times in each case about 5 sec/min with the abovementioned nutrient solution), a 28-minute resting or incubation phase follows, within which the contractions as a rule reach the starting value again.

The height of the 3rd DRC, in a normal case, is used as a reference quantity for the assessment of the test substance to be investigated in further runs, which substance is applied to the baths in the following DRCs in each case in increasing dose at the start of the incubation period. Each aorta ring is in this case stimulated for the whole day, always with the same agonist.

Agonists and their standard concentrations (administration volume per individual dose - 100 µl):

KCl	22.7; 32.7; 42.7; 52.7	mmol/l
1 Noradrenaline	3×10^{-9}; 3×10^{-8}; 3×10^{-7}; 3×10^{-6};	g/ml
Serotonin	10^{-8}; 10^{-7}; 10^{-6}; 10^{-5}	g/ml
B-HT 920	10^{-7}; 10^{-6}; 10^{-5};	g/ml
Methoxamine	10^{-7}; 10^{-6}; 10^{-5};	g/ml
Angiotensin II	3×10^{-9}; 10^{-8}; 3×10^{-8}; 10^{-7}	g/ml

To calculate the IC_{50} (concentration at which the substance to be investigated causes a 50% inhibition), the effect is in each case based on the 3rd = submaximal agonist concentration.

The compounds according to the invention inhibit the contraction of the isolated rabbit aorta induced by angiotensin II in a dose-dependent manner. The contraction induced by potassium depolarization or other

agonists was not inhibited or only weakly inhibited at high concentrations.

Table A:

Inhibition of the vascular contraction in isolated rabbit aorta rings in vitro

IC_{50} (nM) against contractions induced by: AII

Ex. No.	IC_{50} [nM]
9	260
30	220

Blood pressure measurements on the angiotensin II-infused rat

Male Wistar rats (Moellegaard, Copenhagen, Denmark) having a body weight of 300-350 g are anaesthetized with thiopental (100 mg/kg i.p.). After tracheotomy, a catheter for blood pressure measurements is inserted in the femoral artery and a catheter for angiotensin II infusion and a catheter for substance administration are inserted in the femoral veins. After administration of the ganglionic blocker pentolinium (5 mg.kg i.v.), the angiotensin II infusion (0.3 µg/kg/min) is started. As soon as the blood pressure values have reached a stable plateau, the test substances are administered either intravenously or orally as a suspension or solution in 0.5% Tylose. The blood pressure changes under the action

of substance are indicated as mean values ± SEM in the table.

Determination of the antihypertensive activity in conscious hypertensive rats

The oral antihypertensive activity of the compounds according to the invention was tested in conscious rats having surgically induced unilateral renal artery stenosis. To do this, the right renal artery was constricted with a silver clip of 0.18 mm internal width. In this form of hypertension, the plasma renin activity is increased in the first six weeks after intervention. The arterial blood pressure of these animals was measured in a bloodless manner at defined time intervals after substance administration using the "tail cuff". The substances to be tested were administered intragastrally ("orally") by stomach tube at various doses suspended in a Tylose suspension. The compounds according to the invention reduce the arterial blood pressure of the hypertensive rats at a clinically relevant dosage.

The compounds according to the invention additionally inhibit the specific binding of radioactive angiotensin II in a concentration-dependent manner.

23189-7599

Interaction of the compounds according to the invention with the angiotensin II receptor in membrane fractions of the adrenal gland cortex (bovine)

Adrenal gland cortices from cattle (AGCs), which have been freshly removed and carefully freed from gland medulla, are comminuted in sucrose solution (0.32 M) with the aid of an Ultra-Turrax™ (Janke & Kunkel, Staufen i.B.) to give a coarse membrane homogenate and partially purified to give membrane fractions in two centrifugation steps.

The receptor binding investigations are carried out on partially purified membrane fractions of bovine AGC using radioactive angiotensin II in an assay volume of 0.25 ml, which specifically contains the partially purified membranes (50-80 µg), ^{3}H-angiotensin II (3-5 nM), test buffer solution (50 mM Tris, pH 7.2, 5 mM $MgCl_2$) and the substances to be investigated. After an incubation period of 60 min at room temperature, the unbound radioactivity of the samples is separated by means of moistened glass fibre filters (Whatman™ GF/C) and the bound radioactivity is measured spectrophotometrically in a scintillation cocktail after washing the protein with ice-cold buffer solution (50 mM Tris/HCl, pH 7.4, 5% PEG 6000). The raw data were analysed using computer programs to give K_i or IC_{50} values (K_i: IC_{50} values corrected for the radioactivity used; IC_{50} values: concentration at which the substance to be investigated causes a 50% inhibition of the specific binding of the radioligand).

Table B:

Ex. 9	K_i = 47 nM
Ex. 30	K_i = 19 nM

Investigation of the inhibition of the proliferation of smooth muscle cells by the compounds according to the invention

To determine the antiproliferative action of the compounds, smooth muscle cells are used which are obtained from the aortas of rats by the media explant technique [R. Ross, J. Cell. Biol. 50, 172, 1971]. The cells are inoculated into suitable culture dishes, as a rule 96-hole plates, and cultured at 37°C in 5% CO_2 for 2-3 days in medium 199 containing,7.5% FCS and 7.59% NCS, 2 mM L-glutamine and 15 mM HEPES, pH 7.4. The cells are then synchronized for 2-3 days by withdrawal of serum and then stimulated into growth using serum or other factors. Test compounds are simultaneously added. After 16-20 hours, 1 µCi ^{3}H-thymidine is added and after a further 4 hours the incorporation of this substance into the TCA-precipitable DNA of the cells is determined. To determine the IC_{50} values, the active compound concentration is calculated which, on sequential dilution of the active compound, causes semi-maximum inhibition of the thymidine incorporation produced by 10% FCS.

Table C:

Ex. No.	IC_{50}[nM]
16	410
17	2
21	7
25	26
29	4
31	3

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In this case, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to reach the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent organic solvents can optionally be used as auxiliary solvents.

Administration is carried out in a customary manner, preferably orally or parenterally, in particular

perlingually or intravenously.

In the case of parenteral administration, solutions of the active compound using suitable liquid excipient materials can be employed.

In general, it has proven advantageous in the case of intravenous administration to administer amounts from about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to obtain effective results, and in the case of oral administration the dose is about 0.01 to 20 mg/kg, preferably about 0.1 to 10 mg/kg, of body weight.

In spite of this, it may sometimes be necessary to depart from the amounts mentioned, depending on the body weight or the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of larger amounts, it may be advisable to divide these into several individual doses over the course of the day.

The invention also extends to a commercial package containing, as active pharmaceutical ingredient, a compound of the invention, together with instructions for its use for the treatment of arterial hypertension or atherosclerosis.

Eluent mixtures:

A = Dichloromethane : methanol = 10:1

B = Petroleum ether : ethyl acetate = 4:1

C = Petroleum ether : ethyl acetate = 1:1

D = Dichloromethane: methanol = 10:1

E = Ethyl acetate : dichloromethane = 1:1

F = Dichloromethane : ethanol = 20:1

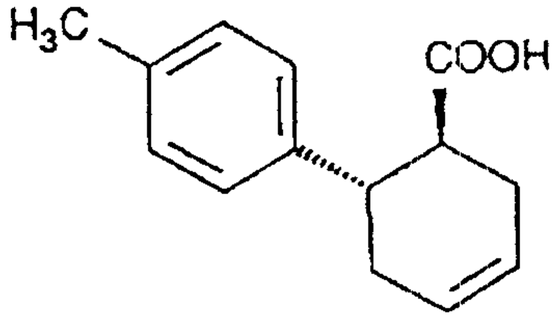
G = Petroleum ether : ethyl acetate = 1:2

H = Dichloromethane : methanol: aq. conc. ammonia = 200:20:1

Starting Compounds

Example I

trans-6-(4-Tolyl)-cyclohex-3-ene-1-carboxylic acid



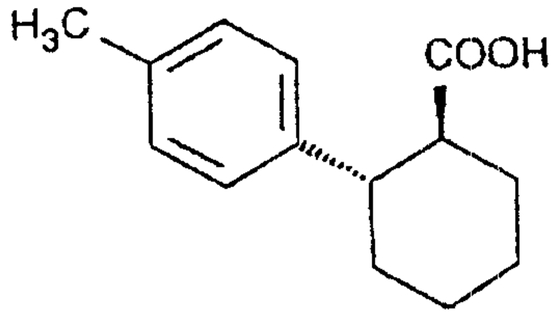
racemic

275 g (1.695 mol) of 3-E-(4-tolyl)acrylic acid (commercially available) are reacted at about 200°C and about 20 bar for 22 h with 580 ml of 1,3-butadiene (measured in condensed form) in 480 ml of toluene with addition of 3 g of hydroquinone by a known process (Eur. J. Med. Chem. 11, 493 (1976)). The crude mixture is diluted with toluene and extracted with 0.5 M aqueous sodium hydroxide solution. The aqueous phases are then acidified with 1 M hydrochloric acid and extracted with ether. The ethereal solutions are dried using sodium sulphate, evaporated and the residue is again dissolved in toluene. After boiling with 5 g of active carbon for 15 minutes, the carbon is filtered off hot with suction and the solvent is evaporated to about 120-160 ml; 124 g (573 mmol) of product crystallize out at 0-4°C. The filtrate is somewhat further concentrated and cooled again to induce additional crystallization. On repetition of this process, altogether a further 42 g (194 mmol) of product are obtained.

R_f = 0.39 (dichloromethane:methanol = 10:1)

Example II

trans-2-(4-Tolyl)-cyclohexane-1-carboxylic acid



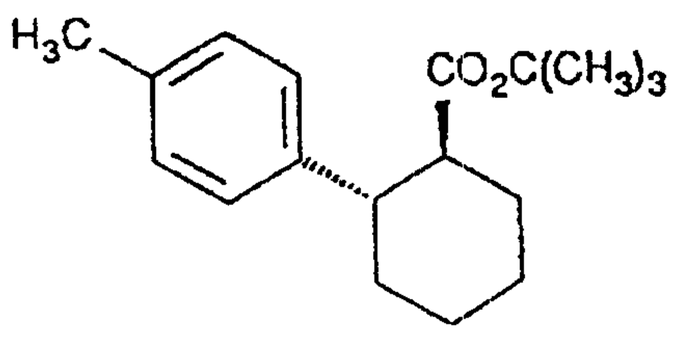
racemic

155 g (717 mmol) of the compound from Example I are dissolved in 1 l of methanol and reacted at 20°C and a hydrogen pressure of about 1 bar on 10 g of palladium (10% on animal charcoal). After a reaction time of altogether 16 h, the catalyst is filtered off and the solvent is evaporated - finally in vacuo.
Yield: 153 g (701 mmol)

R_f = 0.38 (dichloromethane:methanol = 10:1)

Example III

tert-Butyl trans-2-(4-tolyl)-cyclohexane-1-carboxylate



racemic

Method A:

45.8 g (184 mmol) of the compound from Example II are dissolved in 600 ml of toluene and reacted under reflux with 49.5 ml (387 mmol) of oxalyl chloride. After 2 h, the solvent is evaporated with excess reagent; to do this the crude carboxylic acid chloride must if necessary be repeatedly taken up in toluene and the solution concentrated in a rotary evaporator once again. The product thus obtained is dissolved in 500 ml of tetrahydrofuran, stirred at 0°C with 24.8 g (221 mmol) of potassium tert-butoxide and additionally stirred for 20 h (at 20°C). Water and ether are then added and the mixture is extracted several times. The organic phase is dried using sodium sulphate and evaporated, and the residue is purified by chromatography on silica gel 60 (Merck, petroleum ether:ethyl acetate = 20:1).

Yield: 39.6 g (130 mmol)

R_f = 0.47 (petroleum ether:ethyl acetate = 10:1)

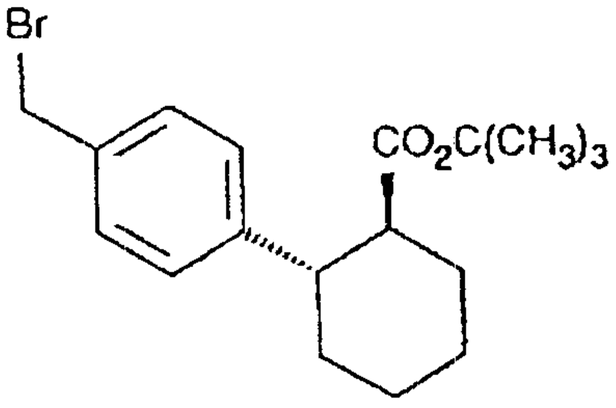
Method B:

20.0 g (91.6 mmol) of the compound from Example II are suspended in 7 ml of conc. sulphuric acid in 100 ml of ether and treated with 80 ml (713 mmol) of isobutene at -30°C (pressure apparatus). The mixture is heated to 20°C in the closed vessel and reacted for 20 hours. It is then cooled again to -30°C, the apparatus is opened and the reaction mixture is stirred into 300 ml of 3 M sodium hydroxide solution/400 ml of ether at 20°C. The aqueous phase is reextracted with ether, and the organic solution is dried with sodium sulphate and evaporated.

Yield: 23.3 g (84.9 mmol)

Example IV

tert-Butyl trans-2-(4-bromomethylphenyl)-cyclohexane-1-carboxylate



racemic

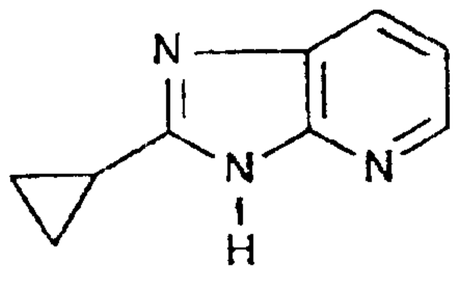
11.70 g (42.6 mmol) of the compound from Example III are reacted with 7.59 g (42.6 mmol) of N-bromosuccinimide and 1.4 g of azobisisobutyronitrile in 100 ml of tetrachloromethane under reflux. After a reaction time of 4 h, the mixture is cooled, the succinimide precipitate obtained is filtered off with suction and the filtrate is evaporated.

Yield: 14.2 g (40.2 mmol)

R_f = 0.48 (petroleum ether:ethyl acetate = 10:1)

Example V

6-Cyclopropyl-imidazo[2,3-b]pyridine

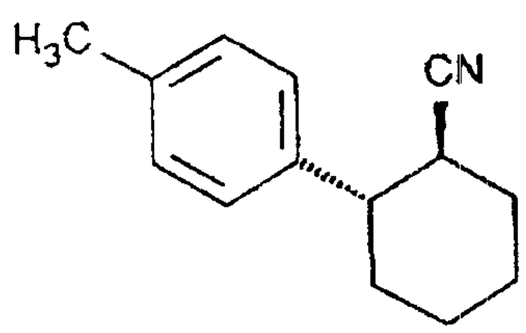


3.27 g (30 mmol) of 2,3-diaminopyridine (Aldrich) and 2.72 g (30 mmol) of cyclopropanecarboxylic acid (Aldrich) are stirred at 120°C for 3 hours with 30 ml of tolylphosphoric acid. The mixture is poured into ice-water, adjusted to pH = 6-7 with sodium hydroxide and basified to pH = 8-9 with sodium carbonate. After extracting several times with ethyl acetate, the combined organic phases are dried using sodium sulphate, filtered and evaporated - finally in a high vacuum. After chromatographic work-up of the crude product (silica gel 60, Merck, dichloromethane to dichloromethane:methanol = 50:1); yield: 3.01 g (19 mmol).

R_f = 0.38 (ethyl acetate:methanol = 10:1)

Example VI

trans-2-(4-Tolyl)-cyclohexane-1-carbonitrile



racemic

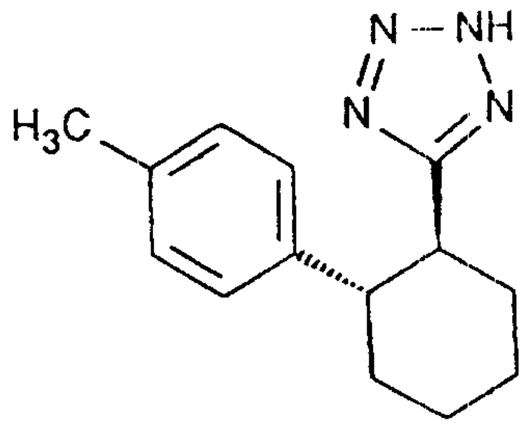
100.0 g (458.0 mmol) of the compound from Example II are reacted at boiling point in 1 l of dichloromethane for 1 h with 84.3 g (595.5 mmol) of chlorosulphonyl isocyanate in 100 ml of dichloromethane. 72 ml (938.9 mmol) of N,N-dimethylformamide are then added dropwise to the cooling reaction mixture and it is subsequently stirred for 18 h. The mixture is poured onto 350 g of ice, the phases are separated after melting and the aqueous phase is extracted with dichloromethane. The organic phases dried using potassium carbonate are evaporated and the residue is distilled. 57.8 g (290.2 mmol) of product are obtained.

Boiling point: 122-131°C (0.2 mbar)

R_f = 0.81 (dichloromethane)

Example VII

5-[trans-2-(4-Tolyl)-cyclohex-1-yl]tetrazole



racemic

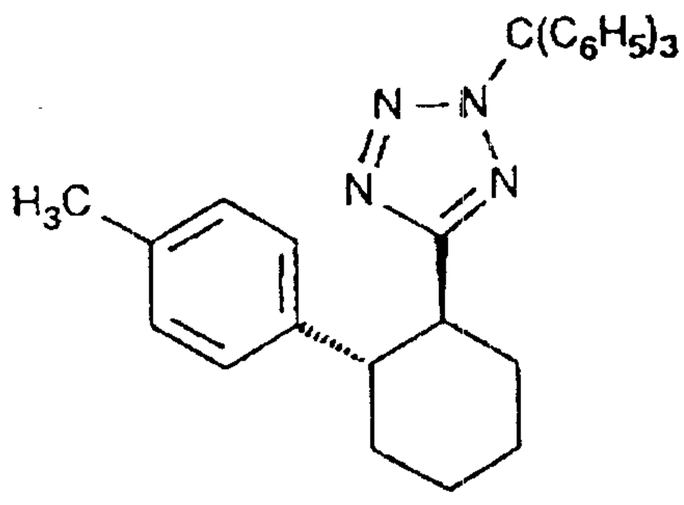
15.34 g (69.6 mmol) of the compound from Example VI are reacted under nitrogen at boiling heat with 22.6 g (348 mmol) of sodium azide and 47.9 g (348 mmol) of triethylammonium chloride in 230 ml of anhydrous N,N-dimethylformamide. After 20 h, the mixture is poured into ether and 1 M sulphuric acid after cooling, and the organic phase is washed with 1 M sulphuric acid and then extracted with 10% strength sodium hydroxide solution. The aqueous phase is adjusted to pH = 1.5 at 0°C using 1 M hydrochloric acid and the precipitate obtained is filtered off with suction, washed with water and dried over phosphorus pentoxide and sodium hydroxide in a high vacuum.

Yield: 11.2 g (46.2 mmol)

R_f = 0.23 (dichloromethane:methanol = 20:1)

Example VIII

5-[trans-2-(4-Tolyl)-cyclohex-1-yl]-2-triphenylmethyl-tetrazole



racemic

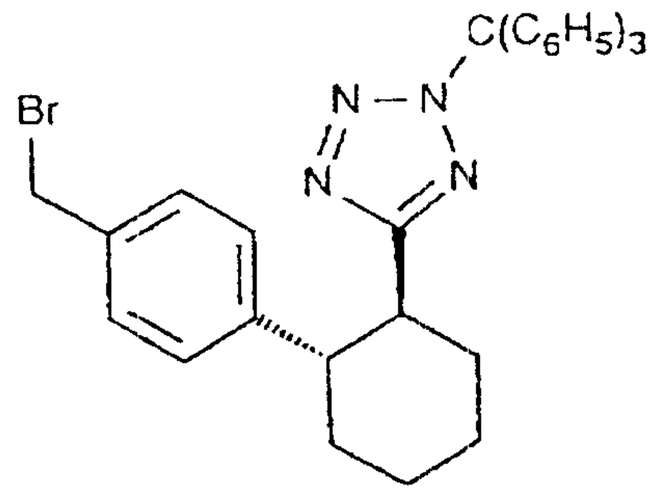
11.0 g (45.7 mmol) of the compound from Example VII are reacted at 0°C with 13.4 g (48.2 mmol) of triphenylmethyl chloride and 7.57 ml (54.6 mmol) of triethylamine in 170 ml of dichloromethane. The mixture is additionally stirred for about 20 h while warming to room temperature and is then extracted with ether and aqueous citric acid. The organic phases are dried using sodium sulphate and evaporated.

Yield: 22.1 g (45.5 mmol)

R_f = 0.67 (petroleum ether:ethyl acetate = 5:1)

Example IX

5-[trans-2-(4-Bromomethylphenyl)-cyclohex-1-yl]-2-triphenylmethyl-tetrazole



racemic

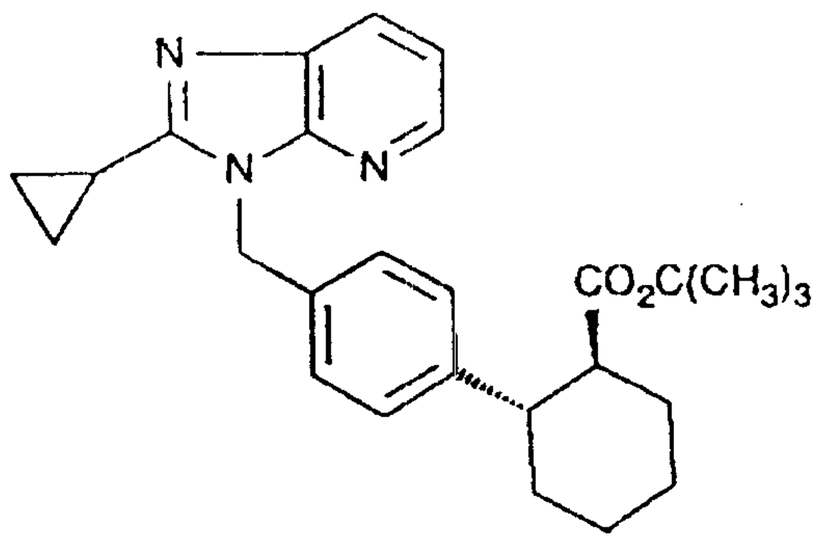
22.1 g (45.5 mmol) of the compound from Example VIII are reacted under reflux with 8.1 g (45.5 mmol) of N-bromo-succinimide and 0.3 g of azobisisobutyronitrile in 300 ml of tetrachloromethane. After a reaction time of 3 hours, the mixture is cooled to room temperature and later to 0°C and the precipitate is filtered off with suction. The filtrate is evaporated and a crude product (26.2 g) is obtained which is further reacted without further work-up.

R_f = 0.47 (petroleum ether:ethyl acetate = 10:1)

Preparation Examples

Example I

tert-Butyltrans-2-{4-[6-cyclopropyl-imidazo[2,3-b]-pyridin)-7-yl-methyl]-phenyl}-cyclohexane-1-carboxylate



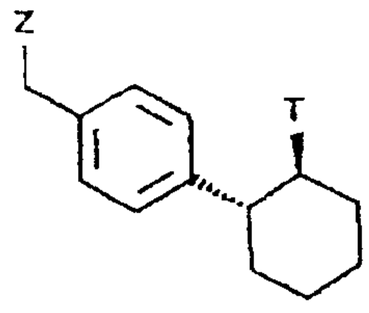
racemic

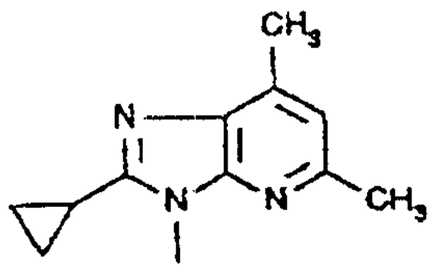
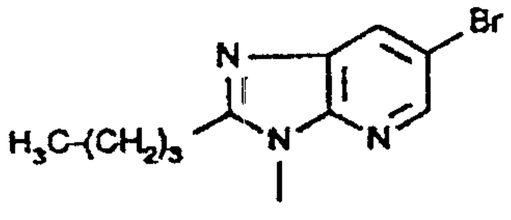
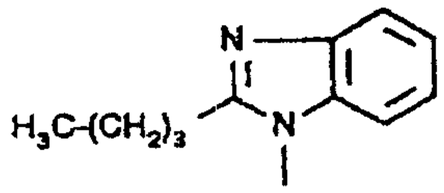
0.90 g (5.7 mmol) of the compound from Example V is reacted at 0°C with 0.17 g (5.7 mmol) of sodium hydride (80% strength, stabilized with paraffin) in 15 ml of dimethylformamide. After evolution of hydrogen is complete, the mixture is additionally stirred for 20 minutes and 2.00 g (5.7 mmol) of the compound from Example IV in 20 ml of dimethylformamide are then added dropwise at 0°C. The mixture is additionally stirred for 20 h while warming to 20°C and then extracted several times with ether after addition of water. The organic phase is dried with sodium sulphate and evaporated, and the residue is purified by chromatography on silica gel 60 (Merck, petroleum ether:ethyl acetate = 1:1); yield: 0.4 g (0.9 mmol).

R_f = 0.60 (petroleum ether:ethyl acetate = 1:2)

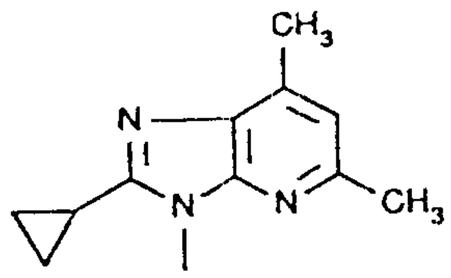
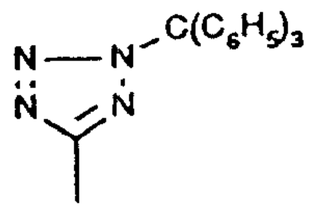
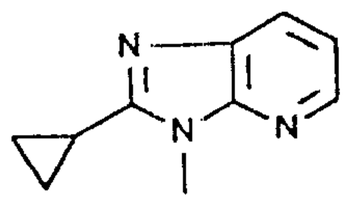
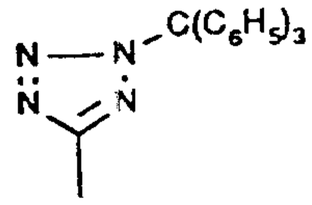
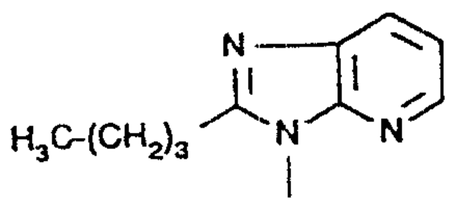
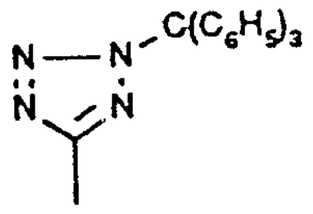
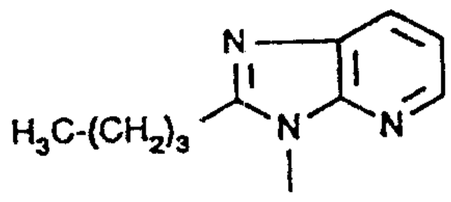
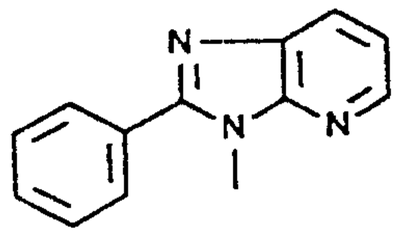
The compounds shown in Table 1 are prepared analogously to Example 1:

Table 1:



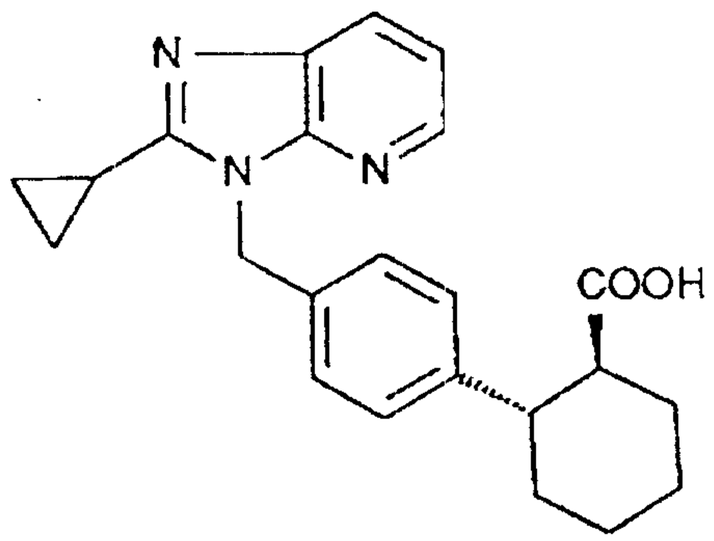
Ex. No.	Z	T	R_f (eluent)
2		$-CO_2C(CH_3)_3$	0.16 (B)
3		$-CO_2C(CH_3)_3$	0.50 (B)
4		$-CO_2C(CH_3)_3$	0.21 (B)

Continuation of Table 1:

Ex. No.	Z	T	R_f (eluent)
5			0.74 (G)
6			0.53 (G)
7			0.50 (C)
8		$CO_2C(CH_3)_3$	0.41 (D)
9		$CO_2C(CH_3)_3$	0.18 (D)

Example 10

trans-2-{4-[(6-Cyclopropyl-imidazo[2,3-b]pyridin-7-yl-methyl]phenyl}-cyclohexane-1-carboxylate

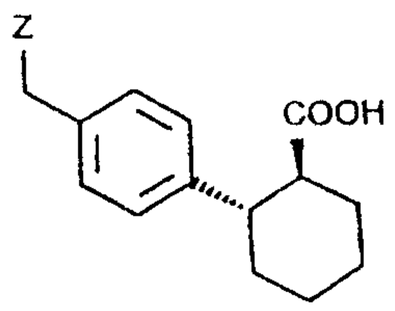


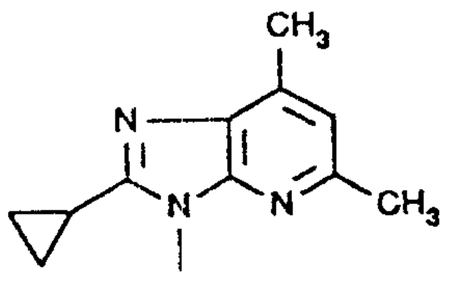
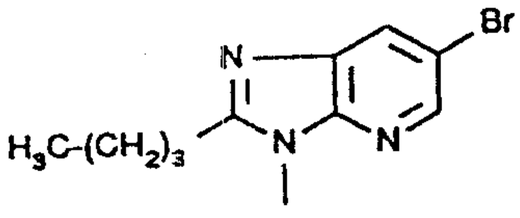
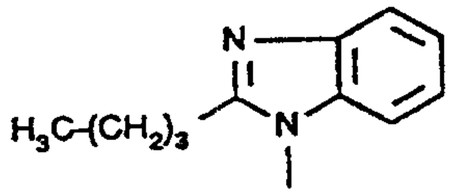
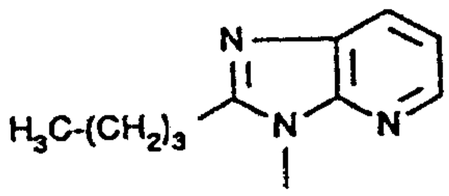
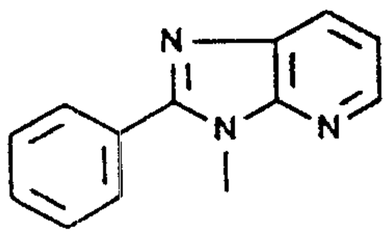
racemic

0.39 g (0.9 mmol) of the compound from Example 1 is reacted with 10 ml of concentrated hydrochloric acid in 10 ml of dioxane at 20°C. After 18 h, the mixture is adjusted to pH = 13 using 2 M sodium hydroxide solution and shaken once with ether. After separation of the phases, the aqueous solution is freed from organic solvent residues in vacuo and adjusted to pH = 5 using concentrated hydrochloric acid at 0°C. The precipitate deposited during the crurse of this is filtered off with suction, washed with water and dried over sodium hydroxide and phosphorus pentoxide in a high vacuum.
Yield: 0.28 g (0.7 mmol)
R_f = 0.08 (dichloromethane:methanol = 10:19)

The compounds shown in Table 2 are prepared in analogy to Example 10:

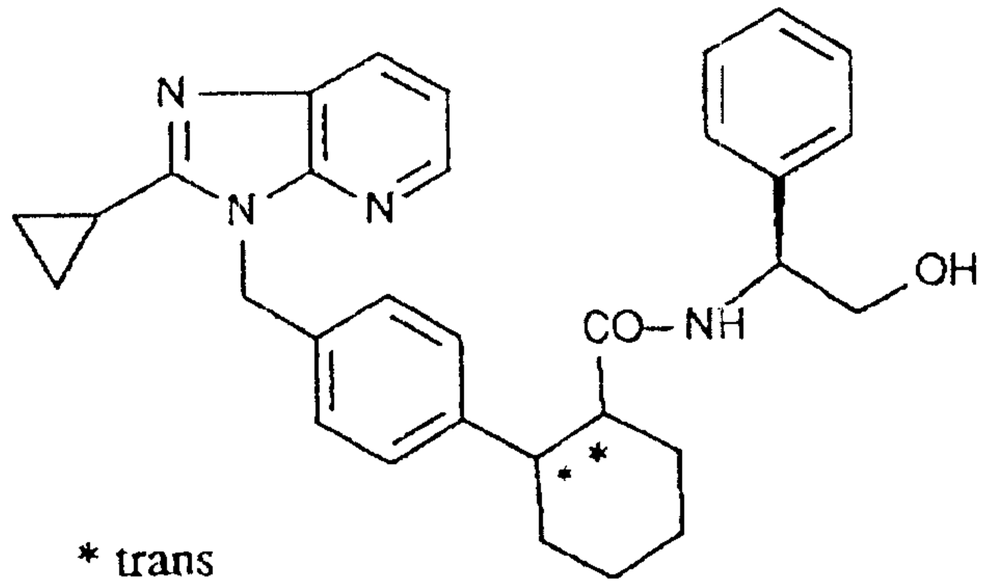
Table 2:



Ex. No.	Z	R_f (eluent)
11		0.33 (A)
12		0.32 (C)
13		0.16 (C)
14		0.18 (B)
15		0.16 (C)

Examples 16 and 17

trans-2-{4-[(6-Cyclopropyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-[(S)-phenylglycinol]-cyclohexane-1-carboxamide



0.12 g (0.32 mmol) of the compound from Example 10 is reacted with 89.6 µl (6.5 mmol) of triethylamine and 26.6 µl (0.35 mmol) of methanesulphonyl chloride at -30°C in 4 ml of tetrahydrofuran. After 30 minutes, 52.6 mg (0.38 mmol) of (S)-phenylglycinol and 39 mg (0.32 mmol) of 4-(N,N-dimethylamino)pyridine in 3 ml of tetrahydrofuran are added and the mixture is additionally stirred for 19 h while warming to 20°C. It is then poured into aqueous sodium hydrogen carbonate solution and extracted several times with ether. The ethereal extracts are dried using sodium sulphate and evaporated, and the residue is purified by chromatography on silica gel 60 (Merck, dichloromethane:methanol = 50:1).

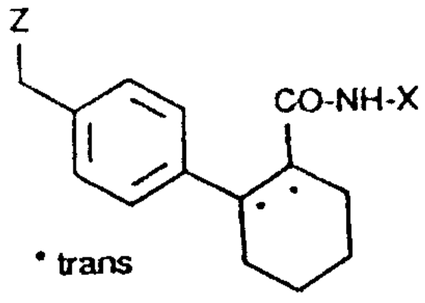
Yield:

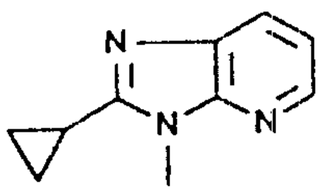
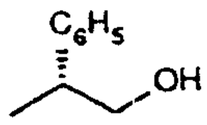
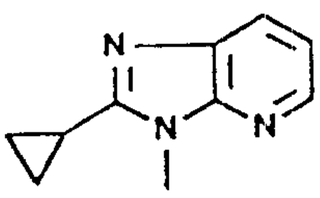
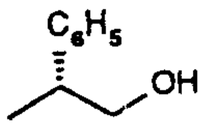
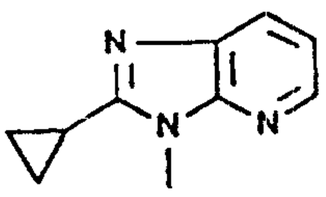
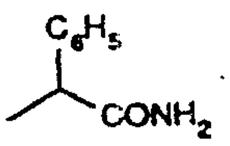
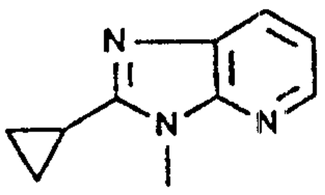
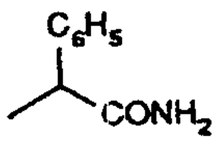
60 mg (0.12 mmol)/R_f = 0.63 (A) diastereomer A (Example 16)

40 mg (0.08 mmol)/R_f = 0.59 (A) diastereomer B (Example 17)

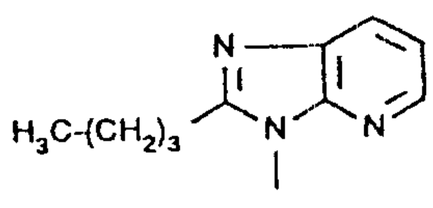
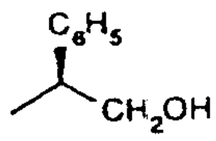
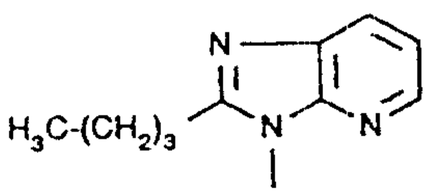
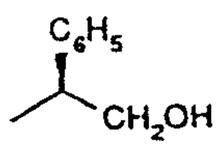
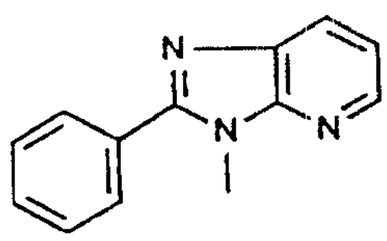
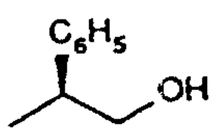
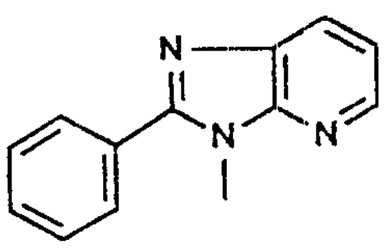
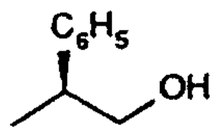
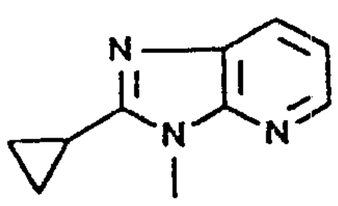
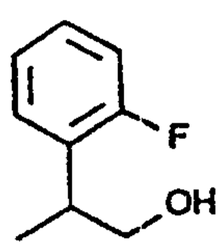
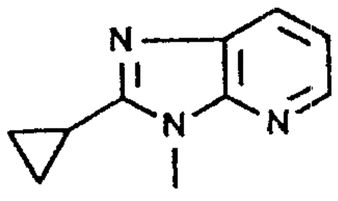
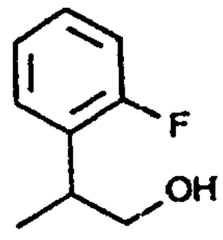
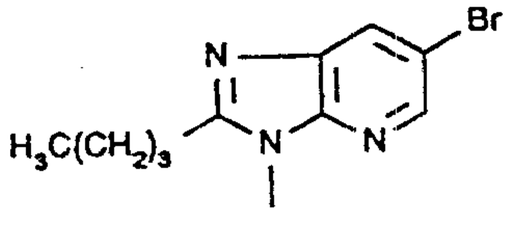
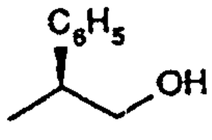
The compounds shown in Table 3 are prepared in analogy to the procedures of Examples 16 and 17:

Table 3:

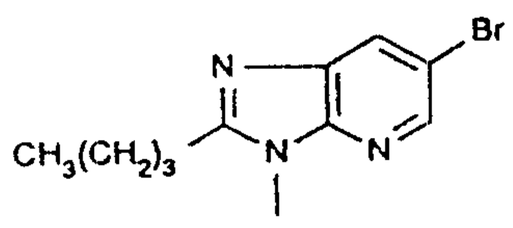
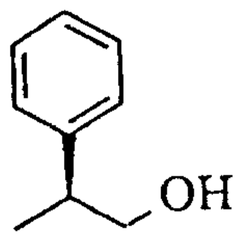
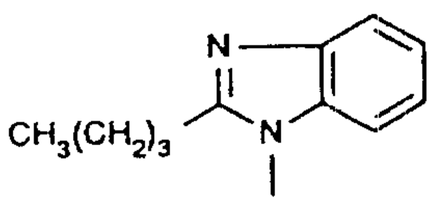
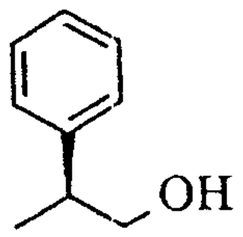
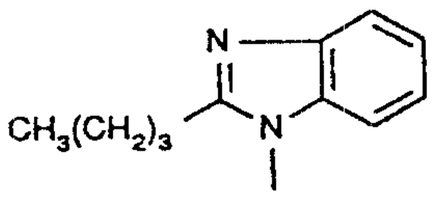
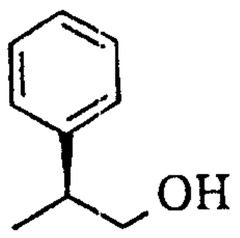
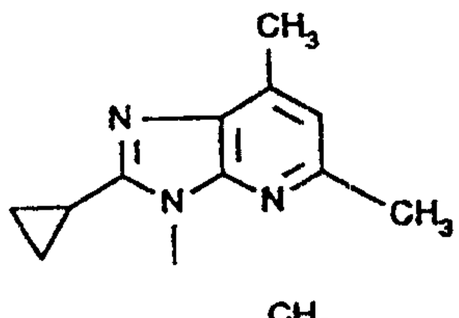
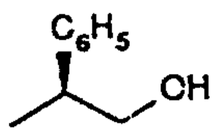
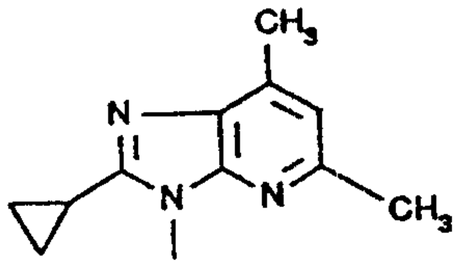
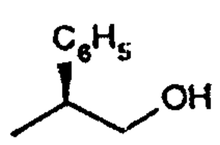
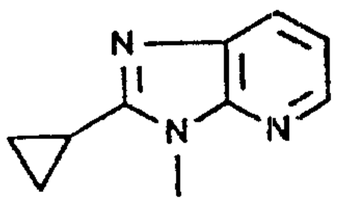
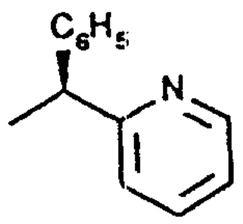
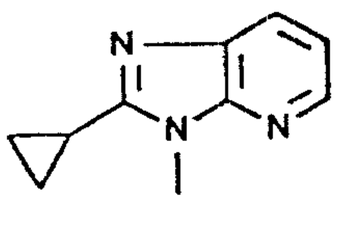
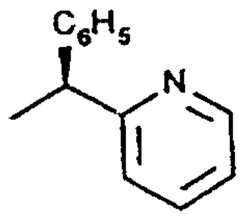


Ex. No.	Z	X	R_f (eluent)
18			0.31 (D)
19			0.27 (D)
20			0.37 (D)
21			0.32 (D)

Continuation of Table 3:

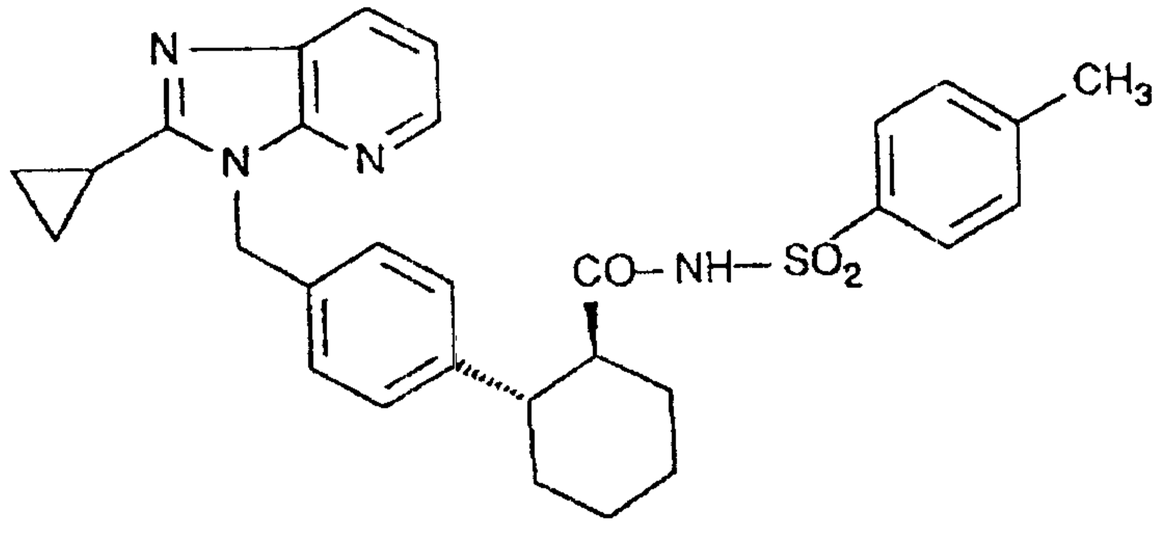
Ex. No.	Z	X	R_f (eluent)
22			0.23 (D)
23			0.15 (D)
24			0.42 (H)
25			0.40 (H)
26			0.28 (D)
27			0.25 (D)
28			0.37 (E)

Continuation of Table 3:

Ex. No.	Z	X	R_f (eluent)
29			0.27 (E)
30			0.61 (F)
31			0.56 (F)
32			0.55 (F)
33			0.51 (F)
34			0.31 (G)
35			0.21 (G)

Example 36

trans-2-{4-[(6-Cyclopropyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-(4-tolylsulphonyl)cyclohexane-1-carboxamide



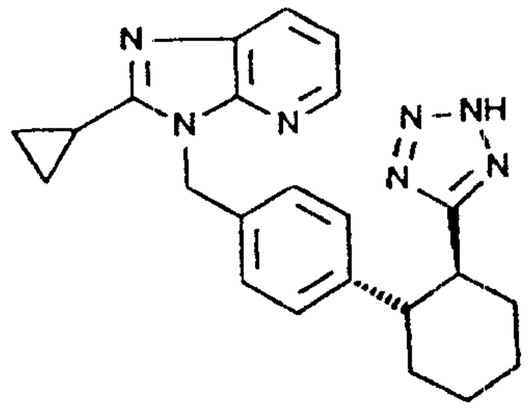
racemic

120 mg (0.32 mmol) of the compound from Example 10 are reacted with 26.6 µl (0.35 mmol) of methanesulphonyl chloride and 194 µl (1.4 mmol) of triethylamine in 4 ml of tetrahydrofuran (-20°C). After 2 h, 66.0 mg (0.39 mmol) of 4-toluenesulphonamide and 155 mg (1.28 mmol) of 4-(N,N-diethylamino)pyridine are added to the reaction mixture and the mixture is additionally stirred for 20 h. It is poured into aqueous sodium hydrogen carbonate solution and extracted with ether. The organic phase is dried using sodium sulphate and evaporated. Chromatographic purification of the residue (silica gel 60, Merck, dichloromethane:methanol = 50:1) yields 34 mg (0.06 mmol) of product.

R_f = 0.45 (petroleum ether:ethyl acetate = 1:8).

Example 37

5-[trans-2-(2-Cyclopropyl-imidazo[2,3-b]pyridin-1-yl-methylphenyl)-cyclohex-1-yl]tetrazole



racemic

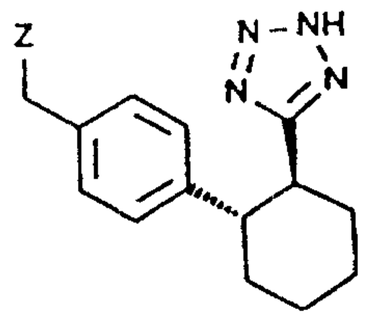
0.64 g (1.0 mmol) of the compound from Example IX is reacted at 20°C with 3 ml of water and 3 ml of trifluoroacetic acid in 7 ml of tetrahydrofuran. After 2 hours, the mixture is diluted with ether and extracted with aqueous sodium hydroxide solution (pH = 13). The alkaline aqueous phase is adjusted to pH = 4.5 using 1 M hydrochloric acid and the precipitate obtained in this way is filtered off with suction, washed with water and dried over sodium hydroxide and phosphorus pentoxide in a high vacuum.

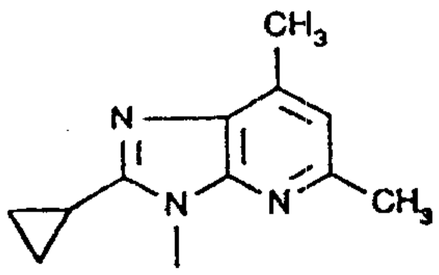
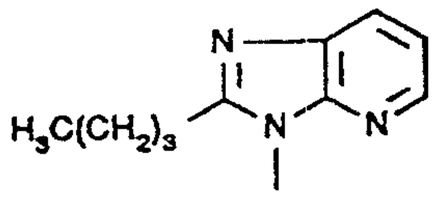
Yield: 0.27 g (0.7 mmol).

R_f = 0.35 (dichloromethane:methanol = 10:1)

The compounds shown in Table 4 are prepared in analogy to the procedure of Example 37:

Table 4:



Ex. No.	Z	R_f (eluent)
38		0.38 (A)
39		0.32 (A)

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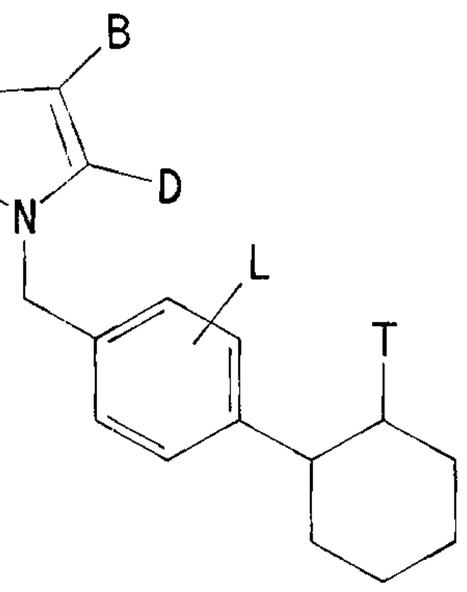
CLAIMS:

1. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative of the general formula (I):



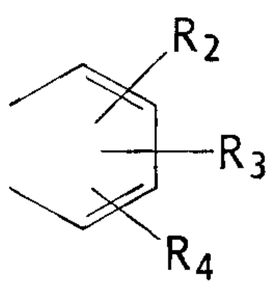
(I)

wherein:

A represents a radical selected from the group consisting of a hydrogen atom, C_{6-10}-aryl, straight-chain-C_{1-8}-alkyl, branched-chain-C_{1-8}-alkyl, straight-chain-C_{2-8}-alkenyl, branched-chain-C_{2-8}-alkenyl and C_{3-8}-cycloalkyl, wherein the C_{6-10}-aryl radical is optionally substituted by a radical selected from the group consisting of a halogen atom, hydroxyl, trifluoromethyl, straight-chain-C_{1-6}-alkyl, branched-chain-C_{1-6}-alkyl, straight-chain-C_{1-6}-alkoxy and branched-chain-C_{1-6}-alkoxy;

E represents a nitrogen atom or a radical of the general formula $-CR^1$, wherein R^1 is as defined above for A;

B and D together form a radical of the general formula: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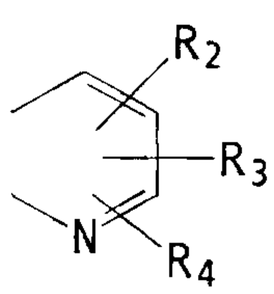
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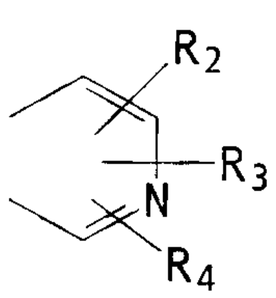
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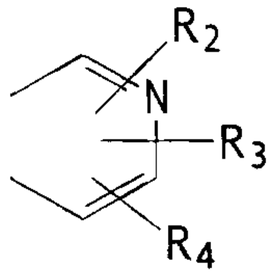
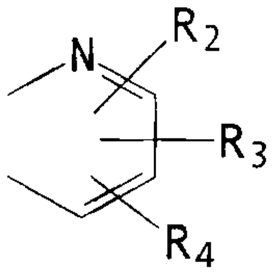
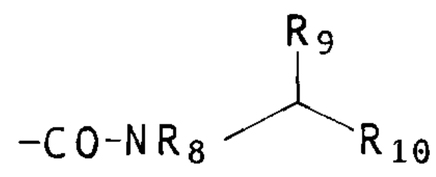

or


wherein R^2, R^3 and R^4, independently, represent a halogen atom or are as defined above for A;

L represents a radical selected from the group consisting of a hydrogen atom, a halogen atom, nitro, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, carboxyl, straight-chain-C_{1-6}-alkyl, branched-chain-C_{1-6}-alkyl, straight-chain-C_{1-6}-alkoxy, branched-chain-C_{1-6}-alkoxy, straight-chain-C_{1-6}-alkoxycarbonyl and branched-chain-C_{1-6}-alkoxycarbonyl; and

T represents a radical of the general formula:

$-CO_2R^5$, $-CO-NR^6SO_2R^7$ or 

wherein:

R^5 represents a radical selected from the group consisting of a hydrogen atom, phenyl, straight-chain-C_{1-8}-alkyl, branched-chain-C_{1-8}-alkyl and C_{3-7}-cycloalkyl,

R^6 and R^8, independently, represent a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl,

R^7 represents a radical selected from the group consisting of trifluoromethyl, phenyl, benzyl, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl, wherein the phenyl and benzyl radicals, independently, are optionally substituted by straight-chain-C_{1-6}-alkyl,

R^9 represents C_{6-10}-aryl, which is optionally substituted by up to 2 radicals selected from the group consisting of a halogen atom, hydroxyl, carboxyl, phenoxy, C_{3-6}-cycloalkoxy, straight-chain-C_{1-6}-alkyl, branched-chain-C_{1-6}-alkyl, straight-chain-C_{1-6}-alkoxy, branched-chain-C_{1-6}-alkoxy, straight-chain-C_{1-6}-alkoxycarbonyl and branched-chain-C_{1-6}-alkoxycarbonyl, and

R^{10} represents pyridyl or a radical of the general formula:

$$-CH_2-OR^{11},\ -CO_2R^{12} \text{ or } -CO-NR^{13}R^{14}$$

wherein:

R^{11} represents a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-8}-alkyl and branched-chain-C_{1-8}-alkyl,

R^{12} represents a radical selected from the group consisting of a hydrogen atom, phenyl, C_{3-6}-cycloalkyl, straight-chain-C_{1-8}-alkyl and branched-chain-C_{1-8}-alkyl, and

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R^{13} and R^{14}, independently, represent a radical selected from the group consisting of a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, straight-chain-C_{1-8}-alkyl and branched-chain-C_{1-8}-alkyl; or

T represents tetrazolyl, which is optionally substituted by a radical selected from the group consisting of triphenylmethyl, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl; and

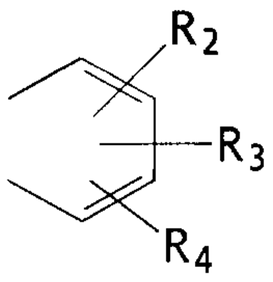
an isomeric form thereof, and a salt thereof.

2. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative of the general formula (I) according to claim 1, wherein:

A represents a radical selected from the group consisting of a hydrogen atom, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, straight-chain-C_{1-6}-alkyl, branched-chain-C_{1-6}-alkyl, straight-chain-C_{2-6}-alkenyl and branched-chain-C_{2-6}-alkenyl, wherein the phenyl radical is optionally substituted by a radical selected from the group consisting of a fluorine atom, a chlorine atom, a bromine atom, hydroxyl, trifluoromethyl, straight-chain-C_{1-4}-alkyl, branched-chain-C_{1-4}-alkyl, straight-chain-C_{1-4}-alkoxy and branched-chain-C_{1-4}-alkoxy;

E represents a nitrogen atom or a radical of the general formula $-CR^1$, wherein R^1 is as defined above for A;

B and D together form a radical of the general formula: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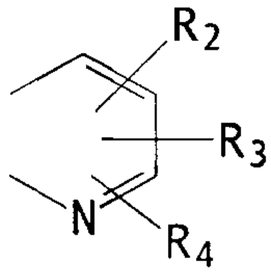
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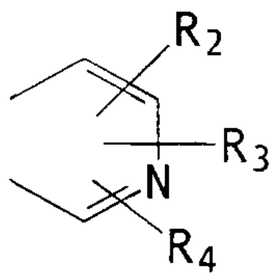
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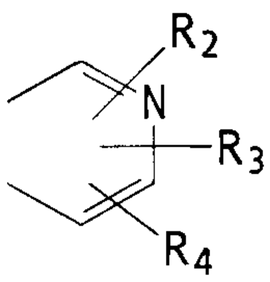
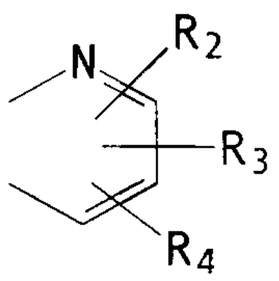
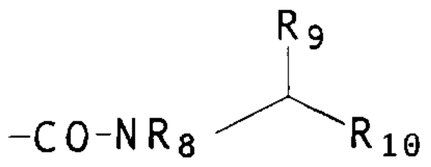

or


wherein R^2, R^3 and R^4, independently, represent fluorine, chlorine, bromine or A as defined above;

L represents a radical selected from the group consisting of a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, trifluoromethyl, carboxyl, straight-chain-C_{1-4}-alkyl, branched-chain-C_{1-4}-alkyl, straight-chain-C_{1-4}-alkoxy, branched-chain-C_{1-4}-alkoxy, straight-chain-C_{1-4}-alkoxycarbonyl and branched-chain-C_{1-4}-alkoxycarbonyl; and

T represents a radical of the general formula:

$-CO_2R^5$, $-CO-NR^6SO_2R^7$ or 

wherein:

R^5 represents a radical selected from the group consisting of a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl,

R^6 and R^8, independently, represent a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl,

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R^7 represents a radical selected from the group consisting of trifluoromethyl, phenyl, benzyl, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl, wherein the phenyl and benzyl radicals, independently, are optionally substituted by straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl,

R^9 represents phenyl, which is optionally substituted by a radical selected from the group consisting of a fluorine atom, a chlorine atom, a bromine atom, hydroxyl, carboxyl, phenoxy, straight-chain-C_{1-4}-alkyl, branched-chain-C_{1-4}-alkyl, straight-chain-C_{1-4}-alkoxy, branched-chain-C_{1-4}-alkoxy, straight-chain-C_{1-4}-alkoxycarbonyl and branched-chain-C_{1-4}-alkoxycarbonyl, and

R^{10} is as defined in claim 1, wherein:

R^{11} represents a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl,

R^{12} represents a radical selected from the group consisting of a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl,

R^{13} and R^{14}, independently, represent a radical selected from the group consisting of a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, straight-chain-C_{1-6}-alkyl and branched-chain-C_{1-6}-alkyl; or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl or methyl; and

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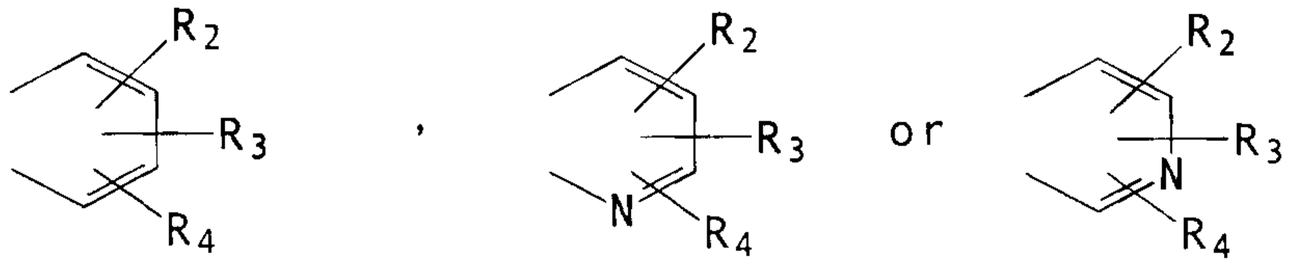
an isomeric form thereof, and a salt thereof.

3. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative of the general formula (I) according to claim 1, wherein:

A represents a radical selected from the group consisting of a hydrogen atom, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl;

E represents a nitrogen atom;

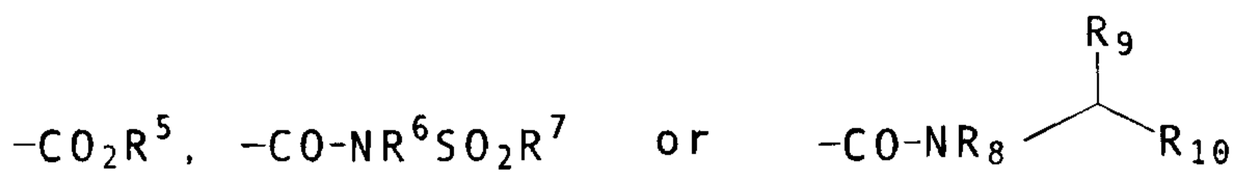
B and D together form a radical of the general formula:



wherein R^2, R^3 and R^4, independently, represent a fluorine atom, a chlorine atom, a bromine atom or A as defined above;

L represents a hydrogen atom, a fluorine atom, a chlorine atom, trifluoromethyl or methyl; and

T represents a radical of the general formula:



wherein:

R^5 represents a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl,

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R^6 and R^8, independently, represent a hydrogen atom or methyl,

R^7 represents trifluoromethyl, methyl, ethyl, benzyl, p-tolyl or phenyl,

R^9 represents phenyl, which is optionally substituted by a radical selected from the group consisting of a fluorine atom, a chlorine atom, a bromine atom, hydroxyl, carboxyl, phenoxy, straight-chain-C_{1-3}-alkyl, branched-chain-C_{1-3}-alkyl, straight-chain-C_{1-3}-alkoxy, branched-chain-C_{1-3}-alkoxy, straight-chain-C_{1-3}-alkoxycarbonyl and branched-chain-C_{1-3}-alkoxycarbonyl, and

R^{10} is as defined in claim 1, wherein:

R^{11} to R^{14}, independently, represent a radical selected from the group consisting of a hydrogen atom, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl; or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl or methyl; and

an isomeric form thereof, and a salt thereof.

4. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative of the general formula (I) according to claim 1

wherein:

A represents a radical selected from the group consisting of a hydrogen atom, cyclopropyl, phenyl, straight-chain-C_{1-4}-alkyl and branched-chain-C_{1-4}-alkyl;

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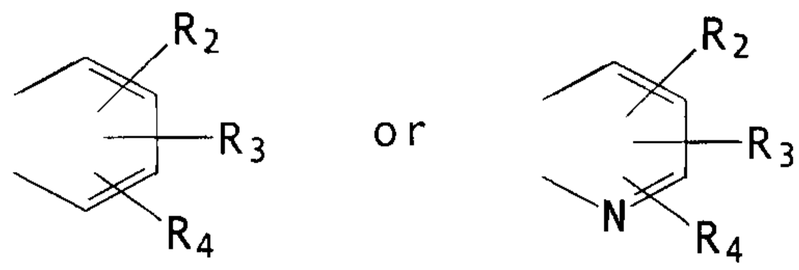
E represents a nitrogen atom;

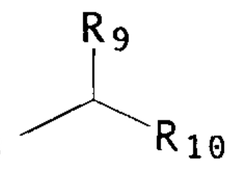
B and D together form a radical of the general formula:



wherein R^2, R^3 and R^4, independently, represent a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom or methyl;

L represents a hydrogen atom, a fluorine atom or a chlorine atom; and

T represents a radical of the general formula:

$-CO_2R^5$, $-CO-NR^6SO_2R^7$ or 

wherein:

R^5, R^6 and R^8 are as defined in claim 3,

R^7 represents trifluoromethyl, methyl or p-tolyl,

R^9 represents phenyl which is optionally substituted by a fluorine atom or a chlorine atom, and

R^{10} represents $-CH_2OH$, $-CONH_2$ or pyridyl; or

T represents tetrazolyl, which is optionally substituted by triphenylmethyl; and

an isomeric form thereof, and a salt thereof.

5. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative according to claim 1, wherein

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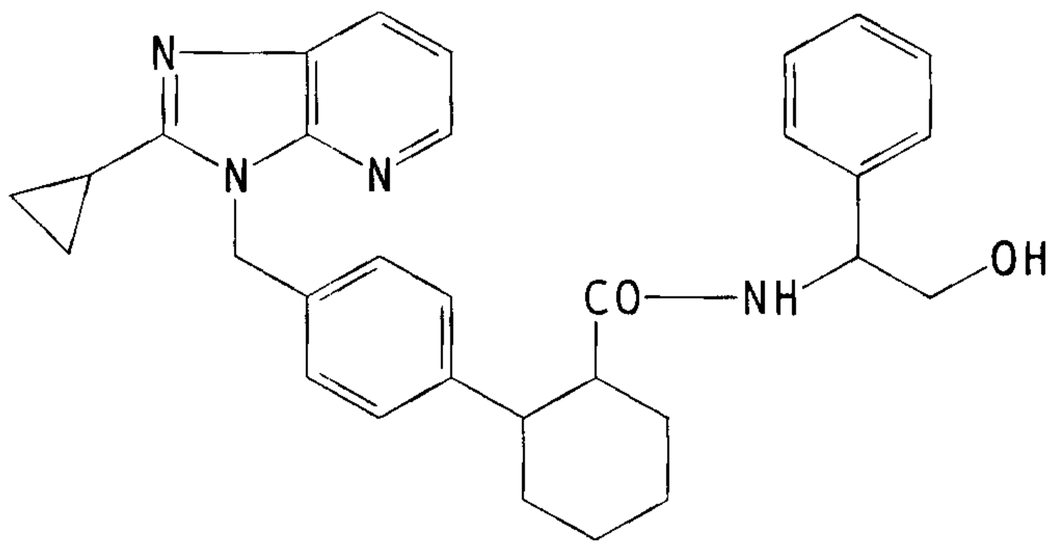
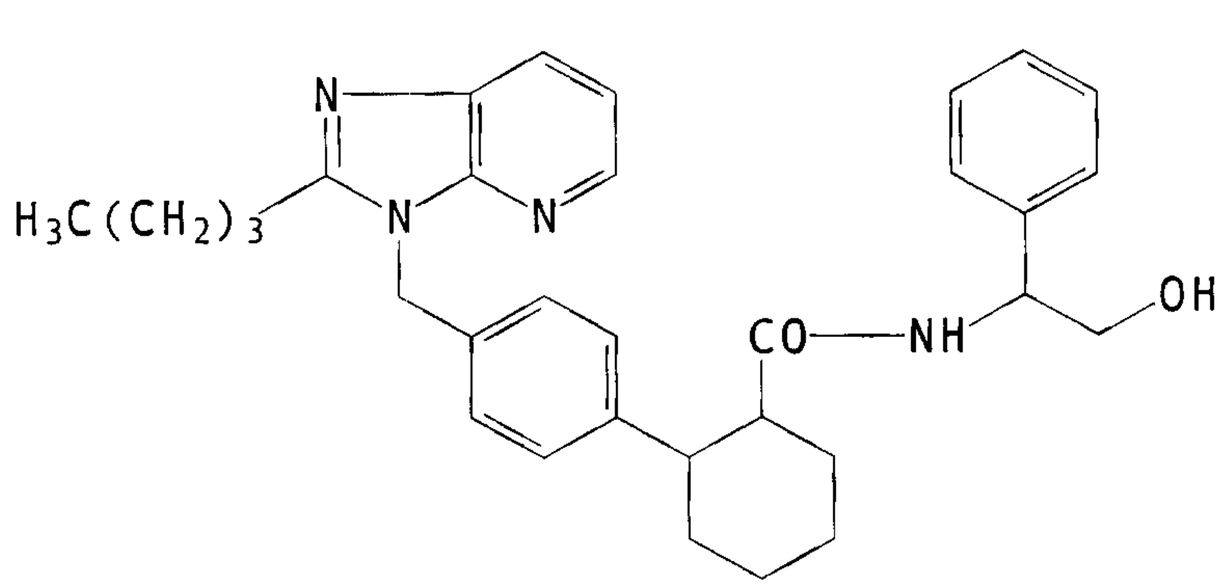
such compound is 2-{4-[(6-cyclopropyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-[(S)-phenylglycinol]-cyclohexane-1-carboxamide of the formula:



an isomer thereof, and a salt thereof.

6. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative according to claim 1, wherein such compound is 2-{4-[(6-butyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-[(S)-phenylglycinol]cyclohexane-1-carboxamide of the formula:



an isomer thereof, and a salt thereof.

7. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative according to claim 1, wherein such compound is 2-{4-[(6-phenyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-[(S)-phenylglycinol]cyclohexane-1-carboxamide of the formula:

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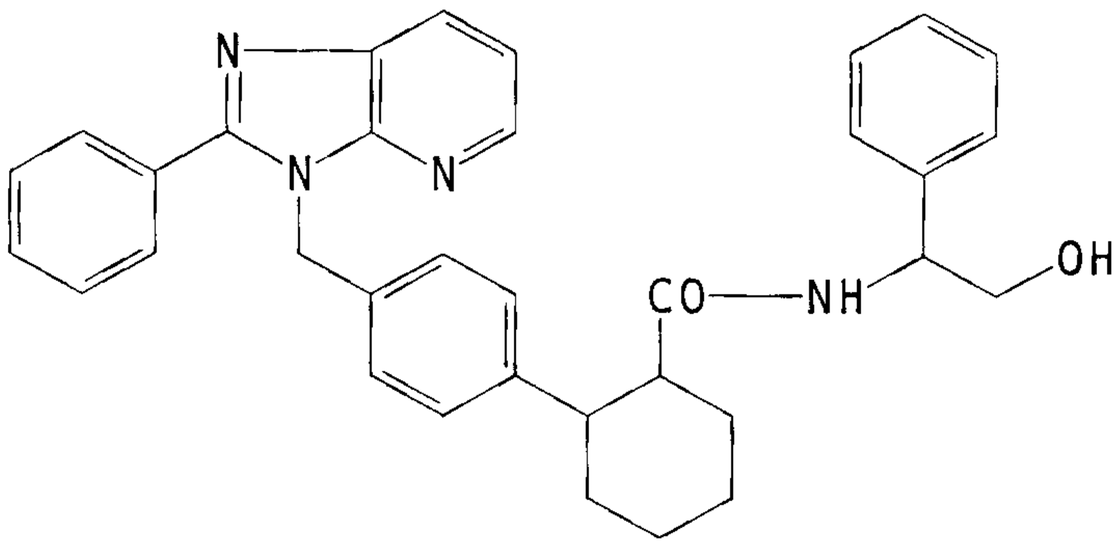
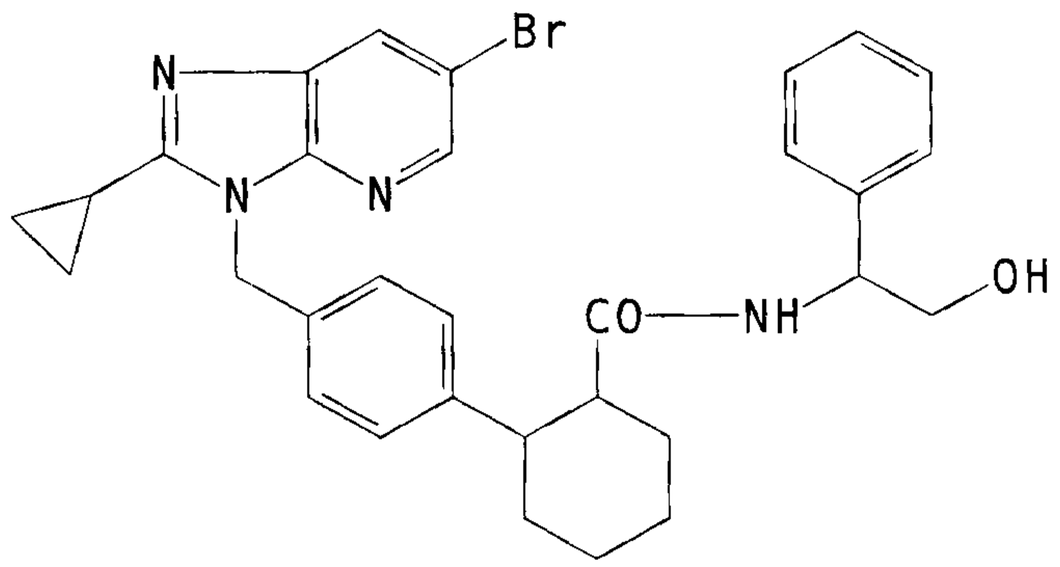


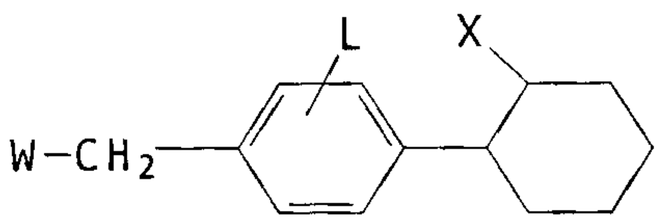
an isomer thereof, and a salt thereof.

8. A heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative according to claim 1, wherein such compound is 2-{4-[(3-bromo-6-cyclopropyl-imidazo[2,3-b]pyridin)-7-yl-methyl]phenyl}-N-[(S)-phenylglycinol]cyclohexane-1-carboxamide of the formula:



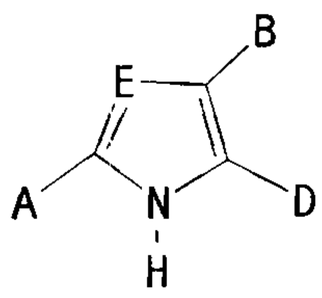
an isomer thereof, and a salt thereof.

9. A process for preparing a heterocyclically substituted phenyl-cyclohexane-carboxylic acid derivative of the general formula (I) as defined in any one of claims 1 to 4, or a salt thereof, which process comprises reacting a compound of the general formula (II):



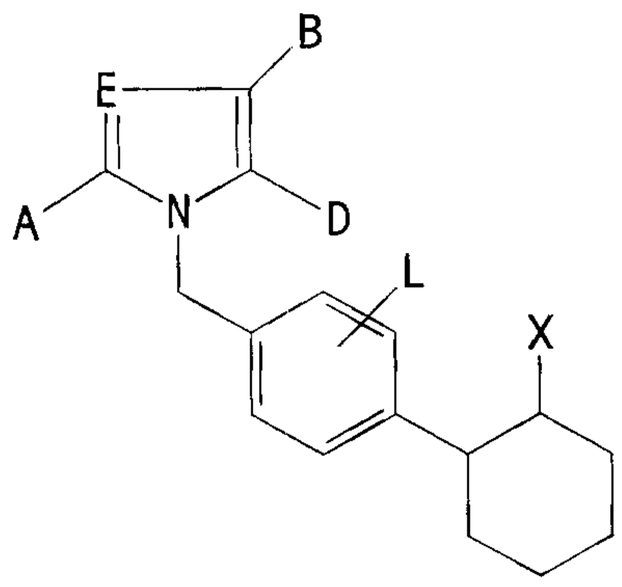
(II)

wherein L is as defined in any one of claims 1 to 4, W represents a leaving group and X represents a C_{1-6}-alkoxycarbonyl group or the triphenylmethyl-tetrazol-1-yl group, with a compound of the general formula (III):



(III)

wherein A, B, D and E are as defined in any one of claims 1 to 4, to obtain a compound of the general formula (IV):



(IV)

wherein A, B, D, E, L and X are as defined above, and

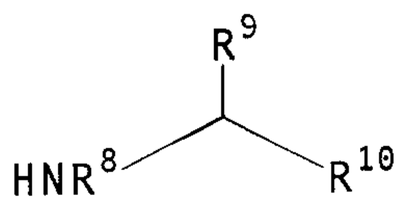
(i) if X is the triphenylmethyl-tetrazol-1-yl group and a compound of formula (I) is required in which T is a tetrazolyl group, removing the triphenylmethyl; or

(ii) if X is a C_{1-6}-alkoxycarbonyl group and a compound of formula (I) is required in which T is other than an alkoxycarbonyl group, hydrolysing the obtained compound of formula (IV) to convert the C_{1-6}-alkoxycarbonyl group to a carboxyl group, if necessary activating the carboxyl group and reacting the compound bearing the carboxyl group with an esterifying agent, to obtain a compound of the general formula (I) in which T represents a group of general formula $-CO_2R^5$, wherein R^5 is as defined in any one of claims 1 to

4, or reacting the compound bearing he carboxyl group with a sulphonamide of the general formula (V):

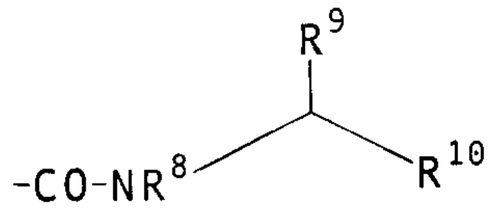
$$HNR^6\text{-}SO_2\text{-}R^7 \qquad (V)$$

wherein R^6 and R^7 are as defined in any one of claims 1 to 4, to obtain a compound of the general formula (I) in which T represents a group of the formula $-CO\text{-}NR^6SO_2R^7$, wherein R^6 and R^7 are as defined in any one of claims 1 to 4, or reacting the compound bearing the carboxyl group with an amine of the general formula (Va):



(Va)

wherein R^8, R^9 and R^{10} are as defined in any one of claims 1 to 4, to obtain a compound of the general formula (I) in which T represents a group of the formula



wherein R^8, R^9 and R^{10} are as defined in any one of claims 1 to 4, followed, if required, by converting an obtained compound of the general formula (I) into a salt thereof.

10. A process according to claim 9, wherein the reaction between the compound of the general formula (II) and the compound of the general formula (III) is carried out in an inert solvent, in the presence of a base and under a protective gas atmosphere.

11. A process according to claim 10, wherein reaction of the compound bearing the carboxyl group with a sulphonamide of the general formula (V) or with an amine of the general formula (Va) is carried out in the presence of a base and a dehydrating agent.

12. A pharmaceutical composition for the treatment of arterial hypertension or atherosclerosis, which composition comprises a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, together with a suitable diluent or carrier.

13. A process for preparing a pharmaceutical composition for the treatment of arterial hypertension or atherosclerosis, which process comprises admixing a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof with a suitable diluent or carrier.

14. Use of a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, or a composition according to claim 12 for the treatment of arterial hypertension or atherosclerosis.

15. Use of a compound according to any one of claim 1 to 8 or a pharmaceutically acceptable salt thereof, or a composition according to claim 12 for preparing a medicament for the treatment of arterial hypertension or a atherosclerosis.

16. A commercial package comprising, as active pharmaceutical ingredient, a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, or a composition according to claim 12, together

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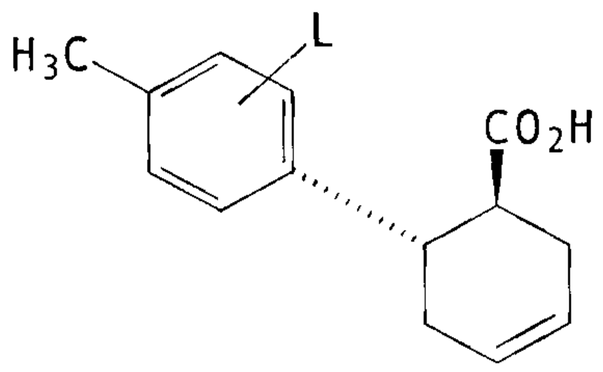
with instructions for the use thereof, for the treatment of arterial hypertension or atherosclerosis.

17. A compound of the general formula (IV) as defined in claim 9.

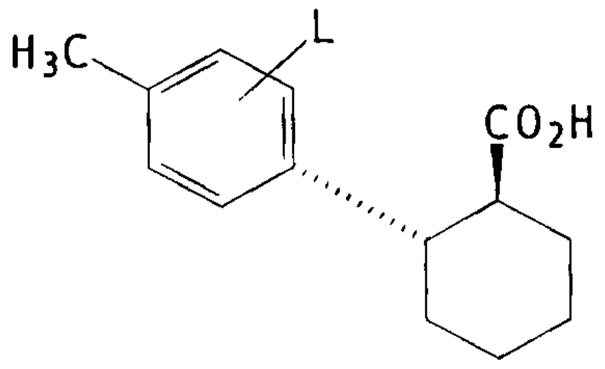
18. A compound of the general formula (VI):



(VI)

wherein L is as defined in any one of claims 1 to 4.

19. A compound of the general formula (VII):



(VII)

wherein L is as defined in any one of claims 1 to 4.

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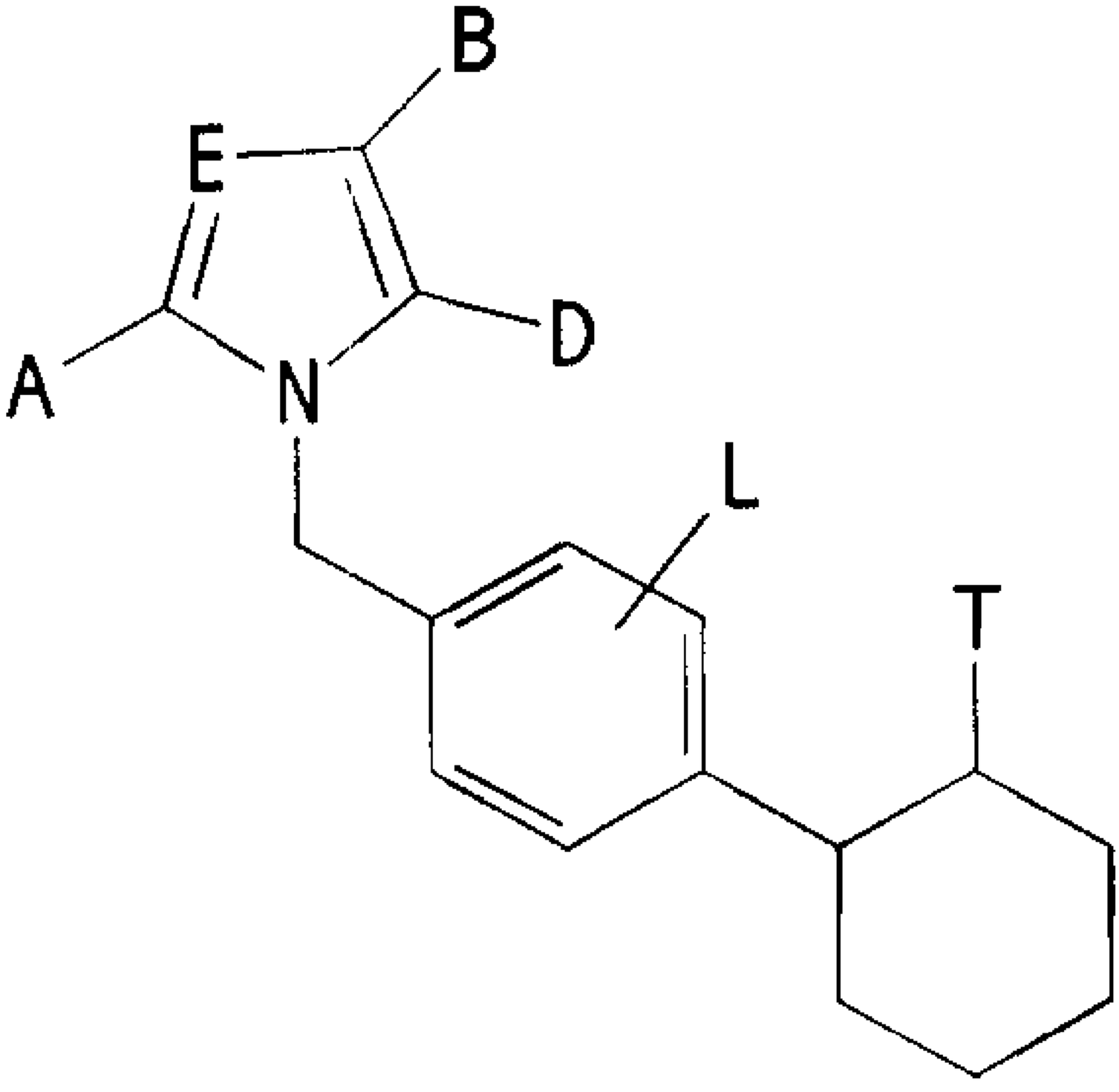

(I)