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Dow

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(54) **CYANO CONTAINING OXAMIC ACIDS AND DERIVATIVES AS THYROID RECEPTOR LIGANDS**

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Related U.S. Application Data

(60) Provisional application No. 60/122,119, filed on Mar. 1, 1999.

(51) **Int. Cl.**[7] **A61K 31/275**; C07C 255/60; A61P 3/06; A61P 3/04

(52) **U.S. Cl.** **514/522**; 558/413; 558/416; 558/417

(58) **Field of Search** 514/522; 558/413, 558/417

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,069,343	1/1978	Sellstedt et al.	424/319
4,554,290	11/1985	Böger et al.	514/487
4,766,121	8/1988	Ellis et al.	514/247
4,826,876	5/1989	Ellis et al.	514/535
4,910,305	3/1990	Ellis et al.	544/239
5,061,798	10/1991	Emmett et al.	544/239
5,232,947	8/1993	Sato et al.	514/549
5,284,971	2/1994	Walker et al.	562/429
5,401,772	3/1995	Yokoyama et al.	514/539
5,569,674	10/1996	Yokoyama et al.	514/539
5,654,468	8/1997	Yokoyama et al.	560/43

FOREIGN PATENT DOCUMENTS

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Wright, S.W. et al., *OPPI Briefs*, 29 (1): 128–131 (1997).

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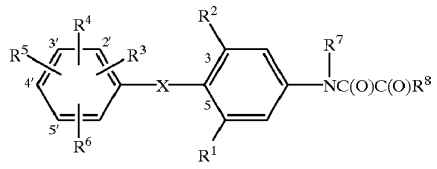
(57) **ABSTRACT**

The present invention provides novel compounds of the Formula

(I)



and prodrugs thereof, geometric and optical isomers thereof, and pharmaceutically acceptable salts of such compounds, prodrugs and isomers, wherein R^1–R^8 and X are as described herein. Pharmaceutical compositions containing such compounds, prodrugs, isomers or pharmaceutically acceptable salts thereof, and methods, pharmaceutical compositions and kits for treating obesity, hyperlipidemia, thyroid disease, hypothyroidism and related disorders and diseases such as diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis are also provided.

45 Claims, No Drawings

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CYANO CONTAINING OXAMIC ACIDS AND DERIVATIVES AS THYROID RECEPTOR LIGANDS

CROSSREFERENCE TO RELATED APPLICATION

This application claims priority from U.S. Provisional Patent Application No. 60/122,119 filed Mar. 1, 1999, the benefit of which is hereby claimed under 37 C.F.R. §1.78 (a)(3).

FIELD OF THE INVENTION

The present invention relates to novel thyroid receptor ligands and, more particularly, relates to novel cyano containing oxamic acids, and derivatives thereof, which are useful in the treatment of obesity, hyperlipidemia, thyroid disease, hypothyroidism and related disorders and diseases such as diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis. Also provided are methods, pharmaceutical compositions and kits for treating such diseases and disorders.

BACKGROUND OF THE INVENTION

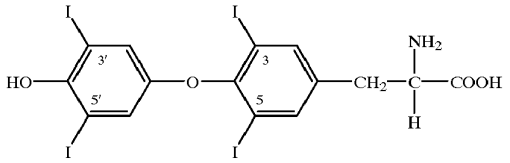
It is generally accepted that thyroid hormones, specifically, biologically active iodothyronines, are critical to normal development and to maintaining metabolic homeostasis. Thyroid hormones stimulate the metabolism of cholesterol to bile acids and enhance the lipolytic responses of fat cells to other hormones.

Thyroid hormones also affect cardiac function both directly and indirectly, e.g., by increasing the metabolic rate. For example, tachycardia, increased stroke volume, increased cardiac index, cardiac hypertrophy, decreased peripheral vascular resistance and increased pulse pressure are observed in patients with hyperthyroidism.

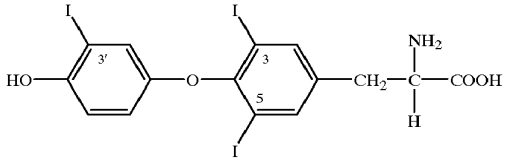
Disorders of the thyroid are generally treated with hormone replacement by administering either naturally occurring thyroid hormones or thyromimetic analogues thereof which mimic the effects of thyroid hormones.

Two naturally occurring thyroid hormones, namely, thyroxine or 3,5,3',5'-tetraiodo-L-thyronine (commonly referred to as "T_4") and 3,5,3'-triiodo-L-thyronine (commonly referred to as "T_3"), are shown below:

T_4



T_3



T_3 is the more biologically active of the two and, as will be appreciated from the structural formulae provided above, differs from T_4 by the absence of the 5' iodine.

T_3 may be produced directly from the thyroid gland, or, in peripheral tissues, by the removal of the 5' iodine by deiodinase enzymes. Thyromimetic analogs are often designed to be structurally similar to T_3. In addition, naturally occurring metabolites of T_3 are known.

As discussed above, thyroid hormones affect cardiac functioning, for example, by causing an increase in the heart rate and, accordingly, an increase in oxygen consumption. While the increase in oxygen consumption may result in certain desired metabolic effects, nonetheless, it does place an extra burden on the heart, which in some situations, may give rise to damaging side effects. Therefore, as is known in the art, such as described by A. H. Underwood et al. in an article published in *Nature*, Vol. 324: pp. 425–429 (1986), efforts have been made to synthesize thyroid hormone analogs which function to lower lipids and serum cholesterol without generating the adverse cardiac effects referred to above.

U.S. Pat. Nos. 4,766,121; 4,826,876; 4,910,305; and 5,061,798 disclose certain thyroid hormone mimetics, namely, 3,5-dibromo-3'-[6-oxo-3(1H)-pyridazinylmethyl]-thyronines.

U.S. Pat. No. 5,284,971 discloses certain thyromimetic cholesterol lowering agents, namely, 4-(3-cyclohexyl-4-hydroxy or -methoxy phenylsulfonyl)-3,5 dibromophenylacetic compounds.

U.S. Pat. Nos. 5,401,772; 5,654,468; and 5,569,674 disclose certain lipid lowering agents, namely, heteroacetic acid derivatives, which compete with radiolabeled T_3 in binding assays using rat liver nuclei and plasma membrane preparations.

Certain oxamic acids and derivatives thereof are known in the art, e.g., U.S. Pat. No. 4,069,343 describes the use of certain oxamic acids to prevent immediate type hypersensitivity reactions; U.S. Pat. No. 4,554,290 describes the use of certain oxamic acids to control pests on animals and plants; U.S. Pat. No. 5,232,947 describes the use of certain oxamic acids to improve damaged cerebral functions of the brain; and European Patent Specification published as EP 580,550 discloses certain oxamic acid derivatives as hypocholesteremic agents.

In addition, certain oxamic acid derivatives of thyroid hormones are known in the art. For example, N. Yokoyama et al. in an article published in the *Journal of Medicinal Chemistry,* 38 (4): 695–707 (1995) describe replacing a —CH_2 group in a naturally occurring metabolite of T_3 with an —NH group resulting in —$HNCOCO_2H$. Likewise, R. E. Steele et al. in an article published in International Congressional Service (*Atherosclerosis* X) 1066: 321–324 (1995) and Z. F. Stephan et al. in an article published in *Atherosclerosis,* 126: 53–63 (1996), describe certain oxamic acid derivatives useful as lipid-lowering thyromimetic agents yet devoid of undesirable cardiac activities.

All of the documents cited herein, including the foregoing, are incorporated by reference herein in their entireties.

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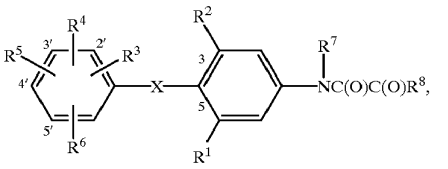
SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



(I)

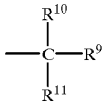
prodrugs thereof, geometric and optical isomers thereof, and pharmaceutically acceptable salts of said compounds, said prodrugs, and said isomers, wherein:

R^1 and R^2 are independently halogen, C_{1-8} alkyl, —CN or C_{1-8} perfluoroalkyl; provided that at least one of R^1 and R^2 is —CN;

R^3 is hydrogen or C_{1-8} alkyl;

R^4 is halogen, C_{1-8} perfluoroalkyl, C_{1-8} alkyl, C_{1-8} alkanoyl, hydroxy-(C_{1-8} alkyl), aryl optionally substituted with Y and Z, aryl-(C_{1-8} alkyl), carbocyclic aroyl optionally substituted with Y and Z, C_{3-10} cycloalkyl optionally substituted with Y and Z, or C_{3-10} cycloalkyl-(C_{1-8} alkyl);

or R^4 is the radical



wherein: R^9 is hydrogen, C_{1-8} alkyl, aryl optionally substituted with Y and Z, aryl-(C_{1-8} alkyl), C_{3-10} cycloalkyl optionally substituted with Y and Z, or C_{3-10} cycloalkyl-(C_{1-8} alkyl); R^{10} is —OR^{14}; R^{11} is hydrogen or C_{1-8} alkyl; or R^{10} and R^{11} may be taken together with the carbon atom to which they are attached to form a carbonyl group;

R^5 is hydroxy, esterified hydroxy or etherified hydroxy;

R^6 is hydrogen, halogen, C_{1-8} alkyl or C_{1-8} perfluoroalkyl;

R^7 is hydrogen, C_{1-8} alkyl or C_{1-8} perfluoroalkyl;

R^8 is —OR^{12} or —$NR^{12}R^{13}$;

R^{12} and R^{13} are each independently hydrogen or C_{1-8} alkyl;

R^{14} is hydrogen, C_{1-8} alkyl or C_{1-8} acyl;

X is O, $S(O)_a$, C═O or NR^{15};

a is 0, 1 or 2;

R^{15} is hydrogen or C_{1-8} alkyl;

Y and Z for each occurrence are independently (a) hydrogen, (b) halogen, (c) trifluoromethyl, (d) —OCF_3, (e) —CN, (f) C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, —OCF_3, —CF_3 and phenyl, (g) C_{1-6} alkoxy, (h) aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, —OCF_3, —CF_3, C_{1-4} alkyl and C_{1-4} alkoxy, (i) —$C(O)_2R^{16}$, (j) —$C(O)NR^{16}R^{17}$, (k) —$C(O)R^{16}$, (l) —$NR^{16}C(O)NR^{16}R^{17}$ or (m) —$NR^{16}C(O)R^{17}$; or Y and Z for any occurrence may be taken together to form (a) a carbocycle of the formula —$(CH_2)_b$—, or (b) a heterocycle selected from the group consisting of —$O(CH_2)_cO$—, $(CH_2)_dNH$— and —CH═CHNH—;

b is 3, 4, 5, 6 or 7;

c and d are each independently 2, 3, 4, 5 or 6;

R^{16} and R^{17} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, —(C_{1-6} alkyl)-C_{1-6} alkoxy, aryl optionally substituted with Y and Z, het optionally substituted with Y and Z, —(C_{1-4} alkyl)-aryl optionally substituted with Y and Z, —(C_{1-4} alkyl)-heterocycle optionally substituted with Y and Z, —(C_{1-4} alkyl)-hydroxy, —(C_{1-4} alkyl)-halo, —(C_{1-4} alkyl)-poly-halo, —(C_{1-4} alkyl)-$CONR^{18}R^{19}$ or C_{3-10} cycloalkyl;

het for each occurrence is a 4-, 5-, 6-, 7- or 8-membered partially or fully saturated, or unsaturated, ring containing from one to four heteroatoms independently selected from the group consisting of N, O and S, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle which is a 4-, 5-, 6-, 7- or 8-membered partially or fully saturated, or unsaturated, ring containing from one to four heteroatoms independently selected from the group consisting of N, O and S; and

R^{18} and R^{19} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or aryl optionally substituted with Y and Z.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the A Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein X is oxygen.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the A Group, designated the B Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is located at the 2' position, R^4 is located at the 3' position, R^5 is located at the 4' position and R^6 is located at the 5' position.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the C Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3, R^5 and R^7 are hydrogen, and R^6 is hydroxy.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the C Group, designated the D Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently —CN, methyl or chloro, provided that at least one of R^1 and R^2 is —CN.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the E Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^8 is —OR^{12}.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the E Group, designated the F Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^{12} is hydrogen, methyl or ethyl, and R^4 is —$CH(CH_3)_2$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the G Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^8 is —$NR^{12}R^{13}$.

A preferred group of the pharmaceutically acceptable salts of the compounds of Formula I, and the prodrugs, geometric

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and optical isomers thereof, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or sodium salt.

A preferred group of compounds of Formula I, prodrugs and geometric and optical isomers thereof, and pharmaceutically acceptable salts of the compounds, prodrugs and isomers, designated the H Group, includes the specific compounds N-[3-cyano-4-(4-hydroxy-3-isopropyl-phenoxy)-5-methyl-phenyl]-oxamic acid and N-[3-chloro-5-cyano-4-(4-hydroxy-3-isopropyl-phenoxy)-phenyl]-oxamic acid, and the ethyl esters thereof.

A preferred group of the pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers of the H Group, designated the I Group, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or sodium salt.

This invention provides methods of treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) which comprise administering to said mammal an effective treating amount of a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, such prodrug, or such isomer, as described above.

In another aspect, this invention provides methods of treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) which comprise administering to said mammal effective treating amounts of a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, such prodrug, or such isomer, as described above, and an anorectic agent.

In another aspect, this invention provides methods of treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) which comprise administering to said mammal effective treating amounts of a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, such prodrug, or such isomer, as described above, and a lipase inhibitor.

In a preferred aspect, this invention provides methods of treating obesity in mammals (including a human being) which comprise administering to said mammal an obesity treating effective amount of compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above.

In another aspect, this invention provides methods of treating obesity in mammals (including a human being) which comprise administering to said mammal obesity treating effective amounts of a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and an anorectic agent.

In another aspect, this invention provides methods of treating obesity, in a mammal (including a human being) which comprise administering to said mammal obesity treating effective amounts of a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, such prodrug, or such isomer, as described above, and a lipase inhibitor.

In another aspect, this invention provides pharmaceutical compositions comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides pharmaceutical compositions comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, an anorectic agent and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides pharmaceutical compositions comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, a lipase inhibitor and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides pharmaceutical compositions for treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides pharmaceutical compositions for treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, an anorectic agent, and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides pharmaceutical compositions for treating a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis, in a mammal (including a human being) comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, a lipase inhibitor, and a pharmaceutically acceptable vehicle, diluent or carrier.

In another preferred aspect, this invention provides pharmaceutical compositions for treating obesity in a mammal (including a human being) comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and a pharmaceutically acceptable vehicle, diluent or carrier.

In yet another aspect, this invention provides pharmaceutical compositions for treating obesity in a mammal (including a human being) comprising a compound of

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Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, an anorectic agent, and a pharmaceutically acceptable vehicle, diluent or carrier.

In yet another aspect, this invention provides pharmaceutical compositions for treating obesity in a mammal (including a human being) comprising a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, a lipase inhibitor, and a pharmaceutically acceptable vehicle, diluent or carrier.

In another aspect, this invention provides kits for the treatment of a condition selected from obesity, hyperlipidemia, thyroid disease, hypothyroidism, diabetes mellitus, atherosclerosis, hypertension, coronary heart disease, hypercholesteremia, depression and osteoporosis which comprise: a first compound, said first compound being a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and a pharmaceutically acceptable vehicle, carrier or diluent, in a first unit dosage form; a second compound, said second compound being an anorectic agent or a lipase inhibitor, and a pharmaceutically acceptable vehicle, carrier or diluent, in a second unit dosage form; and a container.

In another preferred aspect, this invention provides kits for the treatment of a obesity which comprise: a first compound, said first compound being a compound of Formula I, or a prodrug thereof, or a geometric or an optical isomer thereof, or a pharmaceutically acceptable salt of such compound, prodrug, or isomer, as described above, and a pharmaceutically acceptable vehicle, carrier or diluent, in a first unit dosage form; a second compound, said second compound being an anorectic agent or a lipase inhibitor, and a pharmaceutically acceptable vehicle, carrier or diluent, in a second unit dosage form; and a container.

Unless otherwise provided herein:

"acyl" means an organic radical derived from an organic acid by the removal of the hydroxyl group, including, as the case may be, for example, acetyl, C_{1-8} alkanoyl, carbocyclic aryl-C_{1-8} alkanoyl or carbocyclic aroyl;

"alkanoyl" means a univalent or bivalent acyl radical formed by removal of hydroxyl from the carboxyl group which replaced the methyl group at the end of the main chain of the acyclic hydrocarbon; "C_{1-8} alkanoyl" includes, as the case may be for example, acetyl, propionyl, butyryl or pivaloyl;

"alkanoylamino" of "C_{1-8} alkanoylamino" includes, as the case may be, for example, acetamido or propionamido;

"alkoxy" means an alkyl radical which is attached to the remainder of the molecule by oxygen, including as the case may be, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy;

"alkoxycarbonyl" of "C_{1-8} alkoxycarbonyl" preferably contains one to four carbon atoms in the alkoxy moiety and includes, as the case may be, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl;

"alkyl" means a straight or branched hydrocarbon chain radical, including as the case may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl and the like;

"aroyl" means aryl acyl, including, as the case may be, for example, benzenesulfonyl, benzoyl and naphthoyl; preferably benzoyl and benzoyl substituted on the benzene ring by C_{1-8} alkyl, C_{1-8} alkoxy, halogen or trifluoromethyl;

"aryl" includes carbocyclic aryl and heterocyclic aryl, and is preferably phenyl optionally substituted by one or two of C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, C_{1-8} alkanoyloxy, halogen, trifluoromethyl, cyano, C_{1-12} alkanoylamino or C_{1-8} alkoxycarbonyl; "aryl" of "aryl-C_{1-8} alkyl" is preferably benzyl or phenethyl optionally substituted by one or two of C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, C_{1-8} alkanoyloxy, halogen or trifluoromethyl;

"carbocyclic" (carbocycle) means an unsaturated, or a partially or fully saturated, ring having only carbon atoms in its nucleus, including, as the case may be, an aryl (an organic radical derived from an aromatic hydrocarbon by the removal of one atom, e.g., phenyl from benzene, also including, for example, naphthyl);

"carbocyclic aryl" includes, as the case may be, for example, optionally substituted phenyl or optionally substituted naphthyl;

"cycloalkane" means a saturated, monocyclic hydrocarbon, including, as the case may be, for example, cyclohexane;

"C_{3-10} cycloalkyl" means a monocyclic or polycyclic radical derived from a cycloalkane, including as the case may be, for example, cyclopentyl and cyclohexyl;

"C_{3-10} cycloalkyl-(C_{1-8} alkyl) includes, as the case may be, for example, 1- or 2-(cyclopentyl or cyclohexyl) ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)butyl;

"esterified hydroxy" means acyloxy, e.g., acyloxy derived from an organic carboxylic acid, preferably C_{1-12} alkanoyloxy, aroyloxy, or aryl-(C_{1-8} alkanoyloxy); also, 3,7,12(3α, 5β, 7α, 12α)-trihydroxy-cholan-24-oyloxy (derived from cholic acid), and the like;

"etherified hydroxy" includes, as the case may be, for example, C_{1-8} alkoxy, C_{1-8} alkenyloxy, C_{5-7} cycloalkyloxy, carbocyclic aryl-C_{1-8} alkoxy, tetrahydropyranyloxy, C_{5-7} cycloalkyl-C_{1-8} alkoxy, and the like;

"halo" and "halogen" mean a radical derived from the elements fluorine, chlorine, bromine or iodine;

"heterocyclic" ("heterocycle") means a radical derived from an unsaturated, or a partially or fully saturated, ring of different types of atoms, and includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N; examples of heterocyclic groups include, as the case may be, for example, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, furyl, imidazolyl, indolyl, isoquinolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolyl, piperazinyl, piperidyl, pyranyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolyl, quinolyl, tetrahydroisoquinoly, tetrahydroquinolyl, tetrahydrothienyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, thiomorpholinyl, thiophenyl and triazolyl; where heterocyclic groups are specifically recited or covered as substituents for the compounds of Formula I, it is understood that, unless specifically noted otherwise, all suitable isomers of such heterocyclic groups are intended;

"heterocyclic aryl" includes, as the case may be, for example, monocyclic heterocyclic aryl, e.g., optionally substituted thienyl, furanyl, pyridyl, pyrrolyl or N—(C_{1-8} alkyl)pyrrolyl; optionally substituted thienyl

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Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

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.

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Sync your system to PACER to automate legal marketing.