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Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. **01.002.039**

Solicitud del examen de patentabilidad correspondiente a la Patente de Invención para:

"COMPOSICIÓN FARMACEUTICA QUE COMPRENDE UN ANILLO DE HIDROCARBILO Y UN GRUPO SULFAMATO"

Solicitante: **STERIX LIMITED y SCHERING AKTIENGESELLSCHAFT**

SOLICITUD EXAMEN DE PATENTABILIDAD

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago **No. 03 - 82.456** de **Noviembre** 12 **de 2003,** correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente de Invención, y se continúe con su tramitación.

Señor Jefe,

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
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13 NOV. 2003

Bogotá,
MCA/gcb/4804

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SUPERINTENDENCIA DE COMERCIO
Radicacion : 01002839 00000004 Folios: 2
Fecha (AMD): 2003-11-13 14:50:52
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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NIT : 8001/6989-2

RECIBO OFICIAL DE CAJA : 03 - 82,456
FECHA : NOVIEMBRE 12 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAMILO RESTREPO	CONSIGNACION	BANCO POPULAR	050-00110-6	9932778	12/11/2003	12,333,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
			TOTAL : $	335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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PC 332

Industria y Comercio
SUPERINTENDENCIA

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **01-2039**

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **528**, DE

FECHA **30 DE MAYO DE 2003**, EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **29 DE AGOSTO DE 2003.**

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_____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
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US005556847A

United States Patent [19]

Johnson et al.

[11] Patent Number: 5,556,847

[45] Date of Patent: Sep. 17, 1996

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D1

[54] METHODS OF EFFECTING MEMORY ENHANCEMENT MEDIATED BY STEROID SULFATASE INHIBITORS

[75] Inventors: David A. Johnson, Butler; Pui-Kai Li, Library; Michael E. Rhodes, Latrobe, all of Pa.

[73] Assignee: Duquesne University of the Holy Ghost, Pittsburgh, Pa.

[21] Appl. No.: 338,534

[22] Filed: Oct. 27, 1994

[51] Int. Cl.[6] A61K 31/56; A61K 31/57

[52] U.S. Cl. 514/178; 514/182

[58] Field of Search 514/178, 182

[56] References Cited

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92/01387 8/1992 WIPO .
92/07729 9/1992 WIPO .
92/08935 10/1992 WIPO .

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Flood et al., "Dehydroepiandrosterone and its sulfate enhance memory retention in mice", *Brain Research*, vol. 447, pp. 269–278, 1988.

Flood et al., "Dehydroepiandrosterone sulfate improves memory in aging mice", *Brain Research*, vol. 448, pp. 178–181, 1988.

Flood et al., "Memory-enhancing effects in male mice of pregnenolone and steroids metabolically derived from it", *Proc. Nat'l. Acad. Sci. USA*, vol. 89, pp. 1567–1571, 1992.

Majewska, "Neurosteroids: Endogenous Bimodal Modulators of the $GABA_A$ Receptor. Mechanism of Action and Physiological Significance", *Progress in Neurobiology*, vol. 38, pp. 379–395, 1992.

Robel et al., "Neurosteroids: Biosynthesis and Function", *Trends Endocrinol Metab*, vol. 5, pp. 1–8, 1994.

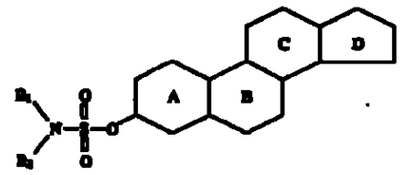
Mellon, "SPECIAL ARTICLE— Neurosteroids: Biochemistry, Modes of Action, and Clinical Relevance", *Journal of Clinical Endocrinology and Metabolism*, vol. 78, No. 5, pp. 1003–1008, 1994.

Primary Examiner—Phyllis G. Spivack

Attorney, Agent, or Firm—Jolene W. Appleman; Eckert Seamans Cherin & Mellott

[57] ABSTRACT

This invention discloses a method for treating a patient for an illness selected from the group consisting of anoxia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia or individuals otherwise seeking memory enhancement. The method comprises providing a compound of formula (1)



(1)

wherein (a) R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms and (b) the ring system ABCD is steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiolester, pregnenolone, substituted estrone, substituted dehydroepiandrosterone, substituted estradiol, substituted estradiolesters and substituted pregnenolone. The invention also discloses the enhancement of memory by the steroid sulfatase inhibitors of the invention acting synergistically with the naturally occurring neurosteroids dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS).

45 Claims, 1 Drawing Sheet

METHODS OF EFFECTING MEMORY ENHANCEMENT MEDIATED BY STEROID SULFATASE INHIBITORS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to memory enhancement in patients suffering from illnesses consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post-stroke dementia or individuals otherwise seeking memory enhancement. More particularly, the invention relates to the enhancement of memory by steroid sulfatase inhibitors and steroid sulfatase inhibitors in combination with the naturally occurring neurosteroids dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) and other structurally similar organic compounds.

2. Description of the Prior Art

Neurosteroids are concentrated within and are known to produce effects mediated by the central nervous system (CNS). Paul Robel and Etienne-Emile Baulieu, *Neurosteroids, Biosynthesis and Function*, Trends Endocrinol Metab., Volume 5, pp. 1–8 (1994), discloses that several neurosteroids are involved in either auto-or paracrine mechanisms involving both regulation of target gene expression and effects on membrane receptors (including those of neurotransmitters).

Among the effects associated with neurosteroids is the enhancement of memory. James F. Flood, Gary E. Smith and Eugene Roberts, *Dehydroepiandrosterone and Its Sulfate Enhance Memory Retention in Mice*, Brain Research, Volume 447 pp. 269–278 (1988); James F. Flood, John E. Morley and Eugene Roberts, *Memory-Enhancing Effects in Male Mice of Pregnenolone and Steroids Metabolically Derived From It*, Proc. Nat'l Acad. Sci. USA, Volume 89, pp. 1567–1571 (1992) and James F. Flood and Eugene Roberts, *Dehydroepiandrosterone Sulfate Improves Memory in Aging Mice*, Brain Research, Volume 448, pp. 178–181 (1988).

The mechanism of this enhancement is not well understood but sulfated neurosteroids which enhance memory such as pregnenolone sulfate (PS) and dehydroepiandrosterone sulfate (DHEAS) are known to both inhibit the actions mediated by the $GABA_A$ receptor and facilitate NMDA receptors. The unsulfated analogs, pregnenolone and dehydroepiandrosterone, also enhance memory, however, they can also be metabolized to neurosteroids which have the opposite effect at the $GABA_A$ receptor. Synthia H. Mellon *Special Article Neurosteroids: Biochemistry, Modes of Action and Clinical Relevance*, Endocrinology and Metabolism, Volume 78, No. 3 pp. 1003–1008 (1994) and Majewska M.D.: *Neurosteroids: Endogenous Bimodal Modulators of the $GABA_A$ Receptor. Mechanism of Action and Physiological Significance*. Progress in Neurobiology, Volume 38, pp. 379–395 (1992).

PCT/US 92107739 published as WO93/04687 on Mar. 18, 1993 discloses methods for modulating NMDA-mediated ion transport and inhibiting non-NMDA glutamate-induced ion transport in neuronal cells. The methods involve contacting a neuronal cell with an effective mount of the neurosteroid pregnenolone sulfate and PCT/US92/08935 published as WO93/07877 on Apr. 29, 1993 discloses memory enhancement by pregnenolone and pregnenolone sulfate. PCT/GB92/01587 published as WO93/05064 on

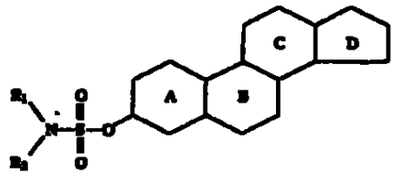
Mar. 18, 1993 disclosed that steroid sulfatase inhibitors are able to treat breast cancer.

Since the metabolism of pregnenolone and DHEA between the sulfated and unsulfated forms occurs bi-directionally within the central nervous system, it was previously unknown whether the sulfated or unsulfated forms produce memory enhancing effects individually or by way of metabolism from one analog to the other.

Therefore, in spite of the prior art disclosures, there remains a very real and substantial need for steroid sulfatase inhibitor which can alter the equilibrium between the endogenous sulfated and unsulfated forms of DHEA in such a way to enhance memory. There is also a need to determine whether the memory enhancing effects of peripherally administered DHEAS and PS can be potentiated by inhibition of the metabolism of DHEAS and PS to DHEA and P, respectively, by way of preadministration of the steroid sulfatase inhibitors of the present invention.

SUMMARY OF THE INVENTION

The present invention has met the hereinbefore described need. The steroid sulfatase enzyme inhibitors of the present invention can inhibit greater than about 98% of the sulfatase after 24 hours. The present invention provides a process of using the steroid sulfatase inhibitors described herein for memory enhancement comprising providing a compound having the formula (1)



(1)

wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms and (b) the ring system ABCD is steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiolesters, pregnenolone, substituted estrones, substituted dehydroepiandrosterones, substituted estradiol, substituted estradiolesters and substituted pregnenolone. The method comprises incorporating the compound in a suitable pharmaceutical carrier, administering a therapeutically or prophylactically effective amount of the compound incorporated in the carrier to a patient; and employing the method in treating a patient for memory enhancement.

Preferably R_1 is methyl and R_2 is hydrogen and most preferably both R_1 and R_2 are hydrogen. In the above structure (1), the steroid ring system is preferably estrone, dehydroepiandrosterone or pregnenolone. Other suitable steroid ring systems are:

Substituted estrones as follows:
- 2-OH-estrone
- 2-methoxy-estrone
- 4-OH-estrone
- 6 alpha-OH-estrone
- 7 alpha-OH-estrone
- 16 alpha-OH-estrone
- 16 beta-OH-estrone

Estradiols and substituted estradiols as follows:
- 2-OH-17-beta estradiol
- 2-methoxy-17 beta-estradiol
- 4-OH-17-beta-estradiol

6 alpha-OH-17 beta-estradiol
7 alpha-OH-17 beta-estradiol
16 alpha-OH-17 beta-estradiol
16 beta-OH-17 alpha-estradiol
16 beta-OH-17 beta-estradiol
17 alpha-estradiol
17 beta-estradiol
17 alpha-ethinyl-17 beta-estradiol

Estradiol esters and substituted estradiol esters, for example:
17-beta-OH-methyl estradiol ester
17-beta-OH-ethyl estradiol ester
17-beta-OH propyl-estradiol ester
17-beta-OH-butyl estradiol ester
17-beta-OH-penthyl-estradiol ester
17-beta-OH-hexyl-estradiol ester

Substituted dehydroepiandrosterones, for example,:
6 alpha-OH-dehydroepiandrosterone
7 alpha-OH-dehydroepiandrosterone
16 alpha-OH-dehydroepiandrosterone
16 beta-OH-dehydroepiandrosterone

Pregnenolone and substituted pregnenolone, for example:
6 alpha-OH-pregnenolone
7 alpha-OH-pregnenolone
16 alpha-OH-pregnenolone
16 beta-OH-pregnenolone

This process provides a method of therapeutically treating a patient for an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia. It also may treat other individuals that seek memory enhancement.

This invention provides a process for using the steroid sulfatase inhibitors described herein as synergistic agents with dehydroepiandrosterone sulfate (DHEAS) and/or pregnenolone sulfate (PS) to enhance the effect obtained treating a patient for one of either memory enhancement or therapeutically treating an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

It is an object of this invention to employ an effective dosage of the steroid sulfatase inhibitors for substantially enhancing the memory function.

It is an object of the present invention to employ steroid sulfatase inhibitors for use in treating a patient therapeutically.

It is an object of the present invention to employ steroid sulfatase inhibitors for use in prophylactically treating a patient.

It is a further object of this invention to employ an effective dosage of DHEAS with the steroid sulfatase inhibitors of this invention for a synergistic effect to further enhance the effect of treating a patient for one of either memory enhancement or therapeutically.

It is a further object of this invention to employ an effective dosage of PS with the steroid sulfatase inhibitors of this invention for a synergistic effect to further enhance the effect of treating a patient for one of either memory enhancement or therapeutically.

It is a further object of this invention to employ an effective dosage of DHEAS and PS with the steroid sulfatase inhibitors of this invention for a synergistic effect to further achieve memory enhancement.

It is yet a further object of this invention to use the steroid sulfatase inhibitors of this invention to increase the concentration of endogenous sulfated neurosteroids by way of inhibition of steroid sulfatase activity to enhance memory function and/or therapeutically.

It is yet another object of this invention to use the steroid sulfatase inhibitors of this invention to show that it is the sulfated form of DHEA and pregnenolone which is responsible for the memory enhancing properties of these neurosteroids.

It is another object of this invention to show that the steroid sulfatase inhibitors of the present invention alter the balance between sulfated and unsulfated neurosteroids.

It is yet another object of this invention to employ neurosteroids enhanced with the steroid sulfatase inhibitors of the present invention to reverse an illness such as amnesia induced by blockade of central muscarinic receptors.

It is a further object of this invention to employ blocking the metabolism of endogenous neurosteroids for enhancement of memory function which is similar to the blockade of monoamine metabolism as a means of treating depression.

These and other objects of the invention will be more fully understood from the drawings and the following description of the invention and the claims appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the effect of DHEAS and the effect of DHEAS and sulfatase inhibitor EMATE on Scopolamine induced amnesia in rats.

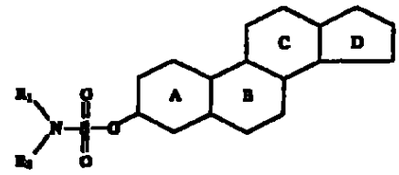
FIG. 2 discloses the effects of the sulfatase inhibitor EMATE alone on scopolamine induced amnesia in rats.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein, the term "patient" means members of the animal kingdom including, but not limited to, human beings.

The steroid sulfatase inhibitor compounds of this invention provide memory enhancing effects by altering the equilibrium between the endogenous sulfated and unsulfated form of the neurosteroids that occur naturally in the brain. These steroid sulfatase inhibitors and pharmaceutically acceptable salts inhibit the metabolism of the sulfated form of the neurosteroid to the unsulfated form and therefore inhibit the actions mediated by the $GABA_A$ receptor and facilitate NMDA receptors in the brain. They have a synergistic effect with DHEAS, PS and other neurosteroid memory enhancers. The compounds of this invention provide for the therapeutic treatment of an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia. It may also treat other individuals that seek memory enhancement.

The method for treating a patient for memory enhancement comprising providing a compound having the formula (I)



(I)

wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen (b) and a

lower alkyl group of one to six carbon atoms. The ring system ABCD is steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiol ester, pregnenolone, substituted estrone, substituted dehydroepiandrosterone, substituted estradiols, substituted estradiol esters and substituted pregnenolone.

Preferably R_1 is methyl and R_2 is hydrogen and most preferably both R_1 and R_2 are hydrogen. In the above structure (1), the steroid ring system is preferably estrone, dehydroepiandrosterone or pregnenolone. Other suitable steroid ring systems are:

Substituted estrones as follows:
- 2-OH-estrone
- 2-methoxy-estrone
- 4-OH-estrone
- 6 alpha-OH-estrone
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- 2-OH-17 beta-estradiol
- 2-methoxy-17 beta-estradiol
- 4-OH-17 beta-estradiol
- 6 alpha-OH-17 beta-estradiol
- 7 alpha-OH-17 beta-estradiol
- 16 alpha-OH-17 beta-estradiol
- 16 beta-OH-17 alpha-estradiol
- 16 beta-OH-17 beta-estradiol
- 17 alpha-estradiol
- 17 beta-estradiol
- 17 alpha-ethinyl-17 beta-estradiol

Estradiol esters and substituted estradiol esters, for example:
- 17-beta-OH-methyl-estradiol ester
- 17-beta-OH-ethyl-estradiol ester
- 17-beta-OH propyl-estradiol ester
- 17-beta-OH-butyl-estradiol ester
- 17-beta-OH-pentyl-estradiol ester
- 17-beta-OH-hexyl-estradiol ester

Substituted dehydroepiandrosterones, for example:
- 6 alpha-OH-dehydroepiandrosterone
- 7 alpha-OH-dehydroepiandrosterone
- 16 alpha-OH-dehydroepiandrosterone
- 16 beta-OH-dehydroepiandrosterone

Pregnenolone and substituted pregnenolone, for example:
- 6 alpha-OH-pregnenolone
- 7 alpha-OH-pregnenolone
- 16 alpha-OH-pregnenolone
- 16 beta-OH-pregnenolone

The method comprises incorporating the compound in a suitable pharmaceutical carrier, administering a therapeutically or prophylactically effective dosage of the compound incorporated in the carrier to a patient and employing the method in treating a patient for memory enhancement. The method also includes therapeutically treating a patient for an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia. This method may also treat other individuals that seek memory enhancement.

The method also includes employing combining a therapeutically or prophylactically effective dosage of DHEAS and/or PS with the compounds of structure (1) to enhance the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

One embodiment of the invention uses a method of treating a patient to enhance memory comprising providing a compound having the structure (2) wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and lower alkyl group of one to six carbon atoms.

A preferred embodiment using structure (2) is wherein R_1 is methyl and R_2 is hydrogen. A particularly preferred embodiment of the invention using structure (2) is wherein R_1 and R_2 are hydrogen.

Another embodiment of the invention uses a method of treating a patient to enhance memory by comprising providing a compound having the structure (3) wherein R_1 and R_2 can be the same or different and is selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms.

A preferred embodiment using structure (3) is wherein R_1 is methyl and R_2 is hydrogen. A particularly preferred embodiment using (3) is wherein R_1 and R_2 are hydrogen.

Another embodiment of the invention uses a method of treating a patient to enhance memory by comprising providing a compound having the structure (4) wherein R_1 and R_2 can be the same or different and selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms.

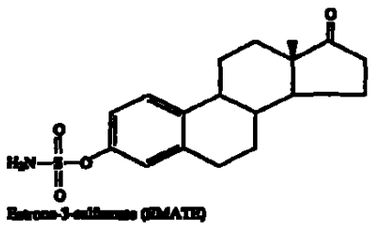
A preferred embodiment using structure 4 is wherein R_1 is methyl and R_2 is hydrogen. A particularly preferred embodiment of the invention using structure 4 is wherein R_1 and R_2 are hydrogen.

Another embodiment of this invention provides a method comprising providing a compound of this invention for therapeutic purposes. This process includes incorporating a compound of structure (2), (3) or (4) of this invention in a suitable pharmaceutical carrier and administering a therapeutically effective amount of the compound of this invention to a patient.

An example of a suitable pharmaceutical carrier is corn oil. The compounds of this invention incorporated into the pharmaceutical carrier may be administered to a patient by parenteral injection, such as for example, intravenously, intrathecally, intramuscularly or intraarterially. Other potential routes of administration include, for example, orally, transdermally or by other means. The dosage of, route of, administration of, and duration of therapy with the compounds of this invention, which can readily be determined by those skilled in the art, will be individualized according to the illness being treated, body weight of the patient, other therapy employed in conjunction with the compounds of this invention and the condition, clinical response and tolerance of the patient.

The following is an example of how a preferred compound is prepared and employed in the present invention:

EXAMPLE I



Estrone-3-sulfamate (EMATE)

The Synthesis of estrone - 3- sulfamate was as follows:

Sodium hydride (0.19 g, 2 eq) and sulfamoyl chloride (1.1 g, 2 eq) were added to a stirred solution of estrone (1.0 g) in anhydrous dimethyl formamide (25 ml) at 0° C. The solution was allowed to stir at room temperature for 24 hours. The reaction mixture was poured into a cold solution of sodium bicarbonate (50 ml) and the resulting aqueous phase was extracted with dichloromethane (3×40 ml). The combined dichloromethane was washed with distilled water (2×50 ml), dried ($MgSO_4$) and solvent evaporated in vacuo to afford 0.8 g of the crude product. The product was purified by silica gel chromatography eluted with dichloromethane—pet ether - ethyl acetate (1: 3: 0.5) mp 179°–181° C.; ^1H NMR (300 MHz; DMSO-d6) 0.83 (s, 3H, 18-CH_3), 6.98–73.6 (m, 3H, aromatic), 7.90 (s, 2H, NH_2). Analysis calculated for $C_{18}H_{23}NO_4S$: C, 61.87, H 6.63, N 4.01. Found C, 61.64, H 6.58, N 4.06.

The test methods were as follows:

Male rats weighing between 80 and 100 grams were purchased from Hilltop Lab Animals Inc. (Scottdale, Pa.) and housed in hanging wire mesh cages in groups of three with water and rat chow available ad libitum. The room in which the animals were housed was controlled for both temperature and humidity, there was a standard 12 hour, light/dark cycle. To assess memory, the Gemini Avoidance System (San Diego Instruments) was utilized in a standard passive avoidance paradigm. Briefly, the avoidance apparatus consisted of a box (53×53×32 cm) with two compartments connected by an opening with a sliding door. The room in which the rat was placed was brightly lit, while the other room was dark. Initially, the animals were allowed to explore the apparatus and were then removed. During the memory acquisition trial, animals were placed in the light compartment. When an animal entered the dark compartment, the sliding door closed and a mild foot shock (1 mA; 1 sec.) was delivered. The rat was then removed from the apparatus and returned to its cage. Twenty-four hours later the rat was again placed in the light side of the apparatus and the time latency to crossing to the dark room recorded. If the rat did not enter the dark room within 10 minutes it was removed from the apparatus. The acquisition of memory for the foot shock was assessed as an increased latency period before entering the dark room on the second day. Significant differences in crossover latency were determined by statistical analysis utilizing one-way analysis of a variance with a Dunnett's test post hoc. Significant differences between groups were interpreted as differences in memory acquisition resulting from the various treatments.

To determine the affect of DHEAS on memory, one hour before the acquisition trial six groups of ten animals were injected intraperitoneally (IP) with one of the following several doses of DHEAS (5, 10, 20, 30, 50, 70 mg/Kg/ml dissolved saline) or saline. All animals in a given group were administered the same dosage. Thirty minutes prior to testing the animals were also injected IP with scopolamine (1 mg/Kg) which preliminary studies determined would produce amnesia in this paradigm. Twenty-four hours later the rats were again placed in the apparatus and the time delay before the animals entered the dark compartment was recorded.

To determine whether EMATE could potentiate the reversal of scopolamine-induced amnesia by DHEAS, additional groups of ten rats per group were administered EMATE (10 mg/Kg) suspended in corn oil IP 48 hours before the acquisition trial. On the day of the acquisition the six groups of trial animals were administered DHEAS and scopolamine as above, except that the dose range of DHEAS was reduced (0.03, 0.1, 0.3, 1.0, 5.0, 10.0 mg/Kg). Twenty-four hours later, crossover latency (the time delay before the rats crossed to the dark compartment) for the groups was determined.

In order to determine whether EMATE alone could enhance memory, four groups of rats (10 animals per group), were injected with EMATE (10 mg/Kg; IP), either four hours before the acquisition trial, or daily for 3, 10 or 15 days before the acquisition trial. Twenty-four hours following the acquisition trial crossover latency was determined. The daily dosage of EMATE was 10 mg/kg which inhibited the sulfatase enzyme for about three to four days. The reversal of the amnestic effect of scopolamine was tested 24 hours later.

The results were as follows:

In a preliminary study, control animals administered saline one hour before the acquisition trial with no scopolamine, had a prolonged retention latency the second day (583.8±16.2 sec), indicating a memory of the foot shock from the previous day. Rats administered saline one hour before the amnestic agent scopolamine (1 mg/Kg; IP) 30 minutes before the acquisition trial had a retention latency 24 hours later of only 21.1±10.9 sec indicating a failure to remember the aversive event of the previous day.

In the groups of animals administered DHEAS (IP) in various doses (5 –70 mg/Kg as administered before) one hour before the acquisition trial and scopolamine 30 minutes before, there was a significant ($p \leq 0.05$), reversal of scopolamine-induced amnesia which followed a bell shaped dose response curve (FIG. 1). The maximum effect occurred at 20 mg/Kg DHEAS with a crossover latency of 299.4±83.5 sec. For those groups of animals treated with both EMATE and DHEAS, there was a 20-fold increase in the potency of DHEAS with a maximum crossover latency of (194.9±54.6 sec at 1 mg/Kg). This result is shown in FIG. 1.

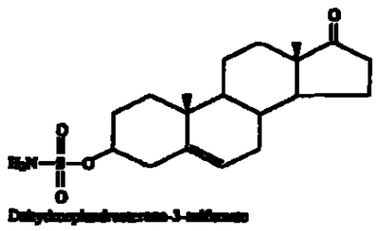
In those groups treated with EMATE alone, as a single dose EMATE failed to increase crossover latency (FIG. 2). However, in the groups administered EMATE daily for 10 and 15 days before the acquisition trial there was a significant ($p \leq 0.05$) reversal of scopolamine-induced amnesia with a crossover latency of 263.1 ±69.7 sec for the 10-day group and 297.0±88.7 sec for the 15-day group. Tacrine hydrochloride [COGNEX] is currently the only drug commercially available to treat Alzheimer's Disease associated dementia. Therefore, its effect on the reversal of scopolamine induced amnesia was included in the figure for comparison with our invention. This is shown in FIG. 2.

Sulfatase inhibitor EMATE can affect the memory enhancement of peripherally administered DHEAS, a neu-

roosteroid, by inhibiting the metabolism of DHEAS to DHEA. EMATE is a potent irreversible inhibitor of steroid sulfatase. A single dose (10 mg/kg) can inhibit greater than 98% of sulfatase after 24 hours. After 10 days of treatment the sulfatase activity in the whole body (including liver, adrenal gland, ovary, uterus and brain) is inhibited. The administration of EMATE alone can alter the equilibrium between the endogenous sulfated and unsulfated forms of neurosteroids in such a way as to enhance memory.

The following sets forth a protocol that could be used in testing DHEA - Sulfamate:

EXAMPLE II



Dehydroepiandrosterone-3-sulfamate

The synthesis of dehydroepiandrosterone - 3- sulfamate [DHEA sulfamate] was as follows:

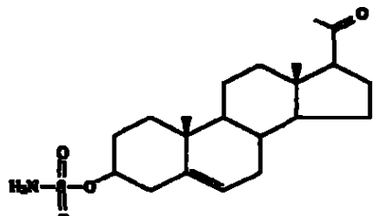
Sodium hydride (0.19 g, 2 eq) and sulfamoyl chloride (1.1 g, 2 eq) was added to a stirred solution of dehydroepiandrosterone (1.0 g) in anhydrous dimethyl formamide (25 ml) at 0° C. The solution was allowed to be stirred at room temperature for 24 hours. The reaction mixture was poured into a cold solution of sodium bicarbonate (50 ml) and the resulting aqueous phase was extracted with dichloromethane (3x40 ml). The combined dichloromethane was washed with distilled water (2x30 ml), dried ($MgSO_4$) and solvent evaporated in vacuo to afford the crude product. The product was purified by silica gel chromatography eluted with dichloromethane—pet ether—ethyl acetate (1: 3: 0.5).

To determine whether DHEA sulfamate would potentiate the reversal of scopolamine-induced amnesia by DHEAS, additional groups of ten rats per group as described above were administered DHEA sulfamate (10 mg/Kg) suspended in corn oil IP. On the day of the acquisition trial animals were administered DHEAS and scopolamine as above, except that the dose range of DHEAS was reduced (0.03, 0.1, 0.3, 1.0, 5.0, 10.0 mg/Kg). Each animal in a group gets the same dosage. On the following day crossover latency (the time delay before the rats crossed to the dark compartment) for the groups was determined.

In order to determine whether DHEA sulfamate alone could enhance memory, four groups of rats (10 animals per group), were injected with DHEA sulfamate (10 mg/Kg; IP), either four hours before the acquisition trial, or daily for 3, 10 or 15 days before the acquisition trial. Twenty-four hours following the acquisition trial crossover latency was determined.

The following sets forth a protocol that could be used in testing pregnenolone-3-sulfamate:

EXAMPLE III



Pregnenolone-3-sulfamate

The synthesis of pregnenolone- 3 - sulfamate was as follows:

Sodium hydride (0.21 g, 2 eq) and sulfamoyl chloride (1.22 g, 2 eq) was added to a stirred solution of pregnenolone (1.0 g) in anhydrous dimethyl formamide (25 ml) at 0° C. The solution was allowed to stir at room temperature for 24 hours. The reaction mixture was poured into a cold solution of sodium bicarbonate (50 ml) and the resulting aqueous phase would be washed with distilled water (2x50 ml), dried ($MgSO_4$) and solvent evaporated in vacuo to afford the crude product. The product was purified by silica gel chromatograph eluted with dichloromethane—pet ether - ethyl acetate (1: 3: 0.5).

To determine whether pregnenolone sulfamate could potentiate the reversal of scopolamine-induced amnesia by DHEAS, additional groups of ten rats per group were administered pregnenolone sulfamate (10 mg/Kg) suspended in corn oil IP. On the day the acquisition groups of ten trial animals were administered DHEAS and scopolamine as above, except that the dose range of DHEAS was reduced (0.03, 0.1, 0.3, 1.0, 5.0, 10.0 mg/Kg). Each animal in a group get the same dosage. On the following day crossover latency (the time delay before the rats crossed to the dark compartment) for the groups was determined.

In order to determine whether pregnenolone sulfamate alone could enhance memory, four groups of rats (10 animals per group), were injected with pregnenolone sulfamate (10 mg/Kg; IP), either four hours before the acquisition trial, or daily for 3, 10, or 15 days before the acquisition trial. Twenty-four hours following the acquisition trial crossover latency was determined.

The experiments as discussed herein lead to the following conclusions:

EMATE and the other steroid sulfatase inhibitors of this invention can significantly enhance the potency of DHEAS in reversing scopolamine-induced amnesia. The significant enhancement of the potency of DHEAS by co-treatment with EMATE suggests that it is the sulfated form of DHEA which is responsible for the memory enhancing properties of this neurosteroid since the inhibition of steroid sulfatase enhanced rather than diminished the response to DHEAS.

The failure of EMATE alone to enhance crossover latency following a single dose indicated that the enzyme inhibitor by itself did not have the same mechanism of action for enhancing memory function as DHEAS. However, 10 days and 15 days of treatment with EMATE did have a significantly positive effect on memory acquisition. This positive effect may reflect an alteration in the balance between naturally occurring sulfated and unsulfated neurosteroids.

Although neurosteroids can alter hippocampal function, this is the first study to demonstrate the neurosteroids can

reverse amnesia induced by blockade of central muscarinic receptors. The mechanism by which this occurs is not yet known precisely. It is thought that memory enhancement can be mediated by a strategy of blocking the metabolism of endogenous neurosteroids. DHEAS and PS enhance memory via inhibition of $GAGA_A$ receptor mediated actions and potentiation of NMDA receptor mediated actions. These effects are associated with memory enhancement. The inhibition of the metabolism of DHEAS and PS to DHEA and P respectively, results in higher concentrations of DHEAS and PS in the brain, therefore enhanced memory function. This strategy is similar to the use of monoamine oxidase inhibitors in the treatment of depression.

It will be understood by those skilled in the art that the compounds described herein may be used as synergistic agents with neurosteroids and other compounds.

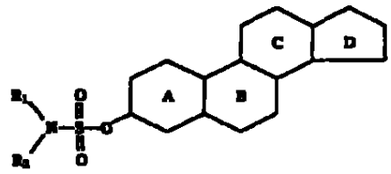
It will be appreciated by those skilled in the art that the compounds of this invention may be used to transport other compounds, such as for example, DHEAS and PS, across the blood-brain barrier for distribution in the cerebrospinal fluid. It will be appreciated by those skilled in the art that both the transported compound and the compound of this invention will be active in the central nervous system after crossing the blood-brain barrier.

In order to effect the objects of this experiment this invention provides the use of the steroid sulfatase inhibitors of this invention for memory enhancement and a method of using these compounds in a patient for therapeutic and prophylactic purposes.

Whereas, particular embodiments of this invention have been described above for purposes of illustration, it will be evident to those skilled in the art that numerous variations of the details of the present invention may be made without departing from the invention as defended in the appended claims.

We claim:

1. A method for treating a patient to effect memory enhancement comprising providing a compound having the formula (1)



(1)

wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms and (b) the ring system ABCD is a steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiolester, pregnenolone, substituted estrones, substituted dehydroepiandrosterones, substituted estradiols, substituted estradiolesters and substituted pregnenolone,

incorporating said compound in a suitable pharmaceutical carrier;

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

2. The method of claim 1, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

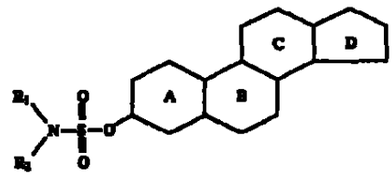
3. The method of claim 1, comprising employing corn oil as said carrier.

4. The method of claim 2, comprising administering said compound incorporated in said carrier to a patient by the parenteral route.

5. The method of claim 2, comprising administering said compound in said carrier to a patient by the oral route.

6. The method of claim 2, comprising administering said compound incorporated in said carrier to enhance said patient's short term memory.

7. A method for treating a patient to effect memory enhancement comprising providing dehydroepiandrosterone sulfate (DHEAS) and a compound having the formula (1)



(1)

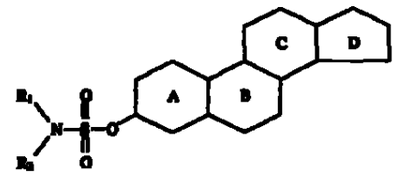
wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms and (b) the ring system ABCD is steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiolester, substituted estrones, pregnenolone, substituted dehydroepiandrosterones, substituted estradiols, substituted estradiolesters and substituted pregnenolone,

incorporating said compound in a suitable pharmaceutical carrier;

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

8. The method of claim 7, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

9. A method for treating a patient to effect memory enhancement comprising providing pregnenolone sulfate (PS) and a compound of the formula (1)



(1)

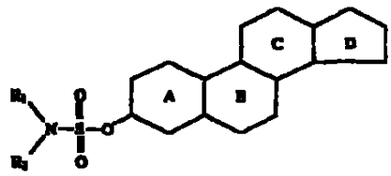
wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms and (b) the ring system ABCD represents steroid nucleus selected from the group consisting of estrone, dehydroepiandrosterone, estradiol, estradiolester, pregnenolone, substituted estrones, substituted dehydroepiandrosterones, substituted estradiols, substituted estradiolesters and substituted pregnenolone.

incorporating said compound in a suitable pharmaceutical carrier;

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

10. The method of claim 9, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

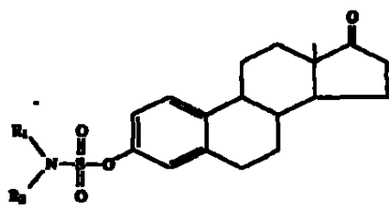
11. The method of claim 9, comprising employing an effective dosage of dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) with the compounds and pharmaceutically acceptable salts of formula (1),



(1)

thereby enhancing the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

12. The method of claim 1 comprising employing an effective dosage of a compound having the species formula (2)



(2)

thereby enhancing the effect obtained treating a patient for one of either memory enhancement for an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

13. The method of claim 12, comprising employing R_1 and R_2 equal to hydrogen in the compound.

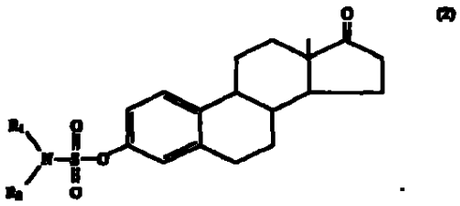
14. The method of claim 12, comprising employing R_1 equal to methyl and R_2 equal to hydrogen in the compound.

15. The method of claim 12, comprising employing corn oil as said carrier.

16. The method of claim 12, comprising administering said compound incorporated in said carrier to a patient by the parenteral route.

17. The method of claim 12, comprising administering said compound in said carrier to a patient by the oral route.

18. A method for treating a patient to effect memory enhancement comprising providing dehydroepiandrosterone sulfate (DHEAS) and a compound having the species formula (2)



(2)

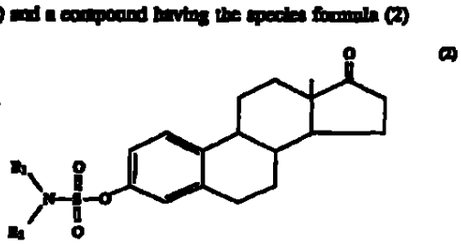
wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms;

incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

19. The method of claim 18, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

20. A method for treating a patient to effect memory enhancement comprising providing pregnenolone sulfate (PS) and a compound having the species formula (2)



(2)

wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms;

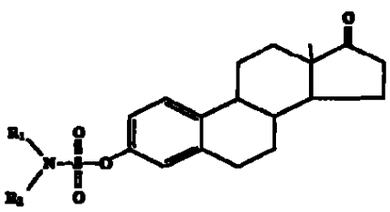
incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

21. The method of claim 20, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

22. The method of claim 20, comprising employing an effective dosage of dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) with the compound of the formula (2)

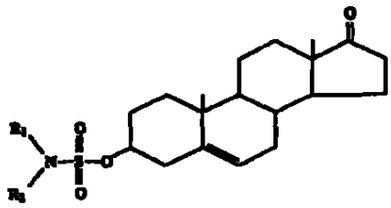
(2)



thereby enhancing the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

23. The method of claim 1 comprising employing an effective dosage of the compound having the species formula (3)

(3)



thereby enhancing the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

24. The method of claim 23, comprising employing R_1 and R_2 equal to hydrogen in the compound.

25. The method of claim 23, comprising employing R_1 equal to methyl and R_2 equal to hydrogen in the compound.

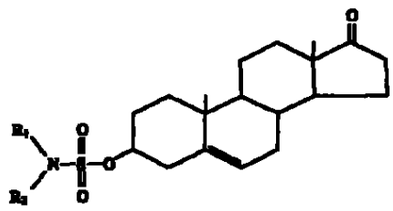
26. The method of claim 23, comprising employing corn oil as said carrier.

27. The method of claim 23, comprising administering said compound incorporated in said carrier to a patient by the parenteral route.

28. The method of claim 23, comprising administering said compound in said carrier to a patient by the oral route.

29. A method for treating a patient to effect memory enhancement comprising providing dehydroepiandrosterone sulfate (DHEAS) and a compound of structure (3)

(3)



wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of one to six carbon atoms;

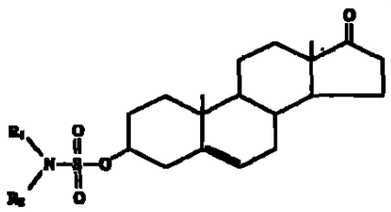
incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

30. The method of claim 29, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

31. A method for treating a patient to effect memory enhancement comprising providing pregnenolone sulfate (PS) and a compound having the species formula (3)

(3)



wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms;

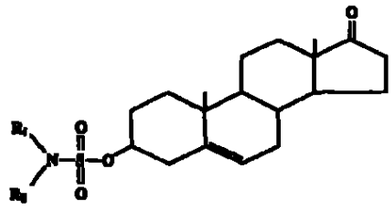
incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

32. The method of claim 31, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

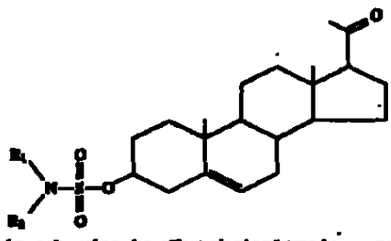
33. The method of claim 31, comprising employing an effective dosage of dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) with the compound of the formula (3)

(3)



thereby enhancing the effect obtained treating a mammal for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

34. The method of claim 1 comprising employing an effective dosage of a compound having the species formula (4)



(4)

thereby enhancing the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, vascular dementia and post stroke dementia.

35. The method of claim 34, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

36. The method of claim 34, comprising employing R_1 and R_2 equal to hydrogen in the compound.

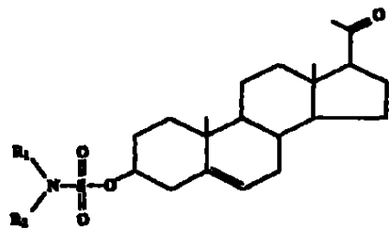
37. The method of claim 34, comprising employing R_1 equal to methyl and R_2 equal to hydrogen in the compound.

38. The method of claim 34, comprising employing corn oil as said carrier.

39. The method of claim 34, comprising administering said compound incorporated in said carrier to a patient by a parenteral route.

40. The method of claim 34, comprising administering said compound in said carrier to a patient by the oral route.

41. A method for treating a patient to effect memory enhancement comprising providing dehydroepiandrosterone sulfate (DHEAS) and a compound of structure species formula (4)



(4)

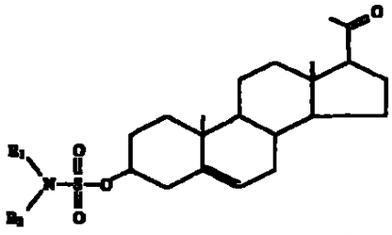
and wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms;

incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

42. The method of claim 41, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

43. A method for treating a patient to effect memory enhancement comprising providing pregnenolone sulfate (PS) and a compound of species formula (4)



(4)

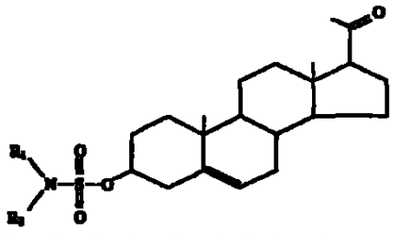
wherein (a) R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen and a lower alkyl group of 1 to 6 carbon atoms;

incorporating said compound in a suitable pharmaceutical carrier; and

administering a dosage of said compound in said carrier which is therapeutically effective to enhance said memory of said patient.

44. The method of claim 43, comprising employing said method in therapeutically treating a patient having an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia in order to enhance said patient's memory.

45. The method of claim 44, comprising employing an effective dosage of dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) with the compound of the formula (4)



(4)

thereby enhancing the effect obtained treating a patient for one of either memory enhancement or an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post-traumatic dementia, senile dementia, vascular dementia and post stroke dementia.

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Empresa Laboratorio Farmacéutico "Mario Muñoz"

ESTRIOL Y SUS DERIVADOS. COMPORTAMIENTO DE LA TECNOLOGÍA EN EL MUNDO

Bárbara Águila Gil,[1] Fernando Verdecia Navarro[2] y Manuel Cué Brugueras[3]

RESUMEN

A partir de la extensa producción de artículos que se han publicado acerca de los estrógenos, el presente trabajo centró la atención en el estudio del estriol, para lo cual empleó la mayor información existente en el país de revistas y documentos de patentes, así como de soporte magnético. Se presenta desde que fue aislada la primera hormona estrogénica hasta la fecha, incluyendo los derivados de estriol, sus nuevas aplicaciones en el campo médico y en la alimentación animal.

Descriptores DeCs: ESTRIOL/síntesis química; ESTEROIDES.

El estudio de las hormonas sexuales data de más de 6 décadas, entre ellas los estrógenos son cada vez más empleados en el tratamiento de diferentes afecciones.

Los *estrógenos esteroidales*[1] son hormonas sexuales femeninas que se caracterizan químicamente por poseer el anillo A aromático en su molécula y en consecuencia carecer del grupo metilo en el C 10 (García M, Verdecia FA. Síntesis de estradiol cipionato, 1992. Trabajo de Diploma para Licenciado en Ciencias Farmacéuticas).

Como es conocido, éstos se encargan en el organismo de controlar el desarrollo y función fisiológica de los órganos reproductores femeninos, así como del desarrollo de caracteres sexuales secundarios.

Se forman en el ovario bajo el estímulo de hormonas gonadotrópicas procedentes del lóbulo anterior de la hipófisis y durante el embarazo se excretan en la orina cantidades significativas de éstos.

Las primeras hormonas estrógenas conocidas fueron la estrona, el estradiol y el estriol (fig. 1).

En 1929, *Doisy*[1] en Estados Unidos y *Butenand*[2] en Alemania aislaron la estrona pura y cristalina de orina de mujer embarazada y detectaron la presencia de otro estrógeno que resultó ser el estriol.

[1] Aspirante a Investigadora.
[2] Investigador Agregado.
[3] Especialista en Información Científica. Centro Nacional de Información de Ciencias Médicas.

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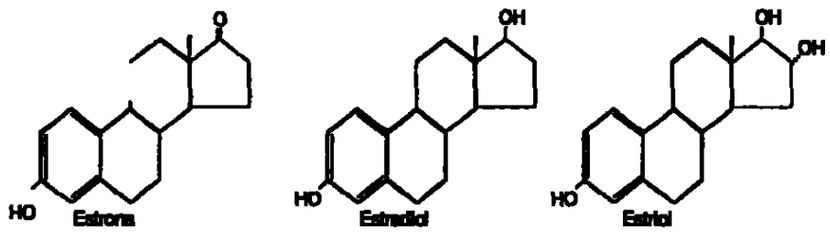

FIG. 1. *Hormonas estrógenas: estrona, estradiol y estriol.*

Se reporta la presencia de estriol en tejido placentario,[1] hígado y riñones de caballo.

Zondek en 1930, observó que la orina de yegua preñada contenía cantidades mayores de estrógenos, señalando que la yegua preñada excreta más estrógeno que la mujer durante el embarazo,[4] obteniéndose de forma reproducible cantidad suficiente de material estrogénico por cada litro de orina.

Los estrógenos se encuentran en cantidades superiores a las antes mencionadas en la orina de los animales machos del género *Equus*[5] como el caballo que a pesar de su virilidad, excreta en su medio más estrógeno que ningún otro ser viviente.

Como se muestra en la figura 1, el estriol presenta 2 grupos hidroxilos en el anillo D, uno en la posición 16 y otro en la posición 17, presentando configuraciones α y β respectivamente. Además existen 2 estereoisómeros, el 16 epiestriol que presenta el grupo hidroxilo en el carbono 16 con una configuración β y el 17- epiestriol el cual posee el grupo hidroxilo enlazado al carbono 17 con una configuración α .[6]

A diferencia del estradiol y la estrona, el estriol es el más activo por vía oral.

Los estrógenos se emplean para el control y diagnóstico del embarazo de alto riesgo[7] en la terapia sustitutiva para los estados de deficiencias: menopausia y posmenopausia, en afecciones y para la anticoncepción combinados con progestágenos. También son utilizados para el tratamiento de neoplasias malignas de la próstata y de mamas en mujeres posmenopáusicas, así como en la prevención de la osteoporosis posmenopáusica y senil, y en el tratamiento de otras afecciones climatéricas del aparato genito-urinario y sistémicas, y en la inducción de la pubertad en hipogonadismo femenino, solo o con otros medicamentos, sin llegar a tener tantos efectos adversos como otros estrógenos más fuertes.[8-19]

Es conocido que los estrógenos activos, como el estradiol y el 17 α–etinil estradiol, ejercen un intenso efecto inhibidor de gónadas, presentando el inconveniente de producir fenómenos de feminización cuando se administran a pacientes varones que presentan carcinoma de la próstata. En una patente holandesa se describe la síntesis de nuevos derivados del 17- epiestriol, los cuales presentan un intenso efecto inhibidor de gónadas y prácticamente ninguna acción estrogénica.[20]

A finales de los 80 se registró una patente que propone el uso del estriol para promover el crecimiento e incrementar la eficacia de utilización del pienso en rumiantes.[21]

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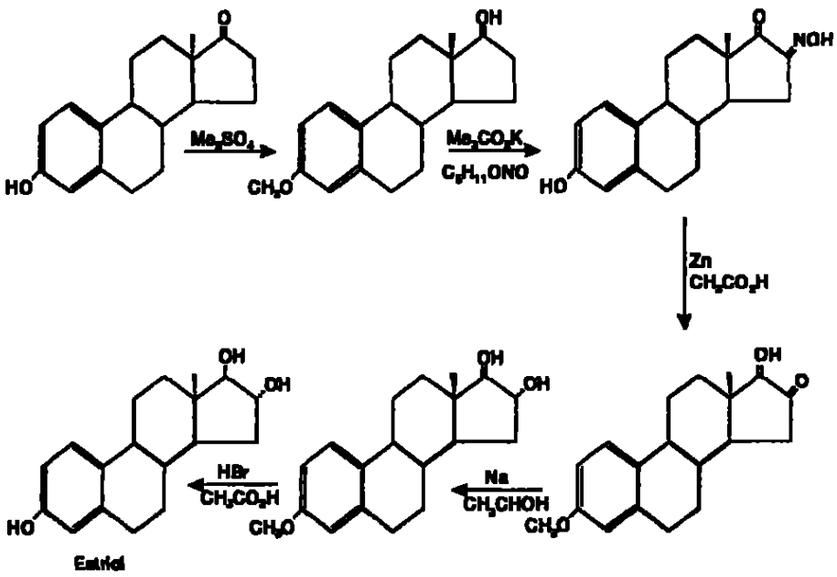

FIG. 2. *Preparación de estriol a partir de estrona reportada por Hufman.*

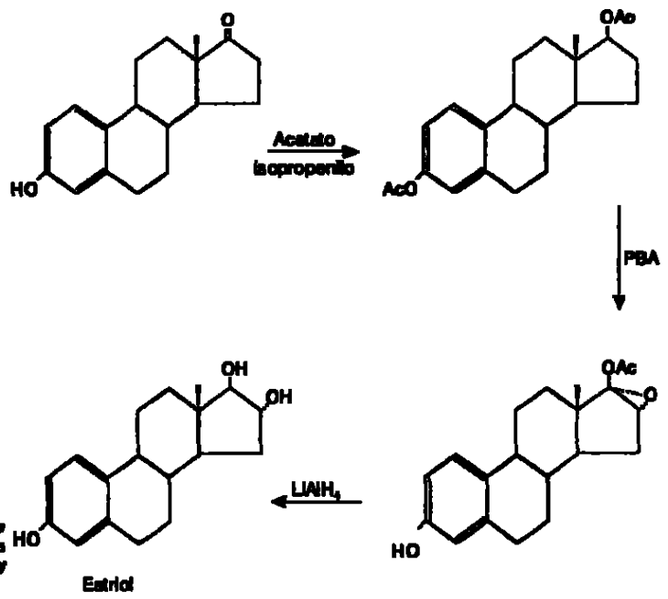

FIG. 3. *Preparación de estriol a partir de estrona reportada por Laveda y otros*

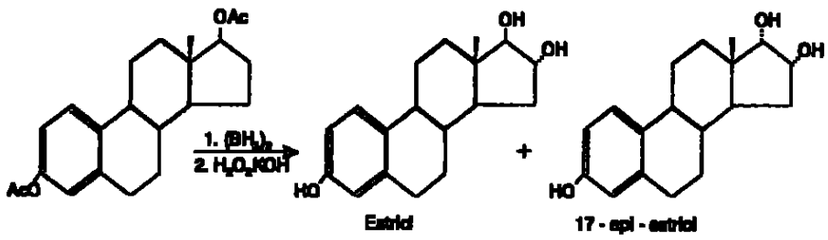

FIG. 4. *Preparación de estriol a partir de estrona reportada por Ling.*

La preparación del estriol a partir de estrona por diferentes vías de semisíntesis fue reportada por: *Huffman*[22] en 1947 (fig. 2). *Leeds y otros*[23] en 1954 (fig. 3) y *Ling*[24] en 1981 (fig. 4).

Los derivados del estriol se obtienen desde la década de los 60 y fundamentalmente se preparan los ésteres, registrándose un gran número de patentes por diferentes firmas de EE.UU., Francia, Holanda y Alemania.

Partiendo de ácidos mono y dicarboxílicos o sus derivados en presencia de una base orgánica terciaria mezclada con un disolvente orgánico, se obtiene un 16, 17- mono o dihemiéster y derivados de éstos solubles en agua por reacción con hidróxido de sodio o bicarbonato de potasio.[25]

Estos se emplean para el tratamiento de toda clase de hemorragias y se administran por vía intravenosa, además aumentan especialmente la resistencia capilar sin ocasionar efectos indeseables.

En 1967 se registra una patente[27] para obtener nuevos derivados del estriol con un hidrocarburo acíclico no saturado de 1 a 6 átomos de carbono enlazado al 17. Estos compuestos están indicados como agentes estrogénicos para el tratamiento de las deficiencias.

La firma francesa Theramex[26] en 1974 registró un procedimiento para la preparación de nuevos derivados nicotínicos del estriol con actividades hipolipidemiantes y estrogénicas moduladas, resultando muy activos en el tratamiento de las hiperlipidemias y de la arteriosclerosis humana para afecciones en las que los efectos indeseables de las 2 moléculas por separado no se manifiestan.

Investigadores de los Laboratorios Abbott[28] en 1983 registraron un procedimiento para obtener un glucorónido del estriol y otras hormonas esteroidales marcados con enzimas útiles como trazadores en inmunoensayos enzimáticos. Estos esteroides glucorónidos están enlazados covalentemente a una fosfatasa alcalina y se caracterizan por poseer la actividad enzimática de la fosfatasa alcalina sola y actividad inmunológica del glucorónido de la hormona esteroidal solo.

La casa Schering[29] en 1984 registró un procedimiento para la obtención de nuevos 3,17β–diésteres del estriol. El radical acilo consta de 2 a 10 átomos de carbono. Estos compuestos son especialmente apropiados como profármacos de estriol para la producción de preparados de depósito, inyectables o implantables.

Estos derivados combinados con el enantato de noretisterona o con el acetato de medroxiprogesterona resultaron ser anticonceptivos de acción prolongada.

Se reportó que el estriol 3 sulfato marcado con radioisótopos puede ser empleado en el diagnóstico del cáncer de mama.[30]

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Simons DM patentó la aplicación de los conjugados del estriol como inmunógenos y para inmunoensayos.[31]

El presente trabajo es el resultado de la búsqueda, recopilación y ordenamiento de la información acerca del estriol, sus derivados y usos, esperamos que sea de interés para los especialistas e investigadores relacionados con esta temática.

SUMMARY

Based on the wide production of articles published about oestrogens, the present paper focused its attention on the study of estriol, for which it was used most of the information existing in the country in journals and documents of patents, and on magnetic support. Data since the first estrogenic hormone was isolated up to now, including the derivates of estriol, and its new applications in the medical field and in animal feeding are included here.

Subject headings: ESTRIOL/chemical synthesis; STEROIDS.

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Lic. *Bárbara Águila Gil.* Empresa Laboratorio Farmacéutico "Mario Muñoz". Hacendados No. 1, municipio Habana Vieja, Ciudad de La Habana, Cuba.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor(a)
Margarita Castellanos Abondano **Oficio Nº** 6276
Apoderado(a)
STERIX LIMITED y
SCHERING AKTIENGESELLSCHAFT

REFERENCIA	**Radicación**	**01 2039**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**008**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 01 2039, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

- El resumen y el capítulo descriptivo de la solicitud en los folios 82 y 6 a 69 respectivamente.
- Los ejemplos que ilustran la invención en los folios 70 a 76.
- Los diagramas y gráficos relacionados con las concentraciones plasmáticas de estrógenos en los folios 83 a 100.
- Las cláusulas 1 a 26 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 77 a 81.
- El primer examen de forma realizado a la solicitud de oficio No. 1035, que se encuentra en el folio 105.
- Las copias de las solicitudes originales mediante las cuales se reivindica prioridad, allegadas mediante memorial de fecha 11/05/2001 de números: GB0000792.2 de 14/01/2000 en los folios 116 a 154 junto con su traducción correspondiente en los folios 107 a 115; GB0002115.4 de 28/01/2000 en los folios 164 a 204 junto con su traducción correspondiente en los folios 155 a 163 y US60/218.730 de 17/07/2000 en los folios 211 a 275 junto con su traducción correspondiente en los folios 205 a 210.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 04/06/2001 que se encuentra en los folios 276 a 325, mediante el cual se anexan los documentos de poder otorgados por las sociedades solicitantes STERIX LIMITED y SCHERING AKTIENGESELLSCHAFT y se modifica el título de la invención.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 13/11/2003, que se encuentra en los folios 328 y 329.

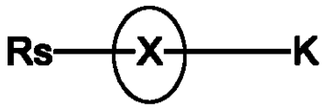
2. BJETO DE LA INVENCIÓN

La solicitud hace referencia a un ***"Composición farmacéutica que comprende un anillo de hidrocarbilo y un grupo sulfamato"***

- **Reivindicaciones 1 a 7:**

Se reivindica una composición farmacéutica que comprende:

i) un compuesto de fórmula (I):



ii) optativamente mezclado con un vehículo diluyente, excipiente o adyuvante farmacéuticamente acceptable

En particular se reclama la composición farmacéutica de acuerdo con la cláusula 1 en la cual el compuesto está presente en una cantidad que produce una dosis de 10 a 200µg/día, y particularmente de 50 a 200µg/día y especialmente 20 a 50µg/día. Es decir que el compuesto está presente en cantidades no mayores a 200µg/día.

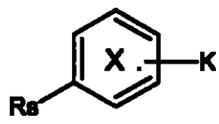
De igual forma se reivindica las composiciones farmacéuticas que generan dosis no mayores a 1mg y particularmente no mayores a 4mg.

- **Reivindicaciones 8 a 11:**

Se reivindica una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la cual X en combinación con K imita una estructura esteroide, teniendo en cuenta que K es un grupo cíclico y X es un anillo de seis miembros conformado por átomos de carbono.

- **Reivindicaciones 12 a 16:**

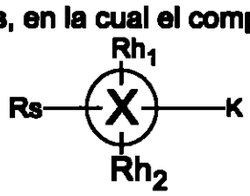
Se reivindica una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la cual el compuesto es de fórmula (II):



En particular se reclama la composición farmacéutica en la cual X en combinación con K es una estructura de anillo esteroide o un derivado sustituido de la misma. En la que Rs está en la posición 3 del anillo X y corresponde a un grupo sulfamato.

- **Reivindicaciones 17 a 19:**

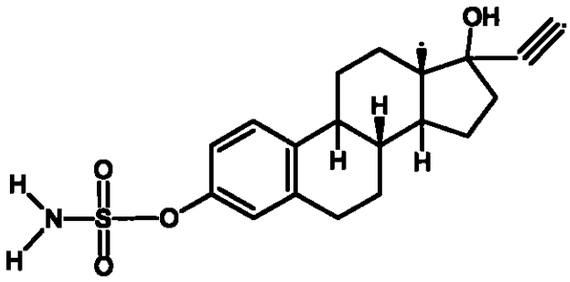
Se reivindica una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la cual el compuesto es de la fórmula (III):



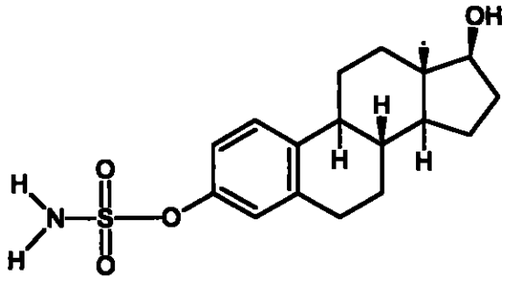
En particular se reclama la composición de acuerdo con la cláusula 17 en la cual Rh1 está en la posición 2 del anillo X y Rh2 está en la posición 4 del anillo.

- **Reivindicación 20:**

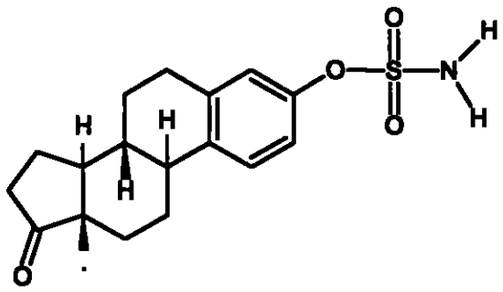
Se reclama una composición farmacéutica de acuerdo con la reivindicación 1 en la cual el compuesto de la fórmula (I) se selecciona entre:



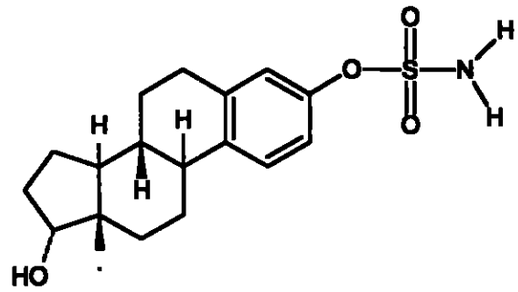
17α-etinil-17β-estradiol-3-sulfamato



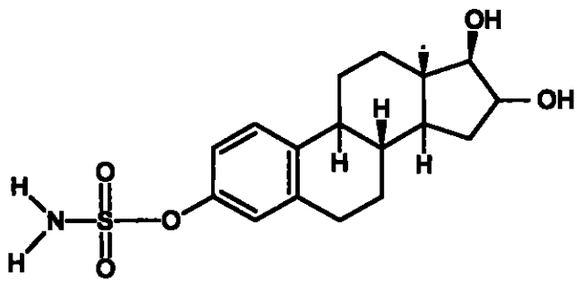
17β-estradiol-3-sulfamato



estrona-3-sulfamato (EMATE)



17α-estradiol-3-sulfamato



Estriol-3-sulfamato

Además se reivindica la composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes para usar en medicina.

- **Reivindicaciones 22 a 26:**

Se reivindica el uso de una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1 a 20 en la elaboración de un medicamento para usar en la anticoncepción oral, la terapia de reemplazo hormonal para la protección ósea sin estimulación del endometrio, el tratamiento de trastornos o enfermedades asociadas a niveles adversos de STS (sulfato de estrona).

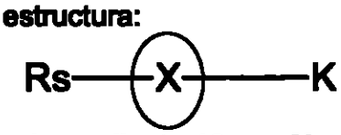
Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K $^{31}/_{56}$ de la Clasificación Internacional de Patentes.**

3. CLARIDAD DE LA SOLICITUD:

El artículo 30 de la Decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción".*

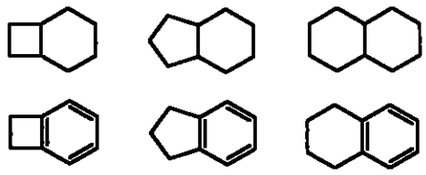
Teniendo en cuenta el alcance de la cláusula independiente 1, esta Dependencia señala las siguientes objeciones:

- La fórmula (I) toma para **X** la connotación de un anillo de hidrocarbilo de por lo menos 4 átomos, de estructura:



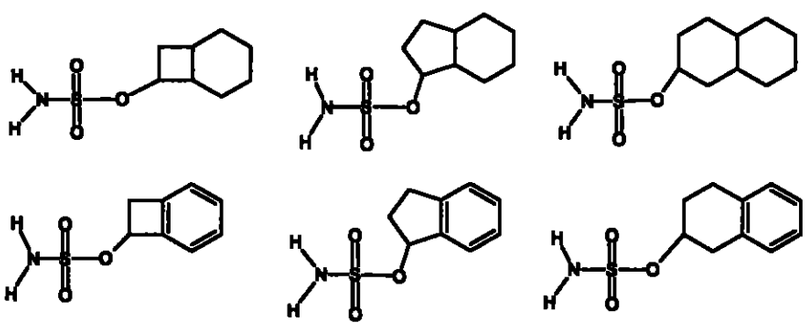
Especificando en la cláusula dependiente 10 que **X** es un anillo de seis átomos de carbono y que el grupo **K** corresponde a un grupo hidrocarbilo particularmente de carácter cíclico.

Siendo que la fórmula (I) comprende cualquier clase de compuestos que enlace dos anillos de hidrocarbilo, para esta Dependencia es claro el alcance amplio y especulativo de la fórmula señalada, por cuanto cualquier anillo aromático o saturado de cuatro a seis miembros que se enlaza a otro hidrocarbilo cíclico cabría dentro de la definición general de la fórmula (I), de esta manera tendríamos entre otras, las siguientes posibilidades:



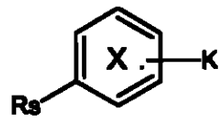
Haciendo la salvedad respecto a que esta Dependencia interpreta la fusión de los anillos **X** y **K**, de acuerdo con la cláusula 8 en la que se señala que **X** y **K** forman estructuras esteroides; porque de la lectura de la cláusula 1 y en particular de la forma como se presenta la fórmula (I) no se infiere la fusión de los anillos, por el contrario, tal como se presenta lo que se está definiendo es un enlace simple entre los anillos que representa **X** y **K**; como tampoco se especifica que el anillo **K** corresponde exclusivamente a un ciclo hidrocarbilo de seis miembros, lo que hace pensar que se ha ampliado aún más el espectro de la invención, al hacerla extensiva a cualquier anillo de hidrocarbilo que cuente con n número de átomos de carbono y que pueda enlazarse con anillos de 4 a seis miembros saturados o insaturados de forma fusionada o mediante enlace simple.

Ahora bien, cuando se incluye el significado del grupo **Rs**, los posibles compuestos de la invención comprenderían entre otras a las estructuras:

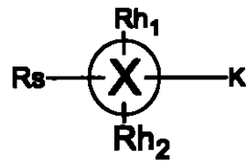


Las cuales constituyen menos de la mitad de la estructura química que realmente conforma el pentaciclo fusionado denominado ciclopentanoperhidrofenantreno, característico de las hormonas esteroidales.

- Cuando se determina en la cláusula dependiente 12 que en particular se prefieren los compuestos que dentro de la fórmula (I) toman la connotación de la fórmula (II), especificando que tanto **Rs** como **X** y **K** son como se definieran en la cláusula 1, tampoco se está generando mayor claridad respecto del alcance real de la invención. En este punto tampoco es posible determinar que los compuestos de la invención, alrededor de los cuales se formula el problema técnico y la solución propuesta, son de carácter esteroide.



- En igual sentido ocurre con la fórmula (III), señalada en la reivindicación dependiente 17 y que toma iguales connotaciones que las especificadas en la cláusula 1 y a partir de la cual tampoco es posible inferir que el objeto de la invención son las composiciones farmacéuticas que contienen como principio activo una estructura esteroide como las reclamadas en la cláusula 20.



Ahora bien, si el problema técnico corresponde a que los estrógenos conocidos exhibían deficits farmacocinéticos y a que los estrógenos naturales sólo podían ser biodisponibles en un pequeñísimo grado por vía oral, igual que los estrógenos sintéticos etinil-estradiol y la estrona 3-sulfamato, cabría preguntarse por qué se reivindican formulas tan generales e inespecíficas que no corresponden al sistema de cinco anillos enlazado al grupo sulfamato.

Con lo cual se concluye que las cláusulas 1 a 19 no define el objeto real de la invención y por consiguiente no permite una interpretación inequívoca del alcance de la misma.

- Se recomienda al interesado revisar la nomenclatura de los compuestos reclamados como sustancias activas de las composiciones farmacéuticas, ya que las denominaciones químicas no se encuentran en correspondencia directa con la estructura que señala, en particular la del compuesto EMATE. Para ello se recomienda revisar el artículo que se encuentra adjunto al presente estudio técnico[1], que presenta las estructuras correspondientes al estriol, estrona y estradiol.

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[1] AGUILA Gil Bárbara, VERDECIA Navarro Fernándo, CUÉ Brugueras Manuel. "Estriol y sus derivados, comportamiento de la tecnología en el mundo". Revista cubana de Farmacia, 1999; 33(3): 195-200. pág195 a200. (Ver folios 336 a 338)

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4. ES UNA INVENCION:

El artículo 14 de la decisión 486 establece: "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

En atención a que la Comunidad Andina no considera posible la protección de objetos diferentes a los productos o procedimientos, las cláusulas relativas al uso de la composición farmacéutica se encuentran excluidas de patentabilidad – reivindicaciones 22 a 26 -, así las cosas, se recomienda al interesado eliminarlas del alcance de protección solicitado.

5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 14.01.2000-, relacionados con la materia técnica reivindicada:

N°	Documento	Título	Fecha de Publicación
D1	US556847	"Methods of efecting memory enhancement mediated by sterold sulfatase inhibitors"	17/09/1996

Anterioridad D1 en los folios 331 a 335.

6. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*".

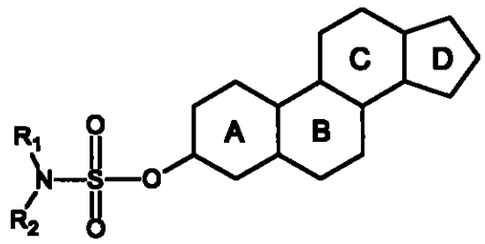
En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

6.1 Evaluación de NOVEDAD:

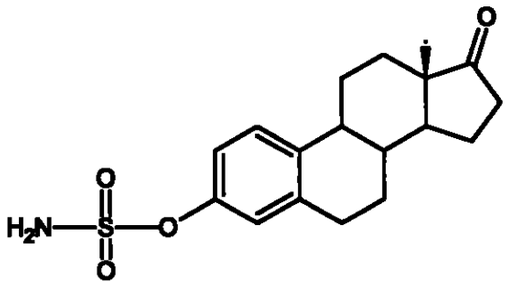
El artículo 16 de la decisión 486 dispone: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

La anterioridad **D1** comprende compuestos de fórmula estructural (1)



Para la cual R_1 y R_2 pueden ser iguales o diferentes, tomando connotaciones como –H y alquilo de 1 a 6 átomos de carbono. Y en donde el sistema de anillos ABCD es un núcleo esteroidal seleccionado entre estrona, dehidroepiandrosterona, estradiol, pregnenolona, estrona sustituida, estradiol, entre otros... Pero en particular, el ejemplo (I) de la anterioridad establece la ruta sintética del compuesto Estrona-3-sulfamato (EMATE) de estructura química:



Y más adelante en su aparte reivindicatorio reclama el método para tratar a un paciente con desórdenes hormonales, que comprende la administración del compuesto definido.

Queda claro entonces, que el estado de la técnica ya establecía la posibilidad de tratar enfermedades asociadas a desórdenes hormonales o al control de la natalidad mediante la administración de análogos de las hormonas endógenas como los que la solicitud en estudio reclama en los folios 77 a 81, en particular estructuras idénticas a las contempladas en la anterioridad **D1** como el EMATE.

Y teniendo en cuenta que existe identidad entre la materia reclamada y aquella contemplada en la anterioridad, queda clara la afectación ejercida por la publicación señalada sobre el requisito de NOVEDAD.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US556847	1 a 21	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 la 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.

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Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 08 JUN. 2006

CONCEPTO TÉCNICO Número 0864	**EXAMINADOR TÉCNICO** Código 202044

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

D ctor(a) **Oficio Nº.** 6277
Margarita Castellanos Abondano
Apoderado(a)
STERIX LIMITED Y
SCHERING AKTIENGESELLSCHAFT

REFERENCIA	**Radicación**	**01 2039**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**002**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 01 2039, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El art. 46 de la Decisión 486 establece que "*La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera...Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente*"

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

1) FOULKES, ROLY ET AL: "Immunological consequences of inhibiting dehydroepiandrosterone (DHEA) sulfatase in vivo". STEROID HORM. T-CELL CYTOKINE PROFILE (1997), 135 – 152. EDITOR(S): ROOK, G.A.W.; LIGHTMAN, STAFFORD L. PUBLISHER: SPRINGER, LONDON, UK., XP001040905.
2) ELGER, WALTER ET AL: "Sulfamates of various estrogens are prodrugs with increased systemic and reduced hepatic estrogenicity at oral application" J. STEROID BIOCHEM. MOL. BIOL. (1995), 55(3/4), 395 – 403, XP000618892.

3) ELGER, WALTER ET AL: "Novel estrogen sulfamates: a new approach to oral hormone therapy". EXPERT OPIN. INVEST. DRUGS (1998), 7(4), 575-589, XP002121926.
4) BARTH, ASTRID ET AL: "Influence of subchronic administration of estradiol, ethinylestradiol and estradiol sulfamate on bile flor, bile acid excretion, and liver and biliary glutathione status in rats". ARCH. TOXICOL. (1997), 71(7), 443-449, XP000986430.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO 0151055, equivalente a la solicitud colombiana aquí estudiada, y no siendo viable la consecución de dicho artículo por este despacho, se requiere que el solicitante, en virtud de lo establecido en el art. 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione la publicación completa, 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 5 del título primero de la Circular Única Nº 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 08 JUN 2006

CONCEPTO TÉCNICO Número 0873	**EXAMINADOR TÉCNICO** Código 202044

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RADICACIÓN: 1-2039 **EDICTO No. 15056**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 24871 de 20-SEP-2006. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPOSICION FARMACEUTICA QUE COMPRENDE UN ANILLO DE HIDROCARBILO Y UN GRUPO SULFAMATO".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Margarita Castellanos Abondano, o a quien haga sus veces, en su calidad de apoderada de Starx Limited y Schering Aktiengesellschaft., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 20 SET 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUEDA ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 04-OCT-2006 **Este edicto se desfija hoy 18-OCT-2006 a las cinco (5:00 p.m.)**
Secretaría General Ad-Hoc
EDICTO No. 15056