

United States Patent [19]

Karjalainen et al.

[11] Patent Number: **4,544,664**

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

[54] **ANTIHYPERTENSIVE SUBSTITUTED
IMIDAZOLE DERIVATIVES**

[75] Inventors: **Arto J. Karjalainen; Kauko O. A. Kurkela**, both of Oulu, Finland

[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

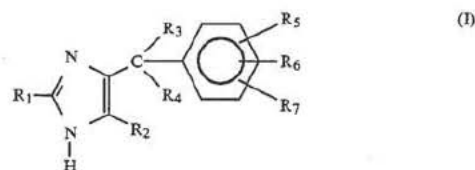
Kelley, J., et al., *J. Pharm. Sci.*, 70(3), 341-343, (1981).

Primary Examiner—Richard A. Schwartz

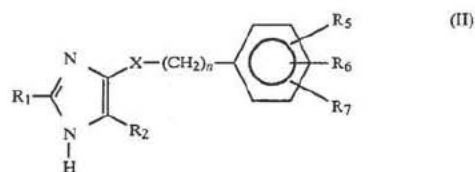
Attorney, Agent, or Firm—Armstrong, Nikaido, Marmelstein & Kubovcik

[57] **ABSTRACT**

The invention provides novel compounds of the formula:



or



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 or 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.

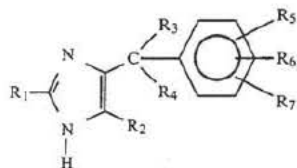
12 Claims, No Drawings

ANTIHYPERTENSIVE SUBSTITUTED IMIDAZOLE DERIVATIVES

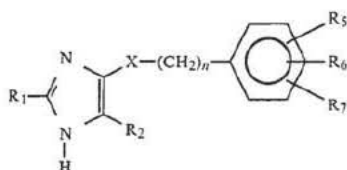
DESCRIPTION

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.

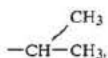
The imidazole derivatives of the present invention have the general formula:



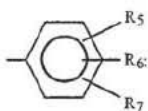
or



wherein R₁ is H, an alkyl of 1 to 4 carbon atoms, e.g. methyl or —CH₂OH; R₂ is H or CH₃; R₃ is —CH₃, —CH₂CH₃, —CH₂CH₂CH₃,



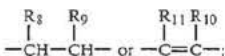
—CH₂CH₂CH₂CH₃, —CH₂CH=CH₂, or



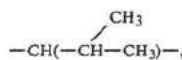
and R₄ is H or OH; or R₃ and R₄ together represent



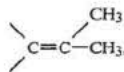
or =CH—CH₂CH₂CH₃; X is



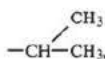
R₅, R₆, and R₇, which can be the same or different are H, —CH₃, —CH₂CH₃, halogen, OH or —OCH₃ or R₅ is hydrogen and R₆ and R₇ together form an —O—CH₂—O—bridge between two adjacent carbon atoms in the phenyl group; —CHR₈— is —CH₂—, —CH(CH₃)—, —CH(—CH₂CH₃)—, —CH(—CH₂CH₂CH₃)—,



5 —CH(—CH₂CH₂CH₂CH₃)— or >C=CH₂,
>C=CH—CH₃, >C=CH—CH₂CH₃,



15 >C=CH—CH₂CH₂CH₂CH₃; R₉ is H, —CH₃, —CH₂CH₃,
(I) —CH₂CH₂CH₃,



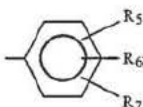
20 —CH₂CH₂CH₂CH₃ or OH; R₁₀ is H, —CH₃,
—CH₂CH₃, —CH₂CH₂CH₃,

(II) 25 —CH(—CH₂CH₂CH₂CH₃)—

or —CH₂CH₂CH₂CH₃; R₁₁ is H, —CH₃, —CH₂CH₃,
—CH₂CH₂CH₃,

30 —CH(—CH₂CH₂CH₂CH₃)—

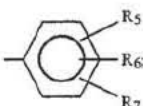
or —CH₂CH₂CH₂CH₃; n is 0 to 4; provided that
when R₄ is OH, R₁ is H or CH₃ and R₃ is



40

then R₅, R₆ and R₇ are not all simultaneously hydro-

45 gen; when R₁, R₂ and R₄ all are hydrogen and R₃ is



55

then R₅, R₆, R₇ are not all simultaneously hydrogen;
R₈ and R₉ are not simultaneously hydrogen; and
R₁₁ and R₁₀ are not simultaneously hydrogen.

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

60 stituted imidazole derivatives.
The non-toxic pharmaceutically acceptable acid addi-

65 tion 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, sul-

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]hydroxymethylimidazole
 4-[[α -(2,3-dimethylphenyl)]- α -methyl]hydroxymethylimidazole
 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

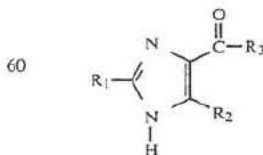
- 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-2-methylimidazole
 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole
 4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole
 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole
 4-[3-(2,6-dimethylphenyl)-1-ethyl-1-propenyl]imidazole
 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]-5-methylimidazole
 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.

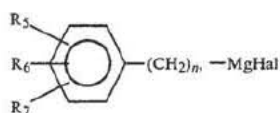
While all of the compounds of formula (I) and (II) essentially satisfy the objectives of the present invention, certain groups of compounds remain preferred. One such preferred group is represented by formula (I) wherein R_4 is hydrogen, R_3 is alkyl and R_5 , R_6 and R_7 , which can be the same or different, 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



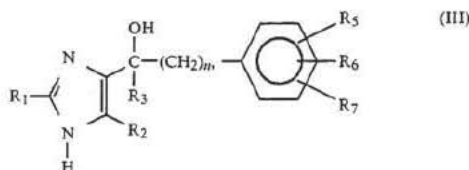
According to the feature of the invention, the compounds of formula (I) wherein R_4 is OH and the compounds of formula (II) are made by a Grignard reaction, in which an imidazolylketone of the formula



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:



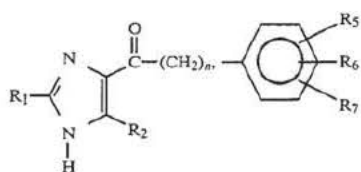
wherein R_5 , R_6 and R_7 are as defined before, n' is 0 to 5 and Hal is a halogen atom to give compounds of the formula (III)



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.

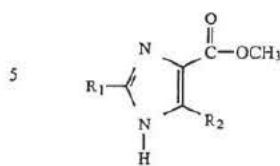
Another process for the preparation of compounds of formula (III) is a Grignard reaction in which a compound of the formula (IV)



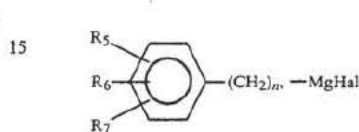
wherein R_1 - R_7 and n' are as before, is reacted with a compound of the formula



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



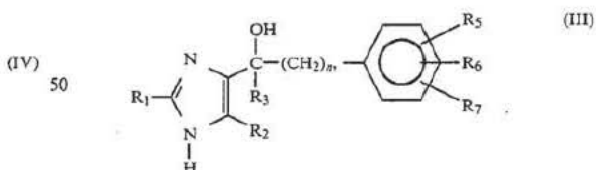
wherein R_3 is as defined before.

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.

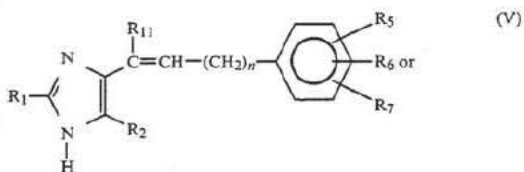
Unsaturated compounds of formula (I) wherein R_3 and R_4 are $=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$,



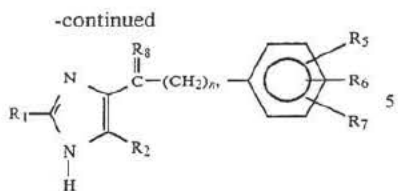
or $=CH-CH_2CH_2CH_3$ or formula (II) wherein R_{10} is hydrogen are prepared by dehydrating compounds of formula (III):



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)



7

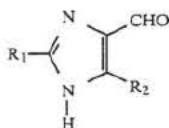


wherein R_1 , R_2 , R_5 , R_6 , R_7 , and n and n' are as defined before; R_{11} is an alkyl as defined before and R_8 is an alkenyl as defined before.

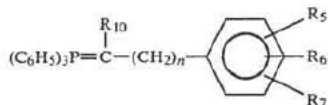
The dehydration is preferably performed by refluxing in an appropriate acidic solution, e.g. concentrated hydrochloric acid or heating for example with potassium-hydrogen sulfate.

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

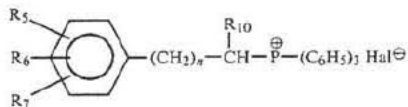


wherein R_1 and R_2 are as before, with an aralkylidene-triphenylphosphorane of the formula:



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 aralkylidene-triphenylphosphoranes are preferably prepared by reacting the corresponding aralkyl-triphenylphosphonium halide of the formula:



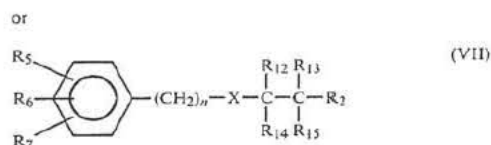
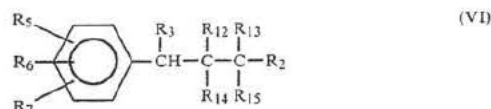
wherein R_5 , R_6 , R_7 , R_{10} and n are as before and Hal is halogen, with a basic reagent, preferably butyllithium.

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.

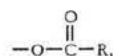
The present invention further provides yet another method for preparing compounds of the invention.

8

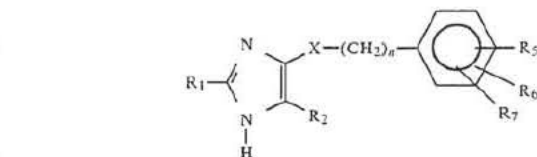
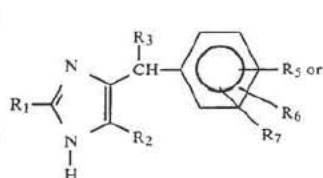
Thus, according to this embodiment of the invention, a starting material of the formula (VI) or (VII)



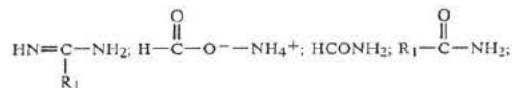
wherein R_2 , R_3 , R_5 , R_6 , R_7 and n are as hereinbefore defined; wherein R_{12} , R_{13} , R_{14} and R_{15} , which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, -O- alkyl of 1 to 7 carbon atoms or



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 imidazole include $\text{NH}_3 + \text{CH}_2\text{O}$ (or a source of ammonia and formaldehyde);



or $R_1\text{CHO}$ 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.