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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-008246- -00003-0000

Fecha: 2007-09-11 15:58:20 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Re: P1.-SMITHKLINE BEECHAM CORPORATION.-Solicitud de
Patente de Invención en Fase Nacional PCT para "COMPUESTOS
DE CICLOALQUILIDENO COMO MODULADORES DEL
RECEPTOR DE ESTRÓGENO".-Clase C07C 59/00.-Expediente
número 06-008.246.-

1. Me refiero a mi memorial de 19 de Abril de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **577** de 29 de Junio de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo I.
4. Anexo me permito acompañar recibo número 07-72.196, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-008246- -00003-0000

Fecha: 2007-09-11 15:58:20 Dep. 2020 NUECREACIONE
Tipo: Petición Ene 378 FASENACIONALI
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 72,196
FECHA : SEPTIEMBRE 7 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLORED A Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47999523	07/09/2007	12,446,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
TOTAL :			\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-08246

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577** DE

FECHA **29 DE JUNIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **27 DE SEPTIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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3,287,397

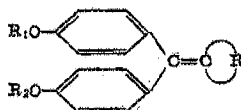
P,p' SUBSTITUTED BENZHYDRYLIDINE CYCLOALKANES

Knut Gunnar Olsson, Hans Erik Alfred Wahlstam, and Bertil Sundbeck, all of Celsiusgatan 35, Malmo, Sweden, and Ernst Herbert Barány, Hallhygatan 28A, and Jean Francois Miquel, Studentvagen, 1A, both of Uppsala, Sweden

No Drawing. Filed Nov. 15, 1961, Ser. No. 152,625
Claims priority, application Great Britain, Nov. 22, 1960, 40,123/60

9 Claims. (Cl. 260-479)

This invention relates to novel chemical compounds having pharmacological activity which may comprise estrogenic and antiestrogenic activity and inhibition of gonadotrophins from the pituitary gland, as well as processes of preparing the same. In particular, said compounds are p,p'-substituted benzhydrylidene cycloalkanes which may be represented by the following general formula



wherein R is a member selected from the group consisting of saturated straight and branch-chained alkylene radicals containing from three to eight carbon atoms in the molecule and wherein R₁ and R₂ are similar and dissimilar members selected from the group consisting of hydrogen, alkyl radicals containing from one to six carbon atoms, alkenyl radicals containing from two to six carbon atoms and phenylalkyl radicals in which the alkyl radical contains from one to three carbon atoms, saturated and unsaturated, straight and branch-chained alkane carbonyl radicals containing from one to eighteen carbon atoms, cyclopentane and cyclohexane carbonyl radicals and radicals of carbonic, sulphuric and phosphoric acids. The new compounds may be regarded as p,p'-dihydroxy-benzhydrylidene cycloalkanes, their mono and bis-ethers, their mono and bis-esters and their mono-ether-monoesters.

The invention also includes compounds wherein at least one of the radicals R₁ and R₂ is derived from a polybasic acid, including both organic polybasic carboxylic acids and carbonic, sulphuric and phosphoric acids. In these compounds the remaining free acid radicals may be converted to the corresponding salts of alkali metals, alkaline earth metals, ammonia or amines, for example.

In the new benzhydrylidene compounds of the invention R may be a saturated straight or branch-chained alkylene (polymethylene) radical containing from three to eight carbon atoms. As examples of suitable alkylene radicals there may be mentioned trimethylene, 1 or 2-methyltrimethylene, 1,3-dimethyltrimethylene, tetramethylene, 2-ethyltetramethylene, 1,4-dimethyltetramethylene, pentamethylene, 3-methylpentamethylene, 2,3-dimethylpentamethylene, 2-methyl-4,4-dimethylpentamethylene, 3-iso-propylpentamethylene, hexamethylene, 1,6-dimethylhexamethylene, heptamethylene and octamethylene radicals.

When R₁ and R₂ in the above general Formula I are hydrogen atoms each phenyl group contains a free hydroxy group in the p-position. One of these two p-hydroxy groups or both may be alkylated with similar or dissimilar alkyl groups containing from one to six carbon atoms, such as methyl, ethyl, propyl, iso-propyl, n-butyl, tert-butyl, n-amyl, iso-amyl, for instance 2-methylbutyl, and cyclohexyl, alkenyl groups containing from two to six carbon atoms, such as allyl and crotonyl, phenylalkyl groups in which the alkyl radical is straight or branched and con-

2

tains from one to three carbon atoms, e.g. benzyl, phenethyl, and phenylisopropyl.

Said p-hydroxy groups may also be mono or diesterified, for instance with alkanoyl or alkenoyl radicals containing from one to eighteen carbon atoms, such as formyl, acetyl, propionyl, pivaloyl, caproyl, palmitoyl, stearyl, undecenoyl and oleyl, cyclopentane and cyclohexane carbonyl radicals, or with aroyl radicals, such as benzoyl radicals, or with aralkanoyl radicals such as phenylpropionyl, cinnamoyl radicals and the like. They may also be mono or diesterified with polybasic organic acids such as succinic, maleic, tartaric, citric, hexahydrophthalic acids or the like, and with carbonic, sulphuric and phosphoric acids such as ortho-phosphoric acid. When an organic or inorganic polybasic acid has been used for the mono or diesterification of the hydroxy group or groups the remaining free acid groups may be converted to salts of pharmaceutically acceptable cations such as Na, K, Ca and ammonium.

The free acid used for the esterification may in advance be converted to another suitable derivative such as a half-ester or half-amide. Upon esterification it is also possible to convert any remaining free acid radical to a half-ester or half-amide.

Thus, in accordance with the above one of said p-hydroxy groups may be etherified while the other is esterified to form mixed mono-ether-monoesters, wherein the ether and ester radicals are the same as those mentioned above.

The invention also includes all steric isomers comprised by the general Formula I.

The new compounds of the invention having the general Formula I may be prepared according to methods known per se for preparing similar compounds. A useful method broadly comprises using as the starting material a compound having the general formula



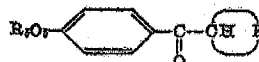
(II)

wherein R₁, R₂ and R have the meanings hereinbefore defined and wherein one of the symbols R₃ and R₄ represents hydrogen and the other a member of the group consisting of OH and esters thereof and halogens, such as Cl and Br. When using such a starting compound the benzhydrylidene cycloalkanes having the general Formula I are prepared by splitting off a compound of the formula R₃-R₄ so as to form a double bond between the carbon atoms to which the groups R₃ and R₄ are attached.

The invention therefore also comprises a process of preparing the compounds having the general Formula I. According to a preferred feature of the invention said compounds are prepared using carbinols having Formula II above as the starting material, viz. wherein one of the symbols R₃ and R₄ represents hydrogen and the other a hydroxy group.

Said carbinols of the general Formula II are novel compounds and are included within the scope of the invention. They are preferably prepared by an organometal reaction and most preferably by a Grignard reaction. In the last-mentioned case the carbinols having the general Formula II may be prepared from ketones and esters as can be seen from the following description of the process preferably used.

(I) According to one embodiment of the invention ketones are used having the general formula



(III)

3

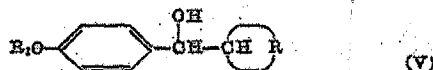
wherein R has the meaning hereinbefore defined and R_2 is the same as R_1 with the exception that it may not represent an acid radical.

Said ketones of Formula III may be prepared by reacting an acid of the formula



wherein R has the meaning hereinbefore defined, or the corresponding chloride with phenol or a phenylalkyl ether in the presence of a suitable catalyst, for example aluminum trichloride or boron trifluoride.

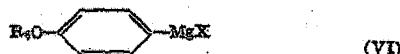
Said ketones of Formula III may also be prepared by oxidation of alcohols having the general formula



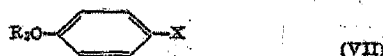
for example by the use of chromium trioxide as the oxidation agent.

As examples of suitable ketones of the general Formula III there may be mentioned p-hydroxyphenyl cyclobutyl ketone, p-methoxyphenyl cyclopentyl ketone, p-hydroxyphenyl-(4-methylcyclohexyl) ketone, p-benzyloxyphenyl cyclohexyl ketone, p-methoxyphenyl-2,4-dimethyl cyclobutyl ketone, p-hydroxyphenyl cyclononyl ketone and the like.

The ketones of Formula III are reacted with a Grignard reagent having the general formula



wherein R_2 is the same as R_2 in Formula I above with the exception that R_2 may not be hydrogen or an acid radical, and wherein X represents chlorine, bromine or iodine. Said Grignard reagents are prepared in conventional manner by reacting a compound having the general formula



with magnesium in a suitable form such as magnesium turnings in an ether, such as diethyl ether.

Upon reaction of the ketones of Formula III with the Grignard reagent of Formula VI in conventional manner the magnesium complex formed is decomposed in the usual manner to form the desired carbinol, for example by the addition of water or dilute acids, such as dilute hydrochloric acid or an aqueous solution of ammonium chloride. The carbinol of Formula II thus formed need not be isolated in pure state to enable it to be used in preparing the benzhydrylidene cycloalkanes of the invention. It is sufficient to recover the carbinol from the aqueous reaction mixture by extraction with a suitable organic solvent for the carbinol, including higher aliphatic alcohols, ethers, ketones, hydrocarbons and halogenated hydrocarbons, for instance butyl alcohol, iso-amyl alcohol, diethyl ether, tetrahydrofuran, methyl isobutyl ketone, petroleum ether, cyclohexane, benzene, toluene, chloroform, carbon tetrachloride, trichloroethylene and the like. The carbinol is then isolated by evaporation of the extract obtained and, if desired, may be purified in conventional manner, for instance by distillation or recrystallization, but is preferably used directly in the form of the evaporation residue as the starting material in preparing the benzhydrylidene cycloalkanes of the invention.

(II) According to another embodiment of the invention, there is used as the starting material p,p'-dihydroxybenzo-phenone or a derivative thereof wherein one of or both the hydroxy groups may be alkylated as described above at item I. As examples of particularly suitable compounds of said kind there may be mentioned: p,p'-dihydroxybenzophenone, p-methoxy-p'-hydroxybenzophenone, p,p'-dimethoxybenzophenone, p,p'-dibenzoyloxybenzophenone and the like.

4

Said benzophenones are reacted with a Grignard reagent having the general formula



wherein R and X have the meanings hereinbefore defined. Said Grignard reagents may be prepared as described above at item I. Examples of suitable Grignard reagents are cyclohexyl magnesium bromide, 2,3-dimethyl cyclohexyl magnesium bromide, cyclooctyl magnesium iodide and the like. The complex formed in this reaction is worked up in the same manner as that described above at item I.

(III) According to still another embodiment of the invention esters are used having the general formula



wherein R has the meaning hereinbefore defined and R_7 represents a residue of any suitable alcohol, preferably a lower aliphatic alcohol such as a residue of methanol, ethanol or the like. Said esters of Formula IX may be prepared in conventional manner from the corresponding acid and alcohol in the presence of an acid catalyst or from the corresponding acid chloride and the alcohol. As examples of suitable esters of Formula IX there may be mentioned ethyl cyclobutylcarboxylate, methyl 2,4-dimethyl-cyclobutylcarboxylate, methyl 3-methyl-cyclopentyl-carboxylate, butyl 2,5-dimethyl-cyclopentyl-carboxylate, ethyl 3,4-dimethyl-cyclohexylcarboxylate, ethyl cycloheptylcarboxylate, propyl cyclooctylcarboxy-oxybenzophenone and the like.

Said esters are reacted with two moles of a Grignard reagent having the general Formula VI. The reaction is carried out in the same manner and the reaction mixture is worked up as described above at item I to obtain the desired carbinol of the general Formula II.

(IV) According to a still further embodiment of the invention ketones are used having the general formula



wherein R has the meaning hereinbefore defined. Said ketones are reacted with an organometal compound containing the above-mentioned benzhydryl residue. In this embodiment of the invention there is preferably used a lithium compound of the general formula



wherein R_1 and R_2 are other residues of the kind hereinbefore defined. Said compounds are prepared from the corresponding compound containing an additional hydrogen atom instead of the Li atom. Said compound is reacted with phenyl lithium in conventional manner for the preparation of Li compounds of said kind.

The carbinol of Formula II prepared in this manner contains the hydroxy group at the cycloalkyl carbon atom and not at the diphenylmethane carbon atom as do the carbinols prepared by the reactions described above at items I-III but the reaction mixture is nevertheless worked up in the same manner as described at item I.

The carbinol thus obtained is preferably used directly in the form of the evaporation residue of the extract for preparing the benzhydrylidene cycloalkanes of the invention.

Said evaporation of the extract of the carbinol formed may be carried out under various conditions as to time, temperature and pressure. The conditions to be used are generally not critical in any manner but it is preferable to carry out the evaporation at a relatively low temperature and in vacuum, e.g. at a temperature up to about 50° C. at water pump vacuum. In certain cases such as

when the solvent employed for the extraction of the carbinol has a boiling point above 50° C. also in vacuum the use of said conditions may be accompanied by some dehydration of the carbinol.

Complete or partial dehydration may also occur when the above-mentioned organometal complex is decomposed by the use of strong acids and insufficient cooling. In this case the desired benzhydrylidene cycloalkane of Formula I is obtained in crude state or in the form of a mixture with the corresponding carbinol. The solvents used for the isolation of said reaction products may be the same as those used for the recovery of the pure carbinol in the manner described at item I.

According to a preferred embodiment of the invention the dehydration is carried out simply by continuing the heating of the residue obtained in the evaporation of the extract of the carbinol. In this case it is suitable to carry out the heating to a temperature between about 50 and 300° C. at atmospheric pressure or preferably in vacuum. Vacuum is suitably employed to assist in removing the water split off from the carbinol from the reaction vessel used, but the pressure to which the reaction vessel is evacuated is not critical in any manner. The dehydration by heating is usually carried out at a pressure of about 5 to 200 mm. of Hg, and preferably at water pump vacuum. The time necessary for dehydration varies according to the quantity of carbinol to be dehydrated but the dehydration should preferably be carried out as fast as possible for instance during a period of from about one to about thirty minutes. In this manner undesirable side reactions are avoided. Any usual distillation equipment may be used for performing the dehydration. However, if the quantity of carbinol to be dehydrated is relatively large a period of time of up to about two hours or more would be necessary. In that case it is more convenient to use a special evaporation apparatus for continuous dehydration where only heating for a short time of the flowing liquid is necessary.

The dehydration may be facilitated by the addition of various materials, such as sulphuric acid, phosphoric acid, phosphorous pentoxide in boiling benzene, alkali metal hydrogen sulphates, e.g. sodium and potassium hydrogensulphate, potassium pyrosulphate, iodine in xylene, hydrogen bromide in acetic acid, p-toluenesulphonic acid, sulphonamide acid, formic acid, acetic acid and anhydrides of lower aliphatic carboxylic acids containing from one to six carbon atoms, e.g. acetic anhydride, and also the corresponding acyl chlorides, e.g. acetyl chloride. The dehydration may also be carried out in aqueous to alcoholic alkali solutions, such as potassium or sodium hydroxide dissolved in water or lower alcohols having one to six carbon atoms or with the corresponding lower potassium or sodium alkoxylates.

The desired benzhydrylidene cycloalkanes of the invention thus formed may be isolated in any conventional manner, such as by distillation at a pressure of for instance 0.001 to 5 mm. of Hg and most preferably at a pressure of from about 0.01 to about 0.2 mm. of Hg. The product may then be further purified by reprecipitation or recrystallization. The desired benzhydrylidene cycloalkanes are obtained as liquids or as solids in good yield and in a pure state.

The product thus obtained may be a mono or dialkyl ether. According to a further embodiment of the invention the alkyl groups may be removed in conventional manner, preferably by reacting the ether with a nucleophilic agent, such as an alkali metal hydroxide, e.g. sodium and potassium hydroxide. The reaction is conveniently carried out in the presence of a polar organic solvent, such as lower alcohols having one to eight carbon atoms, e.g. methanol and ethanol, or in glycol ethers, e.g. triethylene glycol, in aqueous or anhydrous state at increased temperatures and preferably at a temperature of from about 150 to about 250° C. The pressure to be used of course depends on the solvent used. The lower alcohols may be used in an autoclave but the tri-

ethylene glycol can be used at atmospheric pressure. The dealkylated benzhydrylidene cycloalkanes of the invention thus obtained, i.e. the free p,p'-dihydroxy compounds, may be isolated in the following manner.

The reaction mixture is diluted with water and neutralized with a suitable acid for example hydrochloric acid, acetic acid and the like. The benzhydrylidene cycloalkane can be extracted with an organic solvent of the group described in connection with the isolation of the corresponding carbinol of Formula II. Upon drying the solution, for instance with anhydrous sodium sulphate or magnesium sulphate the solvent may be removed by distillation and the benzhydrylidene cycloalkane compound may be distilled at reduced pressure, preferably at about 0.001 to 0.1 mm. of Hg. The dihydroxy compounds thus obtained may also be recrystallized from suitable solvents.

According to still another embodiment of the invention the monoalkyl ethers and the free p,p'-dihydroxy compounds are esterified especially with pharmaceutically acceptable acids to form the corresponding mono and diesters.

In the preparation of the esters of organic mono and polybasic aliphatic, cycloaliphatic and aromatic carboxylic acids, it is possible to use the acids themselves. However, the corresponding acyl chlorides and anhydrides are preferably used. The esterification may be carried out in the presence of usual esterification catalysts, such as mineral acids, e.g. sulphuric acid, p-toluenesulphonic acid, cation exchange resins containing sulphonic acid radicals, and the like. The esterification may be carried out in a suitable organic solvent, such as pyridine, if desired.

As examples of pharmaceutically acceptable acids for the preparation of the esters of the invention there may be mentioned sulphuric acid and ortho-phosphoric acid, formic acid, acetic acid, propionic acid, phenylpropionic acid, butyric acid, isobutyric acid, tert-butylacetic acid, caproic acid, caprylic acid, capric acid, palmitic acid, stearic acid, benzoic acid, succinic acid, glutaric acid, ethoxyacetic acid, ethylmercaptoacetic acid, lactic acid, tartaric acid, citric acid, hexahydrophthalic acid, pivalic acid and the like. Esters with polybasic acids containing free acid groups may be converted to the corresponding salts of pharmaceutically acceptable cations as mentioned above.

The esters may be isolated in the same manner as the corresponding dihydroxy compounds. The reaction mixture is treated with water and the ester is extracted with a suitable solvent, selected from the group used in the isolation of the carbinols of Formula II. The solution is dried and evaporated whereupon the residue obtained is rectified in vacuum preferably at a pressure of from about 0.01 to 0.1 mm. of Hg. Upon distillation the ester can also be recrystallized from suitable solvents so as to obtain the product in a purer state, if necessary.

In accordance with the statements made above the present invention comprises the following groups of compounds:

(1) Compounds of the general Formula I wherein each phenyl group contains a free hydroxy group in the p-position.

(2) Mono and diesterified p,p'-dihydroxy compounds of the general Formula I.

(3) Mono and dietherified p,p'-dihydroxy compounds of the general Formula I.

(4) Monoesterified-monoetherified p,p'-dihydroxy compounds of the general Formula I.

(5) Mono and diesters of p,p'-dihydroxy compounds of the general Formula I with polybasic acids in which remaining free acid radicals may have been converted to the corresponding salts with alkali metals, alkaline earth metals, ammonia or an amine or to an ester with a suitable alcohol, esp. a lower aliphatic alcohol, such as methanol and ethanol and the like, or to an amide with ammonia or a lower aliphatic amine.

398
344

(6) Compounds having the general Formula II, wherein the p,p'-hydroxy groups may be free, or converted to other derivatives as stated above at items 2-5.

The benzhydrylidene cycloalkanes of the invention are valuable compounds. Some are capable of inhibiting the secretion of several pituitary gonadotrophins in the male and female without being at the same time strong estrogens. In some of them the relation between uterotrophic and vaginotrophic activity differs from that of previously known steroidal and non-steroidal agents. Some of them interfere with the remaining production of estrogens in females, probably by an action of the adrenals. Some are able to antagonize the peripheral actions of estrogens. These properties, which can occur singly or in combination, make the compounds useful agents in the treatment of a variety of conditions. A special advantage is that being non-steroidal they cannot by metabolism be changed into compounds having androgenic corticoid or progestational activities. In this respect they differ from steroids having similar activities.

In the male some of them can be useful, where a reduction in the production of androgens is desirable. Since some of the compounds inhibit the secretion of those gonadotrophins which cause spermatogenesis, they can be used for reducing fertility in the male. In all these applications in the male the relative weakness of their estrogenicity is a definite advantage, since feminization is undesirable.

In the female the agents are valuable in their ability to inhibit the secretion of gonadotrophins without being strong estrogens.

The above-mentioned findings have been established by animal tests carried out as described hereinafter.

The animal tests used were a vaginal cornification test in spayed rats, a uterus growth test in infantile mice and a pituitary inhibition test in prepuberal male rats. Estrogenicity in birds was studied in newly hatched chicken. Antiestrogenicity was studied in chicken and mice as described hereinafter. The compounds were compared with stilbestrol and the test for estrogenicity showed that several of the compounds were more active on the pituitary than on the vagina while others are especially weakly acting on the uterus while retaining pituitary inhibitory potency. The benzhydrylidene cyclopentane compound, for instance, was about 5,000 times weaker than stilbestrol on the vagina but only about 1,500 times weaker on the pituitary. Corresponding figures for the benzhydrylidene cyclohexane compound are 1,750 and 750.

It is remarkable that the pituitary inhibition was always achieved without stimulation of the seminal vesicles. This is not the case with estradiol benzoate, stilbestrol and similar compounds and in itself indicates a favorable relation between ability to inhibit the pituitary and stimulatory estrogenic actions.

Some of the compounds are antiestrogenic in tests conducted in the following manner. In the chicken a dose of 0.5 mg./day of estradiol benzoate was combined with 5 mg./day of the compound to be tested, and the resulting oviduct growth over the first 6 days was compared with that resulting in controls from 0.5 mg./day of estradiol benzoate alone. The oviducts of the animals receiving the benzhydrylidene cyclohexane compound weighed 45-50% of the final weight of the controls. The inhibitory potency of the benzhydrylidene cyclopentane compound was less pronounced.

In a uterus growth test 0.12 µg./day of estradiol benzoate was given to control mice and the same dose +30 µg./day of the benzhydrylidene cyclohexane compound to the experimental group. On the fourth day the average uterine weight was 25% smaller in the experimental group.

Thus, some of the compounds have an antiestrogenic action on systemic administration.

The compounds of the invention may be administered as such or together with suitable carriers which are phar-

maceutically acceptable. The carrier is selected according to the route of administration to be used as well as according to the physical properties of the compounds and standard pharmaceutical practice.

The invention is further illustrated by means of the following non-limiting examples.

EXAMPLE I

Preparation of p,p'-dimethoxybenzhydrylidene cyclohexane

To a Grignard solution of 29 grams of magnesium (1.2 moles) and 225 grams of 4-methoxybromobenzene (1.2 moles) in 500 millilitres of dry ether there was added dropwise with vigorous agitation 63 grams of cyclohexane carboxylic acid ethyl ester (0.4 mole) dissolved in 500 millilitres of dry ether. Upon completion of the addition the reaction mixture was refluxed 2.5 hours with stirring and was then cooled, and a solution of 10 moles of ammonium chloride in 2 litres of water was added. The ethereal layer was separated, washed with water, dried over anhydrous sodium sulphate and distilled. Boiling point: 195-207° C. at 0.3 mm. Upon recrystallization from ethanol the product melted at 110-111° C.

EXAMPLE 2

Preparation of p,p'-dibenzoyloxybenzhydrylidene cyclohexane

This compound was prepared from a Grignard solution of 16 grams of mg. (0.66 mole) and 158 grams of 4-benzoyloxybromobenzene (0.6 mole) in 500 millilitres of dry ether and 32 grams of ethyl cyclohexanecarboxylate (0.2 mole) dissolved in 50 millilitres of dry ether as described in Example 1. Upon recrystallization from ethanol the melting point is 143-145° C. Yield: 69 grams.

EXAMPLE 3

Preparation of p-hydroxy-p'-methoxybenzhydrylidene cyclohexane

To a Grignard solution prepared from 110 grams of magnesium (4.5 moles) and 840 grams of p-bromoanisole (4.5 moles) in 1 litre of anhydrous ether, there was added dropwise with vigorous agitation 307 grams of p-hydroxyphenyl cyclohexyl ketone (1.5 moles) dissolved in 1 litre of anhydrous ether. Upon completion of the addition the reaction mixture was refluxed for 2.5 hours with agitation, and was then cooled. Thereupon 15 moles of ammonium chloride dissolved in 3 litres of water were added. The ethereal layer was separated, washed with water, dried over anhydrous sodium sulphate and distilled. Yield: 370 grams. Boiling point 180-190° C. at 0.1 mm. The substance was recrystallized from a mixture of carbon tetrachloride and petroleum ether. Melting point 145-146° C.

EXAMPLE 4

Preparation of p,p'-dibenzoyloxybenzhydrylidene cyclohexane

A Grignard solution prepared from 19 grams of cyclohexyl chloride in 100 millilitres of ether was filtered and evaporated to dryness. A solution of 45.3 grams of dibenzoyloxybenzophenone in 150 millilitres of toluene was added to the cyclohexyl magnesium chloride. After the addition was completed the reaction mixture was refluxed for two hours, whereupon the magnesium complex was decomposed with 2 M hydrochloric acid. The toluene layer was washed with water and dried over anhydrous magnesium sulphate and then evaporated. The residue was recrystallized from a mixture of acetone and chloroform (1:1). The melting point was found to be 139-141° C. The yield was 28 grams.

EXAMPLE 5

*Preparation of p,p'-dihydroxybenzhydri-
dene cyclohexane*

A mixture of 118 grams of p-hydroxy-p'-methoxybenzhydri-
dene cyclohexane (0.4 mole), 120 grams of
potassium hydroxide pellets and 500 millilitres of tri-
ethylene glycol was stirred four hours at 220° C. When
the reaction mixture was poured into water the sub-
stance crystallized, and the crystals were filtered off and
washed with water. The substance was then recrystal-
lized from a mixture of ethanol and petroleum ether.
Yield: 104 grams. Melting point 235-236° C.

EXAMPLE 6

*Preparation of p,p'-dihydroxybenzhydri-
dene cyclohexane*

A solution of 10 grams p,p'-dimethoxybenzhydri-
dene cyclohexane and 25 grams of potassium hydroxide in 100
millilitres ethanol was heated in an autoclave to 200° C.
for 12 hours. After cooling the reaction mixture was
poured into 500 millilitres of water and washed with
ether. The aqueous phase was acidified with 6 N hydro-
chloric acid to about pH 2.5 whereupon the compound
crystallized. The crystals were recovered by suction fil-
tration and were washed with 50% (vol./vol.) ethanol.
Upon recrystallization from cyclohexane the melting point
was 242-245° C.

EXAMPLE 7

*Preparation of p,p'-dihydroxybenzhydri-
dene cyclohexane*

A mixture of 23 grams (0.005 mole) of p,p'-dibenzyl-
oxybenzhydri-
dene cyclohexane and 95 grams of PtO₂ in
150 millilitres of ethanol is hydrogenated at normal pres-
sure and 20° C. After 300 millilitres of hydrogen are
absorbed the catalyst is filtered off and the solution is
evaporated to dryness. The residue is recrystallized from
50% ethanol and has the melting point 242-245° C. Yield:
0.9 grams.

EXAMPLE 8

*Preparation of p,p'-diacetoxybenzhydri-
dene cyclohexane*

56 grams of p,p'-dihydroxybenzhydri-
dene cyclohexane (0.2 mole) was mixed with 250 millilitres of acetic
anhydride and 500 millilitres of pyridine. The mixture
was refluxed for two hours and was then poured into
water the substance crystallizing out. The crystals were
filtered off and washed with water. Finally the substance
was recrystallized from ethanol. Yield: 62 grams.
Melting point 135-136° C.

EXAMPLE 9

*Preparation of p-hydroxy-p'-methoxybenzhydri-
dene cyclohexane*

98 grams of p-hydroxy-p'-methoxybenzhydri-
dene cyclohexane (0.33 mole) was dissolved in 400 millilitres of
acetic anhydride and one drop of concentrated sulphuric
acid was added. The mixture was then heated for half
an hour on the steam bath and poured into water the
substance crystallizing out. The crystals were filtered off,
washed with water and dilute ethanol, and finally recryst-
allized from ethanol. Yield: 105 grams. Melting point
109-110° C.

EXAMPLE 10

*Preparation of p,p'-dicaproyloxybenzhydri-
dene cyclohexane*

To a solution of 1.5 grams of p,p'-dihydroxybenzhy-
dri-
dene cyclohexane 2 grams of caproylchloride were
added. The mixture was stirred at 20° C. for 1 hour
and was poured into an excess of 2 N hydrochloric acid
and ice. The oil formed was extracted with ether. The
etheral extract was washed with water and dried over

sodium sulphate. The ether was then evaporated and
the compound formed distilled at 195-205° C. at a pres-
sure of 0.005 mm. of Hg n_D^{20} =1.5469. The yield after
distillation was 1.5 grams.

EXAMPLE 11

*Preparation of disodium p,p'-dihydroxybenzhydri-
dene cyclohexane disulphate*

To a well stirred mixture of 12 millilitres of chloro sul-
phonic acid and 60 millilitres of pyridine, cooled to -10°
C., there was added a solution of 15.0 grams of p,p'-di-
hydroxybenzhydri-
dene cyclohexane in 20 millilitres of
pyridine. The reaction temperature was kept below 0°
C. during the addition, whereupon the mixture was heated
to 30-40° C., for one hour and then poured into a satu-
rated solution of sodium hydrogen carbonate in water.
The aqueous phase was washed with ether, filtered and
neutralized with dilute hydrochloric acid. The precipi-
tated substance was sucked off, washed with water and
recrystallized from water. The product consisted of the
pyridine salt of the disulphate. This salt was dissolved
in 40 millilitres of 1 M sodium hydroxide. The solution
was filtered and diluted with 1 litre of acetone and 1 litre
of ether. The sodium salt crystallized as long needles
which were sucked off and washed with ether. The yield
was 12 grams.

EXAMPLE 12

*Preparation of p-hydroxy-p'-methoxybenzhydri-
dene cyclopentane*

This substance was prepared from p-hydroxyphenyl
cyclopentyl ketone and anisylmagnesium bromide as de-
scribed in Example 3. Boiling point: 193-197° C. at 0.2
mm. Upon recrystallization from carbon tetrachloride
the substance melted at 139-140° C.

EXAMPLE 13

*Preparation of p-acetoxy-p'-methoxybenzhydri-
dene cyclopentane*

This substance was prepared from p-hydroxy-p'-me-
thoxybenzhydri-
dene cyclopentane as described in Exam-
ple 9. Melting point: 115-116° C.

EXAMPLE 14

*Preparation of p,p'-diacetoxybenzhydri-
dene cyclopentane*

A mixture of 98 grams of p-hydroxy-p'-methoxybenz-
hydri-
dene cyclopentane (0.35 mole), 100 grams of po-
tassium hydroxide pellets and 400 millilitres of triethylene
glycol was stirred for five hours at 220° C. The reaction
mixture was then poured into water and washed with ether.
The aqueous phase was acidified with 5 N hydrochloric
acid to about pH 3 and was then extracted with ether.
Thereupon the ethereal phase was washed with water,
dried over anhydrous sodium sulphate and evaporated
into dryness the residue forming crystals. The crude
product thus obtained in a yield of 93 grams was dissolved
in 400 millilitres of acetic anhydride and one drop of con-
centrated sulphuric acid was added. Upon heating on
the steam bath for half an hour the reaction mixture was
poured into water and the crystalline substance separat-
ing out was recovered by filtration and washed with water
and dilute ethanol. Finally the substance was distilled
at 203-208° C. at a pressure of 0.2 mm. Upon recrystal-
lization from ethanol 65 grams of the desired product
having the melting point 128-129° C. was obtained.

EXAMPLE 15

*Preparation of p,p'-dimethoxybenzhydri-
dene cyclobutane*

This compound was prepared from cyclobutane car-
boxylic acid ethyl ester as described in Example 1. Boil-
ing point: 173-175° C. at 0.03 mm. Upon recrystalliza-
tion from ethanol the product melted at 116-117° C.

11

EXAMPLE 16

Preparation of p,p'-diacetoxybenzhydriidene cyclobutane

This compound was prepared from p,p'-dimethoxybenzhydriidene cyclobutane as described in Example 14. Boiling point: 205–212° C. at 0.2 mm.

EXAMPLE 17

Preparation of p,p'-dimethoxybenzhydriidene cycloheptane

This compound was prepared from cycloheptane carboxylic acid ethyl ester as described in Example 1. Boiling point: 225–235° C. at 0.03 mm. Upon recrystallization from ethanol the product melted at 64–66° C.

EXAMPLE 18

Preparation of p,p'-dihydroxybenzhydriidene cycloheptane

This compound was prepared from p,p'-dimethoxybenzhydriidene cycloheptane as described in Example 6. Upon recrystallization from a mixture of ethanol and benzene the yield was 75 grams. Melting point: 159–198° C.

EXAMPLE 19

Preparation of p,p'-diacetoxybenzhydriidene cycloheptane

This compound was prepared from p,p'-dihydroxybenzhydriidene cycloheptane as described in Example 9. The substance was distilled at 207–215° C. at 0.07 mm. of Hg. Upon recrystallization from ethanol the product melted at 98–101° C. Yield: 42 grams.

EXAMPLE 20

Preparation of p,p'-dimethoxybenzhydriidene cyclooctane

This compound was prepared from 4-methoxybromobenzene and ethyl cyclooctane carboxylate as described in Example 1. Boiling point: 190–200° C. at 0.05 mm. of Hg. Upon recrystallization from ethanol the compound melted at 68–70° C.

EXAMPLE 21

Preparation of p,p'-diacetoxybenzhydriidene cyclooctane

This compound was prepared from p,p'-dimethoxybenzhydriidene cyclooctane as described in Example 14. Boiling point: 214–217° C. at 0.05 mm. of Hg. Upon recrystallization from ethanol the melting point was 111–113° C.

EXAMPLE 22

Preparation of p,p'-dimethoxybenzhydriidene (4-methylcyclohexane)

This compound was prepared from 4-methoxybromobenzene and ethyl 4-methylcyclohexane carboxylate as described in Example 1. Boiling point: 166–168° C. Upon recrystallization from ethanol the product melted at 47–50° C.

EXAMPLE 23

Preparation of p,p'-diacetoxybenzhydriidene (4-methylcyclohexane)

This compound was prepared from p,p'-dimethoxybenzhydriidene (4-methylcyclohexane) as described in Example 14. Boiling point: 196–198° C. at 0.15 mm. Upon recrystallization from isopropylketone and from ethanol the product melted at 121–124° C.

EXAMPLE 24

Preparation of p,p'-dimethoxybenzhydriidene (3,4-dimethylcyclohexane)

This compound was prepared from 4-methoxybromobenzene and ethyl 3,4-dimethylcyclohexanecarboxylate as described in Example 1. Boiling point: 180–190° C.

12

Recrystallized from ethanol the substance melted at 64–66° C.

EXAMPLE 25

Preparation of p,p'-diacetoxybenzhydriidene (3,4-dimethylcyclohexane)

This compound was prepared from p,p'-dimethoxybenzhydriidene (3,4-dimethylcyclohexane) as described in Example 14. Boiling point: 222–224° C. at 0.35 mm. Recrystallized from light petroleum the substance melted at 86–88° C.

EXAMPLE 26

Preparation of p,p'-dimethoxybenzhydriidene (3-methylcyclopentane)

This compound was prepared from 4-methoxybromobenzene and ethyl 3-methylcyclopentane carboxylate as described in Example 1. Boiling point: 172° C. at 0.2 mm. Recrystallized from methanol the substance melted at 73–75° C.

EXAMPLE 27

Preparation of p,p'-dimethoxybenzhydriidene (4-isopropylcyclohexane)

This compound was prepared from 4-methoxybromobenzene and ethyl 4-isopropylcyclohexanecarboxylate as described in Example 1. Recrystallized from ethanol the substance melted at 80–81° C.

EXAMPLE 28

Preparation of p-allyloxy-p'-hydroxybenzhydriidene cyclopentane

3.1 grams of p,p'-dihydroxybenzhydriidene cyclopentane was dissolved in 10 millilitres of methylethyl ketone 3.3 grams of anhydrous potassium carbonate and 2.8 grams of allyl bromide were added to the solution and the reaction mixture was refluxed for 7 hours. Then the reaction mixture was poured into 25 millilitres of water. The precipitate formed was extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate, evaporated to dryness and distilled. Upon recrystallization from ethanol the melting point was 46–48° C. The yield was 3.0 grams.

EXAMPLE 29

200 mg. tablets

200 milligrams of p,p'-dihydroxybenzhydriidene cycloheptane, 100 mg. of powdered sugar, and 64 mg. of corn starch are mixed and granulated with a 10% gelatin solution. The granulation is dried and ground to fine granules for tableting. About 1% of magnesium stearate is added as a lubricant together with sufficient corn starch to give a weight of 600 mg. per tablet. The product is compressed on a single punch or rotary machine using a 5/8 inch punch.

EXAMPLE 30

500 mg. tablets

500 mg. of p,p'-diacetoxybenzhydriidene cyclooctane, in finely powdered form is admixed with 60 mg. of corn starch and 100 mg. of powdered sugar and then granulated with a 10% gelatin solution. The granulation is dried and ground to size suitable for tableting. About 1% of magnesium stearate is added as a lubricant, together with sufficient corn starch to give a weight of 700 mg. per tablet. The product is compressed on a single punch or rotary machine using a 7/16 inch punch.

The tablets of Example 1 and Example 2 may be suitably coated if desired, as, for example, with sugar.

EXAMPLE 31

Injectable suspension, 100 mg. per ml.

The following ingredients are sterilized separately: 100 mg. of p-methoxy-p'-acetoxybenzhydriidene cyclohexane, 0.1 mg. of Tween 80 and q.s. of corn oil to make a

13

final volume of one ml. These ingredients are admixed aseptically. Particle size may be achieved by use of micronized material or by use of a ball mill, maintaining aseptic conditions. The above suspension may be administered subcutaneously and intramuscularly.

EXAMPLE 32

10% ointment

To a melt of 1.5 lbs. of propylene glycol, 6 lbs. of polyethylene glycol 400 USP and 6 lbs. Carbowax 4000 USP is added 1.5 lbs. of micropulverized p,p'-dimethoxybenzhydrylidene cyclopentane. The product is stirred until almost solid and milled if necessary to a smooth ointment. The ointment is filled into suitable containers.

What we claim is:

1. Compounds containing a cycloalkyl group, corresponding to the following formula:



wherein R is a member selected from the group consisting of unsubstituted saturated straight and branch-chained alkylene radicals containing from 4 to 8 carbon atoms wherein said R together with the carbon atom to which it is attached forms a ring containing from 5 to 6 carbon atoms, and R₁ and R₂ are selected from the group consisting of hydrogen, alkyl radicals containing from 1 to 6 carbon atoms, alkenyl radicals containing from 2 to 6 carbon atoms, phenyl alkyl radicals in which the alkyl radical contains from about 1 to about 3 carbon atoms, and pharmaceutically acceptable acyl radicals.

14

2. The compound according to claim 1, wherein R is the divalent $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$.

3. The compound according to claim 1, wherein R is the divalent $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$.

4. The compound p,p'-dihydroxybenzhydrylidene cyclopentane.

5. The compound p,p'-dihydroxybenzhydrylidene cyclohexane.

6. The compound p,p'-diacetoxybenzhydrylidene cyclohexane.

7. The compound p-hydroxy p'-methoxy-benzhydrylidene cyclohexane.

8. The compound p,p'-dicapropyloxybenzhydrylidene cyclohexane.

9. The compound p,p'-dimethoxybenzhydrylidene (4-methyl cyclohexane).

References Cited by the Examiner

UNITED STATES PATENTS

2,429,556 10/1947 Longfellow et al. 260-619
2,950,266 8/1960 Goldblum.

FOREIGN PATENTS

537,976 7/1941 Great Britain.

OTHER REFERENCES

Dodds et al.: Proc. Royal Soc. London, vol. 127 B (1939), pages 140-166 (27 pages).

Solmssen: Chem. Reviews, 37:553, 558 (1945; 2 pages).

LEON ZITVER, Primary Examiner.

CHARLES B. PARKER, Examiner.

H. G. MOORE, J. E. EVANS, Assistant Examiners.

404

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	06008246
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	
	Folios	011

004831

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional		PCT/US2004/024308	
Fecha de Presentación Internal.		27/07/2004.	

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 26 a 288 como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios: 289 a 308 como se radicó inicialmente.
- 1.3. Prioridad: 28/07/2003; US; 60/490,588

2. Objeto de la invención

Título de la invención: "COMPUESTOS DE CICLOALQUILIDENO COMO MODULADORES DEL RECEPTOR DE ESTRÓGENO"

Problema Técnico Planteado: Necesidad de compuestos útiles como moduladores receptivos de estrógeno.

Solución: Compuestos conforme a la reivindicación 1, representados por la formula (I).

403

IPC: C07C59, A61K31/351, A61K31/382, A61P5/30.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

En las reivindicaciones 1-27, se reclama un compuesto de fórmula (I) incluyendo sus sales, solvatos y derivados funcionalmente funcionales de los mismos. Se observa que en la presente descripción no existe soporte para la obtención de solvatos de los compuestos reclamados y que la expresión "derivados farmacológicamente funcionales de los mismos", no es concisa.

La reivindicación 1, y sus dependientes reclaman un compuesto de fórmula (I) incluyendo sus sales, radicales con R1-R7 y variables p y q ; no obstante se encuentra que existe falta de concisión y definición en el alcance de acuerdo a los ejemplos de soporte en la descripción. Por lo cual se hacen las siguientes observaciones:

Existen términos ambiguos como por ejemplo: alquilo, heteroarilo, heterociclilo, cicloalquilo, por lo que es necesario que los sustituyentes de cada radical y variable sea definido de forma específica, acorde con los compuestos ejemplificados, que evidentemente resuelvan el problema planteado con la actividad biológica que se les atribuye.

Además existe sustento, acorde a los ejemplos en la descripción, para la materia reclamada cuando:

R1=OH

R2= CH3, halógeno, q=0, 1,2

R4=halógeno p=0,1

R5= H, R6, R7= H, alquil

R3=-(Y)₂-R8

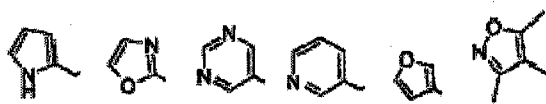
Z=0 entonces R8 = CO₂H, NHCO-CH₃; -O-CH₂-CH₂-O-CH₂-CH₂-OH cuando t=2, Rh= -CR_jR_k y R_j y R_k=H; -PO₃HRa y Ra = alquilo; SO₂-Rd y Rd =alquilo; CONH₂; O(Rh)t OH y Rh=CH₂, t=2 ; -NRa-SO₂-Rd ; CN; halógeno; -(Rh)t OH y Rh=CH₂, t=1; CONRaRb , -SO₂Rd.

Ra, Rb, Re, Rf , R_j, R_k = H ; Rc, Rd=alquil

Rh= R_jR_k

Según los ejemplos cuando R3=R8 y este significa arilo, es solo fenilo, y si R3 es

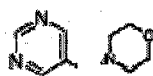
hetroarilo, estos son:



No existe sustento para heterociclilos.

Cuando el sustituyente es arilo este esta sustituido por CN, F, $\equiv$ N,

OH, COOH, CONH₂, NHCOCH₃, NHSO₂CH₃, SO₂CH₃, -(CH₂)CO₂H,



406

La reivindicaciones 29, esta caracterizada por un uso; se aclara que este no es una característica técnica esencial de un compuesto.

4. Excepción a la patentabilidad (artículo 20 D486 literal d))

Las reivindicaciones 36-38 se refieren a métodos de tratamiento.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Las reivindicaciones 33-35 se refieren a Usos.

6. 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: 28/07/2003.

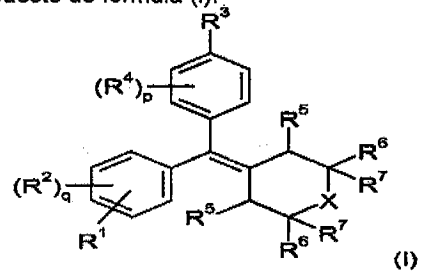
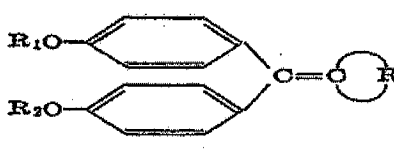
Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US3287397	Substituted Benzhydrylidine cycloalkanes	Noviembre,22,1966

D1 (folios: 396-402)

7. Análisis de patentabilidad (artículo 14 D486)

7.1 Novedad (artículo 16 D486)

CARACTERÍSTICAS ESENCIALES DE LA REIVINDICACION 1	D1
Compuesto de fórmula (I):  (I) Cuando q=0, p=0 R1= OH R3= -(Y)z- R5 cuando z=0, R5= alcoxy, entonces R3= alcoxy de 1 a 6 C R5, R6 y R7 =H X= -(CH2)n n= 0,1, 2,3; se pueden obtener ciclos de 5-8 carbonos.	Compuesto de fórmula (I):  Donde: R1= OH OR2= Oalquilo de 1 a 6 C Hidrógeno R=-(CH2)n n=4-7; se pueden obtener ciclos de 5-8 carbonos.

De la comparación anterior, como se puede observar, las características técnicas esenciales del compuesto reclamado, estaban divulgadas en D1 por lo tanto la reivindicación 1 no es nueva, así como tampoco sus dependientes 2-27, y la composición farmacéutica de la reivindicación 28.

8. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US3287397	1-28	Novedad

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 sesenta 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 N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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

09 ABR. 2010

CONCEPTO TÉCNICO No.969

EXAMINADOR TÉCNICO
Código No.202078

408

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	06008246
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	0 4832
	Folios	002

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

-Muthyala et al: "Los núcleos bicíclicos puenteados que contienen un motivo 1,1-diarileno son ligandos de alta afinidad selectivos del subtipo para receptor de estrógeno". J MED CHEM, Vol 46, 4 de febrero de 2003 (2003-02-04) páginas 1589-1602, XP002313260.

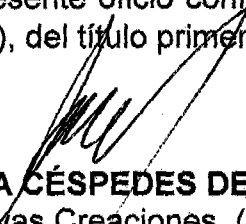
-CHemical Abstracts Service, Columbus, Ohio, US; Gilber, Jacques et al: " Inhibición de prostaglandina sintasa mediante derivados de di- y trifeniletileno: un estudio de estructura-actividad", XP002313261. Journal of medical chemistry, 26(5), 693-9 CODEN: JMCMAR; ISSN:0022-2623, 1983.

- CHemical Abstracts Service, Columbus, Ohio, US; Jendralla, H. et al: " Sintesis y actividad biológica de inhibidores de reductasa HMG-CoA nuevos.3. Lactonas de los ácidos 6-fenoxi-3,5-dihidroxihexanóico", XP002313262. Journal of medical chemistry, 34(10), 2962-83 CODEN: JMCMAR; ISSN:0022-2623, 1991.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO 2005/012220 equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones

completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 09 ABR. 2010

CONCEPTO TÉCNICO No. 969	EXAMINADOR TÉCNICO Código No.202078
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