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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

AS. 104.414



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Ira: 11 PATENTILYII Eje: 378 FASENACIONALI
Act: 538 PLICION Folios: 3

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

REF.: Expediente No. 07 063.474 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US2005/045748.
a nombre de: **COLGATE-PALMOLIVE COMPANY.**

Titulada: MÉTODOS PARA LA UTILIZACIÓN DE COMPOSICIONES DE CUIDADO BUCAL QUE CONTIENEN ANTIOXIDANTES FLAVONOIDES CON ANILLO B LIBRE.

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **COLGATE-PALMOLIVE COMPANY**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar los recibos oficiales de caja No. 08-48,478 y 08-48,479 por valor de \$420,000.

De la Señora Jefe atentamente,

J. R. No. 10

JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 19 de agosto de 2008

MEV/CAG/jpg

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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RECIBO OFICIAL DE CAJA : 09 - 48.478
FECHA : JUNIO 17 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249696	16/06/2008	28,020,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	210,000.00
TOTAL :			\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 890176089-2

RECIBO OFICIAL DE CAJA : 08 - 48.479
FECHA : JUNIO 17 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249606	16/06/2008	28,020,000.00

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SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-63474

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **590** DE

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

EXPIRA EL **27 DE JUNIO 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 _____

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Organization
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- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **YEN, Mao-Hsiung** [CN/CN]; Lane 24-5, Tin-Chou Road, 43 Taipei (TW). **WU, Edwin, S.C.** [US/US]; 102 Timber Hitch Road, Cary, NC 27513 (US).
- (74) Agent: **MYERS BIGEL SIBLEY & SAJOVEC, P.A.**; P.O. Box 37428, Raleigh, NC 27627 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

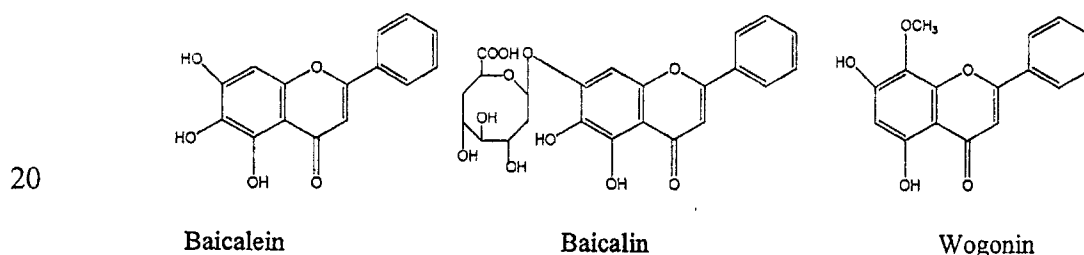


WO 2004/037193 A2

(54) Title: **CHROMONES AND CHROMONE DERIVATIVES AND USES THEREOF**

(57) **Abstract:** The present invention relates to chromones, novel chromone derivatives, and pharmaceutical formulations containing the same and methods of use thereof. Uses of the present invention include, but are not limited to, use for the prevention and treatment of septic shock, organ injury and other disorders. The compounds described herein can be salt forms and also water-soluble compounds.

5 activity by drug delivery system. *Antiviral Res.* **30**: A1-A62 (1995); and Kitamura K et al. Baicalin, an inhibitor of HIV-1 production *in vitro*. *Antiviral Res.* **37**: 131-140 (1998)], and baicalein has been shown to produce a hypotensive effect (Takizawa et al. Prostaglandin I₂ contributes to the vasodepressor effect of baicalein in hypertensive rats. *Hypertension* **31**: 866-871(1998) and Chen ZY et al. Endothelium-dependent
10 contraction and direct relaxation induced by baicalein in rat mesenteric artery. *Eur J Pharmacol.* **374**:41-47 (1999)]. More recently, baicalein has been implicated in the inhibition of expression of adhesion molecules induced by cytokines in human umbilical vein endothelial cells [Ikemoto, S et al. Antitumor effects of *Scutellariae radix* and its components baicalein, baicalin, and wogonin on bladder cancer cell
15 lines. *Urology.* **55**: 951-955 (2002); Middleton, EJ and Kandaswani C. Effects of flavonoids on immune and inflammatory cell functions. *Biochem. Pharmacol.* **43**: 1167-1179 (1992)].



25 **Chart 1.** Bioactive flavonoids of *Scutellaria baicalensis* GEORGI.

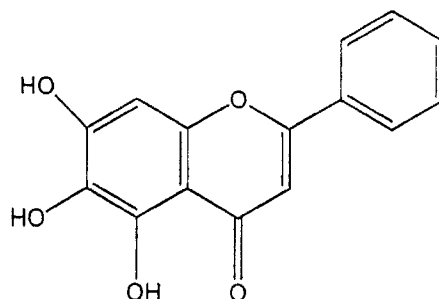
Current therapies for the treatment of septic shock include antibiotics, vasoconstrictors, steroids, and fluid supplementation to maintain the circulation
30 volume; however, in many cases, these therapies have been deemed inefficient (Barron RL. Pathophysiology of septic shock and implications for therapy. *Clin. Pharm.* **12**: 829-845 (1993)). It is desirable to provide compounds useful for the prevention or treatment of septic shock.

During the course of sepsis, nitric oxide (NO) is produced. Its metabolites
35 impair normal vascular reactivity, in conjunction with elevated endotoxin levels. Inhibitors of NO synthase restore blood pressure, lower the cardiac index and increase

- 5 disorders, comprising administering to a subject in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I described above.

According to still other embodiments, the present invention relates to a method of preventing or treating conditions or diseases associated with
10 overproduction of $\text{TNF-}\alpha$, overproduction of superoxide anion radical, organ damage, neurodegenerative diseases, cancer, and cardiac disorders, comprising administering to a subject in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula II:

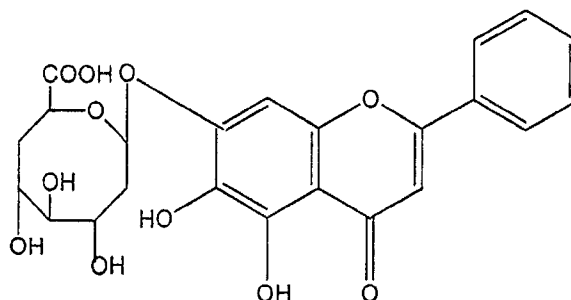
(II)



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According to yet other embodiments, the present invention relates to a method of preventing or treating conditions or diseases associated with overproduction of $\text{TNF-}\alpha$, overproduction of superoxide anion radical, organ damage,
20 neurodegenerative diseases, cancer, and cardiac disorders, comprising administering to a subject in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula III:

(III)



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5 **B. Pharmaceutically acceptable salts**

 The term "active agent" as used herein, includes the pharmaceutically acceptable salts of the compound. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts
10 formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid,
15 methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (b) salts formed from elemental anions such as chlorine, bromine, and iodine. In particular embodiments, pharmaceutically acceptable salts are formed with hydrochloric acid. In other particular embodiments, pharmaceutically acceptable salts are formed with malic acid.

20 Active agents used to prepare compositions for the present invention may alternatively be in the form of a pharmaceutically acceptable free base of active agent. Because the free base of the compound is less soluble than the salt, free base compositions are employed to provide more sustained release of active agent to the target area. Active agent present in the target area which has not gone into solution is
25 not available to induce a physiological response, but serves as a depot of bioavailable drug which gradually goes into solution.

C. Pharmaceutical Formulations

 The flavonoids and flavonoid analogs of the present invention are useful as
30 pharmaceutically active agents and may be utilized in bulk form. More preferably, however, these compounds are formulated into pharmaceutical formulations for administration. Any of a number of suitable pharmaceutical formulations may be utilized as a vehicle for the administration of the compounds of the present invention.

 It will be appreciated that certain compounds of the above Formulae can
35 possess an asymmetric carbon atom(s) and are thus capable of existing as

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5 enantiomers. Unless otherwise specified, this invention includes such enantiomers, including racemates. The separate enantiomers may be synthesized from chiral starting materials, or the racemates can be resolved by procedures that are well known in the art of chemistry such as chiral chromatography, fractional crystallization of diastereometric salts and the like.

10 The compounds of the present invention may be formulated for administration for the treatment of a variety of conditions. In the manufacture of a pharmaceutical formulation according to the invention, the compounds of the present invention and the physiologically acceptable salts thereof, or the acid derivatives of either *
(hereinafter referred to as the "active compound") are typically admixed with, inter •
15 alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. In
20 one particular embodiment, a pharmaceutical composition comprises less than 80% by weight of active compound. In other particular embodiments, a pharmaceutical composition comprises less than 50% by weight of active compound. One or more of each of the active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy
25 consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal **administration**, although the most
30 suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, tablets, dragees, or syrups each containing a
35 predetermined amount of the active compound; as a powder or granules; as a solution

12. A pharmaceutical formulation comprising a compound according to claim 1 and at least one pharmaceutically acceptable carrier, diluent, or excipient.

13. The pharmaceutical formulation comprising a compound according to claim 12, wherein the pharmaceutically acceptable carrier is an aqueous carrier.

14. A method of treating diseases associated with overproduction of TNF- α selected from the group consisting of arthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, insulin resistance, multiple sclerosis, organ failure, pulmonary fibrosis, and atherosclerosis, comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

15. A method of treating diseases associated with overproduction of superoxide anion radical selected from the group consisting of Alzheimer's disease, Parkinson's disease, aging, cancer, myocardial infarction, atherosclerosis, autoimmune disease, radiation injury, emphysema, sunburn, joint disease, and oxidative stress, comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

16. A method of treating septic shock, comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

17. A method of treating inflammation, comprising administering to a subject in need thereof, an effective amount of a compound according to claim 1, when the compound is an isoflavone.

18. A method of treating organ damage, comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

19. The method according to claim 18, wherein the organ damage is liver damage, lung damage, or kidney damage, or combinations thereof.