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DIVISION DE NUEVAS CREACIONES

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Ref: Expediente No. 06-068.392

Solicitud de patente de invención titulada:

"MODULADORES DEL RECEPTOR SELECTIVO PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES."

Solicitante: ELI-LILLY AND COMPANY

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$420.000 pesos

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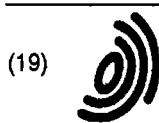
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DECLARATION OF INTEREST
IN THE MATTER OF THE EMBASSY OF THE UNITED STATES

I, JOHN R. CLARK, of the City of Washington, District of Columbia, do hereby declare that I am not a member of, nor am I connected with, any organization, firm, or individual, which is or has been engaged in any activity which is prohibited by the laws of the United States, and that I am not a member of, nor am I connected with, any organization, firm, or individual, which is or has been engaged in any activity which is prohibited by the laws of the United States.

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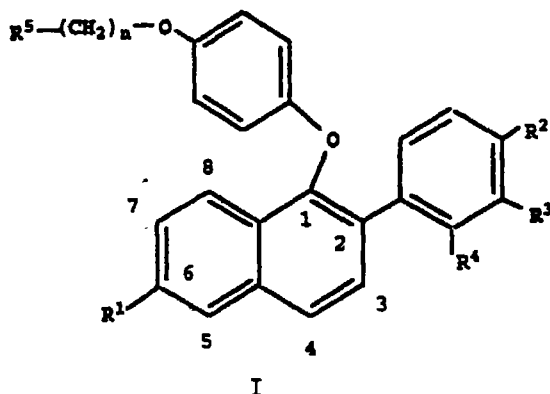
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(54) Naphthyl compounds, intermediates, compositions, and method of use

(57) The instant invention provides novel substituted naphthyl compounds, intermediates, compositions, pharmaceutical formulations, and methods of use. The novel naphthyl compounds have the formula



wherein

R¹ is -H, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -O(CO)OAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl);
R² is -H, -F, -Cl, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -O(CO)OAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl);
R³ and R⁴ are, independently, -H, -F, -Cl, -CH₃, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl), with the proviso that both R³ and R⁴ cannot be hydrogen;
n is 2 or 3; and

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Description

Osteoporosis describes a group of diseases which arises from diverse etiologies, but which are characterized by the net loss of bone mass per unit volume. The consequence of this loss of bone mass and resulting bone fracture is the failure of the skeleton to provide adequate support for the body. One of the most common types of osteoporosis is associated with menopause. Most women lose from about 20% to about 60% of the bone mass in the trabecular compartment of the bone within 3 to 6 years after the cessation of menses. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among postmenopausal women.

There are an estimated 25 million women in the United States alone who are afflicted with this disease. The results of osteoporosis are personally harmful, and also account for a large economic loss due to its chronicity and the need for extensive and long term support (hospitalization and nursing home care) from the disease sequelae. This is especially true in more elderly patients. Additionally, although osteoporosis is generally not thought of as a life threatening condition, a 20% to 30% mortality rate is related to hip fractures in elderly women. A large percentage of this mortality rate can be directly associated with postmenopausal osteoporosis.

The most vulnerable tissue in the bone to the effects of postmenopausal osteoporosis is the trabecular bone. This tissue is often referred to as spongy or cancellous bone and is particularly concentrated near the ends of the bone (near the joints) and in the vertebrae of the spine. The trabecular tissue is characterized by small osteoid structures which interconnect with each other, as well as the more solid and dense cortical tissue which makes up the outer surface and central shaft of the bone. This interconnected network of trabeculae gives lateral support to the outer cortical structure and is critical to the biomechanical strength of the overall structure. In postmenopausal osteoporosis, it is primarily the net resorption and loss of the trabeculae which leads to the failure and fracture of bone. In light of the loss of the trabeculae in the postmenopausal woman, it is not surprising that the most common fractures are those associated with bones which are highly dependent on trabecular support, for example, the vertebrae, the neck of the weight-bearing bones such as the femur and the forearm. Indeed, hip fracture, colles fractures, and vertebral crush fractures are hallmarks of postmenopausal osteoporosis.

The most generally accepted method for the treatment of postmenopausal osteoporosis is estrogen replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low, primarily because estrogen treatment frequently produces undesirable side effects. An additional method of treatment would be the administration of a bisphosphonate compound, such as, for example, Fosamax® (Merck & Co., Inc.).

Throughout premenopausal time, most women have less incidence of cardiovascular disease than men of the same age. Following menopause, however, the rate of cardiovascular disease in women slowly increases to match the rate seen in men. This loss of protection has been linked to the loss of estrogen and, in particular, to the loss of estrogen's ability to regulate the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not well understood, but evidence to date indicates that estrogen can up regulate the low density lipid (LDL) receptors in the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of cholesterol, and other beneficial effects on cardiovascular health.

It has been reported in the literature that serum lipid levels in postmenopausal women having estrogen replacement therapy return to concentrations found in the premenopausal state. Thus, estrogen would appear to be a reasonable treatment for this condition. However, the side effects of estrogen replacement therapy are not acceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent which regulates serum lipid levels in a manner analogous to estrogen, but which is devoid of the side effects and risks associated with estrogen therapy.

In response to the clear need for new pharmaceutical agents which are capable of alleviating the symptoms of, *inter alia*, postmenopausal syndrome, the present invention provides naphthyl compounds, pharmaceutical formulations thereof, and methods of using such compounds for the treatment of postmenopausal syndrome and other estrogen-related pathological conditions such as those mentioned below.

Thus, it would be a significant contribution to the art to provide novel substituted naphthyl compounds useful, for example, in the inhibition, treatment, or prevention of the disease states as indicated herein.

The present invention provides compounds of formula I:

In the first step of the present process, a compound of formula III is converted to a phenol of formula IVc via a three-step protocol, essentially as described by Wang, G., *et al.*, *M. Syn. Commun.*, 21:989 (1991). In essence, a formula III ketone is enolized by refluxing a solution of an acetylenolic ester solvent, in the presence of an acid catalyst. The resulting enolacetate is directly converted to a naphtholacetate which is then hydrolyzed to a phenol of formula IVc.

In converting a ketone of formula III to its respective enol acetate, various known acid catalysts can be used. Preferably, non-aqueous acids, and particularly, *p*-toluenesulfonic acid is preferred. A preferred acetylenolic ester solvent would be isopropenyl acetate.

When run at reflux, the present reaction takes from about 6 to about 48 hours to complete. The enol product from this reaction is not isolated, but upon completion of the reaction, the resulting solution is treated with an appropriate oxidant and heated to reflux for, optimally, about 1 to about 3 hours.

Appropriate oxidants for this second phase of the first reaction step shown in Scheme I are limited to those known in the art which can lead to the elimination of hydrogen from a saturated system to give an aromatized system. Such oxidants include, for example, de-hydrogenation catalysts such as platinum, palladium, and nickel, elemental sulfur and selenium, and quinones. For the present application, quinone oxidants, especially 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) are preferred. About 1 to 2 equivalents of DDQ per equivalent of substrate will drive the present process phase.

The resulting product of the present phase, a 1-naphthol ester, is then subjected to hydrolysis to provide a compound of formula IVc, thus completing the first process step shown in Scheme I. The present hydrolysis phase is accomplished via either acid or basic hydrolysis of the substrate in a polar protic solvent such as water or one or more solvents containing an alcohol such as methanol or ethanol. A cosolvent such as tetrahydrofuran (THF) or dioxane also may be added to the solution to aid solubility. Appropriate bases for this phase include sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like. Appropriate acids include, for example, hydrochloric acid, methanesulfonic acid, *p*-toluenesulfonic acid, and the like. A preferred acid would be hydrochloric acid.

This final phase of the first step shown in Scheme I, *supra*, can be run at ambient temperature and runs in a short period of time, typically from 1 to about 12 hours. Completion of the present reaction can be determined via standard chromatographic techniques such as thin layer chromatography.

In the second step of Scheme I, a phenol of formula IVc is first reacted with a base, followed by the addition of a 4-halobenzaldehyde or 4-halobenzoketone, in a polar aprotic solvent, under an inert atmosphere such as nitrogen, to give a biarylether of formula IIa. This reaction is well known in the art and is carried out essentially as described by Yeager, G.W., *et al.*, *Synthesis*, 63 (1991).

More particularly, 1 equivalent of a formula IVc compound is first treated with at least 1 equivalent of an alkali metal hydride or carbonate in an appropriate solvent, followed by a dropwise addition of a 4-halobenzaldehyde in the same solvent as used with the substrate. Appropriate solvents for this reaction are those solvents or mixture of solvents which remain inert throughout the reaction. *N,N*-dimethylformamide (DMF), especially the anhydrous form thereof, is preferred. Preferably, sodium hydride is used as the required base, and 4-fluorobenzaldehyde is used as the preferred 4-halobenzaldehyde.

The temperature employed in this step of the present process should be sufficient to effect completion of this reaction, without encouraging the formation of undesirable by-products. A preferred temperature range for this reaction is from about 30° C to about 100° C. Under preferred reaction conditions, a formula IIa compound will be prepared via the preferred process in about 24 to about 48 hours.

The final reaction shown in Scheme I, the conversion of the aldehyde moiety of a formula IIa compound to a phenol group, thus forming a compound of formula IIb, is known in the art as a Bayer-Villiger oxidation. See, e.g., Fiesers, L., *et al.*, *Reagents for Organic Synthesis*, 1:467, Wiley (New York, 1967); Hassall, C.H., *Organic Reactions*, 9:73-106 (Wiley, New York, 1967).

In general, the present reaction involves the combination of a benzaldehyde with a peracid such as peracetic acid or *m*-chloroperbenzoic acid in an inert solvent such as chloroform or methylenechloride. The product of this reaction, a formate ester, can then be readily hydrolyzed to the desired phenol. See, for example, Yeager, *et al.*, *supra*; Godfrey, I.M., *et al.*, *J. Chem. Soc. Perkins. Trans. I*:1353 (1974); and Rue, R., *et al.*, *Bull. Soc. Chim. Fr.*, 3617 (1970).

For the present reaction, a preferred variation is described by Matsumoto, M., *et al.*, *J. Org. Chem.*, 49:4741 (1984). This method involves combining a benzaldehyde of formula IIa with at least 1 to about 2 equivalents of 30% hydrogen peroxide in an alcohol solvent, and in the presence of a catalytic acid. Under these conditions, the phenol is formed directly, and the need for an additional hydrolysis step is, therefore, eliminated. The preferred solvent and acid catalyst for the present reaction is methanol and concentrated sulfuric acid, respectively. Under the preferred reaction conditions, the transformation from a formula IIa compound to a formula IIb compound is complete after stirring for about 12 to about 48 hours at ambient temperatures.

Compounds of formula II, IIa, and IIb are useful as intermediate compounds in the preparation of pharmaceutically active compounds of formula I of the present invention. Upon preparation of a formula IIb compound, it is reacted with a compound of formula V

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amount of an additional therapeutic agent, including but not limited to estrogen, progestin, benzothiofene compounds having including raloxifene, naphthyl compounds having antiestrogen activity, bisphosphonate compounds such as alendronate and tiludronate, parathyroid hormone (PTH), including truncated and/or recombinant forms of PTH such as, for example, PTH (1-34), calcitonin, bone morphogenic proteins (BMPs), or combinations thereof. The different forms of these additional therapeutic agents available as well as the various utilities associated with same and the applicable dosing regimens are well known to those of skill in the art.

Various forms of estrogen and progestin are commercially available. As used herein, the term "estrogen" includes compounds having estrogen activity and estrogen-based agents. Estrogen compounds useful in the practice of the present invention include, for example, estradiol estrone, estriol, equilin, equilenin, estradiol cypionate, estradiol valerate, ethynyl estradiol, polyestradiol phosphate, estropipate, diethylstilbestrol, dienestrol, chlorotrianisene, and mixtures thereof. Estrogen-based agents, include, for example, 17-a-ethynyl estradiol (0.01-0.03 mg/day), mestranol (0.05-0.15 mg/day), and conjugated estrogenic hormones such as Premarin® (Wyeth-Ayerst; 0.2-2.5 mg/day). As used herein, the term "progestin" includes compounds having progestational activity such as, for example, progesterone, norethynodrel, norgestrel, megestrol acetate, norethindrone, progestin-based agents, and the like. Progestin-based agents include, for example, medroxyprogesterone such as Provera® (Upjohn; 2.5-10 mg/day), norethynodrel (1.0-10.0 mg/day), and norethindrone (0.5-2.0 mg/day). A preferred estrogen-based compound is Premarin®, and norethynodrel and norethindrone are preferred progestin-based agents. The method of administration of each estrogen- and progestin-based agent is consistent with that known in the art.

The formulations which follow are given for purposes of illustration and are not intended to be limiting in any way. The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. The term "active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules	
Ingredient	Quantity (mg/capsule)
Active Ingredient	0.1-1000
Starch NF	0-500
Starch flowable powder	0-500
Silicone fluid 350 centistokes	0-15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Formulation 2: Tablets	
Ingredient	Quantity (mg/tablet)
Active Ingredient	2.5-1000
Starch	10-50
Cellulose, microcrystalline	10-20
Polyvinylpyrrolidone (as 10% solution in water)	5
Sodium carboxymethylcellulose	5
Magnesium stearate	1
Talc	1-5

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules thus produced are dried at 50-60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethylcellulose, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are added to the above granules and thoroughly mixed. The resultant material is compressed in a tablet forming machine to yield the tablets.

Formulation 3: Aerosol	
Ingredient	Weight %
Active Ingredient	0.25
Ethanol	29.75
Propellant 22 (Chlorodifluoromethane)	70.00

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(continued)

Formulation 3: Aerosol	
Ingredient	Weight %
Total	100.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to - 30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4: Suppositories	
Ingredient	Weight
Active ingredient	150 mg
Saturated fatty acid	glycerides 3000mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the fatty acid glycerides which had previously heated to their melting point. The mixture is poured into a suppository mold and allowed to cool.

Formulation 5: Suspension	
Suspensions each containing 0.1-1000 mg of a compound of formula I per 5 mL dose.	
Ingredient	Weight
Active Ingredient	0.1-1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution (0.1M)	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	Total 5 mL

A compound of formula I is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color diluted in water are added and mixture stirred thoroughly. Additional water is added to bring the formulation to final volume.

The following examples and preparations are provided to better elucidate the practice of the present invention and should not be interpreted in any way as to limit the scope of same. Those skilled in the art will recognize that various modifications may be made while not departing from the spirit and scope of the invention. All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains.

EXAMPLES

NMR data for the following Examples were generated on a GE 300 MHz NMR instrument, and anhydrous d-6 DMSO was used as the solvent unless otherwise indicated.

Preparation 1

2,4-di-(3-methoxyphenyl)butyric Acid

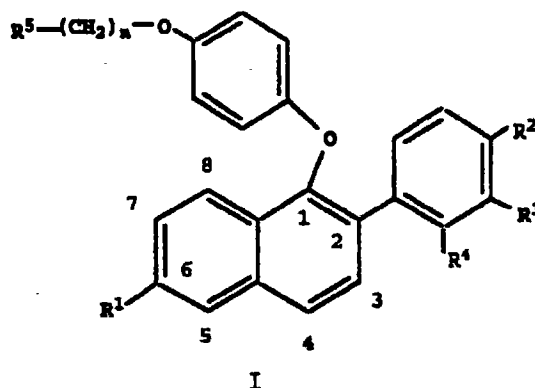
A solution of 50.68 g (305 mmol) of 3-methoxyphenylacetic acid in 1.4 L of anhydrous THF was prepared and cooled to -70° C under a nitrogen atmosphere. Slowly, 400 mL of 1.6 M (640 mmol) of n-butyl lithium was added and the solution was allowed to stir for two hours at -70° C. A solution of 72.1 g (335 mmol) of 2-(3-methoxyphenyl)ethylbromide in 100 mL of THF was added and the reaction was allowed to proceed for sixteen hours, while slowly warming

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Claims

1. A compound of formula I



wherein

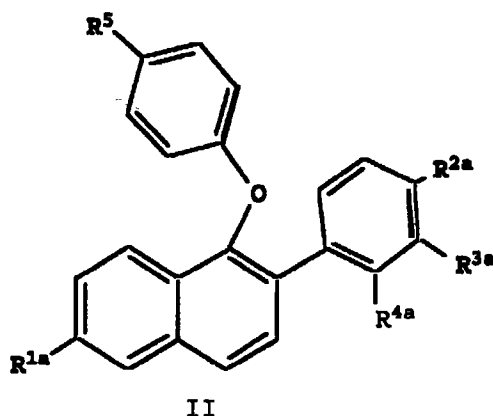
- R¹ is -H, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -O(CO)OAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl);
 R² is -H, -F, -Cl, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -O(CO)OAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl);
 R³ and R⁴ are, independently, -H, -F, -Cl, -CH₃, -OH, -O(C₁-C₄ alkyl), -OCOAr where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl), with the proviso that both R³ and R⁴ cannot be hydrogen;
 n is 2 or 3; and
 R⁵ is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to Claim 1 wherein R¹ and R³ each are -OH.
3. A compound according to Claim 1 wherein R¹ is hydroxy and R³ is methoxy.
4. A compound according to Claim 1 wherein R¹ is methoxy and R³ is hydroxy.
5. A compound according to Claim 1 wherein n is two and R⁵ is 1-piperidinyl.
6. A compound according to Claim 1 wherein said salt thereof is the hydrochloride salt.
7. A compound according to Claim 1 wherein R¹ and R³ each are -OH, R⁵ is piperidinyl, n is two, and said salt thereof is the hydrochloride salt.
8. A compound according to Claim 1 wherein R¹ is hydroxy, R³ is methoxy, R⁵ is piperidinyl, n is two, and said salt thereof is the hydrochloride salt.
9. A compound according to Claim 1 wherein R¹ is methoxy, R³ is hydroxy, R⁵ is piperidinyl, n is two, and said salt thereof is the hydrochloride salt.
10. A compound according to Claim 1 selected from the group consisting of
- 1-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene hydrochloride,
 1-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(3-methoxyphenyl)naphthalene hydrochloride,
 1-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(3-hydroxyphenyl)-6-hydroxynaphthalene hydrochloride,

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1-[4-{2-(1-piperidinyl)ethoxy}phenoxy]-2-(3-hydroxyphenyl)naphthalene hydrochloride,
1-[4-{2-(1-piperidinyl)ethoxy}phenoxy]-2-(3-hydroxyphenyl)-6-methoxynaphthalene hydrochloride, and
1-[4-{2-(1-piperidinyl)ethoxy}phenoxy]-2-(3-methoxyphenyl)-6-hydroxynaphthalene hydrochloride.

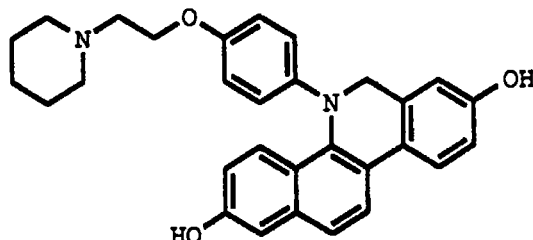
- 5 11. A pharmaceutical composition comprising as an active ingredient a compound as claimed in any of Claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, and optionally an effective amount of estrogen or progestin, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients.
12. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of postmenopausal syndrome.
13. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of the postmenopausal syndrome pathological condition of osteoporosis.
14. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of the postmenopausal syndrome pathological condition related to a cardiovascular disease.
15. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of a cardiovascular disease related to hyperlipidemia.
16. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of the postmenopausal syndrome pathological condition of estrogen-dependent cancer.
17. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of breast or uterine cancer.
18. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of uterine fibroid disease.
19. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of endometriosis.
20. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of aortal smooth muscle cell proliferation.
21. A compound of formula I as claimed in any of Claims 1-10 for use in alleviating the symptoms of restenosis.
22. A compound of formula II



wherein:

Example 14

2,8-Dihydroxy-5-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6H-benzo[*a*]phenanthridine

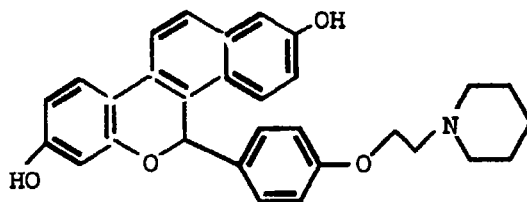


A solution of the product of Example 13 (195 mg, 0.39 mmol) in methylene chloride (25 mL) was treated with ethanethiol (200 mg, 220 mL, 3.2 mmol) and aluminum chloride (320 mg, 2.4 mmol). After stirring for 4 h at ambient temperature, the mixture was quenched carefully with THF (25 mL) and saturated sodium bicarbonate (25 mL). The layers were separated, the aqueous layer was extracted with THF (25 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by radial chromatography (silica gel, 1:1 hexane:ethyl acetate, 10-20% methanol, under an ammonia atmosphere) to provide 110 mg (60%) of the title compound as a tan foam. An analytical sample was crystallized from methanol as a light red solid: ^1H NMR (300 MHz, dimethylformamide- d_7) δ 9.92 (br s, 1H), 9.74 (br s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 9.0, 2.1 Hz, 1H), 6.84 (dd, J = 8.4, 2.1 Hz, 1H), 6.73 (m, 5H), 3.92 (t, J = 5.9 Hz, 2H), 2.57 (t, J = 5.9 Hz, 2H), 2.38 (m, 4H), 1.4-1.5 (m, 4H), 1.3-1.4 (m, 2H); IR (KBr) 3560, 3490 cm^{-1} ; MS (FD+) m/e 466 (M^+); Anal. calc'd. for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 75.75; H, 6.58; N, 5.89. Found: C, 75.82; H, 6.76; N, 5.95.

Example 15

2, 8-dihydroxy-5-[4-[2-(1-piperidinyl)-ethoxy]phenyl]-5H-benzo[*b*]naphtho[2,1-*d*]pyran

This compound is prepared in accordance with the foregoing teaching and examples.



In the examples illustrating the methods, a post-menopausal model was used in which effects of different treatments upon circulating lipids were determined.

Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had *ad libitum* access to food (calcium content approximately 0.5%) and water for one week. Room temperature was maintained at $22.2^\circ \pm 1.7^\circ \text{C}$ with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

Dosing Regimen Tissue Collection.

After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound was initiated. 17 α -ethynyl estradiol or the test compound were given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or dissolved in 20% cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen, animals were weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture and a blood sample was

collected by cardiac puncture. The animals were then sacrificed by asphyxiation with CO₂, the uterus was removed through a midline incision, and a wet uterine weight was determined.

Cholesterol Analysis.

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Blood samples were allowed to clot at room temperature for 2 hours, and serum was obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol was oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotometrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire assay was automated using a Biomek Automated Workstation.

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Uterine Eosinophil Peroxidase (EPO) Assay.

Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH - 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM O-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of eosinophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval was determined over the initial, linear portion of the reaction curve.

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Source of Compound:

17 α -ethynyl estradiol was obtained from Sigma Chemical Co., St. Louis, MO.

Influence of Formula I and II Compounds on Serum Cholesterol and Determination of Agonist/Non-Agonist Activity

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Data presented in Table 1 below show comparative results among ovariectomized rats, rats treated with 17 α -ethynyl estradiol (EE₂; an orally available form of estrogen), and rats treated with certain compounds of the present invention. Although EE₂ caused a decrease in serum cholesterol when orally administered at 0.1 mg/kg/day, it also exerted a stimulatory action on the uterus so that EE₂ uterine weight was substantially greater than the uterine weight of ovariectomized test animals. This uterine response to estrogen is well recognized in the art.

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Not only did the compounds of the present invention generally reduce serum cholesterol compared to the ovariectomized control animals, but uterine weight was only minimally increased to slightly decreased with the majority of the formula compounds tested. Compared to estrogenic compounds known in the art, the benefit of serum cholesterol reduction without adversely affecting uterine weight is quite rare and desirable.

35

As is expressed in the below data, estrogenicity also was assessed by evaluating the adverse response of eosinophil infiltration into the uterus. The compounds of the present invention did not cause any increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, while estradiol cause a substantial, expected increase in eosinophil infiltration.

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The data presented in the Tables 1 below reflects the response of 5 to 6 rats per treatment.

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Table 1

<u>Compound</u>	<u>Dose</u> <u>mg/kg</u>	<u>Uterine Weight</u> <u>(% increase vs. OVX)</u>	<u>Uterine EPO</u> <u>(V. max)</u>	<u>Serum Cholesterol</u> <u>(% decrease vs. OVX)</u>
EE ₂	0.1	86.3	116.4	81.4
Example 1	0.1	25.3	7.8	72.8

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Osteoporosis Test Procedure

Following the General Preparation Procedure, infra, the rats were treated daily for 35 days (6 rats per treatment group) and sacrificed by carbon dioxide asphyxiation on the 36th day. The 35 day time period was sufficient to allow maximal reduction in bone density, measured as described herein. At the time of sacrifice, the uteri were removed, dissected free of extraneous tissue, and the fluid contents were expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight was routinely reduced about 75% in response to ovariectomy. The uteri were then placed in 10% neutral buffered formalin to allow for subsequent histological analysis.

The right femurs were excised and digitized x-rays generated and analyzed by an image analysis program (NIH image) at the distal metaphysis. The proximal aspect of the tibiae from these animals were also scanned by quantitative computed tomography.

In accordance with the above procedures, compounds of the present invention and ethynyl estradiol (EE₂) in 20% hydroxypropyl b-cyclodextrin were orally administered to test animals. Distal femur metaphysis data presented in Tables 2 and 3 below are the results of formula 1 compound treatments compared to intact and ovariectomized test animals. Results are reported as percent protection relative to ovariectomy.

Table 2

Compound/Treatment	Dose /kg	Distal Femur Metaphysis (X-ray Image Analysis-Gray Score)
EE2	0.1 mg	62.4*
Example 1	0.01 mg	14.2
	0.1 mg	49.8*
	1.0 mg	51.7*
	10.0 mg	48.2*

*P <= 0.5 two tailed Student's T Test on raw data.

In summary, ovariectomy of the test animals caused a significant reduction in femur density compared to intact, vehicle treated controls. Orally administered ethynyl estradiol (EE₂) prevented this loss, but the risk of uterine stimulation with this treatment is ever-present.

The compounds of the present invention also prevented bone loss in a general, dose-dependent manner. Accordingly, the compounds of the present invention are useful for the treatment of post-menopausal syndrome, particularly osteoporosis.

MCF-7 Proliferation Assay

MCF-7 breast adenocarcinoma cells (ATCC HTB 22) were maintained in MEM (minimal essential medium, phenol red-free, Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES [(N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid])10 mM], non-essential amino acids and bovine insulin (1 ug/mL) (maintenance medium). Ten days prior to assay, MCF-7 cells were switched to maintenance medium supplemented with 10% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) assay medium) in place of 10% FBS to deplete internal stores of steroids. MCF-7 cells were removed from maintenance flasks using cell dissociation medium (Ca++/Mg++ free HBSS (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA). Cells were washed twice with assay medium and adjusted to 80,000 cells/mL. Approximately 100 mL (8,000 cells) were added to flat-bottom microculture wells (Costar 3596) and incubated at 37° C in a 5% CO₂ humidified incubator for 48 hours to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs or DMSO as a diluent control were prepared in assay medium and 50 mL transferred to triplicate microcultures followed by 50 mL assay medium for a final volume of 200 mL. After an additional 48 hours at 37° C in a 5% CO₂ humidified incubator, microcultures were pulsed with tritiated thymidine (1 uCi/well) for 4 hours. Cultures were terminated by freezing at -70° C for 24 hours followed by thawing and harvesting of microcultures using a Skatron Semiautomatic Cell Harvester. Samples were counted by liquid scintillation using a Wallac BetaPlace b counter. Results in Table 3 below show the IC₅₀ for certain compounds of the present invention.

Table 3

Compound (Example Reference)	IC ₅₀ nM
1	0.2
2	100
3	3.0
4	5.0
5	1000
6	500
11	0.7
14	1

DMBA-Induced Mammary Tumor Inhibition

Estrogen-dependent mammary tumors are produced in female Sprague-Dawley rats which are purchased from Harlan Industries, Indianapolis, Indiana. At about 55 days of age, the rats receive a single oral feeding of 20 mg of 7,12-dimethylbenz[a]anthracene (DMBA). About 6 weeks after DMBA administration, the mammary glands are palpated at weekly intervals for the appearance of tumors. Whenever one or more tumors appear, the longest and shortest diameters of each tumor are measured with a metric caliper, the measurements are recorded, and that animal is selected for experimentation. An attempt is made to uniformly distribute the various sizes of tumors in the treated and control groups such that average-sized tumors are equivalently distributed between test groups. Control groups and test groups for each experiment contain 5 to 9 animals.

Compounds of Formula I are administered either through intraperitoneal injections in 2% acacia, or orally. Orally administered compounds are either dissolved or suspended in 0.2 mL corn oil. Each treatment, including acacia and corn oil control treatments, is administered once daily to each test animal. Following the initial tumor measurement and selection of test animals, tumors are measured each week by the above-mentioned method. The treatment and measurements of animals continue for 3 to 5 weeks at which time the final areas of the tumors are determined. For each compound and control treatment, the change in the mean tumor area is determined.

Uterine Fibrosis Test Procedures

Test 1

Between 3 and 20 women having uterine fibrosis are administered a compound of the present invention. The amount of compound administered is from 0.1 to 1000 mg/day, and the period of administration is 3 months.

The women are observed during the period of administration, and up to 3 months after discontinuance of administration, for effects on uterine fibrosis.

Test 2

The same procedure is used as in Test 1, except the period of administration is 6 months.

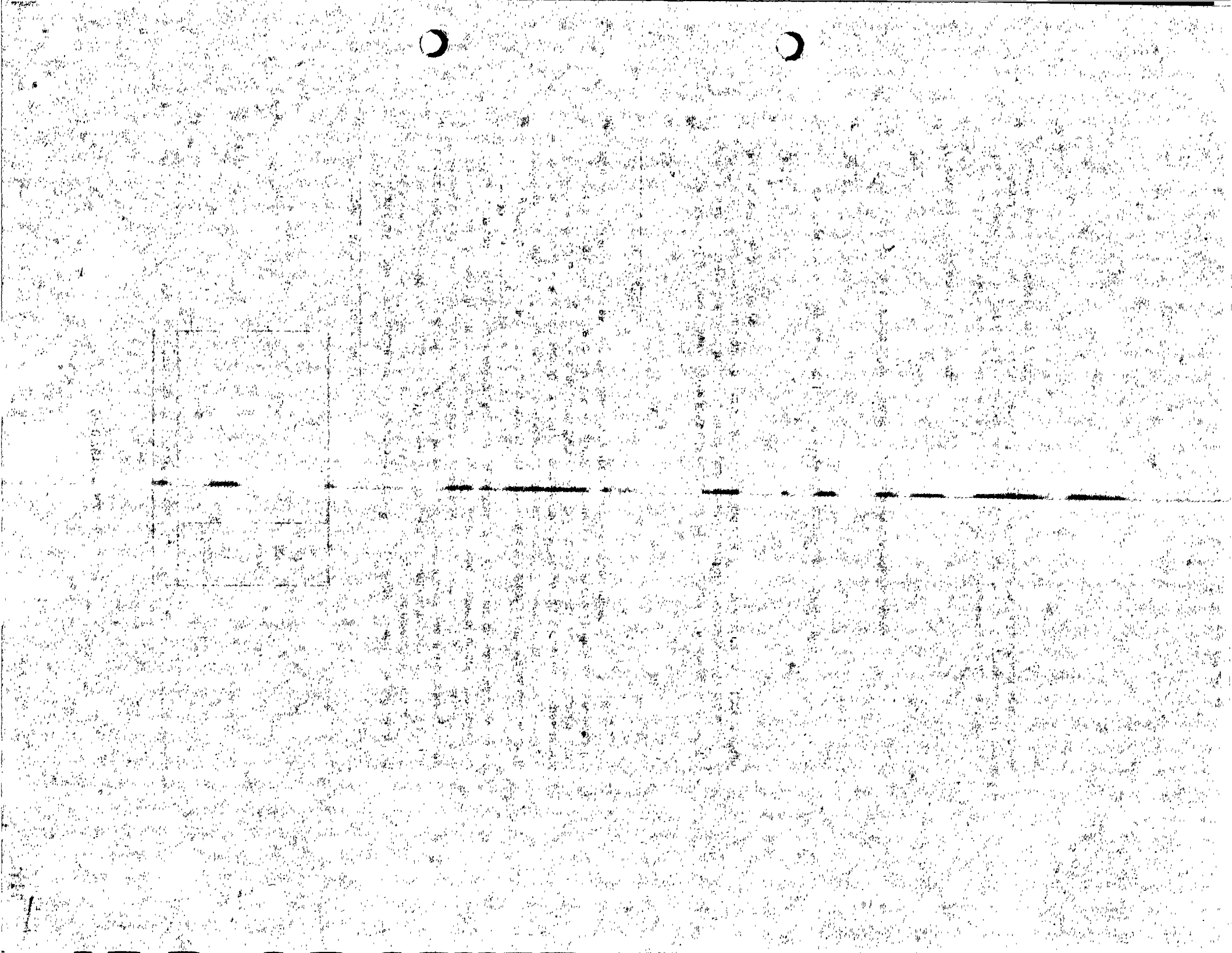
Test 3

The same procedure is used as in Test 1, except the period of administration is 1 year.

Test 4

A. Induction of fibroid tumors in guinea pig.

Prolonged estrogen stimulation is used to induce leiomyomata in sexually mature female guinea pigs. Animals are dosed with estradiol 3-5 times per week by injection for 2-4 months or until tumors arise. Treatments consisting of a compound of the invention or vehicle is administered daily for 3-16 weeks and then animals are sacrificed and the uteri harvested and analyzed for tumor regression.



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B. Implantation of human uterine fibroid tissue in nude mice.

Tissue from human leiomyomas are implanted into the peritoneal cavity and or uterine myometrium of sexually mature, castrated, female, nude mice. Exogenous estrogen are supplied to induce growth of the explanted tissue. In some cases, the harvested tumor cells are cultured *in vitro* prior to implantation. Treatment consisting of a compound of the present invention or vehicle is supplied by gastric gavage on a daily basis for 3-16 weeks and implants are removed and measured for growth or regression. At the time of sacrifice, the uteri are harvested to assess the status of the organ.

10 Test 5

A. Tissue from human uterine fibroid tumors is harvested and maintained, *in vitro*, as primary nontransformed cultures. Surgical specimens are pushed through a sterile mesh or sieve, or alternately teased apart from surrounding tissue to produce a single cell suspension. Cells are maintained in media containing 10% serum and antibiotic. Rates of growth in the presence and absence of estrogen are determined. Cells are assayed for their ability to produce complement component C3 and their response to growth factors and growth hormone. *In vitro* cultures are assessed for their proliferative response following treatment with progestins, GnRH, a compound of the present invention and vehicle. Levels of steroid hormone receptors are assessed weekly to determine whether important cell characteristics are maintained *in vitro*. Tissue from 5-25 patients are utilized.

Activity in at least one of the above tests indicates the compounds of the present invention are of potential in the treatment of uterine fibrosis.

Endometriosis Test Procedure

In Tests 1 and 2, effects of 14-day and 21-day administration of compounds of the present invention on the growth of explanted endometrial tissue can be examined.

Test 1

Twelve to thirty adult CD strain female rats are used as test animals. They are divided into three groups of equal numbers. The estrous cycle of all animals is monitored. On the day of proestrus, surgery is performed on each female. Females in each group have the left uterine horn removed, sectioned into small squares, and the squares are loosely sutured at various sites adjacent to the mesenteric blood flow. In addition, females in Group 2 have the ovaries removed.

On the day following surgery, animals in Groups 1 and 2 receive intraperitoneal injections of water for 14 days whereas animals in Group 3 receive intraperitoneal injections of 1.0 mg of a compound of the present invention per kilogram of body weight for the same duration. Following 14 days of treatment, each female is sacrificed and the endometrial explants, adrenals, remaining uterus, and ovaries, where applicable, are removed and prepared for histological examination. The ovaries and adrenals are weighed.

Test 2

Twelve to thirty adult CD strain female rats are used as test animals. They are divided into two equal groups. The estrous cycle of all animals is monitored. On the day of proestrus, surgery is performed on each female. Females in each group have the left uterine horn removed, sectioned into small squares, and the squares are loosely sutured at various sites adjacent to the mesenteric blood flow.

Approximately 50 days following surgery, animals assigned to Group 1 receive intraperitoneal injections of water for 21 days whereas animals in Group 2 receive intraperitoneal injections of 1.0 mg of a compound of the present invention per kilogram of body weight for the same duration. Following 21 days of treatment, each female is sacrificed and the endometrial explants and adrenals are removed and weighed. The explants are measured as an indication of growth. Estrous cycles are monitored.

Test 3

A. Surgical induction of endometriosis

Autographs of endometrial tissue are used to induce endometriosis in rats and/or rabbits. Female animals at reproductive maturity undergo bilateral oophorectomy, and estrogen is supplied exogenously thus providing a specific and constant level of hormone. Autologous endometrial tissue is implanted in the peritoneum of 5-150 animals and

the first two years after the onset of symptoms. The mean age at onset was 60 years (range 47–80). The mean duration of disease was 19 months (range 1–48). The mean age at death was 69 years (range 55–80).

[illegible]

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1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

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Figure 6 shows the results of the regression analysis. The adjusted coefficient of determination (R^2) was 0.798, indicating that the model explains approximately 80% of the variance in the dependent variable. The F-statistic was 10.12, which is highly significant at the 0.05 level. The p-values for all independent variables were less than 0.05, suggesting that each variable has a statistically significant effect on the dependent variable.

[illegible][illegible]

the 1990s, the number of people in the world who are under 15 years of age is expected to increase from 1.1 billion to 1.5 billion. The number of people aged 65 and over is expected to increase from 250 million to 450 million. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion.

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[illegible]

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

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estrogen supplied to induce growth of the explanted tissue. Treatment consisting of a compound of the present invention is supplied by gastric lavage on a daily basis for 3-16 weeks, and implants are removed and measured for growth or regression. At the time of sacrifice, the intact horn of the uterus is harvested to assess status of endometrium.

5 B. Implantation of human endometrial tissue in nude mice.

Tissue from human endometrial lesions is implanted into the peritoneum of sexually mature, castrated, female, nude mice. Exogenous estrogen is supplied to induce growth of the explanted tissue. In some cases, the harvested endometrial cells are cultured *in vitro* prior to implantation. Treatment consisting of a compound of the present invention
10 supplied by gastric gavage on a daily basis for 3-16 weeks, and implants are removed and measured for growth or regression. At the time of sacrifice, the uteri are harvested to assess the status of the intact endometrium.

Test 4

15 A. Tissue from human endometrial lesions is harvested and maintained *in vitro* as primary nontransformed cultures. Surgical specimens are pushed through a sterile mesh or sieve, or alternately teased apart from surrounding tissue to produce a single cell suspension. Cells are maintained in media containing 10% serum and antibiotic. Rates of growth in the presence and absence of estrogen are determined. Cells are assayed for their ability to produce complement component C3 and their response to growth factors and growth hormone. *In vitro* cultures are assessed for their pro-
20 liferative response following treatment with progestins, GnRH, a compound of the invention, and vehicle. Levels of steroid hormone receptors are assessed weekly to determine whether important cell characteristics are maintained *in vitro*. Tissue from 5-25 patients is utilized.

Activity in any of the above assays indicates that the compounds of the present invention are useful in the treatment of endometriosis.

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Inhibition of Aortal Smooth Cell Proliferation/Restenosis Test Procedure

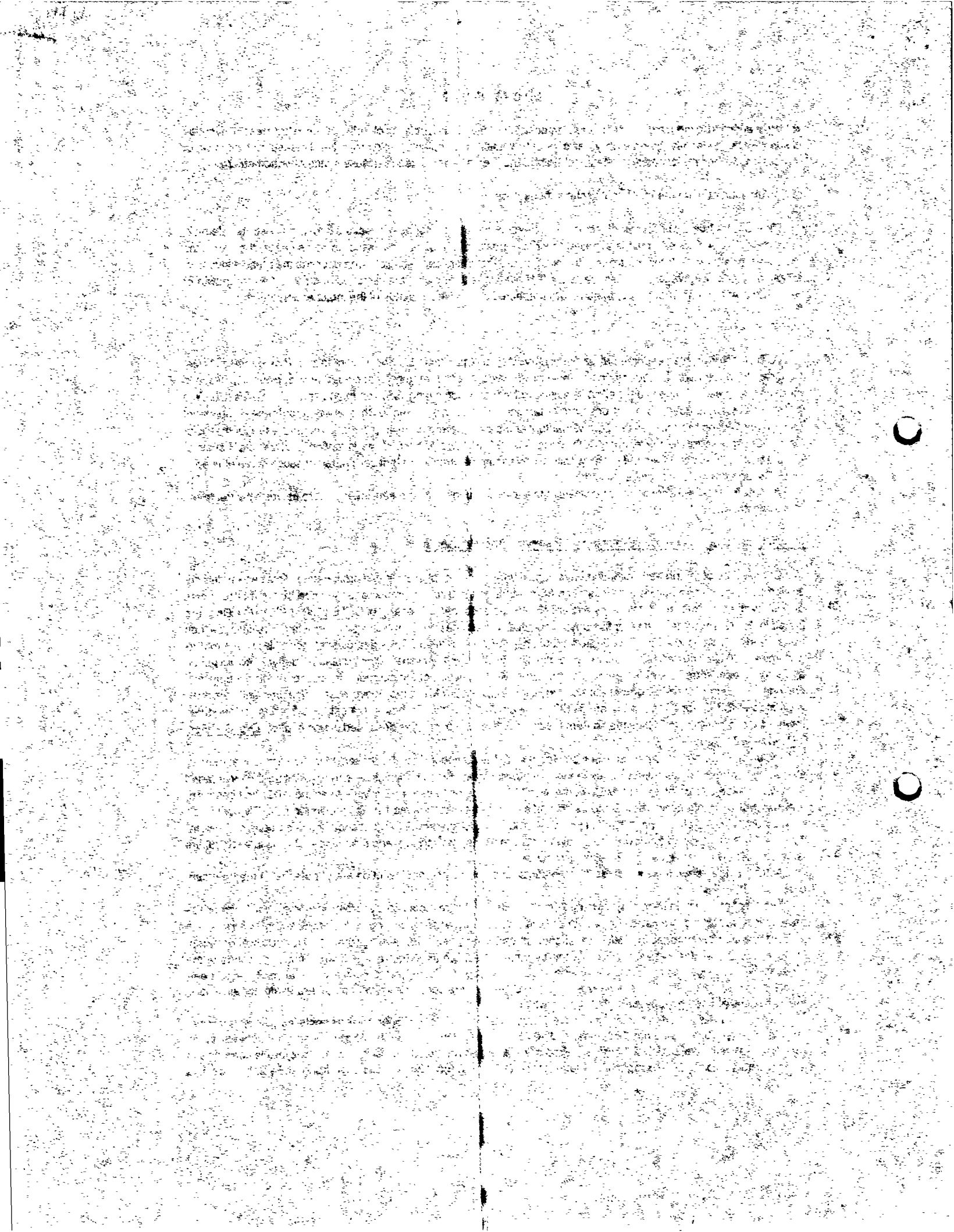
Compounds of the present invention have capacity to inhibit aortal smooth cell proliferation. This can be demon-
30 strated by using cultured smooth cells derived from rabbit aorta, proliferation being determined by the measurement of DNA synthesis. Cells are obtained by explant method as described in Ross, *J. of Cell Bio.* 50: 172 (1971). Cells are plated in 96 well microtiter plates for five days. The cultures become confluent and growth arrested. The cells are then transferred to Dulbecco's Modified Eagle's Medium (DMEM) containing 0.5 - 2% platelet poor plasma, 2 mM L-glutamine, 100 U/ml penicillin, 100 mg/ml streptomycin, 1 mCi/ml ³H-thymidine, 20 ng/ml platelet-derived growth factor, and varying concentrations of the present compounds. Stock solution of the compounds is prepared in dimethyl sul-
35 phoxide and then diluted to appropriate concentration (0.01 - 30 mM) in the above assay medium. Cells are then incubated at 37° C. for 24 hours under 5% CO₂/95% air. At the end of 24 hours, the cells are fixed in methanol. ³H thymidine incorporation in DNA is then determined by scintillation counting as described in Bonin, *et al.*, Exp. Cell Res. 181: 475-482 (1989).

Inhibition of aortal smooth muscle cell proliferation by the compounds of the present invention are further demon-
40 strated by determining their effects on exponentially growing cells. Smooth muscle cells from rabbit aortae are seeded in 12 well tissue culture plates in DMEM containing 10% fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 mg/ml streptomycin. After 24 hours, the cells are attached and the medium is replaced with DMEM containing 10% serum, 2 mM L-glutamine, 100 U/ml penicillin, 100 mg/ml streptomycin, and desired concentrations of the com-
45 pounds. Cells are allowed to grow for four days. Cells are treated with trypsin and the number of cells in each culture is determined by counting using a ZM-Coulter counter.

Activity in the above tests indicates that the compounds of the present invention are of potential in the treatment of restenosis.

The present invention also provides a method of alleviating post-menopausal syndrome in women which comprises the aforementioned method using compounds of Formula I and further comprises administering to a woman an effective
50 amount of estrogen or progestin. These treatments are particularly useful for treating osteoporosis and lowering serum cholesterol because the patient will receive the benefits of each pharmaceutical agent while the compounds of the present invention would inhibit undesirable side-effects of estrogen and progestin. Activity of these combination treat-
ments in any of the post-menopausal tests, *infra*, indicates that the combination treatments are useful for alleviating the symptoms of post-menopausal symptoms in women.

55 Various forms of estrogen and progestin are commercially available. Estrogen-based agents include, for example, ethynyl estrogen (0.01 - 0.03 mg/day), mestranol (0.05 - 0.15 mg/day), and conjugated estrogenic hormones such as Premarin® (Wyeth-Ayerst; 0.3 - 2.5 mg/day). Progestin-based agents include, for example, medroxyprogesterone such as Provera® (Upjohn; 2.5 - 10 mg/day), norethynodrel (1.0 - 10.0 mg/day), and nonethindrone (0.5 - 2.0 mg/day). A



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preferred estrogen-based compound is Premarin, and norethynodrel and norethindrone are preferred progestin-based agents.

The method of administration of each estrogen- and progestin-based agent is consistent with that which is known in the art. For the majority of the methods of the present invention, compounds of Formula I and II are administered continuously, from 1 to 3 times daily. However, cyclical therapy may especially be useful in the treatment of endometriosis or may be used acutely during painful attacks of the disease. In the case of restenosis, therapy may be limited to short (1-6 months) intervals following medical procedures such as angioplasty.

As used herein, the term "effective amount" means an amount of compound of the present invention which is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 5 mg to about 600 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 15 mg to about 80 mg/day.

The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, optionally containing an effective amount of estrogen or progestin, and a pharmaceutically acceptable carrier, diluent, or excipient.

The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations of the present invention can be prepared by procedures known in the art using well known and readily available ingredients. For example, the compounds of formula I and II, with or without an estrogen or progestin compound, can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Compounds of formula I and II, alone or in combination with a pharmaceutical agent of the present invention, generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

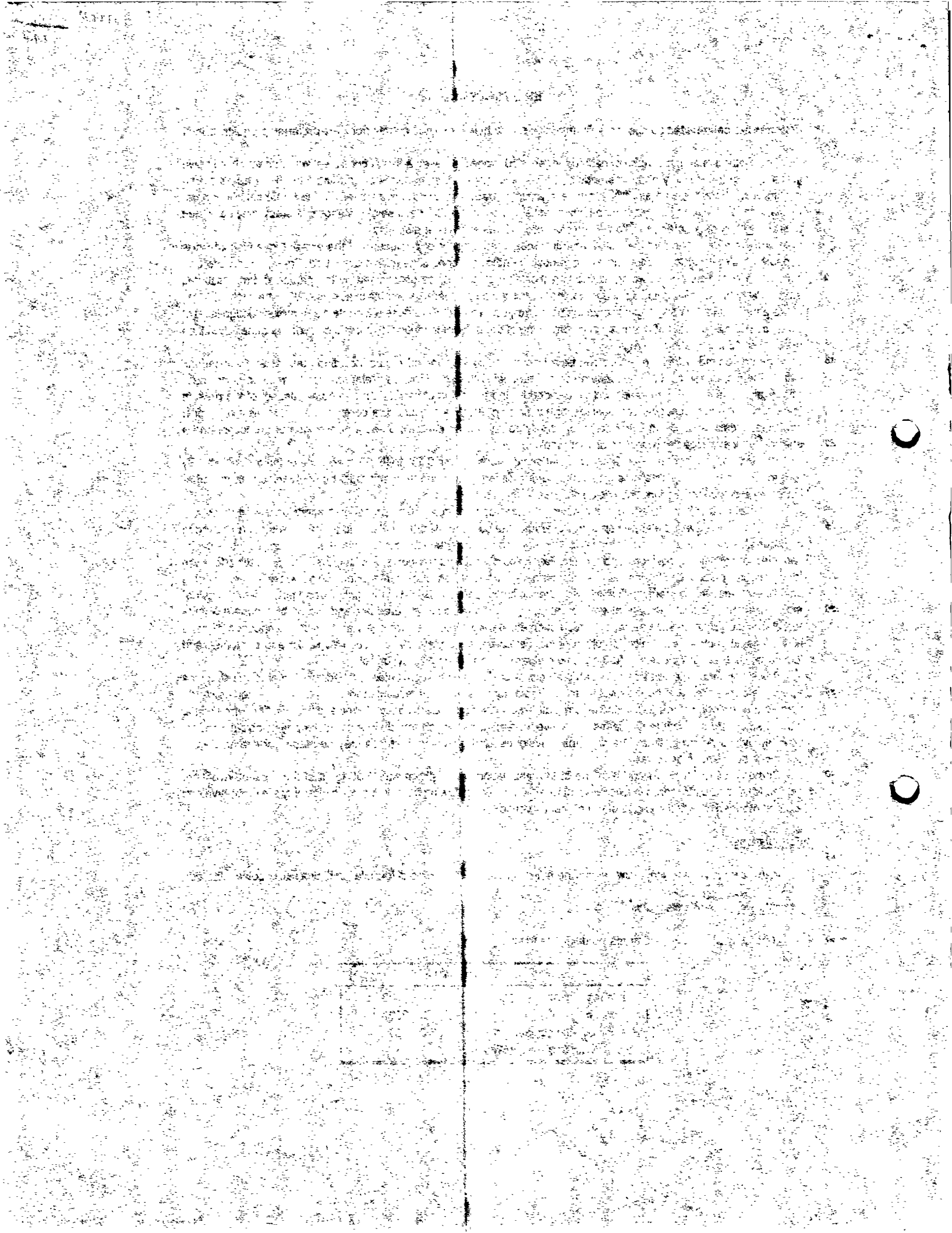
Formulations

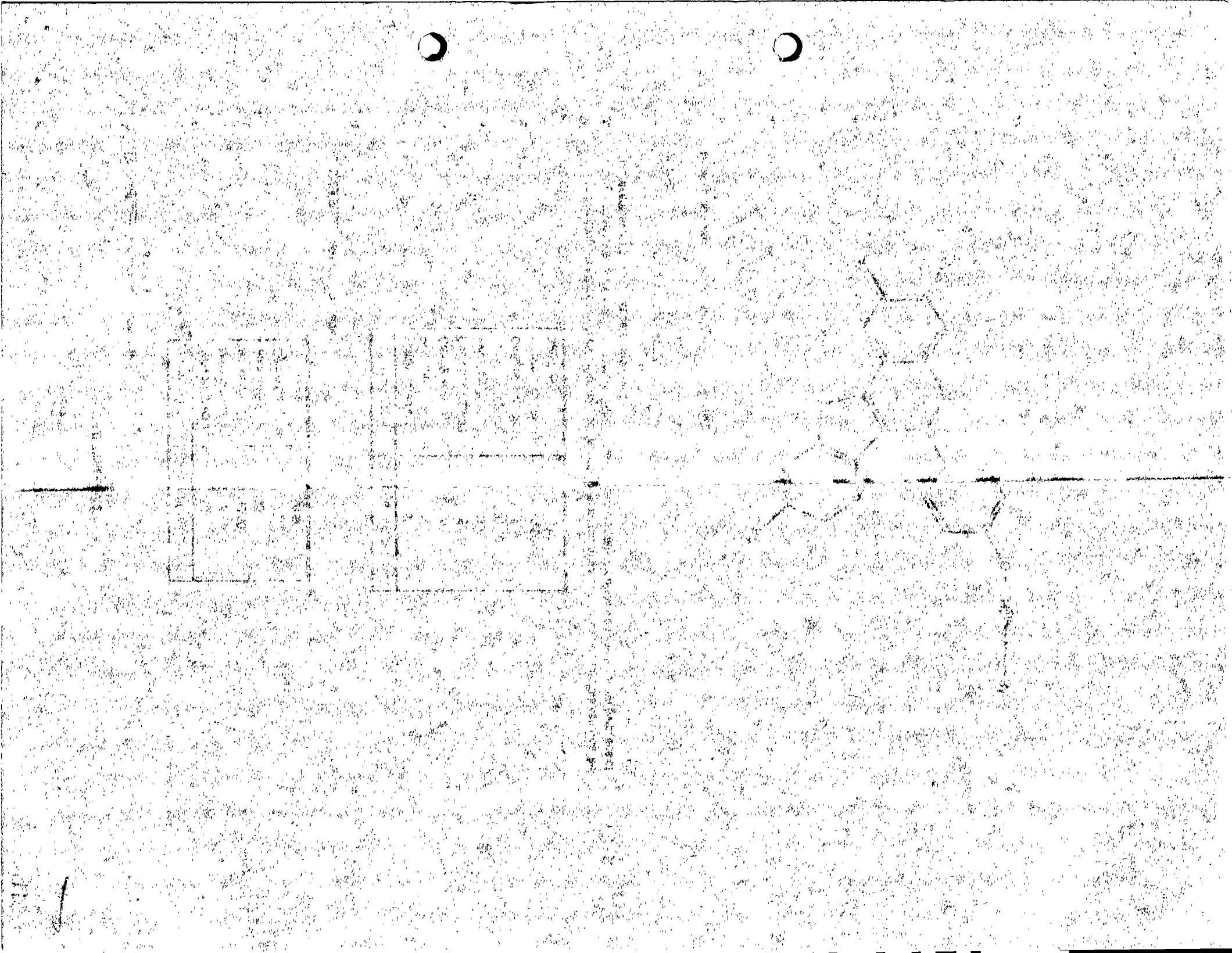
In the formulations which follow, "active ingredient" means a compound of formula I or II, or a salt or solvate thereof.

Formulation 1: Gelatin Capsules

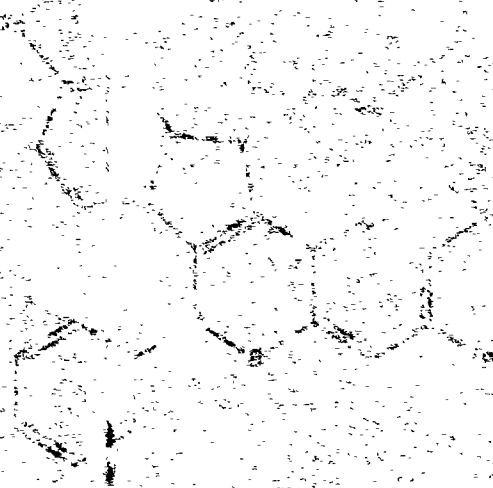
Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

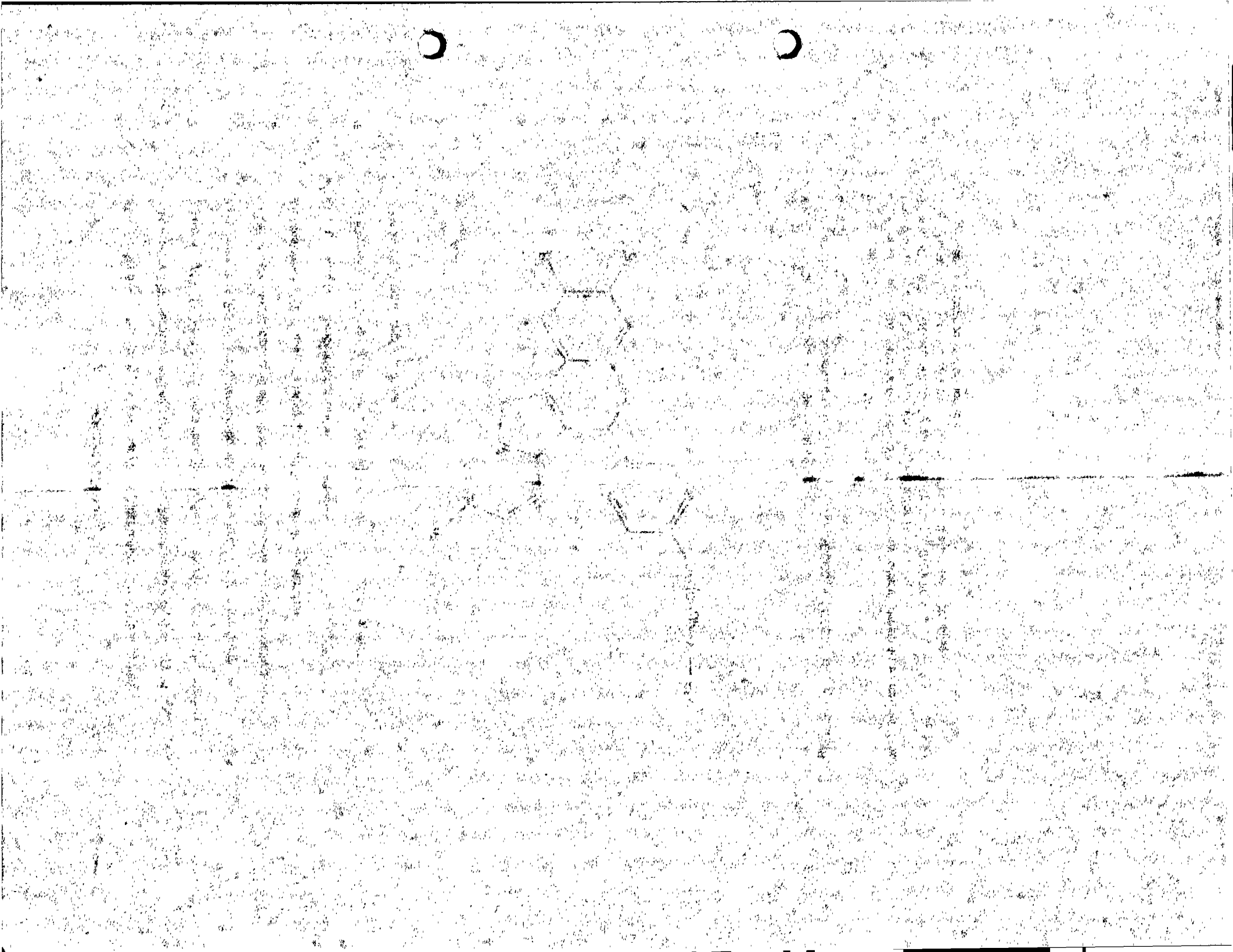


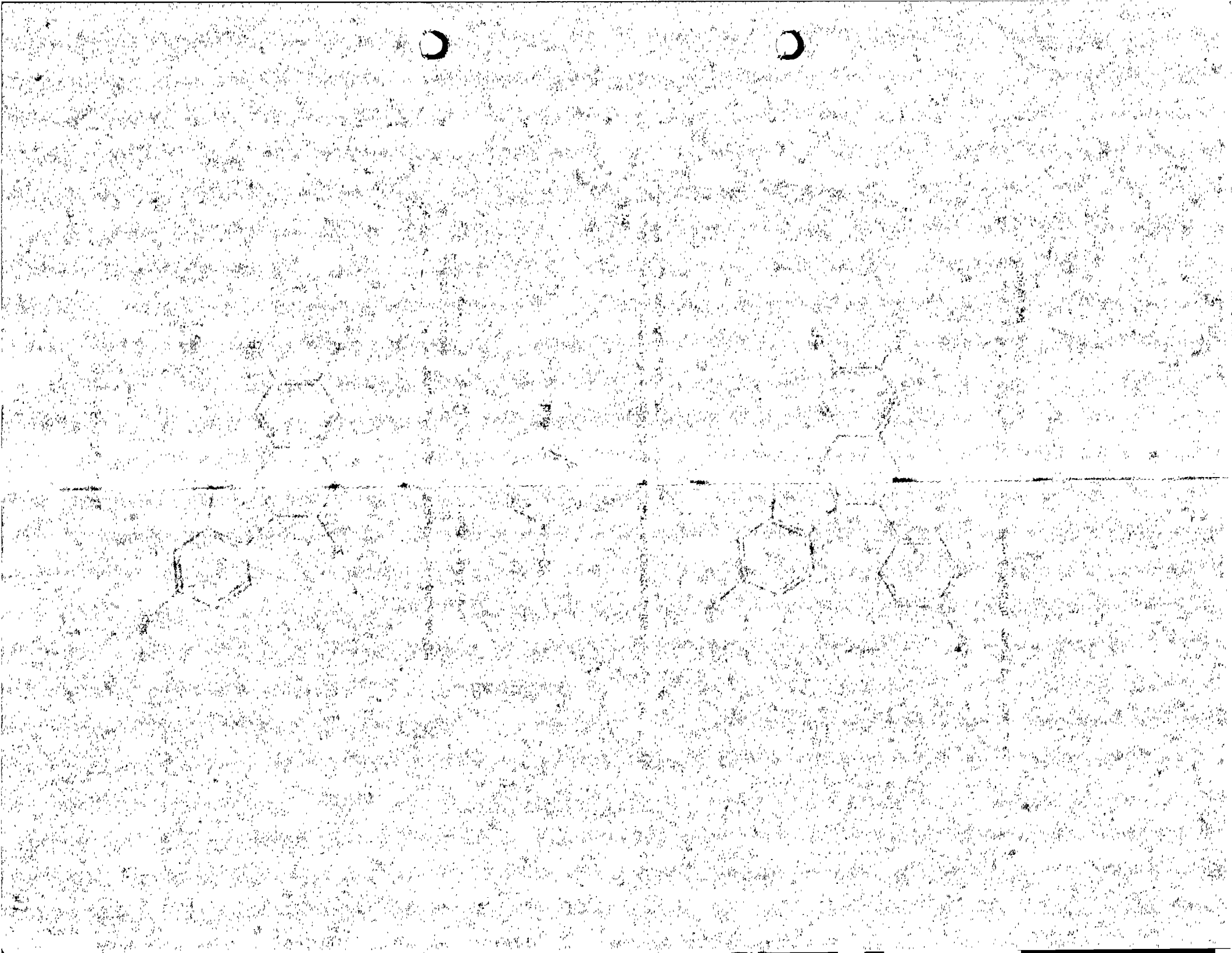


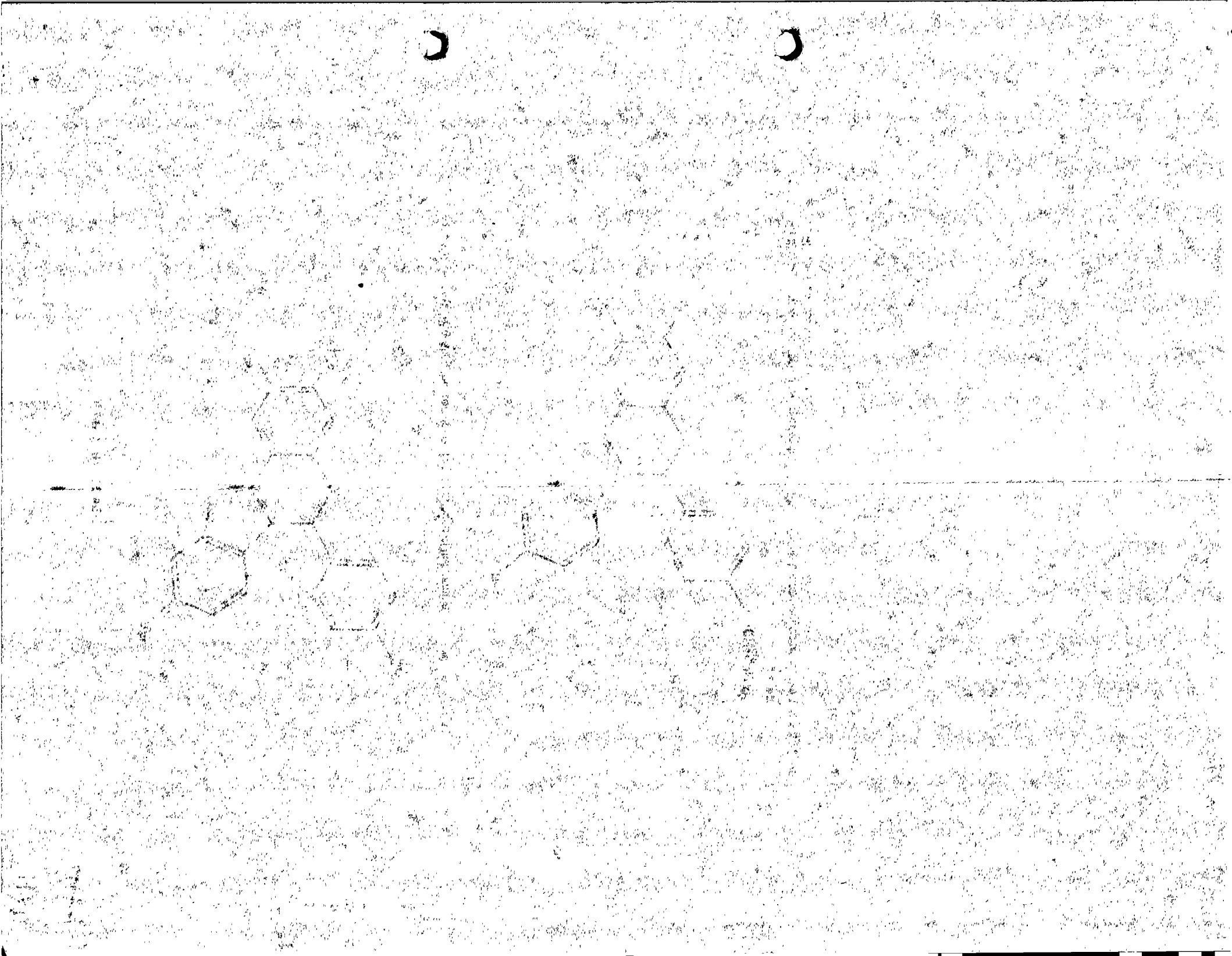
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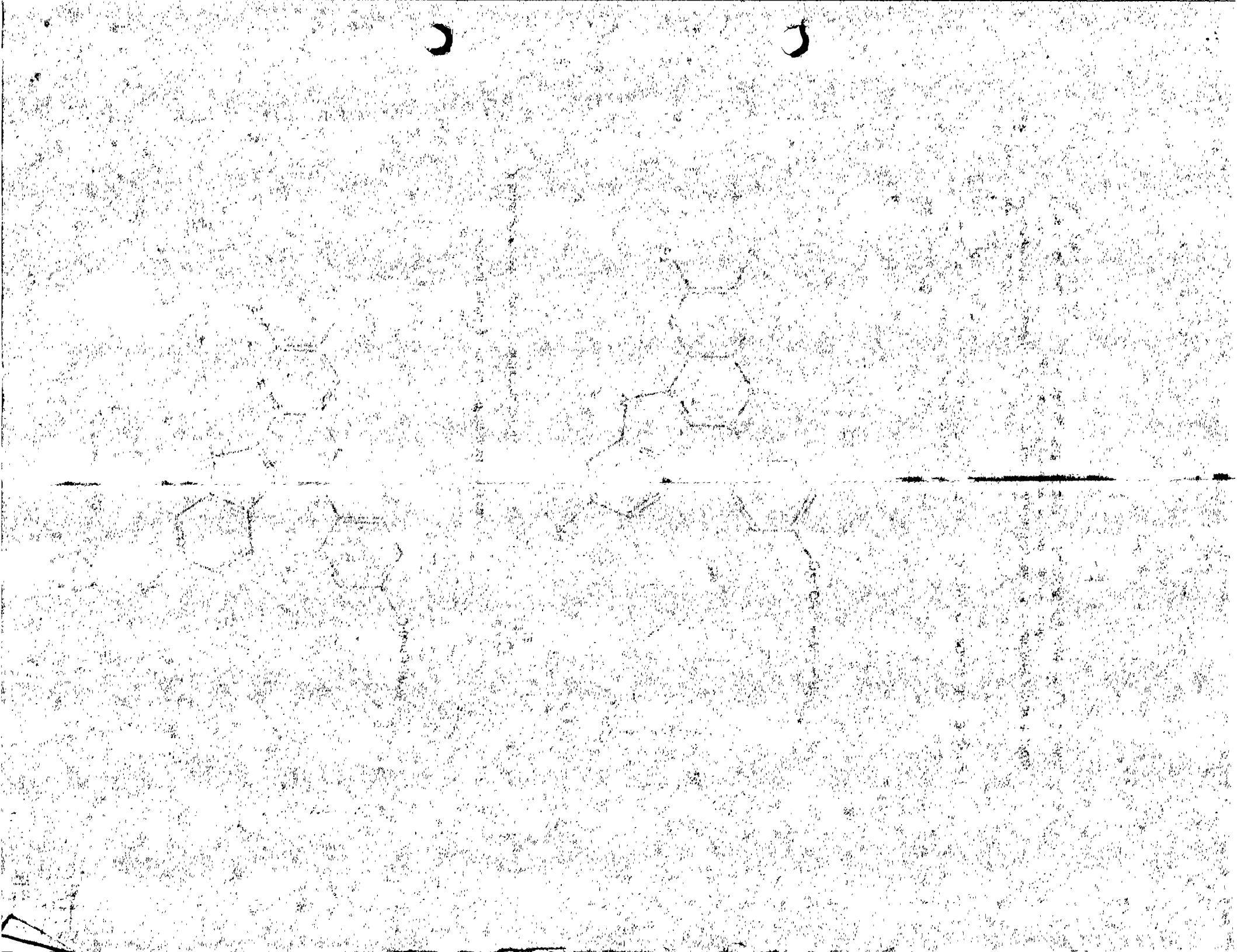


— *Journal of the American Medical Association*









Para solucionar este problema técnico la solicitud en estudio proporciona una compuestos moduladores del receptor selectivo de estrógenos.

Clasificación Internacional de Patentes (IPC.): A61K 31/4453

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicación 14 - 15: Se reivindican compuestos por su posterior uso por lo cual no pueden aceptarse ya que un compuesto se caracteriza únicamente por su fórmula estructural o por su nomenclatura química IUPAC.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2004/01/22

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	EP 0826679	NAPHTHYL COMPOUNDS, INTERMEDIATES, COMPOSITIONS, AND METHOD OF USE	1998/03/04
D ₂	EP 0761669	PENTACYCLIC COMPOUNDS, INTERMEDIATES, PROCESSES, COMPOSITIONS AND METHODS	1997/03/12

5. Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

Reivindicaciones 1 - 12: compuestos de la fórmula general (I).

Reivindicación 16 - 18: compuestos de la fórmula general (II).

D₁ enseña (ver folio 403, abstract) compuestos naftil sustituidos, intermediarios, composiciones, formulaciones farmacéuticas y métodos de uso de fórmula (I)

Así las cosas las formulas I y II reivindicadas se superponen con la formula I del documento D₁, por lo tanto no son novedosas, pues ya se conocían en el estado de la técnica.

- ♦ Los elementos característicos de las fórmulas (I) y (II) habían sido divulgados previamente en el Estado de la Técnica según la tabla 1:

TABLA 1				
SOLICITUD		ANTERIORIDAD (D ₁)		Comparación
(I)		(I)		
(II)				
	F	R ₂ , R ₃ , R ₄	F	IGUAL
X ¹	O		O	IGUAL
R ¹	H, SO ₂ (alquilo), CO(alquilo)	R ¹	H; OSO ₂ (alquilo), OCO(alquilo)	IGUAL
R ^{1a}				IGUAL
R ⁶	H		H	IGUAL
m	0 - 2	R ⁵	Piperidina, pirrolidina, metil pirrolidina	IGUAL
R	H, metilo			
X	O		O	IGUAL
X ²	O		O	IGUAL
	(CH ₂) ₂	n	2	IGUAL

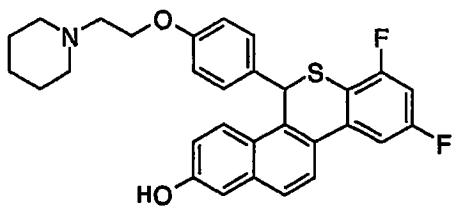
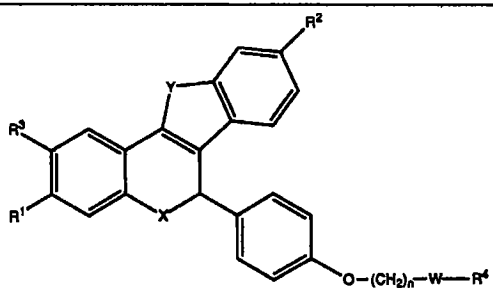
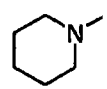
De manera que el objeto de esta solicitud, tal como aparece en las reivindicaciones 1 - 12, 16 - 18, no es nuevo.

Reivindicación 13: compuestos correspondientes a una variante del ejemplo 96 de la fórmula.

D2 enseña (ver folio 410-411, abstract) compuestos pentacíclicos de fórmulas (I) y (II).

Así las cosas el compuesto reivindicado se superpone con la formula I del documento D₂, por lo tanto no es novedoso, pues ya se conocía en el estado de la técnica.

- ♦ Los elementos característicos del compuestos de la reivindicación 13 había sido divulgados previamente en el Estado de la Técnica según la tabla 2:

TABLA 2				
SOLICITUD		ANTERIORIDAD (D ₂)		Comparación
(13)		(I)		
	F	R ₁ , R ₃	F	IGUAL
	S	X	S	IGUAL
	OH	R ²	OH	IGUAL
	CH=CH	Y	CH=CH	IGUAL
	(CH ₂) ₂		(CH ₂) _n -W n= 1 W= CH ₂	IGUAL
		R ⁴	Piperidina	IGUAL

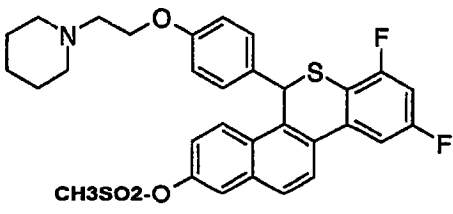
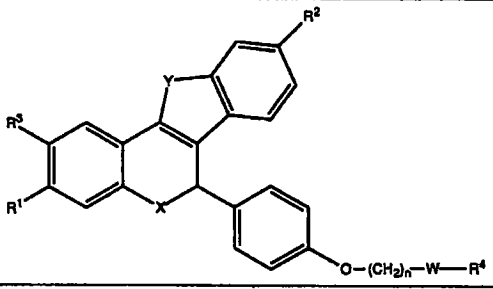
De manera que el objeto de esta solicitud, tal como aparece en la reivindicación 13, no es nuevo.

Nivel inventivo (artículo18 D486)

La presente Solicitud de Patente reivindica (19) Compuestos de acuerdo a la reivindicación 16 correspondientes a una variante del ejemplo 96:

Dicho compuesto se ve afectado por el siguiente documento más cercano del Estado de la Técnica:

D₂ que enseña (ver folio 410-411, abstract) compuestos pentacíclicos de fórmulas (I) y (II).

TABLA 3				
SOLICITUD		ANTERIORIDAD (D ₂)		Comparación
(19)		(I) F421 Pag 66		
	F	R ₁ , R ₃	F	IGUAL

430

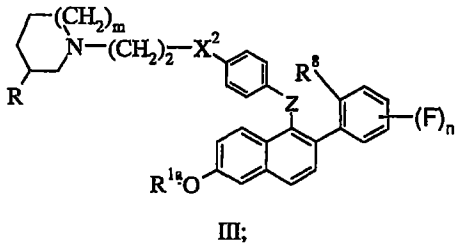
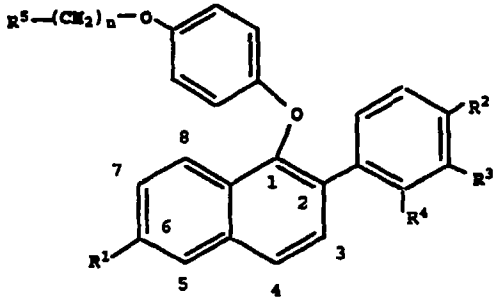
	S	X	S	IGUAL
	CH ₃ SO ₂ -O	R ²	H, OH, O(alquil), OSO ₂ (alquil C ₄ -C ₆), OSO ₂ CF ₃ , Cl, F	DIFERENTE
	CH=CH	Y	CH=CH	IGUAL
	(CH ₂) ₂		(CH ₂) _n -W n= 1 W= CH ₂	IGUAL
		R ⁴	Piperidina	IGUAL

La única diferencia con D₂ es que esta solicitud tiene una sustitución donde existe solamente un CH₃ y no una cadena de 4 pero esta diferencia no parece conceder un efecto técnico inesperado ya que colocar una cadena alquílica independientemente del número de Carbonos se encontraba ya sugerido previamente en D2 según el radical R₂ (folio 411 página 2).

La presente Solicitud de Patente reivindica (20 – 23): compuestos de la fórmula general (III)

Dichos compuestos se ven afectados por el siguiente documento más cercano del Estado de la Técnica:

D₁ que enseña (ver folio 403, abstract) compuestos naftil sustituidos, intermediarios, composiciones, formulaciones farmacéuticas y métodos de uso de fórmula (I)

TABLA 4				
SOLICITUD		ANTERIORIDAD (D ₁)		Comparación
(III)		(I)		
	F	R ₂ , R ₃	F	IGUAL
R ⁸	OH, O(alquilo)	R ₄	OH, O(alquilo)	IGUAL
R ^{1a}	H; OSO ₂ (alquilo), OCO(alquilo)	R ¹	H; OSO ₂ (alquilo), OCO(alquilo)	IGUAL
Z	CHOH, CO		O	DIFERENTE
X ²	O		O	IGUAL
	(CH ₂) ₂	n	2	IGUAL
m	0 - 2	R ⁵	Piperidina, pirrolidina, metil pirrolidina	IGUAL
R	H, metilo			

La única diferencia con D₁ radica en el sustituyente Z.

Esta diferencia no parece conceder un efecto técnico inesperado ya que a pesar de que se muestran ensayos biológicos (pág 186, folio 334 y siguientes) donde aparentemente los compuestos son útiles para el objetivo (tratamiento de síntomas vasomotores) no puede concluirse ninguna superioridad notoria respecto al estado de la técnica.

Por lo tanto el **problema técnico objetivo fundamental** de la invención podría redefinirse en: "como lograr compuestos moduladores del receptor selectivo de estrógenos como alternativa a lo previamente conocido".

Por consiguiente resultaría obvio el diseño de este tipo de compuestos para un experto en la materia.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D ₁	EP 0826679	1-12, 16-18	NOVEDAD
D ₂	EP 0761669	13 19-23	NOVEDAD NIVEL INVENTIVO

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 15 MAYO 2009

CONCEPTO TÉCNICO No. 256	EXAMINADOR TÉCNICO Código No. 202087
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