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(54) **N-SUBSTITUTED PHENYLUREA INHIBITORS OF MITOCHONDRIAL F_1F_0 ATP HYDROLASE**

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(58) **Field of Search** 514/317

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(57) **ABSTRACT**

Compounds having the formula (I),

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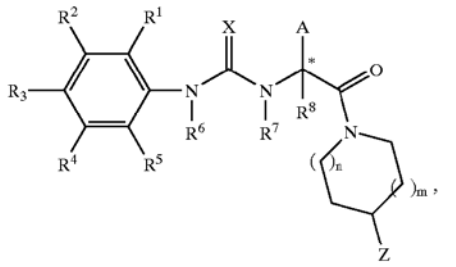

are useful as inhibitors of mitochondrial F_1F_0 ATP hydrolase, wherein R^1–R^8, X, A, Z, n and m are defined herein.

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N-SUBSTITUTED PHENYLUREA INHIBITORS OF MITOCHONDRIAL F_1F_0 ATP HYDROLASE

FIELD OF THE INVENTION

This invention relates to N-substituted phenylurea compounds that inhibit mitochondrial F_1F_0 ATP hydrolase, and are therefore potentially useful for the treatment of a variety of ischemia-related diseases and disorders, including peripheral occlusive arterial disease, intermittent claudication, chronic stable angina pectoris, stroke, myocardial infarction

BACKGROUND OF THE INVENTION

Ischemic heart disease is a common and serious health problem. Every year, large numbers of patients die from ischemic heart disease and its complications. Many others experience acute myocardial infarcation, congestive heart failure, cardiac arrhythmias, or other disorders.

Myocardial ischemia exists when the heart tissue experiences a demand for oxygen and substrates that exceed the supply. Imbalances between oxygen supply and demand span a large range, and thus, there are various syndromes and biochemical pathways involved in the pathogenesis of ischemia, e.g., from low-grade to severe ischemic conditions. For example, chronic stable angina pectoris is a low-grade condition, in which the resting coronary blood flood may be normal but the blood flow reserve is insufficient to meet an increased energy demand. In more extreme situations, the ischemic muscle can develop an impaired contractile function and potential to generate arrhythmias. Major consequences of myocardial ischemia include mechanical and electrical dysfunction, muscle cell damage, and development of necrosis. Acute ischemic events may develop where there is coronary atherosclerosis. Ultimately, if the ischemia is sufficiently severe there will be an immediate reduction (or cessation) of contractile function in the heart.

The impairment of contractile function in ischemic muscle is associated with mitochondrial levels of adenosine triphosphate (ATP) and adenosine triphosphatases (ATPases). ATPases are enzymes that typically catalyze the hydrolysis of ATP, the main energy currency in cells, to adenosine monophosphate (AMP) or adenosine diphosphate (ADP), plus phosphate ions and energy. The contractile function of the heart is regulated by the transport of calcium, sodium, and potassium ions, which in turn is modulated by ATP and ATPases. More particularly, intracellular ATP is split by Na+, K+ ATPase, an enzyme that is responsible for maintaining a gradient of sodium and potassium ions across the cell membrane. The splitting of ATP by Na+, K+ ATPase releases the energy needed to transport K+ and Na+ ions against concentration gradients. This enables the existence of a resting potential in the membrane (i.e, Na+ out, K+ in) which initiates the contractile response. Contraction is triggered by Na/Ca exchange and Ca^{2+} transport, the energy for which is generated by the hydrolysis of ATP by Ca^{2+} ATPase.

To maintain homeostasis, the cells' supply of ATP must be replenished as it is consumed (e.g., with muscle contraction). During the steady state, the rate of ATP synthesis needs to be closely matched to its rate of consumption. Arguably, the most important ATPase is the mitochondrial F_1F_0-ATPase. Unlike other ATPases which function typi-

the mitochondrial F_1F_0-ATPase catalyzes the production of ATP via oxidative phosphorylation of ADP and P_i. Thus, F_1F_0-ATPase is responsible for producing the cell's main energy source, ATP. In normoxic conditions, mitochondrial F_1F_0-ATPase modulates this ATP production via its two units, the F_1 and F_o complexes. F_o is the inner membrane domain, and F_1 is a catalytic domain consisting of five subunits ($\alpha\beta\chi\delta\epsilon$—the catalytic site is on the β unit), that protrude from the F_0 domain into the mitochondrial matrix. When sufficient levels of oxygen are present, electrons from ATPase substrates are transferred to oxygen, and protons are transported out of the mithcondrial matrix. This proton/electron transport creates an electrochemical proton gradient across the mitochondrial membrane and through the F_0 domain which drives the F_1 domain to synthesize ATP.

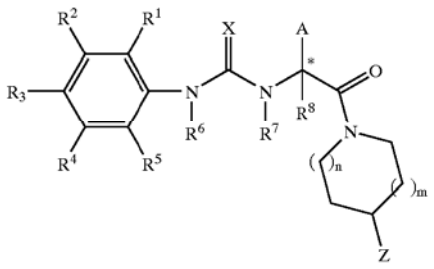
In ischemic conditions, however, this electrochemical gradient collapses, and F_1F_0-ATPase switches to its hydrolytic state. This hydrolysis of ATP seems to serve no useful purpose. Also, as F_1F_0-ATPase operates in its hydrolytic state there is a down-regulation of F_1F_0-ATP synthase. F_1F_0-ATP synthase activities in vesicles from ischemic muscle typically are substantially (up to ~50–80%) less than those of control muscle. A native peptide called IF_1 inhibitor protein (or IF_1) may be bound to the F_1 unit under ischemic conditions to inhibit the ATP hydrolase activity of the enzyme; however, IF_1 is highly pH dependent and in severe conditions can provide only a modicum of control. The conversion of F_1F_0-ATP synthase to F_1F_0-ATP hydrolase is reversible, as addition of substrate and oxygen to the mitochondria of ischemic muscle can reactivate the F_1F_0-ATPase and ATP levels to control levels.

As may be appreciated, in ischemic conditions the activity of F_1F_0-ATPase produces a futile cycling and waste of ATP. It is believed that this depletion of ATP and/or ATP synthase may suppress the Na+K+ pump to increase cardiac contractility, vasoconstriction, sensitivity to vasoactive agents, and arterial blood pressure. Several inhibitors of F_1F_0-ATPase have been described, including efrapeptin, oligomycin, autovertin B, and azide. Oligomycin targets F_0 and reportedly postpones cell injury by preserving ATP during ischemia. However, the only known inhibitors of F_1F_0-ATPase are large proteins or peptides which are not orally bioavailable.

Accordingly, there is an ongoing need for useful inhibitors of F_1F_0-ATPase inhibitors, especially those that are orally bioavailable.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method of treating a mitochondrial F_1F_0 ATP hydrolase associated disorder in a mammal is described comprising administering



(I)

their enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:

X is selected from O or S;

A is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl;

n and m are 0, 1, or 2

R^1 through R^5 are independently selected from hydrogen, halogen, NO_2, CN, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{3-8}cycloalkyl, aryl, heterocyclo, heteroaryl, OR^9, SR^9, COR^{11}, CO_2R^{11}, $CONR^9R^{10}$ or NR^9R^{10};

R^6 and R^7 are independently hydrogen, alkyl or substituted alkyl;

R^8 is hydrogen; C_{1-8}alkyl, substituted C_{1-8}alkyl, aryl, heterocyclo or heteroaryl;

Z is hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, heteroaryl, COR^{11}, CO_2R^{11}, SO_2R^{11}, $S(O)R^{11}$ or $CONR^9R^{10}$;

R^9 and R^{10} are independently hydrogen, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{3-10}cycloalkyl, aryl, heterocyclo, heteroaryl, COR^{13}, SO_2R^{13} or $S(O)R^{13}$; and

R^{11}, R^{12} and R^{13} are independently hydrogen, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{3-10}cycloalkyl, aryl, heterocyclo or heteroaryl;

wherein each occurrence of R^9–R^{13} is chosen independently.

DETAILED DESCRIPTION

The instant invention provides N-substituted phenylurea compounds that are potent and selective inhibitors of F_1F_0-ATP hydrolase. The compounds of the present invention are useful in treating or preventing conditions associated with ischemia, particularly myocardial ischemia and associated conditions, such as muscle cell damage, necrosis, and cardiac arrhythmias. Also, in view of their inhibitory activity, the inventive compounds may be used to treat cancer and tumor growth.

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, three, or four substituents selected from the group consisting of halogen, trifluoromethyl, alkoxyl, alkanoyl, nitro, cyano, keto (=O), thioketo, carboxy, carbamyl, $SO_2NR_aR_b$, CO_2R_a, $C(=O)R_a$, $C(=O)NR_aR_b$, $OC(=O)R_a$, $—OC(=O)NR_aR_b$, $NR_aC(=O)R_b$, $NR_aCO_2R_b$, =N—OH, =N—O-alkyl, aryl, heteroaryl, heterocyclo and cycloalkyl, wherein R_a and R_b are selected from hydrogen, alkyl, alkenyl, cycloalkyl, heterocyclo, aryl, and heteroaryl, and R_c is selected from hydrogen, alkyl, cycloalkyl, heterocyclo aryl and heteroaryl. When a substituted alkyl includes an aryl, heterocyclo, heteroaryl, or cycloalkyl substituent, said ringed systems are as defined below and thus may in turn have zero to four substituents (preferably 0–2 substituents), also as defined below. When either R_a, R_b or R_c is an alkyl or alkenyl, said alkyl or alkenyl may optionally be substituted with 1–2 of halogen, trifluoromethyl, nitro, cyano, keto (=O), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), $N(alkyl)_2$, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl), SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, C(=O)NH_2, C(=O)NH(alkyl), $C(=O)N(alkyl)_2$, OC(=O)alkyl, $—OC(=O)NH_2$, —OC(=O)NH(alkyl), NHC(=O)alkyl, and/or $NHCO_2$(alkyl).

"Alkyl" when used in conjunction with another group such as in arylalkyl refers to a substituted alkyl in which at least one of the substituents is the specifically-named group. For example, the term arylalkyl includes benzyl, or any other straight or branched chain alkyl having at least one aryl group attached at any point of the alkyl chain.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by, for example, one to two substituents, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclo, e.g. indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four triple bonds.

The term "substituted alkynyl" refers to an alkynyl group substituted by, for example, a substituent, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclo, e.g. imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

When reference is made to a substituted alkylene, alkenylene, or alkynylene group, these groups are substituted with one to four substitutents as defined above for alkyl groups. A substituted alkylene, alkenylene, or alkynylene may have a ringed substituent attached in a spiro fashion.

The term "alkoxy" refers to an alkyl, alkenyl, or substituted alkyl or alkenyl group bonded through an oxygen atom (—O—). For example, the term "alkoxy" includes the groups $—O—C_{1-12}$alkyl, $—O—C_{2-8}$alkenyl, and so forth.

The term "alkylthio" refers to an alkyl or alkenyl or substituted alkyl or alkenyl group bonded through a sulfur (—S—) atom. For example, the term "alkylthio" includes the groups $—S—(CH_2)CH_3$, $—S—CH_2$aryl, etc.

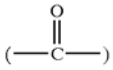
The term "alkylamino" refers to an alkyl or alkenyl or

includes the groups —NR'—C_{1-2}alkyl and —NR'—CH_2-aryl, etc. (where R' is hydrogen, alkyl or substituted alkyl as defined above.) "Amino" refers to the group —NH_2.

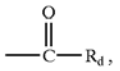
When a subscript is used, as in C_{1-8}alkyl, the subscript refers to the number of carbon atoms the group may contain. Zero when used in a subscript denotes a bond, e.g., C_{0-4}alkyl refers to a bond or an alkyl of 1 to 4 carbon atoms. When used with alkoxy, thioalkyl, or alkylamino (or aminoalkyl), a subscript refers to the number of carbon atoms that the group may contain in addition to heteroatoms. Thus, for example, monovalent C_{1-2}alkylamino includes the groups —NH—CH_3, —NH—CH_2—CH_3, and —N—$(CH_3)_2$. A lower aminoalkyl comprises an aminoalkyl having one to four carbon atoms.

The alkoxy, thioalkyl, or aminoalkyl groups may be monovalent or bivalent. By "monovalent" it is meant that the group has a valency (i.e., power to combine with another group), of one, and by "bivalent" it is meant that the group has a valency of two. For example, a monovalent alkoxy includes groups such as —O—C_{1-12}alkyl, whereas a bivalent alkoxy includes groups such as —O—C_{1-12}alkylene-, etc.

The term "acyl" refers to a carbonyl

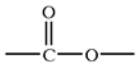


linked to an organic group i.e.,

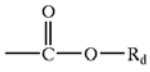


wherein R_d may be selected from alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, heterocyclo, cycloalkyl, or heteroaryl, as defined herein.

The term "alkoxycarbonyl" refers to a group having



linked to an organic radical, R_d, i.e.,



wherein R_d is as defined above for acyl.

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The term "sulfonyl" refers to a sulphoxide group (i.e., —$S(O)_{1-2}$) linked to an organic radical R_e, as defined above.

The term "sulfonamidyl" or "sulfonamido" refers to the group —$S(O)_2NR_eR_f$, wherein R_e and R_f are as defined above. Preferably when one of R_e and R_f is optionally substituted heteroaryl or heterocycle (as defined below), the other of R_e and R_f is hydrogen, alkyl, or substituted alkenyl.

to 7 carbon atoms. The term "cycloalkyl" includes such rings having zero to four substituents (preferably 0–2 substituents), selected from the group consisting of halogen, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, keto, OR_d, SR_d $NR_dR_eNR_cSO_2$, $NR_cSO_2R_c$, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —OC(=O)R_d, =N—OH, =N—O-alkyl, aryl, heteroaryl, heterocyclo, a 4 to 7 membered carbocyclic ring, and a five or six membered ketal, e.g., 1,3-dioxolane or 1,3-dioxane, wherein R_c, R_d and R_e are defined as above. The term "cycloalkyl" also includes such rings having a phenyl ring fused thereto or having a carbon-carbon bridge of 3 to 4 carbon atoms. Additionally, when a cycloalkyl is substituted with a further ring, i.e., aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclo, heterocycloalkyl, cycloalkylalkyl, or a further cycloalkyl ring, such ring in turn may be substituted with one to two of C_{0-4}alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=O), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), N(alkyl)$_2$, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl), SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, C(=O)NH_2, C(=O)NH(alkyl), C(=O)N(alkyl)$_2$, OC(=O)alkyl, —OC(=O)NH_2, —OC(=O)NH(alkyl), NHC(=O)alkyl, and $NHCO_2$(alkyl).

The term "aryl" refers to phenyl, biphenyl, 1-naphthyl, 2-naphthyl, and anthracenyl, with phenyl being preferred. The term "aryl" includes such rings having zero to four substituents (preferably 0–2 substituents), selected from the group consisting of halo, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_d, SR_d, NR_dR_e, NR_dSO_2, $NR_dSO_2R_c$, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —OC(=O)R_d, heteroaryl, heterocyclo, cycloalkyl, phenyl, benzyl, napthyl, including phenylethyl, phenyloxy, and phenylthio, wherein R_c, R_d and R_e are defined as above. Additionally, two substituents attached to an aryl, particularly a phenyl group, may join to form a further ring such as a fused or spiro-ring, e.g., cyclopentyl or cyclohexyl or fused heterocycle or heteroaryl. When an aryl is substituted with a further ring, such ring in turn may be substituted with one to two of C_{0-4}alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=O), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), N(alkyl)$_2$, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl), SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, C(=O)NH_2, C(=O)NH(alkyl), C(=O)N(alkyl)$_2$, OC(=O)alkyl, —OC(=O)NH_2, —OC(=O)NH(alkyl), NHC(=O)alkyl, and $NHCO_2$(alkyl).

The term "heterocyclo" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N). Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quater-

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