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Sher

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[45] Date of Patent: Jun. 14, 1994

[54] **THIAZOLE AND OXAZOLE-BASED β3 ADRENERGIC RECEPTOR AGONISTS**

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[73] Assignee: **Bristol-Myers Squibb Company**, Princeton, N.J.

[21] Appl. No.: **15,940**

[22] Filed: **Feb. 10, 1993**

[51] **Int. Cl.**[5] **A61K 31/42**; C07D 261/08

[52] **U.S. Cl.** **514/365**; 514/378; 548/201; 548/204; 548/236

[58] **Field of Search** 514/365, 378; 548/201, 548/204, 236

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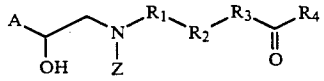
Primary Examiner—Mary C. Lee
Assistant Examiner—Jacqueline Haley
Attorney, Agent, or Firm—Ellen K. Park

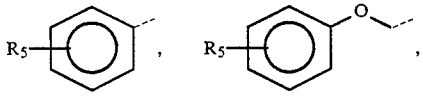
[57] **ABSTRACT**

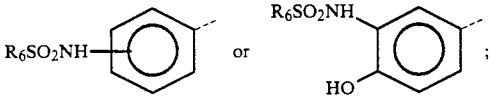
Compounds having the formula

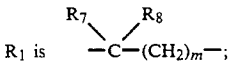


I

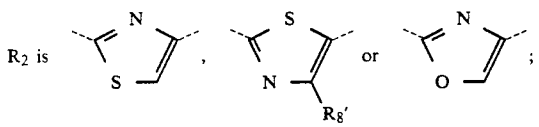
and pharmaceutically acceptable salts thereof where A is







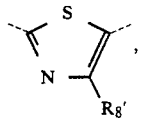
R_1 is



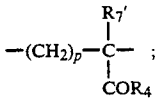
R_2 is

(Abstract continued on next page.)

R_3 is $-(CH_2)_n-$ or in the case where R_2 is



R_3 in addition to the above may be



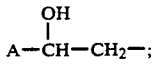
R_4 is hydroxy, alkoxy, amino, alkylamino or dialkylamino;

R_5 is hydrogen, fluorine, chlorine, bromine, iodine, —CN, CF_3, lower alkyl, lower alkoxy, cycloalkyl or aryl;

R_6 is lower alkyl, cycloalkyl or aryl;

R_7, R_7', R_8 and R_8' are independently hydrogen or a lower alkyl or R_7 and R_8 may together be CH_2CH_2;

Z is hydrogen or



m is an integer of 1 or 2;

n is zero or an integer of 1 to 6; and

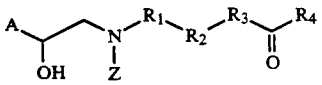
p is an integer of 1 to 5. These compounds are beta 3 adrenergic receptor agonists and are useful, therefore for example, in the treatment of diabetes, obesity and gastrointestinal diseases.

31 Claims, No Drawings

THIAZOLE AND OXAZOLE-BASED β3 ADRENERGIC RECEPTOR AGONISTS

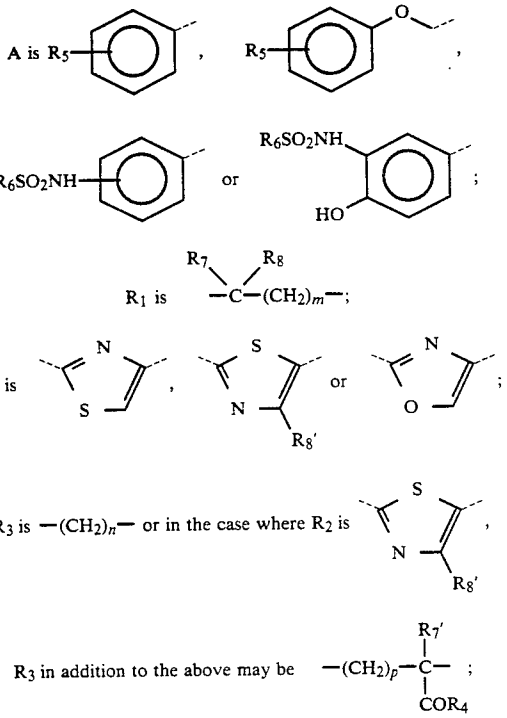
BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula



I

and pharmaceutically acceptable salts thereof. As used in formula I, and throughout the specification, the symbols have the following meanings:



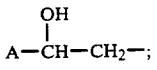
R_4 is hydroxy, alkoxy, amino, alkylamino or dialkylamino;

R_5 is hydrogen, fluorine, chlorine, bromine, iodine, —CN, —CF_3, lower alkyl, lower alkoxy, cycloalkyl or aryl;

R_6 is lower alkyl, cycloalkyl or aryl;

R_7, R_7', R_8 and R_8', are independently hydrogen or lower alkyl or R_7 and R_8 may together be CH_2CH_2;

Z is hydrogen or



m is an integer of 1 or 2;

n is zero or an integer of 1 to 6; and

p is an integer of 1 to 5.

These compounds possess activity at the beta 3 adrenergic receptor. The compounds are useful in the treatment of diabetes, obesity, and intestinal hypermotility disorders. The invention also provides processes for their preparation.

DESCRIPTION OF THE INVENTION

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances either individually or as part of a larger group.

The term "alkyl" refers to both straight and branched chain groups having 1 to 12 carbon atoms in the normal chain, preferably 1 to 7 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like.

The term "lower alkyl" as employed herein includes such alkyl groups as described above containing 1 to 6 carbon atoms in the normal chain.

The term "alkoxy" refers to any of the above alkyl groups linked to an oxygen atom.

The term "lower alkoxy" refers to any of the above lower alkyl groups linked to an oxygen atom.

The term "aryl" refers to monocyclic or bicyclic aromatic groups containing from 6 to 10 carbons in the ring portion, such as phenyl, naphthyl, substituted phenyl or substituted naphthyl wherein the substituent on either the phenyl or naphthyl may be 1, 2 or 3 lower alkyl groups, halogens (e.g., chlorine, bromine or fluorine), or 1, 2 or 3 lower alkoxy groups.

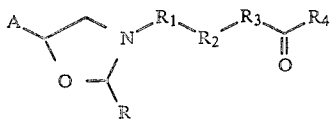
The term "cycloalkyl" refers to saturated cyclic hydrocarbon groups containing one or more rings of 3 to 12 ring carbons, preferably 3 to 8 ring carbons, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, and adamantyl.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as alkane- (of 1 to 4 carbon atoms) or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopro-

pyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form.

It should be understood that the present invention includes prodrug forms of the compounds of formula I such as aldehyde addition products of formula

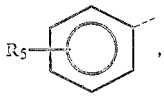


Ia

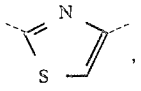
where R is alkyl or aryl such that RCHO is a suitable, for example, non-toxic aldehyde.

The compounds of the instant invention may, for example, be in the free or hydrate form, and may be obtained by methods exemplified by the following descriptions.

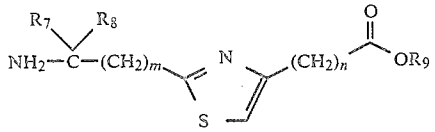
Compounds of formula I where A is



R_2 is

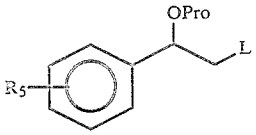


and R_3 is $-(CH_2)_n-$ may be prepared by coupling a compound of formula



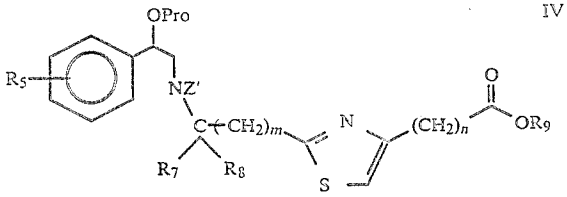
II

where R_9 is a lower alkyl, with a compound of the formula



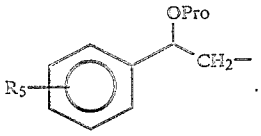
III

where Pro is a suitable oxygen protecting group such as t-butyldimethylsilyl and L is a leaving group such as triflate, mesylate, tosylate, nosylate, bromide or iodide, optionally in the presence of an acid scavenger such as diisopropylethylamine to form a compound of formula

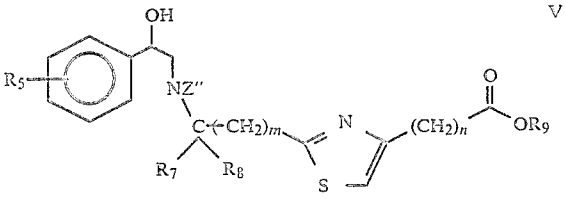


IV

where Z' is hydrogen or

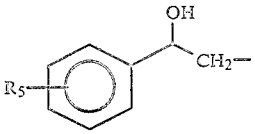


Compounds of formula IV are then deprotected with, for example, fluoride to form compounds of the formula



V

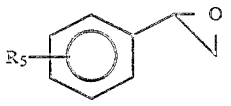
where Z'' is hydrogen or



which are themselves compounds of formula I where R_4 is alkoxy. Compounds of formula V may be deesterified such as by saponification to form the compounds of formula I where R_4 is hydroxy.

Alternatively, compounds of formula V may be amidated, for example with ammonia or a mono or dialkylamine, to form compounds of formula I where R_4 is amino, alkylamino or dialkylamino.

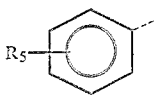
Compounds of formula II may also be coupled with an epoxide of formula



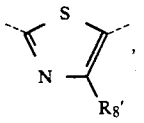
IIIa

to form compounds of formula V. Use of epoxide IIIa would obviate the need for the deprotection step as is necessary after coupling compounds of formula II with compounds of formula III.

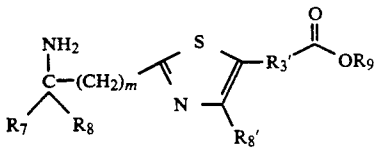
To prepare compounds of formula I where A is



and R_2 is

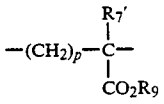


a compound of formula

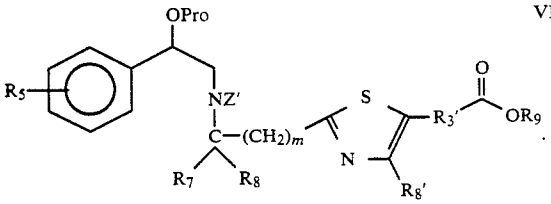


VI

where R_3' is $-(CH_2)_n-$ or

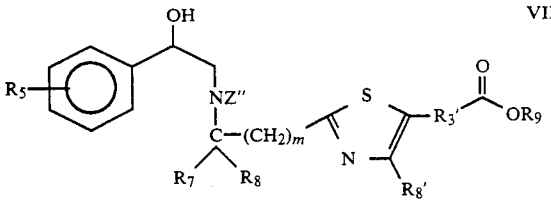


is coupled with a compound of formula III optionally in the presence of an acid scavenger such as diisopropylethylamine to form a compound of formula



VII

Compounds of formula VII are then deprotected, for example, with fluoride to form compounds of the formula



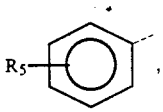
VIII

which are themselves compounds of formula I where R_4 is alkoxy. Compounds of formula VIII may be deesterified such as by saponification to form the compounds of formula I where R_4 is hydroxy.

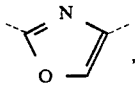
Alternatively, Compounds of formula VIII may be amidated, for example with ammonia or a mono or dialkylamine, to form compounds of formula I where R_4 is amino, alkylamino or dialkylamino.

Compounds of formula VI may also be coupled with an epoxide of formula IIIa to form compounds of formula VIII.

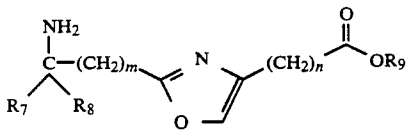
To prepare compounds of formula I where A is



R_2 is

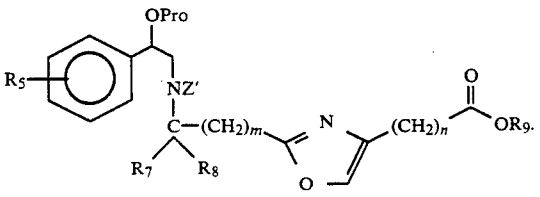


and R_3 is $-(CH_2)_n-$ a compound of formula



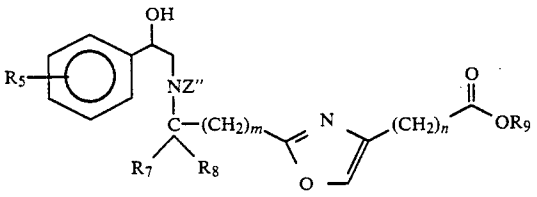
IX

is coupled with a compound of the formula III optionally in the presence of an acid scavenger such as diisopropylethylamine to form a compound of formula



X

Compounds of formula X are then deprotected, for example, with fluoride to form compounds of the formula



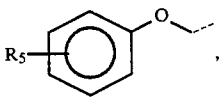
XI

which are themselves compounds of formula I where R_4 is alkoxy. Compounds of formula XI may be deesterified such as by saponification to form the compounds of formula I where R_4 is hydroxy.

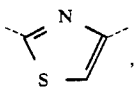
Alternatively, Compounds of formula XI may be amidated, for example with ammonia or a mono or dialkylamine, to form compounds of formula I where R_4 is amino, alkylamino or dialkylamino.

Compounds of formula IX may also be coupled with an epoxide of formula IIIa to form compounds of formula XI.

To prepare the compounds of formula I where A is



R_2 is



and R_3 is $-(CH_2)_n-$, a compound of formula II is coupled with a compound of formula

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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.

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Sync your system to PACER to automate legal marketing.