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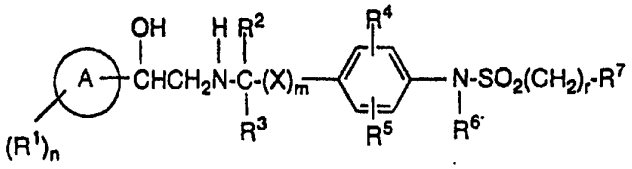
(54) Title: SUBSTITUTED SULFONAMIDES AS SELECTIVE $\beta_3$ AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY




(I)

(57) Abstract

Substituted sulfonamides having formula (I), are selective $\beta_3$ adrenergic receptor agonists with very little $\beta_1$ and $\beta_2$ adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduce neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.

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TITLE OF THE INVENTION

# SUBSTITUTED SULFONAMIDES AS SELECTIVE $\beta_3$ AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

## CROSS REFERENCE

This is a continuation-in-part of co-pending application U.S.S.N. 08/233,166 filed April 26, 1994, which is hereby incorporated by reference in its entirety.

## BACKGROUND OF THE INVENTION

β-Adrenoceptors have been subclassified as $\beta_1$ and $\beta_2$ since 1967. Increased heart rate is the primary consequence of $\beta_1$-receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from $\beta_2$ stimulation. Adipocyte lipolysis was initially thought to be solely a $\beta_1$-mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called $\beta_3$-adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis ($\beta_3$ activity) than for stimulation of atrial rate ($\beta_1$) and tracheal relaxation ($\beta_2$). These early developments disclosed in Ainsworth et al., U.S. Patents 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

Such selectivity for $\beta_3$-adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

A major drawback in treatment of chronic diseases with $\beta_3$ agonists is the potential for stimulation of other β-receptors and subsequent side effects. The most likely of these include muscle tremor ($\beta_2$) and increased heart rate ($\beta_1$). Although these phenylethanolamine

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derivatives do possess some $\beta_3$ selectivity, side effects of this type have been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial $\beta_1$ and/or $\beta_2$ agonism.

More recent developments in this area are disclosed in Ainsworth et al., U.S. Patent 5,153,210, Caulkett et al., U.S. Patent 4,999,377, Alig et al., U.S. Patent 5,017,619, Lecount et al., European Patent 427480 and Bloom et al., European Patent 455006.

Even though these more recent developments purport to describe compounds with greater $\beta_3$ selectivity over the $\beta_1$ and $\beta_2$ activities, this selectivity was determined using rodents, in particular, rats as the test animal. Because even the most highly selective compounds, as determined by these assays, still show signs of side effects due to residual $\beta_1$ and $\beta_2$ agonist activity when the compounds are tested in humans, it has become apparent that the rodent is not a good model for predicting human $\beta_3$ selectivity.

Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human $\beta_3$ receptors which have been expressed in Chinese hamster ovary cells. See Emorine et al, Science, 1989, 245:1118-1121; and Liggett, Mol. Pharmacol., 1992, 42:634-637. The agonist and antagonist effects of the various compounds on the cultivated cells provide an indication of the antiobesity and antidiabetic effects of the compounds in humans.

## SUMMARY OF THE INVENTION

The instant invention is concerned with substituted sulfonamides which are useful as antiobesity and antidiabetic compounds. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted sulfonamides. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

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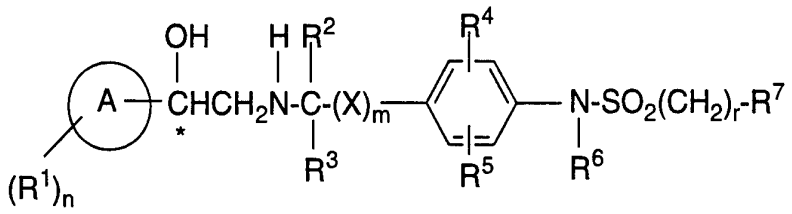
DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:



I

where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) phenyl, or
(5) a benzene ring fused to a $C_3$-$C_8$ cycloalkyl ring;

$R^1$ is (1) hydroxy,
(2) oxo,
(3) halogen,
(4) cyano,
(5) $NR^8R^8$,

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