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Goulet et al.

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[54] O-ARYL, O-ALKYL, O-ALKENYL AND O-ALKYNYLRAPAMYCIN DERIVATIVES

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[51] **Int. Cl.**[5] **A61K 31/395**; C07D 498/16

[52] **U.S. Cl.** **514/291**; 540/456

[58] **Field of Search** 540/456; 514/291

[56] **References Cited**

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3,929,992	12/1975	Sehgal et al.	424/122
4,650,803	3/1987	Stella et al.	514/291
5,100,883	3/1992	Schiehser	514/183
5,102,876	4/1992	Caufield	514/183
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5,118,678	6/1992	Kao et al.	514/183
5,120,725	6/1992	Kao et al.	514/183
5,120,727	6/1992	Kao et al.	514/183
5,120,842	6/1992	Failli et al.	540/452
5,138,051	8/1992	Hughes et al.	540/456
5,151,413	9/1992	Caufield et al.	514/63
5,162,333	11/1992	Failli et al.	514/291
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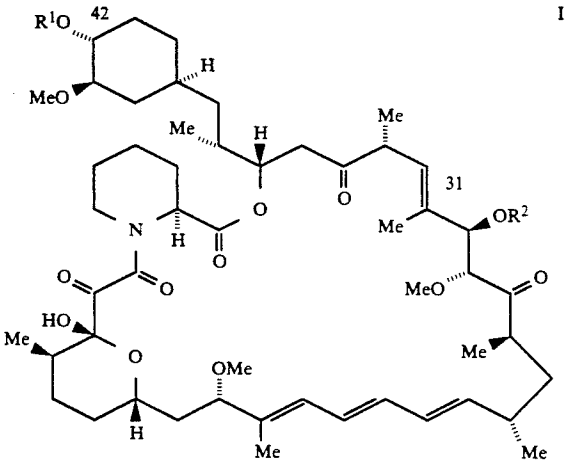
[57] **ABSTRACT**

O-Aryl, O-alkyl, O-alkenyl and O-alkynylrapamycin derivatives of the general structural Formula I:



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have been prepared from suitable precursors by alkylation and/or arylation at C-42 and/or C-31. These compounds are useful in a mammalian host for the treatment of autoimmune diseases and diseases of inflammation, infectious diseases, the prevention of rejection of foreign organ transplants and the treatment of solid tumors.

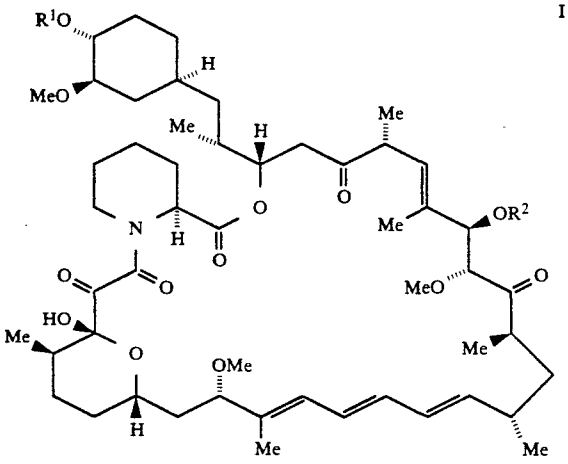
12 Claims, No Drawings

O-ARYL, O-ALKYL, O-ALKENYL AND O-ALKYNYLRAPAMYCIN DERIVATIVES

SUMMARY OF THE INVENTION

The present invention is related to O-aryl, O-alkyl, O-alkenyl and O-alkynylrapamycin derivatives which are useful in a mammalian host for the treatment of autoimmune diseases (such as juvenile-onset or recent-onset diabetes mellitus, multiple sclerosis, rheumatoid arthritis, liver disease, posterior uveitis, allergic encephalomyelitis, and glomerulonephritis), diseases of inflammation, infectious diseases (particularly fungal infections), the prevention of rejection of foreign organ transplants, e.g. bone marrow, kidney, liver, heart, skin, small-bowel, and pancreatic-islet-cell transplants, and the treatment of solid tumors.

More particularly, this invention relates to compounds of the general structural Formula I:



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wherein R^1 and R^2 are hereinafter defined.

This invention also relates to pharmaceutical compositions containing the compounds, and to a method of use of the present compounds and other agents for the treatment and prevention of certain afflictions, diseases and illnesses.

BACKGROUND OF THE INVENTION

Rapamycin characterized by Findlay and coworkers in 1978 is a 35-membered macrolide isolated from *S. hygroscopicus* (*Can. J. Chem.*, 1978, 56, 2491, *J. Antibiotics*, 1975, 28, 721, U.S. Pat. No. 3,929,992, issued Dec. 30, 1975, U.S. Pat. No. 3,993,749, issued Nov. 23, 1975. Rapamycin has been found to have antifungal activity, particularly against *Candida albicans*, both in vitro and in vivo (*J. Antibiotics*, 1978, 31, 539).

Rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with picibanil (U.S. Pat. No. 4,401,653) has been shown to have antitumor activity. R. Martel et al. (*Can, J. Physiol. Pharmacol*, 55, 48 (1977) disclosed that rapamycin is effective in an experimental allergic encephalomyelitis model, a model for multiple sclerosis; in an adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

The immunosuppressive effects of rapamycin have been disclosed (*FASEB* 3, 3411 (1989); *Med. Sci. Res.*, 1989, 17, 877). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection (*FASEB* 3, 3411 (1989); *FASEB* 3, 5256 (1989); and *Lancet* 1183 (1978)).

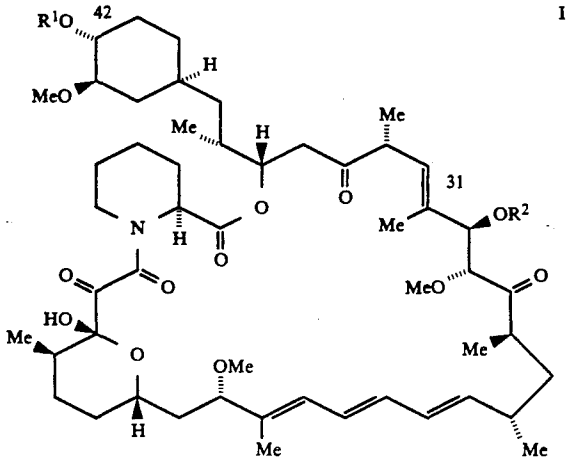
Fujisawa United States patents (U.S. Pat. No. 4,929,611, issued May 29, 1990 and U.S. Pat. No. 4,956,352, issued Sept. 11, 1990) disclose the use of FK-506-type compounds in treating resistance to transplantation. A Sandoz European patent application (*EPO Publication No.* 0,315,978) discloses the use of FR-900506 and related compounds in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illness. A Fisons World patent application (PCT Publication WO 90/14826) discloses the use of FR-900506 and related compounds in the treatment of reversible obstructive airways disease, particularly asthma. A Fujisawa European patent application (EPO Publication No. 0,423,714) discloses the use of FK-506 and derivatives as hair revitalizing agents. Various studies have suggested the efficacy of FK-506 in the treatment of a number of ailments, including rheumatoid arthitis (C. Arita, et al., *Clincial exp. Immunol.*, 1990, 82, 456–461; N. Inamura, et al., *Clin. Immunol. Immunopathol.* 1988, 46, 82–90), recent-onset diabetes (N. Murase, et al., *Diabetes.*, 1990, 39, 1584–86; N. Murase, et al., *Lancet*, 1990, 336, 373–74), posterior uveitis (H. Kawashima, *Invest. Ophthalmul, Vis. Sci.*, 1988, 29, 1265–71), hepatic injury associated with ischemia (M. Sake, et al., *Life Sci.*, 1990, 47, 687–91) allergic encephalomyelitis (K, Deguchi, et al., *Brain Nerve*, 1990, 42, 391–97), glomerulonephritis (J. McCauley, et al., *Lancet*, 1990, 335, 674), systemic lupus erythematosus (K. Takabayashi, et al., *Clin. Immunol, Immunopathol.*, 1989, 51, 110–117), multidrug resistance (M. Naito, et al., *Cancer Chemother, Pharmacol.*, 1992, 29, 195–200), inflammation of mucosa and blood vessels (PCT Publication WO 91/17754), cytomegalovirus infection (UK Publication GB 2,247,620A), and idiopathic thrombocytophenic purpura and Basedow's disease (PCT Publication WO 91/19495).

Mono- and diacylated derivatives of rapamycin (esterified at the 31 and 42 positions) have been shown to be useful as antifungal agents (U.S. Pat. No. 4,316,885) and used to make water soluble prodrugs of rapamycin (U.S. Pat. No. 4,650,803). Reduction products of rapamycin have been prepared (U.S. Pat. Nos. 5,102,876 and 5,138,051). Derivatives of rapamycin at the 31 and 42 positions which have been disclosed include: carboxylic acid esters (PCT Patent Publication WO92/05179); carbamates (U.S. Pat. No. 5.118.678); amide esters (U.S. Pat. No. 5,118,677); fluorinated esters (U.S. Pat. No. 5,100,883); acetals (U.S. Pat. No. 5,151,413); and silyl ethers (U.S. Pat. No. 5,120,842). In addition, bicyclic derivatives of rapamycin connected via the 31, 42 positions (U.S. Pat. No. 5,120,725) and rapamycin dimers connected via the 42 position (U.S. No. Pat. 5,120,727) have been disclosed. Various aryl(lower alkyl) and heteroaryl derivatives of FK-506 type compounds have also been disclosed (UK Patent Publication No. GB 2,245,891A). O-Aryl, O-alkyl, O-alkenyl and O-alkynyl derivatives of FK-506 type compounds will have been disclosed (EPO Patent Publication No. 0,515,071).

DETAILED DESCRIPTION OF THE INVENTION

A. Scope of the Invention

The novel compound of this invention has structural Formula I:



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or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 are independently selected from:

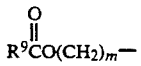
(1) hydrogen;
(2) phenyl;
(3) substituted phenyl in which the substituents are X, Y and Z;
(4) 1- or 2- naphthyl;
(5) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z;
(6) biphenyl;
(7) substituted biphenyl in which the substituents are X, Y and Z;
(8) C_{1-10} alkyl;
(9) substituted C_{1-10} alkyl in which one or more substituent(s) is(are) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} -alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) substituted phenyl-C_{1-3}alkoxy, in which the substituents on phenyl are X, Y and Z,
(f) —OCO—C_{1-6}alkyl,
(g) —NR^6R^7, wherein R^6 and R^7 are independently selected from
(i) hydrogen,
(ii) C_{1-10}alkyl unsubstituted or substituted with one or more of the substituent(s) selected from:
(a′) phenyl, which is unsubstituted or substituted with X, Y and Z,
(b′) —OH,
(c′) C_{1-6}alkoxy,
(d′) $—CO_2H$,
(e′) $—CO_2—C_{1-6}$alkyl,
(f′) $—C_{3-7}$cycloalkyl, and
(g′) $—OR^{11}$,
(iii) C_{3-10}alkenyl unsubstituted or substituted with one or more of the substituent(s) selected from:
(a′) phenyl, which is unsubstituted or substituted with X, Y and Z,
(b′) —OH,
(c′) C_{1-6}alkoxy,
(d′) CO_2H,
(e′) $—CO_2—C_{1-6}$alkyl,
(f′) $—C_{3-7}$cycloalkyl, and
(g′) $—OR^{11}$,
(iv) or where R^6 and R^7 and the N to which they are attached can form an unsubstituted or substituted 3–7-membered saturated heterocyclic ring which can include one or two additional heteroatoms independently selected from the group consisting of O $S(O)_p$, NR^{14}, wherein R^{14} is hydrogen or C_{1-6} alkyl unsubstituted or substituted by phenyl, and p is 0, 1 or 2, the ring being selected from the group consisting of: aziridine, morpholine, thiomorpholine, thiomorpholine-oxide, thiomorpholine-dioxide, piperidine, pyrrolidine, and piperazine,
(h) —$NR^6CO—C_{1-6}$alkyl-R^7, wherein R^6 is as defined above,
(i) —$NR^6CO_2—C_{1-6}$alkyl-R^7,
(j) —$NR^6CONR^6R^7$,
(k) —OCONR R^6R^7,
(l) —$COOR^6$,
(m) —CHO,
(n) phenyl,
(o) substituted phenyl in which the substituents are X, Y and Z,
(p) phenyloxy,
(q) substituted phenyloxy in which the substituents are X, Y and Z,
(r) 1- or 2- naphthyl,
(s) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
(t) biphenyl
(u) substituted biphenyl in which the substituents are X, Y and Z.
(v) —OR^{11}, and
(w) —$S(O)_p—C_{1-6}$alkyl;
(10) C_{3-10} alkenyl;
(11) substituted C_{3-10} alkenyl in which one or more substituent(s) is(are) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) substituted phenyl-C_{1-3}alkoxy, in which the substituents on phenyl are X, Y and Z,
(f) —OCO—C_{1-6}alkyl,
(g) —NR^6R^7, wherein R^6 and R^7 are as defined above
(h) —$NR^6CO—C_{1-6}$alkyl, wherein R^6 is as defined above,
(i) —$COOR^6$, wherein R^6 is as defined above,
(j) —CHO,
(k) phenyl,
(l) substituted phenyl in which the substituents are X, Y and Z,
(m) 1- or 2-naphthyl,
(n) substituted 1- or 2-naphthyl in which the substituents are X, Y and Z,
(o) biphenyl,
(p) substituted biphenyl in which the substituents are X, Y and Z,
(q) —OR^{11}, and
(r) —$S(O)_p—C_{1-6}$alkyl;
(12) C_{3-10}alkyl;

(13) substituted C_{3-10}alkynyl in which one or more substituent(s) is(are) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) substituted phenyl-C_{1-3}alkoxy, in which the substituents on phenyl are X, Y and Z,
(f) —OCO—C_{1-6}alkyl,
(g) —NR^6R^7, wherein R^6 and R^7 are as defined above,
(h) —NR^6CO—C_{1-6}alkyl, wherein R^6 is as defined above,
(i) —$COOR^6$ is as defined above,
(j) —CHO,
(k) phenyl,
(l) substituted phenyl in which the substituents are X, Y and Z,
(m) 1- or 2-naphthyl,
(n) substituted 1- or 2-naphthyl in which the substituents are X, Y and Z,
(o) biphenyl,
(p) substituted biphenyl in which the substituents are X, Y and Z, and
(q) —OR^{11};

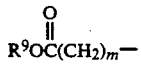
with the proviso that R^1 and R^2 are not simultaneously hydrogen;

R^{11} is selected from:
(a) —$PO(OH)O^-M^+$, wherein $M^+$is a positively charged inorganic or organic counterion,
(b) —$SO_3^-M^+$,
(c) —$CO(CH_2)_qCO_2^-M^+$, wherein q is 1–3, and
(d) —CO—C_{1-6}alkyl—NR^6R^7, wherein R^6 and R^7 are as defined above and the alkyl is unsubstituted or substituted with one or more substituents selected from:
(i) hydroxy,
(ii) C_{1-6}alkoxy,
(iii) —$NR^{16}R^{17}$, wherein R^{16} and R^{17} are independently selected from:
(a′) hydrogen, and
(b′) C_{1-6}alkyl,
(iv) —$COOR^6$, wherein R^6 is as defined above,
(v) phenyl,
(vi) substituted phenyl in which the substituents are X, Y and Z,
(vii) —SH, and
(viii) —S—C_{1-6}alkyl;

X, Y and Z independently are selected from:
(a) hydrogen,
(b) C_{1-7} alkyl,
(c) C_{2-6} alkenyl,
(d) halogen,
(e) —$(CH_2)_m$—NR^6R^7, wherein R^6 and R^7 are as defined above, and m is 0 to 2,
(f) —CN,
(g) —CHO,
(h) —CF_3,
(i) —SR^8, wherein R^8 is hydrogen, C_{1-6}alkyl, trifluoromethyl, or phenyl,
(j) —SOR^8, wherein R^8 is as defined above,
(k) —SO_2R^8, wherein R^8 is as defined above,
(l) —$CONR^6R^7$, wherein R^6 and R^7 are as defined above,
(m) $R^9O(CH_2)_m$- wherein R^9 is hydrogen, C_{1-3} alkyl, hydroxy-C_{2-3}alkyl, trifluoromethyl, phenyl or naphthyl and m is as defined above,
(n) —$CH(OR^{12})(OR^{13})$, wherein R^{12} and R^{13} are C_{1-3}alkyl or taken together form an ethyl or propyl bridge,
(o)



wherein R^9 and m are as defined above, and
(p)



wherein R^9 and m are as defined above, and
(q) —OR^{11};

or any two of adjacent X, Y and Z can be joined to form a ring having 5, 6 or 7 ring atoms, said ring atoms comprising 1 or 2 oxygen atoms, the remaining ring atoms being carbon, selected from the group consisting of: dioxolanyl, dihydrofuranyl, dihydropyranyl, and dioxanyl.

The compounds of the present invention have asymmetric centers and this invention includes all of the optical isomers and mixtures thereof.

In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

When any variable (e.g., alkyl, aryl, R^6, R^7, R^8, R^9, R^{10}, R^{11}, etc.) occurs more than one time in any variable or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyll" includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, sec-and tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, butoxy and pentoxy.

"Alkanoyl" is intended to include those alkylcarbonyl groups of specified number of carbon atoms, which are exemplified by formyl, acetyl, propanoyl and butyryl; "alkanoyloxy" is intended to include those alkylcarbonyl groups of specified number of carbon atoms attached through an oxygen bridge, which are exemplified by formyloxy, acetoxy, propionoyloxy, and butyryloxy. "Alkenyl" is intended to include hydrocarbon chains of a specified number of carbon atoms of either a straight- or branched-configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethyl pentenyl, and the like, and includes E and Z forms, where applicable; and "arylalkyl" represents aryl groups as herein defined which are attached through a straight or branched chain alkyl group of from one to six carbon atoms, such as, for example, benzyl, phenethyl, 3,3-diphenylpropyl, and the like. "Halogen", as used herein, means fluoro, chloro, bromo and iodo.

As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts with inorganic acids such as hydrochlo-

ride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or palmoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with -amines of the formula HNR^6R^7). One embodiment of the present invention encompasses the compounds of Formula I wherein:

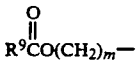
R^1 and R^2 are independently selected from:

(1) hydrogen;
(2) methyl;
(3) phenyl;
(4) substituted phenyl in which the substituents are X, Y and Z;
(5) 1- or 2- naphthyl;
(6) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z;
(7) biphenyl; and
(8) substituted and biphenyl in which the substituents are X, Y and Z;

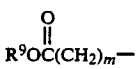
with the proviso that R^1 and R^2 are not simultaneously hydrogen;

X, Y and Z are independently, selected from:

(a) hydrogen,
(b) C_{1-7} alkyl,
(c) C_{2-6} alkenyl,
(d) halogen,
(e) $-(CH_2)_m-NR^6R^7$, wherein R6 and R are, independently selected from
  (i) hydrogen, or
  (ii) C_{1-6} alkyl unsubstituted or substituted with phenyl, and m is 0 to 2,
(f) —CN,
(g) —CHO,
(h) $-CF_3$,
(i) $-SR^8$, wherein R^8 is hydrogen, C_{1-6}alkyl, trifluoromethyl, or phenyl,
(j) $-SOR^8$, wherein R^8 is as defined above,
(k) $-SO_2R^8$, wherein R^8 is as defined above,
(l) $-CONR^6R^7$, wherein R^6 and R^7 are as defined above,
(m) $R^9O(CH_2)_m$- wherein R^9 is hydrogen, C_{1-3} alkyl, hydroxy-C_{2-3}alkyl, trifluoromethyl, phenyl or naphthyl and m is as defined above,
(n) $-CH(OR^{12})(OR^{13})$, wherein R^{12} and R^{13} are C_{1-3} alkyl or taken together form an ethyl or propyl bridge,
(o)



wherein R^9 and m are as defined above, and
(p)



wherein R^9 and m are as defined above, and
(q) $-OR^{11}$;

or any two of adjacent X, Y and Z can be joined to form a ring having 5,6 or 7 ring atoms, said ring atoms comprising 1 or 2 oxygen atoms, the remaining ring atoms being carbon, selected from the group consisting of: dioxolanyl, dihydrofuranyl, dihydropyranyl, and dioxanyl.

Another embodiment of the present invention encompasses the compounds of Formula I wherein:

R^1 and R^2 are independently selected from:

(1) hydrogen;
(2) C_{1-10} alkyl; (3) substituted C_{1-10} alkyl in which one or more substituent(s) is(are) selected from:
  (a) hydroxy,
  (b) oxo,
  (c) C_{1-6}-alkoxy,
  (d) phenyl-C_{1-3}alkoxy,
  (e) substituted phenyl-C_{1-3}alkoxy, in which the substituents on phenyl are X, Y and Z,
  (f) $-OCO-C_{1-6}$alkyl,
  (g) $-NR^6R^7$, wherein R^6 and R^7 are independently selected from
    (i) hydrogen,
    (ii) C_{1-10}alkyl unsubstituted or substituted with one or more of the substituent(s) selected from:
      (a') phenyl, which is unsubstituted or substituted with X, Y and Z,
      (b') —OH,
      (c') C_{1-6}alkoxy,
      (d') $-CO_2H$,
      (e') $-CO_2-C_{1-6}$alkyl,
      (f') $-C_{3-7}$cycloalkyl, and
      (g') $-OR^{11}$,
    (iii) C_{3-10}alkenyl unsubstituted or substituted with one or more of the substituent(s) selected from:
      (a') phenyl, which is unsubstituted or substituted with X, Y and Z,
      (b') —OH,
      (c') C_{1-6}alkoxy,
      (d') $-CO_2H$,
      (e') $-CO_2-C_{1-6}$alkyl,
      (f') $-C_{3-7}$cycloalkyl, and
      (g') $-OR^{11}$,
    (iv) or where R^6 and R^7 and the N to which they are attached can form an unsubstituted or substituted 3–7-membered saturated heterocyclic ring which can include one or two additional heteroatoms independently selected from the group consisting of O $S(O)_p$, NR^{14}, wherein R^{14} is hydrogen or C_{1-6} alkyl unsubstituted or substituted by phenyl, and p is 0, 1 or 2, the ring being selected from the group consisting of: aziridine, morpholine, thiomorpholine, thiomorpholine-oxide, thiomorpholine-dioxide, piperidine, pyrrolidine, and piperazine,
  (h) $-NR^6CO-C_{1-6}$alkyl-R^7, wherein R^6 is as defined above,
  (i) $-NR^6CO_2-C_{1-6}$alkyl-R^7,
  (j) $-NR^6CONR^6R^7$,
  (k) $-OCONR^6R^7$,
  (l) $-COOR^6$,
  (m) —CHO,
  (n) phenyl,
  (o) substituted phenyl in which the substituents are X, Y and Z,
  (p) phenyloxy,
  (q) substituted phenyloxy in which the substituents are X, Y and Z,
  (r) 1- or 2- naphthyl,

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