US006627636B2

(12) **United States Patent**
**Robl**

(10) **Patent No.: US 6,627,636 B2**
(45) **Date of Patent: Sep. 30, 2003**

(54) **HMG-COA REDUCTASE INHIBITORS AND METHOD**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/007,407**

(22) Filed: **Dec. 4, 2001**

(65) **Prior Publication Data**

US 2002/0094977 A1 Jul. 18, 2002

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/875,155, filed on Jun. 6, 2001, now abandoned.
(60) Provisional application No. 60/211,595, filed on Jun. 15, 2000.

(51) **Int. Cl.**[7] ..... **A61K 31/4353**; A61K 31/4365; C07D 491/044; C07D 495/04; A61P 3/06

(52) **U.S. Cl.** ..... **514/291**; 514/292; 514/213.01; 540/577; 546/80; 546/81; 546/89; 546/93

(58) **Field of Search** ..... 514/291, 292, 514/213.01; 546/80, 81, 89, 93; 540/577

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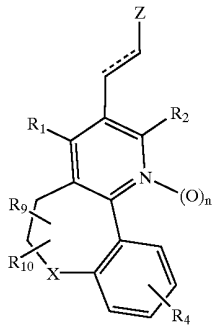
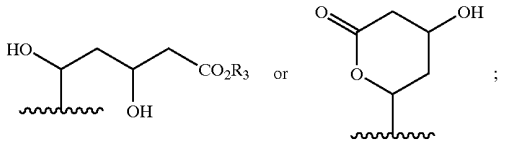
(57) **ABSTRACT**

Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDl cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis




and pharmaceutically acceptable salts thereof, wherein X is O, S, SO, $SO_2$ or $NR_7$; Z is




;

n is 0 or 1; $R_1$ and $R_2$ are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; and $R_3$ to $R_{10}$ are as defined herein.

**25 Claims, No Drawings**

# HMG-COA REDUCTASE INHIBITORS AND METHOD

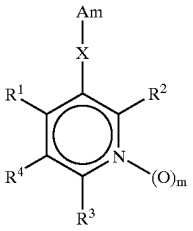
This application is a continuation-in-part of U.S. application Ser. No. 09/875,155 filed Jun. 6, 2001, abandoned which application claims priority from U.S. provisional application No. 60/211,595, filed Jun. 15, 2000.

## FIELD OF THE INVENTION

The present invention relates to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns (1) certain inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) that include a pyridine containing nucleus attached by means of a linker to an HMG-binding domain sidechain, (2) pharmaceutical compositions containing such compounds and (3) a method of lowering blood serum cholesterol levels and modulating blood serum lipid levels employing such pharmaceutical compositions.

## BACKGROUND OF THE INVENTION

U.S. Pat. No. 5,686,433 to Robl discloses the structure




wherein:

Am is a binding domain sidechain;

X is a linker;

$R^1$ and $R^2$ are the same or different and are each independently selected from

(i) hydrogen,
(ii) alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) aralkyl,
(vi) aralkoxy,
(vii) alkenyl,
(viii) cycloalkenyl, and
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

$R^3$ is selected from

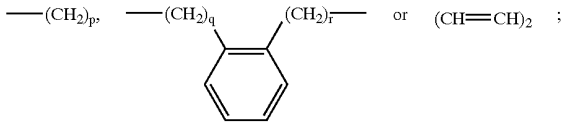
(i) hydrogen,
(ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
(vi) aralkyl,
(vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) halo-substituted alkyl,
(xi) adamantyl, and
(xii) heterocyclo (e.g., thienyl, benzodioxolyl);

$R^4$ is selected from

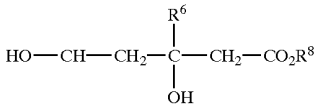
(i) hydrogen,
(ii) lower alkyl,
(iii) aryl,



(iv) cycloalkyl,
(v) alkoxy,
(vi) aralkyl,
(vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) adamantyl,
(xi) halogen,
(xii) halo-substituted alkyl (e.g., trifluoromethyl), and
(xiii) heterocyclo (e.g., thienyl, benzodioxolyl); or $R^3$ and $R^4$ taken together can be




but when $A_m$ is




or a δ lactone thereof, $R^3$ and $R^4$ cannot be $(CH{=}CH)_2$;

$R^6$ is hydrogen or lower alkyl;

$R^8$ is hydrogen, lower alkyl, alkali metal, or alkaline earth metal;

n is 0 or 1;

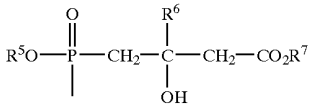
p is 3, 4 or 5;

q is 0, 1, 2, or 3; and

r is 0, 1, 2, or 3.

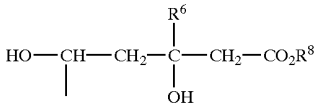
In preferred embodiments (Am) is an HMG-binding domain sidechain having a dihydroxy or a phosphinic acid function.

The phosphinic (or phosphonic when X is $CH_2$—O—) acid HMG-binding domain sidechain ($A_1$) is

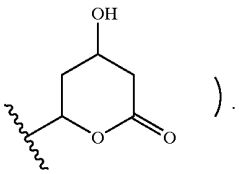



wherein $R^5$ and $R^7$ are independently selected from hydrogen, lower alkyl, alkali metal ion and alkaline earth metal ion; and $R^6$ is hydrogen or lower alkyl.

The dihydroxy acid binding domain sidechain ($A_2$ is




wherein $R^6$ is hydrogen or lower alkyl, $R^8$ is hydrogen or lower alkyl in free acid form or in the form of a physiologically acceptable and hydrolyzable ester or 6 lactone thereof (i.e., when Am is



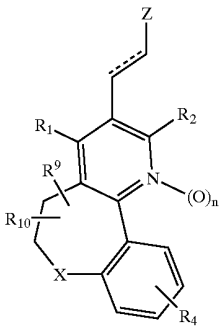
In addition, $R^8$ can be alkali metal ion or alkaline earth metal ion.

A suitable linker (X) is —$(CH_2)_a$—, —CH═CH—, —C≡C—, —$CH_2O$—, wherein O is linked to the phosphorous atom or the aromatic anchor when Am is $A_1$, and wherein O is linked to the aromatic anchor when Am is $A_2$, and wherein "a" is 1, 2, or 3.

## BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided certain pyridine-containing compounds that are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase).

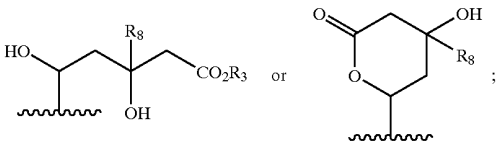
In particular, in its broadest chemical compound aspect, the present invention provides compounds of the formula I



wherein

X is O, S, SO, $SO_2$ or $NR_7$;

Z is



n is 0 or 1;

$R_1$ and $R_2$ are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

$R_3$ is H, or lower alkyl or a metal ion (such as an alkali metal or an alkaline earth metal);

$R_4$ is H, halogen, $CF_3$, hydroxy, alkyl, alkoxy, carboxyl, carboxylalkyl-, aminoalkyl, amino, alkanoylamino, aroylamino, cyano, alkoxyCON($R_{7d}$)-, $R_{7f}R_{7g}NCO$—, $R_{7f}R_{7g}NCO_2$—, $R_{7e}SO_2N(R_{7d})$-, $R_{7f}R_{7g}NSO_2N(R_{7d})$-, $R_{7e}OCO_2$— or $R_{7e}OCO$—;

$R_7$ is H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, $R_{7a}SO_2$—, $R_{7b}R_{7c}NSO_2$— or $R_{7b}R_{7c}NCO$—;

$R_{7a}$ and $R_{7e}$ are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl,

$R_{7b}$ and $R_{7c}$, and $R_{7f}$ and $R_{7g}$, and $R_{7d}$ are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; or $R_{7b}$ and $R_{7c}$ may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring, which where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S; or $R_{7f}$ and $R_{7g}$ may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring which, where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S;

$R_8$ is H or lower alkyl;

$R_9$ and $R_{10}$ are the same or different and are independently selected from H or alkyl, or where at least one of $R_9$ and $R_{10}$ is alkyl, $R_9$ and $R_{10}$ may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

and ⫽ represents a single bond or a double bond (which may be cis or trans);

and including pharmaceutically acceptable salts thereof where $R_3$ is H, esters thereof, prodrug esters thereof, and all stereoisomers thereof.

Preferably, the Z group will be in form of a free acid, a physiologically acceptable and hydrolyzable ester or δ lactone thereof, or an alkali metal salt, alkaline earth metal salt or an amino acid salt.

It is preferred that X is O, $SO_2$ or $NR_7$ where $R_7$ is $R_{7a}SO_2$—.

Preferred are compounds of formula I of the invention wherein

$R_1$ and $R_2$ are independently selected from alkyl, cycloalkyl and aryl;

$R_4$ is H, alkyl or halogen;

X is O; and

n is o.

More preferred are compounds of formula I of the invention wherein $R_1$ is aryl (especially substituted aryl as defined hereinafter);

$R_2$ is alkyl or cycloalkyl;

$R_4$ is H;

$R_9$ and $R_{10}$ are H;

X is O;

n is o; and

⫽ is a double bond.

Still more preferred are compounds of formula I of the invention wherein

$R_1$ is substituted aryl, preferably 4-fluorophenyl, 4-fluoro-3-methylphenyl or 3,5-dimethylphenyl;

$R_2$ is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl;

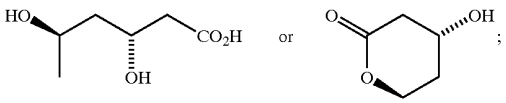
$R_4$ is H;

X is O;

n is o;

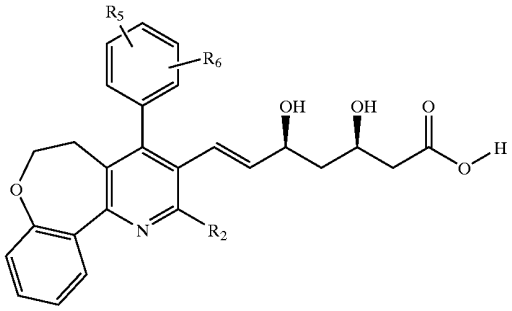
⫽ is a double bond, preferably "trans"; and

Z is



or an alkali or alkaline earth metal salt thereof or an amino acid salt.

Most preferred compounds of formula I of the invention will have the structure



or an alkali or alkaline earth metal (such as Na, K or Ca) salt thereof, or an amino acid salt (such as arginine), wherein $R_5$ and $R_6$ are the same or different and independently selected from H, halogen and/or alkyl (preferably 4-fluoro, 4-fluoro-3-methyl or 3,5-dimethyl); and

$R_2$ is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl.

In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, or hypotriglyceridemic agents, or anti-Alzheimer's agents, or anti-osteoporosis agents as well as other uses as described herein, comprising a hypolipidemic or hypocholesterolemic or hypotriglyceridemic or anti-Alzheimer's disease or anti-osteoporosis amount, or other therapeutically effective amount (depending upon use) of a compound of formula I in accordance with this invention, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels such as lowering LDL cholesterol and/or increasing HDL cholesterol, or treating dyslipidemia, mixed dyslipidemia, hyperlipidemia, hypercholesterolemia, hypo α-lipoproteinemia, LDL Pattern B, LDL Pattern A, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a), or treating or preventing other cholesterol-related diseases, or treating or preventing or reversing progression of atherosclerosis, or preventing or treating Alzheimer's disease, or preventing or treating osteoporosis and/or osteopenia, or reducing inflammatory markers such as C-reactive protein, or preventing or treating low grade vascular inflammation, or preventing or treating stroke, or preventing or treating dementia, or preventing and treating coronary heart disease (including primary and secondary prevention of myocardial infarction), or preventing or treating stable and unstable angina, or primary prevention of coronary events, or secondary prevention of cardiovascular events, or preventing or treating peripheral vascular disease, preventing or treating peripheral arterial disease, or preventing or treating acute vascular syndromes, or preventing or reducing the risk of undergoing myocardial revascularization procedures, or preventing or treating microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome or preventing or treating hypertension in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

In addition, in accordance with the present invention, a method is provided for preventing or treating diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for preventing and treating malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), gastrointestinal malignencies, liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), cancer-induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, other infectious diseases, drug-induced lipodystrophy, and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for improving coagulation homeostasis including reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating cholesterol related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases as defined above and hereinafter and other diseases as set out above, wherein a therapeutically effective amount of a combination of a compound of structure I and a hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent, is administered to a patient in need of treatment.

In the above methods of the invention wherein a combination is administered, the compound of structure I will be employed in a weight ratio to the other therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 500:1, preferably from about 0.5:1 to about 100:1.

## DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme HMG-CoA reductase, which inhibitors are useful as hypocholesterolemic agents, dyslipidemic agents, hypolipidemic agents, hypotriglyceridemic agents, anti-Alzheimer's disease agents, and antiosteoporosis agents as well as other uses as described herein.

The term "coronary events" as employed herein refers to myocardial infarction, myocardial revascularization procedures, angina, cardiovascular death and acute coronary syndrome.

The term "cardiovascular diseases or events" as employed herein refers to atherosclerosis of the coronary arteries, myocardial infarction, including primary MI and secondary MI, recurrent myocardial infarction, angina pectoris (including stable and unstable angina), congestive heart failure, and sudden cardiac death.

The term "cerebrovascular diseases or events" as employed herein refers to cerebral infarction or stroke (caused by vessel blockage or hemmorage), or transient ischemia attack (TIA), syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like.

The term "cholesterol-related diseases" as employed herein refers to diseases involving elevated levels of LDL cholesterol, diseases involving regulation of LDL receptors, diseases involving reduced levels of HDL cholesterol, dyslipidemia, hyperlipidemia, elevated LDL Pattern B, elevated LDL Pattern A, hypercholesterolemia, hypo α-lipoproteinemia (low HDL cholesterol syndrome), hyperlipoproteinemia, elevated Lp(a) levels, hypertriglyceridemia, other aberrations of apolipoprotein B metabolism, heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia (including Frederickson Types IIa and IIb), cholesterol ester storage disease, and cholesterol ester transfer protein disease, and related diseases.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, *J. Clin. Endocrinol. Metab.,* 1997, 82, 727–734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than compounds of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-atherosclerosis agents), other types of anti-atherosclerosis agents, and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis agents, one or more anti-obesity agents, one or more agents for treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

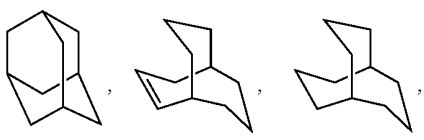
The term "other types of anti-atherosclerosis agents" as employed herein refers to conventional anti-atherosclerosis agents including lipoxygenase inhibitors, ACAT inhibitors, antioxidants, PPAR δ agonists, phospholipase inhibitors including PLA-2 inhibitors and/or other known anti-atherosclerotic agents.

The terms pharmaceutically acceptable "salt" and "salts" refer to basic salts formed with inorganic and organic bases. Such salts include ammonium salts; alkali metal salts, such as lithium, sodium and potassium salts (which are preferred); alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as amine like salts (e.g., dicyclohexylamine salt, benzathine, N-methyl-D-glucamine, and hydrabamine salts); and salts with amino acids like arginine, lysine and the like; and zwitterions, the so-called "inner salts". Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

The term pharmaceutically acceptable "salt" and "salts" also includes 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 such as HCl or HBr, 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 lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C1–C4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or $CF_3$, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, cycloheteroalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl) and tricyclic alkyl, containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



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