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(54) **Title:** NOVEL BIOACTIVE DIPHENYL ETHENE COMPOUNDS AND THEIR THERAPEUTIC APPLICATIONS

(57) **Abstract:** This invention provides a novel group of diphenyl ethene derivatives, pharmaceutically acceptable salts thereof, the process of making these compounds, their pharmaceutical composition and the use of these compounds as agents for treating immune, inflammatory and auto-immune diseases.

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NOVEL BIOACTIVE DIPHENYL ETHENE COMPOUNDS AND THEIR THERAPEUTIC APPLICATIONS

Background of the Invention

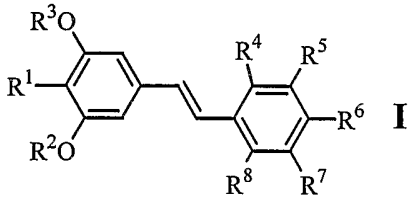
Stilbene derivatives are well-known in the art to have a wide range of activities and are widely distributed in nature. There is a growing interest in stilbene derivatives because of a range of activities that have been observed in some of the naturally occurring as well as some of the synthetic stilbenes. A stilbene derivative, 3,5,4'-trihydroxystilbene, commonly known as resveratrol in which both isomers (cis or trans) has been reported to have a range of biological functions, such as mediating inflammation and cancer chemoprevention (Jang, et al. 1997, Science, 275, 218, US6,008,260).

It is known in the art that substitution on the various position on the two phenyl rings of the basic stilbene structure results in a great diversity of compounds, including those with one or two substituents on one or both of the phenyl rings of the stilbene structure(Shudo K., 1988, US4723028; Hensley, K.L., *et al.*, WO99/59561, Kunihiro N., 1983, JP58159410; Genji I., 1995, JP07053359 and GB1465661) and those with three or more substituents on the phenyl rings (Koichi, S. *et al.*, 1986, EP0170105; Shozo Y., *et al.*, 1986, JP08337523; and Charpentier B. *et al.*, 1992, WO92/19583). Compounds with other substitution on the phenyl ring, such as derivatives of vitamine A (Ney, U.M., *et al.* 1987, Dermatologica, 175:93-99) and vitamine D (WO 00/26167) are well-known in the art. Several publications (WO92/16486, WO99/40056, WO01/95859 and Cushman M. *et. al.* (1992, J. Med. Chem., 35:2293-2306) disclosed compounds that are derived from 3, 4, 5-trimethoxyl stilbene. These compounds showed anti-neoplastic activity and modest activity of modulating cytokines (WO01/95859).

Recently, a group of stilbenes with a unique substitute pattern of two hydroxyl groups, or their derivatives, in position 3 and 5 and a substituent in between have been disclosed. Pending applications of the inventors are directed to compounds having inhibitory activity against kinases, anti-inflammatory activity (WO 01/42231), having effect on T lymphocytes, macrophages, neutrophils and mast cells and modulating a variety of immune and inflammatory activities (WO 02/057219). However, it is not discovered until now that with the unique substitution pattern on one phenyl group the substitution on the other phenyl group with a range of specific substituents, in particular fluoro atoms, resulted in compounds that have surprising immune-modulating activity. The present invention is related to these novel stilbene compounds, their synthesis, their unexpected activity, pharmaceutical composition and their use for treatment of disorders associated with these activities.

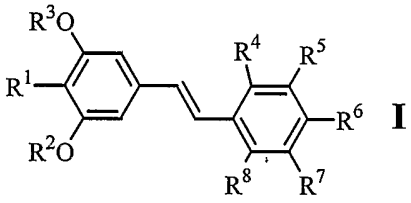
Summary of the Invention

The invention disclosed herein relates to compounds of Formula I, pharmaceutically acceptable salts thereof, pharmaceutical composition of these compounds that have been found useful as immune-modulating agents.



Detailed Description of the Invention

The invention covers new compounds of general formula **I**,



wherein R^1 is selected from the group consisting of unsubstituted or substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, or COR^9;

R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl;

R^4, R^5, R^6, R^7 and R^8 are not H simultaneously and are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\ R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group; with the proviso that R^6 is not hydroxy or alkyoxy group when R^1 is an unsaturated group comprising of 1-3 isoprene unit(s);

R^9 is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, or aralkyl, or $NR^{10}R^{11}$, or OR^{10};

R^{10} and R^{11} are selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl or aralkyl;

R^{12} is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl.

In particular, new compounds of general formula **I**, wherein

R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\ R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group and one or more than one of R^4, R^5, R^6, R^7 and R^8 is F. The configuration of the double bond of the compound of formula I is *E* or *Z*.

Highly preferred compounds include the following:

4-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**6**).

3-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**7**).

5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**13**).

5-[2-(3,5-Dihydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**15**).

5-[2-(2-Fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**37**).

5-[2-(3-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**38**).

5-[2-(4-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**39**).

5-[2-(3,5-Difluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**40**).

5-[2-(2,4-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**41**).

5-[2-(2,6-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**42**).

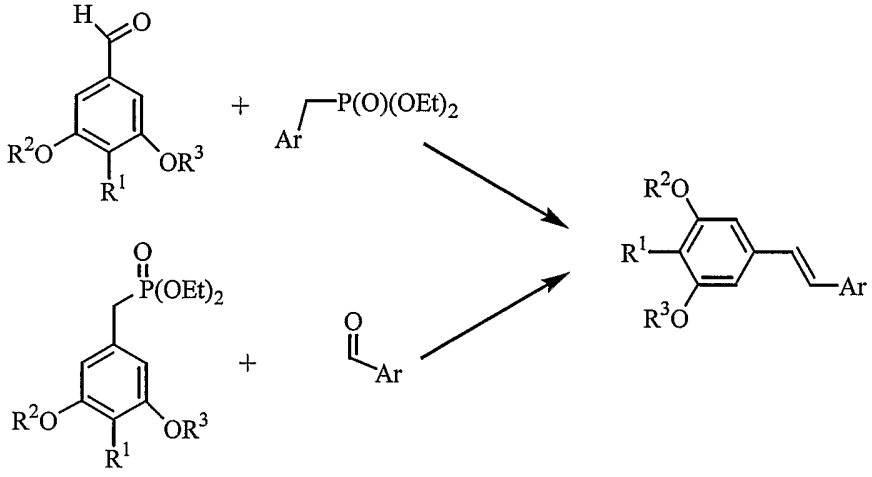
2-*i*-Propyl-5-[2-(2,4,6-trifluorophenyl)ethenyl]-1,3-benzenediol (**43**).

5-[2-(2,3,4,5,6-Pentafluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**44**).

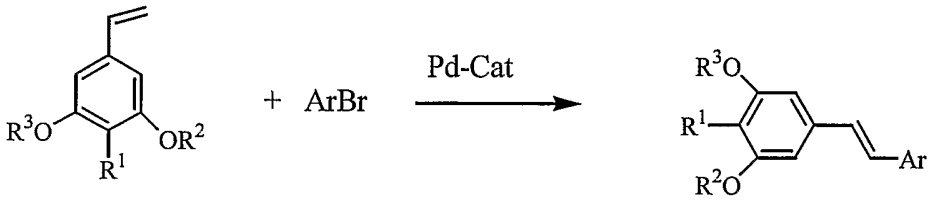
The invention also covers use of the compounds of general formula **I** as immune-modulating agents.

The compounds of this invention may be synthesized using general procedures disclosed in patent publication WO02/057219 with specific modifications. Examples given herein are illustrative only, and are not considered as limitations of this invention. In general, the stilbene structures of the compounds of the invention are constructed *via* Wittig olefination (Scheme 1) and Heck reaction (Scheme 2). The corresponding 1,3-benezendiol can be obtained by a deprotection reaction.

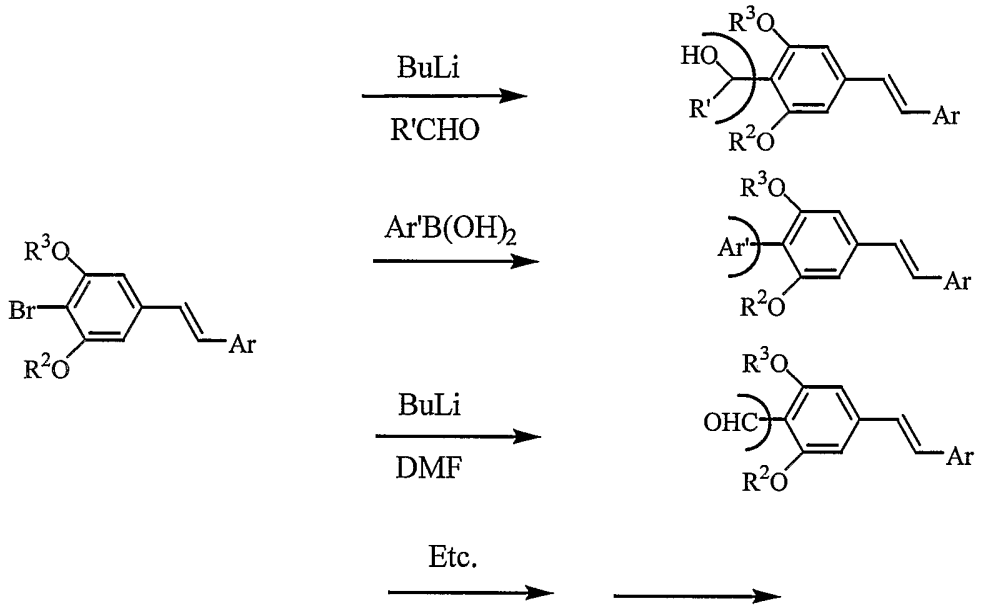
Scheme 1. Wittig olefination:



Scheme 2. Heck reaction:



Scheme 3. Modification:



One modification of R^1 is to start with a bromostilbene (Scheme 3). The bromide can be converted to other functional groups by Suzuki coupling or a bromo-lithium exchange followed by reacting with an electrophile.

The compounds utilized in accordance with the present invention have *Z* or *E* configuration of the double bonds resulting in *trans* and *cis* isomers. The scope of the present invention is intended to cover all such isomers as well as mixtures of cis and trans isomers.

A pharmaceutically acceptable salt may be prepared for any compounds in this invention having a functional capability of forming such salt. Pharmaceutically acceptable salts may be formed with inorganic and/or organic acids and bases. Suitable acids include, for example, hydrochloric, sulfuric, nitric, benzenesulfonic, acetic, maleic, tartaric and the like, which are pharmaceutically acceptable. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in the production of these compounds, or where non-medicament-type uses are contemplated.

Compounds of the present invention have shown a range of immune-modulating activities that are demonstrated and confirmed in the forthcoming examples. Compounds which have immune-modulating activity are well-known in the art, and are described in numerous patent and scientific publications. It is generally known and accepted in the art that immune-modulating activity is useful for treating numerous diseases and conditions of animals, including humans. It is generally known in the art that pharmaceuticals having a compound or compounds with immune-modulating activity, such as those disclosed herein, as the active ingredient are useful agents for the treatment of disorders such as: clinical transplants (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or

osteoarthritis); multiple sclerosis; inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosis); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenalglands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituatarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis, serum sickness; uticaria; allergic diseases such as respiratory allergies (asthma, hay fever, allergic rhinitis) or skin allergies; scleraciерma; mycosis fungoides; acute inflammatory responses (such as acute respiratory distress syndrome and ishchemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; and morphea. In particular, the activity against VEGF expression finds utility in treating cancers and VEGF associated disorders. The inhibition of LTB_4 induced cell migration is useful as anti-inflammatory agents.

The present invention thus provides methods for the treatment of disorders associated with the abovementioned activities, comprising the step of administering to a subject in need thereof at least one compound of the formula I in an amount effective therefore. Other therapeutic agents such as those known to the skilled in the art may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, powder, suppositories etc.) or liquid (solutions, suspensions or emulsions) in a suitable composition for oral, topical, parenteral or rectal administration. These formulations may contain the pure compound or be in combination with a carrier or some other pharmaceutically active compound. These compositions may need to be sterile when administered parenterally.

For topical use, it will be preferred to use in the form of creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to about 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of

active agent compounded with an appropriate and convenient amount of carrier material that may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The invention is now described in greater detail by reference to the following non-limiting examples.

Synthesis of compounds

Example 1. 4-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**1**).

a). Methyl 3,5-dimethoxy-4-*i*-propylbenzoate.

This compound was obtained using method described in WO 01/42231. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.2 Hz, 6H), 3.66 (hept, J = 7.2 Hz, 1H), 3.82 (s, 6H), 3.95 (s, 3H), 7.25 (s, 2H).

b). 3,5-Dimethoxy-4-*i*-propylbenzyl alcohol.

To a suspension of $LiAlH_4$ (95%) (5.00g, 125mmol) in dry ether (100mL) at 0°C was added a solution of methyl 3,5-dimethoxy-4-*i*-propylbenzoate (15.7g, 90.1mmol), in ether (300mL) under N_2. The suspension was stirred at 0°C for one hour then for an additional hour at room temperature. The reaction was quenched by slow addition of a saturated Na_2SO_4 aqueous solution (10mL) at 0°C. The mixture was stirred overnight. The solid was filtered off and the filtrate was evaporated to dryness to give the desired alcohol (13.8g, 88% yield) as white crystals. ^{1}HNMR ($CDCl_3$. ppm): δ 1.34 (d, J = 7.2Hz, 6H), 3.65 (hept., J = 7.2Hz, 1H), 3.88 (s, 6H), 4.70 (s, 2H), 6.62 (s, 2H).

c). 3,5-Dimethoxy-4-*i*-propylbenzyl aldehyde.

A mixture of 3,5-dimethoxy-4-*i*-propylbenzyl alcohol (13.05g, 62.1mmol) and pyridinium chlorochromate (33.92g, 157mmol) was stirred in CH_2Cl_2 (100mL) in the presence of K_2CO_3 (4.18g, 30mmol) for 30 min. Ether (300mL) was added to quench the reaction. The mixture was passed through a short pad of Florisil and the pad was washed thoroughly with ether. Evaporation of the solvent gave 3,5-dimethoxy-4-*i*-propylbenzyl aldehyde (11.89g. 92% yield) as a yellowish crystal. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.2Hz, 6H), 3.68 (hept., J = 7.2Hz, 1H), 3.92 (s, 6H), 7.12 (s, 2H), 9.96 (s, 1H).

d). (3,5-Dimethoxy-4-*i*-propylphenyl)ethene.

To a suspension of methyltriphenylphosphonium bromide (6.89g, 19.3mmol) in THF (100mL) under argon was added BuLi (7.7ml, 2.5M in hexane, 19.3mmol) at room temperature. The resultant red solution was stirred for 10 min. and then 3,5-dimethoxy-4-*i*-propylbenzyl aldehyde (4.02g, 19.3mmol) in THF (20mL) was added. After 2 hours, the reaction was quenched with water (20mL). The mixture was extracted with ether (3 x 100mL). The extract was washed with saturated saline solution (3 x 30mL) and dried over sodium sulphate. Evaporation of ether followed by flash chromatography

using 3% ethyl acetate in hexane afforded pure (3,5-dimethoxy-4-*i*-propylphenyl)ethene (2.64g, 66% yield) as a colorless solid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.31 (d, J = 7.1Hz, 6H), 3.61 (qint, J = 7.1Hz, 1H), 3.86 (s, 6H), 5.25 (d, J = 11Hz, 1H), 5.73 (d, J = 17Hz, 1H), 6.64 (s, 2H), 6.70 (dd, J = 11, 17Hz, 1H).

e). 4-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**1**).

A mixture of (3,5-dimethoxy-4-*i*-propylphenyl)ethene (0.303g, 1.50mmol), 4-bromobenzoic acid (0.269g, 1.30mmol), dihydrogen di-μ-chlorotetrkis(di-*tert*-butylphosphinito-κ*P*)dipalladate (0.0625g, 0.067mmol), Bu_4NI (0.245g, 0.67mmol) and K_2CO_3 (0.614g, 4.40mmol) in DMF (7mL) was heated at 140°C under argon. After the reaction was complete (5h), the reaction mixture was poured into water (100ml). This was washed with ether. The aqueous phase was acidified with 6NHCl and extracted with ether (2 X100mL). The extract was washed with saturated sodium chloride and then dried over anhydrous Na_2SO_4. Evaporation of ether gave the pure acid **1** (0.345g, 71% yield). ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.1Hz, 6H), 3.63 (qint, J = 7.1Hz, 1H), 3.90 (s, 6H),6.76 (s, 2H), 7.08 (d, J = 17Hz, 1H), 7.27 (d, J = 17Hz, 1H), 7.63 (d, J = 8Hz, 2H), 8.13 (d, J = 8Hz, 2H).

Example 2. 3-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**2**).

This compound was synthesized from (3,5-dimethoxy-4-*i*-propylphenyl)ethene and 3-bromobenzoic acid in 77% yield in the same way as described in preparation of **1**. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.1Hz, 6H), 3.63 (qint, J = 7.1Hz, 1H), 3.90 (s, 6H), 6.76 (s, 6H), 7.08 (d, J = 17Hz, 1H), 7.25 (d, J = 17Hz, 1H), 7.50 (t, J = 7.7Hz, 1H), 7.79 (d, J = 7.7Hz, 1H), 8.04 (d, J = 7.7Hz, 1H), 8.31 (s, 1H).

Example 3. 4-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**6**).

A mixture of 4-[2-(3.5-dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid (0.289g, 0.886mmol) and pyridine hydrochloride (0.678, 5.9 mmol) was heated at 200°C for 2 h under a stream of argon. The reaction mixture was cooled to room temperature. 2NHCl (10mL) and ether (50mL) was added. The organic layer was separated and the aqueous mixture was extracted with ether (2 × 50mL). The extract was washed with saturated brine and dried over anhydrous Na_2SO_4. Evaporation of ether followed by flash chromatography using ethyl acetate/hexane/acetic acid (40/60/1) afforded the pure acid **6** (0.03g, 11% yield). ^{1}HNMR (DMSO-d_6, ppm): δ 1.22 (d, J = 7.0Hz), 6.49 (s, 2H), 6.90 (d, J = 18Hz, 1H), 7.19 (d, J = 18Hz, 1H), 7.67 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H), 9.14 (s, 2H).

Example 4. 3-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid (**7**).

This material was prepared from 3-[2-(3.5-dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid **2** and pyridine hydrochloride in 86% yield in the same way as described in example 3. ^{1}HNMR (DMSO-d_6, ppm): δ 1.22 (d, J = 7.0Hz, 6H),6.48 (s, 2H), 7.03 (d, J = 17Hz, 1H), 7.12 (d, J = 17Hz, 1H), 7.46 (t, J = 7.5Hz, 1H), 7.7-7.9 (m, 2H), 8.06 (s, 1H), 9.12 (s, 2H).

Example 5. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-phenylethene (**19**).

a). Diethyl benzylphosphonate.

The mixture of benzyl bromide (12mL, 101mmol) and triethyl phosphite (25mL, 146mmol) was heated at 110-130°C in the presence of Bu_4NI (0.05g) overnight. The excess triethyl phosphite was

removed under reduced pressure at 110°C. The phosphonate (23g) was obtained quantitatively as a colorless liquid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.28 (t, J = 7.2Hz, 6H), 3.20 (d, J = 21.9Hz, 2H), 4.10 (dt., J = 7.2Hz, 7.2Hz, 4H), 7.30 (s, 5H).

b). 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-phenylethene (**19**).

To a solution of diethyl benzylphosphonate obtained above (11.39g, 54.7mmol) in THF (100mL) at 0°C was added NaH (60% in mineral oil) (4.68g, 115mmol) under N_2. After the addition was completed, the suspension was stirred at 0°C for 1 h and 3,5-dimethoxy-4-*i*-propylbenzyl aldehyde obtained in example 1(c) (11.39g, 54.7 mmol) in THF (100mL) was added. The reaction was kept at 0°C for 1 h and then at 45-50°C for 5 h. The reaction was cooled to 0°C. Water was added slowly to quench the reaction followed by addition of 2N HCl (75mL). The mixture was extracted with ether (3 × 200mL). The extract was dried over anhydrous Na_2SO_4. Evaporation of ether gave crude 5-(2-phenylethenyl)-2-*i*-propyl-1,3-dimethoxy benzene (18.07g). This was used for the next reaction without further purification. A small amount of the crude product was purified by flash chromatography using 10% ethyl acetate in hexane to afford pure product. ^{1}HNMR ($CDCl_3$, ppm): δ 1.28 (d, J = 7.0 Hz, 6H), 3.58 (hept, J = 7.0 Hz, 1 H), 3.85 (s, 6 H), 6.69 (s, 2 H), 7.05 (s, 2 H), 7.25 (m, 1 H), 7.35 (m, 2 H), 7.25 (m, H).

Example 6. 5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol (**20**).

To the crude 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-phenylethene (18.07g) in dry CH_2Cl_2 (100mL) at –78°C under N_2 was added BBr_3 (5.2mL, 55mmol) dropwise. After the reaction was stirred at –78°C for 1 h, the temperature was allowed to rise to room temperature and the reaction mixture was stirred at room temperature for 2 days. Water was added to quench the reaction, followed by 20% NaOH to adjust pH > 12. The organic layer was removed and the aqueous layer was washed with hexane (2 × 100mL). The aqueous layer was acidified with 6N HCl to pH 1 and extracted with ether (3 × 200mL). The organic layer was separated and washed with water (50mL) and brine (50mL) and dried over anhydrous Na_2SO_4. Evaporation of ether gave a red syrup. Recrystallization with chloroform yielded pure stilbene product **20** (6.92g) as a white crystal. The mother liquid was concentrated and the residue was recrystallized once more to afford an additional 2.5g of **20** (total 9.42g, 67.7% over two steps). ^{1}HNMR ($CDCl_3$, ppm): δ 1.38 (d, J = 7.3Hz, 6H), 3.46 (hept., J = 7.3Hz, 1H), 4.80 (s, 2H), 6.50 (s, 2H), 6.92 (d, J = 17.2Hz, 1H), 6.97 (d, J = 17.2Hz, 1H), 7.25 (m, 1H), 7.34 (m, 2H), 7.52 (m, 2H).

Example 7. 3-Acetoxy-5-(2-phenylethenyl)-2-*i*-propylphenyl acetate (**10**).

To 5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol obtained in example 11 (1.00g, 3.93mmol) and triethylamine (1.5mL, 10.8mmol) in dichloromethane (100mL) at 0°C was added acetyl chloride dropwise. The reaction was monitored by TLC. Water (50mL) was added after the reaction was complete (~30 min.). The organic layer was separated and washed with 2NHCl (30mL), H_2O (50mL), saturated $NaHCO_3$ (50mL), H_2O (50mL) and brine (50mL), and dried over anhydrous sodium sulfate. Evaporation of the solution followed by flash chromatography using 5% ethyl acetate in hexane

yielded 3-acetoxy-5-(2-phenylethenyl)-2-*i*-propylphenyl acetate. (1.32g, 92%) as a white solid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.26 (d, J = 7.0Hz, 6H), 2.35 (s, 6H), 3.08 (hept., J = 7.0Hz, 1H), 6.98 (d, J =17.4Hz, 1H), 7.04 (d, J = 17.4Hz, 1H), 7.07 (s, 2H), 7.24-7.29 (m, 1H), 7.34-7.38 (m, 2H), 7.45-7.49 (m, 2H).

Example 8. 3-Chloroacetoxy-5-(2-phenylethenyl)-2-*i*-propylphenyl chloroacetate(**11**).

This material was synthesized from anhydrous chloroacetic and 5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol obtained in example 11 in 72%yield by the same procedure as described in example 12. ^{1}HNMR ($CDCl_3$, ppm): δ 1.30 (d, J = 7.0Hz, 6H), 3.08 (hept, J=7.0Hz, 1H), 4.39 (s, 4H), 6.96 (d, J = 17Hz, 1H), 7.14 (d, J = 17Hz, 1H) 7.17 (s, 2 H), 7.2-7.5 (m, 5 H).

Example 9. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethene (**12**).

a). 3,5-Dimethoxy-4-isopropyl benzyl bromide

To 3,5-Dimethoxy-4-*i*-propylbenzyl alcohol (12.57g, 59.8mmol) in dry ether (100mL) at 0°C was added PBr_3 (3.0mL, 31.2mmol) dropwise under nitrogen. The reaction was monitored by TLC. After the reaction was completed (~4h), water (180mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 50mL). The extract was washed with water (20mL), sat. Na_2CO_3 (20mL), water (20mL) and brine (20mL), and dried over anhydrous sodium sulfate. Evaporation of the solution yielded pure bromide (14.93g, 91.4%) as a white solid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.29 (d, J = 7.1Hz, 6H), 3.64 (hept, J = 7.1Hz, 1H), 3.84 (s, 6H), 4.50 (s, 2H), 6.60 (s, 2H).

b). Diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate.

The mixture of 3,5-dimethoxy-4-*i*-propylbenzyl bromide (5.01g, 18.3mmol) and triethyl phosphite (4.7mL, 27.4mmol) was heated at 110-130°C in the presence of Bu_4NI (0.05g) overnight. The excess triethyl phosphite was removed under reduced pressure at 110°C to give the phosphonate (5.58g, 92%). ^{1}HNMR ($CDCl_3$, ppm): δ 1.27 (d, J = 7.1Hz, 6H), 1.29 (t, J = 7.0Hz, 6H), 3.12 (d, J =21.5Hz, 2H), 3.4-3.7 (m, 1H), 3.80 (s, 6H), 4.06 (dt, J =7.1, 7.1Hz, 4H), 6.50 (d, J = 2.6Hz, 2H).

c). 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethene (**12**).

This material was prepared from diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate and 4-anisaldehyde in 63% yield as the same procedure as described in example 5(b). ^{1}H NMR ($CDCl_3$, ppm): δ 1.31 (d, J=7.1Hz, 6H), 3.51-3.74 (m, 1H), 3.86 (s, 3H), 3.91 (s, 6H), 6.71 (s, 2H), 6.84-7.09 (m, 4H), 7.39-7.60 (m, 2H).

Example 10. 5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**13**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethene and pyridine hydrochloride in 30% yield in the same way as described in example 3. ^{1}H NMR (DMSO-d_6, ppm): δ 1.22 (d, J=7.0Hz, 6H), 3.41 (m, 1H), 6.40 (s, 2H), 6.73 (d, J = 6.3Hz, 4H), 7.33 (s, 1H), 7.41 (s, 1H), 8.98 (s, 2H), 9.51 (s, 1H).

Example 11. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3,5-dimethoxyphenyl)ethene (**14**).

This material was prepared from diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate and 3,5-dimethoxybenzaldehyde in 25%yield as the same procedure as described in example 5(b)

Example 12. 5-[2-(3,5-Dihydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**15**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(3,5-dimethoxyphenyl)ethene and BBr_3 by the same procedure as described in example 11.

Example 13. 1-(4-Bromo-3,5-dimethoxyphenyl)-2-phenylethene (**21**).

a). Methyl 4-bromo-3,5-dimethoxybenzoate.

This material was synthesized from 4-bromo-3,5-dihydroxybenzoic acid and Me_2SO_4 in 95% yield by the same method as described in example 1 (a). ^{1}HNMR ($CDCl_3$, ppm): δ 3.96 (s, 3 H), 3.99 (s, 6 H), 7.28 (s, 2 H).

b). 4-Bromo-3,5-dimethoxybenzyl alcohol.

This material was synthesized from methyl 4-bromo-3,5-dimethoxybenzoate obtained above in 85% yield by the same method as described in example 1(b). ^{1}HNMR ($CDCl_3$, ppm): δ1.95 (s, 1H), 3.93 (s, 6H), 4.69 (s, 2H), 6.61 (s, 2H).

c). 4-Bromo-3,5-dimethoxybenzaldehyde.

This material was synthesized from 4-bromo-3,5-dimethoxybenzyl alcohol in 75% yield by the same method as described in example 1(c). ^{1}HNMR ($CDCl_3$, ppm): δ 4.02 (s, 6 H). 7.11 (s, 2H), 9.97 (s, 1 H).

d). 1-(4-Bromo-3,5-dimethoxyphenyl)-2-phenylethene (**21**).

This material was synthesized from 4-bromo-3,5-dimethoxybenzyl aldehyde and diethyl benzylphosphonate in 70% yield by the same method as described in example 5(b). ^{1}HNMR ($CDCl_3$, ppm): δ 3.96 (s, 6 H), 6.72 (s, 2 H), 7.06 (d, J = 17Hz, 1H), 7.11 (d, J = 17Hz, 1H), 7.28 (m, 1 H), 7.37 (m, 2 H), 7.55 (m, 2 H).

Example 14. 2-Bromo-5-(2-phenylethenyl)-1,3-benzenediol (**22**).

This material was synthesized from 1-(4-bromo-3,5-dimethoxyphenyl)-2-phenylethene (**21**) and BBr_3 in 90% yield by the same method as described in example 6. ^{1}HNMR ($CDCl_3$, ppm): δ 5.39 (s, 2H), 6.81 (s, 2H), 7.06 (d, J = 17Hz, 1H), 7.11 (d, J = 17Hz, 1H), 7.28 (m, 1H), 7.37 (m, 2H), 7.55 (m, 2H).

Example 15. 1-[2,5-Dimethoxy-4-(2-phenylethenyl)]phenyl-1-phenylmethanol (**16**).

To a solution of 1-(4-bromo-3,5-dimethoxyphenyl)-2-phenylethene (0.2185g. 0.6845mmol) in dry THF (10mL) at –78°C was added BuLi (0.3mL, 2.5M in hexane, 0.7530mmol). One hour after the addition, benzaldehyde (0.07mL, 0.69mmol) was added. The reaction mixture was stirred at –78°C for another 4 hours and then water (12mL) was added to quench the reaction. This was extracted with ether (3 x 20mL). The extract were combined and dried over anhydrous Na_2SO_4. Evaporation of solvent followed by flash chromatography using 5% ethyl acetate in hexane afforded pure **16** (0.203, 86% yield) as a yellow solid. The ^{1}HNMR ($CDCl_3$, ppm): δ 3.88 (s, 6H), 4.26 (d, J = 5.6Hz, 1H),6.40 (br, 1H), 6.79 (s, 2H), 7.12 (s, 2H), 7.2-7.6 (m, 10H).

Example 16. 2,5-Dimethoxy-4-(2-phenylethenyl) benzaldehyde (**17**).

This compound was synthesized from 1-(4-bromo-3,5-dimethoxyphenyl)-2-phenylethene, BuLi and N,N-dimethylformamide in 38% yield by the same method as described in example 15. ^{1}HNMR

($CDCl_3$, ppm): δ 3.94 (s, 3H), 4.00 (s, 3H), 6.75 (s, 2H), 7.14 (s, 2H), 7.3-7.5 (m, 5H), 10.52 (s, 1H).

Example 17. 1-(3,5-Dimethoxy-4-ethylphenyl)-2-phenylethene (**23**).

To a solution of 1-(4-bromo-3,5-dimethoxyphenyl)-2-phenylethene (0.53g, 1.7mmol) in THF (10mL) was added *t*-Butyl Li (1.1 mL, 1M in THF) at – 78 °C. After the addition complete, the solution was slowly heated to reflux for 30 min and then cooled down to – 78 °C. Ethyl iodide (1.2 eq, 0.27 mL) was added to the solution. Water (10mL) was added after the completion of the reaction. THF was evaporated and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The extract was combined and dried over anhydrous magnesium sulfate. Evaporation of the solution followed by flash chromatography using 20% ether in hexane gave 1,3-dimethoxy-2-ethyl-5-(2-phenylethenyl)benzene in 70% yield. ^{1}HNMR ($CDCl_3$, ppm): δ 1.12 (t, J = 7.2 Hz, 6H), 2.70 (q, J = 7.2 Hz, 2H), 3.91 (s, 6H), 6.74 (s, 2H), 7.07 (s, 2 H), 7.26 (m, 1H), 7.36 (m, 2H′), 7.52 (m, 2 H).

Example 18. 2-Ethyl-5-(2-phenylethenyl)-1,3-benzenediol (**24**).

This material was synthesized from 1-(3,5-dimethoxy-4-ethylphenyl)-2-phenylethene and BBr_3 in 91% yield by the same method as described in example 6. ^{1}HNMR ($CDCl_3$, ppm): δ 1.22 (t, J = 7.5Hz, 6H), 2.70 (q, J = 7.5Hz, 2H), 4.81 (s, 2H), 6.60 (s, 2H), 7.00 (s, 2H), 7.26 (m, 1H), 7.36 (m, 2H), 7.52 (m, 2H).

Example 19. 1-(3,5-Dimethoxy-4-*n*-tetradecanylphenyl)-2-phenylethene (**25**).

This material was prepared from 2-bromo-1,3-dimethoxy-5-(2-phenylethenyl)benzene and 1-bromo-*n*-tetradecane by the same procedure as described in example 15. ^{1}HNMR ($CDCl_3$, ppm): δ 0.91 (m, 6H), 1.29 (m, 22 H), 2.65 (m, 2H), 3.90 (s, 6H), 6.73 (s, 2H), 7.10 (s, 2H), 7.26 (m, 1H), 7.36 (m, 2H), 7.52 (m, 2H).

Example 20. 5-(2-Phenylethenyl)-2-*n*-tetradecanyl-1,3-benzenediol (**26**).

This material was synthesized from 1-(3,5-dimethoxy-4-*n*-tetradecanylphenyl)-2-phenylethene and BBr_3 by the same method as described in example 6. ^{1}HNMR ($CDCl_3$, ppm): δ 0.95 (m, 6H), 1.30 (m, 22H), 2.65 (m, 2H), 4.80 (s, 2H), 6.60 (s, 2H), 7.00 (s, 2H), 7.26 (m, 1H), 7.36 (m, 2H), 7.52 (m, 2H).

Example 21. 2-(3,5-Dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethene (**27**).

To a solution of diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate (0.50g, 1.5mmol) in THF (10mL) at 0°C was added NaH (60% in mineral oil) (0.14g, 3.5mmol) under N_2. After the addition was completed, the suspension was stirred at 0°C for 1 h and then 2-fluorobenzaldehyde (0.2mL, 1.9 mmol) in THF (10mL) was added. The reaction was kept at 0°C for 1 h and then at 50°C for 5h. The reaction was cooled to 0°C. Water (5mL) was added slowly to quench the reaction followed by addition of 2N HCl (8mL). The mixture was extracted with ether (3 × 20mL). The extract was dried over anhydrous Na_2SO_4. Evaporation of ether followed by flash chromatography using 5% ethyl acetate in hexane as eluent afforded 2-(3,5-dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethene (**1**). (0.31g, 68%) as a yellow crystal. ^{1}HNMR ($CDCl_3$, ppm): δ 1.34 (d, J = 7.1Hz, 6H), 3.60 (qint. J= 7.1Hz, 1H), 3.89 (s, 6H), 6.74 (s, 2H), 7.0-7.2 (m, 5H), 7.4-7.6 (m, 1H).

Example 22. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3-fluorophenyl)ethene (**28**).

This material was prepared from diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate and 3-fluorobenzaldehyde in the same way as described in example 21.

Example 23. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-fluorophenyl)ethene (**29**).

This material was prepared from diethyl (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate and 4-fluorobenzaldehyde in the same procedure as described in example 21.

Example 24. 2-(3,5-Difluorophenyl)-1-(3,5-dimethoxy-4-*i*-propylphenyl)ethene (**30**).

This material was prepared from (3,5-dimethoxy-4-*i*-propylbenzyl)phosphonate and 3,5-difluorobenzaldehyde in 27% yield in the same way as described in example 21. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.0Hz, 6H), 3.66 (qint., J = 7.0Hz, 1H), 3.90 (s, 6H), 6.72 (s, 2H), 6.8-7.2 (m, 5H).

Example 25. 1-(2,4-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene (**31**)

(3,5-Dimethoxy-4-*i*-propylphenyl)ethane.

To a suspension of methyltriphenylphosphonium bromide (6.89g, 19.3mmol) in THF (100mL) under argon was added BuLi (7.7ml, 2.5M in hexane, 19.3mmol) at room temperature. The resultant red solution was stirred for 10 min. and then 3,5-dimethoxy-4-*i*-propylbenzylaldehyde (4.02g, 19.3mmol) obtained above in THF (20mL) was added. After 2 hours, the reaction was quenched with water (20mL). The mixture was extracted with ether (3 x 100mL). The extract was washed with saturated saline solution (3 x 30mL) and dried over sodium sulphate. Evaporation of ether followed by flash chromatography using 3% ethyl acetate in hexane afforded pure (3,5-dimethoxy-4-*i*-propylphenyl)ethene (2.64g, 66% yield) as a colorless solid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.31 (d, J = 7.1Hz, 6H), 3.61 (qint, J = 7.1Hz, 1H), 3.86 (s, 6H), 5.25 (d, J = 11Hz, 1H), 5.73 (d, J = 17Hz, 1H), 6.64 (s, 2H), 6.70 (dd, J = 11, 17Hz, 1H).

A mixture of (3,5-dimethoxy-4-*i*-propylphenyl)ethene (0.649g, 3.15mmol), 1-bromo-2,4-diflurobenzene (1.23g, 6.37mmol), dihydrogen di-μ-chlorotetrkis(di-*tert*-butylphosphinito-κ*P*)dipalladate (0.1409g, 0.151mmol), Bu_4NI (0.582g, 1.58mmol) and K_2CO_3 (1.45g, 10.5mmol) in DMF (10mL) was heated at 140°C under argon. After the reaction was complete (6h), the reaction mixture was poured into water (10ml).. The aqueous was acidified with 2NHCl and extracted with ether (2 X 50mL). The extract was washed with saturated sodium chloride and then dried over anhydrous Na_2SO_4. Evaporation of ether followed by flash chromatography using 2% ethyl acetate in hexane afforded 1-(2,4-difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene (**31**) quantitatively as a yellowish crystal. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.1Hz, 6H), 3.63 (qint, J = 7.1Hz, 1H), 3.90 (s, 6H), 6.76 (s, 2H), 7.08 (d, J = 17Hz, 1H), 7.27 (d, J = 17Hz, 1H), 7.63 (d, J = 8Hz, 2H), 8.13 (d, J = 8Hz, 2H).

Example 26. 1-(2,6-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene (**32**).

This compound was synthesized from (3,5-dimethoxy-4-*i*-propylphenyl)ethene and 1-bromo-2,6-diflurobenzene quantitatively in the same procedure as described in preparation of **31**. ^{1}HNMR

($CDCl_3$, ppm): δ 1.32 (d, J = 7.1Hz, 6H), 3.62 (qint, J = 7.1Hz, 1H), 3.90 (s, 6H), 6.73 (s, 2H), 6.8-7.2 (m, 4H), 7.41 (d, J = 16.6Hz, 1H).

Example 27. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,4,6-trifluorophenyl)ethene (**33**).

This compound was synthesized from (3,5-dimethoxy-4-*i*-propylphenyl)ethene and 1-bromo-2,4,6-triflurobenzene in 58% yield in the same procedure as described in preparation of **31**. ^{1}HNMR ($CDCl_3$, ppm): δ 1.32 (d, J = 7.0Hz, 6H), 3.62 (qint, J = 7.1Hz, 1H), 3.89 (s, 6H), 6.73 (s, 2H), 6.79-7.55 (m, 4H).

Example 28. 1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)ethene (**34**).

This compound was synthesized from (3,5-dimethoxy-4-*i*-propylphenyl)ethene and 1-bromo-2,3,4,5,6-triflurobenzene in the same procedure as described in preparation of **31**.

Example 29. 5-[2-(2-Fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**37**).

A mixture of 2-(3,5-dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethene (**27**) (0.308g, 1.03mmol) and pyridine hydrochloride (0.72g, 6.2 mmol) was heated at 200°C for 4 h under a stream of argon. The reaction mixture was cooled to room temperature. 2NHCl (10mL) and ether (15mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10mL). The extract was dried over anhydrous Na_2SO_4. Evaporation of ether followed by flash chromatography using 15% ethyl acetate in hexane afforded pure 5-[2-(2-fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**37**) (0.269g, 95% yield) as an off-white solid. ^{1}HNMR ($CDCl_3$, ppm): δ 1.41 (d, J = 7.2Hz, 6H), 3.51 (qint., J = 7.2Hz, 1H), 5.01 (b, 2H), 6.56 (s, 2H), 6.98 (d, J = 17.6Hz, 1H), 7.0-7.3 (m, 4H), 7.60 (ddd, J = 7.5, 7.5, 2.2Hz, 1H).

Example 30. 5-[2-(3-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**38**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(3-fluorophenyl)ethene (**28**) and pyridine hydrochloride in the same procedure as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.41 (d, 7.2Hz, 6H), 3.49 (qint., J = 7.2Hz, 1H), 6.53 (s, 2H), 6.9-7.5 (m, 6H).

Example 31. 5-[2-(4-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**39**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(4-fluorophenyl)ethene **29** and pyridine hydrochloride (38% yield over 2 steps) in the same procedure as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.41 (d, 7.2Hz, 6H), 3.48 (qint., J = 7.2Hz, 1H), 6.52 (s, 2H), 6.81 (d, J = 17Hz, 1H), 7.00 (d, J = 17Hz, 1H), 7.0-7.2 (m, 2H), 7.4-7.6 (m, 2H); ^{1}HNMR (DMSO-d6, ppm): δ 1.22 (d, J = 7.1Hz, 6H), 3.35 (qint., J = 7.1Hz, 1H), 6.45 (s, 2H), 6.81 (d, J = 16.7Hz, 1H), 6.99 (d, J = 16.7Hz, 1H), 7.17 (dd, J = 8.8, 8.8Hz, 2H), 7.61 (dd, J = 8.8Hz, 5.6Hz, 2H), 9.05 (s, 2H).

Example 32. 5-[2-(3,5-Difluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol (**40**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(3,5-difluorophenyl)ethene and pyridine hydrochloride in 70% yield in the same procedure as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.40 (d, J = 7.1Hz, 6H), 3.56 (qint., J = 7.2Hz, 1H), 4.90 (s, 2H), 6.52 (s, 2H), 6.2-7.1 (m, 5H).

Example 33. 5-[2-(2,4-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**41**).

This material was prepared from 1-(2,4-difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene and pyridine hydrochloride in 44% yield in the same way as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.41 (d, J=7.1Hz, 6H), 3.49 (qint, J = 7.1Hz, 1H), 4.78 (br, 2H), 6.54 (s, 2H), 6.69-7.02 (m, 3H), 7.13 (d, J=16Hz, 1H), 7.41-7.75 (m, 1H).

Example 34. 5-[2-(2,6-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**42**).

This material was prepared from 1-(2,6-difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene and pyridine hydrochloride in 29% yield in the same way as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.42 (d, J = 7.1Hz, 6H), 3.50 (qint, J = 7.1Hz, 1H), 4.77 (br, 2H), 6.57 (s, 2H), 6.8-7.4 (m, 5H).

Example 35. 2-*i*-Propyl-5-[2-(2,4,6-trifluorophenyl)ethenyl]-1,3-benzenediol (**43**).

This material was prepared from 1-(3,5-dimethoxy-4-*i*-propylphenyl)-2-(2,4,6-trifluorophenyl)ethene and pyridine hydrochloride in 14% yield in the same way as described in example 29. ^{1}HNMR ($CDCl_3$, ppm): δ 1.42 (d, J=7.1Hz, 6H), 3.50 (qint, J = 7.1Hz, 1H), 4.77 (br, 2H), 6.55 (s, 2H), 6.59-7.24 (m, 4H).

Example 36. 5-[2-(2,3,4,5,6-Pentafluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**44**).

This material was prepared from 1-(2,3,4,5,6-pentafluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethene and pyridine hydrochloride in 21% yield in the same way as described in example 34. ^{1}HNMR ($CDCl_3$, ppm): δ 1.40 (d, J=7.2Hz, 6H), 3.53 (d, J=7.2Hz, 6H), 4.91 (s, 2H), 6.55 (s, 2H), 6.86 (d, J = 17Hz, 1H), 7.28 (d, J = 17Hz, 1H).

The standard pharmacological procedures, described fully in the examples hereafter, show the compounds of the invention to inhibit T-cell, keratinocyte proliferation, cell migration induced by leukotriene B4 and to inhibit IFN-γ secretion and VEGF expression *in vitro* as well as to inhibit TNF-α and edema *in vivo*.

Example 37. Biological activity of novel compounds.

These assays for the following biological activities are well-established and known in the art, brief descriptions are provided herein for clarity.

(a). Effect on proliferation and IFN-γ production of human peripheral blood mononuclear cells (PBMC) stimulated by phytochemagglutinin (PHA).

Experiment:PBMC were cultured with PHA and cultured with titrated concentrations of compounds or solvent, or media alone using standard cell culture techniques. The MTT assay was performed after 48 hours of culture. Supernatants were collected after 48 hours of culture and levels of IFN-γ were assayed by ELISA.

Results: 5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol (**13**) of the present invention had an IC_{50} of 2.97 against human PBMC proliferation while resveratrol had an IC_{50} of > 50. Compound **13** is 20 times more potent in inhibiting PBMC proliferation (Table 1). Similarly, compound **13** is more than 15 times more potent than is resveratrol in inhibition IFN-γ production

(Table 2). Similarly, the three fluorinated compounds, **37**, **38** and **39** had IC_{50} < 10 μM whereas that of resveratrol was > 50 μM the highest concentration tested. The fluorinated compounds had superior activity in inhibiting PBMC proliferation to that of resveratrol with >5 times more potency (Table 1). Similarly, the IC_{50} value of resveratrol is more than 9 times higher than that of the three fluorinated compounds, indicating that the fluorinated compounds are over 9 times more potent than resveratrol in inhibiting IFN-γ production by human PBMC (Table 2).

Table 1. Effect of the novel compounds and resveratrol against human PBMC proliferation.

Compound	IC_{50} (μM)
13	2.97
37	5.62
38	9.91
39	7.36
Resveratrol	> 50

Table 2. Effect of the novel compounds and resveratrol on IFN-γ production by human PBMC

Compound	IFNγ IC_{50} (μM)
13	2.55
37	3.80
38	4.29
39	4.16
Resveratrol	39.2

(b). Effect on human keratinocyte proliferation

Human keratinocytes were cultured in the presence of IFN-γ and titrated concentrations of drug or the vehicle. The MTT assay was performed after 48 hours of culture.

Results: Compound **13** had an IC_{50} of 4.3 μM compared to that of resveratrol of >50, indicating compound **13** is more than 10 times potent than is resveratrol (Table 3).

Table 3. Effect of the novel compound **13** and resveratrol on human keratinocyte proliferation.

Compound	IC_{50} (μM)
13	4.3
resveratrol	> 50

(c). Effect on migration of human white blood cells (WBC) induced by leukotriene B4

Experiment:WBC collected from donors was mixed with equal volume of 3% dextran (in 0.15M NaCl). The red blood cells were sedimented (45 minutes, room temperature) and removed. Any remaining red blood cells in the plasma were removed by adding 150mM of Tris-NH_4Cl. The leukocyte-rich plasma was washed twice in Hanks balanced salts solution containing 20 mM HEPES. The WBC was then transferred to RPMI-1640 medium and adjusted to a density of $5x10^7$ cells/ml. An agarose plate assay system (Nelson *et al.* 1978)was used to measure the WBC migration. Briefly,

a 0.8% agarose solution was prepared with complete RPMI-1640 cell culture medium. About 3.5 ml of this agarose solution was transferred to a glass slide before it solidified. Wells were made on the slide in a 3×6 array fashion (∅2 mm, inter-well distance 3mm) once the agarose had solidified. LTB4 was dissolved in anhydrous ethanol to 10^4 ng/ml and further diluted with the RPMI-1640 medium to10 ng/ml for the test. Compound **39** was dissolved in DMSO, diluted with RPMI-1640 to 10^3 μg/ml and tested at the following concentrations:100, 10, 1, 0.1 and 0.01 μg/ml. Ten microlitres of cell suspension with different concentrations of compound **39** was added to each well of the center row of the three rows of wells. The same volume of LTB_4 in RPMI-1640 medium or the medium alone was added to wells in the other rows and served as controls. After 5 h incubation (5% CO_2, 37°C) the test slides were fixed with 100% methanol (30 min) and dried at 4°C (overnight). The slides were then examined microscopically. The migration index was defined as the average distances that cells migrated towards the positive LTB_4 well divided by that of spontaneous migration. The percentage migration was compared between treatment and the non-drug control. The dose-effect relationship was determined by plotting the percentage chemotaxis vs concentration for IC_{50} values.

Results: Compound **39** inhibited the migration of WBC towards LTB_4 in a dose-dependent manner (Table 4).

Table 4. Effect of Compound **39** on human white blood cell migration towards LTB_4.

Concentration (μM)	% Migration
40	13.07±5.8
8	58.46±4.3
1.6	83.85±15.9
0.32	88.46±18.6
0	100

Conclusion: Compound **39** showed potent inhibitory activity against WBC migration induced by leukotriene B4, a mediator that plays important role in inflammation, including the auto-immune response.

(d). The effect on vascular endothelial growth factor (VEGF) protein expression

Experiment: Compound **39** was dissolved in DMSO, diluted with keratinocyte-serum-free medium (KC-SFM) to 10^3 μg/ml, further diluted with the culture medium and tested at the following concentrations: 10, 1, 0.1 and 0.01 μg/ml. Prime cultures of keratinocytes were obtained from a commercial source and maintained with KC-SFM at a cell density of 10^6/ml. In the test, cells were cultured in 24-well plates and incubated at 37°C in 5% CO_2 first for 4 h, and then treated with rhTGF-α (final concentration 100 ng/ml) and the test compound at different concentrations (0.01-10 μg/ml). Medium without test compound was the negative control. The culture supernatant from each well was separately collected after an additional 24 h incubation and centrifuged at 2000rpm for 5 minutes before measuring the VEGF concentration. VEGF concentration in the supernatant in each well was

calculated based on measurements taken using an ELISA kit, according to the manufacturer's instructions.

Results: Compound **39** showed a dose-dependent effect on the VEGF concentration in the cell supernatant of keratinocytes induced by rhTGF-α after 24-h treatment. This effect increased substantially and the protein concentration decreased 100% when compound **39** concentration increased to 40 M (Table 5).

Table 5. Effect of Compound **39** on VEGF expression of human keratinocytes induced by rhTGF-α.

Concentration (μM)	VEGF(pg/ml)
40	0±0
8	33.6±1.8
1.6	34.4±2.0
0	38.9±2.8

Conclusion: Compound **39** had a significant inhibitory effect on VEGF expression in human keratinocytes.

(e) *In vivo* efficacy in endotoxemia mouse model.

Experiment: Test compounds were dissolved and formulated in 50% PEG-400 in water. Female Balb/c mice (~20g) were first injected separately intraperitoneally (IP) with 25 mg/kg of each test compound, then challenged by injection with 40 mg/kg lipopolysaccharide (LPS) (IP) 30 minutes later. One drug injection with 12.5 mg/kg of test compound was done at the same time as (LPS challenge and two subsequent sequential injections at 30 minutes intervals. Positive control of dexamethasone was administered in a similar manner starting at 0.4 mg/kg and subsequently 0.2 mg/kg for three additional injections. Mice were sacrificed and blood collected by cardiac puncture 150 minutes after LPS challenge. The serum TNF-α levels were determined by ELISA. Each test group was comprised of six mice. Group of mice injected with the vehicle alone was used as negative control.

Results: Compound **37** and **39** decreased significantly ($P<0.05$) TNF-α levels in mice blood induced by LPS (Table 6).

Table 6. Effect of the novel compounds, **37** and **39** on TNF-α levels induced by LPS in a mouse model.

Compound	TNF-α (pg/mL)	*P*-value
37	638.9±273.0	0.03
39	601.6±211.9	0.01
Carrier	1126.6±396.4	
Dexamethasone	281.3±67.2	0.0004

P-values calculated with Student's *t*-test (unpaired, two-tailed)

Conclusions:The fluorinated compounds, compound **37** and **39** significantly decreased levels of TNF-

α that modulate a broad range of activities in mice, resulting in reduced inflammatory reactions in animals.,

(f). Efficacy on TPA induced edema.

Experiment: Three representative compounds, 5-(2-phenylethenyl)-2-*i*-propyl-1,3-benzenediol, a s previously reported, a closely related stilbene derivative (WO 0142231) and compound **39,** a novel compound of the current invention, were assayed against the edema on female mice (*Balb/c*) aged 10-12 weeks, using 0.01% Calcitriol (a commercial standard) as a positive control. Phorbol-12-myristate-13-acetate (TPA) was used as the edema inducer. TPA and the test compounds were all dissolved in 100% ethanol and 20 μl applied on the right ear of the mouse with six mice per group. The TPA concentration used was 0.01% (w/v). Ear thickness was measured 6 hours after TPA treatment to determine if edema was decreased. In each experiment replicated groups of TPA treated mice were treated with either 5-(2-phenylethenyl)-2-*i*-propyl-1,3-benzenediol, Calcitriol, compound **39** or only ethanol, and the levels of inhibition was obtained by measuring the thickness of the ear and expressing the difference in thickness of the treated ear from that of the ethanol treated ear, as a percentage.

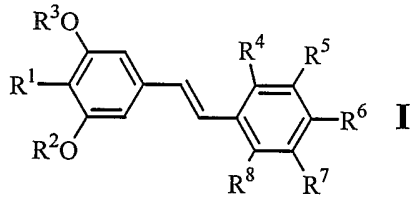
Results: The fluorinated compound reduces the edema significantly. With one of H atoms of the previously reported stilbene, 5-(2-phenylethenyl)-2-*i*-propyl-1,3-benzenediol, replaced by a F to the novel compound **39** of the current invention, the inhibition of edema is increased from 8% to 85% while inhibition of Calcitriol was 31%, demonstrating the surprisingly high levels of activity of the novel compound **39** of the current invention.

Table 6. Anti-inflammatory activity of stilbene compound after a single topical administration in the TPA-induced ear edema model

Treatment	% edema inhibition
TPA(0.01%) + 5-(2-phenylethenyl)-2-*i*-propyl-1, 3-benzenediol (0.3%)	8.0
TPA(0.01%) + Compound **39** (0.3%)	85.2
TPA(0.01%) + Calcitriol (0.01%)	31.2

CLAIMS

1. A compound of formula I, or a salt thereof



wherein R^1 is selected from the group consisting of unsubstituted or substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, or COR^9;

R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl;

R^4, R^5, R^6, R^7 and R^8 are not H simultaneously and are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group; with the proviso that R^6 is not hydroxy or alkyoxy group when R^1 is an unsaturated group comprising of 1-3 isoprene unit(s);

R^9 is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, or aralkyl, or $NR^{10}R^{11}$, or OR^{10};

R^{10} and R^{11} are selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl or aralkyl;

R^{12} is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl; wherein the configuration of the double bond of the compound of formula I is *E* or *Z*.

2. The compound of claim 1, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group provided that one or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

3. The compound of claim 1, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, COR^9, and OR^{12}, provided that one, or more than one of R^3, R^4, R^5, R^6 and R^7 is COR^9.

4. The compound of claim 3, wherein R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, or acyl;

5. The compound of claim 4, wherein R^2 and R^3 are independently selected from the group consisting of H, methyl, or acetate;

6. The compound of claim 2, wherein R^1 is selected from unsubstituted or substituted alkyl of 1 to 14 carbons; R^2 and R^3 are independently each selected from the group consisting of H, unsubstituted or substituted alkyl or acyl;

7. The compound of claim 6, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H and F, provided that one, or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

8. The compound of claim 6, wherein R^1 is isopropyl; R^2 and R^3 are independently each selected from the group consisting of H, methyl or acetate;

9. The compound of claim 1, wherein the compound is selected from the group consisting of :

4-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

4-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethane;

5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3,5-dimethoxyphenyl)ethane;

5-[2-(3,5-Dihydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-[2,5-Dimethoxy-4-(2-phenylethenyl)phenyl]-1-phenylmethanol;

2,5-Dimethoxy-4-(2-phenylethenyl) benzaldehyde;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-phenylethene;

5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol;

1-(4-Bromo-3,5-dimethoxyphenyl)-2-phenylethene;

2-Bromo-5-(2-phenylethenyl)-1,3-benzenediol;

1-(3,5-Dimethoxy-4-ethylphenyl)-2-phenylethene;

2-Ethyl-5-(2-phenylethenyl)-1,3-benzenediol;

2-(3,5-Dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-fluorophenyl)ethane;

2-(3,5-Difluorophenyl)-1-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,4-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,6-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,4,6-trifluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)ethane;

5-[2-(2-Fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(3-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(4-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(3,5-Difluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

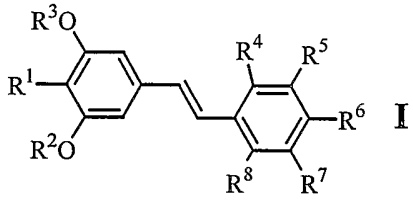
5-[2-(2,4-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(2,6-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

2-*i*-Propyl-5-[2-(2,4,6-trifluorophenyl)ethenyl]-1,3-benzenediol;

5-[2-(2,3,4,5,6-Pentafluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

10. A pharmaceutical composition comprising: a compound of formula I, or a salt thereof



wherein R^1 is selected from the group consisting of unsubstituted or substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, or COR^9;

R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl;

R^4, R^5, R^6, R^7 and R^8 are not H simultaneously and are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group; with the proviso that R^6 is not hydroxy or alkyoxy group when R^1 is an unsaturated group comprising of 1-3 isoprene unit(s);

R^9 is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, or aralkyl, or $NR^{10}R^{11}$, or OR^{10};

R^{10} and R^{11} are selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl or aralkyl;

R^{12} is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl;wherein the configuration of the double bond of the compound of formula I is *E* or *Z*, and a pharmaceutically acceptable diluent or carrier.

11. The composition of claim 10, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group provided that one or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

12. The composition of claim 10, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, COR^9, and OR^{12}, provided that one, or more than one of R^3, R^4, R^5, R^6 and R^7 is COR^9.

13. The composition of claim 12, wherein R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, or acyl;

14. The composition of claim 13, wherein R^2 and R^3 are independently selected from the group consisting of H, methyl, or acetate;

15. The composition of claim 11, wherein R^1 is selected from unsubstituted or substituted alkyl of 1 to 14 carbons; R^2 and R^3 are independently each selected from the group consisting of H, unsubstituted or substituted alkyl or acyl;

16. The composition of claim 15, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H and F, provided that one, or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

17. The composition of claim 15, wherein R^1 is isopropyl; R^2 and R^3 are independently each selected

from the group consisting of H, methyl or acetate;

18. The composition of claim 10, wherein the compound is selected from the group consisting of :

4-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

4-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethane;

5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3,5-dimethoxyphenyl)ethane;

5-[2-(3,5-Dihydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-[2,5-Dimethoxy-4-(2-phenylethenyl)phenyl]-1-phenylmethanol;

2,5-Dimethoxy-4-(2-phenylethenyl) benzaldehyde;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-phenylethene;

5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol;

1-(4-Bromo-3,5-dimethoxyphenyl)-2-phenylethene;

2-Bromo-5-(2-phenylethenyl)-1,3-benzenediol;

1-(3,5-Dimethoxy-4-ethylphenyl)-2-phenylethene;

2-Ethyl-5-(2-phenylethenyl)-1,3-benzenediol;

2-(3,5-Dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-fluorophenyl)ethane;

2-(3,5-Difluorophenyl)-1-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,4-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,6-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,4,6-trifluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)ethane;

5-[2-(2-Fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(3-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(4-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(3,5-Difluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

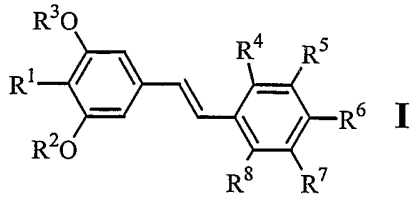
5-[2-(2,4-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(2,6-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

2-*i*-Propyl-5-[2-(2,4,6-trifluorophenyl)ethenyl]-1,3-benzenediol;

5-[2-(2,3,4,5,6-Pentafluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

19. A use of a compound of formula I,



I

wherein R^1 is selected from the group consisting of unsubstituted or substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, or COR^9;

R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl;

R^4, R^5, R^6, R^7 and R^8 are not H simultaneously and are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group; with the proviso that R^6 is not hydroxy or alkyoxy group when R^1 is an unsaturated group comprising of 1-3 isoprene unit(s);

R^9 is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, or aralkyl, or $NR^{10}R^{11}$, or OR^{10};

R^{10} and R^{11} are selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl or aralkyl;

R^{12} is selected from H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl or acyl; wherein the configuration of the double bond of the compound of formula I is *E* or *Z*, in the preparation of a medication for treating a disorder comprising immune, inflammatory or autoimmune diseases.

20. The use according to claim 19, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, alkenyl, alkynyl, aryl or aralkyl group, halo, nitro, CN, COR^9, $NR^{10}R^{11}$, $S(O)_2N\,R^{10}R^{11}$, $S(O)_nR^{10}$, n = 0-2, OR^{12}, a cyclic, or a heterocyclic group provided that one or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

21. The use according to 19, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, COR^9, and OR^{12}, provided that one, or more than one of R^3, R^4, R^5, R^6 and R^7 is COR^9.

22. The use according to claim 21, wherein R^2 and R^3 are independently selected from the group consisting of H, unsubstituted or substituted alkyl, or acyl;

23. The use according to claim 22, wherein R^2 and R^3 are independently selected from the group consisting of H, methyl, or acetate;

24. The use according to claim 20, wherein R^1 is selected from unsubstituted or substituted alkyl of 1 to 14 carbons; R^2 and R^3 are independently each selected from the group consisting of H, unsubstituted or substituted alkyl or acyl;

25. The use according to claim 24, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H and F, provided that one, or more than one of R^4, R^5, R^6, R^7 and R^8 is F.

26. The use according to claim 24, wherein R^1 is isopropyl; R^2 and R^3 are independently each selected from the group consisting of H, methyl or acetate;

27. The use according to claim 19, wherein the compound is selected from the group consisting of :

4-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dimethoxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

4-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

3-[2-(3.5-Dihydroxy-4-*i*-propylphenyl)ethenyl]benzoic acid;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-methoxyphenyl)ethane;

5-[2-(4-Hydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3,5-dimethoxyphenyl)ethane;

5-[2-(3,5-Dihydroxyphenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

1-[2,5-Dimethoxy-4-(2-phenylethenyl)phenyl]-1-phenylmethanol;

2,5-Dimethoxy-4-(2-phenylethenyl) benzaldehyde;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-phenylethene;

5-(2-Phenylethenyl)-2-*i*-propyl-1,3-benzenediol;

1-(4-Bromo-3,5-dimethoxyphenyl)-2-phenylethene;

2-Bromo-5-(2-phenylethenyl)-1,3-benzenediol;

1-(3,5-Dimethoxy-4-ethylphenyl)-2-phenylethene;

2-Ethyl-5-(2-phenylethenyl)-1,3-benzenediol;

2-(3,5-Dimethoxy-4-*i*-propylphenyl)-1-(2-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(3-fluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(4-fluorophenyl)ethane;

2-(3,5-Difluorophenyl)-1-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,4-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(2,6-Difluorophenyl)-2-(3,5-dimethoxy-4-*i*-propylphenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,4,6-trifluorophenyl)ethane;

1-(3,5-Dimethoxy-4-*i*-propylphenyl)-2-(2,3,4,5,6-pentafluorophenyl)ethane;

5-[2-(2-Fluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(3-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(4-Fluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(3,5-Difluorophenyl)ethenyl]-2- *i*-propylphenyl-1,3-diol;

5-[2-(2,4-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

5-[2-(2,6-Difluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

2-*i*-Propyl-5-[2-(2,4,6-trifluorophenyl)ethenyl]-1,3-benzenediol;

5-[2-(2,3,4,5,6-Pentafluorophenyl)ethenyl]-2-*i*-propyl-1,3-benzenediol;

28. The method for treating a disorder comprising immune, inflammatory or autoimmune diseases in mammals comprising administering to a mammal so afflicted an effective amount of a compound of Formula I as defined in claim 1 or a salt thereof.

29. The method for treating a disorder comprising immune, inflammatory or autoimmune diseases in

mammals comprising administering to a mammal so afflicted an effective amount of a compound according to claim 2-9 or a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01497

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C65/28 C07C65/19 C07C43/215 C07C43/225 A61K31/19
A61K31/085 A61K31/11 A61K31/05 C07C39/27 C07C39/373

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199821 Derwent Publications Ltd., London, GB; Class B05, AN 1998-234684 XP002267830 & JP 10 072330 A (KANSAI KOSO KK), 17 March 1998 (1998-03-17) abstract ---	1,4,5, 10,13, 14,19, 22,23, 28,29
X	SYAH, Y. M. ET AL: "Andalasin A, a new stilbene dimer from Morus macroura" FITOTERAPIA (2000), 71(6), 630-635 , XP002267826 page 632, compounds 1 and 2 page 634, paragraphs 2,3 --- -/--	1,10,19, 28,29

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2004	13/02/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Delanghe, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01497

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LIKHITWITAYAWUID, KITTISAK ET AL: "A new dimeric stilbene with tyrosinase inhibitory activity from Artocarpu gomezianus" JOURNAL OF NATURAL PRODUCTS (2001), 64(11), 1457-1459 , XP002267827 figure 1 page 1458, column 2, paragraph 2 ---	1,10,19, 28,29
X	DUDEK, STEPHEN P. ET AL: "Synthesis of Ferrocenethiols Containing Oligo(phenylenevinylene) Bridges and Their Characterization on Gold Electrodes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY (2001), 123(33), 8033-8038 , XP002267828 Chart 1, compounds 2c,3a,3b,4,5,13 ---	1
X	TREADWELL, EDWARD M. ET AL: "A Cascade Cyclization Approach to Schweinfurthin B" ORGANIC LETTERS (2002), 4(21), 3639-3642 , XP002267829 figure 1 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01497

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds of formula 1 in claim 1 and its pharmaceutical composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 03/01497

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 10072330 A	17-03-1998	NONE	