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Magnin et al.

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[54] **α-PHOSPHONOSULFONATE SQUALENE SYNTHETASE INHIBITORS**

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[21] Appl. No.: **266,888**

[22] Filed: **Jul. 5, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 109,762, Aug. 20, 1993, abandoned, which is a continuation-in-part of Ser. No. 967,904, Oct. 28, 1992, abandoned.

[51] **Int. Cl.**[6] **C07F 9/38**; C07F 9/553; C07F 9/6506; C07F 9/6512; A61K 31/66

[52] **U.S. Cl.** **546/22**; 514/94; 514/114; 514/127; 514/79; 514/80; 514/81; 514/86; 514/89; 514/92; 544/232; 544/243; 544/244; 546/23; 540/450; 540/471; 540/474; 540/542; 548/112; 548/113; 558/45; 562/17; 562/21; 562/23; 562/35

[58] **Field of Search** 558/45; 562/17, 562/21, 23, 35; 546/22, 23; 548/112, 113; 544/232, 243, 244; 540/450, 471, 474, 542; 514/27, 80, 81, 86, 89, 92, 94, 114, 127

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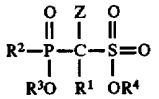
Primary Examiner—Floyd D. Higel

Attorney, Agent, or Firm—Burton Rodney

[57] **ABSTRACT**

α-Phosphonosulfonate compounds are provided which inhibit the enzyme squalene synthetase and thereby inhibit cholesterol biosynthesis. These compounds have the formula



wherein R^2 is OR^5 or R^{5a}; R^3 and R^5 are independently H, alkyl, arylalkyl, aryl or cycloalkyl; R^{5a} is H, alkyl, arylalkyl or aryl; R4 is H, alkyl, aryl, arylalkyl, or cycloalkyl;, Z is H, halogen, lower alkyl or lower alkenyl; and R^1 is a lipophilic group which contains at least 7 carbons and is alkyl, alkenyl, alkynyl, mixed alkenyl-alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl; as further defined above; including pharmaceutically acceptable salts and or prodrug esters of the phosphonic (phosphinic) and/or sulfonic acids.

26 Claims, No Drawings

α-PHOSPHONOSULFONATE SQUALENE SYNTHETASE INHIBITORS

This is a continuation of application Ser. No. 109,762, filed Aug. 20, 1993, now abandoned, which is a continuation-in-part of application Ser. No. 967,904, filed Oct. 28, 1992, now abandoned.

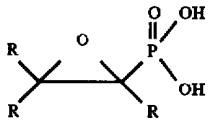
FIELD OF THE INVENTION

The present invention relates to new α-phosphonosulfonate compounds which are useful in inhibiting cholesterol biosynthesis by inhibiting de novo squalene production, to hypocholesterolemic and antiatherosclerotic compositions containing such compounds and to a method of using such compounds for inhibiting cholesterol biosynthesis and atherosclerosis.

BACKGROUND OF THE INVENTION

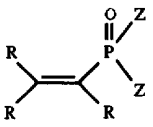
Squalene synthetase is a microsomal enzyme which catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) in the presence of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) to form squalene (Poulter, C. D.; Rilling, H. C., in "Biosynthesis of Isoprenoid Compounds", Vol. I, Chapter 8, pp. 413–441, J. Wiley and Sons, 1981, and references therein). This enzyme is the first committed step of the de novo cholesterol biosynthetic pathway. The selective inhibition of this step should allow the essential pathways to isopentenyl tRNA, ubiquinone, and dolichol to proceed unimpeded. Squalene synthetase along with HMG-CoA reductase have been shown to be down-regulated by receptor mediated LDL uptake (Faust, J. R.; Goldstein, J. L.; Brown, M. S. *Proc. Nat. Acad. Sci. U.S.A.* 1979, 76, 5018–5022), lending credence to the proposal that inhibiting squalene synthetase will lead to an up-regulation of LDL receptor levels, as has been demonstrated for HMG-CoA reductase, and thus ultimately should be useful for the treatment and prevention of hypercholesterolemia and atherosclerosis.

U.S. Pat. No. 3,657,282 (Merck) (Division U.S. Pat. No. 3,822,296) discloses antibiotics of the structure



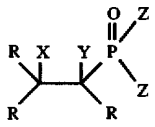
wherein R=SO_3H, SO_2R*, H, hydrocarbyl other than alkyl (eg. alkenyl, alkynyl, phenyl and naphthyl), substituted hydrocarbyl, CO_2H, CO_2R*, SO_3NR_2, heterocycle*, amino*, OH, OR, SH, SR, CHO, halogen, NO_2, CN, PO_3H_2, AsO_3H_2, acyl, —CHR^1R^3 where R^1=H, Me; R^3=R as above, preferably at least one R not =H, R preferably contains 1–10 carbons. *=optionally substituted.

Starting materials employed to prepare the above antibiotics include



via epoxidation

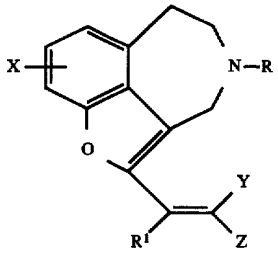
-continued



via ring closure

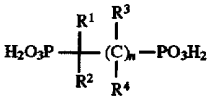
wherein R can be SO_3H, and X and Y are hydroxy or functional equivalent precursor to epoxide: eg. OH, halo, azide, RCO_2—, RSO_2O—, R_2S^+—, R_3N^+—, ArO—, R_2PO_2—, RSO_2NR^1—. One of X and Y must be an oxygen radical.

EP 89/0-344-980 (Smith Kline) discloses α-antagonists of the structure



wherein Y or Z may be —SO_2R, —P(R)O(OR), —PR_2O, —$PO(OR)_2$, and amides.

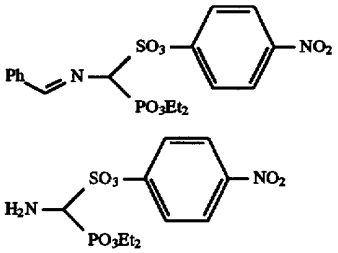
WO 88/00061 (Amersham) discloses Technetium-99 complexes for bone scanning having the structure



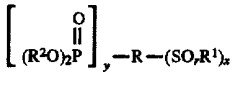
wherein R^1 and R^3=H, SO_3H or alkyl substituted with SO_3H and optionally one or more heteroatoms; R^4 can also be SO_3H or OH, NH_2, NHMe, NMe_2, lower alkyl substituted with a polar group;

R^2=same as R^4 except not SO_3H and n=0, 1.

U.S. Pat. No. 4,032,521 (Merck) discloses inter-mediates, in cephalosporin synthesis, of the structures



WO 90/07513 (Gas Research Institue) discloses electrolytes for fuel cells of the structure



wherein R=organic radicals with 1 or more F atoms;

R^1=H, alkali metal, Zn, Cd;

R^2=H, lower alkyl;

r=2, 3; and x, y=1, 2, 3.

U.S. Pat. No. 4,254,215 (Ciba Geigy AG) discloses a process for photographic developers wherein one component of a developer solution is:

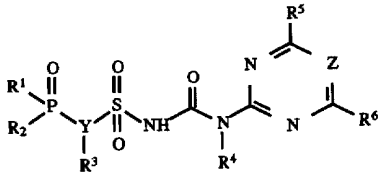
$$HS—D—(W)_n$$

wherein n=1 to 4.

D=optionally substituted, saturated or unsaturated aliphatic radical (<40 carbons), can be interrupted by heteroatoms such as O, SO_2, NH, NR.

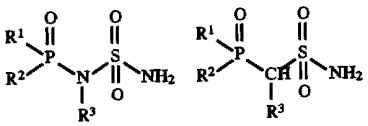
W=PO_3R_2, SO_3R, SO_2R, —NY—SO_3R, —SO_2NR_2, —SSO_3R, CO_2R, OH, NR_3^+, NR_2, $CONR_2$.

DE 89/3739691-A (Hoechst) (Derwent #89-173507/24) discloses herbicides and plant growth regulators of the structure



wherein Y=CH, N; X=O, S; Z=CH, N; R^1, R^2=C1–C6 alkyl or alkoxy; R^3=H, C1–C6 alkyl or alkoxy, C2–C6 alkenyl, alkynyl, alkenyloxy, alkynyloxy; all optionally substituted with one or more halogens; and R^4=H, C1–C4 alkyl or physiologically acceptable cation.

New intermediates are disclosed of the structures



Burton, D. J., J. Am. Chem. Soc. 1989, 111, 1773–1776 discloses electrolytes and chelators of the structures

$(HO)_2P(O)CF_2SO_3Na$ $(HO)_2P(O)CF_2SO_3H$

Su, D.; Cen. W.; Kirchmeier, R. L.; Shreeve, J. M., Can. J. Chem. 1989, 67, 1795–1799, disclose electrolytes and chelators of the structures

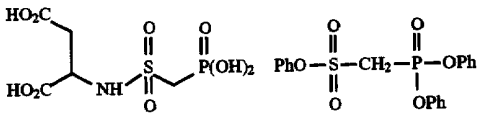
$(C_2H_5O)_2P(O)CFBrSO_3Na$ $(C_2H_5O)_2P(O)CFHSO_3Na$

$(HO)_2P(O)CFHSO_3Na$ $(HO)_2P(O)CFHSO_3H$

$(C_2H_5O)_2P(O)CF(SO_3Na)(SO_2Na)$

$(C_2H_5O)_2P(O)CF(SO_3Na)_2$

Farrington, G. K.; Kumar, A.; Wedler, F. C., J. Med. Chem. 1985, 28, 1668–1673 discloses compound 10 as an inhibitor of aspartate transcarbamylase. Compound 24 is a synthetic intermediate.



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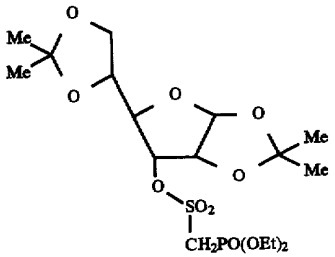
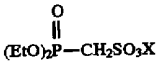
Musicki, B.; Widlanski, T. S. Tetrahedron Lett. 1991, 32, 1267–1270 discloses compound 4 as a synthetic intermediate.



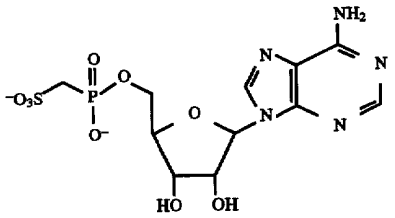
Carretero, J. C.; Demillequand, M.; Ghosez, L., Tetrahedron 1987, 43, 5125–5134 discloses



1a X = Et
1b X = i-Pr
2a X = Li
2b X = n-Bu_4N

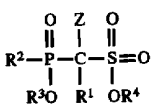
for use in the synthesis of vinyl phosphonates via a Horner-Emmons reaction.

Callahan, L.; Ng, K.; Geller, D. H.; Agarwal, K.; Schwartz, N. B., Analytical Biochemistry 1989, 177, 67–71 discloses an analog of ADP (adenosine diphosphate) of the structure



DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided α-phosphonosulfonate compounds which inhibit cholesterol biosynthesis, and thus are useful as hypocholesterolemic and antiatherosclerotic agents and have the following structure I.



I

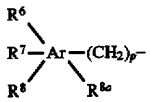
wherein R^2 is OR^5 or R^{5a}, R^3 and R^5 are the same or different and are H, alkyl, arylalkyl, aryl, cycloalkyl, a metal ion or other pharmaceutically acceptable cations as defined below, or a prodrug ester;

R^{5a} is H, alkyl, arylalkyl or aryl;

R^4 is H, alkyl, cycloalkyl, aryl, aryl-alkyl, metal ion or other pharmaceutically acceptable cations as defined below, or a prodrug ester;

Z is H, halogen, lower alkyl or lower alkenyl;

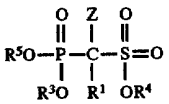
R^1 a lipophilic group containing at least 7 carbons and is alkyl containing 7 to 25 carbons in the chain; alkenyl containing from 7 to 25 carbon atoms in the chain and from 1 to 6 double bonds; alkynyl containing 1 to 6 triple bonds; mixed alkenyl-alkynyl containing 1 to 5 double bonds and 1 to 5 triple bonds; and where in the above groups alkenyl and/or alkynyl may be substituted or unsubstituted; cycloalkyl; cycloheteroalkyl linked through a carbon on the ring or a heteroatom; aryl; heteroaryl; heteroarylalkyl; cycloalkylalkyl; cycloheteroalkylalkyl; or a group of the structure



wherein Ar is aryl (such as phenyl or naphthyl), heteroaryl (5 or 6 membered) and may include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl) and wherein $(CH_2)_p$ contains from 1 to 15 carbons, preferably 2 to 12 carbons, in the chain and may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain, and may contain an ether or amino function in the chain, and/or may include 0, 1, 2 or 3 substituents as defined below for R^6; and R^6, R^7, R^8 and R^{8a} are the same or different and are H, alkyl containing 1 to 40 carbons, preferably from 3 to 25 carbons, alkoxy containing 1 to 40 carbons, preferably from 3 to 25 carbons, alkenyl containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkenyloxy containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkynyl containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkynyloxy containing 2 to 40 carbons, preferably from 3 to 25 carbons, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, cycloalkyl, cycloalkylalkyl, Ar-alkyl, (such as arylalkyl), ArO (such as aryloxy), Ar-amino (such as arylamino), hydroxy, halogen, nitro, Ar (such as aryl), amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, alkenyl, aryl or any of the Ar groups mentioned above), thiol, alkylthio, Ar-thio (such as arylthio), alkylsulfinyl, Ar-sulfinyl (such as arylsulfinyl), alkylsulfonyl, Ar-sulfonyl (such as arylsulfonyl), carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, Ar-carbonyloxy (such as arylcarbonyloxy), Ar-carbonylamino (such as arylcarbonylamino) or alkylcarbonylamino, as well as any of the Ar groups as defined above, and preferably wherein the total number of carbons in the substituted Ar—$(CH_2)_p$— group exceeds 10 carbons; including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other FDA approved cations such as ammonium, choline, diethanolamine, ethylenediamine, and salts of naturally occuring amino acids such as arginine, lysine, alanine and the like.

The $(CH_2)_p$ group may contain 1, 2, 3 or more alkyl, alkoxy, alkenyl, alkynyl, hydroxy and/or halogen substituents as well as any of the substituents defined for R^6.

Thus, the compounds of the invention include the following sub-genuses:



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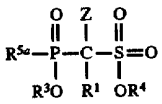

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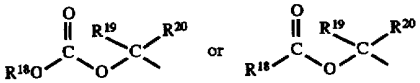
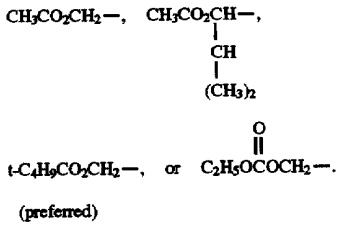
The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for both phosphorus and carboxylic acids. Examples include the following groups: (1-alkanoyloxy)alkyl such as,

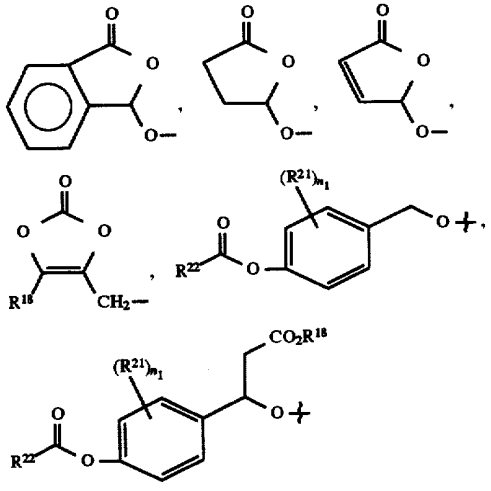


wherein R^{18}, R^{19} and R^{20} are H, alkyl, aryl or aryl-alkyl; however $R^{18}O$ cannot be HO. Examples of such prodrug esters include

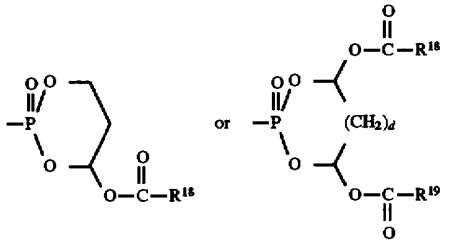


(preferred)

Other examples of suitable prodrug esters include



wherein R^{18} can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^{21} is H, alkyl, halogen or alkoxy, R^{22} is alkyl, aryl, arylalkyl or alkoxyl, and n_1 is 0, 1 or 2; or R^3 and R^5 can be linked together as in



(d is 0 to 3)

Unless otherwise indicated, the term "lower alkyl" or "alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, in the normal chain, more preferably 1 to 12 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as F, Br, Cl or I or CF_3, alkoxy, aryl, arylalkyl, alkenyl, cycloalkyl, amino, hydroxy, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated cyclic hydrocarbon groups containing 3 to 12 carbons, preferably 3 to 8 carbons, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl, any of which groups may be substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "aryl" as employed herein refers to monocyclic or bicyclic aromatic groups containing from 6 to 10 carbons in the ring portion, such as phenyl, naphthyl, or phenyl or naphthyl substituted with 1 to 4 substituents such as alkyl, halogen (Cl, Br or F), alkoxy, hydroxy, amino, alkanoylamino, arylcarbonylamino, aryl, arylalkyl, cycloalkyl, alkylamido, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

The term "aralkyl", "aryl-alkyl" or "aryl-lower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, alkyl, aralkyl or aryl groups linked to a sulfur atom.

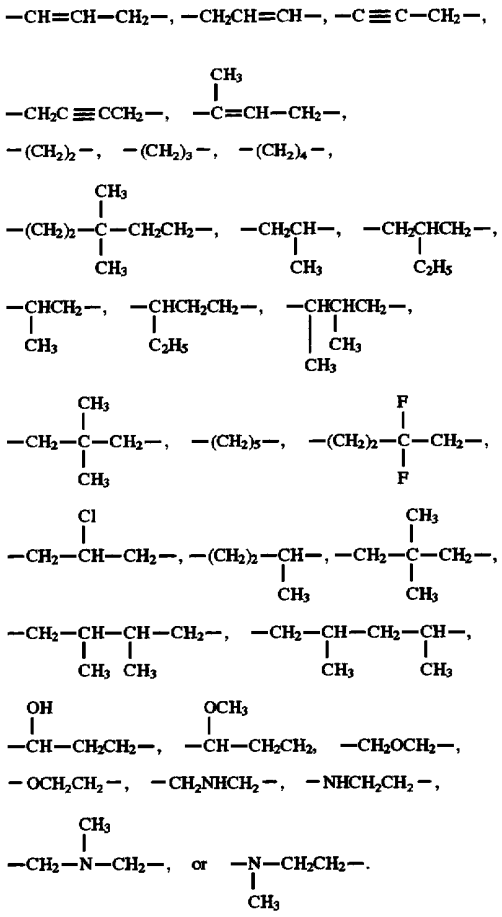
The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 40 carbons, preferably 3 to 30 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 40 carbons, preferably 2 to 20 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for R^6.

Examples of suitable $(CH_2)_p$ groups include



The term "halogen" or "halo" as used herein refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

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