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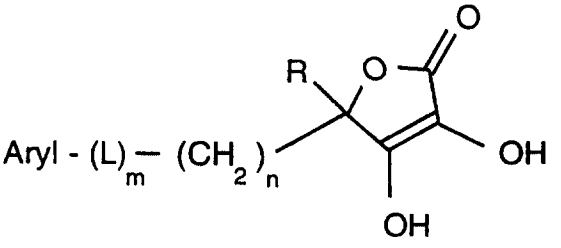
(54) **3,4-DIHYDROXY-2(5H)-FURANONES SUBSTITUEES EN 5 ET DISUBSTITUEES EN 5,5 ET PROCEDE D'UTILISATION DESDITES SUBSTANCES**

(54) **5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5H)-FURANONES AND METHODS OF USE THEREFOR**



(I)

(57) Procédé de synthèse pour la production de 3,4-dihydroxy-2(5H)-furanones disubstituées en 5,5, de 5-[(4-aryl)-3-butynyl]-3,4-dihydroxy-2(5H)-furanones, de 5-(2-arylthio)éthyl-3,4-dihydroxy-2(5H)-furanones et de 5-(2-aryloxy)éthyl-3,4-dihydroxy-2(5H)-furanones à la fois optiquement actives et racémiques. La présente invention concerne en outre l'utilisation des composés susmentionnés en tant qu'agents anti-inflammatoires grâce à leur action en tant qu'inhibiteurs mixtes de la peroxydation des lipides, de la 5-lipoxygénase, de la

(57) The present invention relates to synthetic methods for the production of both optically active and racemic 5,5-disubstituted-3,4-dihydroxy-2(5H)-furanones; 5-[(4-aryl)-3-butynyl]-3,4-dihydroxy-2(5H)-furanones; 5-(2-arylthio)ethyl-3,4-dihydroxy-2(5H)-furanones; and 5-(2-aryloxy)ethyl-3,4-dihydroxy-2(5H)-furanones. This invention further relates to the use of the above mentioned compounds as anti-inflammatory agents through their action as mixed inhibitors of lipid peroxidation, 5-lipoxygenase, cyclooxygenase-1 and

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cyclooxygénase-1 et de la cyclooxygénase-2. Elle concerne encore l'utilisation de tels composés dans le traitement des états inflammatoires chroniques tels que l'asthme, la polyarthrite rhumatoïde, la maladie intestinale inflammatoire, l'athérosclérose, le syndrome de détresse respiratoire aiguë et les troubles du système nerveux central tels que la maladie d'Alzheimer et la maladie de Parkinson, dans lesquels des espèces oxygène réactives et des médiateurs inflammatoires sont des facteurs délétères aggravants.

cyclooxygenase-2. The invention further relates to the use of such compounds in the treatment of chronic inflammatory disorders such as asthma, rheumatoid arthritis, inflammatory bowel diseas, atherosclerosis, acute respiratory distress syndrome, and central nervous system disorders such as Alzheimer's and Parkinson's diseases wherein reactive oxygen species and inflammatory mediators are contributing deleterious factors.

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(54) Title: 5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5H)-FURANONES AND METHODS OF USE THEREFOR

(57) Abstract

The present invention relates to synthetic methods for the production of both optically active and racemic 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones; 5-[(4-aryl)-3-butynyl]-3,4-dihydroxy-2(5*H*)-furanones; 5-(2-arylthio)ethyl-3,4-dihydroxy-2(5*H*)-furanones; and 5-(2-aryloxy)ethyl-3,4-dihydroxy-2(5*H*)-furanones. This invention further relates to the use of the above mentioned compounds as anti-inflammatory agents through their action as mixed inhibitors of lipid peroxidation, 5-lipoxygenase, cyclooxygenase-1 and cyclooxygenase-2. The invention further relates to the use of such compounds in the treatment of chronic inflammatory disorders such as asthma, rheumatoid arthritis, inflammatory bowel diseas, atherosclerosis, acute respiratory distress syndrome, and central nervous system disorders such as Alzheimer's and Parkinson's diseases wherein reactive oxygen species and inflammatory mediators are contributing deleterious factors.

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5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5*H*)-FURANONES AND METHODS OF USE THEREFOR

This Application claims priority from Provisional Applications Serial Nos. 60/024,440 and 60/024,586 both filed on August 22, 1996.

FIELD OF THE INVENTION

The present invention relates generally to 5-substituted and 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones, methods of preparation therefor, and methods for their use.

BACKGROUND OF THE INVENTION

The *aci*-reductone 4-(4-chlorophenyl)-2-hydroxytetronic acid compound (CHTA) possesses antilipidemic and antiaggregatory properties which differ from those of the classical phenoxyactetic acids as has been disclosed in Witiak *et al.* J. Med. Chem., 1988, 31:1434-1445 and Kamanna *et al.*, Lipids, 1989, 24:25-32. Although unsubstituted-, 2-alkyl- and 2-acyltetronic acids are frequently found in nature, the 2-hydroxy substituted tetronic acid redox system is found only in vitamin C and its closely related relatives (isoascorbic acid, erythroascorbic acid) and derivatives, and the macrolide antibiotic, chlorothricin.

The antiaggregatory activities of 2-hydroxytetronic acid *aci*-reductone compound (CHTA) are of interest since blood platelets are involved in the genesis of atherosclerosis. 2-Hydroxytetronic acid *aci*-reductones inhibit collagen-induced human platelet aggregation and secretion of [^{14}C]-serotonin in a concentration-dependent manner at equivalent doses, as reported in Witiak *et al.*, J. Med. Chem., 1982, 25:90-93. The CHTA compound inhibits platelet function by a similar mechanism, involving arachidonic acid release. Redox analogues, such as 2-hydroxytetronic acid, function as antioxidants in membranes or interfere with free radical processes involved in the biosynthetic elaboration of cyclic prostaglandin

endoperoxides (PGG_2 and PGH_2), and, subsequently, thromboxane A_2 from arachidonic acid.

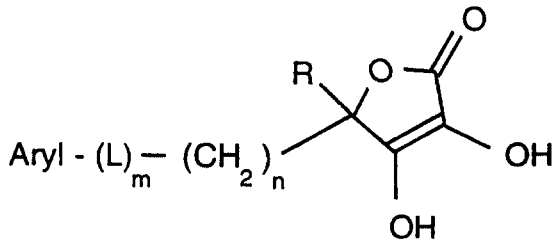
The development of dual antioxidant-arachidonic acid (AA) metabolism inhibitors may provide added benefits over existing drugs for the treatment of diseases associated with oxidative stress and inflammation. Numerous conditions including asthma, rheumatoid arthritis, irritable bowel disease (IBD), adult respiratory distress syndrome (ARDS), atherosclerosis, ischemia/reperfusion injury, restenosis, neurodegenerative disorders and initiation and promotion of carcinogenesis correlate with abnormally high levels of reactive oxygen species (ROS). Antioxidant- based therapies including both natural antioxidants (*e.g.*, vitamin E, vitamin C and SOD), and synthetic antioxidants (*e.g.*, 4-aryl-2-hydroxytetronic acids[1], 2-*O*-alkyl ascorbic acids, probucol and tirilazad mesylate) have been, or are currently being, investigated for the treatment of a number of these conditions.

Previously, the *S*-arachidonic acid *aci*-reductone analog (*S*)-3, 4-dihydroxy-5 [(all Z)-3, 6, 9, 12-octadecatraenyl]-2 (5H)-furanone, was identified as a stereoselective and potent acachidonic acid metabolic inhibitor. This compound inhibits both PGE_2 and LTB_4 production in stimulated macrophages (IC_{50} = 20 μM) and blocks AA-induced platelet aggregation (AAIPA) with an IC_{50} < 10 μM. Dual cyclooxygenase (COX) and lipoxygenase (LO) activity could be important in preventing substrate shunting in the arachidonic acid cascade. Although this compound demonstrates an encouraging biological profile, both its instability and labored synthesis render this compound less than satisfactory as a therapeutic agent.

Thus, there exists a need for new therapeutic agents which exhibit activity as antioxidants and arachidonic acid metabolism inhibitors. It is to this aim that the present invention is directed.

SUMMARY OF THE INVENTION

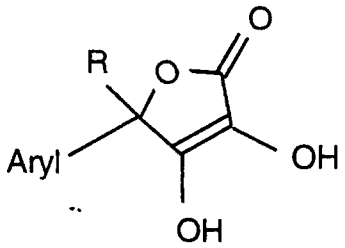
The present invention relates to 5-substituted and 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of the general formula I



(I)

wherein R is hydrogen, phenyl or lower alkyl; L is a linker moiety selected from the group consisting of oxygen, sulfur, nitrogen, acetylene, a cis or trans carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1; n is 0 to 4; Aryl is a mono-substituted or unsubstituted aryl group; with the *proviso* that when R is hydrogen, then either m or n is not zero, and the pharmaceutically acceptable salts thereof.

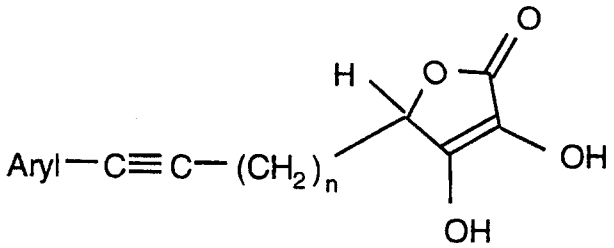
In various preferred embodiments of the present invention, these compounds are represented by four structural subclasses of compounds. Thus, in one preferred embodiment, the compounds are 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Ia



(Ia)

wherein R and Aryl are as hereinbefore defined. Most preferably, in the compounds of formula (Ia), R is a methyl, 1-propyl or 2-methylpropyl group; and Aryl is a phenyl, or substituted phenyl, such as 1, 1'-biphenyl, 4-chlorophenyl or 2- methylpropylphenyl group.

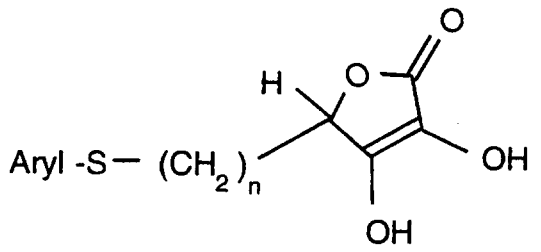
In a second preferred embodiment, the compounds are 5-(aryl alkynyl)-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Ib



(Ib)

wherein n and Aryl are as hereinbefore defined. Most preferably, in the compounds of formula 1b, n is 2 and Aryl is naphthyl or a substituted phenyl such as 2-methylphenyl, 2-hexenyl phenyl, 2-phenylthiomethylphenyl or pentylthiomethyl phenyl.

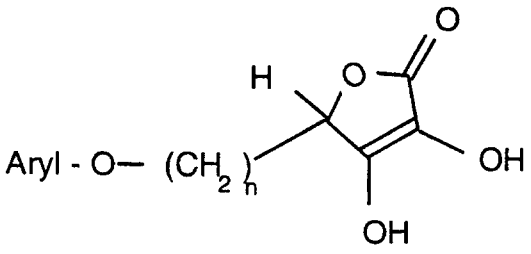
In a third preferred embodiment, the compounds are 5-(arylthio)alkyl-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Ic



(Ic)

wherein n and Aryl are as hereinbefore defined. Most preferably, in the compounds of Formula Ic, n is 2 and the Aryl substituent is napthyl or 4, 5-diphenylisoxazole.

In a fourth preferred embodiment, the compounds are 5-(aryloxy)alkyl-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Id



(Id)

wherein n and Aryl are as hereinbefore defined. Most preferably, in the compounds of formula Id, n is 2 and Aryl is a substituted phenyl or heteroaryl compound such as 1,12 biphenyl-4 yl, 4-phenoxyphenyl, flavonyl, dibenzofuranyl, quinolinyl and naphthyl.

The racemic 5,5-disubstituted analogs of formula Ia are prepared by reacting an ethyl benzoylformate with a Grignard reagent and trapping the intermediate alkoxide anion with benzyloxyacetyl chloride, and subsequently adding lithium diisopropylamide to generate the corresponding 3-benzyloxy-5,5-disubstituted-4-hydroxy-2(5*H*)-furanones. Cleavage of the benzyl group by hydrogenolysis provides racemic 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of formula Ia.

The enantiomerically pure 5,5-disubstituted analogs of formula Ia are synthesized by reacting ethyl benzoylformate with a Grignard reagent, followed by ester saponification and resolution of the resultant 2-aryl-2-substituted-2-hydroxy acid by crystallizing with a suitable optically pure chiral amine to provide the optically pure compounds with non-racemisable stereocenters. Acid esterification, acylation of the hydroxyl group with benzyloxyacetyl chloride, LDA-induced intramolecular Claisen cyclization and reductive cleavage of the benzyl protecting group generates the 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of formula Ia having high enantiomeric purity.

The 5-(aryl alkynyl)-3,4-dihydroxy-2(5*H*)-furanones of formula Ib are synthesized in a convergent manner by coupling 5-(alkynyl)-3,4-dihydroxy-2(5*H*)-furanone with aryliodides by employing a catalytic amount of $Pd(PPh_3)_4$. The starting material, 5-(alkynyl)-3,4-dihydroxy-2(5*H*)-furanone, is synthesized in four steps. For instance, intermolecular Claisen reaction between α-trimethylsilyloxy-γ-butyrolactone and ethyl benzyloxyacetate yields 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone. Iodination (I_2, PPh_3, imidazole), subsequent iodo displacement with lithium acetylide, and benzyl group cleavage yields, for instance, the 5-(3-butynyl)-3,4-dihydroxy-2(5*H*)-furanone coupling precursor.

The 5-(arylthio)alkyl-3,4-dihydroxy-2(5*H*)-furanones of formula Ic are produced by reacting a 3,4-dihydroxy-5-(iodoalkyl)-2(5*H*)-furanone with the lithium salt of a substituted arylthiol. The starting material, 3,4-dihydroxy-5-(2-iodoalkyl)-2(5*H*)-furanone is produced by benzyl group cleavage of 3-benzyloxy-4-hydroxy-5-(2-iodoalkyl)-2(5*H*)-furanone.

The 5-(aryloxy)alkyl-3,4-dihydroxy-2(5*H*)-furanones of formula Id are prepared by coupling 3,4-dibenzyloxy-5-(hydroxyalkyl)-2(5*H*)-furanone with an appropriately substituted phenol according to the Mitsunoble reaction. Subsequent benzyl group

cleavage by hydrogenation yields the desired 5-(aryloxy) alkyl-3, 4-dihydroxy-2(5H)-furanone.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "alkenyl" means an organic, alkanyl group containing one or more double bonds and which can optionally be substituted by one or more halogen, lower alkanyl, alkoxy, aromatic or heteroaromatic groups. Examples of unsubstituted alkenyl groups include those such as 3-butenyl, 3- or 4-pentenyl, and the like. In a similar fashion, the term "alkynyl" refers to an organic, alkanyl group containing one or more triple bonds, of which 3-butynyl, 3- or 4- pentynyl and the like are representative.

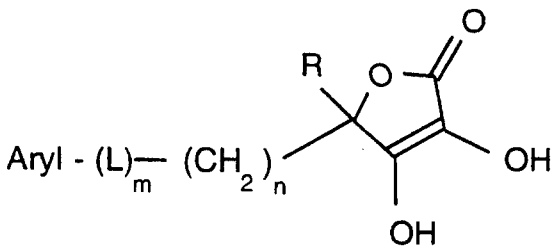
The term "substituted or unsubstituted aryl", as utilized herein, means an organic, aromatic group which can be unsubstituted or substituted by one or more lower alkyl, lower alkenyl, lower alkenynyl, loweralkylthio, loweralkylsulfonyl, loweralkylsulfonylamino, aromatic or heteroaromatic groups. Examples of unsubstituted aryl groups include phenyl, pyridyl, thiophenyl, furyl, pyrrolyl and the like. Examples of substituted aryl groups include those such as alkyl-substituted aryl, *e.g.*, tolyl, 3-methylpyridyl, 2,3-dimethylphenyl, 4-ethylphenyl, 4-isobutylphenyl; alkoxysubstituted aryl, *e.g.*, 4-methoxyphenyl; loweralkylthio or loweralkylsulfonyl-substituted aryl, *e.g.*, 1-propylthiophenyl, 1-pentylsulfonylphenyl, lower alkenyl substituted phenyl, *e.g.*, 4-(2-(2Z-hexenyl] phenyl and aryl-substituted aryl, *e.g.*, 1,1'-biphenyl and naphthyl. Complex aryl groups such as those derived from flavone, dibenzofuran, 1,8-natphthalimide, 1,8-naptholsultam, quinoline, 4,5-diphenyl-2-thio-1, 3- isoxazole, and napthalenethiol can also be utilized as substituant groups. Particularly preferred are compounds wherein a 2- or 2,3-disubstitution pattern (relative to the alkenenyl or alkynenyl group) is present.

As used herein, the term lower "alkyl" means straight- or branched-chain saturated aliphatic hydrocarbon groups preferably containing 1-6 carbon atoms. Representative of such groups are methyl, ethyl, isopropyl, isobutyl, butyl, pentyl, hexyl and the like.

The term "alkoxy" means a lower alkyl group attached to the remainder of the molecule by oxygen. Examples of alkoxy include methoxy, ethoxy, propoxy, isopropoxy and the like.

The compounds of formula I can be formed as mixtures of enantiomers, as well as cis/trans isomers, due to the asymmetric carbon atoms of the ring structure and the double bonds present in the substituents. The present invention contemplates the use of both the individual isomers, as well as the racemic or cis/trans mixtures or both.

The present invention relates to 5-substituted-and 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of the general formula,

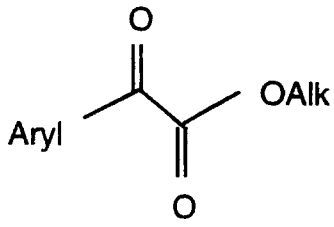


(I)

wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the group consisting of oxygen, sulfur, nitrogen, acetylene, a *cis* or *trans* carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4, Aryl is a substituted or unsubstituted aryl group; with the *proviso* that when R is hydrogen, then either m or n is not zero; and the pharmaceutically acceptable salts thereof.

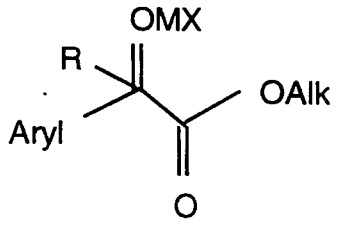
In general, the compounds of formula I wherein m and n are zero are prepared by:

a) reacting a benzoylformate of the formula,



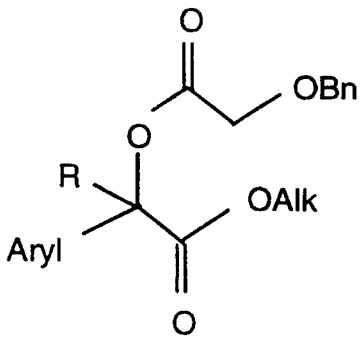
(II)

wherein Alk is a lower alkyl group, Aryl is as hereinbefore defined with an organometalic reagent RMX wherein M is a group I or group II metal, X is a halogen, and R is as hereinbefore defined, to form an intermediate alkoxide of the formula,



(III)

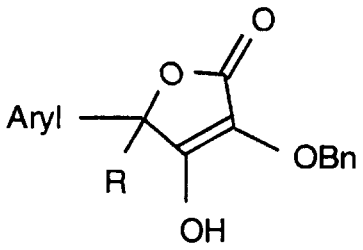
wherein Aryl, R, M, Alk and X are as hereinbefore defined. The intermediate alkoxide is treated with a benzyloxyacetyl chloride, wherein Bn is a protecting group such as benzyl or a substituted derivative thereof, to provide an intermediate diester of the formula,



(IV)

wherein Aryl, R and Alk are as hereinbefore defined;

(b) Intramolecular Claisen cyclization of the diester of formula IV to the tetronic acid of the formula,



(V)

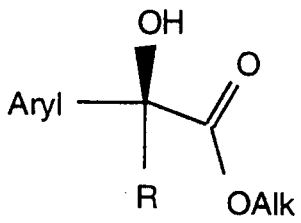
wherein Aryl, R and Bn are as hereinbefore defined; and

(c) cleaving the benzyl protecting group of formula V by catalytic hydrogenation to yield the desired 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein Aryl and R are as hereinbefore defined, and m and n are 0.

Step (a) of the instant process utilizes as starting material, the appropriate benzoyl formate of the formula II wherein Aryl and Alk are as hereinbefore defined which can be purchased through commercial suppliers, or, if not commercially available, synthesized according to literature procedures. Benzoylformates are prepared by mixing an aryl compound, alkyl oxalylchloride and $AlCl_3$ (or suitable Lewis acid) in a 1.0/1.1/1.1 mixture in 1,2-dichloroethane (or suitable solvent) at 0_ to 10_C with vigorous stirring and subsequently stirring the reaction mixture at 25_C for 24 hours according to the method of Kuchar et al., *Coll. Czech. Chem. Commun.*, 49: 122-136 (1984).

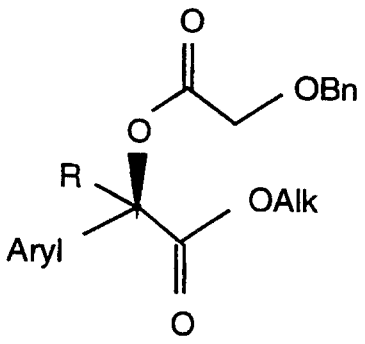
A process for the synthesis of enantiomerically pure analogs of the formula I wherein m and n are both zero comprises:

(a) reacting an optically pure 2-hydroxyester of the formula



(VI)

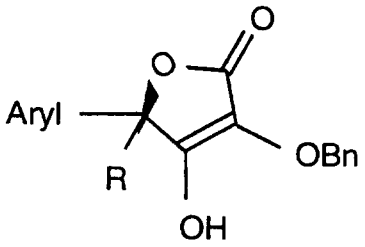
wherein Aryl, R and Alk are as hereinbefore defined with a benzyloxyacetyl chloride, wherein Bn is as hereinbefore defined, to provide an intermediate diester of the formula,



(VII)

wherein Aryl, R, Bn, Alk and R are as hereinbefore defined;

(b) Intramolecular Claisen cyclization of the diester of formula VII to the tetronic acid of the formula,



(VIII)

wherein Aryl, R and Bn are as hereinbefore defined; and

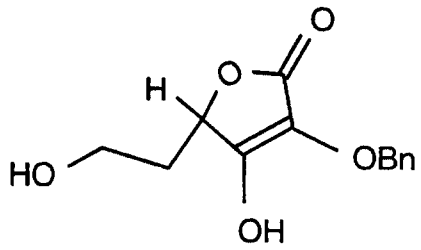
(c) cleaving the benzyl protecting group of formula VIII by catalytic hydrogenation to yield the desired optically pure 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein Aryl and R are as hereinbefore defined, and m and n are both zero.

Step (a) of this process utilizes as starting material, an optically pure 2-hydroxyester of the formula VI, wherein Aryl, R and Alk are as hereinbefore defined, which can be purchased through commercial suppliers or, if not commercially available, synthesized according to literature procedures. Reaction of a benzoylformate with an organometalic reagent RMX, wherein R, M, and X are as hereinbefore defined, produces racemic 2-hydroxyesters of the formula VI, wherein aryl, R and Alk are as hereinbefore defined. Ester saponification with, for example, 1.0M NaOH, resolution with an

optically pure amine base using the method of Saigo et al., *Bull. Chem. Soc. Jpn.*, 55: 1188-1190 (1982) and esterification of the acid with, for example an etheral solution of CH_2N_2, provides optically pure 2-hydroxyesters of the formula VI.

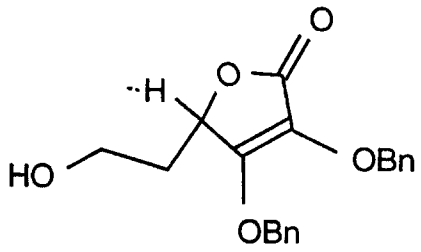
A process for the synthesis of analogs of formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1 n = 2, and L is an oxygen, ester, N-sulfonamide or N-imide linkage comprises:

(a) reacting a 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula,



(IX)

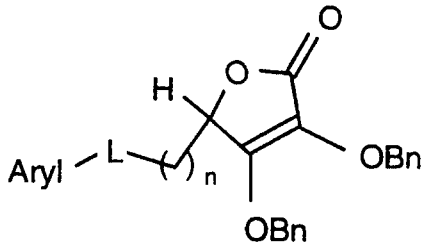
wherein Bn is as hereinbefore defined with one equivalent of BnBr and one equivalent of triethlyamine in THF for 5 hours at 65_C to provide 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula,



(X)

wherein Bn is as hereinbefore defined;

(b) reacting the 3,4-dibenzyloxy-2(5*H*)-furanone of the formula X with an aryl alcohol (i.e. phenol), carboxylic acid, sulfonamide, or phthalimide, wherein aryl is as hereinbefore defined, under Mitsunoble conditions to provide 3,4-dibenzyloxy-2(5*H*)-furanones of the formula,



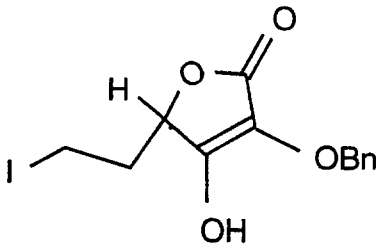
(XI)

wherein Aryl and Bn are as hereinbefore defined, L is an oxygen, ester, N-sulfonamide or N-imide linkage and n = 2; and

(c) cleaving the benzyl protecting groups of formula XI by catalytic hydrogenation to yield the desired 5-substituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1, n = 2, and L is an oxygen, ester, N-sulfonamide or N-imide linkage.

A process for the synthesis of analogs of the formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1, n = 2, and L is a sulfur linkage comprises:

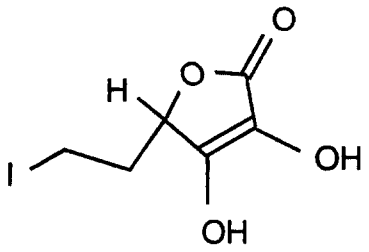
(a) Iododination of the 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula IX with I_2, PPh_3 and imidazole in CH_3CN/ether (1/5) to produce the 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2-(5*H*)-furanone of formula,



(XII)

wherein Bn is as hereinbefore defined;

(b) benzyl group cleavage by first treating the furanone of formula XII with acetyl anhydride and pyridine in CH_2Cl_2 for 2 hours, followed by removal of all volatile substances in vacuo and subsequent treatment with boron trichloride to yield 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone of the formula;

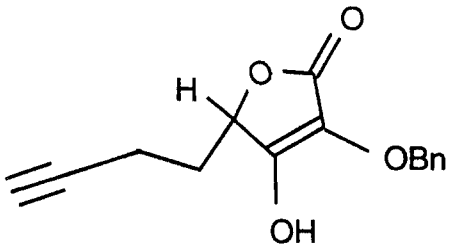


(XIII)

(c) reaction of a compound with the formula XIII with three mole equivalents of the lithium salt of an arylthiol, wherein aryl is as hereinbefore defined, provides compounds of the formula I wherein Aryl is as hereinbefore defined, n = 2, R = H, and L is sulfur.

A process for the synthesis of analogs of the formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1, n = 2, and L is an acetylene or carbon-carbon double bond linkage comprises:

(a) reaction of 5-(2-iodoethyl)-2-(5*H*)-furanone of the formula XII with lithium acetylide ethylenediamine complex in HMPA at -5_C to make 3-benzyloxy-4-hydroxy-5-(3-butynyl)-2-(5*H*)-furanone of formula,

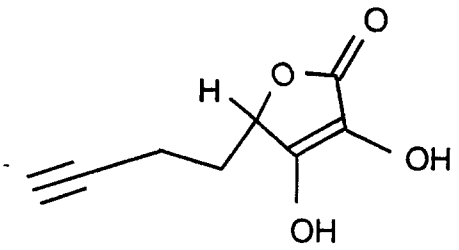


(XIV)

wherein Bn is as hereinbefore defined;

(b) benzyl group cleavage by first treating the furanone of formula XIV with acetyl anhydride and pyridine in CH_2Cl_2 for 2 hours, followed by removal of all volatile

substances in vacuo and subsequent treatment of the remaining residue with boron trichloride to yield compounds of the general formula;



(XV)

(c) coupling the 5-(3-butynyl)-2(5*H*)-furanone of formula XV with an aryliodide to provide analogs of the formula I, wherein Aryl is as hereinbefore defined, n = 2, R = H and L is an acetylene linker;

(d) reduction of the acetylene moiety by the addition of 1 mole equivalent of H_2 by catalytic hydrogenation under Lindlar conditions to yield compounds of formula I wherein Aryl is as hereinbefore defined, n = 2, R = H and L is a carbon-carbon *cis* double bond; and

(e) reduction of the acetylene moiety by the addition of 2 mole equivalent of H_2 by catalytic hydrogenation to yield compounds of formula I wherein Aryl is as hereinbefore defined, m = 0, n = 4, and R is hydrogen.

In a composition aspect, the present invention encompasses novel pharmaceutical compositions comprising the compounds of the general formula I, together with a physiologically acceptable carrier or excipient, in an amount sufficient to have antilipidemic, antiaggregatory or antiinflammatory activities in an animal or patient. The compounds and their compositions of the present invention are thus useful in the treatment or prevention of atherosclerotic disorders, as well as in the treatment of various pathologies in which acute and chronic inflammation occur.

The starting materials utilized in the synthesis of the compounds of formula I are known in the art and/or are preparable by methods described herein. Where the pure optical isomers of these compounds are desired, numerous methods exist for the manufacture of optically active and optically pure derivatives of the necessary starting materials. Also, a wide range of chiral bases can be used to starting materials and

intermediate products. Partial separation of enantiomers can typically accomplished with optically active solvents such as (-)-menthone, (-)-menthyl acetate and (+)-limonene. Anion-exchange chromatography using a chiral stationary phase constructed of 1-p-nitrophenyl-2-amino-1,3-propanediol, or chromatography through starch successfully separates mandelic acid enantiomers.

The invention also provides for pharmaceutical compositions comprising the compounds of formula I above, as well as their physiologically acceptable salts (such as, for example, Na^+, K^+, NH_4^+).

The compounds of the invention have antilipidemic and antiaggregatory activity and are thus useful in the treatment or prevention of atherosclerotic disorders. Additionally, the compounds of the invention possess the ability to inhibit the activity of cyclooxygenase and 5-lipooxygenase in standardized assays for such activity, thus making them useful for the treatment of pathologies involving acute or chronic inflammation, such as inflammatory bowel disease, asthma, adult respiratory distress syndrome (ARDS) and various forms of arthritis.

BIOLOGICAL EVALUATION

The compounds of the invention were screened for their anti-inflammatory activity using a series of *in vitro* tests the details of which are given below. The activity of various compounds against 5-lipoxygenase, cycloxygenase-1, cycloxygenase-2 and lipid peroxidase was evaluated. Results of the screening procedures are included in TABLE I, and the activity against 5-lipoxygenase at a test concentration of 1μM in Table II.

5-LIPOXYGENASE SCREEN

5-Lipoxygenase catalyzes the oxidative metabolism of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HETE), the initial reaction leading to the

formation of the leukotrienes. Briefly, the testing procedure utilizes a crude enzyme preparation from rat basophilic leukemia cells (RBL-1) according to the methods of T. Shimuzu et al. *Pro. Natl. Acad. Sci.* 81:689-693 (1984) and R.W. Egan et al, *J. Biol. Chem.* 260: 11554-11559 (1985). Test compounds are pre-incubated with the enzyme preparation for 5 minutes at room temperature and the reaction is initiated by the addition of arachidonic acid. Following an 8 minute incubation at room temperature, the reaction is terminated by the addition of citric acid and concentrations of 5-HETE are determined by RIA. Compounds are screened at 30μM. Under these conditions the reference compound phenidone has an IC_{50} of 30μM.

CYCLOOXYGENASE-1 SCREEN

Cyclooxygenase-1 is involved in the formation of prostaglandins and thromboxane via the oxidative metabolism of arachidonic acid. Briefly, cyclooxygenase from ram seminal vesicles is incubated with arachidonic acid (100μm) for 2 minutes at 37°C in the presence or absence of test compounds according to the methods of A.T. Evans et al., *Biochem. Pharm.* 36:2035-2037 (1987) and R. Boopathy et al., *Biochem J.* 239:371-377 (1968). The assay is terminated by the addition of trichloroacetic acid and cyclooxygenase activity is determined by reading the absorbance at 530nm. Compounds are screened at 300μM. Under these condition the reference compound aspirin has an IC_{50} value of 240μM.

CYCLOOXYGENASE-2 SCREEN

Cyclooxygenase-2, also known as prostaglandin H synthetase-2, catalyzes the rate-limiting step in the synthesis of inflammatory prostaglandins. In this reaction cyclooxygenase-2 catalyzes the oxygenation of unesterified precursors to form cyclic endoperoxide derivatives, including prostaglandin H. Briefly, cyclooxygenase-2 from sheep placenta, 14μg/assay tube, is incubated with arachidonic acid (500μM) for 1.5 minutes at 27°C in the absence or presence of test compounds according to the methods of A.T. Evans, et al., *Biochem Pharm.* 36:2035-2037 (1987) and M.G. O'Sullivan et al., *Biochem. Biophys. Res. Cxomm.* 187: 1123-1127 (1992). The assay

is terminated by the addition of trichloroacetic acid and cyclooxygenase activity is determined by reading the absorbance at 532nm. Compounds are screened at 300μM. Under these conditions the reference compound NS-398 exhibited 77% inhibition at 300μM.

LIPID PEROXIDATION SCREEN

Lipid peroxidation is a consequence of various stimuli, including reactive free radicals. Polyunsaturated fatty acids associated with plasma membranes are degraded due to enzymatic induction by reactive agents such as CCl_4, leading to cellular damage. Briefly, microsomes are prepared from rat livers and the protein concentration is determined according to the method of D. Mansuy et al., *Biochem. Biophys. Res. Comm.* 135:1015-1021 (1986). A reaction mixture consisting of 2mg of the microsomal preparation, an NADPH generating system, 20mM CCl_4 and test compound are incubated for 12 minutes at 37°C. The reaction is terminated by the addition of a mixture of thiobarbituric acid and trichloroacetic acid. The absorbance is read at 535nm and is proportional to the concentration of malondialdehyde. Compounds are screened at 300μM. Under these conditions the reference compound, alpha-tocopherol has an IC_{50} value of 280μM.

TABLE I

Example #	Compound Name	(PERCENT INHIBITION) COX-1 (300μM)	COX-2 (300μM)	5-LO (30μM)	LPO (300μM)
1	3,4-Dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone	-12	3	58	63
2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	33	22	107	78
3	3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	2	-4	99	78
4	5-(4-Chlorophenyl)-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	2	24	2	54
5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5*H*)-furanone	13	22	99	70
6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5*H*)-furanone	67	46	96	82
7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone	52	34	102	73
8	3,4-Dihydroxy-5,5-diphenyl-2(5*H*)-furanone	15	17	94	70
9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone	25	19	82	79
10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone	43	34	106	89
11	(*S*)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	34	10	101	71
12	(*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	10	12	101	62
13	(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	12	14	102	76
14	(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	12	18	96	66
15	3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone	9	-4	100	-5
16	3,4-Dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone	17	2	100	76
17	5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone	17	21	99	74
18	3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone	11	-12	99	71
19	3,4-Dihydroxy-5-[2-(1,8-naphthalimide)-*N*-ethyl]-2(5*H*)-furanone	9	2	86	68

20	3,4-Dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone	-15	13	91	61
21	3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone	12	10	101	68
22	5-[2-((1,1'-Biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone	18	10	99	74
23	3,4-Dihydroxy-5-[2-(quinoline-2-oxy)ethyl]-2(5*H*)-furanone	8	-2	93	69
24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone	76	68	113	78
25	3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone	6	19	102	74
26	3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone	12	12	101	77
27	3,4-Dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone	5	20	42	59
28	3,4-Dihydroxy-5-[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone	4	15	58	61
29	3,4-Dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone	55	26	81	72
30	3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone	26	16	100	62
31	3,4-Dihydroxy-5-[(4-(2-phenylsulfonamide-(*N*-butyl))-3-butynyl]-2(5*H*)-furanone	7	23	81	73
32	3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone	34	23	98	75
33	3,4-Dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone	37	20	84	74
34	3,4-Dihydroxy-5-[(4-(2-(1-pentylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone	67	43	92	63
35	3,4-Dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone	25	13	30	60
36	3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone	NT	NT	85@1	NT
37	3,4-Dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone	NT	NT	NT	NT
38	3,4-Dihydroxy-5-[(4-phenyl)-3Z-butenyl]-2(5*H*)-furanone	NT	NT	NT	NT
39	3,4-Dihydroxy-5[(4-(2-methyl)phenyl)-3Z-butenyl]-2(5*H*)-furanone	NT	NT	NT	NT
40	3,4-Dihydroxy-5[(4-(2-(2*Z*-hexenyl))phenyl)-3Z-butenyl]-2(5*H*)-furanone	38	25	99	65

TABLE II

The effect of various aci-reductones on 5-Lipoxygenase (5-LO)

at a test concentration of 1μM

Example #	Compound Name	Percent Inhibition of **5-LO** at a test Conc. of (1μM)
2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	15
5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5*H*)-furanone	68
6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5*H*)-furanone	70
7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone	61
8	3,4-Dihydroxy-5,5-diphenyl-2(5*H*)-furanone	15
9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone	40
10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone	64
11	(*S*)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	59
12	(*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	60
13	(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	59
14	(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	50
15	3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone	52
16	3,4-Dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone	54
17	5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone	60
18	3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone	49
20	3,4-Dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone	38
21	3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone	62
22	5-[2-((1,1'-Biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone	55
24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone	71
25	3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone	56

26	3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone	54
29	3,4-Dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone	56
30	3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone	70
32	3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone	66
46	3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone	91; IC_{50} = 160nM

Nuclear factor-κB exists in the cytoplasm of most cells bound to a natural inhibitor protein IκB. In a complex cascade, extracellular stimulation by cytokines such as TNF-α or interleukin-1 (IL1), viruses, lipopolysaccharide (LPS) or UV-radiation results in the production of second messenger reactive oxygen species (ROS). Increased ROS concentrations are important mediators, which instigate the process of IκB disassociation from the NF-κB complex enabling NF-κB to migrate into the cell nucleus. Recent findings demonstrate that low levels of H_2O_2 activate NF-κB and that a number of antioxidants inhibit this activation process. The antioxidants pyrrolidone dithiocarbamate (PDTC) and N-acetyl-cysteine (NAC) inhibit both the H_2O_2 and extracellular cytokine-induced activation of NF-κB in a concentration dependent manner. Steroids such as dexamethasone are potent anti-inflammatory agents in part, because they stimulate the gene synthesis of IκB, leading to inhibition of NF-κB. The mechanism by which these aci-reductones block NF-κB nuclear translocation is not clear, but is likely related to their antioxidant properties. However, the possibility that they specifically interact with a biomolecule involved in NF-κB activation has not been disregarded.

Test Compound	Concentration	% Inhibition
3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone	30nM	90%
Reference Compounds		
Dexamethasone	1000nM	60%
Pyrrolidone dithiocarbamate (PDTC)	10,000nM	50%
N-Acetyl-cysteine (NAC)	1000nM	0%

Experiments measuring test agents effect on NF-κB nuclear membrane translocation were performed with NR8383 cells, which are transformed rat alveolar macrophages. Cells were treated simultaneously with LPS (1 μg/ml) and the test compounds (10 and 30 nM). In addition, some compounds were tested at doses of 10 and 30 μM. Untreated control cells and cells treated with LPS alone were tested in each experiment. Cells were harvested 6 hours after treatment. Nuclear proteins were extracted, frozen and quantified using the Bradford assay. Electrophoretic

mobility shift assays (EMSA) were subsequently analyzed using a radiolabeled NF-κB probe. Nuclear proteins were reacted with the radiolabeled probe, run on a 5% polyacrylamide gel, and subjected to audoradiography. Specificity of protein binding for the NF-κB binding site was assayed by cold and nonspecific competition using the LPS treated sample in each experiment . All EMSA were duplicated at least once to verify results. Laser densitometry of NF-κB bands was done on autoradiographs to quantify NF-κB binding activity.

The human T lymphoid cell line Jurkat was transfected with a response element lacZ reporter in which transcription of the β-galactosidase gene is directed by the binding site for the NF-κB transcription factor. The cell line containing κB-Z is stimulated with calcium ionophore A23187 and phorbol ester PMA; this stimulation is inhibited by the immunosuppressive drug cyclosporin A. In the screening assay transfected κB-Z Jurkat cells (1 x 10^6 cells/assay well) are incubated with 2μM A23187, 20 ng/mL PMA and test compound or vehicle in the well of a microplate for at least 4 hours according to the procedure of M.J. Lenardo and D. Baltimaore, NF-κB: a pleiotropic mediator of inducible and tissure specific gene control. *Cell* **58**, 227-229, (1989). At the end of the incubation, the cells are spun down and resuspended in the buffer and FDG (fluorescein di-β-*D*-galactopyranoside) solution. The covered plates are further incubated in the dark for 16 hours at 25°C. The fluorescent product resulting from the end of reaction is read at 485/530 in a Cyto2300 fluorescence reader. Compounds were screened at 10μM. The standard, cyclosporin A has an IC_{50} of 50nM in this assay.

TABLE III

The effect of various aci-reductones on Nuclear Factor-kappa B

Percent Inhibition (%)

Example #	Compound Name	(PERCENT INHIBITION) NF-κB (10 μM)
2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	90
5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5*H*)-furanone	68
6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5*H*)-furanone	59
7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone	21
8	3,4-Dihydroxy-5,5-diphenyl-2(5*H*)-furanone	33
9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone	26
10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone	16
11	(*S*)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	72
12	(*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone	56
13	(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	49
14	(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone	60
24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone	44
41	3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone	61; IC_{50} = 6μM

The ability of the compounds of formula I to inhibit the action of various inflammatory cytokines make them useful in a wide variety of therapeutic methods. Specifically, their ability to mediate or inhibit the actions of TNF-α makes these compounds useful in the treatment of various invasive diseases, infections, and inflammatory states. Particularly important is the inhibition of the large amount of TNF produced during serious bacterial infections, which can trigger a state of shock and tissue injury (septic shock syndrome).

A further important use of the compounds of formula I is to inhibit the TNF which is known to mediate cachexia produced during chronic disease states. Thus, these compounds are particularly useful in adjunctive therapy for AIDS and cancer patients to reduce and/or ameliorate the consequences of cachexia produced during these chronic disease states.

A further specific method of treatment for which the compounds of the instant invention are particularly useful is in the treatment of rheumatoid arthritis wherein increased amounts of the inflammatory cytokines, TNF-α and IL-1 are present. By virtue of their ability to mediate and/or inhibit the action of these cytokines, inflammation and the severity of the disease state can be reduced or eliminated.

The compounds of the instant invention can also be utilized in the treatment of multiple sclerosis (MS), Crohn's disease and ulcerative colitis by inhibiting and the activity of the inflammatory cytokines which underlie these disease states.

The compounds of the invention may be formulated in a conventional manner, optionally together with one or more other active ingredients, for administration by any convenient route for example of oral, intravenous or intramuscular administration.

Thus, according to another aspect, the invention provides a pharmaceutical composition comprising a compound of formula I and/or a pharmaceutically

acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with physiologically acceptable excipients.

The compounds may be formulated for intravenous or intramuscular administration in dry form for reconstitution before use, or as a sterile solution or suspension.

A proposed daily dose based on similar pharmacokinetic parameters to CHTA for administration to man is about 10 to 25 mg/kg, for example, 700 mg to 1 gm daily, which may be conveniently administered in 1 to 3 doses per day. The precise dose administered will, of course, depend on the age and condition of the patient.

The following examples are illustrative of the present invention.

EXAMPLES

General Methods. Unless otherwise noted all reagents were purchased from commercial suppliers and used as received. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with either an IBM-Bruker model NR/100 or Varian model 200 FT NMR spectrometer. Tetramethylsilane (TMS) in $CDCl_3$, DMSO-d_6, acetone-d_6, CD_3OD or D_2O was used as internal standard. Chemical shifts are reported on the δ scale with peak multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd doublet of doublet of doublets; t, triplet; q, quartet, m, multiplet. Anhydrous solvents were purchased from Aldrich Chemical, Inc., Milwaukee, WI and used as such. Optical rotations were performed on a Perkin-Elmer model 241

polarimeter using a 10 cm, 1mL cell. Elemental Analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

PREPARATION OF STARTING MATERIALS

EXAMPLE A

Ethyl 4-phenylbenzoylformate

A mixture of 77g (500mmol) of biphenyl and 68mL (540mmol) of ethyl oxalylchloride was dissolved in 300mL of 1,2-dichloroethane and cooled with stirring to between 0° and 10°C. $AlCl_3$ (73g, 550mmol) was added at such a rate to maintain the reaction temperature below 15°C. The mixture was stirred at 10°C for 1 hour and at 25°C for 24 hours, then poured into 1000mL of a ice cold 10% HCl solution. The aqueous suspension was extracted with 4 x 500mL of ether and the combined ether extracts were washed with 100mL of 10% HCl solution, 100mL of brine, dried ($MgSO_4$) and concentrated to a yellow oil which was purified by chromatography over SiO_2 using initially acetone/hexanes (2/98) and increasing the polarity of the solvent to acetone/hexanes (10/90) upon elution of the nonpolar impurities to liberate 82g (68% yield) of a yellow oil, which crystallized on standing.

EXAMPLE B

Ethyl 4-isobutylbenzoylformate

A mixture of 27g (200mmol) of isobutylbenzene and 24mL (215mmol) of ethyl oxalylchloride underwent Friedel-Crafts acylation reaction in an analogous fashion as described for the synthesis of ethyl 4-phenylbenzoylformate to yield 38g (81% yield) of ethyl 4-isobutylbenzoylformate as a colorless oil.

EXAMPLE C

3-Benzyloxy-4-hydroxy-5-(2-hydroxy)ethyl-2(5*H*)-furanone

A. A solution of 10.0g (98mmol) of α-hydroxy-γ-butyrolactone in 100mL of anhydrous THF under argon was cooled to 0-5°C with magnetic stirring. Addition of 14mL (110mmol) of trimethylsilyl chloride and 16mL (115mmol) of triethylamine

immediately produced a white precipitate. The suspension was warmed to room temperature and stirred for 4 hours. The suspension was poured into a separatory funnel containing 100mL of H_2O and 500mL of ether. The organic layer was washed with 50mL of H_2O, 50mL of brine, dried ($MgSO_4$) and concentrated. Purification (Kugelrohr distillation) provided 14.7g (90% yield) of α-trimethylsilyloxy-γ-butyrolactone bp 80-100°C (8 mm Hg).

B. To a 500mL 2-necked flask flame dried under argon and equipped with a magnetic stir bar, was added 200mL of THF and 18.7mL (89mmol) of hexamethyldisilazide. The flask was cooled to -78°C and 55.4mL (89mmol) of a 1.6M nBuLi solution in hexanes was added with stirring over 15 min. The light yellow solution was stirred for an additional 15 min and 16.7g (86mmol) of ethyl benzyloxyacetate was added over 5 min. The solution was stirred for 20 min at -78°C, and 14.7g (84.4mmol) of α-silyloxy-γ-butyrolactone was added via syringe. The reaction mixture was quenched after 30 minutes by pouring into a mixture of 100mL of 10% aqueous HCl solution and 500mL of ether. The aqueous layer was separated and washed with 2 x 100mL of ether. The combined ether extracts were washed with 50mL of brine, dried ($MgSO_4$) and concentrated leaving a yellow oil, which was dried *in vacuo* for 15 hours.

C. The yellow oil was placed under argon, diluted with 400mL of MeOH, cooled to 0°C with stirring and 11.7g (85mmol) of anhydrous K_2CO_3 was added. After 30 minutes the suspension was concentrated to a volume of about 75mL, diluted with 100mL of H_2O and 50mL of saturated sodium bicarbonate solution, and washed with 2 x 100 mL of ether. The aqueous phase was acidified with 37% HCl solution to a pH near 1 and extracted with 10 x 150mL of ether. The combined ether extracts were washed with 100mL of brine, dried ($MgSO_4$) and concentrated to a yellow oil (18.7 g, 86%) which solidified upon standing. Recrystallization from benzene and hexanes provided 15.8 g, (75% yield) of 3-benzyloxy-4-hydroxy-5-(2-hydroxy)ethyl-2(5*H*)-furanone as a white solid: mp 98-99°C, ^{1}H NMR (acetone- d_6) δ 7.46-7.27 (m, 5H),

5.06 (s, 2H), 4.83 (t, J = 6.3 Hz, 1H), 3.85-3.69 (m, 2H), 2.05-1.95 (m, 1H), 1.89-1.76 (m, 1H). Anal Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.51; H, 5.50.

EXAMPLE D

3,4-Dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone

A mixture of 1.25g (5mmol) of 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone, 15mL of THF, 871μL (5.0mmol) of diisopropylethylamine and 631μL (5.2mmol) of benzyl bromide were combined under argon. The reaction mixture was warmed to reflux for 5 hours, and upon cooling, a suspension formed which was poured into 50mL of 5% aqueous HCl solution and extracted with 100mL of ether. The ether fraction was separated and sequentially washed with 30mL of 5% aqueous HCl, 30mL of H_2O, 30mL of saturated $NaHCO_3$ solution, 30mL of H_2O, 30mL of brine, dried ($MgSO_4$) and concentrated to a colorless oil. Purification over silica gel using EtOAc/hexanes (2/3) provided 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone as a faint pink colored oil (1.0g, 60% yield).

EXAMPLE E

3-Benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone

To an oven dried 250mL round bottom flask flushed with argon was added 5.8g (22mmol) of PPh_3, 1.5g (22mmol) of imidazole and 80mL of ether/CH_3CN (3/1). The mixture was cooled in an ice water bath with magnetic stirring and 5.6g (22mmol) of iodine was added in 4 equal portions with vigorous stirring. The resulting slurry was warmed at room temperature for 20 minutes, cooled to 0°C, and 5.0g (20mmol) of 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone dissolved in 20mL of CH_3CN/ether (1/1) was added in one portion and the remainder was rinsed in with 5mL of ether. The mixture was stirred at 0°C for 10 minutes, then at room temperature for 30 minutes and quenched by pouring into 150mL of 10% HCl solution and extracting with 500mL of ether/hexanes (1/1). The aqueous layer was separated and extracted with 100mL of ether. The combined organic fractions were washed with 50mL of H_2O and extracted with 5 x 50mL of saturated $NaHCO_3$

solution. The combined bicarbonate extracts were washed with 50mL of ether/hexanes (1/1), acidified to pH below 2 with 10% HCl solution and extracted with 3 x 200mL of ether. The combined ether extracts were washed with 100mL of brine, dried ($MgSO_4$) and concentrated to give 6.7g, (93% yield) of 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone as a white solid, which was not further purified: mp 101-104°C, ^1H NMR ($CDCl_3$) δ 7.40-7.27 (m, 5H), 5.06, (dd, J = 11.4 Hz, 2H), 4.69 (dd, J = 3.4, 8.0 Hz, 1H), 3.06 (t, J = 7.3 Hz, 2H), 2.41-2.29 (m, 1H), 2.02-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.33, 160.61, 136.32, 128.77, 128.69, 128.58, 120.11, 75.76, 73.39, 35.77, -2.03; Anal Calcd for $C_{13}H_{13}O_4I$: C, 43.35; H, 3.64. Found: C, 43.94; H, 3.69.

EXAMPLE F

3,4-Dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone

To a dry flask flushed with argon was added 0.72g (2.0mmol) of 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone and 10mL of CH_2Cl_2. The solution was cooled with stirring in an ice-water bath, and 0.38mL (4.0mmol) of acetic anhydride and 0.34mL (4.2mmol) of pyridine were added. The ice bath was removed and the solution was stirred for 1 hour. All volatile substances were removed *in vacuo* (2h at 1 mm Hg, 25°C). Argon was introduced to the reaction flask and the residue was taken up in 20mL of dry CH_2Cl_2, cooled to -78°C and 5.2mL (2.6mmol) of 1.0M BCl_3 in CH_2Cl_2 was added with stirring. The reaction mixture was kept at -78°C for 1 hour and at room temperature for 30 minutes. The mixture was poured into 50mL of brine and extracted with 3 x 30mL of ether. The combined ether extracts were washed with 5mL of H_2O and extracted into saturated $NaHCO_3$ solution (3 x 15mL). The bicarbonate fractions were pooled and washed with 15mL of ether, acidified to pH 1 with 25% aqueous HCl solution, and extracted with 3 x 30mL of ether. The ether extracts were combined and washed with 15mL of brine, dried ($MgSO_4$) and concentrated to provide 360mg (67% yield) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone as a white crystalline solid: mp 150-151°C; ^1H NMR (acetone-d_6) δ 4.80

(dd, 1H, J = 3.5, 8.0 Hz), 3.50-3.25 (m, 2H), 2.60-2.35 (m, 1H), 2.20-1.95 (m, 1H). Anal Calcd for $C_6H_7O_4I$: C, 26.69; H, 2.61. Found: C, 26.54; H, 2.59.

EXAMPLE G

3-Benzyloxy-5-(3-butyne)-4-hydroxy-2(5*H*)-furanone

To a flame-dried three-necked round bottom flask with magnetic stir bar, argon inlet, and septum containing 5.7g (55.8mmol) of 90% lithium acetylide ethylenediamine complex, was added 20mL of HMPA. The suspension was stirred for 15 minutes at room temperature, cooled in an ice bath (acetone/CO_2) to between -5°C and -10°C, and 6.7g (18.6 mmol) of 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone dissolved in 15mL of HMPA was added over a two minute period. A dark brown-orange slurry formed and the temperature was maintained between 0°C and -5°C for 30 minutes. The mixture was quenched by the careful addition of 150mL of 10% aqueous HCl solution, which was immediately extracted with 2 x 200mL of ether. The combined ether extracts were washed with 2 x 50mL of 5% aqueous HCl solution and extracted with 4 x 50mL of $NaHCO_3$ solution. The combined bicarbonate extracts were washed with 50mL of ether, acidified with 20% aqueous HCl solution to pH 1 and extracted with 3 x 150mL of ether. The combined ether extracts were washed with 50mL of brine, dried ($MgSO_4$) and concentrated leaving 4.1 g (85% crude yield) of 3-benzyloxy-5-(3-butyne)-4-hydroxy-2(5*H*)-furanone as a yellow solid. This material was used without further purification in subsequent steps: mp 85-88°C; ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (m, 5H), 5.06, (q, J_{ab} = 11.6 Hz, 2H), 4.75 (dd, J = 3.5, 8.1 Hz, 1H), 2.27-2.20 (m, 2H), 2.12-2.01 (m, 1H), 1.98 (t, J = 2.6 Hz, 1H), 1.73-1.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.93, 160.90, 136.39, 128.77, 128.73, 128.64, 120.13, 82.31, 74.30, 73.43, 69.71, 30.78, 13.72.

EXAMPLE H

5-(3-Butyne)-3,4-dihydroxy-2(5*H*)-furanone

An oven dried 250mL flask equipped with a magnetic stir bar was flushed with argon and charged with 2.6g (10.0mmol) of 3-benzyloxy-5-(3-butyne)-4-hydroxy-2(5*H*)-

furanone and 50mL of anhydrous CH_2Cl_2. The solution was cooled in an ice bath to 5°C with magnetic stirring and 1.9mL (20.0mmol) of acetic anhydride was added followed by 1.7mL (21mmol) of pyridine. The ice bath was removed after 1 hour, and the mixture was concentrated on a rotary evaporator and dried at 0.5 mm Hg at 25°C for 12 hours. Argon was introduced followed by 100mL of dry CH_2Cl_2. The solution was cooled to -78°C with stirring and 25mL (25mmol) of 1.0M BCl3 in CH_2Cl_2 was added. The reaction mixture was allowed to gradually warm to 10°C over a 2 hour period and maintained at 10°C for 1 hour. The mixture was poured into 50mL of brine and extracted with 4 x 100mL of ether. The combined ether fractions were extracted with 3 x 25mL of saturated $NaHCO_3$ solution. The combined bicarbonate extracts were washed with 25mL of ether and acidified to pH 1 with aqueous HCl solution and extracted with 5 x 100mL of ether. The combined ether washes were dried ($MgSO_4$) and filtered through 100g of silica gel to remove a polar impurity using 1L of ether as eluant. Removal of solvent *in vacuo* left 1.4g (80% yield) of 5-(3-butyne)-3,4-dihydroxy-2(5*H*)-furanone as an off white solid: mp 124-128 °C dec.; ^{1}H NMR (acetone- d_6) δ 4.79 (dd, J = 3.4, 8.3 Hz, 1H) 2.42 (t, J = 2.6 Hz, 1 H) 2.37-2.30 (m, 2H), 2.20-2.09 (m, 1H), 1.81-1.67 (m, 1H); ^{13}C NMR (acetone- d_6) δ 170, 153.7, 119, 83.4, 74.7, 70.9, 32.4, 14.4; Anal Calcd for $C_8H_8O_4$: C, 57.14; H, 4.79. Found: C, 57.04; H, 5.01.

EXAMPLE I

2-(2*Z*-Hexenyl)iodobenzene

A dry 25mL 2-necked flask equipped with a magnetic stir bar, argon inlet and septum was cooled to 0°C and 3 mL of 1.0M BH_3 in THF was added. Cyclohexene, 607μL (6 mmol) was added via syringe and the suspension stirred at 0-5°C for 35 minutes. 2-Hexynyliodobenzene, (0.852g, 3.0 mmol) was added to the reaction mixture dropwise over a 5 minute period, the ice bath was removed and the yellow reaction mixture stirred at room temperature for 1 hour. The solution was subsequently cooled in an ice bath, and 1.4 mL (25 mmol) of glacial AcOH was added. The mixture stirred at room temperature for 1 hour, was poured into 75mL of H_2O, and extracted

with 3 x 30mL of hexanes. The combined hexanes fractions were washed with 25mL of H_2O, 25mL of saturated $NaHCO_3$ solution, 25mL of H_2O, 2 x 20mL of brine, dried ($MgSO_4$) and concentrated to an oil (do not warm above 30°C to avoid isomerization of the double bond). Purification over 40g of silica gel using hexanes as eluant provided 670 mg (78%) of 2-(2*Z*-hexenyl)iodobenzene as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.30-7.20 (m, 2H), 6.91-6.86 (m, 1H), 5.62-5.46 (m, 2H), 3.47 (d, J = 6.5 Hz, 2H), 2.17-2.10 (m, 2H), 1.49-1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 143.8, 139.3, 131.8, 129.2, 128.3, 127.7, 126.6, 100.8, 38.8, 29.6, 22.7, 13.9; Anal Calcd for $C_{12}H_{15}I$: C, 50.37; H, 5.28. Found: C, 49.97; H, 5.24.

SYNTHESIS OF COMPOUNDS OF THE INVENTION

EXAMPLE 1

3,4-Dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone

A. To a 2-necked flask flame dried under argon with septum and charged with a solution of 3.6g (20mmol) of ethyl benzoylformate in 50mL of anhydrous THF at -30°C was slowly added 7 mL (21mmol) of a 3.0 M solution of methylmagnesium iodide. The reaction mixture was stirred at 0°C for 45 minutes, then at room temperature for 30 minutes and again cooled to 0°C. Benzyloxyacetyl chloride (3.4mL, 21mmol) was added and the reaction mixture was stirred at room temperature for 1 hour, cooled to -78°C and 33mL of a 1.5M solution of LDA in THF was added with rapid stirring. The mixture was worked up after 1 hour by the addition of 100 mL of aqueous 10% HCl solution and 300mL of ether. The layers were separated and the organic phase was washed with 50mL aqueous 10% HCl solution, 30mL of H_2O, and extracted with 3 x 40mL of saturated $NaHCO_3$ solution. The bicarbonate extracts were combined and washed with 40mL of ether, acidified to pH 1 with 10% aqueous HCl solution, and extracted with 2 x 80mL of ether. The organic fractions were combined, washed with 25 mL of H_2O, 25 mL of brine, dried ($MgSO_4$), and

concentrated leaving 1.2g (20% yield) of 4-hydroxy-5-methyl-5-phenyl-3-phenylmethoxy-2-(5*H*)-furanone as a yellow oil.

B. The 4-hydroxy-5-methyl-5-phenyl-3-phenylmethoxy-2-(5*H*)-furanone (1.2g) was subjected to hydrogenation over 100 mg of 5% $Pd/BaSO_4$ in 100 mL of MeOH at room temperature and under 30 psi H2. The reaction was monitored periodically by TLC analysis. The suspension was filtered through two #1 filter papers, concentrated to a white solid and recrystallized from $MeOH/H_2O$ to give 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone as a white crystalline material: mp 173-175°C dec. ^1H NMR (acetone-d_6) δ 7.53-7.36 (m, 5H), 1.84 (s, 3H). Anal Calcd for $C_{11}H_{10}O_4 + 0.125\ H_2O$: C, 63.38; H, 4.96. Found: C, 63.30; H, 4.96.

EXAMPLE 2

5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide in THF was added to a THF solution of 2.4g (10mmol) of ethyl 4-phenylbenzoylformate in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis, 1.1g (30% yield) of 5-[(1,1'-biphenyl)-4-yl]-3-phenylmethoxy-4-hydroxy-5-methyl-2(5*H*)-furanone as a white granular solid: m.p. 182-183°C (benzene/hexanes) ^1H NMR ($CDCl_3$) δ 7.56-7.26 (m, 14H), 5.10 (ab quartet, 2H, J = 11.4 Hz), 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.5, 163.8, 141.5, 140.3, 137.0, 136.3, 129.0, 128.8, 128.8, 128.8, 127.6, 127.2, 127.1, 125.6, 119.0, 81.1, 73.5, 24.3. Anal Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.99; H, 5.61.

B. Hydrogenolysis of 500 mg of the 5-[(1,1'-biphenyl)-4-yl]-3-phenylmethoxy-4-hydroxy-5-methyl-2(5*H*)-furanone was performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 240mg (63% yield) of 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a white powder: mp 206-212°C dec. ($MeOH/H_2O$), ^1H NMR (acetone-d_6) δ 7.69-7.33 (m, 9H), 1.88 (s, 3H). ^{13}C NMR (acetone-*d*6) δ 169.5, 157.1, 141.6, 141.0, 139.8,

129.6, 128.3, 127.6, 127.6, 126.6, 117.9, 81.2, 24.5. Anal Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.07; H, 5.14.

EXAMPLE 3

3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone

A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide in THF was added to a THF solution of 2.34 g (10 mmol) of ethyl 4-isobutylbenzoylformate in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 4-hydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-3-phenylmethoxy-2(5*H*)-furanone in 45% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.37-7.02 (m, 9H), 5.01 (s, 2H), 2.42 (d, 2H, J = 7.2 Hz), 1.86-1.77 (m, 1H), 1.72 (s, 3H), 0.87 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 170.0, 165.1, 142.1, 136.3, 135.2, 129.2, 128.9, 128.6, 127.2, 125.0, 118.6, 81.7, 73.5, 45.0, 30.2, 24.1, 22.4. Anal Calcd for $C_{22}H_{24}O_4$ + 0.5 H_2O: C, 73.11; H, 6.97. Found: C, 72.92; H, 6.87.

B. Hydrogenolysis of 800mg (2.3mmol) of 4-hydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 500mg (84% yield) of 3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone as a light yellow crystalline material: mp 135-150°C dec. ^{1}H NMR (acetone-d_6) δ 7.40-7.17 (m, 4H), 2.46 (d, 2H, J = 7.1 Hz), 1.87-1.82 (m, 1H), 1.82 (s, 3H), 0.87 (d, 6H, J = 6.6 Hz). ^{13}C NMR (acetone-d_6) δ 169.5, 157.2, 142.4, 138.0, 129.8, 125.9, 117.9, 81.3, 45.3, 30.8, 24.5. 22.5. Anal Calcd for $C_{15}H_{18}O_4$ + 0.25 H_2O: C, 67.53; H, 6.99. Found: C, 67.78; H, 7.09.

EXAMPLE 4

5-(4-Chlorophenyl)-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide was added to a solution of 2.34g (10mmol) of ethyl 4-chlorobenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-

furanone to give prior to hydrogenolysis 1.3g (40% yield) of 5-(4-chlorophenyl)-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37-7.21 (m, 9H), 5.10 (s, 2H), 1.73 (s, 3H).

B. Hydrogenolysis of 330 mg of 5-(4-chlorophenyl)-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 110mg (46% yield) of 5-(4-chlorophenyl)-3,4-dihydroxy-5-methyl-2(5*H*)-furanone a light tan solid: mp 154-155°C dec.(benzene/hexanes) ^{1}H NMR (acetone-d_6) δ 7.52-7.34 (m, 4H), 1.82 (s, 3H). ^{13}C NMR (acetone-d_6) δ 169.0, 156.6, 139.8, 134.3, 129.2, 127.8, 117.9, 80.8, 24.6. Anal Calcd for $C_{11}H_9ClO_4$: C, 54.90; H, 3.77. Found: C, 54.74; H, 4.08.

EXAMPLE 5

5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5*H*)-furanone

A. A total of 5.2mL (10.4mmol) of 2.0M n-propylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.30g (8% yield) of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-propyl-2(5*H*)-furanone as an off white solid after crystallization from $CHCl_3$ and hexanes.

B. Hydrogenolysis of 250 mg of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-propyl-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 100mg (52% yield) of a white powder: mp 203-204°C dec.(acetone/$CHCl_3$/hexanes). ^{1}H NMR (acetone-d_6) δ 7.65-7.40 (m, 9H), 2.25-1.95 (m, 2H), 1.45-1.10 (m, 2H), 0.95 (t, J=6.9Hz, 3H). Anal Calcd for $C_{19}H_{18}O_4 + 0.125$ H_2O: C, 73.01; H, 5.88. Found: C, 72.99; H, 5.86.

EXAMPLE 6

5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5*H*)-furanone

A. A total of 5.2mL (10.4mmol) of 2.0M isobutylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.35g (8% yield) of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-(2-methylpropyl)-2(5*H*)-furanone as an off white solid after crystallization from $CHCl_3$ and hexanes.

B. Hydrogenolysis of 350mg of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-(2-methylpropyl)-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 190mg (69% yield) of a white powder: mp 198-199°C dec.($CHCl_3$/hexanes). ^{1}H NMR (acetone-d_6) δ 7.73-7.34 (m, 9H), 2.44-2.28 (m, 1H), 1.50-0.80 (m, 8H). ^{13}C NMR (acetone-d_6) δ 169.21, 155.47, 140.81, 139.57, 129.17, 127.73, 127.18, 127.08, 126.04, 118.47, 86.01, 40.66, 23.72, 12.11, 11.87. Anal Calcd for $C_{20}H_{20}O_4$ + 0.125 H_2O: C, 73.55; H, 6.25. Found: C, 73.25; H, 6.36.

EXAMPLE 7

5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone

A. A total of 3.4mL (10.2 mmol) of 3.0M phenylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.88g (20% yield) of 5-[(1,1'-biphenyl)-4-yl]- 4-hydroxy-3-phenylmethoxy-5-phenyl-2(5*H*)-furanone as an off white solid: mp 190-195°C ($CHCl_3$/hexanes).

B. Hydrogenolysis of 500mg of 5-[(1,1'-biphenyl)-4-yl]- 4-hydroxy-3-phenylmethoxy-5-phenyl-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 150mg (38% yield) of 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone as colorless needles: mp 188-191°C dec.($CHCl_3$/hexanes). ^{1}H NMR (acetone-d_6) δ 7.75-7.36 (m, 14H). ^{13}C NMR (acetone-d_6) δ 168.34, 154.84, 141.50,

140.66, 140.30, 139.42, 129.18, 128.74, 128.59, 127.92, 127.40, 127.25, 127.07, 119.45, 84.59. Anal Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.44; H, 4.50.

EXAMPLE 8

3,4-Dihydroxy-5,5-diphenyl-2(5*H*)-furanone

A. A total of 3.5mL (10.5mmol) of 3.0M phenylmagnesium bromide was added to a solution of 1.6mL (10 mmol) of ethyl benzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give 5,5-diphenyl-4-hydroxy-3-phenylmethoxy-2(5*H*)-furanone as an oil, which was purified over SiO_2 using acetone/hexanes (3/7).

B. Hydrogenolysis of 5,5-diphenyl-4-hydroxy-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 150mg (5.6% overall yield) of 3,4-dihydroxy-5,5-diphenyl-2(5*H*)-furanone as colorless needles: mp 192-193°C dec.($CHCl_3$/hexanes). ^{1}H NMR (acetone-d_6) δ 7.41 (s, 10H). ^{13}C NMR (acetone-d_6) δ 168.38, 154.92, 140.44, 128.72, 128.58, 127.43, 119.46, 84.74. Anal Calcd for $C_{16}H_{12}O_4 + 0.25\ H_2O$ C, 70.46; H, 4.62. Found: C, 70.42; H, 4.52.

EXAMPLE 9

3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone

A. A total of 5.2mL (10.4mmol) of 2.0M 1-propylmagnesium bromide was added to a solution of 2.3g (10 mmol) of ethyl 4-isobutylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 4-hydroxy-5-(4-isobutylphenyl)-3-phenylmethoxy-5-(1-propyl)-2(5*H*)-furanone as an oil, which was purified over SiO_2 using acetone/hexanes (1/4).

B. Hydrogenolysis of 4-hydroxy-5-(4-isobutylphenyl)-3-phenylmethoxy-5-(1-propyl)-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 200mg

(6.9% yield) of 3,4-dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone as an oil, which was purified by preparative TLC using hexanes/acetone/acetic acid (70/29/1) as eluant: ^{1}H NMR (acetone-d_6) δ 7.48-7.13 (m, 4H), 2.47 (d, J = 10.3Hz, 2H), 2.10-1.66 (m, 1H), 1.29-0.85 (m, 13H). ^{13}C NMR (acetone-d_6) δ 169.20, 155.54, 141.58, 137.91, 129.24, 125.32, 118.25, 83.37, 45.02, 39.60, 30.26, 22.03, 16.84, 13.63. Anal Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.01; H, 7.61.

EXAMPLE 10

3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone

A. A total of 3.5mL (10.5mmol) of 3.0M phenylmagnesium bromide was added to a solution of 2.3g (10 mmol) of ethyl 4-isobutylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide an oil, which was purified over 400g of SiO_2 by eluting with 500mL of $CHCl_3$, 500mL of EtOH/$CHCl_3$ (3/97) and 500mL of EtOH/$CHCl_3$ (8/92) to provide 1.2g (29% yield) of 4-hydroxy-5-(4-isobutylphenyl)-5-phenyl-3-phenylmethoxy-2(5*H*)-furanone as a tan powder recrystallized from $CHCl_3$ and hexanes.

B. Hydrogenolysis of 500mg (1.2mmol) of 4-hydroxy-5-(4-isobutylphenyl)-5-phenyl-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 200mg (51% yield) of 3,4-dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone as a white powder: mp 138-139 °C ($CHCl_3$/hexanes). ^{1}H NMR (acetone-d_6) δ 7.40-7.15 (m, 9H), 2.49 (d, J = 7.1Hz, 2H), 1.94-1.74 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H). Anal Calcd for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 73.7; H, 6.3.

EXAMPLE 11

(*S*)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

A. To a flame dried 500mL flask flushed with N_2, was added 24g (100mmol) of ethyl 4-phenylbenzoylformate and 300mL of anhydrous THF. The solution was cooled with stirring to -25°C and 37mL (110mmol) of a 3.0M solution of methylmagnesium

iodide was added at a rate to maintain the reaction temperature below -10°C. The reaction progress was monitored by TLC and upon disappearance of starting material, 100mL of saturated NH_4Cl solution and 200mL of ether were added. The organic layer was separated and washed with 2 x 50mL of brine, dried ($MgSO_4$) and concentrated leaving racemic ethyl 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate as an oil.

B. The crude ethyl 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate was saponified by treating with 100mL of ethanol and 100mL of 4.0M NaOH solution. The suspension was stirred for 3 hours, after which a clear solution formed The solution was concentrated, diluted with 150mL of H_2O, washed with 2 x 50mL of ether, and acidified to pH 1 with 10% HCl solution. The aqueous phase was extracted with 3 x 100mL portions of ether and the combined ether extracts were washed with 50mL of H_2O, 50mL of brine, dried ($MgSO_4$) and concentrated leaving 18.3g (72% yield) of racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid as a white solid after was recrystallization from $CHCl_3$ and hexanes.

C. Racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid 12.1g (50mmol) was resolved by dissolving in 225mL of a 2:2:1 mixture of isopropanol:benzene:hexanes. The solution was warmed to reflux and 6.9g (50mmol) of (R)-(-)-phenylglycinol was added in one portion. The mixture was allowed to cool slowly over 15 hours during which white crystals formed, which were isolated by filtration and washed with several small portions of isopropanol. The isolated white solid was recrystallized four additional times from isopropanol until a constant melting point of 189.5-191°C was observed, leaving 4.3g (45.3% yield for the resolution) of diastereomerically pure (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate (*R*)-(-)-phenylglycinol salt.

D. Diastereomerically pure (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate (*R*)-(-)-phenylglycinol salt (1.9g, 5mmol) was added to a separatory funnel containing 70mL of 15% aqueous HCl solution and 150mL of ether. The suspension was shaken until completely solvated, and the aqueous layer was separated. The ether portion was

washed with 2 x 50mL of 15% aqueous HCl solution, 50mL of H_2O, 50mL of brine, dried ($MgSO_4$) and filtered into a 500mL flask. The ether solution was cooled in an ice bath and a freshly prepared etheral solution of diazomethane was added with stirring until the yellow color of the reagent persisted. The solution was concentrated leaving 1.3g (99%) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate as a white crystalline material.

E. In a dry flask under argon, were mixed 1.3g (5mmol) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate, 1.7mL (10mmol) of 95% benzyloxyacetyl chloride and 6.1mL of pyridine. The reaction stirred for 48 hours and was quenched by pouring into 100mL of 10% aqueous HCl and 200mL of ether. The ether fraction was separated and washed with 50mL of 10% aqueous HCl, 50mL of H_2O, 2 x 50mL of $NaHCO_3$ solution, 50mL of H_2O, 50mL of brine, dried ($MgSO_4$) and concentrated. The product was purified over 250g of SiO_2 using initially EtOAc/hexanes (1/9) followed by EtOAc/hexanes (1.5/8.5) as eluant to yield 1.5g (80% yield) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-(2-phenylmethoxyacetoyl)oxypropionate.

F. (*S*)-(+)-2-[(1,1'-Biphenyl)-4-yl]-2-(2-phenylmethoxyacetoyl)oxypropionate (1.5g, 4mmol) was dissolved in 10mL of anhydrous THF and added to 33mL of a 0.3M solution of LiHMDA in THF at -78°C. The light yellow solution stirred for 45 minutes and was quenched by the addition of 30mL of 10% aqueous HCl solution. The mixture was taken into 200mL of ether and washed with 30mL of 10% aqueous HCl solution, 30mL of H_2O, 30mL of brine, dried ($MgSO_4$) and concentrated. The resultant oil was taken up in 50mL of ether and extracted with 4 x 30mL of saturated $NaHCO_3$ solution. The combined $NaHCO_3$ fractions were washed with 25mL of ether, acidified to pH below 1 with 10% aqueous HCl solution and extracted with 2 x 100mL of ether. The combined ether extracts were washed with 25mL of H_2O, 25mL of brine, dried ($MgSO_4$) and concentrated to give (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone.

G. The (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone was subjected to hydrogenation over 100 mg of 5% $Pd/BaSO_4$ in 100mL of MeOH at room temperature under 30 psi of H_2. The reaction was monitored periodically by TLC analysis. Upon reaction completion, the suspension was filtered through two #1 filter papers, concentrated and recrystallized from $CHCl_3$ and hexanes to provide 300mg (20% overall yield from methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate) of (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a light weight white crystalline material: mp 204-206°C dec.; $[\alpha]^{25}_D$ + 121° (c=0.66; MeOH); ^{1}H NMR (acetone-d_6) δ 7.72-7.41 (m, 9H), 1.89 (s, 3H). Anal Calcd for $C_{17}H_{14}O_4$ + 0.75 H_2O: C, 69.03; H, 5.28. Found: C, 68.69; H, 4.95.

EXAMPLE 12

(*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

A. The combined filtrates from the resolution of racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid with (*R*)-(-)-phenylglycinol (example 11, section C) were concentrated to a thick brown paste and partitioned between 100mL of 20% HCl solution and 400mL of ether. The aqueous phase was separated and the ether layer was subsequently washed with 4 x 30mL of 20% HCl solution, 50mL of brine, dried ($MgSO_4$) and concentrated. A total of 8.5g (35mmol) of 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid was recovered and dissolved in 300mL of isopropanol by warming to reflux and 4.5g (35mmol) of (*S*)-(+)-phenylglycinol was added. The diastereomeric salts were allowed to crystallize at 25°C over a period of 72 hours and isolated by filtration and washed with 2 x 40mL of isopropanol to provide 6.7g of light brown crystals. Two subsequent recrystallizations from isopropanol provided 3.6g of the diastereomerically pure salt of (*R*)-(-)- 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid with (*S*)-(+)-phenylglycinol.

B. (*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone was prepared in an analogous manner as described for (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-

dihydroxy-5-methyl-2(5*H*)-furanone starting with 1.9g (5.0mmol) of the diastereomerically pure salt of (*R*)-(-)- 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid and (*S*)-(+)-phenylglycinol to provide 280mg (19% yield) of (*R*)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a white crystalline material: mp 197-199 °C dec. ($CHCl_3$/hexanes); $[\alpha]^{25}_D$ -182° (c=1.42; MeOH); ^1H NMR (acetone-d_6) δ 7.65-7.41 (m, 9H), 1.89 (s, 3H). Anal Calcd for $C_{17}H_{14}O_4$ + 0.25 H_2O: C, 71.20; H, 5.10. Found: C, 71.19; H, 4.74.

EXAMPLE 13

(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone

(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone was synthesized in an analogous manner used for the production of (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone starting with ethyl 4-isobutylbenzoylformate. (*R*)-(-)-Phenylglycinol was used to resolve the methyl (*R*)-(-)-2-(4-isobutylphenyl)propionate enantiomer, of which 1.2g, (5mmol) was converted into 190mg (15% yield) of (*R*)-(-)-3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone as a white crystalline material: mp 180-181°C dec. ($CHCl_3$/hexanes); $[\alpha]^{25}_D$ -137° (c=1.27; MeOH); ^1H NMR (acetone-d_6) δ 7.44-7.14 (m, 4H), 2.48 (d, 2H, J = 7.1 Hz), 1.87-1.82 (m, 1H), 1.83 (s, 3H), 0.88 (d, 6H, J = 6.5 Hz). Anal Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.52; H, 7.01.

EXAMPLE 14

(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone

(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone was synthesized in an analogous manner used for the production of (*R*)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone starting with ethyl 4-isobutylbenzoylformate. (*S*)-(+)-Phenylglycinol was used to resolve the methyl (*S*)-(+)-2-(4-isobutylphenyl)propionate enantiomer, of which 1.2g (5mmol) was converted into 250mg (19% yield) of (*S*)-(+)-3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone as a white crystalline material: mp 175-177°C

dec. ($CHCl_3$/hexanes); $[\alpha]^{25}_D$ +132° (c=1.55; MeOH) ^{1}H NMR (acetone-d_6) δ 7.44-7.14 (m, 4H), 2.48 (d, 2H, J = 7.1 Hz), 1.87-1.82 (m, 1H), 1.83 (s, 3H), 0.88 (d, 6H, J = 6.5 Hz). Anal Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.08; H, 6.90.

EXAMPLE 15

3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone

A. A mixture consisting of 340mg (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone, 320mg (1.3mmol) of triphenylphosphine and 225mg (1.2mmol) of 4-phenoxyphenol was dissolved in 8mL of anhydrous THF under argon. Diisopropyl azodicarboxylate (276μL 1.4mmol) was added to the solution dropwise with stirring at 25°C. After 36 hours the reaction mixture was poured into 30mL of H_2O and extracted with two 30mL portions of ether. The combined ether fractions were washed with 25mL of saturated $NaHCO_3$ solution, 25mL of H_2O, 25mL of aqueous 10% HCl solution, 25mL of H_2O, 25mL of brine, dried ($MgSO_4$) and concentrated to an oil. The product was purified over silica gel using EtOAc/hexanes (2/3) as eluant to provide 3,4-dibenzyloxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone as an oil.

B. The 3,4-dibenzyloxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone was hydrogenated in 50mL of MeOH over 50mg of 5% Pd/$BaSO_4$ under 30psi H_2. After completion of the reaction, as determined by TLC analysis, the suspension was filtered through celite, washed with three 10mL portions of MeOH and concentrated to a white solid. Trituration with ether and hexanes provided 150mg (44% yield) of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone as a white powder: mp 125-127 °C, ^{1}H NMR (acetone-d_6) δ 7.42-7.28 (m, 2H), 7.12-6.88 (m, 7H), 4.95 (dd, 1H), 4.17 (q_{ab}, 2H), 2.55-2.36 (m, 1H), 2.05-1.87 (m, 1H); ^{13}C NMR (acetone-d_6) δ 169.41, 158.91, 155.57, 153.39, 150.61, 129.98, 122.73, 120.94, 117.71, 116.32, 115.99, 72.43, 63.97, 32.43; Anal Calcd for $C_{18}H_{16}O_6$ + 0.5 H_2O; C, 64.12; H, 5.04: Found C, 64.28; H, 5.04.

EXAMPLE 16

3,4-Dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.33g (1.4mmol) of 6-hydroxyflavone with 0.40g (1.17mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone as a tan solid: mp 200-220°C dec. (acetone/hexanes), ^{1}H NMR (DMSO-d_6) δ 8.13-7.36 (m, 8H), 7.01 (s, 1H), 4.92 (dd, 1H), 4.17 (t, 2H), 2.47-2.27 (m, 1H), 1.98-1.85 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 177.23, 170.22, 162.71, 156.02, 155.36, 150.80, 132.06, 131.51, 129.42, 126.59, 124.31, 123.85, 120.49, 117.44, 106.43, 105.85, 72.24, 64.20, 31.71. Anal Calcd for $C_{21}H_{16}O_7$ + 0.25 H_2O: C, 65.55; H, 4.44. Found: C, 65.59; H, 4.49.

EXAMPLE 17

5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone

Mitsunoble coupling of 0.22g (1.2mmol) of 2-hydroxydibenzofuran with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 40 mg (10% yield) of 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone a white solid.: mp 191-192°C (ether/hexanes), ^{1}H NMR (acetone-d_6) δ 8.23-8.18 (m, 1H), 7.83-7.44 (m, 5H), 7.28-7.23 (m, 1H), 5.12 (dd, J=5.3, 8.7Hz, 1H), 4.42 (dd, J=2.6, 4.7Hz, 2H), 2.69-2.59 (m, 1H), 2.21-2.08 (m, 1H). ^{13}C NMR (acetone-d_6) δ 169.68, 157.31, 155.75, 153.70, 151.31, 127.76, 125.05, 124.83, 123.07, 121.34, 118.46, 116.42, 112.39, 111.90, 105.40, 72.72, 64.57, 32.64. Anal Calcd for $C_{18}H_{14}O_6$ + 0.25 H_2O: C, 65.36; H, 4.57. Found: C, 65.52; H, 4.23.

EXAMPLE 18

3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.17g (1.2mmol) of 1-naphthol with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 75mg (26% yield) of 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone as colorless cubes: mp 163-164°C (ether/hexanes) ^{1}H NMR (acetone-d_6) δ 8.38-8.25 (m, 1H), 7.92-7.79 (m, 1H), 7.60-7.34 (m, 4H), 7.05-6.93 (m, 1H), 5.11 (dd, J=5.3, 8.7Hz, 1H), 4.39 (dd, J=2.6, 4.7Hz, 2H), 2.75-2.52 (m, 1H), 2.25-2.05 (m, 1H). ^{13}C NMR (acetone-d_6) δ 169.62, 154.92, 153.61, 135.13, 127.83, 126.78, 126.50, 125.92, 125.05, 122.41, 120.66, 118.53, 105.28, 72.85, 63.93, 32.58. Anal Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.89. Found: C, 66.70; H, 4.88.

EXAMPLE 19

3,4-Dihydroxy-5-[2-(1,8-naphthalimide)-*N*-ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.24g (1.2mmol) of 1,8-naphthalimide with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 150mg (45% yield) of 3,4-dihydroxy-5-[2-(1,8-naphthalimide)-*N*-ethyl]-2(5*H*)-furanone as a white powder: mp 235-250°C dec. (acetone/hexanes), ^{1}H NMR (DMSO-d_6) δ 8.62-8.35 (m, 4H), 7.92-7.82 (m, 2H), 4.82 (dd, J=5.3, 8.7Hz, 1H), 4.19 (t, J=4.2Hz, 2H), 2.32-2.16 (m, 1H), 1.90-1.75 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 170.29, 163.72, 154.91, 134.56, 131.52, 130.96, 127.60, 127.45, 122.29, 117.46, 73.64, 36.03, 30.58. Anal Calcd for $C_{18}H_{13}NO_6$: C, 63.71; H, 3.86; N, 4.12. Found: C, 63.84; H, 3.83; N, 4.00.

EXAMPLE 20

3,4-Dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.28g (1.3mmol) of 1,8-naphthosultam with 0.37g (1.1mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 100mg (29% yield) of 3,4-dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone as a light yellow powder: mp 85-95°C dec. (acetone/hexanes), ^{1}H NMR (acetone-d_6) δ 8.29-7.55 (m, 5H), 7.12-7.01 (m, 1H), 4.97 (dd, J=4.9, 8.7Hz, 1H), 4.10 (t, J=4.2Hz, 2H), 2.72-2.50 (m, 1H), 2.18-1.95 (m, 1H). ^{13}C NMR (acetone-d_6) δ 169.28, 152.93, 136.42, 131.65, 131.10, 130.84, 130.00, 128.82, 120.03, 119.10, 118.60, 118.42, 103.71, 73.01, 37.72, 31.45. Anal Calcd for $C_{16}H_{13}NO_6S + 1H_2O$: C, 52.60; H, 4.14; N, 3.83. Found: C, 52.62; H, 3.86; N, 3.56.

EXAMPLE 21

3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.28g (1.3mmol) of 2-hydroxy diphenylmethane with 0.37g (1.1mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 140mg (43% yield) of 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone as a white powder, which was purified by trituration with ether and hexanes: ^{1}H NMR (acetone-d_6) δ 7.33-6.82 (m, 9H), 4.78 (dd, J=5.3, 8.7Hz, 1H), 4.19 (dd, J=2.6, 4.7Hz, 2H), 3.96 (s, 2H); 2.57-2.36 (m, 1H), 2.10-1.82 (m, 1H). Anal Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.6. Found: C, 69.75; H, 5.52.

EXAMPLE 22

5-[2-((1,1'-Biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone

Mitsunoble coupling of 0.20g (1.2mmol) of 4-hydroxy-1,1'-biphenyl with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent

benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 100mg (32% yield) of 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone as a white powder after trituration with ether and hexanes: ^{1}H NMR (acetone-d_6) δ 7.71-7.02 (m, 9H), 4.97 (dd, J=4.9, 8.7Hz, 1H), 4.25 (dd, J=2.6, 4.7Hz, 2H), 2.58-2.41 (m, 1H), 2.10-1.92 (m, 1H). Anal Calcd for $C_{18}H_{16}O_5$ + $1H_2O$: C, 67.49; H, 5.66. Found: C, 67.34; H, 5.42.

EXAMPLE 23

3,4-Dihydroxy-5-[2-(quinoline-2-oxy)ethyl]-2(5*H*)-furanone

Mitsunoble coupling of 0.17g (1.2mmol) of 2-hydroxyquinoline with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 50mg (17% yield) of 3,4-dihydroxy-5-[2-(quinoline-2-oxy)ethyl]-2(5*H*)-furanone as a fluffy white solid after recrystallization from ether and hexanes: ^{1}H NMR (acetone-d_6) δ 8.25-8.17 (m, 1H); 7.88-7.38 (m, 4H), 7.01-6.93 (m, 1H); 4.97 (dd, J=4.9, 8.7Hz, 1H), 4.81-4.55 (m, 2H); 2.62-2.45 (m, 1H), 2.20-1.95 (m, 1H). Anal Calcd for $C_{15}H_{13}NO_5$ + $0.5H_2O$: C, 60.81; H, 5.10; N, 4.72. Found: C, 61.04; H, 5.04; N, 4.32.

EXAMPLE 24

3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone

A suspension of 3.14g (12.4mmol) 4,5-diphenyl-2-thio-1,3-isoxazole in 12mL of THF under argon with stirring at -78°C was treated with 4.9mL (12.2mmol) of 2.5M nBuLi. The reaction mixture was warmed to -5°C and 1.1g (4mmol) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone dissolved in 12mL of HMPA was added at a rate to maintain the reaction temperature below 0°C. Stirring continued at 0 to -5°C for 60 minutes followed by the addition of 100mL of saturated NH_4Cl solution. The mixture was extracted with 2 x 100 mL portions of ether/EtOAc (1/1). The organic

fractions were combined and extracted with 3 x 50 mL of saturated $NaHCO_3$ solution. The bicarbonate extracts were combined, washed with 2 x 50mL of ether, acidified to pH 1 with 10% HCl solution and extracted into 2 x 100mL portions of ether. The ether extracts were combined and washed successively with 40mL of H_2O, 40mL of brine, dried ($MgSO_4$) and concentrated to an oil.

Purification over SiO_2 using acetone/hexanes (1:1 to 2:3 to 7:3) provided a brown colored solid upon evaporation of solvent. The solid was taken up in 100mL of ether and extracted with 3 x 50mL of $NaHCO_3$ solution. The combined aqueous extracts were acidified with 10% HCl solution and extracted with 2 x 100mL portions of ether. The organic portions were washed with 40mL of H_2O, 40mL of brine, dried ($MgSO_4$) and concentrated to provide 875mg (55% yield) of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone as a white foam: mp 88-91 °C, ^{1}H NMR (acetone-d_6) δ 7.67-7.39 (m, 10H), 4.95 (dd, J=3.7, 8.7Hz, 1H), 3.61-3.28 (m, 2H), 2.72-2.19 (m, 2H). ^{13}C NMR (acetone-d_6) δ 169.17, 159.13, 152.70, 147.65, 136.83, 132.60, 129.14 (2C), 128.85 (2C), 128.61, 128.11, 126.92, 118.91, 74.25, 32.69, 27.32. Anal Calcd for $C_{21}H_{17}NO_5S$ + 0.25 H_2O: C, 63.07; H, 4.41; N, 3.50. Found: C, 63.23; H, 4.70; N, 3.24.

EXAMPLE 25

3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone

1-Naphthalenethiol (430μL, 3.1mmol) and 0.27g (1mmol) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone were reacted in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone to provide 90mg (30% yield) of 3,4-dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone as a colorless oil. Additional purification by chromatography over SiO_2 was not necessary for this compound: ^{1}H NMR (acetone-d_6) δ 8.44-8.32 (m, 1H), 7.98-7.43 (m, 6H), 4.92 (dd, J=3.7, 8.7Hz, 1H), 3.28-3.06 (m, 2H), 2.39-2.19 (m, 1H), 2.02-1.84 (m, 1H). Anal Calcd for $C_{16}H_{14}O_4S$ + 0.25 H_2O: C, 62.63; H, 4.76. Found: C, 63.06; H, 5.19.

EXAMPLE 26

3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone

2-Naphthalenethiol (430μL, 3.1mmol) and 0.27g (1mmol) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone were reacted in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone to provide 140mg (46% yield) of 3,4-dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone as a white powder after trituration with ether and hexanes. Additional purification by chromatography over SiO_2 was not necessary for this compound: ^{1}H NMR (acetone-d_6) δ 7.95-7.82 (m, 4H), 7.58-7.40 (m, 3H), 4.92 (dd, J=3.7, 8.7Hz, 1H), 3.34-3.08 (m, 2H), 2.42-2.21 (m, 1H), 2.02-1.86 (m, 1H). ^{13}C NMR (acetone-d_6) δ 169.53, 153.03, 134.48, 134.09, 132.29, 128.99, 128.13, 127.49, 127.41, 127.08, 126.65, 126.14, 118.68, 74.25, 32.33, 27.81. Anal Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.44; H, 4.58.

EXAMPLE 27

3,4-Dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone

To a flame dried reaction flask fitted with an argon inlet, septum and magnetic stir bar, were added 58mg (0.05mmol) of $Pd(PPh_3)_4$, 225μL (2.0 mmol) of iodobenzene, 0.17g (1.0mmol) of 5-(3-butynyl)-3,4-dihydroxy-2(5*H*)-furanone, 2 mL of pyrrolidine and 20mg (0.10mmol) of copper (I) iodide. The flask was protected from light (foil) and the yellow mixture was stirred at room temperature until the starting 5-(3-butynyl)-3,4-dihydroxy-2(5*H*)-furanone was not visible by TLC analysis ($CHCl_3$:MeOH 9:1). The reaction mixture was poured into a mixture of 50g of ice and 10mL of 37% HCl, and extracted with 2 x 50mL of ether. The ether extracts were combined and washed with 2 x 20mL of 10% aqueous HCl solution, 20mL of H_2O, 20mL of brine, dried ($MgSO_4$) and concentrated.

The residue was dissolved in 30mL of ether and extracted with 3 x 15mL of saturated $NaHCO_3$ solution. The bicarbonate extracts were pooled and washed with 10mL of ether, acidified to pH 2 with 10% HCl solution and extracted with 2 x 25mL of ether.

The ether extracts were combined and washed with 10mL of H_2O, 3mL of 10% (w/w) $NaHCO_3$ solution, 10mL of H_2O, 10mL of brine, dried ($MgSO_4$) and concentrated to provide 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone as a white solid: mp 145-146°C; ^1H NMR (acetone-d_6) δ 7.35-7.15 (m, 5H) 4.75 (dd, J=3.4, 8.2 Hz, 1H), 2.50-2.40 (m, 2H), 2.20-2.05 (m, 1H), 1.75-1.60 (m, 1H); ^{13}C NMR (acetone-d_6) δ 170.2, 153.8, 132.3, 129.2, 128.7, 124.6, 119.0, 89.3, 82.1, 74.9, 32.4, 15.3.

EXAMPLE 28

3,4-Dihydroxy-5-[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0mmol) and 256μL (2.0 mmol) of 2-iodotoluene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH (96/4) as eluant to provide 3,4-dihydroxy-5-[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone as a light yellow solid: mp 111-112°C, ^1H NMR ($CDCl_3$) δ 7.37-7.07 (m, 4H), 5.01 (dd, J=3.5, 8.5 Hz, 1H), 2.69-2.65 (m, 2H), 2.40 (s, 3H), 2.39-2.27 (m, 1H), 1.97-1.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.6, 155.8, 140.0, 131.9, 129.3, 127.9, 125.5, 123.1, 117.5, 91.5, 80.9, 76.4, 31.3, 20.7, 15.3; Anal Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.41; H, 5.58.

EXAMPLE 29

3,4-Dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.34g, 2.0mmol) and 1.1g (4.0 mmol) of 2-(2*Z*-hexenyl)iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH (96/4) as eluant and dried at 0.05 mm Hg at 58°C for 2h to provide 100 mg (17% yield) of 3,4-dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone as a yellow oil: ^1H NMR (acetone-d_6) δ 7.43-7.15 (m, 4H), 5.70-5.45 (m, 2H), 4.91 (dd, 1H, J = 3.4, 8.3 Hz), 3.57 (d, 2H, J =

5.9 Hz), 2.66 (t, 2H, J = 7.0 Hz), 2.37-2.11 (m, 3H), 2.00-1.85 (m, 1H), 1.48-1.29 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); Anal Calcd for $C_{20}H_{22}O_4$ +0.2 H_2O: C, 72.80; H, 6.84. Found: C, 72.99; H, 6.96.

EXAMPLE 30

3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.12g, 0.71 mmol) and 0.35g (1.1mmol) of 2-(phenylthio)methyl-1-iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (96/3/1) as eluant and dried at 0.05 mm Hg at 58°C for 2h to provide 180 mg (69%) of 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone a light yellow oil: ^{1}H NMR (acetone-d_6) δ 7.44-7.19 (m, 9H), 4.90 (dd, J=3.3, 8.3 Hz, 1H), 4.36 (s, 2H), 2.63 (t, J=7.6 Hz, 2H), 2.28-2.21 (m, 1H), 1.90-1.81 (m, 1H); Anal Calcd for $C_{21}H_{18}O_4S$: C, 68.85; H, 4.95. Found: C, 68.63; H, 5.11.

EXAMPLE 31

3,4-Dihydroxy-5-[(4-(2-phenylsulfonamide-(*N*-butyl))-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0 mmol) and 400mg (1.2mmol) of N-butyl-2-iodobenzenesulfonamide were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 3,4-dihydroxy-5-[(4-(2-phenylsulfonamide-(*N*-butyl))-3-butynyl]-2(5*H*)-furanone as a light yellow oil: ^{1}H NMR (acetone-d_6) δ 8.00-7.96 (m, 1H), 7.59-7.55 (m, 1H), 7.33-7.24(m, 2H), 6.66(s, 1H), 4.82 (dd, J=3.4, 8.3 Hz, 1H), 3.44-3.36 (m, 2H), 3.23-3.14 (m, 2H), 2.52-2.45 (m, 1H), 2.00-1.94 (m, 1H), 1.69-1.53 (m, 2H), 1.43-1.29 (m, 2H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 169.8, 153.5, 141.6, 137.6, 130.0, 124.2, 123.8, 120.9, 118.6, 114.4, 108.7, 74.8, 53.6, 32.0, 24.9, 24.1, 20.9, 12.9; Anal Calcd for $C_{18}H_{21}NO_6S$: C, 56.99; H, 5.58; N, 3.69. Found: C, 56.71; H, 5.65; N, 3.48.

EXAMPLE 32

3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0 mmol) and 300μL (2.0mmol) of 2-iodonaphthalene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (96/3/1) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 230 mg (75%) of 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone as a yellow wax: ^{1}H NMR (acetone-d_6) δ 8.4-8.3 (m, 1H), 7.96-7.88 (m, 2H), 7.70-7.43 (m, 4H), 4.98 (dd, J=3.4, 8.3 Hz, 1H), 2.82-2.75 (m, 2H), 2.48-2.29 (m, 1H), 2.00-1.85 (m, 1H); Anal Calcd for $C_{18}H_{14}O_4$ + 0.5 H_2O: C, 71.27; H, 4.98. Found: C, 71.33; H, 4.87.

EXAMPLE 33

3,4-Dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0 mmol) and 440mg (1.5mmol) of 2-(propylthio)methyl]-iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 240 mg (72% yield) of 3,4-dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone as a yellow oil: ^{1}H NMR (acetone-d_6) δ 7.44-7.21 (m, 4H), 4.90 (dd, J=3.4, 8.3 Hz, 1H), 3.89 (s, 2H), 2.70-2.63 (m, 2H), 2.48-2.41 (m, 2H), 2.26-2.21 (m, 1H), 1.90-1.81 (m, 1H) 1.64-1.53 (m, 2H), 0.93 (t J=7.3 Hz, 3H); Anal Calcd for $C_{18}H_{20}O_4S$: C, 65.05; H, 6.07. Found: C, 64.51; H, 6.28.

EXAMPLE 34

3,4-Dihydroxy-5-[(4-(2-(1-pentylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (84mg, 0.5 mmol) and 240mg (0.75mmol) of 2-(methyl-1-pentylsulfide)iodobenzene were coupled in an analogous

fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2hours to provide 3,4-dihydroxy-5-[(4-(2-(pentylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone: ^{1}H NMR (acetone-d_6) δ 7.43-7.21 (m, 4H), 4.95 (dd, J=3.4, 8.4 Hz, 1H), 3.89 (s, 2H), 2.70-2.63 (m, 2H), 2.50-2.43 (m, 2H), 2.26-2.21 (m, 1H), 2.00-1.81 (m, 1H) 1.66-1.45 (m, 2H), 1.43-1.20 (m, 4H), 0.87 (t, J=7.2 Hz, 3H); Anal Calcd for $C_{20}H_{24}O_4S$ + 0.5 H_2O: C, 65.02; H, 6.82. Found: C, 65.38; H, 6.69.

EXAMPLE 35

3,4-Dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (236mg, 1.2 mmol) and 600mg (1.5mmol) of 2-methyl-(1-propylsulfone)iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 250 mg (50% yield) of 3,4-dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone as a light yellow oil: ^{1}H NMR (acetone-d_6) δ 7.56-7.34 (m, 4H), 4.96 (dd, J=3.4, 8.2 Hz, 1H), 4.57 (s, 2H), 3.03-2.95 (m, 2H), 2.71-2.64 (m, 2H), 2.35-2.26 (m, 1H), 1.94-1.70 (m, 3H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 169.9, 153.5, 132.9, 132.1, 131.0, 128.9, 128.5, 125.3, 118.6, 94.0, 79.6, 74.4, 57.2, 54.0, 31.5, 15.7, 14.8, 12.7; Anal Calcd for $C_{18}H_{20}O_6S$: C, 59.34; H, 5.53. Found: C, 58.93; H, 5.76.

EXAMPLE 36

3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (750mg, 4.5mmol) and 2.6g (8.2mmol) of 4-(4-fluorophenylmethyl)-2-iodothiophene were coupled in an analogous fashion as

described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using $CHCl_3$/MeOH/AcOH (500/15/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 1.2g (75% yield) of 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone as a brown wax: mp 119-121°C 1H NMR (acetone-d_6) δ 7.38-7.25 (m, 2H), 7.13-6.99 (m, 3H), 6.78-6.74 (m, 1H), 4.84 (dd, J=3.3, 8.1 Hz, 1H), 4.14 (s, 2H), 2.59 (t, J=7.1 Hz, 2H), 2.38-2.14 (m, 1H), 1.90-1.69 (m, 1H); ^{13}C NMR (acetone-d_6) δ 169.19, 164.04 157.29, 152.78, 145.79, 136.74, 131.80, 130.80, 130.47, 125.54, 122.74, 118.84, 115.89, 115.03, 92.44, 74.90, 74.31, 35.14, 31.84, 15.02; Anal Calcd for $C_{19}H_{15}FO_4S$: C, 63.69; H, 4.22. Found: C, 63.42; H, 4.33.

EXAMPLE 37

3,4-Dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone

Quinoline (70 μL, 0.6 mmol), 15mg of 5% Pd/$BaSO_4$ and 61mg (0.25mmol) of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone were combined in 20mL of ethanol and hydrogenated at atmospheric pressure until 12 mL (0.5mmol) of H_2 was consumed as measured by a H_2O filled burette. The catalyst was removed by filtration through two #1 fluted filter papers and the solution was concentrated to a volume of about 5mL, taken up in 50mL of ether and washed with 3 x 15mL of 5% aqueous HCl, 20mL of H_2O and 20mL of brine, dried ($MgSO_4$) and concentrated to provide 3,4-dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone as a brown wax: ^{1}H NMR (acetone- d_6) δ 7.28-7.13 (m, 5H), 4.66 (dd, J=3.4, 7.2 Hz, 1H), 2.62 (t, J=7.7, 2H), 2.00-1.93 (m, 1H), 1.69-1.42 (m, 5H); ^{13}C NMR (acetone- d_6) δ 170.7, 154.9, 143.3, 129.2, 129.1, 126.5, 118.6, 76.2, 36.3, 32.7, 32.1, 24.6. Anal Calcd for $C_{14}H_{16}O_4$ + 0.25 H_2O: C, 66.52; H, 6.58. Found: C, 66.71; H, 6.75.

EXAMPLE 38

3,4-Dihydroxy-5-[(4-phenyl)-3*Z*-butenyl]-2(5*H*)-furanone

Quinoline (70 μL, 0.6 mmol), 15mg of 5% Pd/$BaSO_4$ and 62mg (0.25mmol) of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone were combined in 20mL of

ethanol and hydrogenated at atmospheric pressure until 6 mL (0.25mmol) of H_2 was consumed as measured by a H_2O filled burette. The catalyst was removed by filtration through 2 fluted filter papers and the solution was concentrated, taken up in 50mL of ether and washed with 3 x 15mL of 5% aqueous HCl, 20mL of H_2O and 20mL of brine, dried ($MgSO_4$) and concentrated to give 3,4-dihydroxy-5-[(4-phenyl)-3*Z*-butenyl]-2(5*H*)-furanone as the major constituent in a mixture of alkyne, cis alkene and alkane (1.0/5.0/0.5) as determined by ^{1}H NMR spectra: ^{1}H NMR ($CDCl_3$) δ 7.34-7.14 (m, 5H), 6.46 (d, J=11.5 Hz, 1H), 5.65-5.57 (m, 1H), 4.77 (dd, 3.5, 8.0 Hz, 1H), 2.49 (dd, J_{ab}=7.6 Hz, 2H), 2.16-2.09 (m, 1H), 1.80-1.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.4, 155.9, 137.1, 130.4, 130.3, 128.7, 128.3, 128.3, 126.8, 117.5, 77.2, 31.8, 23.5.

EXAMPLE 39

3,4-Dihydroxy-5[(4-(2-methyl)phenyl)-3*Z*-butenyl]-2(5*H*)-furanone

3,4-Dihydroxy-5[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone (65mg, 0.25mmol) was reduced in a similar manner as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3*Z*-butenyl]-2(5*H*)-furanone to produce 3,4-dihydroxy-5[(4-(2-methyl)phenyl)-3*Z*-butenyl]-2(5*H*)-furanone as an oil consisting of only the cis isomer as observed by the ^{1}H NMR spectra. ^{1}H NMR ($CDCl_3$) δ 7.34-7.20 (m, 4H), 6.59 (d, J=11.4 Hz, 1H), 5.81-5.73 (m, 1H), 4.81 (dd, J=3.4, 8.2 Hz, 1H), 2.49-2.35 (m, 2H), 2.33 (s, 3H), 2.17-2.13 (m, 1H), 1.81-1.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.6, 156.0, 136.2, 136.2, 130.2, 129.9, 129.6, 128.8, 127.1, 125.5, 117.4, 77.3, 31.9, 23.4, 19.9.

EXAMPLE 40

3,4-Dihydroxy-5[(4-(2-(2*Z*-hexenyl))phenyl)-3*Z*-butenyl]-2(5*H*)-furanone

3,4-Dihydroxy-5[(4-(2-(2-hexynyl))phenyl)-3*Z*-butenyl]-2(5*H*)-furanone (75mg, 0.25mmol) was reduced in a similar manner as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3*Z*-butenyl]-2(5*H*)-furanone to produce 3,4-dihydroxy-5[(4-(2-(2*Z*-hexenyl))phenyl)-3*Z*-butenyl]-2(5*H*)-furanone as an oil consisting of only the cis isomer as observed by the ^{1}H NMR spectra and contaminated with less than 5% of starting material, which was not separable from the product: ^{1}H NMR (acetone-d_6) δ

7.25-7.15 (m, 4H), 6.59 (d, 1H, J = 11.4 Hz), 5.81-5.76 (m, 1H), 5.51-5.43 (m, 2H), 4.71 (dd, 1H, J = 3.5, 7.6 Hz), 3.44-3.25 (m, 2H), 2.40-1.90 (m, 5H), 1.76-1.58 (m, 1H), 1.50-1.32 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz). Anal Calcd for $C_{20}H_{24}O_4$ + 0.25 H_2O: C, 71.20; H, 7.47. Found: C, 70.97; H, 7.32.

The following is a list of references related to the above disclosure. These references should be considered as incorporated by reference in their entirety.

1. Shimuzu, T., et al. Enzyme with dual lipoxygenase activities catalyzes leukotriene A4 synthetase from arachidonic acid. Pro. Natl. Acad. Sci. 81:689-693, (1984).

2. Egan, RW and Gale PH, Inhibition of mammalian 5-lipoxygenase by aromatic disulfides, J. Biol. Chem. 260: 11554-11559, (1985).

3. Evans, AT, et al Actions of cannabis constituents on enzymes of arachidonic metabobilism: anti-inflammatory potential. Biochem Pharm. 36:2035-2037, (1987).

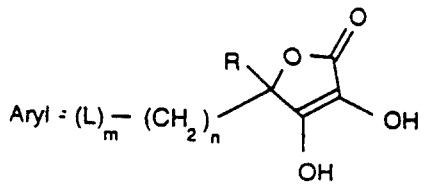
4. Boopathy, R and Baiasubramanian AS. Purification and characterization of sheep platelet cyclooxygenase. Biochem J. 239:371-377, (1968).

5. O'Sullivan, MG et al, Lipopolysaccharide induces prostaglandin H synthase-2 in alveolar macrophages. Biochem. Biophys. Res. Comm. 187: 1123-1127, (1992).

6. Mansuy D. et al, A new potent inhibitor of lipid peroxidation in vitro and in vivo, the hepatoprotecticve drug anisyldithiolthione. Biochem. Biophys. Res. Comm. 135:1015-1021, (1986).

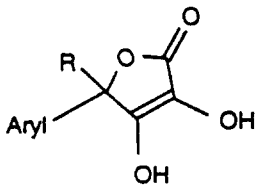
WHAT IS CLAIMED IS:

1. A racemic or optically active compound of the formula I:

(I) 

wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the group consisting of oxygen, nitrogen, acetylene, a *cis* or *trans* carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4, Aryl is a substituted or unsubstituted aryl group; with the proviso that when R is hydrogen, then either m or n is not zero; and with the further proviso that when R is hydrogen and L is sulfur, Aryl is substituted other than with a hydroxy or lower alkoxy group; or a pharmaceutically acceptable salt thereof.

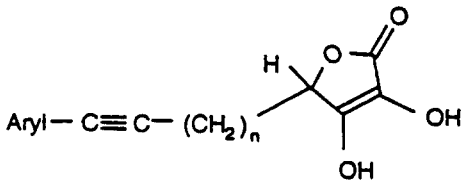
2. A compound according to Claim 1 of the formula Ia

 (Ia)

wherein R is phenyl or a lower alkyl; and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

3. A compound according to Claim 2 which is racemic 5-[(1,1'-diphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone; racemic 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; racemic 3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; (S)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (R)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (S)-(+)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; or (R)-(-)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone.

4. A compound according to Claim 1 of the formula Ib

 (Ib)

wherein n is 0 to 4 and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

5. A compound according to Claim 4 which is 3,4-dihydroxy-5-[(4-(2-(2Z-

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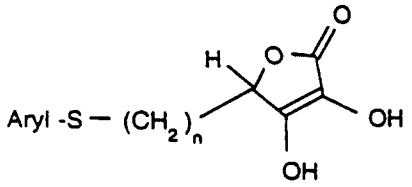
hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone.

6. A compound according to Claim 4 which is 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone.

7. A compound according to Claim 4 which is 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone.

8. A compound according to Claim 4 which is 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone.

9. A compound according to Claim 1 of the formula Ic



(Ic)

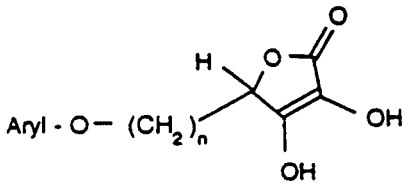
wherein n is 0 to 4 and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

10. A compound according to Claim 9 which is 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone.

11. A compound according to Claim 9 which is 3,4-dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone.

12. A compound according to Claim 9 which is 3,4-dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone.

13. A compound according to Claim 1 of the general formula Id



(Id)

wherein n is 0 to 4 and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

14. A compound according to Claim 13 which is 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone.

15. A compound according to Claim 10 which is 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone.

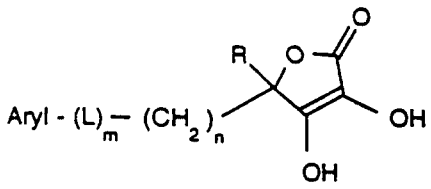
16. A compound according to Claim 10 which is 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

17. A compound according to Claim 10 which is 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone.

18. A compound according to Claim 10 which is 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone.

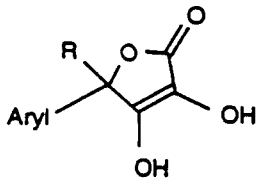
19. A compound according to Claim 10 which is 5-[2-((1,1`-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

20. A pharmaceutical composition comprising an effective amount of a racemic or optically active compound of the general formula I:

(I) 

wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the group consisting of oxygen, nitrogen, acetylene, a *cis* or *trans* carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4, Aryl is a substituted or unsubstituted aryl group; with the proviso that when R is hydrogen, then either m or n is not zero; and with the further proviso that when R is hydrogen and L is sulfur, Aryl is substituted other than with a hydroxy or lower alkoxy group; or a pharmaceutically acceptable salt thereof; together with a pharmaceutically acceptable carrier therefor.

21. A composition according to Claim 20 of the formula Ia



(Ia)

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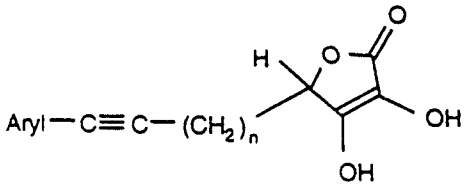
wherein R is phenyl or a lower alkyl; and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

22. A composition according to Claim 21 which is racemic 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone; racemic 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; racemic 3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; (S)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (R)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (S)-(+)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; or (R)-(-)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone.

23. A composition according to Claim 20 of the formula Ib



(Ib)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

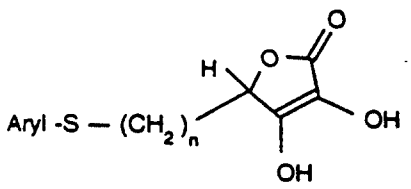
24. A composition according to Claim 23 which is 3,4-dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone.

25. A composition according to Claim 23 which is 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone.

26. A composition according to Claim 23 which is 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone.

27. A composition according to Claim 23 which is 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone.

28. A composition according to Claim 20 of the formula Ic



(Ic)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

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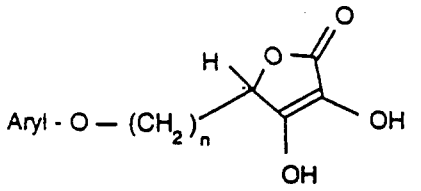
29. A composition according to Claim 28 which is 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone.

30. A composition according to Claim 28 which is 3,4-dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone.

31. A composition according to Claim 28 which is 3,4-dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone.

32. A composition according to Claim 20 of the general formula Id



(Id)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

33. A composition according to Claim 32 which is 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone.

34. A composition according to Claim 27 which is 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone.

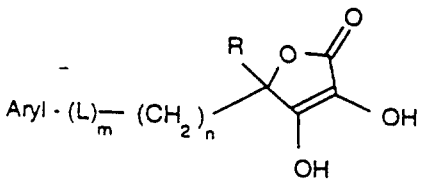
35. A composition according to Claim 27 which is 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

36. A composition according to Claim 27 which is 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone.

37. A composition according to Claim 27 which is 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone.

38. A composition according to Claim 27 which is 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

39. A method of treating a pathology in which reactive oxygen species and inflammatory mediators are contributing deleterious factors which comprises administration to a patient in need of such therapy an effective amount of a racemic or optically active compound of the formula



(I)

wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the group consisting of oxygen, nitrogen, acetylene, a *cis* or *trans* carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4, Aryl is a substituted or unsubstituted aryl group; with the proviso that when R is hydrogen, then either m or n is not zero; and with the further proviso that when R is hydrogen and L is sulfur, Aryl is substituted other than with a hydroxy or lower alkoxy group; or a pharmaceutically acceptable salt thereof.

40. The method of claim 39 wherein said pathology comprises acute or chronic inflammatory disorders.

41. The method of claim 40 wherein said acute or chronic inflammatory disorder is asthma, rheumatoid arthritis, inflammatory bowel disease, or acute respiratory distress syndrome.

42. The method of claim 39 wherein said pathology comprises neurodegenerative disorders.

43. The method of claim 42 wherein said neurodegenerative disorder is Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury or multiple sclerosis.

44. The method of claim 39 wherein said pathology comprises cardiovascular disease.

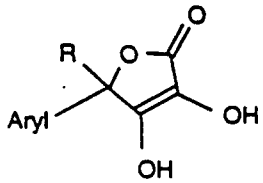
45. The method of claim 44 wherein said cardiovascular disease is atherosclerosis.

46. The method of claim 39 wherein said pathology comprises a viral disease.

47. The method of claim 46 wherein said viral disease is AIDS.

48. The method of claim 39 wherein said pathology comprises a skin disease.

49. A method according to Claim 39 of the formula Ia



(Ia)

wherein R is phenyl or a lower alkyl; and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

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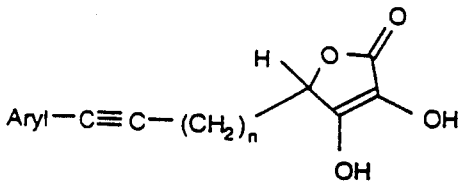
50. A method according to Claim 49 which is racemic 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone; racemic 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; racemic 3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; (S)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (R)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone; (S)-(+)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone; or (R)-(-)-3,4-dihydroxy-5-methyl-5-[4'-(2'-methylpropyl)phenyl]-2(5H)-furanone.

51. A method according to Claim 39 of the formula Ib



(Ib)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

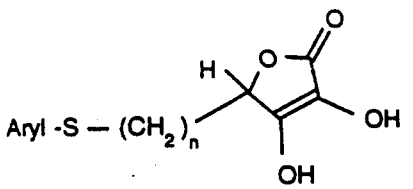
52. A method according to Claim 51 in which said compound is 3,4-dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone.

53. A method according to Claim 51 in which said compound is 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone.

54. A method according to Claim 51 in which said compound is 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone.

55. A method according to Claim 51 in which said compound is 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone.

56. A method according to Claim 39 comprising a compound of the formula Ic



(Ic)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

57. A method according to Claim 56 in which said compound is 3,4-dihydroxy-5-[2-(4,5-

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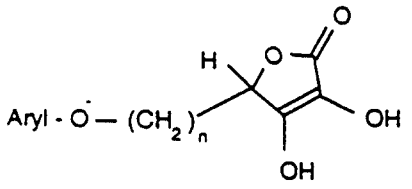
diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone.

58. A method according to Claim 56 in which said compound is 3,4-dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone.

59. A method according to Claim 56 in which said compound is 3,4-dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5*H*)-furanone.

60. A method according to Claim 39 comprising a compound of the general formula Id



(Id)

wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

61. A method according to Claim 60 in which said compound is 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone.

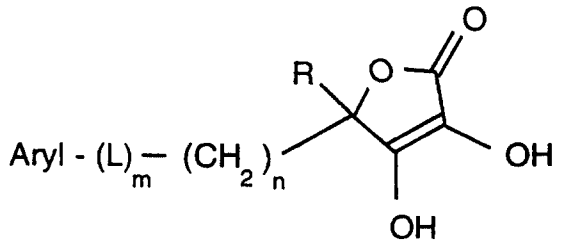
62. A method according to Claim 60 in which said compound is 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone.

63. A method according to Claim 60 in which said compound is 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

64. A method according to Claim 60 in which said compound is 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone.

65. A method according to Claim 59 in which said compound is 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone.

66. A method according to Claim 59 in which said compound is 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.



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