Substituted Indenyl Phosphonic Acids Having Anti-Inflammatory Activity

Inventors: Tsung-Ying Shen, Westfield; Howard Jones, Holmdel, both of N.J.

Assignee: Merck & Co., Inc., Rahway, N.J.

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Abstract

New substituted indenyl tetrazoles, sulfonic and phosphonic acids and derivatives thereof which have anti-inflammatory, anti-pyretic and analgesic activity. Also included are methods of preparing said indenyl compounds, pharmaceutical compositions having said indenyl compounds as an active ingredient and methods of treating inflammation by administration of said indenyl compounds.

3 Claims, No Drawings
SUBSTITUTED INDENYL PHOSPHONIC ACIDS HAVING ANTI-INFLAMMATORY ACTIVITY

SUMMARY OF THE INVENTION

This invention relates to new substituted 1-(Ar)-alkylidene (or heteroalkylidene) indenyl tetrazoles, sulfonic and phosphoric acids and derivatives thereof to processes for producing the same. This invention also relates to pharmaceutical compositions containing said indenyl compounds as an active ingredient and to methods of treating pain, fever or inflammation by administering these particular compounds to patients.

DESCRIPTION AND PREFERRED EMBODIMENTS

The invention is more particularly directed to new substituted indenyl compounds having the following general formula:

\[
R_1 \quad R_2 \quad R_3 \quad R_4 \quad R_5 \quad R_6 \quad R_7
\]

wherein:
- \( R_4 \) may be hydrogen, alkyl haloalkyl, alkenyl, alkynyl, or trihalomethyl;
- \( R_4, R_5, R_6, R_7, R_8 \) and \( R_9 \) each may be hydrogen, alkyl, acyloxy, aryloxy, alkoxy, nitro, amino, acylamino, alkylamino, dialkylamino, alkenyl, alkylnyl, alkenyloxyl, dialkylalkyloxyl, sulfamyl, alkylthio, alkysulfinyl, alkylsulfonyl, hydroxy, hydroxyalkyl, acyl, halo, cyano, carboxy, carbalkoxy, carbamido, haloalkyl, cycloalkyl, trifluoromethyl, aroyl or cycloalkoxy; X may be alkenyl, alkenyloxyl, alkenyloxyl, O, S, carbonyl or NR wherein R is hydrogen or alkyl; n is 0 or 1; \( \text{Ar} \) may be aryl or heteroaryl;
- \( R_3 \) may be
- \(-\text{CH}_2\) - C - R' - N - NH -
- \(-\text{CH}_2\) - C - S - O - M;

or

- \( R' \) - SO\(_3\)M

wherein
- \( M \) may be hydrogen, alkyl or a cation; and \( R' \) and \( R'' \) each may be hydrogen, alkyl, aryl, alkylthio, hydroxy, alkoxy, halogen or to ether a carbyl.
- The aryl or heteroaryl substituent, \( \text{Ar} \) may include an aryl ring system such as benzene, naphthalene or biphenyl or a heteroaryl ring system such as a pyrrole, furan, thiophene, pyridine, imidazole, pyrazole, pyrazine, thiazole, pyrimidine, benzothiazole, pyrazole, oxazole, pyrane, pyridazine, indole, thionaphthene, benzofuran, benzimidazole, azaindole, benzoxyrene, quinoline, isoquinoline, quinoxaline, naphthyridine or benzoazole and may be substituted with any of the aforementioned R4 and R5 substituents.

In the preferred compounds of this invention \( R_3 \) is hydrogen, \( C_{1-5} \) loweralkyl or \( C_{1-5} \) chloro, bromo, or fluoro loweralkyl; \( R_6, R_7, R_8 \) and \( R_9 \) may be hydrogen, halo (chloro, bromo, fluoro), \( C_{1-5} \) loweralkyl, halo \( C_{1-5} \) loweralkoxy, \( C_{1-5} \) loweralkoxy, cyano, nitro, amino, \( C_{1-5} \) loweralkylamino, \( C_1\text{-diloweralkylamino, } C_{1-5}\text{-loweralkenylamino, } C_{1-5}\text{-loweralkanoyloxy, } C_{1-5}\text{-loweralkanoylamino, } C_{1-5}\text{-loweralkenoyloxy or trifluoromethyl; } R_6 \) and \( R_7 \) are each hydrogen, chloro, bromo, fluoro, \( C_{1-5} \) loweralkythio, \( C_{1-5}\text{-loweralkylsulfanyl, } C_{1-5}\text{-loweralkylsulfamyl, } C_1\text{-diloweralkylsulfamyl, } C_1\text{-diloweralkysulfonyl, } C_{1-5}\text{-loweralkylsulfamoyloxy or trifluoromethyl; } R_6 \) and \( R_7 \) are each hydrogen, chloro, bromo, fluoro, \( C_{1-5} \) loweralkythio, \( C_{1-5}\text{-loweralkylsulfanyl, } C_{1-5}\text{-loweralkylsulfamyl, } C_1\text{-diloweralkylsulfamyl, } C_{1-5}\text{-loweralkylsulfamoyloxy or trifluoromethyl; } X \) is \( C_1\text{-alkylene, } C_{1-5}\text{-alkylene, } C_{1-5}\text{-alkylene or } -O--; n \) is 0 or 1; \( \text{Ar} \) is the phenyl; \( R_3 \) is as previously defined; \( R' \) and \( R'' \) may each be hydrogen or \( C_{1-5} \) loweralkyl; and \( M \) is hydrogen or \( C_{1-5} \) loweralkyl.

In the most preferred aspect of this invention \( R_3 \) is hydrogen or \( C_{1-5} \) loweralkyl; \( R_6, R_7, R_8 \) and \( R_9 \) are each hydrogen, chloro, bromo, fluoro, \( C_{1-5} \) loweralkylamino, halo \( C_{1-5} \) loweralkoxy, nitro, amino \( C_{1-5} \) loweralkylamino, halo \( C_{1-5} \) loweralkoxy, halo \( C_{1-5} \) loweralkylamino, halo \( C_{1-5} \) loweralkoxy, halo \( C_{1-5} \) loweralkylamino, halo \( C_{1-5} \) loweralkoxy, nitro or \( C_{1-5} \) loweralkoxy, \( C_1\text{-diloweralkylamino, } C_{1-5}\text{-diloweralkylamino, } C_{1-5}\text{-loweralkanoyloxy, } C_{1-5}\text{-loweralkanoylamino, } C_{1-5}\text{-loweralkenoyloxy or trifluoromethyl, at most only 2 of } R_6, R_7, R_8 \) or \( R_9 \) being other than hydrogen at any one time; \( R_6, R_7, R_8, R_9 \) are each hydrogen, \( C_{1-5} \) loweralkyl, \( C_{1-5} \) loweralkoxy, \( C_1\text{-diloweralkylsulfamyl, } C_{1-5}\text{-diloweralkylsulfamoyloxy or trifluoromethyl, at most only 2 of } R_6, R_7, R_8 \) or \( R_9 \) being other than hydrogen at any one time; \( R_6, R_7, R_8, R_9 \) are each hydrogen, \( C_{1-5} \) loweralkyl, \( C_{1-5} \) loweralkoxy, \( C_1\text{-diloweralkylsulfamyl, } C_{1-5}\text{-diloweralkylsulfamoyloxy or trifluoromethyl, at most only 2 of } R_6, R_7, R_8 \) or \( R_9 \) being other than hydrogen at any one time; \( R_6, R_7, R_8, R_9 \) are each hydrogen, \( C_{1-5} \) loweralkyl, \( C_{1-5} \) loweralkoxy, \( C_1\text{-diloweralkylsulfamyl, } C_{1-5}\text{-diloweralkylsulfamoyloxy or trifluoromethyl, at most only 2 of } R_6, R_7, R_8 \) or \( R_9 \) being other than hydrogen at any one time.

This invention also relates to a method of treating pain, fever or inflammation in patients using a compound of Formula I, particularly and especially the preferred compounds as the active constituent.

The compounds of the instant invention can be used to treat inflammation by reducing inflammation and relieving pain in such diseases as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis and rheumatic fever. The compounds of Formula I can also be used as an anti-pyretic and would be administered and used in the same manner and in same dosage ranges as if they were being used to treat inflammation as discussed further on.

The treatment of inflammation in accordance with the method of the present invention is accomplished by topically, orally, rectally or parenterally administering to patients a composition of a compound of Formula I, particularly the especially preferred compounds in a non-toxic pharmaceutically acceptable carrier.

The non-toxic pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid car-
rriers are lactose, corn starch, gelatin, talc, stearbit, stearic acid, magnesium stearate, terra alba, sucrose, agar, pectin, cab-o-sil and acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly, the carrier or diluent may include a time delay material such as glycerin monostearate or glyceryl distearate alone or with a wax.

Several pharmaceutical forms of the therapeutically useful compositions can be used. For example, if a solid carrier is used, the compositions may take the form of tablets, capsules, powders, troches or lozenges, prepared by standard pharmaceutical techniques. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, a syrup, an aqueous solution or liquid suspension. Suppositories may be prepared in a conventional manner by mixing the compounds of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature. Such materials are cocoa butter and polyethylene glycol. Gels and lotions for topical application may be prepared in conventional manners.

The compounds of Formula I and of the compositions of this invention are to be administered in an amount sufficient to treat inflammation, that is to reduce inflammation. Advantageously, the compositions will contain the active ingredient, namely, the compounds of Formula I in an amount of from about 0.1 mg. to 50 mg. per kg. body weight per day (5 mg. to 35 mg. per patient per day), preferably from about 1 mg. to 15 mg./kg. body weight per day (50 mg. to 1 g. per patient per day).

The method of treatment of this invention comprises administering to a patient (animal or human), a compound of Formula I, particularly an especially preferred compound admixed with a non-toxic pharmaceutical carrier such as exemplified above. The compounds of Formula I and particularly the especially preferred compounds will be administered in an amount of from 0.1 mg. to 50 mg./kg. body weight per day, preferably from about 1 mg. to about 15 mg. per kilogram body weight per day. The most rapid and effective anti-inflammatory effect is obtained from oral administration of a daily dosage of from about 1 to 15 mg./kg./day. It should be understood, however, that although preferred dosage ranges are given, the dose level for any particular patient depends upon the activity of the specific compound employed. Also, many other factors that modify the actions of drugs will be taken into account by those skilled in the art in the therapeutic use of medicinal agents, particularly those of Formula I, for example, age, body weight, sex, diet, time of administration, route of administration, rate of excretion, drug combination, reaction sensitivities and severity of the particular disease. 3-indenyl methyl tetrazole compounds are known from U.S. Pat. No. 3,631,167 issued Dec. 28, 1971. These compounds differ structurally from the 3-indenyl ethyl tetrazole compounds of this invention in that the 3-position of the indene contains a methyl group rather than an ethyl group, and are prepared by an overall different process.

The compounds of this invention may be prepared from their corresponding acids or esters. For example, in the case of the 3-indenyl ethyl tetrazole compounds, a 1-unsubstituted 3-indenyl acetic acid or ester may be first converted to its corresponding alcohol by methods well known in the art for reduction of an acid group or ester to an alcohol group (such as with complex hydrides, for example, lithium aluminium hydride or calcium borohydride, in such solvents as tetrahydrofuran ether and the like), halogenation of the alcohol to ethyl halide formation of the corresponding nitrile by methods well known to the art, followed by reactions with an alkali azide to form the tetrazole nucleus, and finally condensation and dehydration with the appropriate aldehyde in the 1-position of the indene. This latter reaction may readily be carried out by using a strong base such as alkali hydroxide or alkoxide and the like, as the catalyst, the reaction can be carried out in a solvent, if desired. Alternatively, the 1-substituent may be placed in the indene moiety at any stage of the process, for example the 1-substituent may be placed on the 3-indenyl acetic acid or ester followed by the subsequent reactions to result in the final 3-indenyl ethyl tetrazole compounds of this invention.

The starting material, i.e., 1-unsubstituted 3-indenyl acetic acids or esters are known compounds as indicated by such U.S. Patents as U.S. Pat. No. 3,654,349, 3,312,730, and others. The 1-substituted derivatives thereof may be readily prepared by condensation and dehydration of the 1-unsubstituted 3-indenyl acetic acids or esters.

The following examples are given by way of illustration.

**EXAMPLE 1**

5-Fluoro-2-methyl-1-(p-methylylsulfonylbenzyldiene)-indenyl-3-ethyl-5-tetrazole

A. 5-Fluoro-2-methylindenyl-β-ethanol methyl 5-fluoro-2-methyl indenyl-3-acetate (9.8 g.) is added in ether (75 ml.) to a suspension of lithium aluminium hydride (1.0 g.) in ether (50 ml.) over 30 min. The reaction is then refluxed and stirred for 30 min., cooled methanol (50 ml.) slowly added and filtered through celite. The solution is dried (MgSO₄) filtered and concentrated to give an oil. The oil is chromatographed on silica-gel 10 in. × 2 in. column (Baker analyzed 60 to 200 mesh). Elution with 200 ml. portions of benzene gives the title compound m.p. 64°–66°.

B. 5-Fluoro-2-methylindenyl-β-ethyl chloride The above compound (0.1 mole) is refluxed in benzene (100 ml.) with thionyl chloride (0.11 mole) with a drop of dimethylformamide for 2 hrs. and evaporated to dryness. The oily ethyl chloride compound is used crude in the next reaction.

C. 5-Fluoro-2-methylindenyl-β-propionitrile 5-Fluoro-2-methylindenyl-β-ethylichloride (0.1 mole) and dry sodium cyanide (0.11 mole) are stirred together at 60° in dry redistilled dimethylformamide (100 ml.) for 1 hr. The reaction mixture is cooled, the sodium chloride filtered off, and the filtrate evaporated to one-third volume. The crude propionitrile is extracted into ethyl acetate (100 ml.) and washed well with water 12 × 25 ml. The filtrate is evaporated and put on a 1 ft. × 2 in. silica gel column (Baker analyzed 60–200 mesh) elution with mixtures of ether:alcohol gives the compound pure.

D. 5-Fluoro-2-methylindenyl-3-ethyl-5-tetrazole A mixture of the above nitrile (0.003 ml.) sodium azide (0.051 ml.) and ammonium chloride (0.049 ml.) are heated at 120° with stirring for 16 hrs. in dry dimethylformamide (80 ml.). After this time, the reaction mixture is concentrated to dryness, 100 ml. water added and the mixture filtered (pH of filtrate 8). The filtrate is acidified and the precipitate filtered. The combined precipitates are recrystallized from ethanol-water to give 5-fluoro-2-methylindenyl ethyl-5-tetrazole.
3,860,636

E. 5-Fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)indenyl-3-ethyl-5-tetrazole
5-Fluoro-2-methylindenyl-3-ethyl-5-tetrazole (5.0 mmole) is dissolved in 10 ml. of dry pyridine followed by p-methylsulfinylbenzaldehyde (5.0 mmole). The flask is placed under nitrogen and Triton B (5.1 mmole) in methanol is added. The reaction mixture is allowed to stand overnight and then water (3 ml.) is added. After standing for 15 minutes it is poured into an excess of water. The organics are extracted with ether (2 × 50 ml.). The aqueous phase is added to 10% HCl ice. The precipitated material is extracted into methylene chloride and dried (MgSO₄). The solution is filtered and the solvent removed. The product is recrystallized from benzene to yield the desired compound.

Similarly, when benzaldehyde, p-methylthiobenzaldehyde, p-chlorobenzaldehyde, m-chlorobenzaldehyde, p-fluorobenzaldehyde, p-ethylthiobenzaldehyde, m-nitrobenzaldehyde, m-diethylaminobenzaldehyde, p-methylbenzaldehyde or p-methoxybenzaldehyde is used on an equivalent amount in place of p-methylsulfinylbenzaldehyde in 1E above, there is obtained the corresponding appropriately 1-substituted 3-indenyl-3-ethyl-5-tetrazole compound.

Similarly when
methyl 5-hydroxy-2-methyl-3-indenyl acetate, methyl 5-methoxy-2-methyl-3-indenyl acetate, methyl 5-cyano-2-methyl-3-indenyl acetate, ethyl 5-fluoro-3-indenyl acetate, methyl 5,6-difluoro-2-methyl-3-indenyl acetate, methyl 5-chloro-2-methyl-3-indenyl acetate, methyl 5-trifluoromethyl-2-methyl-3-indenyl acetate, methyl 2,5-dimethyl-3-indenyl acetate, methyl 5,7-difluoro-2-methyl-3-indenyl acetate, methyl 5-dimethylamino-2-methyl-3-indenyl acetate, methyl 5-allyloxy-2-methyl-3-indenyl acetate and methyl 5-methoxy-6-fluoro-2-methyl-3-indenyl acetate are used in place of methyl 5-fluoro-2-methylindenyl-3-acetate in an equivalent amount, in step IA above, and the product therefrom carried out through step 1B-1E, there is obtained the corresponding substituted indenyl-3-ethyl-5-tetrazoles.

EXAMPLE 2
5-Fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-indenyl-3-methanesulfonic acid
A. 5-Fluoro-2-methylindenyl-3-methylamine
5-Fluoro-2-methylindenyl-3-acetic acid (0.12 mole) is dissolved in acetone (dry 270 ml.) and triethylamine (0.0124 mole) is added with stirring i-butyl chloroformate is then added (0.12 mole). The precipitate is collected after 10 minutes and the triethylamine hydrochloride rinsed out with acetone (50 ml.). Sodium azide (0.127 mole) in water (50 ml.) is added over 10 min. to the salt in acetone. After 2 hr. at room temperature ether (2 liter) and water (1 liter) are added and the mixture separated. The ether layer is washed with water (2 × 100 ml.) separated, dried (MgSO₄), filtered and evaporated to an oil. This oil is heated at 100° with stirring for 5 min. alone and then with benzyl alcohol (35 ml.) in benzene (500 ml.) at reflux for 3 hr. The solvents are removed under vacuum and the crude product is catalytically reduced in methanol (150 ml.) over Pd/c (5%) (4 g.) and concentrated hydrochloric acid (3 ml.) at room temperature. After removing the catalyst, the solution is extracted with chloroform (3 × 40 ml.) from water (50 ml.) and more 2.5 N HCl (70 ml.). The aqueous solution is made basic with saturated sodium bicarbonate solution and extracted with ethyl acetate (4 × 100 ml.) separated and washed with H₂O (2 × 20 ml.) The organic layer is dried (MgSO₄), filtered and evaporated to dryness to give the crystalline amine.
B. 5-Fluoro-2-methylindenyl-3-methanol
The above amine (0.1 mole) is dissolved in 2.5N hydrochloric acid (50 ml.) and the solution cooled and stirred in an ice bath at 0° while 10% aqueous sodium nitrite is added slowly (0.15 mole). The solution is then heated to 60° with stirring for 1 hr. and the alcohol extracted with chloroform (2 × 50 ml.). The chloroform layer is separated, dried (MgSO₄), filtered and evaporated to give the crystalline alcohol.
C. 5-Fluoro-2-methylindenyl-3-methylchloride
The above alcohol (0.1 mole) in benzene (50 ml.) and thionyl chloride (0.11 mole) is refluxed for 1 hr. and the solution then evaporated to give an oil.
D. 5-Fluoro-2-methylindenyl-3-methyl-5-thiouronium chloride
The above chloro compound (0.1 mole) in isopropanol (100 ml.) is stirred and refluxed with thiourea (0.11 mole) for 3 hrs. The 5-thiouronium chloride is precipitated as it is formed and is used as is.
E. 5-Fluoro-2-methylindenyl-3-methylmercaptan
The above thionium salt (0.1 mole) is stirred and refluxed under nitrogen in aqueous alcoholic potassium hydroxide (1:1 10% 100 ml.) for 4 hrs. The alcohol is evaporated off under reduced pressure and the gummy material extracted into ether (2 × 50 ml.). Evaporation of the ether gave the crystalline mercaptan.
F. 5-Fluoro-2-methylindenyl-3-methyloctanonic acid
The above mercaptan (0.1 mole) in isopropanol (300 ml.) is oxidized with 30% hydrogen peroxide (100 ml.) at room temperature for 24 hrs. The isopropanol is evaporated off and the aqueous layer neutralized with sodium bicarbonate. The aqueous layer is extracted with ethyl acetate (3 × 100 ml.), acidified with concentrated hydrochloric acid and again extracted with ethyl acetate (2 × 100 ml.). The ethyl acetate solution is dried (MgSO₄), filtered and evaporated to dryness to give the crystalline sulfonic acid.
G. 5-Fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)indenyl-3-methanesulfonic acid
The product from Example 2F is reacted with p-methylsulfinylbenzaldehyde by the procedure given in Example 1E, to yield the desired product.

Similarly, when benzaldehyde, p-methylthiobenzaldehyde, p-chlorobenzaldehyde, m-chlorobenzaldehyde, p-fluorobenzaldehyde, p-ethylthiobenzaldehyde, m-nitrobenzaldehyde, m-diethylaminobenzaldehyde, p-methylbenzaldehyde or p-methoxybenzaldehyde is used in an equivalent amount in place of p-methylsulfinylbenzaldehyde 2G above, there is obtained the corresponding appropriately 1-substituted indenyl-3-methyl sulfonic acid.

Similarly when an equivalent amount of
5-hydroxy-2-methyl-3-indenyl acetic acid,
5-methoxy-2-methyl-3-indenyl acetic acid,
5-cyano-2-methyl-3-indenyl acetic acid,
5-fluoro-3-indenyl acetic acid,
5,6-dichloro-2-methyl-3-indenyl acetic acid,
5-chloro-2-methyl-3-indenyl acetic acid,
3,860,636

5-trifluoromethyl-2-methyl-3-indenyl acetic acid, 5-methyl-2-methyl-3-indenyl acetic acid, 5,7-difluoro-2-methyl-3-indenyl acetic acid, 5-tetrafluoro-2-methyl-3-indenyl acetic acid, 5,3-alloxy-2-methyl-3-indenyl acetic acid and 5-methoxy-6-fluoro-2-methyl-3-indenyl acetic acid are used in place of 5-fluoro-2-methylindenyl-3-acetic acid in Example 2A, and the product further reacted in accordance with Example 2 B-G, there is obtained the corresponding substituted indenyl-3-methane sulfonic acid.

EXAMPLE 3

5-Fluoro-2-methyl-1-(p-methylsulfinylbenzyldiene)-indenyl-3-methylphosphonic acid

A. 5-Fluoro-2-methyl-3-methyl phosphonic acid

5-Fluoro-2-methylidenyl-3-methyl chloride (see Example 2C) (0.5 mole) is heated in isopropylphosphate (300 ml) at 180° for 2 days while removing isopropanol. At the end of this time all the excess isopropylphosphate is removed by distillation at 40° and 2 mm. and the crude ester is chromatographed on Baker analyzed silica gel (2 ft. x 3 in.) using mixtures of benzene petroleum benzene as eluants. In this way, pure isopropylphosphonate ester is obtained by evaporation of pure fractions.

The ester is heated to reflux in 5N hydrochloric acid (200 ml) with strong stirring for 8 hours. At the end of this time the solution is evaporated to dryness and the crude phosphonic acid recrystallized from ethyl alcohol.

B. 5-Fluoro-2-methyl-1-(p-methylsulfinylbenzyldiene)-indenyl-3-methylphosphonic acid

The product of Example 3A is reacted with p-methylsulfinylbenzaldehyde in accordance with the procedure of Example 1E to obtain the desired product.

Similarly when benzaldehyde, p-methylthiobenzaldehyde, p-methylsulfonylbenzaldehyde, p-chlorobenzaldehyde, m-chlorobenzaldehyde, p-fluorobenzaldehyde, p-ethylthiobenzaldehyde, m-nitrobenzaldehyde, m-diethylaminothiobenzaldehyde, p-methylsulfinylbenzaldehyde, p-methylbenzaldehyde or methoxybenzaldehyde is used in an equivalent amount in place of p-methylsulfinylbenzaldehyde in 3B above, there is obtained the corresponding appropriately 1-substituted-indenyl-3-methyl phosphonic acid.

Similarly when an equivalent amount of 5-hydroxy-2-methyl-3-indenyl acetic acid, 5-methoxy-2-methyl-3-indenyl acetic acid, 5-cyano-2-methyl-3-indenyl acetic acid, 5-fluoro-3-indenyl acetic acid, 5,6-dichloro-2-methyl-3-indenyl acetic acid, 5-chloro-2-methyl-3-indenyl acetic acid, 5-trifluoromethyl-2-methyl-3-indenyl acetic acid, 5,5-dimethyl-2-methyl-3-indenyl acetic acid, 5,5-dimethyl-2-methyl-3-indenyl acetic acid and 5-methoxy-6-fluoro-2-methylindenyl-3-indenyl acetic acid are used in place of 5-fluoro-2-methylindenyl-3-acetic acid in Example 2A, the product further reacted in accordance with Example 2 B and C and the 3-methylether compound obtained is reacted according to Example 3A and B, there is obtained the corre-

EXAMPLE 4

cis- and trans-5-Fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-ethyl-5-tetrazole

To a solution of 0.02 mole of 5-fluoro-2-methylindenyl-3-ethyl-5-tetrazole in methanol (60 ml) is added sodium methoxide (2.16 g, 0.04 mole) and after solution p-methylsulfinylcinnamaldehyde (0.02 mole). The mixture is heated at reflux for 5 hours, cooled, poured into ether, extracted with ether, dried (MgSO4), and concentrated to an oil in vacuo. The oil is taken up in methylene chloride and chromatographed on silica gel and eluted with ethyl acetate. The fractions of eluate are concentrated to yield cis- and trans-5-fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-ethyl-5-tetrazole.

Similarly, when an equivalent amount of any of the other tetrazole compounds obtained from Example 1 are used in place of 5-fluoro-2-methylindenyl-3-ethyl-5-tetrazole there is obtained the corresponding 1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-ethyl-5-tetrazole compound.

Similarly, when an equivalent amount of the aldehyde of Table 1 below is used in place of 4-methylsulfinylcinnamaldehyde in the above procedure, the corresponding 1-substituted-2-methyl-5-fluoro-indenyl-3-ethyl-5-tetrazole is obtained.

| TABLE 1 |
|-----------------|-----------------|
| α-toluicdehxy  | cinnamaldehyde  |
| cinnamaldehyde  | hydrocinnamaldehyde |
| 2-methoxy cinnamaldehyde | 4-methoxy cinnamaldehyde |
| 4-ethoxy cinnamaldehyde | 3,4-dimethoxy cinnamaldehyde |
| 4-methyl cinnamaldehyde | 4-t-butyl cinnamaldehyde |
| 2-nitro cinnamaldehyde | 3-nitro cinnamaldehyde |
| 4-nitro cinnamaldehyde | 4-dimethylaminocinnamaldehyde |
| 2-chloro cinnamaldehyde | 6-dimethylaminocinnamaldehyde |
| 4-chloro cinnamaldehyde | 2,4-dichloro cinnamaldehyde |
| 4-bromocinnamaldehyde | 4-methylthiocinnamaldehyde |
| 4-methylsulfinyl cinnamaldehyde | 4-methylsulfinyl cinnamaldehyde |
| 4-chloro α-methyl cinnamaldehyde | 4-chloro cinnamaldehyde |
| 4-chloro-2-nitro cinnamaldehyde | 4-chloro-3-nitro cinnamaldehyde |
| 5-chloro-2-methyl cinnamaldehyde | 5-chloro cinnamaldehyde |
| 4-nitro α-methyl cinnamaldehyde | 4-nitro cinnamaldehyde |
| 4-nitro-β-methyl cinnamaldehyde | 4-nitro-β-phenyl cinnamaldehyde |
| α methyl cinnamaldehyde | α-ethyl cinnamaldehyde |
| β-methylecinnamaldehyde | β-ethylecinnamaldehyde |
| β-ethylecinnamaldehyde | d | α-β-dimethyl cinnamaldehyde |
3,860,636

α-pentylcinnamaldehyde
α-cyclopentylcinnamaldehyde
3,4-methylenedioxy cinnamaldehyde
3,4,5-trimethoxy cinnamaldehyde
3,4-dimethoxy-α-methylcinnamaldehyde
4-isopropyl-α-methylcinnamaldehyde
4-methoxyhydrocinnamaldehyde
2-methylhydrocinnamaldehyde
4-methylhydrocinnamaldehyde
4-sec-butydrocinnamaldehyde
6-nitrohydrocinnamaldehyde
4-chlorohydrocinnamaldehyde d
4-methylthiohydrocinnamaldehyde
4-methylsulfinylhydrocinnamaldehyde
4-methylsulfonylhydrocinnamaldehyde
4-nitro-α-methylhydrocinnamaldehyde
4-nitro-β-methylhydrocinnamaldehyde
4-chloro-α-methylhydrocinnamaldehyde
4-chloro-β-methylhydrocinnamaldehyde
α-methylhydrocinnamaldehyde
β-methylhydrocinnamaldehyde
α,α-dimethylhydrocinnamaldehyde
4-chloro-α-toluic aldehyde
4-methoxy-α-toluic aldehyde
4-methythio-α-toluic aldehyde
α-ethyl-α-toluic aldehyde
4-nitro-α-methyl-α-toluic aldehyde
4-chloro-α-methyl-α-toluic aldehyde
4-phenylbutanal
4-phenyl-2-butanal
2'-thienylacetoraldehyde
β-(2'-thienyl) propenal
β-(2'-thienyl) propanal
3'-pyridylacetoraldehyde
4'-pyridylacetoraldehyde
2'-pyridylacetoraldehyde
2'-furylacetoraldehyde
5'-chloro-2'-thienylacetalddehyde
α-naphthylacetalddehyde
β-naphthylacetalddehyde
β-(2'-furyl) propenal
β-(2'-pyridyl) propenal
β-(α'-napthyl) propenal
β-(3'-pyridyl) propenal
β-(4'-pyridyl) propenal
β-(2'-furyl) propional
β-(2'-pyridyl) propional
β-α'-napthyl propional
β-(2'-quinolyl) propional
β-(2'-pyrrolidinyl) propional
β-(2'-benzofuranyl) propional
β-(2'-quinolyl) propional
β-(2'-pyrrolidinyl) propional
β-(2'-napthyl) propional
ββ-β-diphenylpropenal
2'-indanacetalddehyde
β-(2'-benzothiazol)e propenal
β-(3'-nitro-2'-thienyl) propenal
β-(1'-methyl-2'-pyrrolyl) propenal
β-(1'-methyl-2'-pyridyl) propenal

EXAMPLE 5

A. (3-Chloro-4-methylthio)-phenylpropargaldehyde

A mixture of 3-chloro-4-methylthiocinnamaldehyde (2.0 mole) and acetic acid (1.5 liter) is stirred vigorously while bromine (320 g., 2.0 mole) is added dropwise at 25°. Powdered anhydrous potassium carbonate is added at 25°. When the evolution of gas stops the mixture is refluxed for 30 minutes, cooled and poured into cold water (2.5 liters). The mixture is cooled to 0°-5° with stirring and stirred at this temperature overnight. The precipitate is separated by filtration without drying and crystallized from ethanol-water. 3-Chloro-4-methylthio-α-bromocinnamaldehyde is filtered, washed and dried in air. The aldehyde (1.6 mole) methyl orthoformate (244 g., 2.3 mole), absolute ethanol (320 ml.) and ammonium chloride (4.0 g.) are refluxed for 30 minutes, low boiling components distilled at atmospheric pressure and distilled in vacuo to yield 1,1-dimethoxy-3-(3'-chloro-4'-methylthiophenyl)-2-propene. To this compound (1.35 mole) is added potassium hydroxide (132 g., 2.0 moles) in methanol (1400 ml.). The mixture is refluxed for 3 hours and poured into water (11.3 liters). The mixture is extracted with chloroform (3 × 1.5 liter), the combined chloroform extracts washed with water (3 × 660 ml.) and dried (NaSO4). The chloroform is distilled and the residue fractionated in vacuo to obtain 1,1-dimethoxy-3-(3'-chloro-4'-methylthiophenyl)-2-propyne. This compound (1.0 mole) is added to water (1 liter) containing concentrated sulfuric acid (70 ml.) and the mixture is heated on the steam bath for 30 minutes with occasional mixing. The mixture is extracted with ether (3 × 750 ml.), the ether extract washed with water and saturated salt solution, dried (Na2SO4) and concentrated to an oil at atmospheric pressure. The oil is distilled in vacuo to yield (3-chloro-4-methylthio)-phenylpropargaldehyde.

B. cis- and trans-5-Fluoro-2-methyl-1-(3'-chloro-4'-methy lthiophenylpropargylidine)-indanyl-3-ethyl-5-tetrazole

(3-Chloro-4-methylthio)-phenylpropargaldehyde 0.2 mole and 5-fluoro-2-methyl-indenyl-β-ethyl-5-tetrazole (0.2 mole) are condensed by the method of Example 4 to yield the subject compound.

Similarly, when the other tetrazole compounds obtained from Example 1 are used in place of 5-fluoro-2-methyl-indenyl-3-ethyl-5-tetrazole in the above Example, there is obtained the corresponding 1-(3'-chloro-4'-methylthiophenylpropargylidine substituted indenyl tetrazole compounds.

Similarly, when an equivalent amount of 5-fluoro-2-methyl-indenyl-3-methylsulfonic acid or 5-fluor o-2-methylindeny1-3-methyl phosphonic acid obtained from Example 2 and 3 respectively are used in place of 5-fluoro-2-methyl-indenyl-3-ethyl-5-tetrazole in the above Example, there is obtained 5-fluoro-2-methyl-1-(3'-chloro-4'-methylthiophenylpropargylidine)-indenyl-3-methylsulfonic acid or 5-fluoro-2-methyl-1-(3'-chloro-4'-methylthiophenylpropargylidine)-indenyl-3-methylphosphonic acid respectively.

EXAMPLE 6

A. t-Butyl 5-fluoro-2-methyl-3-indenyl acetate
Ethyl 5-fluoro-2-methyl-3-indenyl acetate (1.0 mole), t-butyl acetate (700 g., 6.0 mole) and sodium methoxide (108 g., 2 mole) under nitrogen are stirred and refluxed at 101° ratio through a 1.5' column packed with glass one-eighth inch helices. The mixture is distilled for 18 hours and 250 ml. of distillate is collected. The excess of t-butylacetate is distilled in vacuo and the residue is taken up in methylene chloride, filtered through diatomaceous earth then through acid-washed alumina. The methylene chloride is removed...
and the residue crystallized from acetone-n-hexane to yield t-butyl 5-fluoro-2-methyl-3-indenyl acetate. 

B. t-Butyl 5-fluoro-1-hydroxymethylene-2-methyl-3-indenyl acetate, Sodium Salt

To a mixture of t-butyl 5-fluoro-2-methyl-3-indenyl acetate (0.2 mole) in benzene (500 ml.) and ethyl formate (74.1 g., 1.0 mole) is added oil-free sodium hydride (7.2 g., 0.3 mole). The mixture is stirred at room temperature 1 hour each day for 2 days. Any remaining sodium hydride is decomposed by the addition of methanol (20 ml.) in ether (100 ml.). The salt is filtered washed with ether and dried in vacuo. 

C. cis- and trans-t-Butyl-5-fluoro-2-methyl-1-(p-methylthiophenoxy)methylidine)-3-indenyl acetate

The sodium salt (0.01 mole) from Example 6B in dimethoxyethane (200 ml.) is heated at reflux with stirring for 15 hours with p-methylthiophenyl iodide (25.0 g., 0.01 mole). The mixture is concentrated in vacuo to remove solvent, taken up in methylene chloride-water, the layers separated and the water layer extracted with methylene chloride (2 x 100 ml.). The combined methylene chloride layers are concentrated to one-third volume and chromatographed over silica gel and eluted by methanolic chloroform to separate cis- and trans- isomers.

D. 5-Fluoro-2-methyl-1-(p-methylthiophenoxy)methylidine)-3-indenyl-5-tetrazole

The product of Step C above is reacted in accordance with Example A-D to yield the subject product. Similarly, when an equivalent amount of p-methylsulfinylphenylidiole is used in place of p-methylthiophenylidiole in Example 6C above, and the product reacted by the method of 6D above, there is obtained the corresponding 1-(p-methylsulfinylphenoxy)methylidine) compound. Similarly, when an equivalent amount of any one of the methyl or ethyl acetate compounds from Example 1 is used in place of ethyl-5-fluoro-2-methyl-3-indenyl acetate in Example 6A above and the resulting product used in Example 6B-D, there is obtained the corresponding 3-indenyl-5-tetrazole compound. Similarly, when the product of step 6C is reacted in accordance with Example 2-A, (or Example 2-A-C and 3A), there is obtained the corresponding 3-methylsulfonic acid or 3-methylphosphonic acid respectively.

EXAMPLE 7

5-Fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methane sulfonic acid

To a solution of 0.02 moles of 5-fluoro-2-methylindenyl-3-methanesulfonic acid in methanol (60 ml.) is added sodium methoxide (2.16 g., 0.04 mole) and after solution p-methylsulfinylcinnamaldehyde (0.02 mole). The mixture is heated at reflux for 5 hours, cooled, poured into ether-water, extracted with ether, dried (MgSO4), and concentrated to an oil in vacuo. The oil is taken up in methylene chloride and chromatographed on silica gel and eluted with ethyl acetate. The fractions of eluate are concentrated to yield 5-fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methane sulfonic acid. 

Similarly, when an equivalent amount of the aldehyde compounds from Table I are used in place of 4'-methylsulfinylcinnamaldehyde in the above Example, there is obtained the corresponding substituted-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methanesulfonic acid.

EXAMPLE 8

5-Fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methylphosphonic acid

To a solution of 0.02 mole of 5-fluoro-2-methylindenyl-3-methylphosphonic acid in methanol (60 ml.) is added sodium methoxide (2.16 g., 0.04 mole) and after solution p-methylsulfinylcinnamaldehyde (0.02 mole). The mixture is heated at reflux for 5 hours, cooled, poured into ether-water, extracted with ether, dried (MgSO4), and concentrated to an oil in vacuo. The oil is taken up in methylene chloride and chromatographed on silica gel and eluted with ethyl acetate. The fractions of eluate are concentrated to yield 5-fluoro-2-methyl-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methylphosphonic acid.

Similarly, when an equivalent amount of the aldehyde compounds obtained from Table I are used in place of p-methylsulfinylcinnamaldehyde in the above Example, there is obtained the corresponding substituted-1-(4'-methylsulfinylcinnamylidenyl)-indenyl-3-methylphosphonic acid. 

EXAMPLE 9

A mixture of 260 parts of 5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-indenyl-3-ethyl-5-tetrazole and 25 parts of lactose is granulated with suitable water and to this is added 100 parts of maize starch. The mass is passed through a 16 mesh screen. The granules are dried at a temperature below 60°C. The dry granules are passed through a 16 mesh screen and mixed with 3.8 parts of magnesium stearate. They are then compressed into tablets suitable for oral administration. Similarly, tablets are prepared by employing an equivalent amount of 5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-indenyl-3-methylsulfonic acid or 5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-indenyl-3-methylphosphonic acid.

What is claimed is:

1. A compound of the formula

![Chemical Structure](attachment:chemical_structure.png)
wherein:

R₁ is hydrogen, C₁₋₅ loweralkyl or C₁₋₅ chloro, bromo or fluoro loweralkyl;
R₂, R₃, R₄ and R₅ are each hydrogen, halo, C₁₋₅ loweralkyl, halo C₁₋₅ loweralkyl, C₁₋₅ loweralkoxy, nitro, amino, C₁₋₅ loweralkylamino, C₁₋₅ diloweralkylamino, C₁₋₅ loweralkanoyl, C₁₋₅ loweralkanoyl, hydroxy, C₁₋₅ loweralkanoyl, C₂₋₅ loweralkenoyl, C₁₋₅ loweralkenylxyloxy or trifluoromethyl;
R₆ and R₇ are each hydrogen, halo, C₁₋₅ loweralkyl, halo C₁₋₅ loweralkyl, C₁₋₅ loweralkoxy, nitro, amino, C₁₋₅ loweralkylamino, C₁₋₅ diloweralkylamino, C₁₋₅ loweralkanol, halo C₁₋₅ loweralkanol, C₁₋₅ loweralkanolamino, hydroxy, C₁₋₅ loweralkanol, C₂₋₅ loweralkenoyl, C₁₋₅ loweralkenylxyloxy or trifluoromethyl;
R₈ and R₉ are each hydrogen, halo, bromo, fluoro, C₁₋₅ loweralkyl, halo C₁₋₅ loweralkyl, C₁₋₅ loweralkoxy, C₁₋₅ loweralkylthio, C₁₋₅ diloweralkylthio, C₁₋₅ trifluoromethyl, C₁₋₅ loweralkysulfanyl, C₁₋₅ loweralkylsulfanyl, C₁₋₅ diloweralkylsulfamyl, nitro or C₁₋₅ loweralkoxy;
X is C₁₋₄ alkylene, C₂₋₄ alkenylene, C₃₋₄ alkynylene or —O—;
(A) is phenyl;
R¹ and R¹' are each hydrogen or C₁₋₅ loweralkyl;
n is 0 or 1; and m is hydrogen

2. The compound of claim 1 wherein
R₁ is hydrogen or C₁₋₅ loweralkyl;
R₄, R₅, R₆ and R₇ are each hydrogen, halo, C₁₋₅ loweralkyl, halo C₁₋₅ loweralkyl, C₁₋₅ loweralkoxy, nitro, amino, C₁₋₅ loweralkylamino, C₁₋₅ diloweralkylamino, C₁₋₅ loweralkanol, halo C₁₋₅ loweralkanol, C₁₋₅ loweralkanolamino, hydroxy, C₁₋₅ loweralkanol, C₂₋₅ loweralkenoyl, C₁₋₅ loweralkenylxyloxy or trifluoromethyl;
R₈ and R₉ are each hydrogen, halo, bromo, fluoro, C₁₋₅ loweralkyl, halo C₁₋₅ loweralkyl, C₁₋₅ loweralkoxy, C₁₋₅ loweralkylthio, C₁₋₅ diloweralkylthio, C₁₋₅ trifluoromethyl, C₁₋₅ loweralkysulfanyl, C₁₋₅ loweralkylsulfanyl, C₁₋₅ diloweralkylsulfamyl, nitro or C₁₋₅ loweralkoxy;
n is 0;
(A) is phenyl; and
R¹ and R¹' are each hydrogen.

3. The compound of claim 1 wherein
R₁ is methyl;
R₄, R₅, R₆ and R₇ are each hydrogen;
R₈ is methylsulfanyl;
R₉ is fluoro; and
n is 0.