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# United States Patent [19]

Lee et al.

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[54] **SULFONATE ACAT INHIBITORS**

[75] Inventors: **Helen T. Lee**, Ann Arbor; **Joseph A. Picard**, Canton; **Drago R. Sliskovic**, Ypsilanti, all of Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **359,144**

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[51] **Int. Cl.**[6] ..... **C07C 309/69**; C07C 309/70; A61K 31/095; C07D 487/04

[52] **U.S. Cl.** ..... **514/517**; 514/510; 514/513; 514/300; 514/404; 514/312; 514/457; 514/341; 514/256; 514/252; 514/314; 514/246; 514/248; 514/259; 514/274; 514/351; 514/387; 514/445; 514/443; 514/473; 514/470; 514/469; 514/247; 514/255; 514/424; 514/407; 514/372; 514/365; 514/376; 514/380; 514/384; 514/359; 514/392; 514/386; 514/367; 514/418; 514/415; 514/311; 514/309; 514/307; 558/50; 558/49; 558/52; 546/122; 546/153; 546/294; 546/157; 546/172; 546/141; 546/147; 546/146; 548/370.1; 548/370.4; 548/550; 548/551; 548/213; 548/187; 548/228; 548/229; 548/243; 548/255; 548/264.4; 548/324.1; 548/166; 548/178; 548/180; 548/251; 548/486; 548/484; 548/510; 548/265.4; 549/471; 549/399; 549/410; 549/65; 549/66; 549/52; 549/51; 549/479; 549/466; 544/215; 544/237; 544/235; 544/283; 544/315; 544/319; 544/298; 544/239; 544/408

[58] **Field of Search** ..... 558/49, 50; 514/517, 514/510

[56] **References Cited**

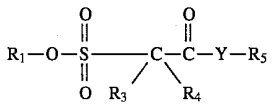
U.S. PATENT DOCUMENTS

4,567,004 1/1986 Blank et al. ..... 260/465 R

*Primary Examiner*—Cecilia Tsang
*Assistant Examiner*—King Lit Wong
*Attorney, Agent, or Firm*—Charles W. Ashbrook; Todd M. Crissey

[57] **ABSTRACT**

β-Carboxy sulfonates of the formula



wherein $R_1$ is aryl, $R_3$ and $R_4$ are hydrogen or alkyl, Y is -O-, -S-, or $-NR_2-$, and $R_5$ is alkyl or aryl are potent inhibitors of the enzyme acyl CoA:cholesterol acyltransferase (ACAT) and are thus useful for treating hypercholesterolemia and atherosclerosis.

**13 Claims, No Drawings**

# SULFONATE ACAT INHIBITORS

## BACKGROUND OF THE INVENTION

This invention provides new chemical compounds characterized as being β-carboxy sulfonates. The compounds inhibit acyl-CoA: cholesterol acyltransferase (ACAT), the enzyme responsible for the esterification of dietary cholesterol. Such agents thus decrease the absorption of dietary cholesterol and therefore provide a therapy for individuals with hypercholesterolemia and atherosclerosis.

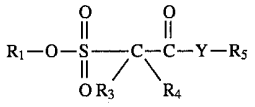
High levels of cholesterol have been associated with heightened risk for development of several disease states, most notably coronary heart disease. A great deal of effort has been devoted to finding ways to lower cholesterol levels in biological systems. The approach of lowering cholesterol intake by modifying diet has met with only limited success. The ACAT enzyme is known to catalyze the esterification of dietary cholesterol, and has been implicated in several aspects of the atherosclerotic process in animals. One approach to lowering cholesterol then is to inhibit the ACAT enzyme. While several ACAT inhibitors have been identified (see for example EP 0570245), the need continues to identify and develop new ACAT inhibitors having improved therapeutic properties.

An object of this invention is therefore to provide a new series of compounds which are β-carboxy sulfonate derivatives and which have demonstrated excellent ACAT inhibitory properties. Another object is to provide pharmaceutical formulations comprising the sulfonates and a carrier or excipient, and a method for inhibiting the ACAT enzyme by administering a compound of the invention.

## SUMMARY OF THE INVENTION

This invention concerns new compounds which are β-carboxy sulfonates and which inhibit the ACAT enzyme.

The compounds of the invention have the Formula I



I

wherein $R_1$ is selected from

(a) phenyl which is unsubstituted or is substituted with from 1 to 3 substituents selected from

$C_1$–$C_4$ alkyl,

$C_1$–$C_4$ alkoxy,

$C_1$–$C_4$ alkyl thio,

hydroxy,

halo,

nitro,

cyano,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,

$-(CH_2)_mNR_xR_y$ wherein m is 0 or 1, and each of $R_x$ and $R_y$ is independently hydrogen or $C_1$–$C_4$ alkyl;

(b) 1- or 2-naphthyl which is unsubstituted or substituted with from 1 to 3 substituents selected from

$C_1$–$C_4$ alkyl,

$C_1$–$C_4$ alkoxy,

$C_1$–$C_4$ alkylthio,



hydroxy,

halo,

nitro,

cyano,

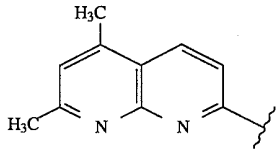
trifluoromethyl,

-COOH,

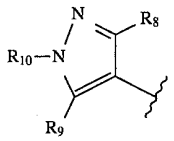
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,

$-(CH_2)_mNR_xR_y$ wherein m is 0 or 1, and each of $R_x$ and $R_y$ is independently hydrogen or $C_1$–$C_4$ alkyl;

(c) the group



(d) the group



wherein $R_8$ and $R_9$ independently are $C_1$–$C_4$ alkyl or phenyl, and R10 is a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds; phenyl; phenyl substituted with from 1 to 3 substituents selected from

$C_1$–$C_4$ alkyl,

$C_1$–$C_4$ alkoxy,

hydroxy,

halo,

nitro,

cyano,

trifluoromethyl,

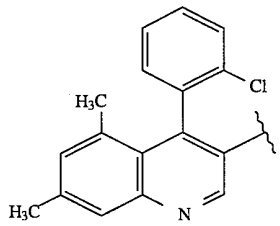
-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

$-(CH_2)_mNR_xR_y$ wherein m, $R_x$, and $R_y$ are as defined above; or

a heterocyclic group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2-, or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 3- or 4-pyridazinyl, and the N-oxides thereof;

(e) the group

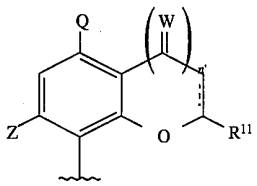


(f) a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated

containing one double bond or two nonadjacent double bonds;

(g) a cycloalkyl group having from 3 to 10 carbon atoms;

(h) the group

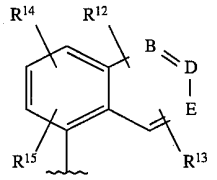


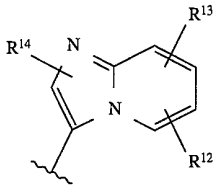
wherein — denotes a single or double bond; Q and Z are each independently hydrogen, $C_1$–$C_4$ alkyl, $C_1$–$C_4$ alkoxy, or halo;

W is oxygen or two hydrogen atoms;

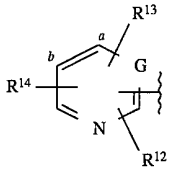
$R^{11}$ is hydrogen or $C_1$–$C_4$ alkyl, and n' is 0 or 1;

(i) is selected from the group





and



wherein $R^{12}$, $R^{13}$, $R^{14}$, and $R^{15}$ are each independently hydrogen,

halo,

$C_1$–$C_4$ alkyl,

$C_1$–$C_4$ alkoxy,

$C_1$–$C_4$ alkylthio,

cycloalkylthio of 5 to 7 carbon atoms,

phenylalkylthio in which alkyl is 1 to 4 carbon atoms,

substituted phenylthio, heteroarylthio, or heteroaryloxy;

and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G =N, the group is attached to the nitrogen atom of Formula I at the four or five position of the pyrimidine ring (a and b); or

(j) a 5- or 6-membered monocyclic or fused bicyclic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_3$ and $R_4$ independently are $C_3$–$C_6$ cycloalkyl, hydroxy-$C_1$–$C_4$ alkyl, $C_1$–$C_4$ alkoxy, hydrogen, $C_1$–$C_4$ alkyl, phenyl, 1- or 2 -naphthyl, or phenyl or naphthyl substituted with from 1 to 3 substituents selected from $C_1$–$C_4$ alkyl, $C_1$–$C_4$ alkoxy, $C_1$–$C_4$ alkylthio, halo, nitro, cyano, trifluoromethyl, phenyl, or $C_3$–$C_6$ cycloalkyl

or $R_3$ and $R_4$ taken together with the carbon to which they are attached complete a $C_3$–$C_8$ carbocyclic ring;

Y is -O-, -S-, or -$NR_2$-, wherein $R_2$ is hydrogen, $C_1$–$C_4$ alkyl, phenyl, $C_1$–$C_4$ alkyl, phenyl, wherein the phenyl may be substituted with 1, 2, or 3 groups selected from $C_1$–$C_4$ alkyl, $C_1$–$C_4$ alkoxy, $C_1$–$C_4$ alkylthio, hydroxy, halo, nitro, cyano, trifluoromethyl, and COOH;

$R_5$ is $R_6$, $C_1$–$C_{20}$ alkyl, $C_2$–$C_{20}$ alkenyl, $C_2$–$C_{20}$ alkynyl and alkyl, alkenyl and alkenyl substituted with one or two groups defined by $R_6$, where $R_6$ is hydrogen, $C_3$–$C_6$ cycloalkyl, phenyl, 1 - or 2 - naphthyl, and phenyl and naphthyl substituted with from 1 to 3 substituents selected from:

$C_1$–$C_4$ alkyl,

$C_1$–$C_4$ alkoxy,

$C_1$–$C_4$ alkylthio,

phenyl,

hydroxy,

halo,

nitro,

cyano,

trifluoromethyl,

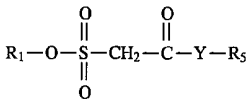
-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,

-$(CH_2)_m NR_xR_y$ wherein m is 0 or 1, and each of $R_x$ and $R_y$ is hydrogen or a straight chain alkyl group having 1 to 4 carbon atoms; and

$R_6$ is heteroaryl selected from a 5- or 6-membered monocyclic or fused bicyclic heterocyclic group containing at least 1 to 4 heteroatoms in at least one ring, said heteroatoms being nitrogen, oxygen, or sulfur and combinations thereof, said heterocyclic group being unsubstituted or substituted with amino, halo, nitro, hydroxy, cyano, trifluoromethyl, or an alkyl group having from 1 to 20 carbon atoms and the N-oxides thereof.

Preferred compounds of the invention have the Formula II



II

wherein $R_1$, Y, and $R_5$ are as defined above. Further preferred are those of the above formula in which Y is -O-, -S-, or -NH-, and especially where Y is -NH-. Additionally preferred are compounds of Formula II wherein $R_1$ is phenyl or substituted phenyl, Y is -O- or S, and $R_5$ is $C_6$–$C_{20}$ alkyl, phenyl, or substituted phenyl. Preferred substituted phenyl groups are di- and trialkyl, such as diisopropyl and triisopropyl.

Particularly preferred compounds have Formula II wherein:

A. $R_1$ is phenyl or phenyl substituted with 1 or 2 $C_1$–$C_4$ alkyl groups;

A(1) Y is NH and $R_5$ is $C_6$–$C_{20}$ alkyl;

A(2) Y is NH and $R_5$ is phenyl or phenyl substituted with 1 or 2 $C_1$–$C_4$ alkyl or $C_1$–$C_4$ alkoxy groups;

A(3) Y is NH and $R_5$ is pyridyl or pyridyl substituted with 1 or 2 $C_1$–$C_4$ alkyl groups;

A(4) Y is S and $R_5$ is $C_6$–$C_{20}$ alkyl;

A(5) Y is O and $R_5$ is $C_6$–$C_{20}$ alkyl;

A(6) Y is O and $R_5$ is phenyl or phenyl substituted with 1 or 2 $C_1$–$C_4$ alkyl groups;

A(7) Y is NH and $R_5$ is tetrazolyl or tetrazolyl substituted with a $C_6$–$C_{20}$ alkyl group;

B. $R_1$ is phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkoxy groups;

B(1) Y is NH and $R_5$ is phenyl or phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkoxy groups;

B(2) Y is NH and $R_5$ is $C_6$–$C_{20}$ alkyl;

B(3) Y is S and $R_5$ is $C_6$–$C_{20}$ alkyl;

B(4) Y is O and $R_5$ is $C_6$–$C_{20}$ alkyl;

B(5) Y is O and $R_5$ is phenyl or phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkoxy groups;

C. $R_1$ is 1- or 2-naphthyl or 1- or 2-naphthyl substituted with 1, 2, or 3 groups selected from $C_1$–$C_4$ alkyl or $C_1$–$C_4$ alkoxy;

C(1) Y is NH and $R_5$ is $C_6$–$C_{20}$ alkyl, phenyl, or phenyl substituted with 1, 2, or 3 groups selected from $C_1$–$C_4$ alkyl or $C_1$–$C_4$ alkoxy;

C(2) Y is S and $R_5$ is $C_6$–$C_{20}$ alkyl;

C(3) Y is O and $R_5$ is $C_6$–$C_{20}$ alkyl, phenyl, tetrazolyl, or phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkyl groups;

C(4) Y is O and $R_5$ is hydrogen;

D. $R_1$ is $C_1$–$C_{20}$ alkyl;

D(1) Y is O and $R_5$ is phenyl or phenyl substituted with 1 or 2 $C_1$–$C_4$ alkyl groups;

D(2) Y is S and $R_5$ $C_6$–$C_{20}$ alkyl;

E. $R_1$ is pyridyl or pyridyl substituted with 1 or 2 $C_1$–$C_4$ alkyl groups;

E(1) Y is O or S and $R_5$ $C_6$–$C_{20}$ alkyl;

F. $R_1$ is 4,6-dialkylpyridin-5-yl;

F(1) Y is NH and $R_5$ $C_6$–$C_{20}$ alkyl;

F(2) Y is S and $R_5$ is phenyl or phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkyl groups;

G. $R_1$ is 4-(2-chlorophenyl)-5,7-dimethylquinolin-2-yl;

G(1) Y is O and $R_5$ is $C_6$–$C_{20}$ alkyl;

G(2) Y is NH and $R_5$ is phenyl or phenyl substituted with 1, 2, or 3 $C_1$–$C_4$ alkoxy groups;

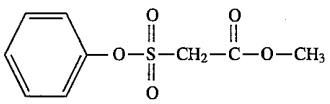
G(3) Y is S and $R_5$ is $C_2$–$C_{20}$ alkenyl;

The most preferred compounds of the invention are defined by Formula II when $R_1$ is phenyl or substituted phenyl, Y is -NH- and $R_5$ is phenyl or dialkylphenyl.

Also provided by this invention are pharmaceutical formulations comprising a compound of Formula I together with a pharmaceutically acceptable excipient, carrier, or diluent. Preferred formulations are those having a compound of Formula II or any of the preferred compounds of A-G as the active ingredient. The invention also provides a method of treating hypercholesterolemia, atherosclerosis, and inhibiting the ACAT enzyme, comprising administering to a subject an effective amount of a compound of Formula I to treat such conditions and to inhibit such enzyme.

## DETAILED DESCRIPTION

The compounds of this invention are named as sulfonates, and more specifically as carbonylmethyl sulfonates. For example, the invention compound of the formula



will be named phenyl methoxycarbonylmethyl sulfonate.

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention. Suitable acids for forming salts of the compounds of Formula I containing a basic group such as amino or pyridyl include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. Additional acids for use to form acid salts of the compounds of Formula I include, but are not necessarily limited to, those acids found in Tables 3 and 4 of Grant & Hackh's Chemical Dictionary, Fifth Edition, 1987:11–13. The acid addition salts are formed by procedures well known in the art.

Certain compounds of the present invention may also exist in different isomeric forms, specifically stereoisomeric forms, by virtue of the presence of asymmetric centers in the compound. The present invention contemplates all stereoisomers that may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

In Formula I, $R_5$ can be $C_1$–$C_{20}$ alkyl, $C_2$–$C_{20}$ alkenyl, or $C_2$–$C_{20}$ alkynyl. Each of these groups can have one or two groups defined by $R_6$ attached, for example a substituted or unsubstituted phenyl, or a substituted or unsubstituted naphthyl, or a cycloalkyl such as cyclopropyl can be attached to the carbon chain. Illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, 2-cyclobutyl-2-phenylethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, 5-phenylpentyl, 2-cyclopropyl-5-phenylpentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

Illustrative examples of straight or branched hydrocarbon alkenyl chains having from 2 to 20 carbon atoms and having one double bond or two nonadjacent double bonds include ethenyl, 2-propenyl, 2-butenyl, 4-cyclobutyl-2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 9-phenyl-9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl. Typical alkynyl groups are those having from 2 to 20 carbon atoms with one triple bond or two monoadjacent triple bonds and include 2-octynyl, 5-hepta-3-decynyl, and 4-phenyl-2-butynyl.

$R_1$ in Formula I includes phenyl substituted with 1, 2, or 3 groups such as $C_1$–$C_4$ alkyl, $C_1$–$C_4$ alkoxy and $C_1$–$C_4$ alkylthio. Straight or branched $C_1$–$C_4$ alkyl groups include methyl and isopropyl. Straight or branched alkoxy groups having 1 to 4 carbon atoms include methoxy, ethoxy, n-propoxy, n-butoxy, and isopropoxy. $C_1$–$C_4$ alkylthio includes groups such as methylthio, ethylthio, isopropylthio, and the like.

Cycloalkyl groups having from 3 to 10 carbon atoms which $R_1$ and $R_4$ may represent include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

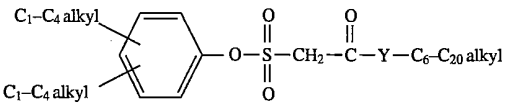
Halo is fluoro, chloro, bromo, or iodo, but preferably bromo and chloro.

A 5- or 6-membered monocyclic or fused bicyclic heterocycle is a monocyclic or fused bicyclic aromatic ring containing at least one to four heteroatoms in at least one

ring, such as nitrogen, oxygen, or sulfur, or a combination thereof. Such a heterocyclic group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrazolyl, isothiazolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, indolyl, quinolinyl, isoquinolinyl, or N-oxides of heterocycles containing a nitrogen atom.

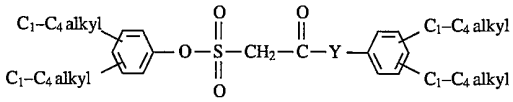
More specifically, such a heterocycle may be a 2- or 3-thienyl; 2- or 3-furanyl; 2-, 3-, or 4-pyridyl or 2-, 3-, or 4-pyridinyl-N-oxide; 2-, 4-, or 5-pyrimidinyl; 3- or 4-pyridazinyl; 2-pyrazinyl; 2-pyrazinyl-N-oxide; 2- or 3-pyrrolyl; 3-, 4-, or 5-pyrazolyl; 2-, 4-, or 5-thiazolyl; 3-, 4-, or 5-isoxazolyl; 2-, 4-, or 5-oxazolyl; 3-, 4-, or 5-isothiazolyl; 5-tetrazolyl; 3- or 5-(1,2,4)-triazolyl; 4- or 5-(1,2,3)-triazolyl; 2-, 4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; or 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl.

A preferred embodiment of this invention includes compounds having the formula



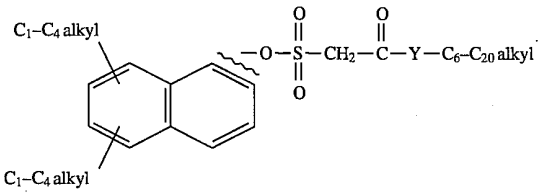

where Y is O, S, or NH, and especially NH.

Also preferred are compounds of the formula

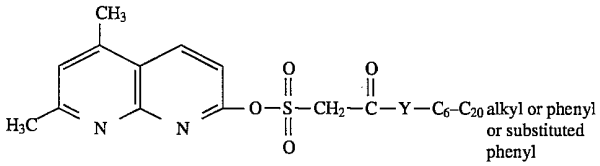



where Y is O, S, or NH, and especially NH.

Another class of compounds provided by the invention have the formula

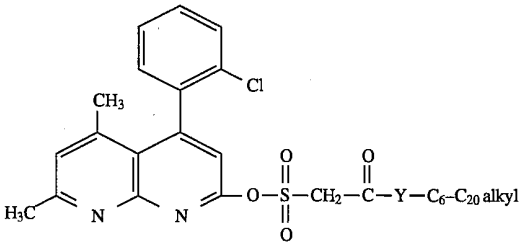



Another class of invention compounds have the formula

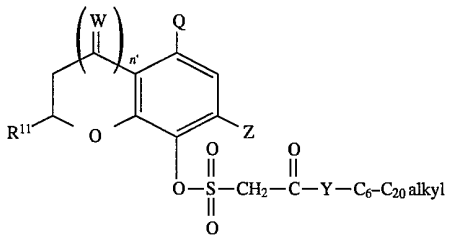



where Y is O, S, or NH, and substituted phenyl is phenyl having 1, 2, or 3 substituents as defined above.

Another preferred group of compounds of the invention have the formula



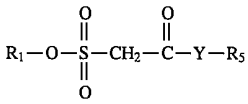

Still other compounds of the invention have the formula



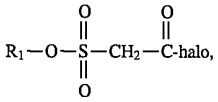

wherein $R_2$, $R_3$, $R_4$, $R_{11}$, W, n', Q, and Z are as defined above, and Y is O, S, or NH.

The compounds of this invention are prepared by any of several synthetic routes utilizing routine methodology well known to those skilled in the art of organic chemistry. The compounds are prepared from readily available starting materials and reactants.

In a preferred embodiment, compounds of Formula II




are prepared by reacting an alcohol, thiol, or amine of the formula H-Y-$R_5$ with an sulfonic acetyl halide of the formula




where $R_1$ is as defined above and halo is preferably bromo or chloro. The sulfonic acetyl halides are readily prepared by starting with a sulfonic acetic acid, which can be reacted with an alcohol to give the corresponding sulfonic acetic acid ester, which reacts with a halogenating agent to give the

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