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Title: A METHOD FOR THE TREATMENT OF ENDOTOXIC SHOCK IN A MAMMAL

BRIEF SUMMARY OF THE INVENTION

This invention relates to a method of treatment of endotoxic shock in mammals which is useful to retard and/or inhibit the development of clinical lesions associated with endotoxic shock. More particularly, it relates to therapeutic compositions containing a combination of a Platelet Activating Factor antagonist and a monoclonal or polyclonal antibody directed to either Tumor Necrosis Factor α, interleukin-1β,gamma interferon or bacterial cell wall lipopolysaccharide/s. The invention includes a new method for the treatment of endotoxic shock in mammals therewith.

DETAILED DESCRIPTION OF THE INVENTION

Platelet Activating Factor (PAF) is a potent mediator of inflammation in mammals and it is synthesized by a variety of cells including macrophages, neutrophils, endothelial cells and platelets (Cammussi, G. 1986, Kidney Int. 29, 469). When injected into mammals, PAF induces hemodynamic and hematological changes including hypotension, platelet aggregation, neutropenia, disseminated intravascular coagulation, increases in vascular permeability, bronchoconstriction, tissue injury (hypoxia and necrosis) and eventually death (reviewed by Cammussi, G. Kidney Int. 29, 469, 1986). In recent years, it has been postulated that PAF is the mediator of tissue

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injury in mammals undergoing endotoxic shock due to bacterial sepsis (Terashita, Z., Y. Imura, K. Nishikawa and S. Sumida 1985, Eur. J. Pharmacol. 109:257-261; Doebber, T. W., M.S.Wu, J. C. Robbins, B. M. Choy, M. N. Chang and T. Y. Shen 1985, Biochem. Biophys. Res. Comm 127:799-808; Inarrea, P., Gomez-Cambronero, J. Pascual, M. del Carmen Ponte, L. Hernando and M. Sanchez-Crespo. 1985, Immunopharmacology, 9:45-52). These studies, in mammals, have shown that PAF is produced in large amounts when the mammal has been treated with endotoxin. In addition, mammals undergoing endotoxic shock exhibit all of the clinical symptoms associated with the administration of PAF.

Studies (Tracey, K. J., B. Beutler, S. F. Lowry, J. Merryweather, S. Wolpe, I. W. Milsark, R. J. Hairi, T. J. Fahey, A. Zentalla, J. D. Albert and A. Cerami 1986, Science (Wash., D.C. 234;47-473) have shown that the clinical symptoms associated with endotoxic shock or with PAF can be reproduced in mammals by the administration of the macrophage cytokine, Tumor Necrosis Factor α (TNFα; also known as cachectin). Since macrophages can be activated in vitro and in vivo, to synthesize and secrete TNFα (Carswell, E. A., L. J. Old, R. L. Kassel, S. Green, D. Fiore and B. Williamson 1975, Proc. Natl. Acad. Sci. USA 72;:3666-3671), it has been suggested that TNFα may be one of the mediators synthesized after endotoxin shock. Evidence supporting this claim is derived from the studies of Beutler et al. (Beutler, B., I. W. Milsark and A. C. Cerami 1985, Science (Wash. D.C.) 229;869-872). These studies have shown that if mice are pretreated with polyclonal antisera directed against TNFα (antiTNFα), they were protected from the lethal effects of endotoxin. However, if antiTNFα was administered at the time of endotoxin treatment or if antiTNFα was administered after endotoxin treatment, no

significant protection was detected. Thus, the time of administration of antiTNFα was critical in the protection against endotoxin induced lethality.

Recent studies by Camussi et al. (Camussi, G., F. Bussolino, G. Salvidio and C. Baglioni 1987, J. Exp. Med. 166, 1390-1404) have shown that when TNFα is added to cultures of rat peritoneal macrophages, neutrophils or human endothelial cells, large amounts of PAF are synthesized and released. These observations indicate that the clinical symptoms associated with the administration of TNFα to mammals are due in part to PAF that is synthesized by a variety of cells when exposed to TNFα.

Since endotoxin shock is initiated by the cell wall lipopolysaccharide (LPS) a monoclonal or a polyclonal antibody directed against LPS in combination with a PAF antagonist can also be a desired form of treatment for endotoxic shock in mammals.

Since macrophages can be activated by gamma interferon (A. G. Morris, Interferons, Immunology 1988 Supplement 1,43-45), a monoclonal or polyclonal antibody directed to human gamma interferon in combination with a PAF antagonist can also be a desired form of treatment for endotoxic shock in mammals.

Another cytokine that is synthesized and released by macrophages exposed to endotoxin is interleukin-1β (IL-1β). Studies conducted by Okusawa et al. (S. Okusawa, J. A. Gelfand, T. Ikejima, R. J. Connolly and C. A. Dinarello, 1988, Clin. Invest. 81, 1162-1172) have shown that the administration of 1L-1β to mammals induces a shock like state (hemodynamic and hematological changes) that is similar to that seen when TNFα is administered. When 1L-1β was combined with TNFα, the shock syndrome in rabbits was of a greater intensity than if either agent was used alone. Thus, it is likely that 1L-1β is an additional mediator

that can induce the synthesis and release of PAF by a variety of cells.

Thus, endotoxin shock due to bacterial sepsis involves the synthesis and release of IL-1β and TNFα by macrophages. The released IL-1β and TNFα can interact with a variety of cells such as macrophages, endothelial cells, neutrophils and platelets to stimulate the synthesis and release of PAF. The released PAF induces hemodynamic and hematological changes, causes tissue damage (hypoxia), increased vascular permeability and organ failure. Due to these induced changes in the mammal, PAF is lethal.

Concurrently, with the realization that PAF is an important mediator of the clinical effects in mammals undergoing endotoxic shock, a number structurally different antagonists of PAF have been developed. References to some of these antagonists are listed hereinbelow.

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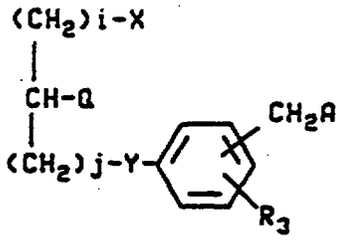
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In addition to the references given above, PAF antagonists of the formula:

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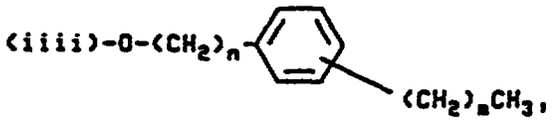


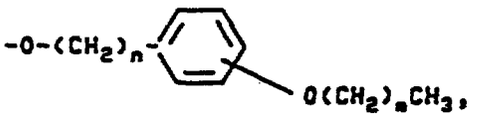
wherein: (A) X is selected from the group consisting of

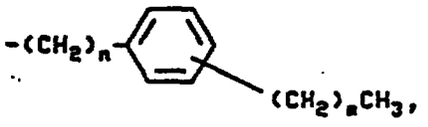
(i) C_1-C_{24} alkyl;

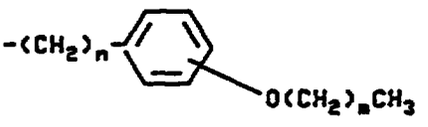
(ii) C_1-C_{24} alkoxy;

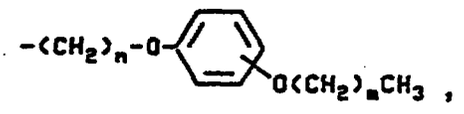
(iii) C_1-C_{24} carboamoyloxy;

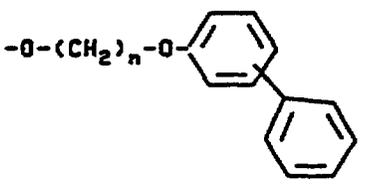


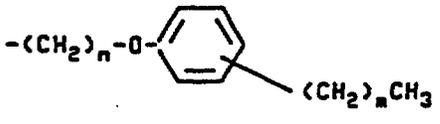










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wherein n is an integer from 1 to 25 and m is an integer from 0 to 24 and the sum of n and m is less than or equal to 25;

(v) phenyl;

(vi) mono-or polysubstituted phenyl wherein the substituents are selected from the group consisting of C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl and benzyloxy;

(vii) phenoxy;

(viii) mono-or polysubstituted phenoxy wherein the substituents are selected form the group consisting of C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl and benzyloxy;

(ix) naphthaloxy;

(x) mono-or polysubstituted naphthaloxy wherein the substituents are selected from the group consisting of C_1-C_{20} alkyl, C_1-C_{20} alkoxy and halogen;

(xi) $-O-(CH_2)_r-O-((CH_2)_pO)_t-(CH_2)_a-W$ wherein W is selected from the group consisting of methyl and phenyl optionally substituted with C_1-C_3 alkyl, C_1-C_3 alkoxy and phenyl, r, p, t and a are integers such that the expression r+(p+1)t+a is also an integer and has a value of 3 to 20; r is greater than or equal to 2; p is greater than or equal to 2; t is greater than or equal to zero; and a is greater than or equal to zero;

(B) i is an integer from 1 to 3 and j is an integer from 1 to 6;

(C) Q is selected from the group consisting of $-OR_2$, $-OCH_2\overset{O}{\overset{\|}{C}}OR_2$

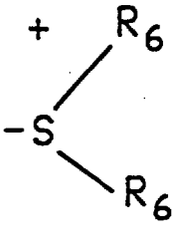
and $O-\overset{O}{\overset{\|}{C}}-R_2$, wherein R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

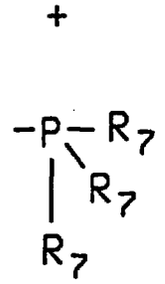
(D) Y is a divalent radical selected from the group consisting of $-O-\overset{O}{\overset{\|}{C}}-$, $-OCH_2-$, and $-O-\overset{O}{\overset{\|}{\underset{\underset{\ominus O}{|}}{P}}}-O-$;

(E) the moiety R_3 represents one or more substituents of the aromatic ring selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy and halogen;

(F) the moiety $-CH_2A$ represents a substituent of the aromatic ring which may be in the ortho, meta or para position wherein A is selected from the group consisting of:

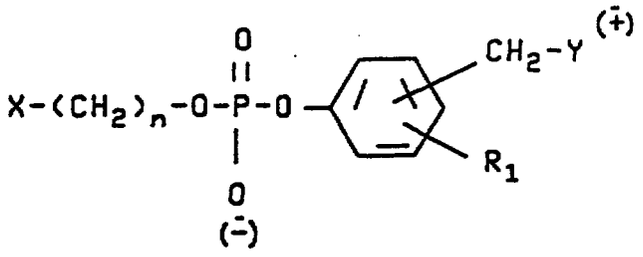
(i) a 5-7 member aromatic heterocyclic ring containing at least one nitrogen atom and one or more nitrogen or sulfur atoms;

(ii)  ; or

(iii) 

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and PAF antagonists of the formula:



wherein: (A) X is a phenyl or naphthyl ring optionally substituted in any position with one or more substituents (i) $-R_2$, wherein R_2 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, C_1-C_{25} alkoxy, C_1-C_{25} alkenyloxy, C_1-C_{25} thioalkyl, phenyl, phenoxy, substituted phenyl or substituted phenoxy wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

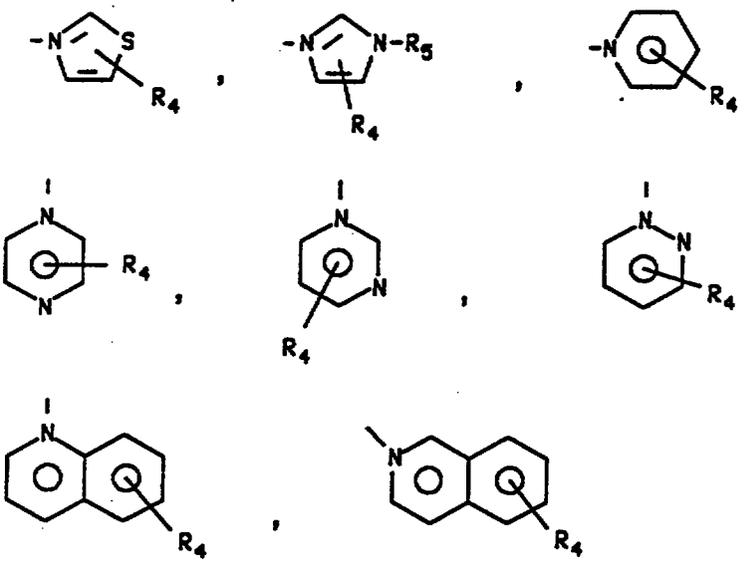
(ii) hydrogen, halogen, trifluoromethyl, cyano, or nitro;

(iii) $-CO_2R_3$, $-CONHR_3$, $-CHO$, $-OCONHR_3$, or $-NHCOR_3$ wherein R_3 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, phenyl, or substituted phenyl, wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, or trifluoromethyl;

(B) R_1 represents one or more substituents of the aromatic ring which may be in any position and is C_1-C_5 alkyl, C_1-C_5 alkoxy or halogen.

$-CH_2-Y$ represents a single substituent of the aromatic ring which may occupy any position wherein Y is a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms; a preferred embodiment is compounds of formula I, above, wherein Y is

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wherein R_4 represents one or more substituents of the heterocyclic ring which may occupy and non-hetero atom position and is C_1-C_5 alkyl, C_1-C_5 alkoxy, hydrogen or halogen; the moiety R_5 is C_1-C_5 alkyl or hydrogen.

(C) n is the integer 0 or 1.

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Our invention relates to the unexpected discovery that when a PAF antagonist is administered in combination with a monoclonal or polyclonal antibody directed toward either Tumor Necrosis Factor α, Interleukin-1β, gamma interferon, or bacterial cell wall lipopolysaccharides, the animals can be protected from the effects of endotoxin in a manner better than if the PAF antagonist or the antibody are administered alone; this combination therapy represents a new method for the treatment of endotoxic shock in mammals.

Antibody directed toward Tumor Necrosis Factor α can be obtained from Endogen Inc., 451 D Street, Boston, MA 02210. Antibody directed toward Interleukin-1β can be obtained from Genzyme, 75 Kneeland St., Boston, MA 02114. Antibody directed toward gamma interferon can be obtain from Alpha Therapeutic Corp., 5555 Valley Road, Los Angeles, CA 90032. Antibody directed toward bacterial cell wall lipopolysaccharides can be obtained from Oxoid Ltd., Wade Road, Basingstoke, Hampshire, RG 24, OPN, England.

The PAF antagonists used to implement the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, these antagonists may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred

compositions according to this invention are prepared so that an oral dosage unit contains between about 1 and 500 mg of active compound.

The tablets, capsules and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor.

These PAF antagonists may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms of PAF antagonists suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the

conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The PAF antagonists of this invention may also be administered directly to the airways in the form of an aerosol.

The monoclonal or polyclonal antibodies directed towards Tumor Necrosis Factor α (also known as Cachectin), Interleukin-1β, Gamma Interferon, and bacterial cell wall lipopolysaccharides which are needed to implement this invention and are best administered parenterally in a dosage range of 2 to 500 mg/kg.

Solutions or suspensions of these antibody compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms of the antibodies suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, saline, water, ethanol, polyol (e.g. glycerol,

propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The PAF antagonists and antibodies may be administered in the same vehicle or different vehicles. The PAF antagonists and antibodies may be administered at the same time or at different times during the course of therapy.

The invention will be further described by the following examples.

Example 1

Balb/c mice (male, 20 g) were obtained from Charles River Laboratories, Wilmington, Massachusetts. They were housed in groups of 5 in individual cages and fed ad libitum. E. coli endotoxin was obtained from Sigma Chemical Co., St. Louis, MO. The endotoxin was dissolved in Phosphate buffered saline (GIBCO) and administered to mice intravenously at a dose of 50 mg/kg. Fifteen to twenty minutes after the administration of endotoxin, the mice were divided into several groups. One group received intravenous saline (Control). The second group received 3-[[3-[[hydroxy[-2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]-phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt (PAF antagonist) intravenously at a dose of 20 mg/kg (Compound suspended in phosphate buffered saline and sonicated for approximately 15 seconds to provide a flocculent or cloudy solution). The third group received a monoclonal antibody directed against murine TNFα administered intravenously at a dose of 25 mg/kg. The fourth group received intravenously 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt (20 mg/kg) and the monoclonal antibody directed against murine TNFα (25 mg/kg). The monoclonal antibody used in these studies was provided by Dr. Robert Schreiber, Department of Pathology, Washington University School of Medicine, St. Louis, MO

and Cell-Tech, Great Britain. The mice were monitored for survival for up to 72 hours post endotoxin treatment. The results of these studies are shown in Table I.

Control mice that had received saline died within 24 hours after endotoxin challenge. Consistent with the observations of Beutler et al. (see reference above), mice that had received endotoxin followed by antiTNFα (antiTNFα administered 15 to 20 minutes after endotoxin) were not protected. By 72 hours, all of the mice had succumbed to the lethal effects of endotoxin. Mice treated with 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt were also not protected from lethality induced by endotoxin. However, mice that had received both 3-[[3-[[hydroxy-[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]-phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt and antiTNFα were completely protected from endotoxin induced lethality. No mortality was observed in this group at 24 hours or 72 hours post endotoxin treatment. They appeared healthy and for up to 13 days post endotoxin treatment. The experiment was terminated at this time.

Example 2

Several Balb/c mice were treated intravenously with either 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt (20 mg/kg) or with saline. After two hours, all of these mice were treated intravenously with endotoxin at a dose of 50 mg/kg. One hour after endotoxin treatment, the mice were divided into several groups. Some mice that had received saline followed by endotoxin were treated intravenously with various doses of antiTNFα (doses ranging from 2.5 to 25 mg/kg). Some mice that had been treated with

3-[[3-[[hydroxy[2-methoxy-3-(tetradecyl-oxy)phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt followed by endotoxin were also treated intravenously with various doses of antiTNFα (doses ranging from 2.5 to 25 mg/kg). Two types of controls were included. One control consisted of mice that were treated with 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]-phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt followed by endotoxin and saline (saline administered 1 hour post endotoxin treatment). Another control consisted of mice treated with saline followed by endotoxin and saline (saline administered 1 hour post endotoxin). The mice were monitored for 48 hours. The results of these experiments are shown in Table II.

Control mice that had been pretreated either with 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)-phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt or saline followed by endotoxin died within 24 or 48 hours. All mice treated with saline followed by endotoxin and various doses of antiTNFα (antiTNFα administered 1 hour post endotoxin treatment) also died within 48 hours. The only survivors at 48 hours (five out of ten treated mice survived) belonged to the group that had been treated with 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phen-oxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt followed by endotoxin and anti-TNFα (25 mg/kg). These observations indicate that mammals can be pretreated in a prophylactic manner with a PAF antagonist followed by antiTNFα to prevent any potential endotoxin toxicity.

Table I

Combination Effect of 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt (PAF antagonist)[1] and antiTNFα on Endotoxin Induced Lethality

Treatment	Alive/Treated 24 hours	48 hours	72 hours
TDOPT (PAF antagonist) 20 mg/kg 20′ after LPS	0/5	0/5	0/5
TDOPT (PAF antagonist) (20 mg/kg) + antiTNF (25 mg/kg) 20′ after LPS	5/5	5/5	5/5[2]
AntiTNF (25 mg/kg) 20′ after LPS	2/5	2/5	0/5
PBS Control 20′ after LPS	0/5	0/5	0/5

Drug and antibody were given by i.v. route at indicated doses 15-20′ after 50 mg/kg i.v. endotoxin in male Balb/c mice.

1 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt (PAF antagonist) will be called TDOPT (PAF antagonist).

2 Still 5/5 by day 12.

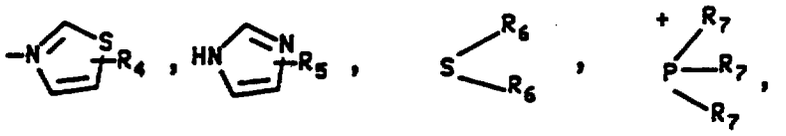
Table II

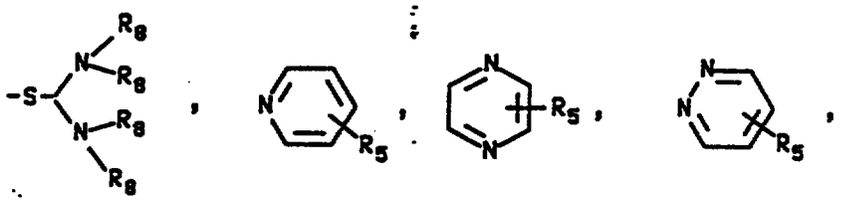
Prophylaxis Protocol: PAF Antagonist 3-[[3-[[hydroxy[2-methoxy-3-(tetradecyloxy)phenoxy]-phosphinyl]oxy]-phenyl]methyl]-5-methyl-thiazolium, hydroxide, inner salt
20 mg/kg (iv) and anti-TNFα (iv)[1]

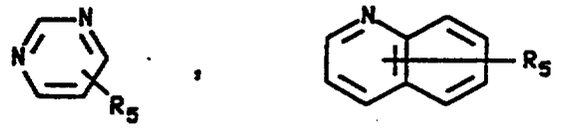
TDOPT or PBS (iv)	LPS (iv)	antiTNFα (iv) TDOPT (iv)	observation period		
HOURS					
treatment			live/treated		
0 hrs.	2 hrs.	3 hrs.	24 hrs.	48 hrs.	72 hrs.
PBS	LPS	PBS	0/20		
TDOPT	LPS	PBS	1/10	0/10	
TDOPT	LPS	TDOPT	0/10		
PBS	LPS	antiTNFα (500)	0/10		
		(250)	2/10	0/10	
		(100)	0/10		
		(50)	0/10		
TDOPT	LPS	antiTNFα (500)	6/10	5/10	5/10
		(250)	3/10	0/10	
		(100)	4/10	0/10	
		(50)	2/10	0/10	

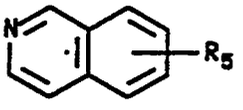
1 The (PAF antagonist) will be called TDOPT (PAF antagonist) in the above table

The preparation of compounds of this invention encompassed by formulas IA-C is described hereinbelow in Flowsheet A wherein X, i, j, R_3, R_6 and A are as described hereinabove; Q^1 is selected from the group $-O-\overset{O}{\overset{\|}{C}}-R^1{}_2$, $-OCH_2\overset{O}{\overset{\|}{C}}-OR_2$ and $-OR^1{}_2$, wherein $R^1{}_2$ is C_1-C_6 alkyl or C_1-C_6 alkenyl; the moieties $-CH_2-J$ and $-CH_2-A^1$ are substituents of the aromatic ring coming off the <u>meta</u> and <u>para</u> positions, wherein A^1 is a nitrogen containing heterocycle, a sulfide, thiourea, or a phosphine selected from the group:







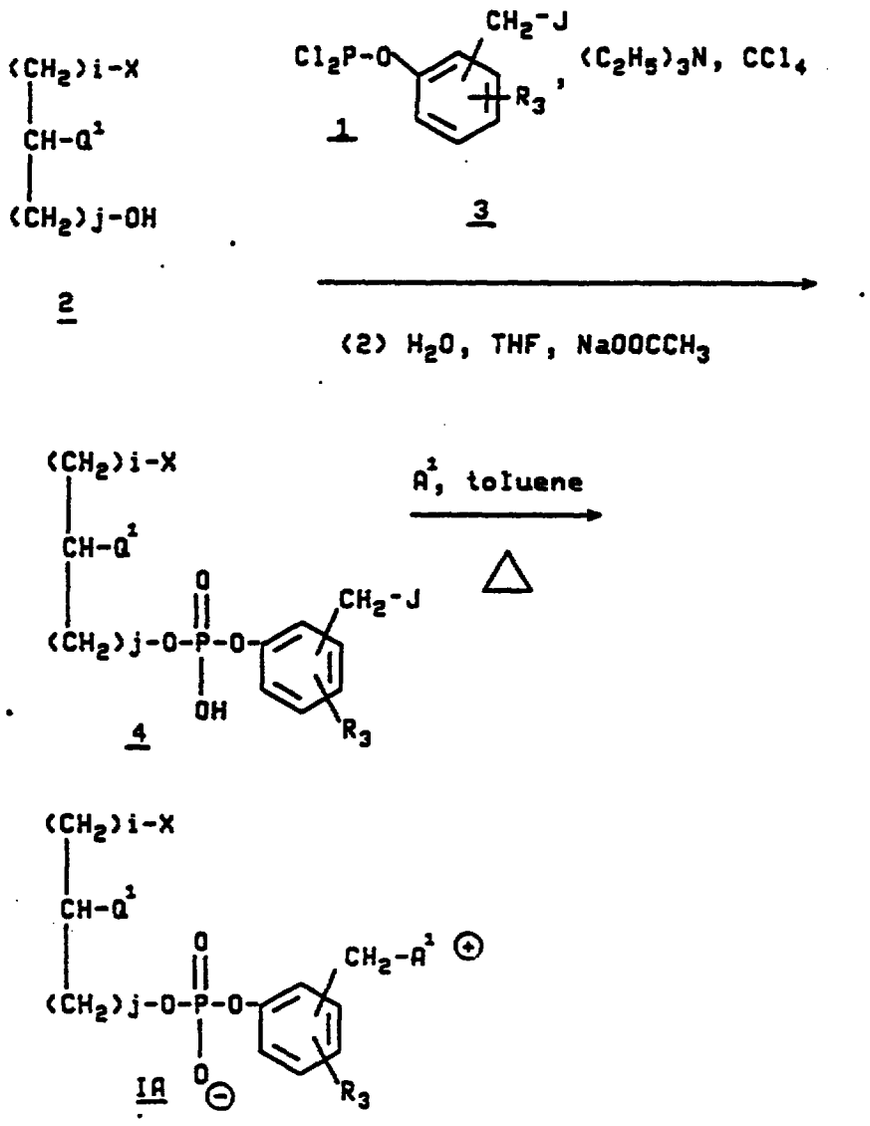
and 

wherein R_4 represents one or more substituents of the heterocyclic ring which may occupy any non-hetero atom position and is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, hydrogen, halogen and $-CH_2CH_2OH$; R_5 represents one or more substituents of the heterocyclic ring which may occupy any non-hetero atom position and is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, hydrogen, and halogen; R_6 is C_1 to C_5 alkyl; R_7 is C_1-C_5 alkyl, phenyl and substituted phenyl R_8 is hydrogen or C_1-C_6 alkyl and J is a leaving group such as a chlorine, bromine or iodine atom.

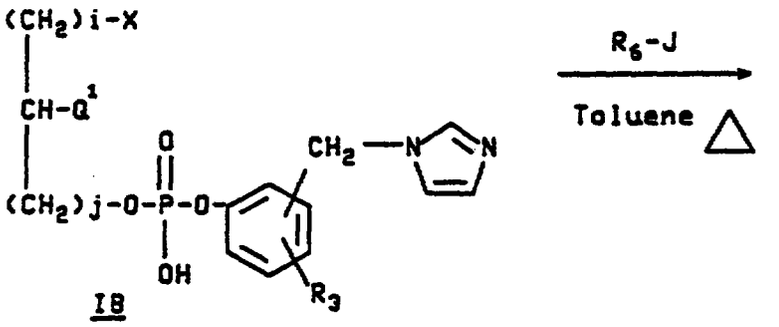
According to the sequence of reactions outlined in Flowchart A, the alcohol 2 is treated with an equivalent of the phosphorus reagent 3 in the presence of a base such as triethylamine in an inert solvent such as carbon tetrachloride to give, after hydrolysis of the resulting intermediate in a buffered solvent system such as tetrahydrofuran-water-sodium acetate, the phosphate 4. The reaction of 4 with a large excess of a nitrogen containing heterocycle, a sulfide, thiourea, or a phosphine in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula IA. These compounds are obtained as internal salts except when A is an imidazole moiety.

In those cases where the compounds contain an imidazole ring (Formula IB), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the internal salts IC.

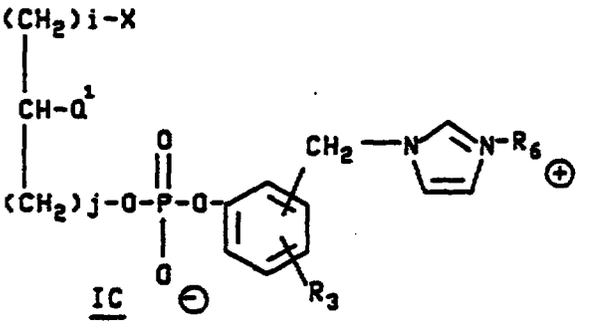
Flowsheet A


(CH2)i-X
CH-Q1
(CH2)j-OH
2
Cl2P-O
CH2-J
R3
1
3
(C2H5)3N, CCl4
(2) H2O, THF, NaOOCCH3
A1, toluene
4
IA

Flowchart A (continued)



IB



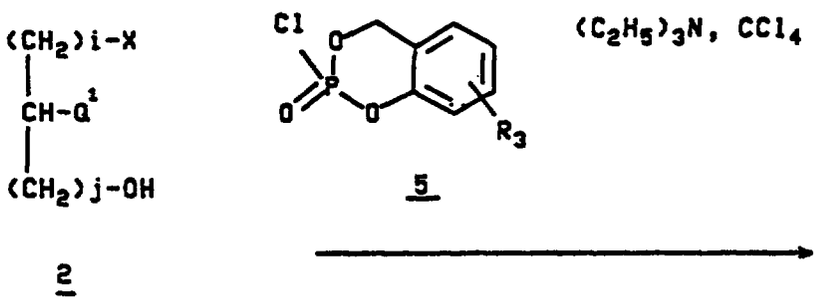
IC

The preparation of compounds of this invention encompassed by formulas ID-IF is described hereinbelow in Flowchart B wherein X, i, j, R_3, R_6, A, A^1, Q^1 and J are as defined hereinabove.

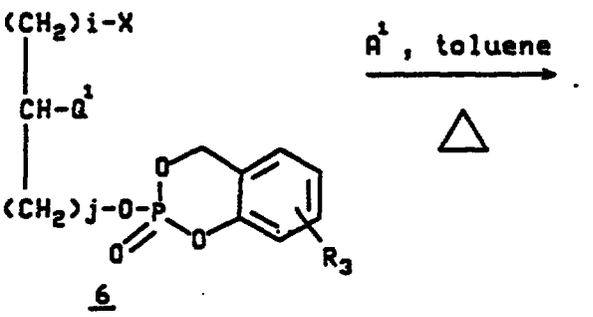
According to the sequence of reactions outlined in Flowchart B, the alcohol 2 is treated with and equivalent of the phosphorus reagent 5 in the presence of a base such as triethylamine in an inert solvent such as carbon tetrachloride to give the cyclic phosphate 6. The reaction of 6 with a large excess of a nitrogen containing heterocycle, a sulfide, thiourea or a phosphine in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula ID. These compounds are obtained as internal salts except when A is an imidazole moiety. In those cases where the compounds

contain an imidazole ring (formula IE), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the internal salts IF.

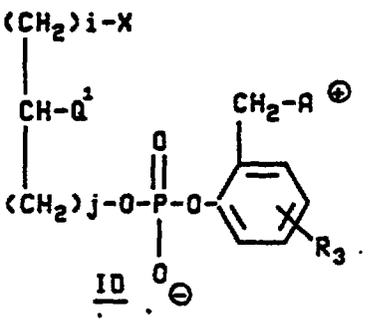
Flowsheet B



2 5

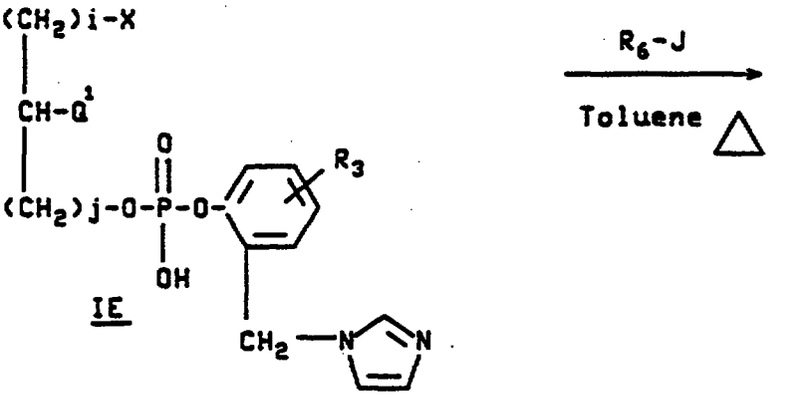


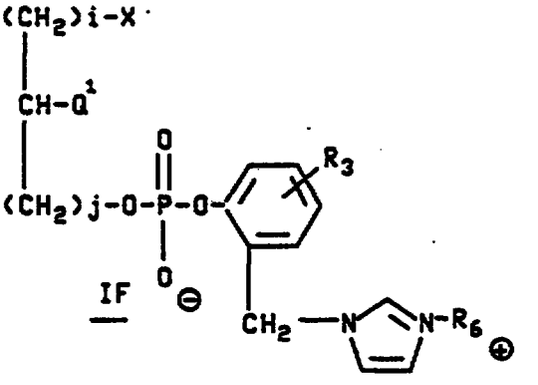
6



ID

Flowchart B (continued)



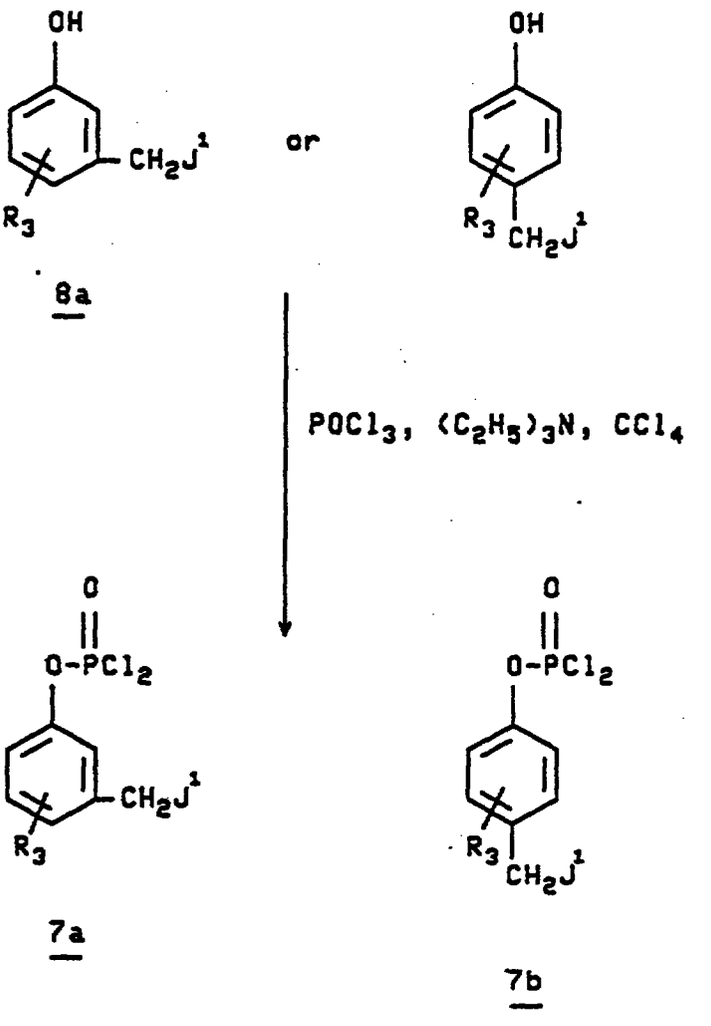


The phosphorous reagents represented by formulas 7a and 7b needed to prepare some of the compounds of this invention are prepared as described hereinbelow in Flowsheet C and in copending application Serial No. 679,788, filed December 10, 1984 (Case 29,706) wherein R_3 is as defined hereinabove and J^1 is chlorine or bromine.

According to the reaction outlined in Flowsheet C, the phenols 8a or 8b are reacted with phosphorousoxychloride and at least one equivalent of an amine base such as triethylamine in an inert solvent such as carbon tetrachloride to give the phosphorous reagents 7a and 7b.

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Flowchart C

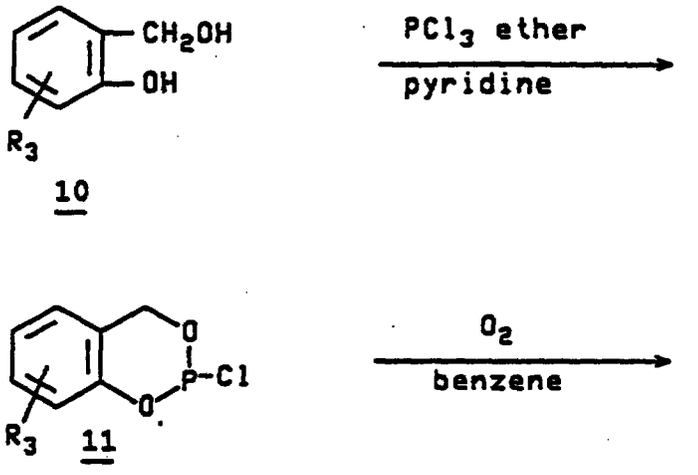


The cyclic phosphorous reagents represented by formula 9 needed to prepare some of the compounds of this invention are prepared as described hereinbelow in flowsheet D wherein R_3 is as defined hereinabove.

According to the reactions outlined in flowsheet D, the hydroxy phenol 10 is treated with an equivalent of phosphorous trichloride in an inert solvent such as ether in the presence of at least two equivalents of pyridine to give compound 11. Oxidation of 11 with a dry stream of oxygen in benzene then furnishes the phosphorous reagent 9.

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Flowsheet D

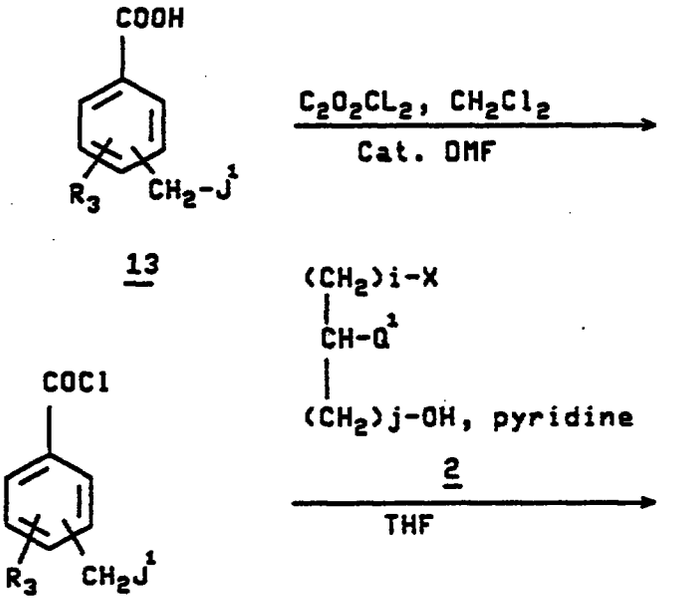


Compounds of this invention represented by formulas 16a-c are prepared as described hereinbelow in flowsheet E, wherein R_3, J', J, X, Q', i, j, A' and A are as defined hereinabove.

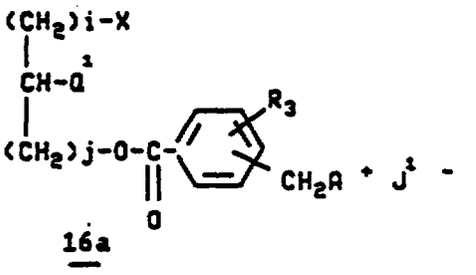
According to the reactions outlined in flowchart E the carboxylic acid 13 is converted to the acid chloride 14 by the reaction with oxalyl chloride in dichloromethane in the presence of a catalytic amount of dimethylformamide. The acid chloride 14 is then treated with an equivalent of the alcohol 2 in an inert solvent such as tetrahydrofuran in the presence of at least one equivalent of an amine base such as pyridine to give the ester 15. The reaction of 15

with a large excess of a nitrogen containing heterocycle, a sulfide, thiourea, or a phosphine in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula 16a. These compounds are obtained as salts except when A is an imidazole moiety. In those cases where the compound contains an imidazole ring (formula 16b), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the salts 16c.

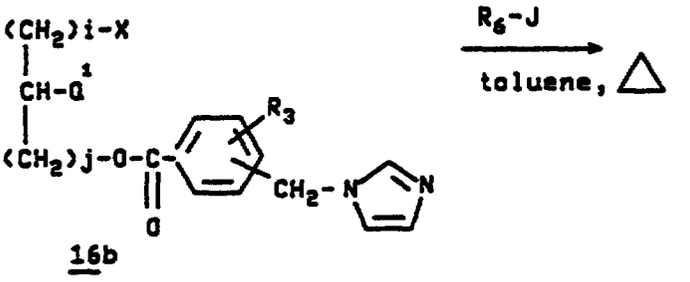
Flowsheet E



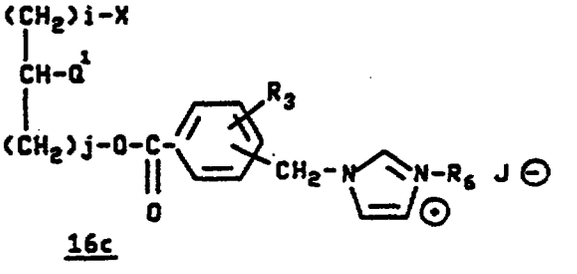
Flowchart E (continued)



16a



16b



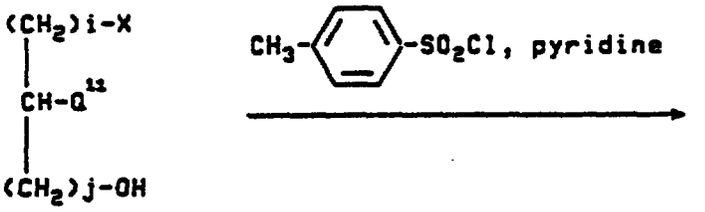
16c

Compounds of this invention represented by formulas 22a-c are prepared as described hereinbelow in flowsheet F wherein R_2, R_3, J', J, X, i, j, A' and A are as defined hereinabove and Q'' is OR_2''', where R_2''' is selected from the group consisting of C_1-C_6alkyl, C_1-C_6 alkenyl, or tetrahydropyranyl.

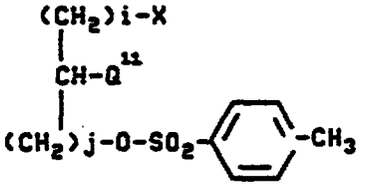
According to the reactions outlined in flowsheet F, the alcohol 17 is converted to the corresponding tosylate using p-toluensulfonyl chloride in pyridine. Addition of 18 to a dimethylformamide solution of the sodium salt of diol 19 gives the monoalkylated product 20 which is separated from the dialkylated product and unreacted 19 by chromatography on silica gel. The reaction of 20 with methane sulfonyl chloride and triethylamine in tetrahydrofuran in the presence of an excess of lithium chloride or lithium bromide gives the halide 21. The reaction of 21 with a large excess of a nitrogen containing heterocycle, a sulfide, thiourea, or a phosphine in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula 22a. These compounds are obtained as salts except when A is an imidazole moiety. In those cases where the compounds contain an imidazole ring (formula 22b), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the salts 22c.

In those cases where Q'' is tetrahydropyranyl (formula 23), the tetrahydropyranyl group can be hydrolyzed using a hydrochloric acid-tetrahydrofuran mixture. The resulting alcohols 24 are useful to prepare the esters 25 of this invention by refluxing 24 with an excess of the anhydride 26 in the presence of an excess of an amine base such as triethylamine in an inert solvent such as chloroform.

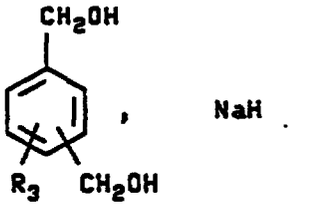
Flowsheet F

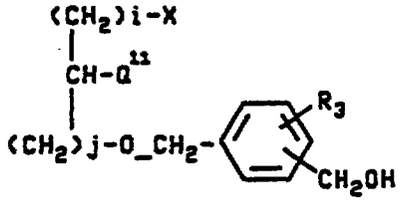


17

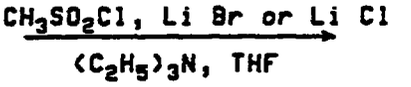


18

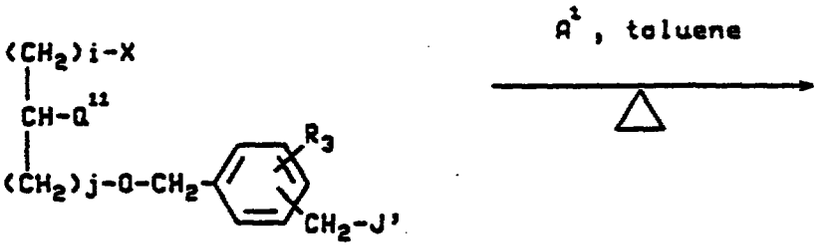




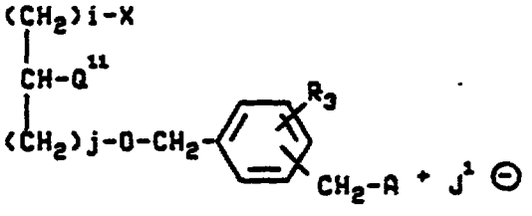
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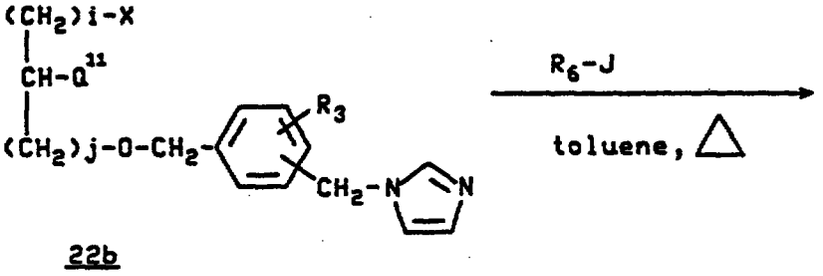
Flowchart F (continued)



21

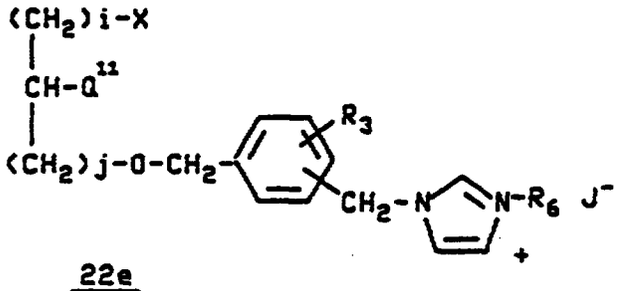


22a

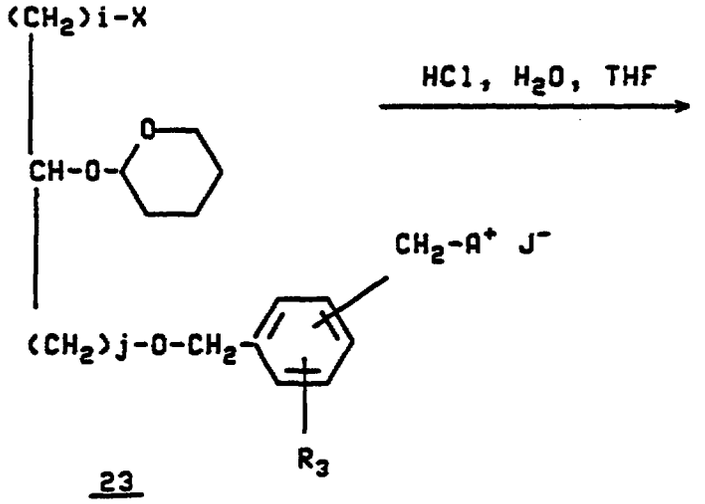


22b

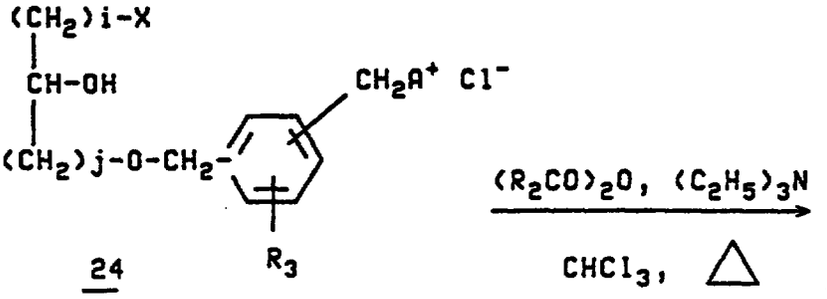
Flowchart F (continued)



22e

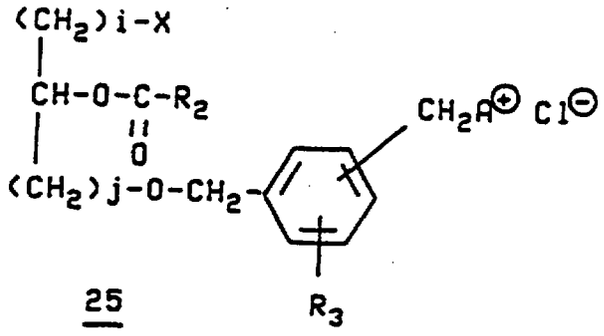


23



24

Flowchart F (continued)



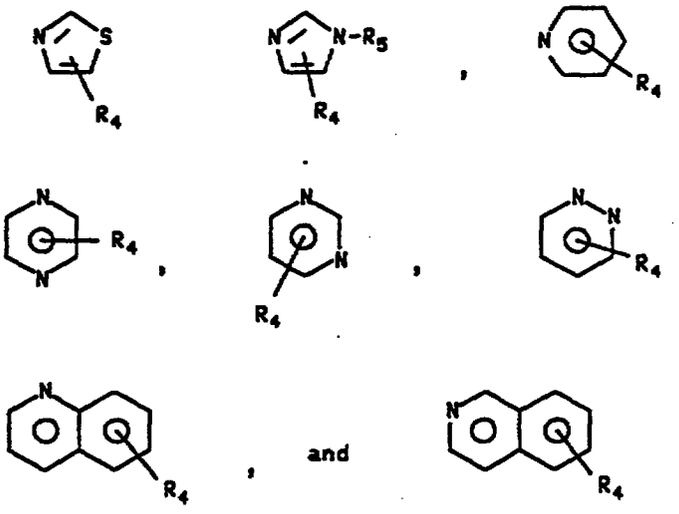
25

The preparations of the various alcohols for formulas 2 and 17 which are needed to prepared the compounds of this invention have been described in U.S. Patents 4,640,913, 4,697,031, 4,703,130 and 4,699,990, copending applications Serial No. 679,788, filed December 10, 1984 (Case 29,706), and Serial No. 679,790, filed December 10, 1984 (Case 29,617), and Terashita, Z., et. al., Life Sci., 32, 1975 (1983). The above patent and applications describe the preparation of alcohols of formulas 2 and 17 in both the racemic and optically active forms. Consequently, the compounds of this invention can be prepared both as the racemates and as the individual R and S enantiomers.

In addition to the synthetic methods discussed hereinabove, many of the methods and procedures described in the aforementioned U.S. Patent and copending applications are applicable to the preparation of the compounds of this invention by one skilled in the art.

This Sheet Has Been Replaced

The preparation of compounds of this invention encompassed by Formulas IA-C is described hereinbelow in Flowsheet A, wherein n, X, R_1 and R_5 are described hereinabove. The moieties $-CH_2-J$ and $-CH_2-Y'$ represent substituents of the aromatic ring which are meta or para to the phosphate group wherein J is a leaving group such as the halogens chlorine or bromine and Y' is a nitrogen containing heterocycle which can be

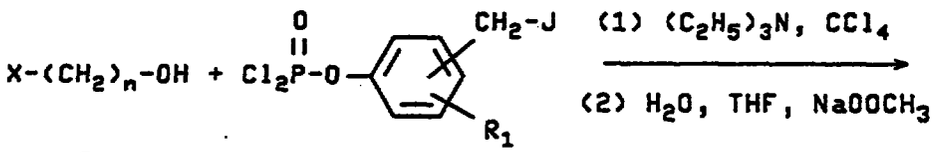


wherein R_4 and R_5 are as described hereinabove.

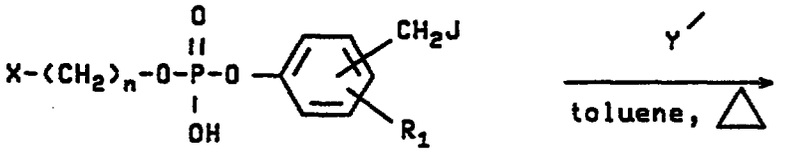
According to the sequence of reactions outlined in Flowchart A, the phenol or alcohol 2 is treated with an equivalent of the phosphorus reagent 3 in the presence of a base such as triethylamine in an inert solvent such as carbon tetrachloride to give, after hydrolysis of the resulting intermediate in a buffered solvent system such as tetrahydrofuran-water-sodium acetate, the phosphate 4. The reaction of 4 with a large excess of a nitrogen containing heterocycle in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula IA. These compounds are obtained as internal salts except when A is an imidazole moiety.

In those cases where the compounds contain an imidazole ring (Formula IB), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the internal salts IC.

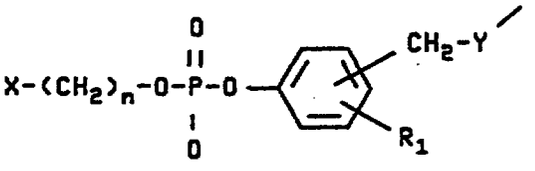
Flowsheet A



2 3



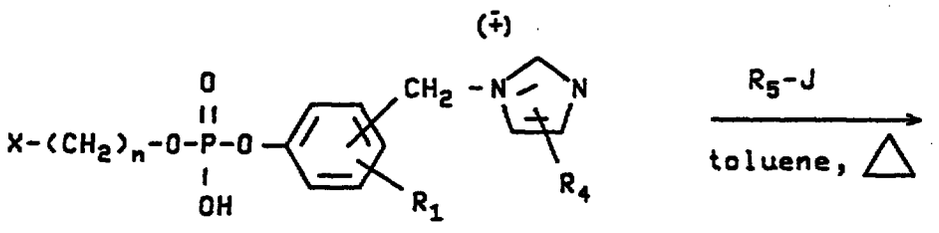
4



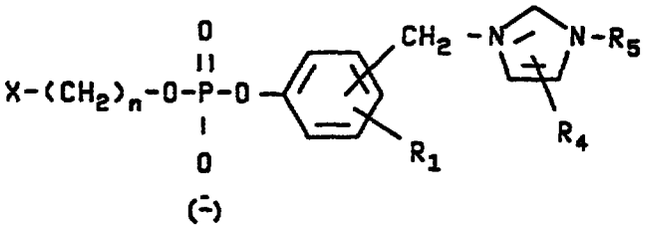
(⁻)

IA

Flowsheet A (Cont'd)



IB

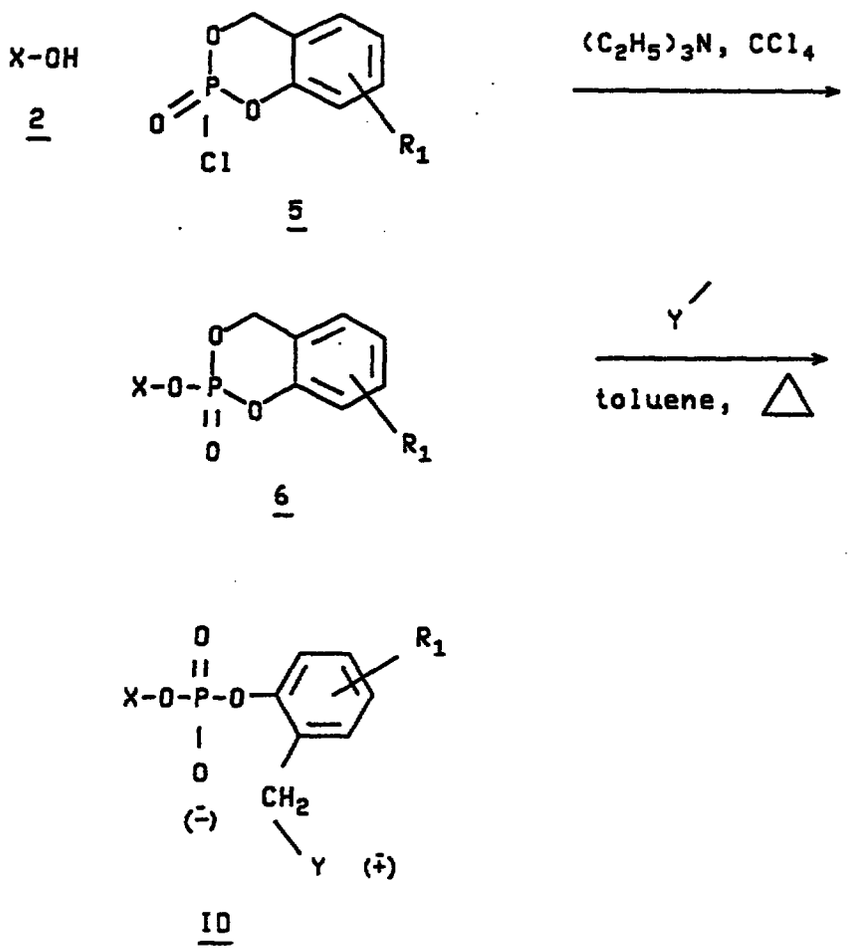


IC

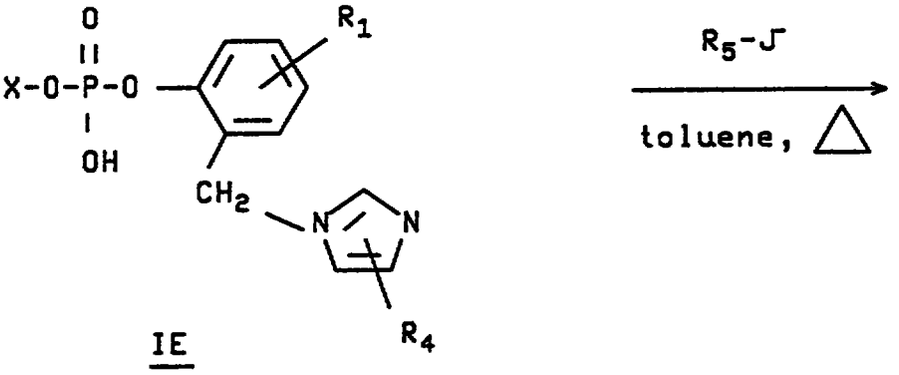
The preparation of compounds of this invention encompassed by formulas ID-IF is described hereinbelow in Flowchart B wherein R_4, Y', X, R_1, and R_5, and J are as defined hereinabove.

According to the sequence of reactions outlined in Flowchart B, the phenol 2 is treated with an equivalent of the phosphorus reagent 5 in the presence of a base such as triethylamine in an inert solvent such as carbon tetrachloride to give the cyclic phosphate 6. The reaction of 6 with a large excess of a nitrogen containing heterocycle in an inert solvent such as toluene at 50°-150°C gives the compounds of this invention represented by formula ID. These compounds are obtained as internal salts except when Y' is an imidazole moiety. In those cases where the compounds contain an imidazole ring (formula IE), the imidazole moiety can be further alkylated with an excess of alkyl halide by heating in an inert solvent such as toluene to give the internal salts IF.

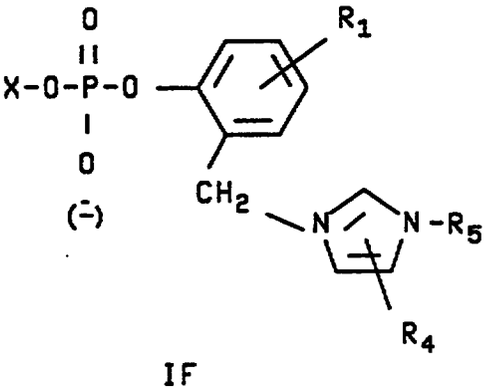
Flowsheet B



Flowsheet B (Cont'd)



IE



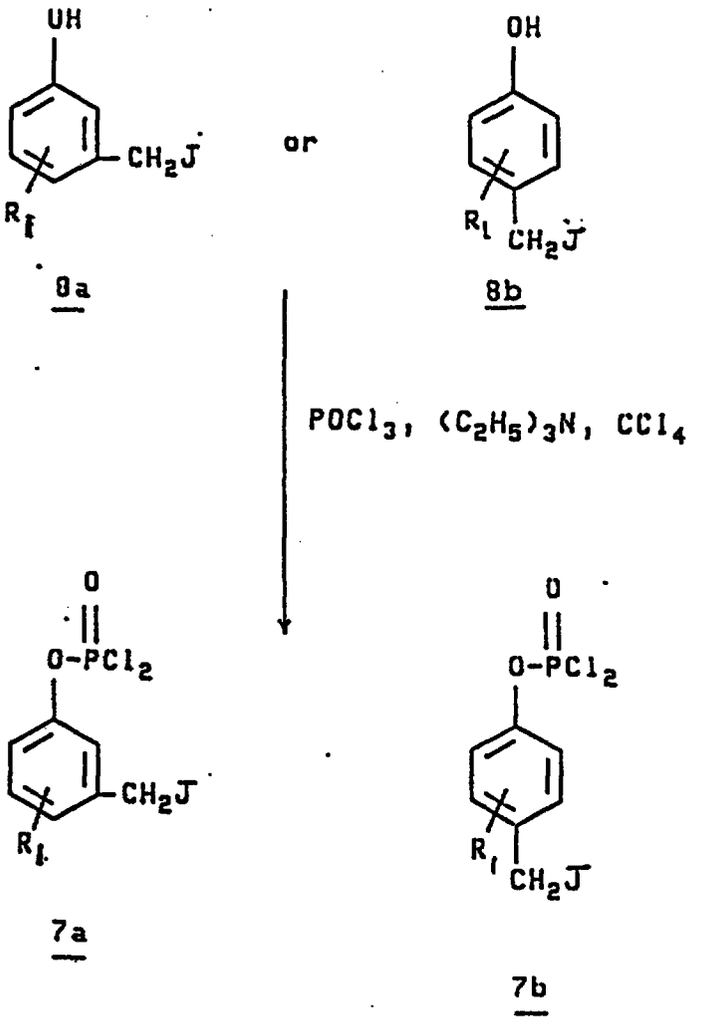
IF

The phosphorous reagents represented by formulas 7a and 7b needed to prepare some of the compounds of this invention are prepared as described hereinbelow in Flowsheet C and in copending application Serial No. 679,788, filed December 10, 1984 and in Serial No. 177,299 wherein R_1 is as defined hereinabove and J is chlorine or bromine.

According to the reaction outlined in Flowsheet C, the phenols 8a or 8b are reacted with phosphorous oxychloride and at least one equivalent of an amine base such as triethylamine in an inert solvent such as carbon tetrachloride to give the phosphorous reagents 7a and 7b.

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Flowsheet C

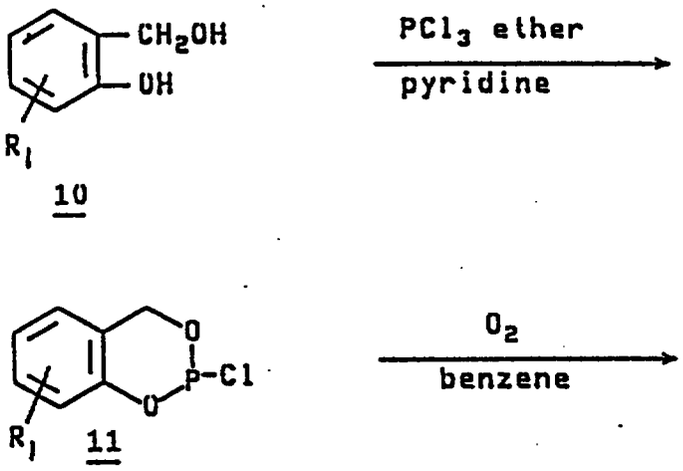


The cyclic phosphorous reagents represented by formula 9 needed to prepare some of the compounds of this invention are prepared as described hereinbelow in Flowsheet D wherein R_1 is as defined hereinabove.

According to the reactions outlined in Flowsheet D, the hydroxy phenol 10 is treated with an equivalent of phosphorous trichloride in an inert solvent such as ether in the presence of at least two equivalents of pyridine to give compound 11. Oxidation of 11 with a dry stream of oxygen in benzene then furnishes the phosphorous reagent 9.

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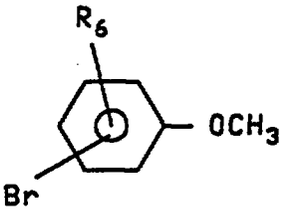
Flowsheet D


CH2OH
OH
R1
10
PCl3 ether
pyridine
O
P-Cl
O
R1
11
O2
benzene
O
P=O
O
Cl
R1
9

The substituted phenols and hydroxy naphthalenes of Formula 12 needed to prepare the compounds of this invention can be prepared as described in the following U.S. patents: 4,697,031; 4,699,990 and 4,640,913 and as described hereinbelow in Flowsheet E, wherein R_6 represents one or more substituents which may occupy any position and are selected from the group consisting of hydrogen, $-R_2$, trifluoromethyl, and fluorine wherein R_2 is as described hereinabove, and R_7 is C_1-C_{25} alkyl or C_1-C_{25} alkenyl. J' is chlorine, bromine or iodine.

According to the sequence of reactions outlined in Flowsheet E, a substituted bromo anisol 10 is reacted with magnesium in tetrahydrofuran to form the Grignard reagent which in turn is reacted with an alkyl halide in the presence of Li_2CuCl_4. The resulting methyl ether 11 is cleaved to the desired phenol using boron tribromide in an inert solvent such as methylene chloride. An identical sequence of reaction can be applied to furnish substituted hydroxy naphthalenes needed to prepare some of the compounds of this invention.

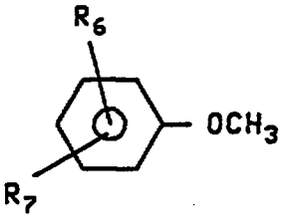
Flowsheet E



10

(1) Mg/THF

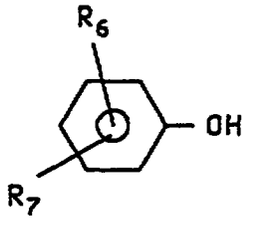
(2) R_7-J, Li_2CuCl_4



11

BBr_3

CH_2Cl_2



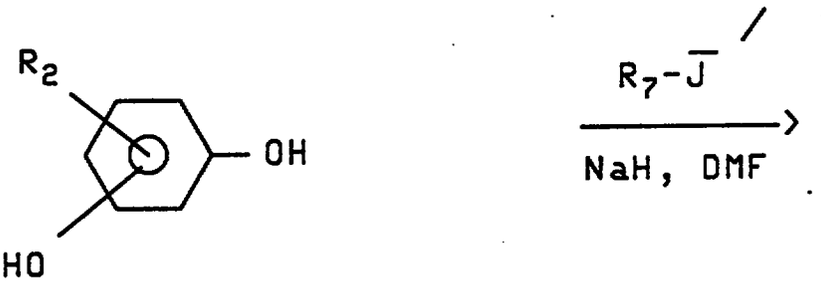
12

The substituted phenols and hydroxy naphthalenes of Formula 14 needed to prepare the compounds of this invention can be prepared as described in the following U.S. patents: 4,697,031; 4,699,990 and 4,640,913, in the following patent application Serial No. 679,792, and as described hereinbelow in Flowsheet F wherein R_2 and J' are as hereinabove defined and R_7 is C_1-C_{25} alkyl and C_1-C_{25} alkenyl. According to the sequence of reactions shown in Flowsheet F, treatment of the dihydroxy compound 13 with sodium hydride in an inert solvent such as dimethylformamide in the presence of an alkyl halide produces the monoalkylated product 14 which can readily be separated from the unreacted 13 and the dialkylated product by a combination of distillation and chromatography. In those cases where two isometric monoalkylated products result, they can be separated using chromatographic procedures. An identical sequence of reactions can be applied to the synthesis of the hydroxy naphthalenes needed to prepare the compounds of this invention.

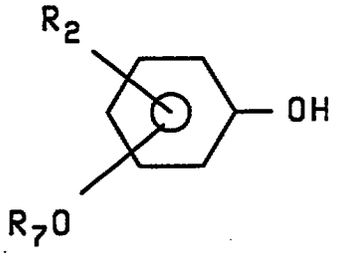
Some of the phenols and hydroxy naphthalenes that can be used to prepare the compounds of this invention are listed hereinbelow in Table I.

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Flowsheet F



13



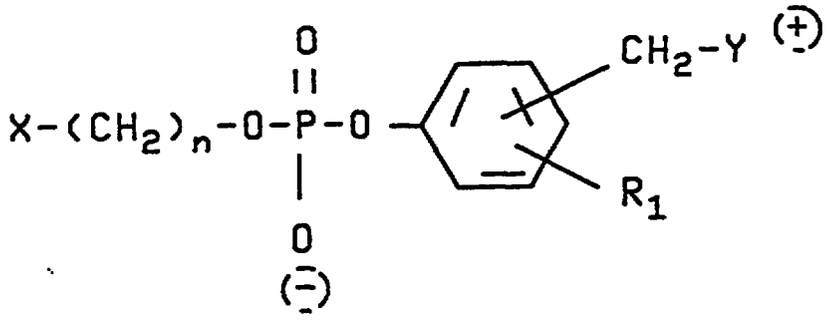
14

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We Claim:

1. A method of treating endotoxic shock in a mammal which comprises administering to the mammal a therapeutically effective amount of an antagonist to Platelet Activating Factor in combination with a therapeutically effective amount of one or more monoclonal or polyclonal antibodies directed towards either Tumor Necrosis Factor α, Interleukin-1β, Gamma Interferon, or bacterial cell wall lipopolysaccharides.

2. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards Tumor Necrosis Factor α is in combination with an antagonist of Platelet Activating Factor of the formula



wherein:

X is a phenyl or naphthyl ring optionally substituted in any position with one or more substituents of:

i) $-R_2$ wherein R_2 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, C_1-C_{25} alkoxy, C_1-C_{25} alkenyloxy, C_1-C_{25} thioalkyl, phenyl, phenoxy, substituted phenyl or substituted phenoxy wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

ii) hydrogen, halogen, trifluoromethyl, cyano or nitro;

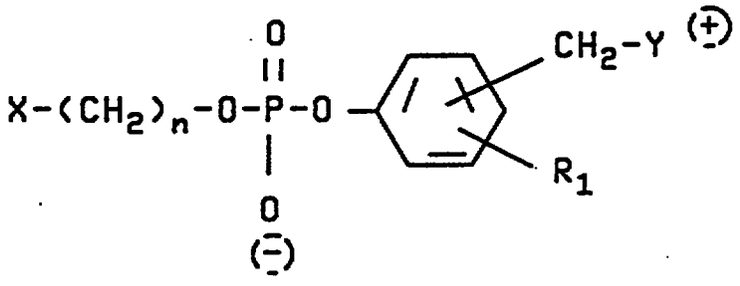
iii) $-CO_2R_3$, $-CONHR_3$, $-CHO$, $OCONHR_3$, or $-NHCOR_3$ wherein R_3 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, phenyl or substituted phenyl wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, or trifluoromethyl;

* C L M S *

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R_1 is one or more substituents of the aromatic ring which may be in any position and is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or halogen;
$-CH_2-Y$ is a single substituent of the aromatic ring which may occupy any position wherein Y is a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

3. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards Interleukin-1β is in combination with an antagonist of Platelet Activating Factor of the formula



wherein:

* C L M S *

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X is a phenyl or naphthyl ring optionally substituted in any position with one or more substituents of:

i) $-R_2$ wherein R_2 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, C_1-C_{25} alkoxy, C_1-C_{25} alkenyloxy, C_1-C_{25} thioalkyl, phenyl, phenoxy, substituted phenyl or substituted phenoxy wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

ii) hydrogen, halogen, trifluoromethyl, cyano, or nitro;

iii) $-CO_2R_3$, $-CONHR_3$, $-CHO$, $OCONHR_3$, or $-NHCOR_3$ wherein R_3 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, phenyl or substituted phenyl wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

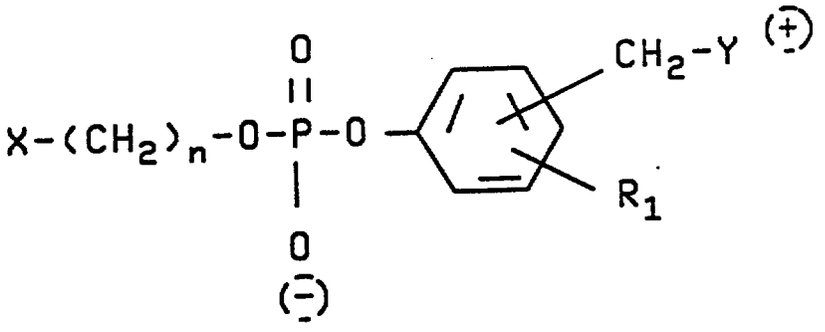
R_1 is one or more substituents of the aromatic ring which may be in any position and is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or halogen;

$-CH_2-Y$ is a single substituent of the aromatic ring which may occupy any position wherein Y is a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

4. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards Gamma Interferon is in combination with an antagonist of Platelet Activating Factor of the formula

* C L M S *

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wherein:

X is a phenyl or naphthyl ring optionally substituted in any position with one or more substituents of:

i) $-R_2$ wherein R_2 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, C_1-C_{25} alkoxy, C_1-C_{25} alkenyloxy, C_1-C_{25} thioalkyl, phenyl, phenoxy, substituted phenyl or substituted phenoxy wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

ii) hydrogen, halogen, trifluoromethyl, cyano, or nitro;

iii) $-CO_2R_3$, $-CONHR_3$, $-CHO$, $OCONHR_3$, or $-NHCOR_3$ wherein R_3 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, phenyl or substituted phenyl wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen and trifluoromethyl;

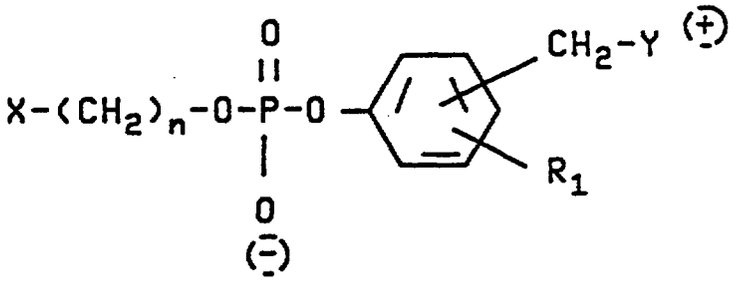
R_1 is one or more substituents of the aromatic ring which may be in any position and is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or halogen;

$-CH_2$-Y is a single substituent of the aromatic ring which may occupy any position wherein Y is a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

* C L M S *

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5. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards bacterial cell wall lipopolysaccharide is in combination with an antagonist of Platelet Activating Factor of the formula:



wherein:

X is a phenyl or naphthyl ring optionally substituted in any position with one or more substituents of:

i) $-R_2$ wherein R_2 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, C_1-C_{25} alkoxy, C_1-C_{25} alkenyloxy, C_1-C_{25} thioalkyl, phenyl, phenoxy, substituted phenyl or substituted phenoxy wherein the substituents are C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

ii) hydrogen, halogen, trifluoromethyl, cyano or nitro;

iii) $-CO_2R_3$, $-CONHR_3$, $-CHO$, $OCONHR_3$ or $-NHCOR_3$ wherein R_3 is C_1-C_{25} alkyl, C_1-C_{25} alkenyl, phenyl or substituted phenyl wherein the substituents are selected C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen or trifluoromethyl;

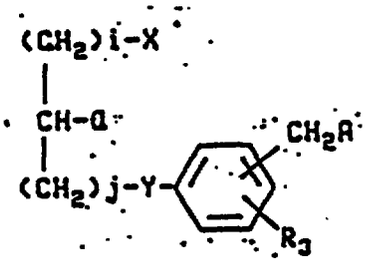
R_1 is one or more substituents of the aromatic ring which may be in any position and is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy or halogen;

* C L M S *

$-CH_2-Y$ is a single substituent of the aromatic ring which may occupy any position wherein Y is a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

* C L M S *

6. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards Tumor Necrosis Factor α is in combination with an antagonist of Platelet Activating Factor of the formula:



Formula II

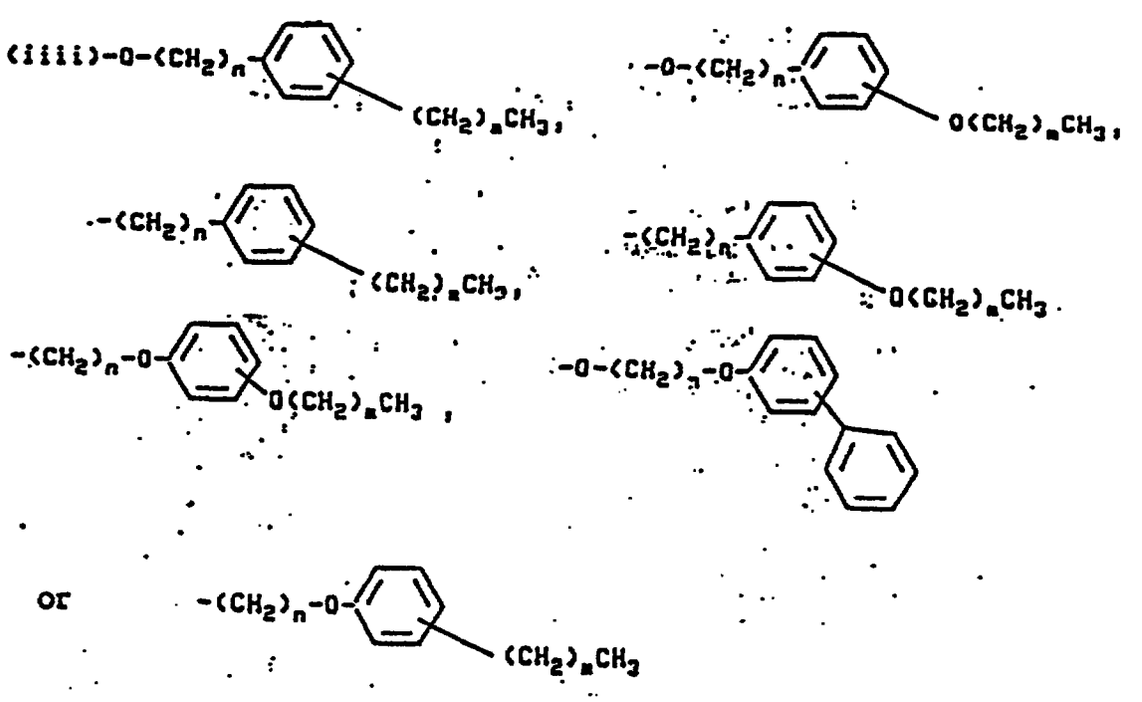
wherein:

(A) X is

i) C_1-C_{24} alkyl;

ii) C_1-C_{24} alkoxy;

iii) C_1-C_{24} carboamoyloxy;



or

n is an integer from 1 to 25 and m is an integer from 0 to 24 and the sum of n and m is less than or equal to 25;

v) phenyl;

vi) mono- or polysubstituted phenyl substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

vii) phenoxy;

viii) mono- or polysubstituted phenoxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

ix) naphthaloxy;

x) mono- or polysubstituted naphthaloxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy or halogen;

xi) $-O-(CH_2)_r-O-((CH_2)_pO)_t-(CH_2)_a-W$ wherein W is methyl or phenyl optionally substituted with C_1-C_3 alkyl, C_1-C_3 alkoxy or phenyl, r, p, t and a are integers such that the expression r+(p+1)t+a is also an integer and has a value of 3 to 20; r is greater than or equal to 2; p is greater than or equal to 2; t is greater than or equal to zero; and a is greater than or equal to zero;

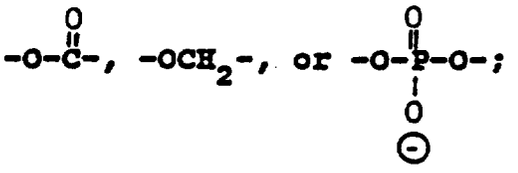
(B) i is an integer from 1 to 3 and j is an integer from 1 to 6;

(C) Q is $-OR_2$,

$-OCH_2\overset{O}{\overset{\|}{C}}OR_2$

or $O-\overset{O}{\overset{\|}{C}}-R_2$, wherein R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

(D) Y is a divalent radical

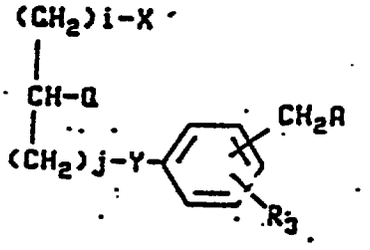


(E) R_3 is one or more C_1-C_5 alkyl, C_1-C_5 alkoxy or halogen substituents of the aromatic ring;

(F) $-CH_2A$ may be in the ortho, meta or para position wherein A is

a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

7. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody is directed towards Interleukin-1β in combination with an antagonist of Platelet Activating Factor of the formula:



Formula II

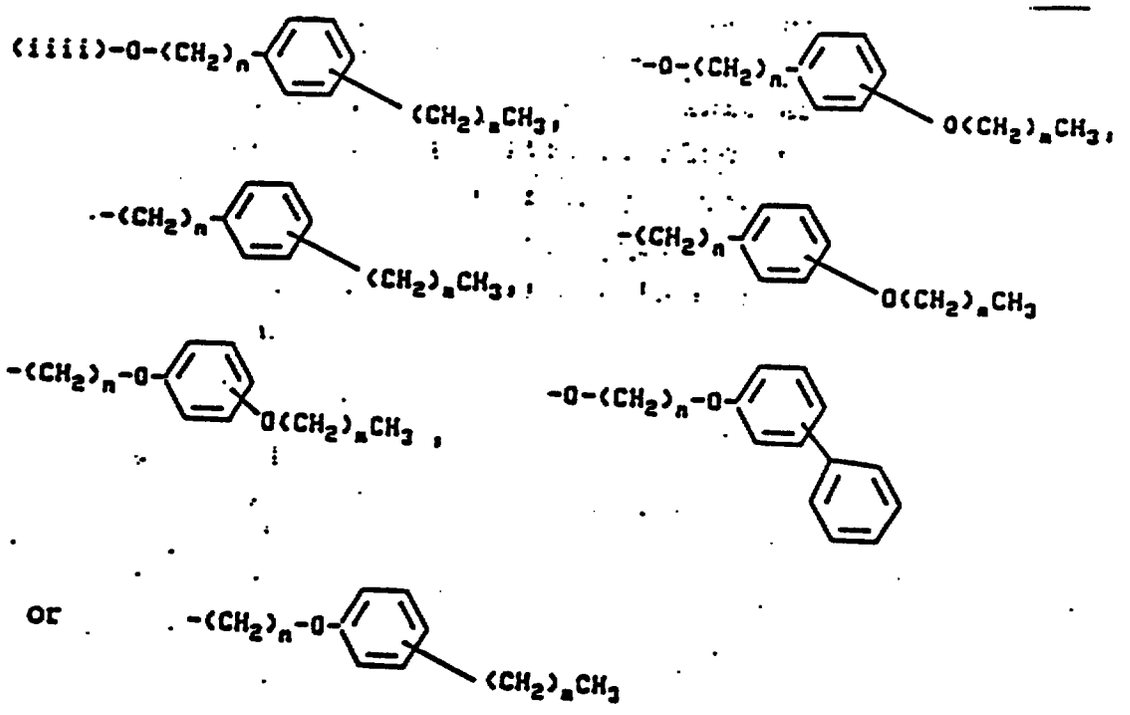
wherein:

(A) X is

i) C_1-C_{24} alkyl;

ii) C_1-C_{24} alkoxy;

iii) C_1-C_{24} carboamoyloxy;



wherein n is an integer from 1 to 25 and m is an integer from 0 to 24 and the sum of n and m is less than or equal to 25;

v) phenyl;

vi) mono- or polysubstituted phenyl substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

vii) phenoxy;

viii) mono- or polysubstituted phenoxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

ix) naphthaloxy;

x) mono- or polysubstituted naphthaloxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy or halogen;

xi) $-O-(CH_2)_r-O-((CH_2)_pO)_t-(CH_2)_a-W$ wherein W is methyl or phenyl optionally substituted with C_1-C_3 alkyl, C_1-C_3 alkoxy or phenyl, r, p, t and a are integers such that the expression r+(p+1)t+a is also an integer and has a value of 2 to 20; r is greater than or equal to 2; p is greater than or equal to 2; t is greater than or equal to zero; and a is greater than or equal to zero;

(B) i is an integer from 1 to 3 and j is an integer from 1 to 6;

(C) Q is $-OR_2$,

$-OCH_2\overset{O}{\overset{\|}{C}}OR_2$

or $O-\overset{O}{\overset{\|}{C}}-R_2$, wherein R_2 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

(D) Y is a divalent radical

$-O-\overset{O}{\overset{\|}{C}}-$, $-OCH_2-$, or $-O-\overset{O}{\overset{\|}{\underset{O^{\ominus}}{P}}}-O-$;

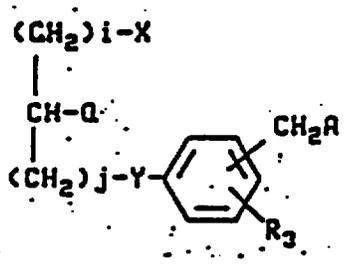
(E) R_3 is one or more C_1-C_5 alkyl, C_1-C_3 alkoxy or halogen substituents of the aromatic ring;

(F) $-CH_2A$ may be in the ortho, meta or para position wherein A is

a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

* C L M S *

8. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody is directed towards Gamma Interferon in combination with an antagonist of Platelet Activating Factor of the formula:



Formula II

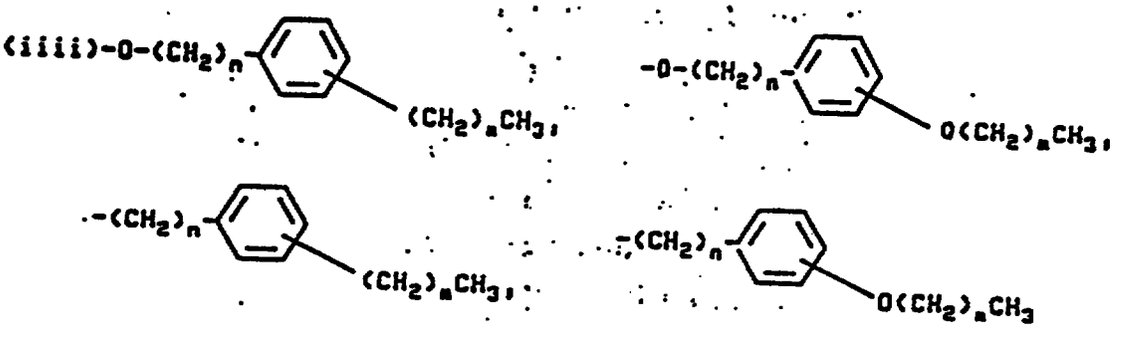
wherein:

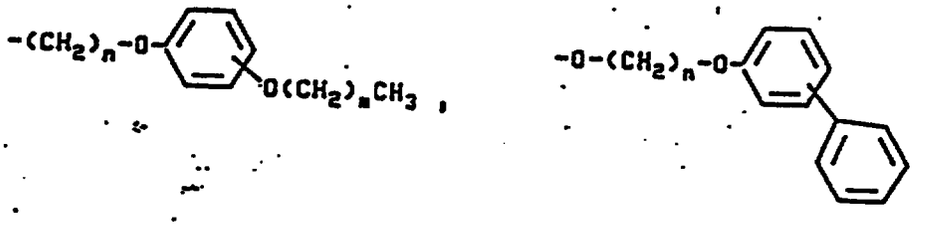
(A) X is

i) C_1-C_{24} alkyl;

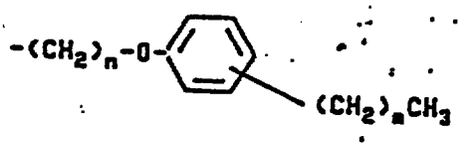
ii) C_1-C_{24} alkoxy;

iii) C_1-C_{24} carboamoyloxy;





or



wherein n is an integer from 1 to 25 and m is an integer from 0 to 24 and the sum of n and m is less than or equal to 25;

v) phenyl;

vi) mono- or polysubstituted phenyl substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

vii) phenoxy;

viii) mono- or polysubstituted phenoxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

ix) naphthaloxy;

x) mono- or polysubstituted naphthaloxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy or halogen;

xi) $-O-(CH_2)_r-O-((CH_2)_pO)_t-(CH_2)_a-W$ wherein W is methyl or phenyl optionally substituted with C_1-C_3 alkyl, C_1-C_3 alkoxy or phenyl, r, p, t and a are integers such that the expression r+(p+1)t+a is also an integer and has a value of 3 to 20; r is greater than or equal to 2; p is greater than or equal to 2; t is greater than or equal to zero; and a is greater than or equal to zero;

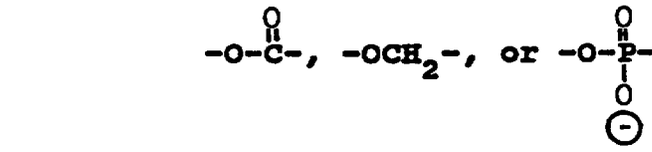
(B) i is an integer from 1 to 3 and j is an integer from 1 to 6;

(C) Q is $-OR_2$,



or  wherein R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

(D) Y is a divalent radical



* C L M S *

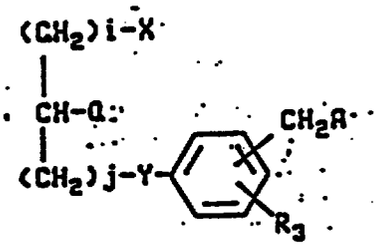
(E) R_3 is one or more C_1-C_5 alkyl, C_1-C_5 alkoxy or halogen substituents of the aromatic ring;

(F) $-CH_2A$ may be in the ortho, meta or para position wherein A is

a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

* C L M S *

9. A method according to Claim 1, of treating endotoxic shock in a mammal wherein the monoclonal or polyclonal antibody directed towards bacterial cell wall lipopolysaccharides is in combination with an antagonist of Platelet Activating Factor of the formula:



Formula II

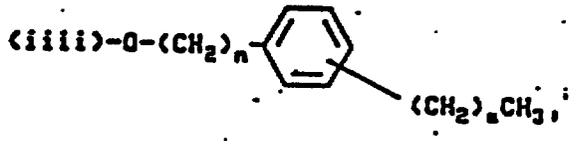
wherein:

(A) X is

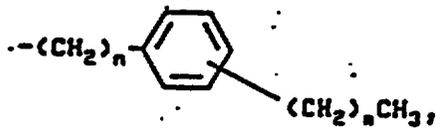
i) C_1-C_{24} alkyl;

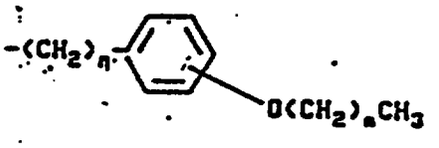
ii) C_1-C_{24} alkoxy;

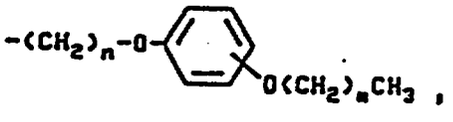
iii) C_1-C_{24} carboamoyloxy;

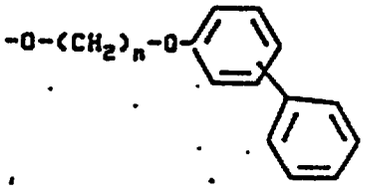


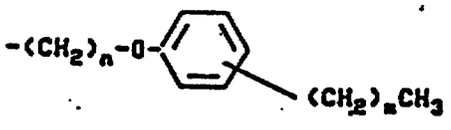










or 

wherein n is an integer from 1 to 25 and m is an integer from 0 to 24 and the sum of n and m is less than or equal to 25;

v) phenyl;

vi) mono- or polysubstituted phenyl substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

vii) phenoxy;

viii) mono- or polysubstituted phenoxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy, halogen, trifluoromethyl, phenyl, substituted phenyl or benzyloxy;

ix) naphthaloxy;

x) mono- or polysubstituted naphthaloxy substituted with C_1-C_{20} alkyl, C_1-C_{20} alkoxy or halogen;

xi) $-O-(CH_2)_r-O-((CH_2)_pO)_t-(CH_2)_a-W$ wherein W is methyl or phenyl optionally substituted with C_1-C_3 alkyl, C_1-C_3 alkoxy or phenyl, r, p, t and a are integers such that the expression r+(p+1)t+a is also an integer and has a value of 3 to 20; r is greater than or equal to 2; p is greater than or equal to 2; t is greater than or equal to zero; and a is greater than or equal to zero;

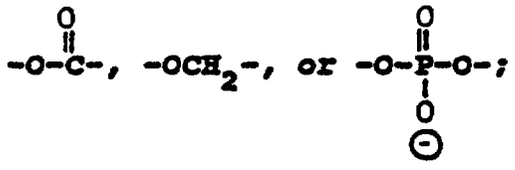
(B) i is an integer from 1 to 3 and j is an integer from 1 to 6;

(C) Q is $-OR_2$,

$-OCH_2\overset{O}{\overset{\|}{C}}OR_2$

or $O-\overset{O}{\overset{\|}{C}}-R_2$, wherein R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

(D) Y is a divalent radical



(E) R_3 is one or more C_1-C_5 alkyl, C_1-C_5 alkoxy or halogen substituents of the aromatic ring;

(F) CH_2A may be in the ortho, meta or para position wherein A is

a mono or bicyclic aromatic heterocycle with 5-7 membered rings containing at least one nitrogen atom which is bonded to the methylene group and optionally one or more other nitrogen or sulfur atoms.

10. A composition comprising a therapeutic combination of an antagonist to Platelet Activating Factor and one or more monoclonal or polyclonal antibodies.

* C L M S *