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ABOGADOS

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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **Expediente 07-135-405**

TÍTULO SOLICITADO: **UNA TABLETA QUE CONTIENE UN INGREDIENTE *DIFÍCILMENTE* SOLUBLE"**

PUBLICACIÓN: **Gaceta 590 de 31-03-2008, Página 539– N.P. 162**

PRIORIDAD: **JP 2004-359487 DE 13/12/2004**

SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

APODERADO: **EMILIO FERRERO**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.,** dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente *ante ese Despacho, en* los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los articulos 14 y 18, de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

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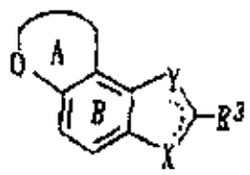
❖ En primer término, y como lo reconoce cualquier persona medianamente versada en la materia, cualquier principio activo que se pretenda comercializar para su utilización en clínica debe pasar por una serie de etapas encaminadas a la obtención de un medicamento seguro y eficaz. Esta etapa que abarca el conocimiento de las características básicas tanto biofarmacéuticas como fisicoquímicas que van a influir en la elección y desarrollo de la forma farmacéutica final del medicamento se conocen como estudios de preformulación. Dentro de las consideraciones biofarmacéuticas a tener en cuenta dentro de este tipo de ensayos se encuentra la biodisponibilidad del principio activo, y dentro de esta biodisponibilidad, un factor crítico es la capacidad de disolución del principio activo en el medio acuoso fisiológico que permita su posterior absorción.

Teniendo en cuenta que la solicitud colombiana en trámite reivindica una formulación de carácter sólido (tableta) cuya composición regula o soluciona una variación en el comportamiento de la disolución de un ingrediente activo tal como el (S)-N-[2-(1,6,7,8-tetrahidro-2H-indeno[5,4-b]furan-8-il)etil]-propionamida (Ramelteon) a través de la incorporación de excipientes como estereato de magnesio e hidroxipropilcelulosa, que tiene una viscosidad de aproximadamente 1 a 4 mPas, es relevante resaltar que, primero, las formulaciones tipo tableta son formulas reconocidas y ampliamente descritas en el estado de la técnica, y segundo, que si la manera de estabilizar dicha variabilidad en la disolución del principio activo en cuestión, ya se ha aplicado en el estado de la técnica en otros principios activos, la composición farmacéutica de la solicitud colombiana en cuestión, se reduce a la aplicación de los respectivos ensayos de preformulación para este tipo de formulación farmacéutica, así como a la utilización de información reconocida para guiar dichos ensayos; con lo cual la invención carecería de nivel inventivo.

❖ La publicación internacional WO 97/32871 publicada el 12 de Septiembre de 1997 y titulada "TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE" revela:

The present invention relates to a novel compound which is characterized in having a R^1-CO-amino-C_{1-4} alkylene group (in which R^1 is of the same meanings as defined hereinafter) at Y of the basic skeleton moiety of the formula:



(...)

Preferable examples of the compound (I) include,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

(...)

The compound (I) of the present invention has low toxicity and can be administered safely through peroral or parenteral routes (e.g., for local administration, rectal administration, intravenous administration, etc.), either directly or as pharmaceutical compositions to be mixed with pharmaceutically acceptable carriers by using per se known methods, for example, as tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, plasters and also as chewing gum, etc. The amount of the

(...)

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Pharmaceutically acceptable carriers employable in the production of the composition of the present invention include various organic and inorganic carrier substances which are known to be usable in pharmaceutical compositions. For example, they include excipients, lubricants, binders, disintegrants, etc. in solid compositions; solvents, solubilizers, suspending

(...)

Lubricants include, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, sodium carboxymethyl cellulose, etc.

(...)

34. A pharmaceutical composition which comprises a compound as claimed in claim 1.

Como se puede apreciar, en esta anterioridad y de manera general, se incluyen formulaciones farmacéuticas para administración oral tipo tableta que contienen entre otros, el mismo principio activo (Ramelteon) y excipientes como los mencionados por la solicitud colombiana (estearato de magnesio e hidroxipropilcelulosa).

❖ Por su parte la patente Japonesa JP 11322584 publicada el 24 de Noviembre de 1999 y titulada "BEZAFIBRATE SUSTAINED RELEASE PHARMACEUTICAL PREPARATION" *revela:*

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(54) **BEZAFIBRATE SUSTAINED RELEASE PHARMACEUTICAL PREPARATION**

(57) Abstract

PROBLEM TO BE SOLVED: To obtain the subject compact and readily administrable pharmaceutical preparation capable of achieving proper substained release and stably providing sufficient initial effects and sustained effects and having uniform and stable quality by including bezafibrate and a specific hydroxypropyl cellulose(HPC) therein.

SOLUTION: This pharmaceutical preparation contains (A) bezafibrate and (B) an HPC having about 1 to about 5 cP, preferably about 1 to about 3 cP, more preferably 2.0-2.8 cP viscosity of a 2 wt.% aqueous solution at 20°C. The content of the ingredient B is usually 0.01-0.5 pt.wt., preferably 0.05-0.4 pt.wt., more preferably 0.1-0.3 pt.wt. based on 1 pt.wt. of the ingredient A. An HPC having a viscosity different from that of the HPC, hydroxypropyl methyl cellulose or polyvinyl alcohol may be contained in addition to the HPC in the pharmaceutical preparation. The resultant pharmaceutical preparation is useful as a therapeutic agent for hyperlipemia.

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Y la patente Japonesa JP 2002326927 publicada el 15 de Noviembre de 2002 y titulada "QUICK-RELEASING TABLET CONTAINING METFORMIN HYDROCHLORIDE" revela:

(54) **QUICK-RELEASING TABLET CONTAINING METFORMIN HYDROCHLORIDE**

(57) Abstract

PROBLEM TO BE SOLVED: To provide quick-releasing tablets of metformin hydrochloride, capable of improving dosing feeling, because the tablets can be prepared in small size, being medically remarkably useful and exhibiting effects such as excellent productivity and storage stability.

SOLUTION: The quick-releasing tablets are characterized by comprising (A) metformin hydrochloride and (B) hydroxypropyl cellulose in which viscosity of 2 mass % aqueous solution at 20°C is 2.0-10.0 mPas.

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Como se puede apreciar, y si bien es cierto en estos dos documentos no se hace mención de Ramelteon, es importante resaltar que estas dos anterioridades se incluye al excipiente hidroxipropilcelulosa (HPC) con una viscosidad entre 1 y 5 cP (para el primer caso) y entre 2-10mPas (para el segundo caso), el cual es capaz de regular o hacer uniforme la tasa de elución del ingrediente activo en sus respectivas formulaciones y/o en distintos lotes. Si tenemos en cuenta lo anterior, nos damos cuenta que la solicitud colombiana en trámite persigue el mismo fin, modificar las propiedades biofarmacéuticas del principio activo dentro de la formulación propuesta, específicamente su intención es la de demostrar que la cantidad de HPC influye en la capacidad de elusión o en el comportamiento de disolución de los mismos.

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En conclusión, las formulaciones farmacéuticas reivindicadas por la solicitud colombiana en trámite carecen por completo de nivel inventivo, ya que resultan ser formulaciones farmacéuticas para administración oral tipo tableta convencionales, en donde se emplean excipientes que se sabe influyen y/o mejoran las características de las mismas, todo esto, producto de la información científica y farmacotécnica *disponible en el mismo estado de la técnica, que permiten definir* características óptimas a través de los correspondientes y convencionales ensayos de preformulación descritos para este tipo de formas farmacéuticas.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- *La publicación internacional WO 97/32871 publicada el 12 de Septiembre* de 1997 y titulada "TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE" paginas 7, 46, 168, 169 y capitulo reivindicatorio.
- Portadas de: La patente Japonesa JP 11322584 publicada el 24 de Noviembre de 1999 y titulada "BEZAFIBRATE SUSTAINED RELEASE PHARMACEUTICAL PREPARATION" y la patente Japonesa JP 20022326927 publicada el 15 de Noviembre de 2002 y titulada "QUICK-RELEASING TABLET CONTAINING METFORMIN HYDROCHLORIDE".

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

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(71) Applicant: TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

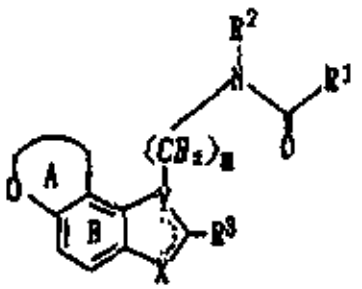
(72) Inventors: OHKAWA, Shigenori; 45-20, Makamicho 6-chome, Takatsuki-shi, Osaka 569 (JP). UCHIKAWA, Osamu; 15-16, Kozukayama 2-chome, Tarumi-ku, Kobe-shi, Hyogo 655 (JP). FUKATSU, Kohji; 8-4, Tsukushigaoka 5-chome, Kita-ku, Kobe-shi, Hyogo 651-12 (JP). MIYAMOTO, Masaomi; 12-11, Gotenyama 4-chome, Takarazuka-shi, Hyogo 665 (JP).

(74) Agent: ASAHINA, Tadao; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(54) Title: TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND USE

(57) Abstract

A compound of formula (I) wherein R^1 is an optionally substituted hydrocarbon, amino or heterocyclic group; R^2 is H or an optionally substituted hydrocarbon group; R^3 is H or an optionally substituted hydrocarbon or heterocyclic group; X is CHR^4, NR^4, O or S in which R^4 is H or an optionally substituted hydrocarbon group; Y is C, CH or N; ring A is an optionally substituted 5- to 7-membered ring; ring B is an optionally substituted benzene ring; and m is 1 to 4, or a salt thereof, a process for producing it, an intermediate for the production and a pharmaceutical composition comprising it are provided.

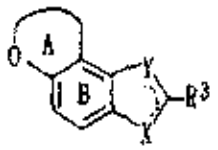


(I)

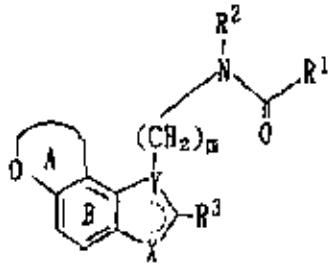
agonistic or antagonistic activity towards melatonin receptor and which are therefore fully satisfactory for use in medicines such as pharmaceutical preparations.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound which is characterized in having a R^1-CO-amino-C_{1-4} alkylene group (in which R^1 is of the same meanings as defined hereinafter) at Y of the basic skeleton moiety of the formula:



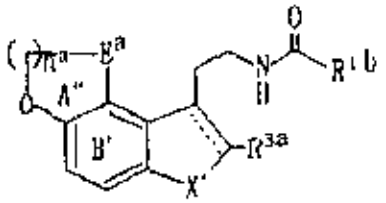
wherein all symbols are of the same meanings as defined hereinafter and is represented by the formula:



(I)

wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;
R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group;
R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
X represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;

formula:



wherein R^{1b} is C_{1-6} alkyl, X' is CH_2, NH or NCHO, ... is a single bond or double bond, R^{3a} is a hydrogen atom or a phenyl, E^a is CH_2CH_2, CH=CH, CH_2O, CH=N, CONH or CH_2NH, n^a is 0 or 1, ring A" is a 5- or 6-membered oxgen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and ring B' is a benzene ring which may be substituted by a halogen, and a salt thereof. Among them, the compound wherein ..... is a single bond or double bond when X' is CH_2 or NCHO, and ..... is a single bond when X' is NH is also preferred.

Preferable examples of the compound (I) include,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-

therefore, it can be used for preventing and curing biorhythmic control disorders and various other *disorders that may be affected by melatonin, for* example, sleep-awake rhythm disorders, jet-lag, shift-work syndrome, seasonal melancholia, genital and neuroendocrine disorders, senile dementia, Alzheimer's disease, various disorders accompanied by aging (e.g., for preventing aging, etc.), cerebrovascular disorders (e.g., cerebral hemorrhage, etc.), cranial injury, spinal injury, stress, epilepsy, convulsions, anxiety, depression, Parkinsonism, hypertension, glaucoma, cancer, insomnia and diabetes. It is also acts as melatonin antagonists in mammals. In addition, it is also effective for immunoregulation, nootropic, tranquilization and ovulatory regulation (e.g., contraception). The compound (I) of the present invention can be used, for example, in biorhythm regulators, preferably medicines for sleep disorder (e.g., sleep-inducing medicines, etc.), sleep-awake rhythm regulators (including those for controlling sleep-awake rhythm), medicines for physilogical syndromes caused by time-zone changes, for example, so-called jet-lag, etc.

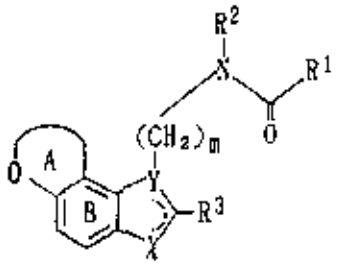
The compound (I) of the present invention has low toxicity and can be administered safely through peroral or parenteral routes (e.g., for local administration, rectal administration, intravenous administration, etc.), either directly or as pharmaceutical compositions to be mixed with pharmaceutically acceptable carriers by using per se known methods, for example, as tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, plasters and also as chewing gum, etc. The amount of the compound (I) in the composition of the present

invention is approximately 0.01 to nearly 100% by weight of the total weight of the composition. The dose of the composition varies, depending on the subject to which the composition is administered, the administration route, the disorder, etc. For example, when the composition is administered to an adult patient suffering from sleep disorders, it is preferable to administer once daily or severally divided dosages in an amount of approximately 0.0005 to 2 mg/kg body weight, preferably approximately 0.001 to 1 mg/kg body weight, more preferably approximately 0.001 to 0.5 mg/kg body weight, in terms of the amount of the active ingredient, compound (I). The composition may be used with other active ingredients (e.g., benzodiazepine-type medicines comprising benzodiazepine compounds such as triazolam, diazepam, alprazolam, estazolam, etc.; regulating agents of sleep rhythm comprising fatty acid derivatives such as butoctamide and its salt, etc.; sleep ruducing substances comprising cis-9,10-octadecenamide, etc.) Such other active ingredient and the compound (I) may be mixed by means of per se known methods to give pharmaceutical compositions (e.g., tablets, powders, granules, capsules including soft capsules, liquids, injections, suppositories, sustained release preparations, etc.); or they are separately formulated into different preparations, which may be administered to one and the same subject either simultaneously or at different times.

Pharmaceutically acceptable carriers employable in the production of the composition of the present invention include various organic and inorganic carrier substances which are known to be usable in pharmaceutical compositions. For example, they include excipients, lubricants, binders, disintegrants, etc. in solid compositions; solvents, solubilizers, suspending

claim:

1. A compound of the formula:



wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;
R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group;
R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;
X represents CHR^4, NR^4, O or S in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group;
Y represents C, CH or N, provided that when X is CH_2, Y is C or CH;
..... represents a single bond or a double bond;
ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;
ring B represents an optionally substituted benzene ring; and
m represents an integer of 1 to 4,
or a salt thereof.

2. A compound as claimed in claim 1, wherein R^1 is (i) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an

optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkylcarbamoyl, di-C_{1-6} alkylcarbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino,
(ii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, or
(iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11} aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6}

alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^2 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

R^3 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (iii) a 5- to 14-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, C_{7-11} aralkyl, C_{6-10} aryl, C_{1-6} alkoxy, C_{6-10} aryloxy, formyl, C_{1-6} alkyl-carbonyl, C_{6-10} aryl-carbonyl, formyloxy, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, carboxyl, C_{1-6} alkoxy-carbonyl, C_{7-11}

aralkyloxy-carbonyl, carbamoyl, an optionally halogenated C_{1-4} alkyl, oxo, amidino, imino, amino, mono-C_{1-4} alkylamino, di-C_{1-4} alkylamino, 3- to 6-membered cyclic amino, C_{1-3} alkylenedioxy, hydroxy, nitro, cyano, mercapto, sulfo, sulfino, phosphono, sulfamoyl, mono-C_{1-6} alkylsulfamoyl, di-C_{1-6} alkylsulfamoyl, C_{1-6} alkylthio, C_{6-10} arylthio, C_{1-6} alkylsulfinyl, C_{6-10} arylsulfinyl, C_{1-6} alkylsulfonyl and C_{6-10} arylsulfonyl;

R^4 is (i) a hydrogen atom or (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino;

ring A is a 5- to 7-membered heterocyclic group optionally containing, besides carbon atoms and an oxygen atom, 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which group may be substituted by 1 to 4 substituents selected from the group consisting of (i) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally

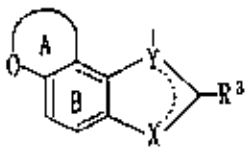
halogenated C_{1-6} alkyl-carbonylamino, (ii) a halogen, (iii) C_{1-6} alkoxy, (iv) C_{6-10} aryloxy, (v) formyl, (vi) C_{1-6} alkyl-carbonyl, (vii) C_{6-10} aryl-carbonyl, (viii) formyloxy, (ix) C_{1-6} alkyl-carbonyloxy, (x) C_{6-10} aryl-carbonyloxy, (xi) carboxyl, (xii) C_{1-6} alkoxy-carbonyl, (xiii) C_{7-11} aralkyloxy-carbonyl, (xiv) carbamoyl, (xv) an optionally halogenated C_{1-4} alkyl, (xvi) oxo, (xvii) amidino, (xviii) imino, (xix) amino, (xx) mono-C_{1-4} alkylamino, (xxi) di-C_{1-4} alkylamino, (xxii) 3- to 6-membered cyclic amino, (xxiii) C_{1-3} alkylenedioxy, (xxiv) hydroxy, (xxv) nitro, (xxvi) cyano, (xxvii) mercapto, (xxviii) sulfo, (xxix) sulfino, (xxx) phosphono, (xxxi) sulfamoyl, (xxxii) mono-C_{1-6} alkylsulfamoyl, (xxxiii) di-C_{1-6} alkylsulfamoyl, (xxxiv) C_{1-6} alkylthio, (xxxv) C_{6-10} arylthio, (xxxvi) C_{1-6} alkylsulfinyl, (xxxvii) C_{6-10} arylsulfinyl, (xxxviii) C_{1-6} alkylsulfonyl and (xxxix) C_{6-10} arylsulfonyl; and

ring B is a benzene ring which may be substituted by 1 or 2 substituents selected from the group consisting of (i) a halogen, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino,

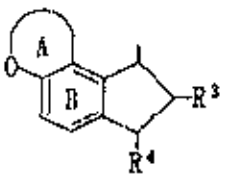
(iii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{6-14} aryl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of

a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino, (iv) a C_{1-6} alkanoylamino group, (v) a C_{1-6} alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen, nitro, cyano, hydroxy, an optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, carboxyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, carbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, C_{6-10} aryl, C_{6-10} aryloxy and an optionally halogenated C_{1-6} alkyl-carbonylamino or (vi) a C_{1-3} alkylenedioxy group.

3. A compound as claimed in claim 1, wherein



is



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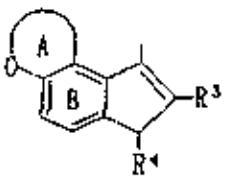

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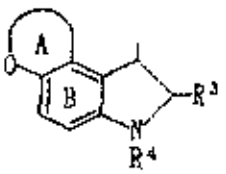
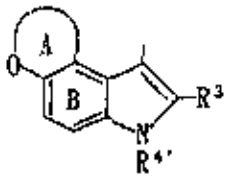
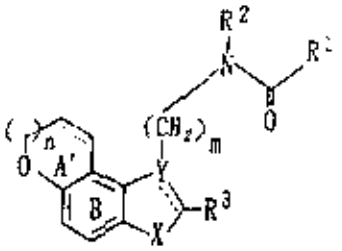


or



wherein $R^{4'}$ is an optionally substituted hydrocarbon group and the other symbols are as defined in claim 1.

4. A compound as claimed in claim 1 which is a compound of the formula:



wherein ring A' is an optionally substituted, oxygen-containing heterocyclic ring;
n is an integer of 0 to 2;
—— and ..... are the same or different and each is a single bond or a double bond;
and the other symbols are as defined in claim 1.

5. A compound as claimed in claim 1, wherein R^1 is
(i) an optionally substituted C_{1-6} alkyl group,
(ii) an optionally substituted C_{3-6} cycloalkyl group,
(iii) an optionally substituted C_{7-6} alkenyl group,
(iv) an optionally substituted C_{6-14} aryl group,
(v) an optionally substituted mono- or di-C_{1-6} alkylamino group,
(vi) an optionally substituted C_{6-14} arylamino group or
(vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group.

6. A compound as claimed in claim 1, wherein R^1 is an optionally halogenated C_{1-6} alkyl group.

7. A compound as claimed in claim 1, wherein R^2 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

8. A compound as claimed in claim 1, wherein R^2 is a hydrogen atom.

9. A compound as claimed in claim 1, wherein R^3 is a hydrogen atom or an optionally substituted hydrocarbon group.

10. A compound as claimed in claim 1, wherein R^2 is a hydrogen atom.

11. A compound as claimed in claim 1, wherein R^3 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

12. A compound as claimed in claim 1, wherein X is CHR^4.

13. A compound as claimed in claim 1, wherein X is CHR^4 and ..... is a single bond.

14. A compound as claimed in claim 13, wherein X is CH_2.

15. A compound as claimed in claim 1, wherein X is NR^4.

16. A compound as claimed in claim 1, wherein Y is C or CH.

17. A compound as claimed in claim 1, wherein Y is CH.

18. A compound as claimed in claim 1, wherein m is 2.

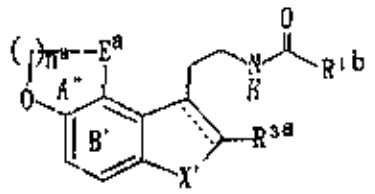
19. A compound as claimed in claim 1, wherein ring A is a tetrahydrofuran ring.

20. A compound as claimed in claim 1, wherein ring A is unsubstituted.

21. A compound as claimed in claim 1, wherein ring B is unsubstituted.

22. A compound as claimed in claim 4, wherein n is 0 or 1.

23. A compound as claimed in claim 1 which is a compound of the formula:



wherein R^{1b} is C_{1-6} alkyl,

X' is CH_2, NH or NCHO,

..... is a single bond or double bond,

R^{3a} is a hydrogen atom or phenyl,
E^a is CH_2CH_2, CH=CH, CH_2O, CH=N, CONH or CH_2NH,
n^a is 0 or 1,
ring A" is a 5- or 6-membered oxgen-containing heterocyclic ring which may be substituted by 1 or 2 C_{1-6} alkyl optionally substituted by a hydroxy, and
ring B' is a benzene ring which may be substituted by a halogen.

24. A compound claimed in claim 23, wherein ⋯⋯ is single bond and X' is NH.

25. A compound claimed in claim 1, which is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

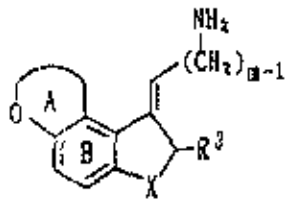
26. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide.

27. A compound claimed in claim 1, which is N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butyramide.

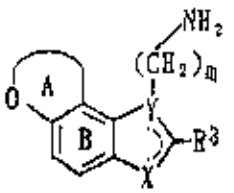
28. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

29. A compound claimed in claim 1, which is N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide.

30. A process for producing a compound as claimed in claim 1, which comprises reacting a compound of the formula (i):



wherein all symbols are as defined in claim 1, or (ii):

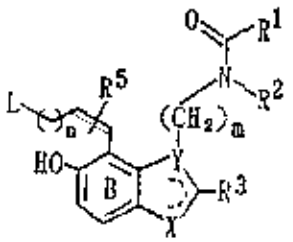


wherein all symbols are as defined in claim 1, or a salt thereof, with a compound of the formula:

R^1COOH

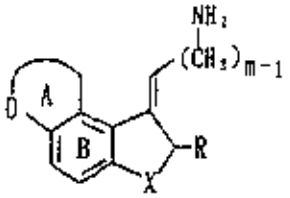
wherein R^1 is as defined in claim 1, or a salt thereof or a reactive derivative thereof, and if necessary, subjecting the resultant compound to reduction and/or alkylation.

31. A process for producing a compound as claimed in claim 4, which comprises subjecting a compound of the formula:



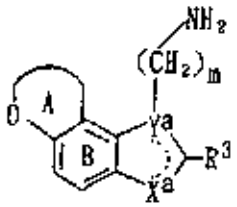
wherein R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxy group, a nitro group, a cyano group or an optionally substituted amino group; L represents a leaving group; and the other symbols are as defined in claim 4, or a salt thereof to cyclization, and if necessary, subjecting the resultant compound to reduction.

32. A compound of the formula:



wherein the symbols are as defined in claim 1, or a salt thereof.

33. A compound of the formula:



wherein X^a represents CHR^{4a}, NR^{4a}, O or S in which R^{4a} represents a hydrogen atom or an optionally substituted hydrocarbon group; Y^a represents C, CH or N, provided that when X^a is NH, Y^a is CH or N; and the other symbols are as defined in claim 1, or a salt thereof.

34. A pharmaceutical composition which comprises a compound as claimed in claim 1.

35. A composition as claimed in claim 34 which has a binding affinity for melatonin receptor.

36. A composition as claimed in claim 35 which is a regulating agent of circadian rhythm.

37. A composition as claimed in claim 35 which is a regulating agent of sleep-awake rhythm.

38. A composition as claimed in claim 35 which is a regulating agent of time zone change syndrome.

39. A composition as claimed in claim 35 which is a therapeutic agent of sleep disorders.

40. Method for treating or preventing diseases related to the action of melatonin in mammals which comprises administrating to a subject in need a therapeutically effective amount of a compound as claimed in claim 1

PATENT ABSTRACTS OF JAPAN

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A61K 9/22, A61K 31/195, A61K 47/38

(21) Application number: 10124860
(22) Date of filing: 07.05.1998

(71) Applicant: SAWAI PHARMACEUTICAL CO LTD
(72) Inventor: OSONO HIROSHI
SUZUKI TOSHIYUKI
ARAKI TERUO
TATSUMI MASASHI

(54) BEZAFIBRATE SUSTAINED RELEASE PHARMACEUTICAL PREPARATION

(57) Abstract:

PROBLEM TO BE SOLVED: To obtain the subject compact and readily administrable pharmaceutical preparation capable of achieving proper sustained release and stably providing sufficient initial effects and sustained effects and having uniform and stable quality by including bezafibrate and a specific hydroxypropyl cellulose(HPC) therein.

SOLUTION: This pharmaceutical preparation contains (A) bezafibrate and (B) an HPC having about 1 to about 5 cP, preferably about 1 to about 3 cP, more preferably 2.0-2.8 cP viscosity of a 2 wt.% aqueous solution at 20°C. The content of the ingredient B is usually 0.01-0.5 pt.wt., preferably 0.05-0.4 pt.wt., more preferably 0.1-0.3 pt.wt. based on 1 pt.wt. of the ingredient A. An HPC having a viscosity different from that of the HPC, hydroxypropyl methyl cellulose or polyvinyl alcohol may be contained in addition to the HPC in the pharmaceutical preparation. The resultant pharmaceutical preparation is useful as a therapeutic agent for hyperlipemia.

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(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

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(71) Applicant: TOA EIYO LTD
(72) Inventor: MATSUI TAOASHI
YUASA SHIYUUICHIROU

(54) QUICK-RELEASING TABLET CONTAINING METFORMIN HYDROCHLORIDE

(57) Abstract:

PROBLEM TO BE SOLVED: To provide quick-releasing tablets of metformin hydrochloride, capable of improving dosing feeling, because the tablets can be prepared in small size, being medically remarkably useful and exhibiting effects such as excellent productivity and storage stability.

SOLUTION: The quick-releasing tablets are characterized by comprising (A) metformin hydrochloride and (B) hydroxypropyl cellulose in which viscosity of 2 mass % aqueous solution at 20°C is 2.0-10.0 mPas.