Abstract

Substituted hydridanes, particularly of formula (I) in which X, Y, R₄, R₅, R₆, R₇, R₈ and R₉ are as defined in the description, and their use in controlling angiogenesis dependent diseases in warm blooded animals, as well as a method for preparing 3-bromo-(2,2-dimethyl)propyl benzoate are disclosed.
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SUBSTITUTED HYDRINDANES FOR THE TREATMENT OF
ANGIOGENESIS-DEPENDENT DISEASES

Background of the Invention

Field of Invention

This invention is directed to substituted hydrindanes and their use in preventing and treating angiogenesis-dependent diseases in warm blooded animals.

Description of Related Art


Summary of Invention

This invention is directed to substituted hydridanes useful in the inhibition of neovascularization. These compounds can be used in the treatment of angiogenesis-dependent diseases. These compounds are particularly useful for the treatment and control of angiogenesis associated with ocular neovascular diseases, solid tumor growth, diabetes and arthritis.

This invention is also directed to methods for controlling and preventing angiogenesis dependent diseases through the systemic or local administration of the compositions herein disclosed.

Detailed Description of Preferred Embodiments

The development and formation of new blood vessels for the purpose of sustaining vital tissue is known as angiogenesis or neovascularization. Angiogenesis is a very important process in the development of an organism; however, a large number of diseases are associated with the aberrant growth of new blood vessels. These diseases are referred to as angiogenesis dependent diseases. The substituted hydridanes of the present invention are useful in preventing and treating, collectively referred to herein as "controlling," neovascularization associated with disease in warm blooded animals, including humans.

Two classes of compounds which are known to inhibit angiogenesis in the chick embryo choioallantoic membrane (CAM) model of neovascularization are angiostatic steroids, such as tetrahydrocortesolone, and dihydroxy-vitamin D analogs, such as calcitriol. Vitamin D is a steroid in which the B ring of the steroid nucleus is photochemically cleaved (i.e. a B-seco steroid).
Tetrahydrocortisolone (THS)  

Calcitriol

Our structure-activity relationship studies of angiostatic steroids and vitamin D analogs in the chick CAM model of neovascularization allowed us to predict that certain fragments of angiostatic steroids or vitamin D analogs would be angiostatic (i.e. inhibit neovascularization). Compounds lacking the A and B rings of the steroid nucleus and containing the six carbon C ring and the five carbon D ring (i.e. substituted hydrindanes) were prepared and evaluated for angiostatic activity in the chick CAM model (details of the methods of the CAM assay may be found in McNatt, et al., Angiostatic activity and metabolism of cortisol in the chorioallantoic membrane (CAM) of the chick embryo. J Steroid Biochem. Molec. Biol. Vol. 42:687-693, 1992). These substituted hydrindanes had angiostatic activity 1000-10,000 times as potent as angiostatic steroids tested in this system.
The substituted hydridanes of the present invention have the following formula:

where X is OH, OR₁, OR₂, OS(O)₂R₃, ON=CHR₁, ON=CR₁R₂, CN, R₁, R₂,
CH(OH)R₂, CH(OR₁)R₂, CH(OR₂)R₂, C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂,
C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂, C(OH)R₁R₂, C(OR₁)R₁R₂,
C(OR₂)R₁R₂, S(=O)ₙH, S(=O)ₙR₁, SR₂, P(=O)R₁R₂, P(=O)(OH)₂,
P(=O)(OH)(OR₁), P(=O)(OR₁)(OR₂), P(=O)(OH)(NH₂), P(=O)(OR₁)(NH₂),
P(=O)(OH)(NHR₁), P(=O)(OH)(NR₁R₂), P(=O)(OR₁)(NHR₁)
P(=O)(OR₁)(NR₁R₂), NH₂, NHR₁, NH₂R₁, NR₁R₂, NR₁R₂, NHOH, N(OH)R₁,
N(OH)R₂, NH(OR₁), NH(OR₂), N(OR₁)R₂, N(OR₂)R₁, N(OR₁)R₂, N(OR₂)R₁,
*S(R₁)(R₂)Q*, *N(R₁)(R₂)(R₃)Q* wherein Q* is a halide, sulfonate, or
carboxylate anion; C(=O)R₁, C(=O)R₂, C(=O)NH₂, C(=O)NHR₁, C(=O)NR₁R₂,
C(=O)N(OH)R₁, C(=O)N(OR₁)R₂, C(=O)N(OR₂)R₁; or

n = 0, 1 or 2;
R₁ is aryl, haloaryl, C₁₋C₁₀ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or
haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR₃,
or 6 OR₂; or imidazolyl, triazolyl, thia dialkyl, oxa dialkyl, thiazolyl,
isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C₁ - C₆ alkyl groups;

R₂ is C(=O)H, C(=O)R₁, C(=O)OR₁, C(=O)OH, C(=O)NH₂, C(=O)NHR₁, C(=O)NR₁R₂;

R₃ is aryl, haloaryl, C₁ - C₁₀ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

R₄ is H, (=O), OR₂, OR₁, OH, =NOH, =NOR₁, =NOR₂;

R₅ and R₆ are independently H, CH₃ or CH₂CH₃;

Y is H, OH, OR₁, OR₂ or (=O), with the proviso that if Y is OH, then X is R₁, R₂,

CH(OH)R₂, CH(OR₁)R₂, CH(OR₂)R₂, C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂,

C(OH)₂R₂, C(OR₁)₂R₂, C(OR₂)₂R₂, and if Y is (=O) then X is R₁, R₂,

CH(OH)R₂, CH(OR₁)R₂, CH(OR₂)R₂, C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂,

C(OH)₂R₂, C(OR₁)₂R₂, C(OR₂)₂R₂, NH₂, NHR₁, NR₁R₂, NHOR₁, N(OH)R₁,

NH(OR₁), NH(OR₂)₂, N(OR₁)₂, or N(OR₂)₂; and

R₇ and R₈ are independently H or C₁ to C₆ alkyl, branched alkyl, hydroxyalkyl,

optionally unsaturated; or R₇ and R₈ together form a double bond.

Unless otherwise specified, all substituent groups can be attached to the hydridane ring system in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts and esters of the substituted hydridanes.
Compounds of Formula 1 having the following structure are preferred (Formula 2):

\[
\begin{align*}
\text{H}_3\text{C} & - \text{CH}_2\text{X} \\
\text{R}_7 & \\
\text{R}_4 & \\
\text{R}_1 & \\
\text{R}_2 & \\
\text{R}_3 & \\
\end{align*}
\]

where \( X \) is \( \text{C} (\text{OH}) \text{R}_1 \text{R}_1, \text{C} (\text{OR}_1) \text{R}_1 \text{R}_1, \text{C} (\text{OR}_2) \text{R}_1 \text{R}_1, \text{C} (\text{OH}) \text{R}_1 \text{R}_2, \text{C} (\text{OR}_1) \text{R}_1 \text{R}_2, \text{C} (\text{OR}_2) \text{R}_1 \text{R}_2, \text{C} (\text{OR}_2) \text{R}_2 \text{R}_2, \text{C}(=\text{O})_{\text{n}} \text{H}, \text{S}(=\text{O})_{\text{n}} \text{H}, \text{SR}_2, \text{P}(=\text{O}) \text{R}_1 \text{R}_1, \text{P}(=\text{O}) (\text{OH})(\text{OR}_1), \text{P}(=\text{O}) (\text{OH})(\text{OR}_2) \\
\text{P}(=\text{O}) (\text{OH})(\text{NH}_2), \text{P}(=\text{O}) (\text{OR}_1)(\text{NH}_2), \text{P}(=\text{O}) (\text{OH})(\text{NHR}_1), \text{P}(=\text{O}) (\text{OH})(\text{NHR}_2), \text{NHOH}, \text{NH}(\text{OH}) \text{R}_1, \text{N}(\text{OH}) \text{R}_2, \text{NH}(\text{OR}_1), \text{NH}(\text{OR}_2) \\
\text{N}(\text{OR}_1) \text{R}_2, \text{N}(\text{OR}_2) \text{R}_2, \text{N}^* (\text{R}_1)(\text{R}_1) \text{Q}^*, \text{N}^* (\text{R}_1)(\text{R}_2) \text{Q}^*, \text{C}(=\text{O}) \text{R}_1, \text{C}(=\text{O}) \text{R}_2, \text{C}(=\text{O}) \text{NH}_2, \text{C}(=\text{O}) \text{NHR}_1, \text{C}(=\text{O}) \text{NR}_1 \text{R}_1, \text{C}(=\text{O}) \text{N}(\text{OH}) \text{R}_1, \text{C}(=\text{O}) \text{N}(\text{OR}_1) \text{R}_1, \text{C}(=\text{O}) \text{N}(\text{OR}_2) \text{R}_1;
\end{align*}
\]

\( n = 0, 1 \) or 2;

\( \text{R}_1 \) is aryl, haloaryl, \( \text{C}_1 - \text{C}_{10} \) alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR, or 6 OR; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or \( \text{C}_1 - \text{C}_8 \) alkyl groups;

\( \text{R}_2 \) is \( \text{C}(=\text{O}) \text{H}, \text{C}(=\text{O}) \text{R}_1, \text{C}(=\text{O}) \text{OR}_1, \text{C}(=\text{O}) \text{OH}, \text{C}(=\text{O}) \text{NH}_2, \text{C}(=\text{O}) \text{NHR}_1, \text{C}(=\text{O}) \text{NR}_1 \text{R}_1; \)

\( \text{R}_3 \) is aryl, haloaryl, \( \text{C}_1 - \text{C}_{10} \) alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

\( \text{R}_4 \) is \( \text{H}, \text{OR}_2, \text{OR}_1, \text{OH}, =\text{NOH}, =\text{NOR}_1, =\text{NOR}_2; \) and provided that if \( X \) is \( \text{S}(=\text{O})_{\text{n}} \) (optionally substituted phenyl) then \( \text{R}_4 \neq \text{OH} \), or \( (=\text{O}); \) and

\( \text{R}_7 \) and \( \text{R}_8 \) are \( \text{H} \) or together are optionally a double bond;

and wherein aryl denotes phenyl, naphthyl, furyl, thiényl, pyridyl, benzofuryl, indoly, benzothienyl, quinolyl or isoquinolyl;
R₁R₁ attached to the same C, S, P or N atom can form a ring of from 3 through 7 members; and
for those substituents containing more than one R₁, R₂, or R₃, each R₁, R₂, or R₃ may be the same or different.

More preferred compounds are compounds of Formula 2 where the stereochemistry is as specified below.

\[
\begin{align*}
\text{H₃C} & \quad \text{CH₂X} \\
\text{CH₃} & \quad \text{H} \\
\text{H} & \quad \text{R₄} \\
\text{H} & \quad \text{H}
\end{align*}
\]

where X and R₄ are the same as above.

Especially preferred are De-A,B-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
De-A,B-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
and De-A,B-23-thiacholestan-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate.

The compounds of Formula 2 can be prepared from diol 3a. Stereoisomers of compounds of Formula 2, as well as related compounds of Formula 1 having substituents R₅=CH₃ and R₆=CH₃, can be prepared by total synthesis using appropriately modified materials and procedures, and/or in some cases from materials (e.g. Compound 3a) derived from Vitamin D₂, at the discretion of one skilled in the art.

The compounds of Formula 2 can be prepared starting with the known "Inhoffen-Lythgoe diol" 3a which can be prepared from Vitamin D₂. Alternatively, 3a can be prepared by total synthesis, for example, as described in:

Conversion of the primary hydroxyl group of diol 3a to a good leaving group, as in the known monotosylate 3b, allows the preparation of thioether and amine derivatives of hydrindanes. For example, reaction of 3b with benzyl mercaptan and a base produces benzyl thioether 3c. Compound 3c can be treated with an
3a, R^4 = OH, X = OH
3b, R^4 = OH, X = OTs
3c, R^4 = OH, X = SCH_2Ph
3d, R^4 = OC(=O)NHC_6H_4Br-p, X = SCH_2Ph
3e, R^4 = OC(=O)NHC_6H_4Br-p, X = S(O)2CH_2Ph
3f, R^4 = OH, X = SH
3g, R^4 = OH, X = SCH_2C(CH_3)2OH
3h, R^4 = OC(=O)NHC_6H_4Br-p, X = OTs
3i, R^4 = OC(=O)NHC_6H_4Br-p, X = SH
3j, R^4 = OC(=O)NHC_6H_4Br-p, X = SCH_2C(CH_3)2CH_2OC(=O)Ph
3k, R^4 = OC(=O)NHC_6H_4Br-p, X = S(O)2CH_2C(CH_3)2CH_2OC(=O)Ph
3l, R^4 = OC(=O)NHC_6H_4Br-p, X = S-(2-(5-methyl-1,3,4-thiadiazolyl))
3m, R^4 = OC(=O)NHC_6H_4Br-p, X = NH+(CH_3)2CH_2CH_2OH, OTs^-
3n, R^4 = OC(=O)NHC_6H_4Br-p, X = NHCH_2C(CH_3)2CH_2OH
3o, R^4 = OH, X = CN
3p, R^4 = OH, X = COOH
3q, R^4 = OH, X = C(=O)N(CH_3)OCH_3
3r, R^4 = OH, X = C(=O)NHCH_2C(CH_3)2CH_2OH
3s, R^4 = OC(CH_3)3, X = OTs
3t, R^4 = OC(CH_3)3, X = I
3u, R^4 = OC(CH_3)3, X = P(O)(O-i-Pr)2
3v, R^4 = OCH_2Ph, X = CHO
3w, R^4 = OCH_2Ph, X = C(=O)CH_2C(CH_3)2OH
appropriate acylating agent, such as 4-bromophenyl isocyanate to produce thioether carbamate 3d. Reaction of a thioether such as 3d with an oxidant, for example, 3-chloroperoxybenzoic acid, yields a sulfone, e.g. 3e, or the corresponding sulfoxide.

Alternatively, hydridane thioethers can be formed by reacting a hydridane thiol, e.g. 3f, with an alkylating agent. For example, use of such as isobutylene oxide, gives thioether 3g. Thiol 3f can be prepared via cleavage of benzyl thioether 3c, using, for example, sodium in liquid ammonia.

Tosylate 3b can be treated with an appropriate acylating agent, such as 4-bromophenyl isocyanate to produce the tosylxy carbamate 3h. Displacement of the tosyl group of 3h with a thiocarboxylate salt, such as potassium thiolacetate, followed by cleavage of the acetyl group, provides thiol carbamate 3j.

Thiol carbamate 3j can be alkylated on sulfur to provide various hydridane thioethers. For example, treatment of 3j with 3-bromo-(2,2-dimethyl)propyl benzoate (prepared from 5,5-dimethyl-2-phenyl-1,3-dioxane according to the method of Hanessian, (Org. Synth. 65, 243) and potassium tert-butoxide in dimethyl sulfoxide solution yields thioether 3k, which can be oxidized as above to sulfone 3m, or the corresponding sulfoxide.

Reaction of tosylate 3h with a heterocyclic thiol, e.g., 2-mercapto-5-methyl-1,3,4-thiadiazole, produces heterocyclic thioethers of hydridanes, such as 3n.

Hydridane quaternary ammonium salts, such as 3p, can be made by reacting tosylate 3h with a tertiary amine, in this case 2-(N,N-dimethylamino)ethanol. Use of a primary amine leads instead to secondary amino compounds, e.g., 3q.

Hydrolysis of the known nitrile 3r (prepared from tosylate 3b: P.M. Wovkulich et al., cited above) provides carboxylic acid 3s, which can be converted into hydridane amides such as 3t and 3u by treatment with an amine such as N,O-dimethylhydroxylamine or 3-amino-2,2-dimethylpropanol, respectively, in the presence of a coupling reagent, for example, a 1,3-dialkyl carbodiimide such as 1-ethyl-3-(dimethylamino)propyl) carbodiimide hydrochloride.

Hydridane phosphonic acid derivatives, e.g., 3x, can be prepared from primary halo compounds such as iodide 3w, using Arbusov reaction conditions such as those described by Karanewsky et al., J. Med. Chem, 33, 2952 (1990); this
reference also teaches methods for converting dialkyl phosphonates to other phosphorus compounds such as monocalkyl phosphonates, phosphinates and phosphonamides.

Hydrindane ketones, e.g., 3z, can be prepared in a variety of ways. For example, reaction of known hydrindane aldehyde 3y (Johnson, et al., cited above) with an organometallic reagent, for example, that derived from isobutylene oxide by the method of T. Cohen et al., J. Org. Chem. 55, 1528 (1990), followed by oxidation of the intermediate secondary alcohols with, e.g., a chromium (VI) reagent, provides ketone 3z. Other methods of preparing ketones are well known in the art, for example, reaction of organolithium reagents with N-alkoxy-N-alkyl amides such as 3t, or with acids such as 3s.

Without being bound by any theory, it is believed that angiostatic agents work by inhibiting one or more steps in the process of neovascularization, regardless of the cause; therefore the angiostatic substituted hydrindanes of this invention are useful in the treatment and prevention of neovascularization associated with a variety of diseases and surgical complications. The formation of new blood vessels (i.e. angiogenesis) is a natural developmental process; however, once a tissue has formed, there is generally no need for additional new blood vessels. A number of diseases are characterized by the growth of new blood vessels, and these diseases can be effectively treated through the inhibition of neovascularization (Doctrow & Kulakowski, "Angiogenesis modulators - New drugs for controlling blood vessel growth?," Drug News & Perspectives 2:74-81, March 1989; Maione & Sharpe, "Development of angiogenesis inhibitors for clinical applications," Trends in Pharmaceutical Sciences, 11:457-461, November 1990). Many different substances have been found to induce and promote neovascularization (Folkman, et al., "Angiogenic factors," Science 235:442-447, 1987; BenEzra, "Neovascularogenic ability of prostaglandins, growth factors and synthetic chemoattractants," American J. Ophthalmology. 86:445-461, October 1978). Inhibition may differ in the various neovascular diseases; however, it is believed that once initiated, the basic process of neovascularization is similar in all tissues regardless of the associated disease (Furcht, "Critical factors controlling angiogenesis: cell products, cell matrix and growth factors," Laboratory Investigation, 55:505-509, 1986).
The substituted hydridanes of the present invention can be used in treating neovascularization associated with, for example: cancer, solid tumors, arthritis, diabetes, arteriosclerosis, angiofibroma, arteriovenous malformations, corneal graft neovascularization, delayed wound healing, diabetic retinopathy, age related macular degeneration, granulations, burns, hemangioma, hemophilic joints, hypertrophic scars, neovascular glaucoma, nonunion fractures, Osler-Weber Syndrome, psoriasis, pyogenic granuloma, retrolental fibroplasia, pterygium, scleroderma, trachoma, vascular adhesions, ocular neovascularization, parasitic diseases, hypertrophy following surgery, inhibition of hair growth, inhibition of ovulation and corpus luteum formation and inhibition of embryo implantation and development in the uterus.

In particular, these compounds are useful in preventing and treating any ocular neovascularization, including, but not limited to: retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, age related macular degeneration); rubeosis iritis; inflammatory diseases; chronic uveitis; neoplasms (retinoblastoma, pseudoglioma); Fuchs' heterochromic iridocyclitis; neovascular glaucoma; corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris); neovascularization resulting following combined vitrectomy and lensectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia); pterygium; neovascularization of the optic nerve; and neovascularization due to penetration of the eye or contusive ocular injury.

The substituted hydridanes of the present invention can be incorporated into various formulations for delivery. The type of formulation (topical or systemic) will depend on the site of disease and its severity. These compounds can be systemically delivered orally in a tablet or capsule form or by parenteral injection. The compounds can be formulated into gels, ointments, or creams for topical administration to the skin. For administration to the eye, topical formulations can be used and can include ophthalmically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic
ointment formulations, an angiostatic substituted hydridane is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations comprising the angiostatic substituted hydridanes of the present invention can be prepared by suspending an angiostatic hydridane in a hydrophilic base prepared from a combination of, for example, Carbopol® 940 (a carboxy vinyl polymer available from BF Goodrich Company), according to published formulations for analogous ophthalmic preparations. Preservatives and antimicrobial agents can also be incorporated in such gel formulations. Angiostatic substituted hydridanes can also be formulated for sterile ophthalmic intraocular injections. Systemic formulations for treating ocular neovascularization can also be used, for example, orally ingested tablets and parenteral injections.

The specific type of formulation selected will depend on various factors, such as the angiostatic substituted hydridane (or its salt or ester) being used, the dosage frequency and the severity and the location of the disease. For ocular neovascular diseases, topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms for the treatment of neovascularization of the front of the eye (e.g. the cornea, iris, trabecular meshwork) or the back of the eye if the angiostatic agent can be formulated such that it can be delivered topically and penetrate the tissues of the front of the eye to get to the back of the eye. The angiostatic agent will normally be contained in these formulations in an amount from about 0.0001 to 1 weight percent. For topical ocular administration, these formulations are delivered to the surface of the eye one to six times a day, depending on the discretion of the skilled clinician. Systemic administration, for example in the form of tablets, is particularly useful in the treatment of neovascularization of the back of the eye, such as the retina. Tablets containing 1-2000 mg of the angiostatic agent can be taken 1-4 times per day depending on the discretion of the skilled clinician.

The substituted hydridanes of this invention are also useful in controlling intraocular pressure associated with primary open angle glaucoma (POAG) and in
controlling the rise in intraocular pressure sometimes associated with the use of glucocorticoids.

The formulations set forth in the following examples for topical ocular suspensions, intraocular injections, and oral tablets can be prepared according to procedures known to those skilled in the art of formulating drugs.

**Example 1: Topical Ocular Suspension**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substituted hydridane</td>
<td>0.001-1.0</td>
</tr>
<tr>
<td>Tyloxapol</td>
<td>0.01 to 0.05</td>
</tr>
<tr>
<td>HPMC</td>
<td>0.5</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.8</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td>0.01</td>
</tr>
<tr>
<td>NaOH/HCl</td>
<td>q.s. pH 7.4</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. 100 ml</td>
</tr>
</tbody>
</table>

**Example 2: Formulation for Sterile Intraocular Injection**

Each mL contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substituted hydridane</td>
<td>0.01-10.0 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>7.14 mg</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.38 mg</td>
</tr>
<tr>
<td>Calcium chloride dihydrate</td>
<td>0.154 mg</td>
</tr>
<tr>
<td>Magnesium chloride dihydrate</td>
<td>0.20 mg</td>
</tr>
<tr>
<td>Dried sodium phosphate</td>
<td>0.42 mg</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>2.1 mg</td>
</tr>
<tr>
<td>Dextrose</td>
<td>0.92 mg</td>
</tr>
<tr>
<td>NaOH/HCl</td>
<td>q.s. pH 7.2</td>
</tr>
<tr>
<td>Purified water for injection</td>
<td>q.s. 1 mL</td>
</tr>
</tbody>
</table>

**Example 3: Formulation for Tablet**
1-2000 mg of substituted hydridane with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formation.

**Examples 4-6: Angiostatic Activity for 3 Classes of Compounds**

Angiostatic activity of the test compounds was evaluated in the chicken embryo chorioallantoic membrane (CAM) model of neovascularization as described by McNatt et al. Briefly, 1.0 ng of the indicated substituted hydridane was added to a 10 μL bead containing 1% agarose and liposomes (2.5% dimyristoyl phosphatidyl choline) and placed on the CAM of a shell-less, 5-6 day chick embryo. After an additional 2 days of incubation at 37°C, the zone of avascularity surrounding the dose bead was evaluated. Angiostatic activity is expressed as the angiostatic response frequency per nmole of test compound.

<table>
<thead>
<tr>
<th>Example</th>
<th>Compound Class</th>
<th>Class Representative</th>
<th>Angiostatic Factor (Response Frequency/nmole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Angiostatic steroid</td>
<td>Tetrahydrocortisol</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Vitamin D analogs</td>
<td>Calcitriol</td>
<td>23,000</td>
</tr>
<tr>
<td>6</td>
<td>Substituted hydridanes</td>
<td>De-A,β-cholestan-8β,23S,25R,26-tetrol</td>
<td>33,000</td>
</tr>
</tbody>
</table>

**Examples 7-23: Angiostatic Activity of Substituted Hydridanes Evaluated in Chick Embryo Model of Neovascularization**

A number of compounds of Formula II were prepared and evaluated in the CAM model as in Examples 4-6 above. Angiostatic activity results for these compounds are shown in the table below. Angiostatic activity is expressed as the angiostatic response frequency per nmole of test compound relative to positive and negative controls.
<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>COMPOUND</th>
<th>R.A.F.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>De-A,B-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate</td>
<td>2.91</td>
</tr>
<tr>
<td>10.</td>
<td>De-A,B-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate</td>
<td>2.18</td>
</tr>
<tr>
<td>11.</td>
<td>De-A,B-23,24-dinor-22-(carbethoxymethyl)thiacholan-8β-ol-(4-bromophenyl) carbamate</td>
<td>1.97</td>
</tr>
<tr>
<td>12.</td>
<td>De-A,B-23,24-dinor-22-(2-(1-methylimidazolyl)thio)cholan-8β-ol-(4-bromophenyl) carbamate</td>
<td>1.83</td>
</tr>
<tr>
<td>13.</td>
<td>De-A,B-23-thiacholen-8β,25-diol-8β,25-bis-(4-bromophenyl) carbamate</td>
<td>1.75</td>
</tr>
<tr>
<td>14.</td>
<td>De-A,B-23,24-dinor-22-(2-(5-methyl-1,3,4-thiadiazolyl)thio)cholan-8β-ol-(4-bromophenyl) carbamate</td>
<td>1.67</td>
</tr>
<tr>
<td>15.</td>
<td>De-A,B-23-thiacholen-8β,25-diol-23-dioxide-8β-(4-bromophenyl) carbamate</td>
<td>1.57</td>
</tr>
<tr>
<td>17.</td>
<td>De-A,B-23,24-dinorcholan-8β,22-diol-bis(phenyl carbamate)</td>
<td>1.25</td>
</tr>
<tr>
<td>18.</td>
<td>De-A,B-cholestan-8β,23S,25R,26-tetrol</td>
<td>1.00</td>
</tr>
<tr>
<td>19.</td>
<td>De-A,B-cholestan-25-en-8β,23S-diol</td>
<td>0.85</td>
</tr>
<tr>
<td>20.</td>
<td>De-A,B-23,24-dinor-8β-hydroxycholan-22-(N-methyl-N-methoxy) carboxamide</td>
<td>0.82</td>
</tr>
<tr>
<td>21.</td>
<td>De-A,B-23,24-dinor-8β-hydroxycholan-22-(N-(2,2-dimethyl-3-hydroxy)propyl) carboxamide</td>
<td>0.49</td>
</tr>
<tr>
<td>22.</td>
<td>De-A,B-23,24-dinorcholan-8β,22-diol</td>
<td>0.39</td>
</tr>
<tr>
<td>23.</td>
<td>De-A,B-23,24-dinor-8β-hydroxycholan-22-carboxylic acid</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* = relative angiostatic factor (angiostatic activity at 1 ng relative to De-A,B-cholestan-8β,23S,25R,26-tetrol)
Examples 24-42: Preparation of Substituted Hydrindanes

Example 24:


Benzyl mercaptan (15 mL) was added in 2-mL portions to a stirred suspension of 5.4 g of NaH (60%, oil dispersion) in 200 mL of dry DMF under Ar, keeping T<35°C. After evolution of H₂ ceased, the solution was cooled to 10 °C and a solution of tosylate 3b in 80 mL of dry DMF was added in 4 portions. The solution was stirred (to 24°C) for 15 h, then quenched carefully with water. The mixture was poured into 1L of water and extracted with ether and ethyl acetate. The combined organic extracts were washed with 1M NaOH (twice), water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica (10%-25% EtOAc-hexane) to give 27.7 g of an oil.

NMR (CDCl₃): δ 0.90 (s, 3H), 1.02 (d, 3H), 1.1-2.0 (m, 14H), 2.35 (ABX, 2H), 3.68 (s, 2H), 4.05 (br s, 1H), 7.3 (br s, 5H).

Example 25:

De-A,B-24-phenyl-23-thiacholan-8β-ol-8β-(4-bromophenyl) carbamate (3d).

4-Bromophenyl isocyanate (3.07 g) was added to a stirred solution of De-A,B-23,24-dinor-24-phenyl-23-thiacholan-8β-ol (3c, 3.79 g) in 24 mL of dry pyridine under Ar. After 68 h, water (5mL) was added and the mixture was stirred for 20 min. The mixture was diluted with ether and washed with water, 1M HCl (to pH 1), water (to pH7), brine, dried (MgSO₄), filtered and concentrated. The residue was suspended in 1:3 EtOAc-hexane, eluted through a silica pad and the eluate concentrated to give 5.88 g of a foam.

NMR (CDCl₃): δ 0.85 (s, 3H), 1.03 (d, 3H), 1.0-2.0 (m, 13 H), 2.35 (ABX, 2H), 3.68 (s, 2H), 5.14 (br s, 1H), 6.48 (br s, 1H), 7.3 (br s, 5H), 7.35 (AB, 4H).
Example 26:

De-A,B-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate (3e).

3-Chloroperoxybenzoic acid (1.98 g) was added in portions to a stirred solution of De-A,B-24-phenyl-23-thiacholan-8β-ol-8β-(4-bromophenyl) carbamate (3d, 1.97 g) in 15 mL of CH₂Cl₂. After 15 h, the mixture was diluted with EtOAc and washed with 1M NaOH (twice), water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was triturated (5% ether-hexane) to give 1.89 g of a pink solid, m.p. 78-84 °C.

Found: C, 59.02; H, 6.28; N, 2.52; S, 5.82.

Example 27:

De-A,B-23,24-dinor-22-mercaptocholan-8β-ol (3f).

Sodium was added in 0.5-g portions to a stirred solution of De-A,B-24-phenyl-23-thiacholan-8β-ol (3c, 9.35 g) in 50 mL of dry THF and 250 mL of liquid NH₃ at -33 °C under Ar, until the blue color persisted (3.5 g Na added). The mixture was quenched carefully with solid NH₄Cl, and the excess NH₃ was allowed to evaporate. The residue was dissolved in ether and water, the mixture was acidified to pH 2 with 1M HCl, and partitioned between ether and water. The ethereal solution was washed with brine, dried (MgSO₄), filtered and concentrated to give 6.75 g of an oil.

NMR (CDCl₃) δ 0.94 (s, 3H), 0.99 (d, 3H), 1.0-2.0 (m, 15H), 2.5 (ABX, 2H), 4.08 (br s,1H).

Example 28:

De-A,B-23-thiacholestan-8β,25-diol (3g).

NaOCH₃ (2.4 mL of a 25% solution in CH₃OH) was added to a stirred solution of De-A,B-23,24-dinor-22-mercaptocholan-8β-ol (3f, 2.25 g) in 15 mL of CH₃OH under Ar. Isobutylene oxide (1.49 g) was added and the solution was heated to reflux for 2 h, then cooled to 24 °C over 15 h. The mixture was poured into water, extracted with ether and ethyl acetate and the organic extracts washed with water.
(to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica (25%–50% EtOAc-hexane) to give 2.47 g of a viscous oil.

NMR (CDCl₃) δ 0.95 (s, 3H), 1.06 (d, 3H), 1.27 (s, 6H), 1.0-2.1 (m, 15H), 2.54 (ABX, 2H), 2.63 (br s, 2H), 4.08, (1 H).

Example 29:
De-AB-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (3h).

4-Bromophenyl isocyanate (6.35 g) was added to a stirred solution of tosylate 3b (9.40 g) in 50 mL of dry pyridine under Ar. After 2.5 h, 5 mL of water was added and stirring continued for 0.5 h. The mixture was diluted with ether and washed with water, 1M H₂SO₄, water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was recrystallized from ethanol to give 10.7 g of a white solid, m.p. 159-161 °C.

Anal. Calcd: C, 57.44; H, 6.07; N, 2.48; S, 5.68.

Found: C, 57.52; H, 6.12; N, 2.47; S, 5.73.

Example 30:
De-AB-23,24-dinor-22-mercaptocholan-8β-ol-8β-(4-bromophenyl) carbamate (3j).

Potassium thiolacetate (1.75 g) was added to a stirred solution of De-AB-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (3h, 4.32 g) in 13 mL of dry DMF under Ar. After 70 min, the mixture was diluted with ether and ethyl acetate, washed with water (3 times), brine, dried (MgSO₄), filtered and concentrated, giving 3.58 g of a yellow foam. This material was dissolved in 40 mL of absolute EtOH and 20 mL of dry THF, and the solution was deoxygenated by sparging with argon. A solution of 0.85 g of NaOH in 8 mL of water was added. After 5 min, the mixture was poured into sat. KH₂PO₄, extracted with ether, and the ethereal solution dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica (10% EtOAc-hexane) to give 2.1 g of compound 3j as a foam.

NMR (CDCl₃) δ 0.90 (s, 3H), 1.03 (d, 3H), 1.1-2.1 (m, 13H), 2.50 (ABX, 2H), 5.15 (br s, 1H), 6.49 (br s, 1H), 7.35 (AB, 4H).
Example 31:
3-bromo-(2,2-dimethyl)propyl benzoate.

N-Bromosuccinimide (20.7 g) was added to a stirred solution of 5,5-dimethyl-2-
phenyl-1,3-dioxane (19.2 g) in 200 mL of CCl₄ containing 8.5 g of BaCO₃ in
suspension. The mixture was heated to reflux under Ar for 2.2 h, then cooled to
24 °C over 15 h, filtered and concentrated. The residue was partitioned between
ether and water, and the ethereal solution was washed with brine, dried (MgSO₄),
filtered and concentrated to give 24.8 g of a yellow oil which was stored in the dark
at 0 °C under Ar.

NMR (CDCl₃) δ 1.16 (s, 6H), 3.45 (s, 2H), 4.20 (s, 2H), 7.5 (m, 3H), 8.04 (dd, 2H).

Example 32:
De-A,B-26-(benzoyloxy)-25-methyl-23-thiacholen-8β-ol-8β-(4-bromophenyl)
carbamate (3k).

Potassium tert-butoxide (0.32 g) was added to a stirred solution of De-A,B-
23,24-dinor-22-mercaptoplan-8β-ol-8β-(4-bromophenyl) carbamate (3j, 1.03 g) in
5.0 mL of dry DMSO under Ar. After 1 min, 3-bromo-(2,2-dimethyl)propyl benzoate
(1.23 g) was added via syringe. The mixture was stirred for 2 h, then diluted with
ether, washed with water (to pH 7), brine, dried (MgSO₄), filtered and concentrated.
The residue was purified by chromatography on silica (10% EtOAc-hexane) to give
0.82 g of a foam.

NMR (CDCl₃) δ 0.85 (s, 3H), 1.04 (d, 3H), 1.10 (s, 6H), 1.0-2.1 (m, 13H), 2.45
(ABX, 2H), 2.60 (s, 2H), 4.16 (s, 2H), 5.12 (br s, 1H), 6.5 (s, 1H), 7.35 (AB, 4H),
7.4-7.6 (m, 3H), 8.04 (dd, 2H).

Example 33:
De-A,B-26-(benzoyloxy)-25-methyl-23-thiacholen-8β-ol-23-dioxide-8β-(4-
bromophenyl) carbamate (3m).

3-Chloroperoxybenzoic acid (0.35 g) was added in portions to a stirred solution
of De-A,B-26-(benzoyloxy)-25-methyl-23-thiacholen-8β-ol-8β-(4-bromophenyl)
carbamate (3k, 0.41 g) in 16 mL of CH₂Cl₂, keeping T ≤ 40 °C. After stirring at
24 °C for 15 h, the mixture was diluted with EtOAc, washed with 1M NaOH (twice),
water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was
triturated with hexane containing 2-5% ether to give (after cooling to 0 °C) 0.36 g of a white solid, m.p. 75-78 °C.

Anal. Calcd: C, 59.25; H, 6.53; N, 2.16; S, 4.94.
Found: C, 59.30; H, 6.55; N, 2.12; S, 5.03.

**Example 34:**

De-A,B-23,24-dinor-22-(2-(5-methyl-1,3,4-thiadiazolylthio)cholan-8β-ol-(4-bromophenyl) carbamate (3n).

A stirred solution of 2-mercapto-5-methyl-1,3,4-thiadiazole (0.27 g), N,N-diisopropylethylamine (0.35 mL), and De-A,B-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (3h, 0.57 g) in 2.0 mL of dry CH₂CN was heated to reflux under Ar for 20 min. The cooled mixture was diluted with EtOAc, washed with water, 1M HCl, water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was recrystallized from ether-hexane to give 0.28 g of a pale yellow solid, m.p. 145-149 °C.

Anal. Calcd: C, 52.66; H, 5.77; N, 8.01.
Found: C, 52.77; H, 5.78; N, 7.95.

**Example 35:**

De-A,B-23,24-dinor-8β-(4-bromophenylcarbamoyloxy)-22-(N,N-dimethyl-N-(2-hydroxy)ethyl)cholanammonium p-toluenesulfonate (3p).

A stirred solution of (N,N-dimethylamino)ethanol (2.5 mL) and De-A,B-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (3h, 0.57 g) in 5.0 mL of absolute EtOH was heated to reflux under Ar for 6 h. The cooled mixture was partitioned between ether and water. The aqueous solution was concentrated, dried azeotropically with toluene (twice) followed by EtOH (twice) and the residue was triturated with ether to give 0.38 g of a foam.

NMR (DMSO-d₆) δ 0.98 (s, 3H), 1.09 (d, 3H), 1.1-2.1 (m, 13H), 2.27 (s, 3H), 3.05 (s, 6H), 3.4 (m, 4H), 3.8 (br s, 2H), 5.03 (br s, 1H), 5.3 (br s, 1H, exchanges), 7.3 (AB, 4H), 7.45 (s, 4H), 9.52 (s, 1H, exchanges).
Example 36:
**De-A,8-25-methyl-23-azacholesterol-8β-26-diol-8β-(4-bromophenyl) carbamate (3q).**

A stirred solution of 3-amino-2,2-dimethyl-1-propanol (1.0 g) and De-A,8-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (3h, 0.80 g) in 4.5 mL of dry 1,2-dimethoxyethane was heated to reflux under Ar for 6 h. The cooled mixture was diluted with EtOAc, washed with water (3 times), brine, dried (MgSO₄) filtered and concentrated to give 0.76 g of a foam.

NMR (DMSO-d₆) δ 0.75 (d, 3H), 0.77 (s, 3H), 0.79 (s, 3H), 0.91 (s, 3H), 1.0-2.5 (m, 18H), 3.16 (s, 2H), 5.02 (br s, 1H), 7.45 (s, 4H), 9.48 (s, 1H, exchanges).

Example 37:
**De-A,8-23,24-dinor-8β-hydroxycholan-22-carboxylic acid (3s).**

A stirred suspension of nitrile 3r (6.57 g) and 6.7 g of KOH pellets in 80 mL of ethylene glycol was heated to 160 °C under Ar for 17 h. The base-soluble product was isolated giving 6.15 g of a solid. A sample was recrystallized from n-BuCl: m.p. 129.5-131 °C.

Anal. Calcd: C, 69.96; H, 10.07

Found: C, 69.86; H, 10.13.

Example 38:
**De-A,8-23,24-dinor-8β-hydroxycholan-22-(N-methyl-N-methoxy)carboxamide (3t).**

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (1.15 g) was added to a stirred solution of acid 3s (0.95 g), N,N-diisopropylethylamine (1.05 mL) and N,O-dimethyhydroxylamine hydrochloride (0.59 g) in CH₂CN (2.0 mL) and CH₂Cl₂ (2.0 mL) under Ar. After 16 h, the mixture was diluted with EtOAc, extracted with 1M H₂SO₄, water (twice), brine, dried (MgSO₄), filtered and concentrated. The residue was crystallized (hexane - n-BuCl) to give 0.45 g of white crystals, m.p. 91-94 °C.

Anal. Calcd: C, 67.81; H, 10.31; N, 4.94.

Found: C, 67.89; H, 10.35; N, 4.90.
Example 39:
De-A,B-23,24-dinor-8β-hydroxycholan-22-(N-(2,2-dimethyl-3-hydroxy)propyl)carboxamide (3u).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (0.30 g) was added to a stirred solution of acid 3s (0.26 g) and 3-amino-2,2-dimethyl-1-propanol (0.15 g) in 1.0 mL of dry CH₂CN and 1.0 mL of dry CH₂Cl₂ under Ar. After 2 h, the mixture was diluted with EtOAc, washed with water, 1M H₂SO₄ (to pH 1), water (to pH 7), brine, dried (MgSO₄), filtered and concentrated. The residue was recrystallized from n-BuCl-EtOAc to give 0.22 g of white crystals, m.p. 172.5-175 °C.

Anal. Calcd: C, 70.11; H, 10.84; N, 4.30.
Found: C, 70.12; H, 10.85; N, 4.23.

Example 40:
De-A,B-23,24-dinor-22-(tosyloxy)-8β-(tert-butoxy)cholane (3v).

Isobutylene (40 mL) was condensed into a stirred, cooled (-78°C) solution of tosylate 3b (3.66 g) in 25 mL of dry CH₂Cl₂ under Ar. Phosphoric acid (0.25 mL, dried with P₂O₅) was added, followed by 0.40 mL of BF₃ etherate. The solution was stirred overnight while warming to 24 °C and the excess isobutylene was allowed to evaporate through a drying tube. The solution was poured into 2M NH₄OH, extracted with ether, and the organic extracts washed with water (to pH 9), brine, dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica (20% ether-hexane) to give 3.63 g of a viscous oil.

NMR (CDCl₃) δ 0.82 (s, 3H), 0.94 (d, 3H), 1.09 (s, 9H), 0.9-1.9 (m, 13H), 3.74 (br s, 1H), 3.9 (ABX, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

Example 41:
Diisopropyl De-A,B-23,24-dinor-8β-tert-butoxycholan-22-phosphonate (3x).

(A) A solution of NaI (2.7 g) and De-A,B-23,24-dinor-22-(tosyloxy)-8β-(tert-butoxy)cholane (3v, 3.62 g) in 40 mL of 2-butanone was heated to reflux under Ar for 45 min, then cooled to 24 °C for 15 h. The mixture was diluted with ether, washed with water, 2M Na₂S₂O₃, water and brine, dried (MgSO₄), filtered and
concentrated to give 3.10 g of De-A,B-23,24-dinor-22-iodo-8β-(tert-butoxy)cholane (3w), m.p. 84-89 °C. The analytical sample, m.p. 89-91 °C, was secured by recrystallization from methanol.


Found: C, 54.08; H, 8.27.

(B) A solution of 3w (2.85 g) and triisopropyl phosphite (21 mL) was stirred and heated to 150 °C under Ar for 1.5 h. The excess triisopropyl phosphite was removed by rotary evaporation (100 °C, -1 mmHg) and the residue was purified by chromatography on silica (25% EtOAc-hexane) to give 2.65 g of 3x as an oil.

NMR (CDCl₃) δ 0.89 (s, 3H), 1.10 (s, 9H), 1.12 (d, 3H), 1.31 (dd, 12H); 1.0 - 2.0 (m, 15H), 3.75 (br s, 1H), 4.7 (m, 2H). NMR (³¹P, CDCl₃) δ 30.52.

Example 42:
De-A,B-8β-(benzylloxy)-23-oxcholestan-25-oI (3z).

Lithium wire (1% Na) (0.21 g) was added in 0.2-cm portions to a stirred, ice-cooled solution of 4,4′-di-t-butylbiphenyl (8.5 g) in 90 mL of anhydrous THF under Ar. After stirring vigorously for 5.5 h, the deep blue-green solution was cooled to -70 °C. Isobutylene oxide (1.35 g) was added via syringe, keeping T ≤ 65 °C. After 6 min, a solution of De-A,B-23,24-dinor-8β-(benzylloxy)cholan-22-carboxaldehyde (3y, 2.41 g) in 10 mL of anhydrous THF was added rapidly. The stirred mixture was allowed to warm to 8 °C over 4 h, and was then quenched with sat. KH₂PO₄ and stirred for 15 h. The phases were separated and the aqueous solution was extracted with ether. The combined organic extracts were dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silica to give 2.14 g of a viscous oil. Pyridinium chlorochromate (PCC) (0.85 g) was added to a stirred solution of 0.60 g of this oil in 25 mL of dry CH₂Cl₂. After 3 h, a 0.89-g portion of PCC was added, and stirring was continued for 15 h. The mixture was eluted through Florisil with ether, and the concentrated eluate was purified by chromatography on silica (25% EtOAc-hexane) to give 0.36 g of the title compound as an oil.

NMR (DMSO-d₆) δ 0.81 (d, 3H), 0.90 (s, 3H), 1.12 (s, 6H), 1.2-2.0 (m, 13H), 2.3 (ABX, 2H), 2.45 (m, 2H), 3.63 (br s, 1H), 4.4 (AB, 2H), 4.60 (s, 1H), exchanges), 7.30 (s, 5H)
We Claim:

1. Use of a pharmaceutically effective amount of a substituted hydrindane or a pharmaceutically acceptable salt or ester of a substituted hydrindane for controlling neovascularization in warm blooded animals.

2. The use of Claim 1 wherein the substituted hydrindane has the following structure

\[
\begin{align*}
\text{where } X & \text{ is } \text{OH, OR}_1, \text{ OR}_2, \text{OS(O)}_2\text{R}_3, \text{ON=CHR}_1, \text{ON=CR}_1\text{R}_1, \text{CN, R}_1, \text{R}_2, \\
& \text{CH(OH)R}_2, \text{CH(OR)}_2\text{R}_2, \text{CH(OR)}_2\text{R}_2, \text{C(OH)R}_1\text{R}_1, \text{C(OR)}_1\text{R}_1\text{R}_1, \text{C(OR)}_2\text{R}_1\text{R}_1, \\
& \text{C(OH)}_2\text{R}_1\text{R}_2, \text{C(OR)}_1\text{R}_1\text{R}_2, \text{C(OR)}_2\text{R}_1\text{R}_2, \text{C(OH)}_2\text{R}_1\text{R}_2, \text{C(OH)}_1\text{R}_2\text{R}_2, \\
& \text{C(OR)}_2\text{R}_2\text{R}_2, \text{S=O)}_n\text{H}, \text{S=O)}_n\text{R}_1, \text{SR}_2, \text{P(=O)R}_1\text{R}_1, \text{P(=O)(OH)}_2, \\
& \text{P(=O)(OH)}\text{(OR)}_1, \text{P(=O)(OR)}_1\text{(OR)}_1, \text{P(=O)(OH)(NH)}_2, \text{P(=O)(OR)}_1\text{(NH)}_2, \\
& \text{P(=O)(OH)(NHR)}_1, \text{P(=O)(OH)(NR)}_1\text{R}_1, \text{P(=O)(OR)}_1\text{(NHR)}_1, \\
& \text{P(=O)(OR)}_1\text{(NR)}_1\text{R}_1, \text{NH}_2, \text{NHR}_1, \text{NHR}_2, \text{NR}_1\text{R}_1, \text{NR}_1\text{R}_2, \text{NHOH, N(OH)R}_1, \\
& \text{N(OH)}_2\text{R}_2, \text{NH(OR)}_1\text{R}_1, \text{NH(OR)}_2\text{R}_2, \text{N(OR)}_1\text{R}_1, \text{N(OR)}_2\text{R}_1, \text{N(OR)}_2\text{R}_2, \text{N(OR)}_1\text{R}_1, \\
& *\text{S(R)}_1\text{(R)}_1\text{Q}^*, *\text{N(R)}_1\text{(R)}_1\text{(R)}_1\text{Q}^* \text{wherein } Q^* \text{ is a halide, sulfonate, or carboxylate anion; C(=O)R}_1, \text{C(=O)R}_2, \text{C(=O)NH}_2, \text{C(=O)NHR}_1, \text{C(=O)NR}_1\text{R}_1, } \\
& \text{C(=O)N(OH)R}_1, \text{C(=O)N(OR)}_1\text{R}_1, \text{C(=O)N(OR)}_2\text{R}_1;} \text{ or }
\end{align*}
\]
n = 0, 1 or 2;
R₁ is aryl, haloaryl, C₁ - C₁₀ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR₃, or 6 OR₂; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C₁₋C₆ alkyl groups;
R₂ is C(=O)H, C(=O)R₁, C(=O)OR₁, C(=O)OH, C(=O)NH₂, C(=O)NHR₁, C(=O)NR₁R₂;
R₃ is aryl, haloaryl, C₁ - C₁₀ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;
R₄ is H, (=O), OR₂, OR₁, OH, =NOH, =NOR₁, =NOR₂;
R₅ and R₆ are independently H, CH₃ or CH₂CH₃;
Y is H, OH, OR₁, OR₂ or (=O), with the proviso that if Y is OH, then X is R₁, R₂, CH(OH)R₂, CH(OR₁)R₂, CH(OR₂)R₂, C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂, C(OH)R₂R₂, C(OR₁)R₂R₂, C(OR₂)R₂R₂, and if Y is (=O) then X is R₁, R₂, CH(OH)R₂, CH(OR₁)R₂, CH(OR₂)R₂, C(OH)R₁R₂, C(OR₁)R₁R₂, C(OR₂)R₁R₂, C(OH)R₂R₂, C(OR₁)R₂R₂, C(OR₂)R₂R₂, NH₂, NHR₁, NR₁R₁, NH₂OH, N(OH)R₁, NH(OR₁), NH(OR₂), N(OR₁)R₁, or N(OR₂)R₁; and
R₇ and R₈ are independently H or C₁ to C₆ alkyl, branched alkyl, hydroxyalkyl, optionally unsaturated; or R₇ and R₈ together form a double bond.

3. Use according to Claim 1 wherein the concentration of substituted hydridane being administered is from 0.0001 to 1 weight percent.

4. Use according to Claim 1 wherein the amount of substituted hydridane being administered is from 1 - 2000 mg.

5. Use of a pharmaceutically effective amount of a substituted hydridane selected from the group consisting of De-A,B-26-(benzoyloxy)-25-
methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
De-A, B-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
and De-A, B-23-thiacholestan-8β, 25-diol-23-dioxide-8β, 25-bis(4-bromophenyl)
carbamate.

6. A substituted hydridane having the formula

\[
\begin{align*}
\text{where } X \text{ is } & \text{C(OH)}R_1R_1, \text{C(OR)}R_1R_1, \text{C(OR)}_2R_1R_2, \text{C(OH)}R_1R_2, \text{C(OR)}_2R_1R_2, \\
& \text{C(OH)}R_2R_2, \text{C(OR)}R_2R_2, \text{C(OR)}_2R_2R_2, \text{C(OH)}R_2R_2, \text{C(OR)}_2R_2R_2, S(=O)\_nH, S(=O)\_nR_1, SR_2, \\
& P(=O)R_1R_1, P(=O)(OH)R_1, P(=O)(OH)(OR), P(=O)(OR)(OR), \\
& P(=O)(OH)(NH_2), P(=O)(OH)(NH)(OR), P(=O)(OH)(NR)(NR), \\
& P(=O)(OR)NRNR, P(=O)(OR)NRNR, NH_2, NHNR, NRNR, NRNR, NRNR, \\
& \text{NHOH, N(OH)R}1, \text{N(OH)R}2, \text{NH(OR)}, \text{NH(OR)}, \text{N(OR)R}2, \text{N(OR)R}1, \\
& \text{N(OR)R}2, \text{N(OR)R}1, \text{N}(=O)R_1R_1, \text{N}(=O)R_2R_2, \text{N}(=O)R_1R_1, \\
& \text{N}(=O)R_2R_2, \text{N}(=O)R_1R_1, \text{N}(=O)NR_1R_1, \text{N}(=O)NR_1R_1, \\
& \text{N}(=O)NR_2R_2, \text{N}(=O)NR_1R_1, \text{N}(=O)NR_2R_1, \text{n} = 0, 1 \text{ or } 2;
\end{align*}
\]

\[R_1\text{ is aryl, haloaryl, } C_1 - C_{10} \text{ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or}
\]
haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR, or 6 OR;

or 6 OR; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl,
isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to

three halogen or C_1 - C_6 alkyl groups;

\[R_2 \text{ is } C(=O)\_nH, C(=O)R_1, C(=O)OR_1, C(=O)OH, C(=O)NH_2, C(=O)NR_1R_1; \]

\[R_3 \text{ is aryl, haloaryl, } C_1 - C_{10} \text{ alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or}
\]
haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

\[R_4 \text{ is } H, \text{ OR}_2, \text{ OR}_1, \text{ OH, } =\text{NOH}, =\text{NOR}_1, =\text{NOR}_2; \text{ and provided that if } X \text{ is}
\]

\[\text{S(=O)}_2\text{(optionally substituted phenyl)} \text{ then } R_4 \neq \text{ OH, or } (=O); \text{ and}
\]

\[R_7 \text{ and } R_8 \text{ are H or together are optionally a double bond;}
\]
and wherein aryl denotes phenyl, naphthyl, furanyl, thiophenyl, pyridyl, benzofuryl, indolyl, benzothiophenyl, quinolyl or isoquinolyl;

R₁R₂, attached to the same C, S, P or N atom can form a ring of from 3 through 7 members; and

for those substituents containing more than one R₁, R₂, or R₃, each R₁, R₂, or R₃ may be the same or different;
or a pharmaceutically acceptable salt or ester thereof.

7. A substituted hydridane according to Claim 6 wherein the hydridane has the formula

![Chemical Structure](image)

8. A substituted hydridane according to Claim 7 wherein the hydridane is selected from the group consisting of De-A,B-26-(benzoyloxy)-25-methyl-23-thiacholen-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
De-A,B-24-phenyl-23-thiacholen-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate,
and De-A,B-23-thiacholen-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate.

9. A process for preparing 3-bromo-(2,2-dimethyl)propyl benzoate which comprises the step of
reacting 5,5-dimethyl-2-phenyl-1,3-dioxane with N-bromosuccinimide in an inert solvent.
### I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC:
- Int.Cl.5: A 61 K 31/325, A 61 K 31/045, A 61 K 31/16
- A 61 K 31/19: C 07 C 323/52, C 07 C 317/18, C 07 C 309/73

### II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched.

### III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>D, A</td>
<td>EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 178, no. 2, 20 March 1990 Amsterdam, NL, pages 247 - 250 T. OIKAWA, ET AL.: 'Inhibition of angiogenesis by vitamin D3 analogues' cited in the application see the whole document</td>
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<td>A</td>
<td>EP,A,0230600 (TEVA PHARMACEUTICAL INDUSTRIES) 5 August 1987 see compounds II, IX; examples 1, 2</td>
<td>6</td>
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* 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
  - "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

### IV. CERTIFICATION

- Date of the Actual Completion of the International Search: 02-11-1993
- Date of Mailing of this International Search Report: 7. 02. 94
- International Searching Authority: EUROPEAN PATENT OFFICE
- Signature of Authorized Officer: R. English
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| A        | EP, A, 0115314 (HOFFMANN-LA ROCHE) 8  
August 1984  
see compounds VII, X; examples 6, 8 | 6                     |
INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/07759

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. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 1-5 are directed to methods of treatment of the human or animal body (Rule 39.1(iv)PCT), the search has been carried out and based on the alleged effects of the compounds.

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:

   For further information please see Form PCT/ISA/206 dated 06/12/93.

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 searches 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. X 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.:

   1-5(part.), 6-8

Remark on Protest

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

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. US 9307759  
SA 78350

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office FIJP file on 02/02/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82