

341

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-021211- -00003-0000

Fecha: 2008-06-05 16:43:24 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

Referencia: Expediente No. 07.021.211

Solicitud de Patente de Invención titulada: "Fenoles de carbonilo
fenantridina como moduladores de citoquina"

Solicitante: Wyeth

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN

486. GACETA NO. 588

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad arriba mencionada, solicito que se examine la invención de la referencia según los requisitos de patentabilidad previstos en la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de \$420.000 para cubrir la tasa correspondiente según la Resolución 44372 del 26 de diciembre de 2007.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexo: Recibo de caja No. 08-27964 por valor de \$420.000

2008 / 007 342

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-021211- -00003-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 27,964
FECHA : ABRIL 7 DE 2008

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	3161944	07/04/2008	30,417,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-21211

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **588** DE

FECHA **31 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **29 DE ABRIL DE 2008**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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Organization
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401/04, 405/04, 409/04, A61K 31/473, A61P 9/00, 29/00,
11/00, 25/00

(74) Agents: **LUCCL, Joseph et al.**; Woodcock Washburn LLP,
46th floor, One Liberty Place, Philadelphia, PA 19103
(US).

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KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
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GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
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(71) Applicant (*for all designated States except US*): **WYETH**
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(72) Inventors; and

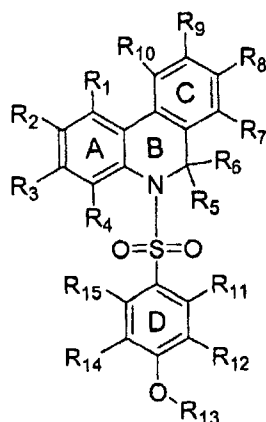
(75) Inventors/Applicants (*for US only*): **MOLINARI, Al-**
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Published:

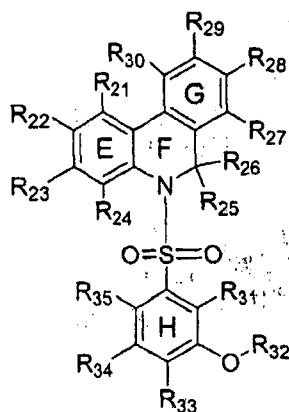
— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED DIHYDROPHENANTHRIDINESUL FONAMIDES



(I)

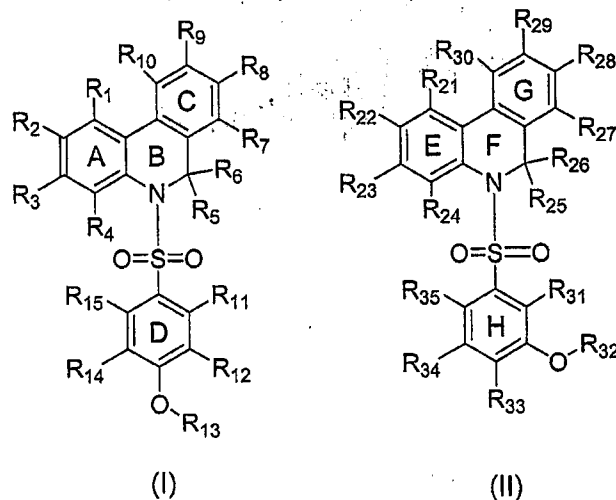


(II)

(57) Abstract: This invention provides a compound of formulae (I) or (II) having the structure or a pharmaceutically acceptable salt thereof which are useful for the treatment of the inflammatory component of diseases and are particularly useful in treating atherosclerosis, myocardial infarction, congestive heart failure, inflammatory bowel disease, arthritis, type II diabetes, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

disease, arthritis, type II diabetes, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

[0007] This invention provides novel compounds of formulae (I) or (II) having the structure



wherein

R₁, R₂, R₃, R₄, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₄, and R₁₅ are each, independently, hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, R₁₇-SO₃-, R₁₇-S(O)₂NR-, -N(R)₂, -NR-C(NH₂)=NR, cyano, nitro, halogen, -OR, -SR, -SO₃R, -S(O)₂N(R)₂, -C(O)R, -C(R)=N-OR, -C(NH₂)=NR, -CO₂R, -OC(O)R, or -C(O)N(R)₂; or are taken together with either R_{p+1} or R_{p-1} linked with an -alkylene-, or -X-alkylene- group;

R₅ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₅ may be taken together with either R₆ or R₇ and linked with an -alkylene- or -X-alkylene- group;

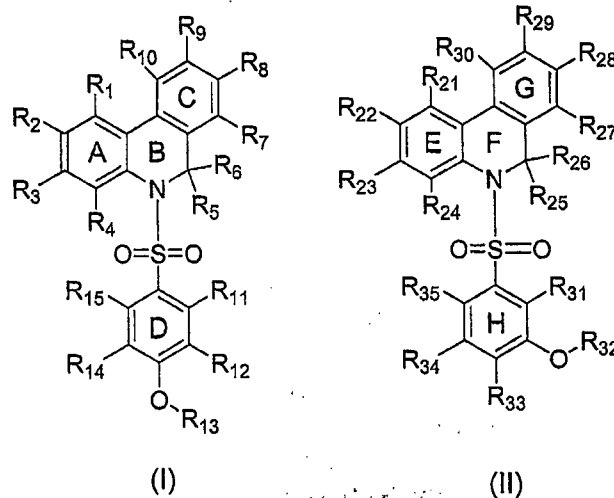
R₆ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₆ may be taken together with either R₅ or R₇ and linked with an -alkylene- or -X-alkylene- group;

R₁₃ is R, R₁₇-X-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, -SO₃R, -S(O)₂N(R)₂, or D-glucuronidate;

CLAIMS

What is claimed is:

1. A compound of formulae (I) or (II) having the structure



wherein

R₁, R₂, R₃, R₄, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₄, and R₁₅ are each, independently, hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, R₁₇-SO₃-, R₁₇-S(O)₂NR-, -N(R)₂, -NR-C(NH₂)=NR, cyano, nitro, halogen, -OR, -SR, -SO₃R, -S(O)₂N(R)₂, -C(O)R, -C(R)=N-OR, -C(NH₂)=NR, -CO₂R, -OC(O)R, or -C(O)N(R)₂; or are taken together with either R_{p+1} or R_{p-1} linked with an -alkylene-, or -X-alkylene- group;

R₅ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₅ may be taken together with either R₆ or R₇ and linked with an -alkylene- or -X-alkylene- group;

R₆ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-X-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₆ may be taken together with either R₅ or R₇ and linked with an -alkylene- or -X-alkylene- group;

R₁₃ is R, R₁₇-X-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, -SO₃R, -S(O)₂N(R)₂, or D-glucuronidate;

R₁₆ is -alkylene-, -cycloalkylene-, -alkylene-X-alkylene-, -alkylene-X-cycloalkylene-, -cycloalkylene-X-alkylene-, or -cycloalkylene-X-cycloalkylene-;

R₁₇ is alkyl, aryl, heteroaryl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, alkenyl-X-alkylene-, cycloalkenyl-X-alkylene-, or perfluoroalkyl;

R is, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, monofluoroalkyl, perfluoroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy-(C₂-C₆)alkyl, alkoxyalkyl, alkylthioalkyl, formyl, acyl, alkoxycarbonyl, -C(O)NH₂, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminoalkyl, or dialkylaminoalkyl; or when an atom contains two R groups, the R groups may be taken together linked with an -alkylene- group;

X is O, -NR-, -S(O)_m-, -C(O)-, -OC(O)-, -C(O)O-, -NRC(O)-, or -C(O)NR-;

m is 0, 1, or 2;

p is 2, 3, 6, 7, 8, 9, 12, 13, or 14;

R₂₁, R₂₂, R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₃, R₃₄, and R₃₅ are, independently, hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-Y-R₁₆-, HS-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, R₁₇-SO₃-, R₁₇-S(O)₂NR-, -N(R)₂-, -NR-C(NH₂)=NR, cyano, nitro, halogen, -OR, -SR, -SO₃R, -S(O)₂N(R)₂-, -C(O)R, -C(R)=N-OR, -C(NH₂)=NR, -CO₂R, -OC(O)R, or -C(O)N(R)₂; or are taken together with either R_{q+1} or R_{q-1} linked with an -alkylene-, or -Y-alkylene- group;

R₂₅ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-Y-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₂₅ may be taken together with either R₂₆ or R₂₇ and linked with an -alkylene- or -Y-alkylene- group;

R₂₆ is hydrogen, R₁₇, monofluoroalkyl, monofluoroalkenyl, aryl-R₁₆-, heteroaryl-R₁₆-, hydroxyalkyl, HO-R₁₆-, R₁₇-Y-R₁₆-, HS-R₁₆-, -CR(O), -CO₂R, or -C(O)N(R)₂; or R₂₆ may be taken together with either R₂₅ or R₂₇ and linked with an -alkylene- or -Y-alkylene- group;

R₃₂ is R, R₁₇-Y-R₁₆-, R₁₇-S(O)-, R₁₇-S(O)₂-, -SO₃R, -S(O)₂N(R)₂, or D-glucuronidate;

Y is O, -NR-, -S(O)_n-, -C(O)-, -OC(O)-, -C(O)O-, -NRC(O)-, or -C(O)NR-;

n is 0, 1, or 2;

q is 22, 23, 26, 27, 28, 29, 32, 33, or 34;

or a pharmaceutically acceptable salt thereof.

United States Patent [19]

Johnson et al.

[11] 4,228,169

[45] Oct. 14, 1980

- [54] 1,9-DIHYDROXYOCTAHYDROBENZO[c]-
QUINOLINES AND
1-HYDROXYHEXAHYDROBENZO[c]-
QUINOLINE-9(8H)-ONES AS ANTIEMETIC
AGENTS

- [75] Inventors: Michael R. Johnson, Gales Ferry;
George M. Milne, Niantic, both of
Conn.

- [73] Assignee: Pfizer Inc., New York, N.Y.

- [21] Appl. No.: 52,324

- [22] Filed: Jun. 26, 1979

- [51] Int. Cl.² A61K 27/00; A61K 31/47
[52] U.S. Cl. 424/258; 424/248.50;
424/248.51; 424/248.54; 424/248.57
[58] Field of Search 424/248.51, 248.54,
424/248.57, 248.50, 258

[56] References Cited

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4,087,545 5/1978 Archer 424/283

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854655 11/1977 Belgium .

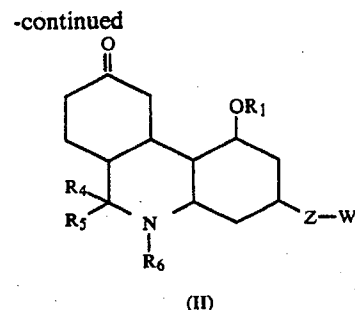
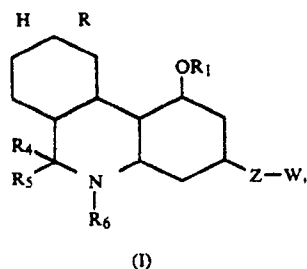
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Sallen et al., N. Eng. J. Med. 293, 795 (1975).
Borison et al., N. Eng. J. Med. 298, 1480 (1978).

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Connolly and Hutz

[57] ABSTRACT

1,9-Dihydroxyoctahydro[c]quinolines (I) and 1-hydroxyhexahydrobenzo[c]quinoline-9(8H)-ones (II), useful as antiemetic agents and derivatives thereof having the formulae

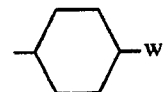


wherein R is hydroxy or alkanoyloxy having from one to five carbon atoms;

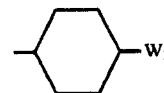
R₁ is hydrogen, benzyl, benzoyl, alkanoyl having from one to five carbon atoms or —CO—(CH₂)_p—NR₂R₃ wherein p is 0 or an integer from 1 to 4; each of R₂ and R₃ when taken individually is hydrogen or alkyl having from one to four carbon atoms; R₂ and R₃ when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring (piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group); R₄ is hydrogen, alkyl having from 1 to 6 carbon atoms and —(CH₂)_x—C₆H₅ wherein x is an integer from 1 to 4; R₅ is hydrogen, methyl or ethyl; R₆ is hydrogen, —(CH₂)_y—carbalkoxy having from 1 to 4 carbon atoms in the alkoxy group wherein y is 0 or an integer from 1 to 4; carbobenzyloxy, formyl, alkanoyl having from two to five carbon atoms, alkyl having from one to six carbon atoms; —(CH₂)_x—C₆H₅ wherein x is an integer from 1 to 4; and —CO(CH₂)_{x-1}—C₆H₅;

Z is (a) alkylene having from one to nine carbon atoms; (b) —(alk₁)_m—X—(alk₂)_n— wherein each of (alk₁) and (alk₂) is alkylene having from one to nine carbon atoms, with the proviso that the summation of carbon atoms in (alk₁) plus (alk₂) is not greater than 9; each of m and n is 0 or 1; X is O, S, SO or SO₂; and

W is hydrogen, methyl,



wherein W₁ is hydrogen, chloro or fluoro; pyridyl, piperidyl, cycloalkyl having from 3 to 7 carbon atoms, or monosubstituted cycloalkyl wherein the substituent is



wherein W₂ is hydrogen, chloro or fluoro; and pharmaceutically-acceptable acid addition salts of compounds of formulae I and II and the ketals of compounds of formula II wherein the ketal moiety has from two to four carbon atoms.

27 Claims, No Drawings

EXAMPLE 16

General Hydrochloride Salt Formation

Excess hydrogen chloride is passed into a solution of the appropriate benzo[c]quinoline of formulae I and II and the resulting precipitate separated and recrystallised from an appropriate solvent, e.g. methanol-ether (1:10).

In this manner the following salt is prepared:

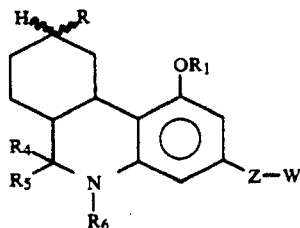
d,l-trans-5,6,6a,7,8,9,10,10a-octahydro-1-acetoxy-9 β -hydroxy-6 β -methyl-3-(5-phenyl-2-pentyloxy)-benzo[c]quinoline, m.p. 191°-193° C.

m/e-437 (m+).

Analysis: Calc'd. for C₂₇H₃₆O₄NCl: C, 68.48; H, 7.70; N, 2.89%; Found: C, 68.42; H, 7.66; N, 2.96%.

We claim:

1. A process for the prevention and treatment of nausea in a mammal subject to said nausea which comprises administering to said mammal a compound in an amount effective to prevent nausea, said compound being selected from the group consisting of



and the pharmaceutically acceptable acid addition salts thereof.

wherein R is selected from the group consisting of hydroxy and alkanoyloxy having from one to five carbon atoms;

R₁ is selected from the group consisting of hydrogen, benzyl, benzoyl, alkanoyl having from one to five carbon atoms and $-\text{CO}-(\text{CH}_2)_p-\text{NR}_2\text{R}_3$ wherein p is 0 or an integer from 1 to 4; each of R₂ and R₃ when taken individually is selected from the group consisting of hydrogen and alkyl having from one to four carbon atoms; R₂ and R₃ when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring selected from the group consisting of piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group;

R₄ is selected from the group consisting of hydrogen, alkyl having from 1 to 6 carbon atoms and $-(\text{CH}_2)_z-\text{C}_6\text{H}_5$ wherein z is an integer from 1 to 4;

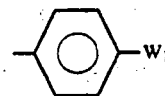
R₅ is selected from the group consisting of hydrogen, methyl and ethyl;

R₆ is selected from the group consisting of hydrogen, $-(\text{CH}_2)_y$ -carbalkoxy having from one to four carbon atoms in the alkoxy group and wherein y is 0 or an integer from 1 to 4, carbobenzyloxy, formyl, alkanoyl having from two to five carbon atoms, alkyl having from one to six carbon atoms and $-(\text{CH}_2)_x-\text{C}_6\text{H}_5$ wherein x is an integer from 1 to 4; and $\text{CO}(\text{CH}_2)_{x-1}-\text{C}_6\text{H}_5$;

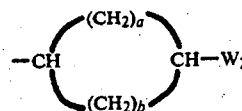
Z is selected from the group consisting of (a) alkylene having from one to nine carbon atoms; (b) $-(\text{alk}_1)_m-\text{X}-(\text{alk}_2)_n-$ wherein each of (alk₁) and (alk₂) is alkylene having from one to nine carbon atoms, with the proviso that the summa-

tion of carbon atoms in (alk₁) plus (alk₂) is not greater than nine; each of m and n is 0 or 1; X is selected from the group consisting of O, S, SO and SO₂; and

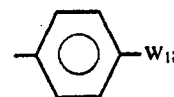
W is selected from the group consisting of hydrogen, methyl, pyridyl, piperidyl,



wherein W₁ is selected from the group consisting of hydrogen, fluoro and chloro; and



wherein W₂ is selected from the group consisting of hydrogen and



a is an integer from 1 to 5 and b is 0 or an integer from 1 to 5; with the proviso that the sum of a and b is not greater than 5.

2. A process according to claim 1 in which a compound wherein R₁ is hydrogen or alkanoyl; R is hydroxy or alkanoyloxy; R₅ is methyl or hydrogen; and each of R₄ and R₆ is hydrogen or alkyl is administered.

3. A process according to claim 2 in which a compound wherein R₁ is hydrogen or acetyl; R is hydroxy or acetoxy; Z is $-(\text{alk}_1)_m-\text{X}-(\text{alk}_2)_n-$ and W is hydrogen or phenyl is administered.

4. A process according to claim 3 in which a compound wherein Z is $-(\text{alk}_1)_m-\text{O}-(\text{alk}_2)_n-$ is administered.

5. A process according to claim 4 in which a compound wherein Z is $-\text{O}-(\text{alk}_2)_n-$, W is phenyl, R₁ is acetyl and R is hydroxy is administered.

6. A process according to claim 5 in which a trans-(6a,10a)diastereomer compound wherein Z is $-\text{OCH}(\text{CH}_3)(\text{CH}_2)_3-$ is administered.

7. A process according to claim 6 in which the compound wherein R is β -hydroxy; R₁ is acetyl; R₄ is β -methyl; and each of R₅ and R₆ is hydrogen is administered.

8. A process according to claim 6 in which the compound wherein R is β -hydroxy; R₁ is acetyl; R₅ is hydrogen; R₆ is methyl; and R₄ is β -methyl is administered.

9. A process according to claim 7 wherein (2'R,6S,6aR,9R,10aR)-(-)-1-acetoxy-5,6,6a,7,8,9,10,10a-octahydro-9-hydroxy-6-methyl-3-(5'-phenyl-2'-pentyloxy)-benzo[c]quinoline hydrochloride, a single stereoisomer according to claim 7 is administered.

10. A process according to claim 8 wherein (2'R,6S,6aR,9R,10aR)-(-)-1-acetoxy-5,6,6a,7,8,9,10,10a-octahydro-9-hydroxy-5,6-dimethyl-3-(5'-phenyl-2'-pentyloxy)benzo[c]quinoline hydrochloride, a single stereoisomer according to claim 8 is administered.