United States Patent [19]

Karjalainen et al.

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[45] **Date of Patent: * Oct. 1, 1985**

[54] **ANTIHYPERTENSIVE SUBSTITUTED IMIDAZOLE DERIVATIVES**

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[73] Assignee: **Farmos Group, Ltd.,** Turku, Finland

[*] Notice: The portion of the term of this patent subsequent to Jun. 8, 1999 has been disclaimed.

[21] Appl. No.: **396,000**

[22] Filed: **Jul. 7, 1982**

[30] **Foreign Application Priority Data**

Jul. 10, 1981 [GB] United Kingdom 8121333

[51] **Int. Cl.**[4] **A61K 31/415;** C07D 233/56; C07D 233/64

[52] **U.S. Cl.** **514/396;** 514/397; 514/400; 548/335; 548/336; 548/342

[58] **Field of Search** ..... 548/335, 336, 341, 342, 548/345; 542/458, 400, 468; 424/273 R; 514/397, 400, 396

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,946,804	7/1960	Zaugg et al.	548/342
4,333,947	6/1982	Karjalainen et al.	542/548
4,443,466	4/1984	Karjalainen et al.	424/274

FOREIGN PATENT DOCUMENTS

0024829	3/1981	European Pat. Off.	548/335
0034474	8/1981	European Pat. Off.	548/335
0034473	8/1981	European Pat. Off.	548/335

OTHER PUBLICATIONS

Kelley, J., et al., *J. Pharm. Sci.*, 70(3), 341–343, (1981).

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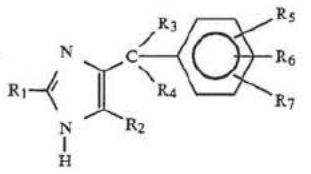
Attorney, Agent, or Firm—Armstrong, Nikaido, Marmelstein & Kubovcik

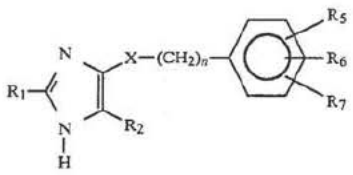
[57] **ABSTRACT**

The invention provides novel compounds of the formula:



(I)

or



(II)

wherein the various substituents are defined herein below. Processes for the preparation of these compounds are described, as are novel pharmaceutical compositions comprising at least one of the compounds of their salts. The compounds and their non-toxic salts exhibit valuable pharmacological activity and are useful in the treatment of mammals, especially as antihypertensive agents. Furthermore, some of the compounds have proved to possess antithrombotic and diuretic activity. Antimycotic and antifungal properties have also been found.

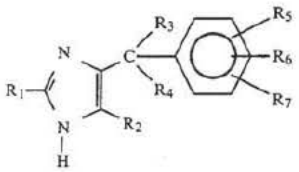
12 Claims, No Drawings

ANTIHYPERTENSIVE SUBSTITUTED IMIDAZOLE DERIVATIVES

DESCRIPTION

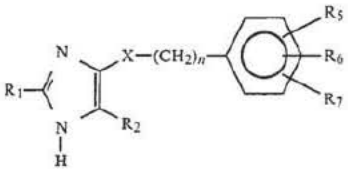
The present invention relates to substituted imidazole derivatives and their non-toxic, pharmaceutically acceptable acid addition salts, and their preparation, to pharmaceutical compositions containing the same, and to their use.

The imidazole derivatives of the present invention have the general formula:



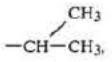
(I)

or

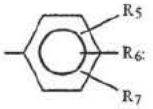


(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms, e.g. methyl or $-CH_2OH$; R_2 is H or CH_3; R_3 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

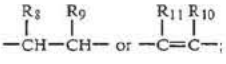


$-CH_2CH_2CH_2CH_3$, $-CH_2CH{=}CH_2$, or

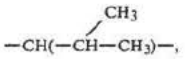


and R_4 is H or OH; or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$,

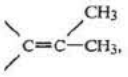
or $=CH-CH_2CH_2CH_3$; X is



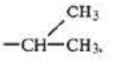
R_5, R_6, and R_7, which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$bridge between two adjacent carbon atoms in the phenyl group; $-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$,



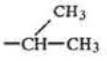
$-CH(-CH_2CH_2CH_2CH_3)-$ or $>C{=}CH_2$, $>C{=}CH-CH_3$, $>C{=}CH-CH_2CH_3$,



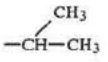
$>C{=}CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,



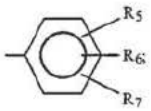
$-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,



or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

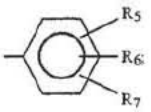


or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; provided that when R_4 is OH, R_1 is H or CH_3 and R_3 is



then R_5, R_6 and R_7 are not all simultaneously hydrogen;

when R_1, R_2 and R_4 all are hydrogen and R_3 is



then R_5, R_6, R_7 are not all simultaneously hydrogen; R_8 and R_9 are not simultaneously hydrogen; and R_{11} and R_{10} are not simultaneously hydrogen.

Because of the tautomerism in the imidazole ring the compounds of the general formula I and II are 4(5)-substituted imidazole derivatives.

The non-toxic pharmaceutically acceptable acid addition salts of these compounds are also within the scope of the invention.

The compounds of the formula (I) and (II) form acid addition salts with both organic and inorganic acids. They can thus form many pharmaceutically usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The invention includes within its scope pharmaceutical compositions comprising at least some of the compounds of formula (I) or (II) or a non-toxic, pharmaceutically acceptable salt thereof, and a compatible pharmaceutically acceptable carrier therefor.

The invention provides, for example, the following specific compounds of formula (I):

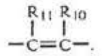
4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole
4-[[α-(2-methylphenyl)]-2-methylbenzyl]imidazole
4-(α-phenylbenzyl)-5-methylimidazole
4-[[α-(2,6-dimethylphenyl)]-α-methyl]hydroxymethyl-]imidazole
4-[[α-(2,3-dimethylphenyl)]-α-methyl]hydroxymethyl-]imidazole
4-[α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole
4-[[α-(2-methylphenyl)]-2-methylbenzyl]-5-methylimidazole
4-[(α-methyl)-2,6-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]imidazole
4-[(α-ethyl)-3-methylbenzyl]imidazole
4-[(α-butyl)-2,3-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]-2-methylimidazole
4-[(α-propyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2,5-dimethylbenzyl]imidazole
4-[α-ethyl-α-(3-methylphenyl)-hydroxymethyl-]imidazole
4-[α-butyl-α-(2,3-dimethylphenyl)-hydroxymethyl-]imidazole
4-[α-methyl-α-(2,3-dimethylphenyl)-hydroxymethyl]-2-methylimidazole
4-[α-propyl-α-(2-methylphenyl)-hydroxymethyl-]imidazole
4-(α-methyl-2-chlorobenzyl)imidazole
4-[α-methyl-α-(2-methylphenyl)-hydroxymethyl-]imidazole
4-[α-methyl-α-(2,5-dimethylphenyl)-hydroxymethyl-]imidazole
4-[α,α-bis-(2,3-dimethylphenyl)hydroxymethyl-]imidazole
4-[α-(2,3-dimethylphenyl)-2,3-dimethylbenzyl-]imidazole
4-[(α-ethyl)-2,6-dimethylbenzyl]imidazole
4-[(α-ethyl)-2,3-dimethylbenzyl]imidazole
1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene
1-(4-imidazolyl)-1-(2,6-dimethylphenyl)ethylene
1-(4-imidazolyl)-1-(2,3-dimethylphenyl)propene
1-(4-imidazolyl)-1-(2,3-dimethylphenyl)pentene

The following specific compounds of formula (II):

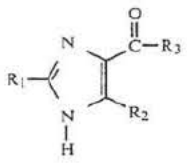
4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole
4-[2-(2,6-dimethylphenyl)propyl]imidazole
4-[2-(2,3-dimethylphenyl)propyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-methylpropyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-hydroxyethyl]imidazole
4-(2-phenylpropyl)imidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-propenyl]imidazole
4-(2-methyl-4-phenyl-1-butenyl)imidazole
4-[2-(4-chlorophenyl)-1-methylpropyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl-]imidazole
4-[3-(2,6-dimethylphenyl)-2-methyl-1-propenyl-]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole
4-[2-(2,3-dimethylphenyl)-1-methylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-isopropylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-2-methylimidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole
4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl-]imidazole
4-[3-(2,6-dimethylphenyl)-1-ethyl-1-propenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]-5-methylimidazole
4-[5-(2,6-dimethylphenyl)-1-methylpentyl]imidazole
4-[4-(2,6-dichlorophenyl)-1-methyl-1-butenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-ethylethyl]imidazole
4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole
4-[2-(2-bromo-4,5-methylenedioxyphenyl)propyl-]imidazole

The compounds of the present invention have been found to possess excellent antihypertensive activity. Preliminary tests have shown that they also possess other valuable pharmacological properties, for example, antithrombotic and diuretic effect. Antimycotic and antifungal properties have also been found.

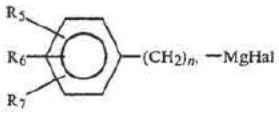
While all of the compounds of formula (I) and (II) essentially satisfy the objectives of the present invention, certain groups of compounds remain preferred. One such preferred group is represented by formula (I) wherein R_4 is hydrogen, R_3 is alkyl and R_5, R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Another preferred group of compounds is represented by formula (II), wherein R_5, R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. In such compounds, those in which R_1 is hydrogen or methyl, R_2 is hydrogen or methyl, R_8 or R_{11} is methyl, ethyl or isopropyl, R_9 and R_{10} are hydrogen and n is 0 may be mentioned. Especially the compounds wherein n is greater than 0 possess valuable antimycotic properties. Especially good antihypertensive properties have been found in compounds of formula (II) wherein n is 0 and X is



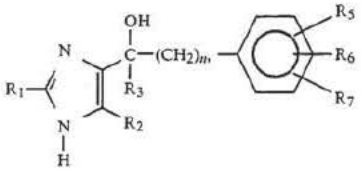
According to the feature of the invention, the compounds of formula (I) wherein R_4 is OH and the compounds of formula (II) are made by a Grignard reaction, in which an imidazolylketone of the formula



wherein R_1, R_2 and R_3 are as defined before, is reacted with an arylalkyl magnesium halide derivative or aryl magnesium halide derivative of the formula:



wherein R_5, R_6 and R_7 are as defined before, n' is 0 to 5 and Hal is a halogen atom to give compounds of the formula (III)

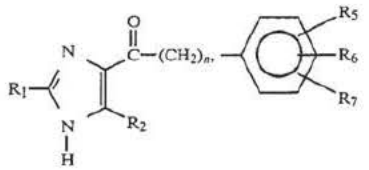


(III)

wherein R_1, R_2, R_3, R_5, R_6, R_7 and n' are as before.

The arylalkylmagnesium halide derivative can be, for example, an arylalkylmagnesiumbromide derivative, which is prepared by reacting the corresponding arylalkylbromide derivative with magnesium. Suitable solvents for the reaction include a variety of ethers, preferably tetrahydrofuran. The arylalkylmagnesiumhalide derivative is prepared in the usual way by adding the arylalkylmagnesiumhalide derivative in a suitable solvent, e.g. tetrahydrofuran, dropwise onto magnesium turnings covered by tetrahydrofuran, at the boiling point of the reaction mixture. When the magnesium turnings have reacted, the mixture is cooled slightly and the 4-imidazole derivative is added in solid form in small portions or in tetrahydrofurane solution. After the addition, the reaction mixture is refluxed until all of the 4-imidazole derivative has reacted. The reaction time varies between one and five hours.

Another process for the preparation of compounds of formula (III) is a Grignard reaction in which a compound of the formula (IV)

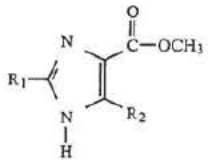


(IV)

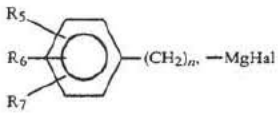
wherein R_1–R_7 and n' are as before, is reacted with a compound of the formula

R_3MgHal

wherein R_3 is an alkyl or aryl as defined before and Hal is halogen. Yet another process for the preparation of compounds of formula (III) is a Grignard reaction in which an imidazole carboxylic acid alkyl ester, preferably the methyl ester of the formula



wherein R_1 and R_2 are as before, is reacted in a first step/with a Grignard reagent of the formula



wherein R_5, R_6, R_7 and n' are as before, to give a compound of formula (IV), which in a second step without isolation is reacted with a Grignard reagent of the formula

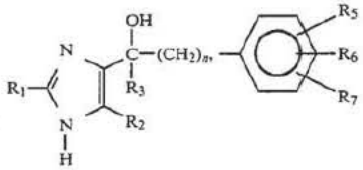
R_3MgHal

wherein R_3 is as defined before.

Compounds of formula (I) wherein R_4 is H can be prepared by reduction of compounds of formula (III) wherein n' is 0 with hydrogen. A suitable catalyst is e.g. palladium-on-carbon.

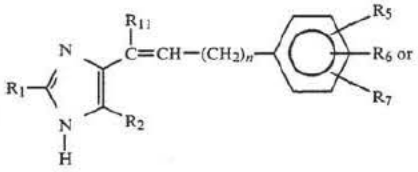
Unsaturated compounds of formula (I) wherein R_3 and R_4 are $=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$,

or $=CH-CH_2CH_2CH_3$ or formula (II) wherein R_{10} is hydrogen are prepared by dehydrating compounds of formula (III):



(III)

wherein R_1, R_2, R_5, R_6, R_7 are as defined before, R_3 is an alkyl or aryl as defined before and n' is 0 to 5, to give a compound of the formula (V)



(V)

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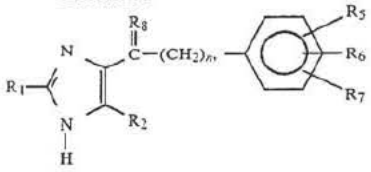
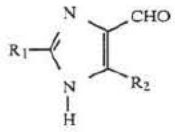


wherein R_1, R_2, R_5, R_6, R_7, and n and n' are as defined before; R_{11} is an alkyl as defined before and R_8 is an alkenyl as defined before.

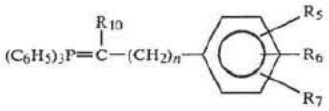
The dehydration is preferably performed by refluxing in an appropriate acidic solution, e.g. concentrated hydrochloric acid or heating for example with potassium-hydrogen sulfate.

The compounds of formula (V) can further be reduced with hydrogen in the presence of a palladium-on-carbon catalyst to the corresponding saturated compounds of formulae (I) and (II).

Compounds of formula (II) wherein R_{11} is hydrogen are prepared by a Wittig reaction which comprises reacting an imidazole aldehyde of the formula

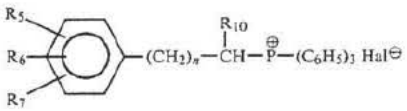


wherein R_1 and R_2 are as before, with an aralkylidene-triphenylphosphorane of the formula:



wherein R_5, R_6, R_7, R_{10} and n are as defined before, to give the unsaturated compounds of formula (II), which in a further step can be reduced to the corresponding saturated compounds of formula (II) as described above.

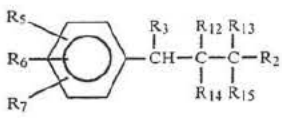
The aralkylidenetriphenylphosphoranes are preferably prepared by reacting the corresponding aralkyltriphenylphosphonium halide of the formula:



wherein R_5, R_6, R_7, R_{10} and n are as before and Hal is halogen, with a basic reagent, preferably butyllithium.

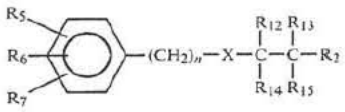
In the Grignard- and Wittig-syntheses described above, the free nitrogen atom in the imidazole starting material can be protected by different methods. Suitable protecting groups are for example benzyl, triphenylsilyl or dialkoxymethane. The removal of the protecting group can be performed in different ways, and depends on the kind of protecting group used. For example, a dialkoxymethane group is removed by acidic hydrolysis and a benzyl group by sodium in liquid ammonia.

The present invention further provides yet another method for preparing compounds of the invention. Thus, according to this embodiment of the invention, a starting material of the formula (VI) or (VII)



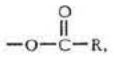
(VI)

or

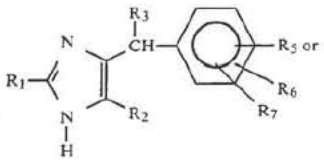


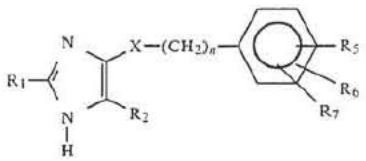
(VII)

wherein R_2, R_3, R_5, R_6, R_7 and n are as hereinbefore defined; wherein R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, —O— alkyl of 1 to 7 carbon atoms or

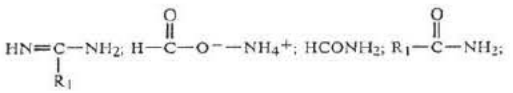


wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups; is reacted with a reagent capable of converting said starting material to the corresponding imidazole of the formula:





wherein R_1, R_2, R_3, R_5, R_6, R_7, X and n are defined as before. Reagents capable of converting the depicted starting material to the corresponding imdidazole include $NH_3 + CH_2O$ (or a source of ammonia and formaldehyde);



or R_1CHO and NH_3. Choice of an appropriate reagent varies with the particular starting material employed.

When R_1 is hydrogen it is preferable to employ formamide as the reagent in cases where, in place of the bromine atom in the aforementioned starting materials, there is instead a hydroxyl, amino or acetyl group. In

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