**Title:** FLAVONES AND COUMARINS AS AGENTS FOR THE TREATMENT OF ATHEROSCLEROSIS

**Abstract**

Flavones and coumarins or a pharmaceutically acceptable salt thereof are inhibitors of VCAM-1 and ICAM-1 and are thus useful in the treatment of atherosclerosis, restenosis, and immune disorders such as arthritis and transplant rejection.
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FLAVONES AND COUMARINS AS AGENTS FOR THE TREATMENT OF ATHEROSCLEROSIS

BACKGROUND OF THE INVENTION

The present invention relates to medical methods of treatment. More particularly, the present invention concerns the use of flavones and/or coumarins, or a pharmaceutically acceptable salt thereof for the treatment of atherosclerosis, restenosis, and immune disorders such as arthritis and transplant rejection.

Additionally, the present invention relates to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier for administering an effective amount of the aforementioned compounds in unit dosage form in the treatment methods mentioned above.

Adhesion of monocytes to vascular endothelium represents an early event in pathologies involving chronic inflammation. These include atherosclerosis, restenosis, and immune disorders like arthritis and transplant rejection. The adhesion of monocytes to endothelium is mediated by expression of cell-surface molecules on endothelial cells. These adhesion molecules are vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and E-selectin. Of these three adhesion molecules, VCAM-1 seems to be involved in binding monocytes (Faruqi R.M., and Di Corleto P.E., Br. Heart J., 1993;69:s19-s29).

Atherosclerosis is viewed as a chronic inflammatory disease of the artery involving monocyte accumulation, smooth muscle proliferation, and cholesteryl ester accumulation by both these cell types. Monocyte accumulation in atherosclerosis begins
with the adherence of blood-borne monocytes to defined areas of aortic endothelium (Ross R., Nature, 1993;362:801-809). The attachment of monocytes is mediated by VCAM-1 expression on endothelial cell-surface as suggested by studies in animal models of atherosclerosis (Li H., et al., Arteriosclerosis Throm., 1993;13:197-204) as well as the expression of VCAM-1 in human atherosclerotic lesions (O'Brien K.D., et al., J. Clin. Invest., 1993;92:945-951). Once the monocytes bind to the endothelium, they migrate into the subendothelial space and transform into cholesteryl ester loaded "foam cells." Monocyte derived foam cells secrete a variety of cytokines, growth factors, and proteases which promote atherosclerotic lesion formation and growth. Therefore, inhibiting the binding of monocytes to VCAM-1 may block monocyte recruitment and lesion formation (Collins T., Lab. Invest., 1993;68:499-508). Selective inhibition of VCAM-1 functions will also decrease nonspecific effects on inflammation.

Intimal thickening response in the artery known as restenosis, following balloon angioplasty is a common and frequent complication that leads to occlusion of coronary vessels. After balloon injury, the endothelial cells regenerate and express VCAM-1 at the surface. This expression of VCAM-1 could contribute to leukocyte recruitment and immune activation in restenosis (Tanaka H., et al., Circulation, 1993;88:1788-1803). Therefore, inhibitors of VCAM-1 expression may be therapeutically useful in restenosis.

Monoclonal antibodies to VCAM-1 have been disclosed by other investigators for therapeutic utility in atherosclerosis. Similarly, pyrrolidine thiocarbamate (PDTC) and two of its analogs which inhibit VCAM-1 expression in vitro (Marui, et al., J. Clin. Invest., 1993;91:1866-1874 and U.S. Patent
5,380,747) have been disclosed for the treatment of atherosclerosis, postangioplasty restenosis, and inflammation. The potential utility of VCAM-1 inhibitors in heart transplant rejection was reported in studies which demonstrated that monoclonal antibodies to VCAM-1 markedly reduced the rejection of transplanted hearts in a rat model and improved the survival rate of these animals (Pelletier R.P., et al., J. Immunol., 1992;149:2473-2481).

We have surprisingly and unexpectedly found that flavones and/or coumarins are inhibitors of VCAM-1 and ICAM-1 and additionally are active in blocking leukocyte adhesion in a rat model and are thus useful as agents for the treatment of atherosclerosis, restenosis, and immune disorders such as arthritis and transplant rejection.

SUMMARY OF THE INVENTION

Accordingly, a first embodiment of the present invention provides a method of treatment of atherosclerosis, restenosis, immune disorders, and transplant rejection in mammals in need thereof comprising administering to such mammal an effective amount of a compound selected from the group consisting of: a flavone; and a coumarin; or a pharmaceutically acceptable salt thereof.

A still further embodiment of the present invention is a method of treatment of atherosclerosis in mammals in need thereof comprising administering to such mammal an effective amount of a compound selected from the group consisting of: a flavone and a coumarin in combination with one or more agents selected from the group consisting of:

(a) ACAT inhibitor;
-4-

(b) HMG-CoA reductase inhibitor;
(c) Lipid regulator; and
(d) Bile acid sequestrant;

or a pharmaceutically acceptable salt thereof.

Finally, the present invention is directed to a pharmaceutical composition for administering an effective amount of a compound of Formula I or Formula II in unit dosage form in the treatment methods mentioned above.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I or Formula II, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, and the like.

The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 12 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

The terms "alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl as defined above for alkyl.

The term "aryl" means an aromatic radical which is a phenyl group, or a naphthyl group, and the like, unsubstituted or substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, carboxy, trifluoromethyl, cyano, thiol, nitro, halogen, amino, alkyl amino wherein alkyl is as defined above, dialkyl amino wherein alkyl is as defined above, 0

-NH-C-alkyl wherein alkyl is as defined above,
-C-O-alkyl wherein alkyl is as defined above, or aryl.

The term "arylalkyl" means an aromatic radical attached to an alkyl radical wherein aryl and alkyl are as defined above, for example, benzyl, and the like.

"Halogen" is fluorine, chlorine, bromine, or iodine.

The term "flavone" means 2-phenyl-4H-1-benzopyran-4-one or a substituted 2-phenyl-4H-1-benzopyran-4-one, i.e.,

wherein the ring may be unsubstituted or substituted at the 3, 5, 6, 7, 8, 2', 3', 4', 5', or 6' positions.

The term "coumarin" means 2H-1-benzopyran-2-one or a substituted 2H-1-benzopyran-2-one, i.e.,

wherein the ring may be unsubstituted or substituted at the 3, 4, 5, 6, 7, or 8 positions.

The term "mammal" includes animals and humans.

Some of the compounds of Formula I or Formula II are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of
these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I or Formula II include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," J. Pharma. Sci., 1977;66:1).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but
otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloro-procaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see Berge, Supra, 1977).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

A preferred compound of the first embodiment used in the method of the present invention is a compound selected from the group consisting of:
wherein R is hydrogen,

alkyl,
alkoxy,
hydroxy,
-N-R^{10} \text{ wherein } R^{10} \text{ and } R^{11} \text{ are each}
R^{11} \text{ independently the same or different and each is hydrogen,}
alkyl,
cycloalkyl,
aryl,
arylalkyl, or
R^{10} \text{ and } R^{11} \text{ taken together with } N \text{ can form a 3- to 6-membered ring, or}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{OH}};
\node at (-1.5,-1.5) {\text{HO}};
\node at (1.5,-1.5) {\text{OH}};
\end{tikzpicture}
\end{center}

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 \text{ are each independently the same or different and each is}

hydrogen,
alkyl,
alkoxy,
hydroxy,
halogen,
CF_3,
CN,
NO_2,
-N-R\textsuperscript{10} wherein R\textsuperscript{10} and R\textsuperscript{11} are as
\begin{align*}
\text{R} & \text{ defined above,} \\
\text{-CH}_2\text{-NR} & \text{ wherein R\textsuperscript{10} and R\textsuperscript{11} are as} \\
\text{R} & \text{ defined above,} \\
\text{-CH}_2\text{OR} & \text{ wherein R\textsuperscript{10} is as defined} \\
\text{above,} \\
\text{-SR} & \text{ wherein R\textsuperscript{10} is as defined above,} \\
\text{-CO}_2\text{R} & \text{ wherein R\textsuperscript{10} is as defined above,} \\
\text{-CONR} & \text{ wherein R\textsuperscript{10} and R\textsuperscript{11} are as defined} \\
\text{R} & \text{ above,} \\
\text{-CH}_2\text{NH-C-(CH}_2\text{OH)} & \text{2,} \\
\text{CH}_3 & \\
\text{-CH}_2 & \text{N} \\
\text{-OCH}_2 & \text{-CO}_2\text{alkyl,} \\
\text{-O(CH}_2\text{)} & \text{n-N(alkyl)} \text{2 wherein n is zero or an} \\
\text{integer of 1,} \\
\text{-NH-CH}_2 & \text{-Oalkyl,} \\
\text{-NH-C-C-} & \text{Oalkyl,} \\
\text{-NH-aryl, or} \\
\text{-N=CH-aryl, or} \\
\text{R} & \text{2 and R} \text{3 may be joined to form a ring selected} \\
\text{from the group consisting of:} \\
\text{and} \\
\text{or} \\
\text{further, R} & \text{2 and R} \text{3 or R} \text{7 and R} \text{8 may be joined by a} \\
\text{methylenedioxy group; and}
wherein \( R \) is hydrogen, alkyl, aryl, arylalkyl, hydroxy, \(-\text{CH}_2\text{-NH-CH}_2\text{-aryl},\) \(-\text{(CH}_2\text{)}_m\text{-X-aryl} \) wherein \( m \) is zero or an integer of 1, 2, or 3 and \( X \) is \( O \) or \( S \), \(-\text{(CH}_2\text{)}_3\text{ OH},\)

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{C-NH}_2, \text{ or} \\
\text{C-O-octadecyl-9-etyl;}
\end{array}
\]

\( R^1 \) is hydrogen, alkyl, aryl, arylalkyl, hydroxy, \(-\text{CH}_2\text{-NH-aryl},\) \(-\text{SH},\) \(-\text{NH}_2; \) or

\( R \) and \( R^1 \) may be joined to form a ring which is
R², R³, R⁴, and R⁵ are each independently the same or different, and each is hydrogen, alkyl, alkoxy, halogen, hydroxy, -N(alkyl)₂, -O(CH₂)₃N(alkyl)₂, -OCH₂CH-CH₂NHC(CH₃)₃, OH -O(CH₂)₃-C(CH₃)₂-CO₂alkyl, or 

R² and R³ may be joined to form a ring which is ; or further, R³ and R⁴ may be joined to form a ring which is ; or a pharmaceutically acceptable salt of a compound of Formula I or Formula II.

A more preferred compound of the first embodiment used in the method of the present invention is a compound of Formula I wherein

R is hydrogen, methyl, methoxy,
R₁, R₂, R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently the same or different and each is hydrogen, alkyl, OCH₃, hydroxy, halogen, CF₃, CN, NH₂, -N(CH₃)₂, -CH₂N(CH₃)₂, -CO₂H, -CH₂-NH-C(CH₂OH)₂, CH₃ -CH₂-N, -OCH₂-CO₂C₂H₅, -O(CH₂)₂-N(C₂H₅)₂, -NH-C-C-O-C₂H₅, -NH-aryl, or -N=CH-aryl or R² and R³ may be joined to form a ring selected from the group consisting of:
further, $R^2$ and $R^3$ or $R^7$ and $R^8$ may be joined by a methylenedioxy group; and in a compound of Formula II

$R$ is hydrogen, aryl, arylalkyl, -CH$_2$-NH-CH$_2$-phenyl, -(CH$_2$)$_3$-X-aryl wherein X is O or S, -(CH$_2$)$_3$OH, S

-C-NH$_2$, or O

-C-O-octadecyl-9-ethyl;

$R^2$, $R^3$, $R^4$, and $R^5$ are each independently the same or different, and each is hydrogen, alkyl, methoxy, halogen, hydroxy, N-(C$_2$H$_5$)$_2$, -O-(CH$_2$)$_3$N(C$_3$H$_7$)$_2$, -OCH$_2$-CH$_2$NHC(CH$_3$)$_3$, OH

-O(CH$_2$)$_3$C(CH$_3$)$_2$-CO$_2$CH$_3$, or
-14-

\[-\text{CH}_2\text{-N}(-\text{phenyl} \text{, or } R^2 \text{ and } R^3 \text{ may be joined to form a ring which is})\]

5

\[\text{or}\]

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\[\text{or}\]

Further, \(R^3\) and \(R^4\) may be joined to form a ring which is

Particularly valuable compounds of Formula I and Formula II are selected from the group consisting of:

3,5,7-Trihydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one;

2-(3-Amino-phenyl)-8-methoxy-chromen-4-one;

6-Methyl-2-[2-(3,4,5-trimethoxy-benzylamino)-phenyl]-chromen-4-one;

3-Benzy1-7-diethylamino-4-methyl-chromen-2-one;

7,8-Dihydroxy-4-methyl-chromen-2-one;

6-Hydroxy-4-methyl-chromen-2-one;

5,7-Dihydroxy-4-methyl-chromen-2-one;

6-Dodecyl-7-hydroxy-4-methyl-chromen-2-one;

7-Hydroxy-chromen-2-one;

3-(4-Amino-phenyl)-chromen-2-one;

7-Hydroxy-3-(4-hydroxy-phenyl)-chromen-2-one;

3-Hydroxy-benzo[c]chromen-6-one;

7-Hydroxy-4-(4-hydroxy-phenyl)-3-phenyl-chromen-2-one;

4-(4-Methoxy-phenyl)-7-methyl-3-phenyl-chromen-2-one;

7-Methoxy-4-(4-methoxy-benzyl)-3-phenyl-chromen-2-one;

3-(4-Amino-phenyl)-7-hydroxy-chromen-2-one;
7-(3-Tert-butylamino-2-hydroxy-propoxy)-4-methyl-chromen-2-one;
3-Benzyl-4-hydroxy-6-methyl-chromen-2-one;
3-Benzyl-4-hydroxy-8-methyl-chromen-2-one;
3-(Benzylamino-methyl)-4-hydroxy-chromen-2-one;
4-[(3,4-Dimethyl-phenylamino)-methyl]-chromen-2-one;
2-(4-Hydroxy-benzyl)-benzo[f]chromen-3-one;
2,2-Dimethyl-5-(2-oxo-2H-chromen-7-yloxy)-pentanoic acid methyl ester;
2,2-Dimethyl-5-(4-methyl-2-oxo-2H-chromen-7-yloxy)-pentanoic acid methyl ester;
3-(4-Amino-benzyl)-chromen-2-one;
3-(4-Amino-phenyl)-4-hydroxy-chromen-2-one;
3-(4-Hydroxy-phenyl)-chromen-2-one;
3-Pyridin-4-yl-chromen-2-one;
1-Methyl-3-[4-(2-oxo-2H-chromen-3-yl)-phenyl]-thiourea;
3-(4-Amino-phenyl)-8-methoxy-chromen-2-one;
4-Mercapto-chromen-2-one;
7-(3-Dipropylamino-propoxy)-4-methyl-chromen-2-one;
4-Amino-chromen-2-one;
2-Oxo-2H-chromene-3-carboxylic acid octadec-9-enyl ester;
6-(4-Phenyl-piperazin-1-ylmethyl)-chromen-2-one;
4,7-Dihydroxy-8-methyl-chromen-2-one;
4-(4-Amino-phenyl)-7-methoxy-3-phenyl-chromen-2-one;
4-Hydroxy-3-[3-(4-methoxy-phenoxyl)-propyl]-chromen-2-one;
6-Chloro-4-hydroxy-3-(3-phenoxy-propyl)-chromen-2-one;
4-Hydroxy-3-(3-phenylsulfanyl-propyl)-chromen-2-one;
3-[3-(3-Amino-phenoxy)-propyl]-4-hydroxy-chromen-2-one;
4-Hydroxy-3-(3-hydroxy-propyl)-chromen-2-one;
2-Oxo-2H-chromene-3-carbothioic acid amide;
5-Methoxy-furo[3,2-g]chromen-7-one;
5-Hydroxy-2-(4-hydroxy-phenyl)-3,6,7,8-tetramethoxy-chromen-4-one;
2-Phenyl-chromen-4-one;
2-(3-Hydroxy-phenyl)-chromen-4-one;
8-Hydroxy-2-phenyl-chromen-4-one;
7-Hydroxy-2-phenyl-chromen-4-one;
2-(4-Hydroxy-phenyl)-chromen-4-one;
2-(2-Methoxy-phenyl)-chromen-4-one;
5,7-Dihydroxy-3-methoxy-2-phenyl-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-3,5-dihydroxy-7-methoxy-chromen-4-one;
5-Methoxy-2-phenyl-chromen-4-one;
6-Methoxy-2-phenyl-chromen-4-one;
2-(2-Hydroxy-phenyl)-chromen-4-one;
2-(3-Methoxy-phenyl)-chromen-4-one;
5,8-Dihydroxy-2-phenyl-chromen-4-one;
3,5,7-Trihydroxy-2-phenyl-chromen-4-one;
8-Dimethylaminomethyl-7-hydroxy-3-methyl-2-phenyl-chromen-4-one;
8-Amino-5-hydroxy-2-phenyl-chromen-4-one;
2-(2,4-Dihydroxy-phenyl)-3,5,7-trihydroxy-chromen-4-one;
5,7-Dihydroxy-2-(4-hydroxy-phenyl)-chromen-4-one;
3-(4-Dimethylamino-phenylamino)-2-phenyl-chromen-4-one;
6-Bromo-2-(5-chloro-2-hydroxy-phenyl)-chromen-4-one;
6-Chloro-2-(5-chloro-2-hydroxy-phenyl)-chromen-4-one;
2-(2-Amino-phenyl)-chromen-4-one;
6-Bromo-2-(3-hydroxy-4-methoxy-phenyl)-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-5-methoxy-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-6-methoxy-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-8-methoxy-chromen-4-one;
2-(6-Amino-benzo[1,3]dioxol-5-yl)-chromen-4-one;
2-(2-Amino-3-methoxy-phenyl)-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-7-trifluoromethyl-chromen-4-one;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)-benzonitrile;
4-(5-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
4-(6-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
2-(4-Hydroxy-phenyl)-6,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl)-5,7-dimethoxy-chromen-4-one;
6-Chloro-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-6,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl)-6,7,8-trimethoxy-chromen-4-one;
2-[2-(Methoxymethyl-amino)-phenyl]-6-methyl-chromen-4-one;
7-(4-Hydroxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3-Hydroxy-4-methoxy-phenyl)-8-isopropyl-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-6,7,8-trimethoxy-chromen-4-one;
N-[2-(6-Methyl-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
N-[2-(6-Methoxy-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
2-(3,4-Dimethoxy-phenyl)-8-isopropyl-chromen-4-one;
8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenyl-chromen-4-one;
7-(3,4-Dimethoxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3,4,5-Trimethoxy-phenyl)-benzo[g]chromen-4-one;
6-Methyl-2-[(3,4,5-trimethoxy-benzylidene)-amino]-phenyl)-chromen-4-one;
7,8-Dihydroxy-2-phenyl-chromen-4-one;
5,8-Dihydroxy-3-methyl-2-phenyl-chromen-4-one;
(5-Hydroxy-4-oxo-2-phenyl-4H-chromen-8-yloxy)-acetic acid ethyl ester;
5-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one;
8-(2-Diethylamino-ethoxy)-5-hydroxy-2-phenyl-chromen-4-one;
2-(4-Dimethylamino-phenyl)-chromen-4-one;
7-Hydroxy-6-morpholin-4-ylmethyl-2-phenyl-chromen-4-one;
7-Hydroxy-6-[(2-hydroxy-1-hydroxymethyl-1-methyl-ethylamino)-methyl]-2-phenyl-chromen-4-one;
5,6,7-Trihydroxy-2-phenyl-chromen-4-one;
3-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yloxy)-2-(3,4-dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-one;
3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-one; and
5,7-Dihydroxy-2-(4-methoxy-phenyl)-chromen-4-one; or a pharmaceutically acceptable salt thereof.
Preferred compounds used in the second embodiment of the present invention include one or more agents selected from the group consisting of an acyl CoA:cholesterol acyltransferase (ACAT) inhibitor; 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA
reductase) inhibitor; lipid regulator; and bile acid sequestrant.


Examples of lipid regulators include gemfibrozil described in U.S. Patent 3,674,836; bezafibrate
disclosed in U.S. Patent 3,781,328; clofibrate
disclosed in U.S. Patent 3,262,850; fenofibrate
disclosed in U.S. Patent 4,058,552; niacin disclosed in
U.S. Patents 3,674,836, 3,781,328, 3,262,850, and
are hereby incorporated by reference.
Methods of preparing ACAT inhibitors, HMG-CoA
reductase inhibitors, lipid regulators, and bile acid
sequestrants used in the second embodiment of the
present invention are disclosed in the aforementioned
references.
The flavones and coumarins of the present
invention are prepared by standard procedures known to
those skilled in the art. For example, methods of
preparing flavones are disclosed in "The Flavonoids"
eds., Harborne J.B., Marby T.J., and Marby H., Chapman
and Hall, London 1975:693-707; Banerji A., and
Goomer N.C., Synthesis, 1980:874; Allan J. and
Ramakrishman V.T., J. Org. Chem., 1970;35:2898; and
Example of methods of preparing coumarins are disclosed
1949;14:362; Wolbeis O.S. and Marhold H., Chem. Ber.,
Setha S.M., and Shah N.M., Chem. Rev., 1945;36:1; Meuly
1979;7:196-206, eds. Grayson M. and Eckroth D., John
Wiley, New York, New York; and Darbarwar M. and
Sundhramurthy V., Synthesis, 1982;5:337.
The flavones and coumarins are valuable agents for
the treatment of atherosclerosis, restenosis, and
immune disorders such as arthritis and transplant
rejection. The tests employed indicate that the compounds possess activity against VCAM-1 and ICAM-1.

Immunoassays for Detection of Cell-Surface Adhesion Molecules VCAM-1 and ICAM-1

Materials:

Cell Culture:
Human aortic endothelial cells (CellSystem)
Media: 50:50 mix of CS 3.0 (CellSystem) and MCDB-107 (Sigma)
10% fetal bovine serum (FBS) (Hyclone)
Tissue culture plates (24 well) (Costar)
TNF: recombinant Tumor necrosis factor-alpha (Genzyme)

Immunoassays:
10% buffered Formalin (Baxter)
Dulbecco's modified eagle medium (DMEM), Phosphate buffered saline (PBS) (Gibco)
Bovine serum albumin (BSA) (Sigma)
Anti-ICAM-1 antibody (R&D System, BBA#3)
Sheep anti-mouse IgG (Cappel, #55558)
Horseradish peroxidase (HRP)-KIT (Bio-Rad, #172-1064)
Anti-VCAM-1 antibody (R&D System, BBA#6)
Goat anti-mouse IgG+IgM, F(ab)2 fragments, biotin conjugated (Jackson Immuno Research Lab, #115-066-068)
125-I-Streptavidin (Amersham, #IM.236)

Methods:
Human aortic endothelial cells (HAEC) were seeded at 100,000 cells/mL/well in 24 well cluster plates and placed in a 5% CO₂ to 95% O₂ humidified incubator at 37°C. At confluence (typically after 24 hours), the cells were incubated with TNF (250 U/mL) in the
presence or absence of compounds at indicated concentrations (dissolved in dimethylsulfoxide (DMSO), 0.005% final DMSO concentration) overnight (18 hours) in the humidified incubator. After this incubation, media was removed, cells washed 3 times with PBS, and fixed for 15 minutes with 10% buffered formalin at room temperature. After removal of formalin, cells were washed 3 times with 2% BSA-DMEM and then processed separately for VCAM-1 or ICAM-1 cell-surface detection as described below.

VCAM-1 ASSAY

The cells were incubated with anti-VCAM-1 monoclonal antibody (1.25 μg/mL) for 2 hours at 37°C. The unbound antibody was aspirated, cells washed 3 times with 2% BSA-DMEM and incubated with biotin conjugated Goat anti-mouse IgG+IgM, F(ab)2 fragments (1:1000 dilution) for 1 hour at room temperature. The second antibody was then aspirated and cells washed 3 times. [125I]Streptavidin (1:60 dilution) was added and cells incubated for 15 minutes at 4°C. Cells were washed again (4 times) and digested overnight with the addition of 500 μL of 1N NaOH and radioactivity contained in the digests counted. Cell-surface VCAM-1 expression is shown as radioactivity bound to the cell surface under various conditions.

ICAM-1 ASSAY

Anti-ICAM-1 monoclonal antibody (0.5 μg/mL) was added to the cells and incubated for 2 hours at 37°C. The media was aspirated, cells washed 4 times with 2% BSA-DMEM, and second antibody added (sheep anti-mouse IgG, 1:3000 dilution), and cells incubated for 1 hour at 37°C. After removal of the unbound antibody and 4 washes with DMEM alone, the cells were incubated with the HRP color reagent for 15 minutes at 37°C in the
dark. Fifty microliters of the color reagent from each well was transferred to 96 well plates and absorbance read at 414 nm on a TiterTek ELISA reader. Cell-surface ICAM-1 expression is presented as OD$_{414}$. The data in the table show the VCAM-1 and ICAM-1 activity of representative flavones and coumarins of the present invention.
<table>
<thead>
<tr>
<th>Example</th>
<th>Compound</th>
<th>VCAM-1 (IC₅₀ = µM)</th>
<th>ICAM-1 (IC₅₀ = µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,5,7-Trihydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2-(3-Amino-phenyl)-8-methoxy-chromen-4-one</td>
<td>18.9</td>
<td>&gt;100</td>
</tr>
<tr>
<td>3</td>
<td>6-Methyl-2-[2-(3,4,5-trimethoxy-benzylamino)-phenyl]-chromen-4-one</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7,8-Dihydroxy-4-methyl-chromen-2-one</td>
<td>41.7</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5</td>
<td>6-Hydroxy-4-methyl-chromen-2-one</td>
<td>88.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>6</td>
<td>5,7-Dihydroxy-4-methyl-chromen-2-one</td>
<td>97.4</td>
<td>&gt;100</td>
</tr>
<tr>
<td>7</td>
<td>7-Hydroxy-3-(4-hydroxy-phenyl)-chromen-2-one</td>
<td>21.4</td>
<td>&gt;50</td>
</tr>
<tr>
<td>8</td>
<td>7-Hydroxy-4-(4-hydroxy-phenyl)-3-phenyl-chromen-2-one</td>
<td>13.4</td>
<td>30.0</td>
</tr>
<tr>
<td>9</td>
<td>4-{3,4-Dimethyl-phenylamino}-methyl-chromen-2-one</td>
<td>86.46</td>
<td>&gt;50</td>
</tr>
<tr>
<td>10</td>
<td>2,2-Dimethyl-5-(2-oxo-2H-chromen-7-yloxy)-pentanoic acid methyl ester</td>
<td>42.19</td>
<td>&gt;50</td>
</tr>
<tr>
<td>11</td>
<td>3-(4-Hydroxy-phenyl)-chromen-2-one</td>
<td>90.23</td>
<td>&gt;50</td>
</tr>
<tr>
<td>12</td>
<td>2-(3-Hydroxy-phenyl)-chromen-4-one</td>
<td>36.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>13</td>
<td>2-(2-Methoxy-phenyl)-chromen-4-one</td>
<td>46% at 100 µM</td>
<td>&gt;100</td>
</tr>
<tr>
<td>14</td>
<td>5,7-Dihydroxy-3-methoxy-2-phenyl-chromen-4-one</td>
<td>56.34</td>
<td>&gt;50</td>
</tr>
<tr>
<td>15</td>
<td>5-Methoxy-2-phenyl-chromen-4-one</td>
<td>28.57</td>
<td>&gt;100</td>
</tr>
<tr>
<td>16</td>
<td>2-(2-Hydroxy-phenyl)-chromen-4-one</td>
<td>77.43</td>
<td>&gt;100</td>
</tr>
<tr>
<td>17</td>
<td>2-(3-Methoxy-phenyl)-chromen-4-one</td>
<td>80.11</td>
<td>&gt;100</td>
</tr>
<tr>
<td>18</td>
<td>4-(5-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid</td>
<td>60.57</td>
<td>&gt;100</td>
</tr>
<tr>
<td>19</td>
<td>2-(4-Hydroxy-phenyl)-6,7,8-trimethoxy-chromen-4-one</td>
<td>13.71</td>
<td>&gt;50</td>
</tr>
<tr>
<td>20</td>
<td>8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenyl-chromen-4-one</td>
<td>42% at 100 µM</td>
<td>&gt;100</td>
</tr>
<tr>
<td>21</td>
<td>7,8-Dihydroxy-2-phenyl-chromen-4-one</td>
<td>36.89</td>
<td>&gt;100</td>
</tr>
<tr>
<td>22</td>
<td>(5-Hydroxy-4-oxo-2-phenyl-4H-chromen-8-yloxy)-acetic acid methyl ester</td>
<td>46% at 100 µM</td>
<td>&gt;100</td>
</tr>
<tr>
<td>23</td>
<td>8-(2-Diethylamino-ethoxy)-5-hydroxy-2-phenyl-chromen-4-one</td>
<td>14.75</td>
<td>33.61</td>
</tr>
<tr>
<td>24</td>
<td>2-(4-Dimethylamino-phenyl)-chromen-4-one</td>
<td>64.83</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
The flavones and coumarins of the present invention also have been evaluated for their ability to block leukocyte adhesion in a rat model.

It has been established for some time that the attachment and migration of bloodborne monocytes across aortic endothelial cells is among the initial events in the development of the atherosclerotic plaques (Faruqi R.M. and Dicorleto P.E., "Mechanisms of Monocyte Recruitment and Accumulation," British Heart J., 1993;69(Supp):S19-S29). This animal model assesses the effect of compounds of the present invention on the recruitment of leukocytes into vascular tissue. The animal model is based on the fact that only polymorphonuclear neutrophils and monocytes possess the enzyme myeloperoxidase. The accumulation of enzyme in the lungs is dependent on an up regulation of various adhesion molecules. Histopathological analysis has demonstrated that a majority of the cells in the lungs at 24 hours are monocytes.

PROTOCOL

Male Sprague-Dawley rats weighting approximately 300 to 350 g, were obtained from Charles River, Portage, Michigan. Test compounds were suspended in 0.5% methylcellulose and were administered by gavage on a milligram active drug moiety per kilogram body weight basis at 100 mg/kg. Glucan was suspended in sterile saline for injection at a concentration of 3.3 μg/μL. Three hundred microliter is injected in the penile vein. Two experiments were performed using three animals in three groups of control, glucan alone, and glucan and compound. Animals were dosed 18 hours before and concurrent with the glucan injection. At 4 and 24 hours, the hearts and lungs are removed and washed 3 times in normal saline solution. The lungs and hearts are placed in separate tubes containing 3 mL
of a solution of normal saline containing 1 mg/mL of aprotinin and phenylmethyl sulfonyl fluoride (PMSF). The tissue is then homogenized using a polytron on the high setting. All samples are held on ice. The samples are then aliquoted and frozen at 20°C. The myeloperoxidase assay was standardized with the linear portion of the curve identified. Lowry protein assays were performed and the samples were diluted to obtain optical densities in the linear range. To 10 parts of a 0.1 M sodium citrate buffer (pH = 5.5) is added one part of a solution 0.1% o-dianisidine in absolute ethanol and one part of a 1 mM hydrogen peroxide solution. To this working solution is added 100 μL of the diluted protein homogenate solution. The reaction is stopped after 1 minute by the addition of 1 mL of 35% perchloric acid. All reactions were run in triplicate. The absorbance at 460 nm is then measured on a Beckman DU-70 spectrophotometer.

Example 2 (2-(3-amino-phenyl)-8-methoxy-chromen-4-one) was evaluated in this glucan induced lung vasculitis model and produced 46.2% decrease in monocyte influx and no decrease in neutrophil influx.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intra-cutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered trans-dermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or Formula II or a corresponding pharmaceutically
acceptable salt of a compound of Formula I or
Formula II.

For preparing pharmaceutical compositions from the
compounds of the present invention, pharmaceutically
acceptable carriers can be either solid or liquid.
Solid form preparations include powders, tablets,
pills, capsules, cachets, suppositories, and
dispersible granules. A solid carrier can be one or
more substances which may also act as diluents,
flavoring agents, binders, preservatives, tablet
disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid
which is in a mixture with the finely divided active
component.

In tablets, the active component is mixed with the
carrier having the necessary binding properties in
suitable proportions and compacted in the shape and
size desired.

The powders and tablets preferably contain
from 5% or 10% to about 70% of the active compound.
Suitable carriers are magnesium carbonate, magnesium
stearate, talc, sugar, lactose, pectin, dextrin,
starch, gelatin, tragacanth, methylcellulose, sodium
carboxymethylcellulose, a low melting wax, cocoa
butter, and the like. The term "preparation" is
intended to include the formulation of the active
compound with encapsulating material as a carrier
providing a capsule in which the active component with
or without other carriers, is surrounded by a carrier,
which is thus in association with it. Similarly,
cachets and lozenges are included. Tablets, powders,
capsules, pills, cachets, and lozenges can be used as
solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax,
such as a mixture of fatty acid glycerides or cocoa
butter, is first melted and the active component is
dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule.
tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 200 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of atherosclerosis, restenosis, and immune disorders such as arthritis and transplant rejection, the compounds utilized in the pharmaceutical methods of this invention are administered at the initial dosage of about 0.01 mg to about 200 mg/kg daily. A daily dose range of about 0.01 mg to about 50 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art.

Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The ACAT inhibitors, HMG-CoA reductase inhibitors, lipid regulators, and bile acid sequestrants utilized in the second embodiment of the present invention are used in standard dosage amounts known in the art.
1. A method for the treatment of atherosclerosis, restenosis, immune disorders, and transport rejection in mammals in need thereof comprising administering to such mammal an effective amount of a compound selected from the group consisting of: a flavone and a coumarin, or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1, wherein a compound is selected from the group consisting of:

\[
\begin{align*}
\text{I} \\
\end{align*}
\]

wherein \( R \) is hydrogen, alkyl, alkoxy, hydroxy, \(-N-R^{10}\) wherein \( R^{10} \) and \( R^{11} \) are each independently the same or different and each is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or \( R^{10} \) and \( R^{11} \) taken together with \( N \) can form a 3 to 6 membered ring, or
R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{5}, R\textsuperscript{6}, R\textsuperscript{7}, R\textsuperscript{8}, and R\textsuperscript{9} are each independently the same or different and each is hydrogen, alkyl, alkoxy, hydroxy, halogen, CF\textsubscript{3}, CN, NO\textsubscript{2}, -N-R\textsuperscript{10} wherein R\textsuperscript{10} and R\textsuperscript{11} are as R\textsuperscript{11} defined above, -CH\textsubscript{2}-NR\textsuperscript{10} wherein R\textsuperscript{10} and R\textsuperscript{11} are as R\textsuperscript{11} defined above, -CH\textsubscript{2}OR\textsuperscript{10} wherein R\textsuperscript{10} is as defined above, -SR\textsuperscript{10} wherein R\textsuperscript{10} is as defined above, -CO\textsubscript{2}R\textsuperscript{10} wherein R\textsuperscript{10} is as defined above, -CONR\textsuperscript{10} wherein R\textsuperscript{10} and R\textsuperscript{11} are as defined above, -CH\textsubscript{2}NH-C-(CH\textsubscript{2}OH)\textsubscript{2}, \textsubscript{30} CH\textsubscript{3} \begin{array}{c} -CH- \bigcirc \
\bigcirc \end{array}, \textsubscript{35} -OCH\textsubscript{2}-CO\textsubscript{2}alkyl, -O(CH\textsubscript{2})\textsubscript{n}-N(alkyl)\textsubscript{2} wherein n is zero or an integer of 1, -NH-CH\textsubscript{2}-Oalkyl,
-NH-C-C-Oalkyl,  
\[ \text{O} \quad \text{O} \]
-NH-aryl, or
-N=CH-aryl, or \( R^2 \) and \( R^3 \)

may be joined to form a ring selected from
the group consisting of:

\[ \text{aryl} \]
and
\[ \text{aryl} \]
or

further \( R^2 \) and \( R^3 \) or \( R^7 \) and \( R^8 \) may be joined
by a methylenedioxy group; and

\[
\begin{align*}
\text{(2)}
\end{align*}
\]

wherein \( R \) is hydrogen,
alkyl,
aryl,
arylalkyl,
hydroxy,
-CH\(_2\)-NH-CH\(_2\)-aryl,
-(CH\(_2\))\(_m\)-X-aryl wherein \( m \) is zero or an
integer of 1, 2, or 3 and \( X \) is
O or S,
-(CH\(_2\))\(_3\) OH,
S

-C-NH₂, or

-O

-C-O-octadecyl-9-enyl;

R¹ is hydrogen,
alkyl,
aryl,
arylalkyl,
hydroxy,
-CH₂-NH-aryl,
-SH,
-NH₂; or

R and R¹ may be joined to form a ring which is

R², R³, R⁴, and R⁵ are each independently the same or different and each is hydrogen,
alkyl,
alkoxy,
halogen,
hydroxy,
-N(alkyl)₂,
-O(CH₂)₃N(alkyl)₂,
-OCH₂CH-CH₂NHC(CH₃)₃,

-CH-N

N-aryl ; or

R² and R³ may be joined to form a ring which is

R³ and R⁴ may be joined to form a ring which is
; or

a pharmaceutically acceptable salt of a compound of Formula I or Formula II.

3. The method of Claim 2, wherein in a compound of Formula I
R is hydrogen,
methyl,
methoxy,

\[-\text{NH-}\text{N(CH}_3\text{)}_2\;\text{, or}\]

\[-\text{O-O-O}\;\text{, or}\]

and

\[-\text{OH}\;\text{, and}\]

\[-\text{OH}\;\text{, and}\]

\[-\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{and} \text{R}^9 \text{ are each independently the same or different and each is}\]

hydrogen,
alkyl,
OCH\(_3\),
hydroxy,
halogen,
CF\(_3\),
CN,
NH\(_2\),
\(-\text{N(CH}_3\text{)}_2\),
\(-\text{CH}_2\text{N(CH}_3\text{)}_2\),
\(-\text{CO}_2\text{H}\),
\(-\text{CH}_2\text{-NH-}\text{C(CH}_2\text{OH)}_2\),
\text{CH}_3
-35-

-CH-N\(\text{O}\),

-\(\text{OCH}_2\text{-CO}_2\text{C}_2\text{H}_5\),

-\(\text{O(CH}_2\text{)}_2\text{-N(C}_2\text{H}_5\text{)}_2\),

-\(\text{NH-C-C-O-C}_2\text{H}_5\),

-\(\text{NH-aryl, or}\)

-\(\text{N=CH-aryl or R}^2\text{ and R}^3\text{ may be joined to form a ring selected from the group consisting of:}\)

\[
\begin{align*}
\text{and} \\
\text{\(\text{\text{Ring}}\) and \(\text{\text{Ring}}\)}
\end{align*}
\]

-further R\(^2\) and R\(^3\) or R\(^7\) and R\(^8\) may be joined by a methylenedioxy group; and

in a compound of Formula II

R is hydrogen,

aryl,

arylalkyl,

-\(\text{CH}_2\text{-NH-CH}_2\text{-phenyl,}\)

-\((\text{CH}_2)_3\text{-X-aryl wherein X is O or S,}\)

-\((\text{CH}_2)_3\text{OH,}\)

-\(\text{S}\)

-\(\text{C-NH}_2, \text{ or}\)

-\(\text{O}\)

-\(\text{C-O-octadecyl-9-enyl;}\)

R\(^2\), R\(^3\), R\(^4\), and R\(^5\) are each independently the same or different and each is
hydrogen,
alkyl,
methoxy,
halogen,
hydroxy,
N-(C₂H₅)₂,
-O-(CH₂)₃N(C₃H₇)₂,
-OCH₂CH-CH₂NHC(CH₃)₃,

\[ \text{OH} \]

-O(CH₂)₃C(CH₃)₂-CO₂CH₃, or

\[ \text{CH} = \text{N} \square \text{N} \text{-phenyl} \]
ror R² or R³ may be joined to form a ring which is

\[ \text{C} \text{C} \]
orfurther R³ and R⁴ may be joined to form a ring which is

4. The method of Claim 3 wherein a compound of Formula I and Formula II is selected from the group consisting of:

5

3,5,7-Trihydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one;
2-(3-Amino-phenyl)-8-methoxy-chromen-4-one;
6-Methyl-2-[2-(3,4,5-trimethoxy-benzylamino)-phenyl]-chromen-4-one;

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3-Benzyl-7-diethylamino-4-methyl-chromen-2-one;
7,8-Dihydroxy-4-methyl-chromen-2-one;
6-Hydroxy-4-methyl-chromen-2-one;
5,7-Dihydroxy-4-methyl-chromen-2-one;
6-Dodecyl-7-hydroxy-4-methyl-chromen-2-one;
7-Hydroxy-chromen-2-one;
3-(4-Amino-phenyl)-chromen-2-one;
7-Hydroxy-3-(4-hydroxy-phenyl)-chromen-2-one;
3-Hydroxy-benzo[c]chromen-6-one;
7-Hydroxy-4-(4-hydroxy-phenyl)-3-phenyl-
chromen-2-one;
4-(4-Methoxy-phenyl)-7-methyl-3-phenyl-
chromen-2-one;
7-Methoxy-4(4-methoxy-benzyl)-3-phenyl-
chromen-2-one;
3-(4-Amino-phenyl)-7-hydroxy-chromen-2-one;
7-(3-Tert-butylamino-2-hydroxy-proproxy)-4-
methyl-chromen-2-one;
3-Benzyl-4-hydroxy-6-methyl-chromen-2-one;
3-Benzyl-4-hydroxy-8-methyl-chromen-2-one;
3-(Benzylamino-methyl)-4-hydroxy-chromen-2-
one;
4-[(3,4-Dimethyl-phenylamino)-methyl]-
chromen-2-one;
2-(4-Hydroxy-benzyl)-benzo[f]chromen-3-one;
2,2-Dimethyl-5-(2-oxo-2H-chromen-7-yloxy)-
pentanoic acid methyl ester;
2,2-Dimethyl-5-(4-methyl-2-oxo-2H-chromen-7-
yloxy)-pentanoic acid methyl ester;
3-(4-Amino-benzyl)-chromen-2-one;
3-(4-Amino-phenyl)-chromen-2-one;
3-(4-Hydroxy-phenyl)-chromen-2-one;
3-Pyridin-4-yl-chromen-2-one;
1-Methyl-3-[4-(2-oxo-2H-chromen-3-yl)-phenyl-
thiourea;
3-(4-Amino-phenyl)-8-methoxy-chromen-2-one;
4-Mercapto-chromen-2-one;
7-(3-Dipropylamino-proproxy)-4-methyl-chromen-
2-one;
4-Amino-chromen-2-one;
2-Oxo-2H-chromene-3-carboxylic acid octadec-9-enyl ester;
6-(4-Phenyl-piperazin-1-ylmethyl)-chromen-2-one;
4,7-Dihydroxy-8-methyl-chromen-2-one;
4-(4-Amino-phenyl)-7-methoxy-3-phenyl-chromen-2-one;
4-Hydroxy-3-[3-(4-methoxy-phenoxy)-propyl]-chromen-2-one;
6-Chloro-4-hydroxy-3-(3-phenoxy-propyl)-chromen-2-one;
4-Hydroxy-3-(3-phenylsulfanyl-propyl)-chromen-2-one;
3-[3-(3-Amino-phenoxy)-propyl]-4-hydroxy-chromen-2-one;
4-Hydroxy-3-(3-hydroxy-propyl)-chromen-2-one;
2-Oxo-2H-chromene-3-carbothioic acid amide;
4-Methoxy-furo[3,2-g]chromen-7-one;
5-Hydroxy-2(4-hydroxy-phenyl)-3,6,7,8-tetramethoxy-chromen-4-one;
2-Phenyl-chromen-4-one;
2-(3-Hydroxy-phenyl)-chromen-4-one;
8-Hydroxy-2-phenyl-chromen-4-one;
7-Hydroxy-2-phenyl-chromen-4-one;
2-(4-Hydroxy-phenyl)-chromen-4-one;
2-(2-Methoxy-phenyl)-chromen-4-one;
5,7-Dihydroxy-3-methoxy-2-phenyl-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-3,5-dihydroxy-7-methoxy-chromen-4-one;
5-Methoxy-2-phenyl-chromen-4-one;
6-Methoxy-2-phenyl-chromen-4-one;
2-(2-Hydroxy-phenyl)-chromen-4-one;
2-(3-Methoxy-phenyl)-chromen-4-one;
5,8-Dihydroxy-2-phenyl-chromen-4-one;
3,5,7-Trihydroxy-2-phenyl-chromen-4-one;
8-Dimethylaminomethyl-7-hydroxy-3-methyl-2-phenyl-chromen 4-one;
8-Amino-5-hydroxy-2-phenyl-chromen-4-one;
2-(2,4-Dihydroxy-phenyl)-3,5,7-trihydroxy-chromen-4-one;
5,7-Dihydroxy-2-(4-hydroxy-phenyl)-chromen-4-one;
3-(4-Dimethylamino-phenylamino)-2-phenyl-chromen-4-one;
6-Bromo-2-(5-chloro-2-hydroxy-phenyl)-chromen-4-one;
6-Chloro-2-(5-chloro-2-hydroxy-phenyl)-chromen-4-one;
2-(2-Amino-phenyl)-chromen-4-one;
6-Bromo-2-(3-hydroxy-4-methoxy-phenyl)-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-5-methoxy-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-6-methoxy-chromen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-8-methoxy-chromen-4-one;
2-(6-Amino-benzo[1,3]dioxol-5-yl)chromen-4-one;
2-(2-Amino-3-methoxy-phenyl)-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-7-trifluoromethyl-chromen-4-one;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)benzonitrile;
4-(5-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
4-(6-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic acid;
2-(4-Hydroxy-phenyl) 4,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl) 5,7-dimethoxy-chromen-4-one;
6-Chloro-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl) 6,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl) 6,7,8-trimethoxy-chromen-4-one;
2-[2-(Methoxymethyl-amino)-phenyl]-6-methyl-chromen-4-one;
7-(4-Hydroxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3-Hydroxy-4-methoxy-phenyl)-8-isopropyl-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-6,7,8-trimethoxy-chromen-4-one;
N-[2-(6-Methyl-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
N-[2-(6-Methoxy-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
2-(3,4-Dimethoxy-phenyl)-8-isopropyl-chromen-4-one;
8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenyl-chromen-4-one;
7-(3,4-Dimethoxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3,4,5-Trimethoxy-phenyl)benzo[g]chromen-4-one;
6-Methyl-2-{2-[(3,4,5-trimethoxy-benzylidene)-amino]-phenyl}-chromen-4-one;
7,8-Dihydroxy-2-phenyl-chromen-4-one;
5,8-Dihydroxy-3-methyl-2-phenyl-chromen-4-one;
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(5-Hydroxy-4-oxo-2-phenyl-4H-chromen-8-yloxy)-acetic acid ethyl ester;
5-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one;
8-(2-Diethylamino-ethoxy)-5-hydroxy-2-phenyl-chromen-4-one;
2-(4-Dimethylamino-phenyl)-chromen-4-one;
7-Hydroxy-6-morpholin-4-ylmethyl-2-phenyl-chromen-4-one;
7-Hydroxy-6-[(2-hydroxy-1-hydroxymethyl-1-methyl-ethylamino)-methyl]-2-phenyl-chromen-4-one;
5,6,7-Trihydroxy-2-phenyl-chromen-4-one;
3-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-
furan-2-yloxy)-2-(3,4-dihydroxy-phenyl)-5,7-
dihydroxy-chromen-4-one;
3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxy-
phenyl)-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-5,7-dihydroxy-
chromen-4-one; and
5,7-Dihydroxy-2-(4-methoxy-phenyl)-chromen-4-one.

5. A pharmaceutical composition for the treatment of atherosclerosis, restenosis, immune disorders, and transport rejection in mammals in need thereof comprising administering to such mammal a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

6. A method for the treatment of atherosclerosis in mammals in need thereof comprising administering to such mammal an effective amount of a compound selected from the group consisting of: a flavone and a coumarin in combination with one or more agents selected from the group consisting of:
7. The method of Claim 6 wherein a compound is selected from the group consisting of:

\[ \text{I} \]

wherein \( R \) is hydrogen, alkyl, alkoxy, hydroxy, 
-\( \text{N-}R^{10} \) wherein \( R^{10} \) and \( R^{11} \) are each \( R^{11} \) independently the same or different and each is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or 
\( R^{10} \) and \( R^{11} \) taken together with \( N \) can form a 3- to 6-membered ring, or
R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently the same or different and each is hydrogen, alkyl, alkoxy, hydroxy, halogen, CF₃, CN, NO₂, -N-R¹⁰ wherein R¹⁰ and R¹¹ are as defined above, -CH₂-NR¹⁰ wherein R¹⁰ and R¹¹ are as defined above, -CH₂OR¹⁰ wherein R¹⁰ is as defined above, -SR¹⁰ wherein R¹⁰ is as defined above, -CO₂R¹⁰ wherein R¹⁰ is as defined above, -CONR¹⁰ wherein R¹⁰ and R¹¹ are as defined above, -CH₂NH-C-(CH₂OH)₂, -CH₂-CO₂alkyl, -O(CH₂)ₙ-N(alkyl)₂ wherein n is zero or an integer of 1, -NH-CH₂-Oalkyl,
-44-

-NH-C-C-Oalkyl,

-NH-aryl, or

-N=CH-aryl, or R² and R³ may be joined to
form a ring selected from the
group consisting of:

\[
\text{and}
\]

\[
\text{or}
\]

further, R² and R³ or R⁷ and R⁸ may be joined
by a methylenedioxy group; and

\[
(2)
\]

wherein R is hydrogen,

alkyl,
aryl,
arylalkyl,
hydroxy,
-CH₂-NH-CH₂-aryl,
-(CH₂)ₘ-X-aryl wherein m is zero or an
integer of 1, 2, or 3 and X is
0 or S,
-(CH₂)₃OH,

\[
\]
-45-

S
\[ -C-NH_2, \text{ or} \]
\[ O \]
\[ -C-O-octadecyl-9-etyl; \]

R\(^1\) is hydrogen,
aldehyde,
aryl,
arylalkyl,
hydroxy,
-CH\(_2\)-NH-aryl,
-SH,
-NH\(_2\); or

R and R\(^1\) may be joined to form a ring which is

\[ \]

R\(^2\), R\(^3\), R\(^4\), and R\(^5\) are each independently the same
or different and each is hydrogen,
aldehyde,
alkeoxy,
halogen,
hydroxy,
-N(alkyl)\(_2\),
-O(CH\(_2\))\(_3\)N(alkyl)\(_2\),
-OCH\(_2\)CH-CH\(_2\)NHC(CH\(_3\))\(_3\),

\[ \text{OH} \]

-O(CH\(_2\))\(_3\)-C(CH\(_3\))\(_2\)-CO\(_2\)alkyl, or

\[ \]

R\(^2\) and R\(^3\) may be joined to form a ring which is

\[ \]

or further,

R\(^3\) and R\(^4\) may be joined to form a ring which is
in combination with one or more agents selected from the group consisting of:
(a) ACAT inhibitor;
(b) HMG-CoA reductase inhibitor;
(c) Lipid regulator; and
(d) Bile acid sequestrant;
or a pharmaceutically acceptable salt thereof.

8. The method of Claim 7 wherein in a compound of Formula I R is hydrogen, methyl, methoxy,

\[ -\text{NH-} - \text{N}\left(\text{CH}_3\right)_2 \quad \text{or} \]

\[ -\text{O-} - \text{O} \quad \text{and} \]

\[ R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, \text{ and } R^9 \text{ are each independently the same or different and each is hydrogen, alkyl, OCH}_3, \]

\[ \text{hydroxy, halogen, CF}_3, \]

CN, NH\(_2\), -N(CH\(_3\))\(_2\), -CH\(_2\)N(CH\(_3\))\(_2\), -CO\(_2\)H,
-47-

-CH₂-NH-C(CH₂OH)₂,
  \[ \text{CH₃} \]

-CH₂-N\[ \text{O} \]

-OCH₂-CO₂C₂H₅,
-\((\text{CH₂})₂\)-N(C₂H₅)₂,
-NH-C-C-O-C₂H₅,
  \[ \text{O} \]

-NH-aryl, or
-N=CH-aryl or R² and R³ may be joined to form a ring selected from the group consisting of:

\[ \text{and} \]

\[ ; \text{or further,} \]

R² and R³ or R⁷ and R⁸ may be joined by a methylenedioxy group; and in a compound of Formula II R is hydrogen,
aryl,
arylalkyl,
-CH₂-NH-CH₂-phenyl,
-(CH₂)₃-X-aryl wherein X is O or S,
-(CH₂)₃OH,

-\[ \text{O} \]

-S\[ \text{C-NH₂} \], or
-O\[ \text{C-O-octadecyl-9-enyl} \];
R², R³, R⁴, and R⁵ are each independently the same or different and each is hydrogen, alkyl, methoxy, halogen, hydroxy, N-(C₂H₅)₂, O-(CH₂)₃N(C₃H₇)₂, OCH₂CH-CH₂NHC(CH₃)₃, or -CH₂O(CH₂)₃C(CH₃)₂-CO₂CH₃, or

\[ \text{-CH-N} \bigg( \bigg)_{\text{N-phenyl}}, \text{or} \]

R² and R³ may be joined to form a ring which is

\[ \text{C-C}, \text{or} \]

further, R³ and R⁴ may be joined to form a ring which is

9. The method of Claim 8 wherein a compound of Formula I and Formula II is selected from the group consisting of:

3,5,7-Trihydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one;
2-(3-Amino-phenyl)-8-methoxy-chromen-4-one;
6-Methyl-2-[2-(3,4,5-trimethoxy-benzylamino)-phenyl]-chromen-4-one;
3-Benzyl-7-diethylamino-4-methyl-chromen-2-one;
7,8-Dihydroxy-4-methyl-chromen-2-one;
6-Hydroxy-4-methyl-chromen-2-one;
5,7-Dihydroxy-4-methyl-chromen-2-one;
6-Dodecyl-7-hydroxy-4-methyl-chromen-2-one;
7-Hydroxy-chromen-2-one;
3-(4-Amino-phenyl)-chromen-2-one;
7-Hydroxy-3-(4-hydroxy-phenyl)-chromen-2-one;
3-Hydroxy-benzo[c]chromen-6-one;
7-Hydroxy-4-(4-hydroxy-phenyl)-3-phenyl-chromen-2-one;
4-(4-Methoxy-phenyl)-7-methyl-3-phenyl-chromen-2-one;
7-Methoxy-4(4-methoxy-benzyl)-3-phenyl-chromen-2-one;
3-(4-Amino-phenyl)-7-hydroxy-chromen-2-one;
7-(3-tert-Butylamino-2-hydroxy-propoxy)-4-methyl-chromen-2-one;
3-Benzyl-4-hydroxy-6-methyl-chromen-2-one;
3-Benzyl-4-hydroxy-8-methyl-chromen-2-one;
3-(Benzylamino-methyl)-4-hydroxy-chromen-2-one;
4-[(3,4-Dimethyl-phenylamino)-methyl]-chromen-2-one;
2-(4-Hydroxy-benzyl)-benzo[f]chromen-3-one;
2,2-Dimethyl-5-(2-oxo-2H-chromen-7-yloxy)-pentanoic acid methyl ester;
2,2-Dimethyl-5-(4-methyl-2-oxo-2H-chromen-7-yloxy)-pentanoic acid methyl ester;
3-(4-Amino-benzyl)-chromen-2-one;
3-(4-Amino-phenyl)-4-hydroxy-chromen-2-one;
3-(4-Hydroxy-phenyl)-chromen-2-one;
3-Pyridin-4-yl-chromen-2-one;
1-Methyl-3-[4-(2-oxo-2H-chromen-3-yl)-phenyl-thiourea;
3-(4-Amino-phenyl)-8-methoxy-chromen-2-one;
4-Mercapto-chromen-2-one;
7-(3-Dipropylamino-propoxy)-4-methyl-chromen-2-one;
4-Amino-chromen-2-one;
2-Oxo-2H-chromene-3-carboxylic acid octadec-9-ethyl ester;
6-(4-Phenyl-piperazin-1-ylmethyl)-chromen-2-one;
4,7-Dihydroxy-8-methyl-chromen-2-one;
4-(4-Amino-phenyl)-7-methoxy-3-phenyl-chromen-2-one;
4-Hydroxy-3-[3-(4-methoxy-phenoxy)-propyl]-chromen-2-one;
6-Chloro-4-hydroxy-3-(3-phenoxy-propyl)-chromen-2-one;
4-Hydroxy-3-(3-phenylsulfanyl-propyl)-chromen-2-one;
3-[3-(3-Amino-phenoxy)-propyl]-4-hydroxy-chromen-2-one;
4-Hydroxy-3-(3-hydroxy-propyl)-chromen-2-one;
2-Oxo-2H-chromene-3-carbothioic acid amide;
4-Methoxy-furo[3,2-g]chromen-7-one;
5-Hydroxy-2-(4-hydroxy-phenyl)-3,6,7,8-tetramethoxy-chromen-4-one;
2-Phenyl-chromen-4-one;
2-(3-Hydroxy-phenyl)-chromen-4-one;
8-Hydroxy-2-phenyl-chromen-4-one;
7-Hydroxy-2-phenyl-chromen-4-one;
2-(4-Hydroxy-phenyl)-chromen-4-one;
2-(2-Methoxy-phenyl)-chromen-4-one;
5,7-Dihydroxy-3-methoxy-2-phenyl-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-3,5-dihydroxy-7-methoxy-chromen-4-one;
5-Methoxy-2-phenyl-chromen-4-one;
6-Methoxy-2-phenyl-chromen-4-one;
2-(2-Hydroxy-phenyl)-chromen-4-one;
2-(3-Methoxy-phenyl)-chromen-4-one;
5,8-Dihydroxy-2-phenyl-chromen-4-one;
3,5,7-Trihydroxy-2-phenyl-chromen-4-one;
8-Dimethylaminomethyl-7-hydroxy-3-methyl-2-
phenyl-chromen-4-one;
8-Amino-5-hydroxy-2-phenyl-chromen-4-one;
2-(2,4-Dihydroxy-phenyl)-3,5,7-trihydroxy-
chomen-4-one;
5,7-Dihydroxy-2-(4-hydroxy-phenyl)-chomen-4-
one;
3-(4-Dimethylamino-phenylamino)-2-phenyl-
chomen-4-one;
6-Bromo-2-(5-chloro-2-hydroxy-phenyl)-
chomen-4-one;
6-Chloro-2-(5-chloro-2-hydroxy-phenyl)-
chomen-4-one;
2-(2-Amino-phenyl)-chomen-4-one;
6-Bromo-2-(3-hydroxy-4-methoxy-phenyl)-
chomen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-5-methoxy-
chomen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-6-methoxy-
chomen-4-one;
2-(5-Chloro-2-hydroxy-phenyl)-8-methoxy-
chomen-4-one;
2-(6-Amino-benzo[1,3]dioxol-5-yl)chomen-4-
one;
2-(2-Amino-3-methoxy-phenyl)-chomen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-7-
trifluoromethyl-chromen-4-one;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)-
benzonitrile;
4-(5-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic
acid;
4-(6-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic
acid;
3-(8-Methoxy-4-oxo-4H-chromen-2-yl)-benzoic
acid;
2-(4-Hydroxy-phenyl)-6,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl)-5,7-dimethoxy-chromen-4-one;
6-Chloro-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-6,7-dimethoxy-chromen-4-one;
2-(4-Hydroxy-phenyl)-6,7,8-trimethoxy-chromen-4-one;
2-[2-(Methoxymethyl-amino)-phenyl]-6-methyl-chromen-4-one;
7-(4-Hydroxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3-Hydroxy-4-methoxy-phenyl)-8-isopropyl-chromen-4-one;
2-(3-Hydroxy-4-methoxy-phenyl)-6,7,8-trimethoxy-chromen-4-one;
N-[2-(6-Methyl-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
N-[2-(6-Methoxy-4-oxo-4H-chromen-2-yl)-phenyl]-oxalamic acid ethyl ester;
2-(3,4-Dimethoxy-phenyl)-8-isopropyl-chromen-4-one;
8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenyl-chromen-4-one;
7-(3,4-Dimethoxy-phenyl)-4,9-dimethoxy-furo[3,2-g]chromen-5-one;
2-(3,4,5-Trimethoxy-phenyl)-benzo[g]chromen-4-one;
6-Methyl-2-2-[(3,4,5-trimethoxy-benzylidene)-amino]-phenyl)-chromen-4-one;
7,8-Dihydroxy-2-phenyl-chromen-4-one;
5,8-Dihydroxy-3-methyl-2-phenyl-chromen-4-one;
(5-Hydroxy-4-oxo-2-phenyl-4H-chromen-8-yloxy)-acetic acid ethyl ester;
5-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one;
8-(2-Diethylamino-ethoxy)-5-hydroxy-2-phenyl-chromen-4-one;
2-(4-Dimethylamino-phenyl)-chromen-4-one;
7-Hydroxy-6-morpholin-4-ylmethyl-2-phenyl-chromen-4-one;
7-Hydroxy-6-[(2-hydroxy-1-hydroxymethyl-1-methyl-ethylamino)-methyl]-2-phenyl-chromen-4-one;
5,6,7-Trihydroxy-2-phenyl-chromen-4-one;
3-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yloxy)-2-(3,4-dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-one;
3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chromen-4-one;
2-(3,4-Dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-one; and
5,7-Dihydroxy-2-(4-methoxy-phenyl)-chromen-4-one.

10. A pharmaceutical composition for the treatment of atherosclerosis in mammals in need thereof comprising administering to such mammal a therapeutically effective amount of a compound in combination with one or more agents according to Claim 6 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.