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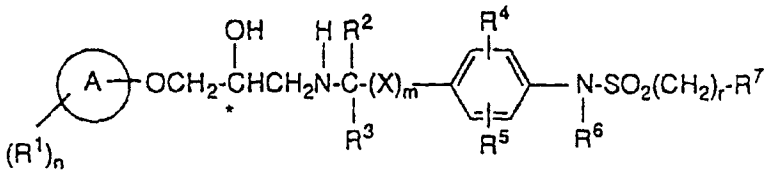
(54) Title: SUBSTITUTED PHENYL SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY



(57) Abstract

Substituted phenylsulphonamides having formula (I) where the variables are as defined in Claim 1; are selective beta-3 adrenergic receptor agonists with very little beta-1 and beta-2 adregenic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have very potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to reduce triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to reduce gut motility. In addition, the compounds can be used to reduce neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenylsulphonamide with an appropriately substituted alkyl epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for the reduction of 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 PHENYL SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our copending application Serial Number 08/015689 filed February 9, 1993.

BACKGROUND OF THE INVENTION

β-Adrenoceptors have been subclassified as β_1 and β_2 since 1967. Increased heart rate is the primary consequence of β_1-receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β_2 stimulation. Adipocyte lipolysis was initially thought to be solely a β_1-mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β_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 (β_3 activity) than for stimulation of atrial rate (β_1) and tracheal relaxtion (β_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 β_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 β_3 agonists is the potential for stimulation of other β-receptors and subsequent side effects. The most likely of these include muscle tremor (β_2) and increased heart rate (β_1). Although these phenylethanolamine derivatives do possess some β_3 selectively, side effects of this type have

been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β_1 and/or β_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 β_3 selectively over the β_1 and β_2 activities, this selectively 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 β_1 and β_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 β_3 selectivity.

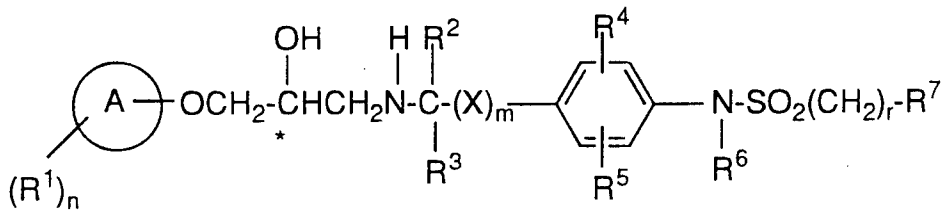
Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. The agonist and antagonist effects of the various compounds on the cultivated cells 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 phenyl 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 phenylsulfonamides. 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.

DESCRIPTION OF THE INVENTION

The compounds of the instant invention are best realized in the following structural formula:



I

where

n is 0 to 7;

m is 0 or 1;

r is 0 to 3;

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

R^1 is hydroxy, oxo, halogen, cyano, nitro, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, SO_2R^9, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$ or C_1-C_6 alkyl substituted by hydroxy, nitro, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or R^1 is a 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

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