Title: CYCLOBUT-3-ENE-1,2-DIONE DERIVATIVES AS SMOOTH MUSCLE RELAXANTS

Abstract

The present invention relates to novel cyclobut-3-ene-1,2-dione-3-y1 substituted benzopyrans, indanes and tetrahydronephthalenones having smooth muscle relaxant activity, pharmaceutical compositions containing them, and to their use in the treatment of diseases and disorders involving excessive smooth muscle contractions in the cardiovascular system, urinary tract, pulmonary system, or gastrointestinal tract such as hypertension, peripheral vascular disease, congestive heart failure, urinary incontinence, irritable bowel syndrome, asthma, and hair loss. The compounds of this invention are represented by Formula (I), wherein variable substitutions R1-R7 are as defined in the summary of the invention; a and b together form an -O- linkage, C=O, or a direct bond; and n = 1-3.
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CYCLOBUT-3-ENE-1,2-DIONE DERIVATIVES AS SMOOTH MUSCLE RELAXANTS

The present invention relates to novel cyclobut-3-ene-1,2-dione-3-yl substituted benzopyrans, indanes and tetrahydronaphthalenones having smooth muscle relaxant activity, pharmaceutical compositions containing them, and to their use in the treatment of diseases and disorders involving excessive smooth muscle contractions in the cardiovascular system, urinary tract, pulmonary system, or gastrointestinal tract such as hypertension, peripheral vascular disease, congestive heart failure, urinary incontinence, irritable bowel syndrome, asthma, and hair loss.

6-Substituted-4-aminobenzopyrans useful in treating hypertension are disclosed in the published PCT patent applications WO 92/19651 and WO 92/20672, published European patent applications EP 0158923 and EP 0427606, and in U. S. patents 4,925,839, 4,908,378 and 4,616,021. 6-Substituted-4-amino tetrahydronaphthalene-1-ones having antihypertensive and bronchodilatory activity are disclosed in U. S. patent 5,208,246 and in the published European patent application EP 0413438. 5-Substituted-3-aminoundanes useful in treating hypertension and respiratory tract disorders are disclosed in published European patent applications EP 0413438 and EP 0426379. Antihypertensive 6-substituted-4-aminobenzopyrans, tetrahydronaphthalenes or tetrahydroquinolines are disclosed in the published European patent application EP 0376524. None of the above patents or published patent applications disclose benzopyrans, benzonaphthalen-1-ones, or indanes having the cyclobut-3-ene-1,2-dione-3-yl substituent on the benzene portion of the fused rings.

Summary of the Invention

The present invention discloses compounds represented by the formula (I):

![Formula Image]

wherein:
R₁ is C₁₋₆ perfluoroalkoxy, C₁₋₆ perfluoroalkyl, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, H, C₁₋₆ alkoxy, hydroxy, C₁₋₆ alkoxycarbonyl, amino, pyrrolidine, piperidine, morpholine, C₁₋₁₂ mono or di-alkyl amino optionally substituted with hydroxy or alkoxy, or mono or bicyclic heteroaryl containing 1-3 heteroatoms selected from N, O, or S;

a and b together form an -O- linkage, C=O, or a direct bond;

R₂ and R₃, independent from each other, are H or C₁₋₆ alkyl optionally substituted with fluorine;

either R₄ is hydrogen, hydroxy, C₁₋₆ alcanoxyloxy, C₇₋₁₁ aroyloxy carbamoyloxy, formylloxy, C₁₋₆ alkoxyacetonyloxy, mono or di C₁₋₁₂ alkylcarbamoyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are selected from the group consisting of C₁₋₆ perfluoroalkoxy, C₁₋₆ perfluoroalkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, C₁₋₆ alkoxycarbonyl, nitro, cyano, halogeno, C₁₋₆ alkylsulfonamido, C₁₋₆ perfluoroalkylsulfonamido, amino, C₁₋₆ acylamino, C₁₋₆ perfluoroacylamino, C₁₋₁₂ mono or di-alkylamino, C₁₋₆ alkylsulfonyl, C₆₋₁₀ arylsulfonyl, carboxyl, C₁₋₁₂ mono or dialkylaminocarbonyl, or hydrogen;

and

n = 1-3.

The more preferred compounds of this invention are those of Formula I wherein:

R₁ is H, C₁₋₆ perfluoroalkoxy, C₁₋₆ perfluoroalkyl, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, mono and bicyclic heteroaryl containing 1-3 heteroatoms selected from N, O or S; C₁₋₆ alkoxy, hydroxy, C₁₋₆ alkoxycarbonyl, amino, pyrrolidine, piperidine, morpholine, or C₁₋₁₂ mono or di-alkylamino optionally substituted with hydroxy or alkoxy;

a and b together form an -O- linkage;
R₂ and R₃, independent from each other, are C₁₋₆ alkyl, optionally substituted by fluorine;

either R₄ is hydrogen, hydroxy, C₁₋₆ alkanoyloxy, or C₇₋₁₁ aroyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are trifluoromethoxy, methoxy, chloro, bromo, fluoro, methyl, trifluoromethyl or H;

and

n = 1.

The most preferred compounds of this invention are those of Formula I wherein:

R₁ is isopropoxy, amino, hydroxyethylamino, pyrrolidinyl, methylamino, hydroxy, or methyl;

R₂ and R₃ is methyl;

R₄ is OH;

R₅ is H;

R₆ and R₇ is H;

n is 1; and

a and b together form an -O- linkage.

The term "mono or bicyclic heteroaryl containing 1-3 heteroatoms selected from N, O, or S" means a compound selected from the group consisting of quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoazole, and benzothiophene. The term alkyl alone or in conjunction with another functional group such as carbonyl, sulfonamido, amino, carbamoyl, sulfonyl or carboxamido encompasses straight and branched chain
hydrocarbons such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, neopentyl, hexyl, decyl, etc. within the limits set forth for the number of carbon atoms. The term perfluoroalkyl means an alkyl group as defined above wherein all of the hydrogen atoms are replaced by fluorine atoms. The term alkoxy means an -O-alkyl group where alkyl is as defined above and a perfluoroalkoxy group is an alkoxy group wherein the alkyl moiety is a perfluoroalkyl group as defined above. The term C₆₋₁₀ aryl means phenyl or naphthyl optionally substituted by halogen, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and may be used in conjunction with a functional group such as amino, sulfonyl, or oxy. The term C₇₋₁₁ arylox used alone or in conjunction with another term means phenylcarbonyl or naphthalenylcarbonyl. The term C₂₋₆ alkenyln encompasses straight and branched chain alkenes such as vinyl, allyl, 2-methyl allyl, n-butenyl, pentene and hexene. The term C₃₋₁₀ cycloalkyl encompasses mono and bicycloalkyl groups such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclooctane and decalin. The term halogen means fluorine, chlorine, bromine or iodine. The term C₁₋₆ alkyl optionally substituted by fluorine means that one or more of the hydrogens of a C₁₋₆ alkyl group may be replaced by fluorine, up to and including C₁₋₆ perfluoroalkyl groups.

It is understood that the definition of the compounds of formula (I), when R₄ is hydroxy and R₅ is a hydrogen encompass all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques.

The compounds of formula (I) are smooth relaxants. They are therefore useful in the treatment of hypertension as well as for treatment of peripheral vascular disease, congestive heart failure and disorders involving excessive smooth muscle contraction of the urinary tract (such as incontinence), or of the gastro-intestinal tract (such as irritable bowel syndrome), asthma, and hair loss.

The present invention accordingly provides for a pharmaceutical composition which comprises a compound of this invention and a pharmaceutically acceptable carrier. The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration for patients suffering from heart failure.

The present invention further provides a compound of the invention for use as an active therapeutic substance. Compounds of formula (I) are of particular use in the treatment of hypertension and/or smooth muscle relaxation.
Detailed Description of the Invention

The compounds of the present invention may be prepared by the methodology of Liebeskind et. al. (J. Org. Chem. 1990, 55, 5359). More particularly, the compounds of formula (II)

\[
\begin{align*}
\text{II} \\
\text{wherein } R_{a8} \text{ is halogen or trifluromethanesulfonate and } R_{a2}, R_{a3}, R_{a4}, R_{a5}, R_{a6}, \text{ and } R_{a7} \text{ are } R_2, R_3, R_4, R_5, R_6 \text{ and } R_7 \text{ respectively, as defined hereinbefore or a group or atom convertible thereto, are reacted with stannane of formula III under palladium catalysis wherein } R_{a1} \text{ is typically O-alkyl or alkyl and } R_9 \text{ is O or an acetal to provide a compound of formula IV}
\end{align*}
\]

\[
\begin{align*}
\text{III} \\
\text{IV} \\
\text{wherein } R_{a1} \text{ is C}_{1-6} \text{ alkyl or O-C}_{1-6} \text{ alkyl. } R_{a1} \text{ may then be convertible to } R_1 \text{ if necessary. For example, when } R_{a1} \text{ is O-C}_{1-6} \text{ alkyl, } R_{a1} \text{ may be converted to hydroxy by treatment with 6 N HCl or converted to amino by treatment with ammonia.}
\end{align*}
\]
The following specific synthetic examples are illustrative of the methods of preparing compounds of this invention. The corresponding tetrahydro and dihydronaphthalene-1-one, indene and indane analogs can be prepared by one skilled in the art using appropriately substituted tetrahydro and dihydronaphthalene-1-one, indene and indane intermediates prepared according to published procedures.

EXAMPLE 1

trans-4-Amino-3,4-dihydro-2,2-dimethyl-6-iodo-2H-1-benzopyran-3-ol.

To a solution of 10.0g (35 mmol) of 2,2-dimethyl-6-iodo-2H-benzopyran as prepared by Soll et al. (US 4908378) in dimethylsulfoxide (98 mL) containing 1.26 mL of water was added 12.4 g (70 mmol) of N-bromosuccinimide. The reaction mixture was stirred for 1 h and was cooled as necessary with an ice bath to prevent an exotherm. The reaction mixture was quenched with water (ca. 250 mL) and then extracted into Et2O. The ethereal extracts were washed with water (3 x), dried over MgSO4 and purified by preparative HPLC (20% CH2Cl2 : 80% hexane to 90% CH2Cl2 : 10% hexane to give 12.7 g (95%) of trans-3-bromo-3,4-dihydro-2,2-dimethyl-6-iodo-2H-1-benzopyran-4-ol: 1H-NMR (DMSO-d6; 300 MHz) δ 7.68 (d, 1 H), 7.48 (dd, 1 H), 6.61 (d, 1 H), 6.21 (d, 1 H), 4.74 (t, 1 H), 4.23 (d, 1 H), 1.51 (s, 3 H), and 1.35 ppm (s, 3 H).

To a solution of 12.7 g (33.2 mmol) of this compound in 20% water - dioxane (67 mL) was added NaOH (1.46 g, 36.6 mmol). The reaction mixture was stirred for 8 h and was judged incomplete by tlc. To the reaction was added another 665 mg (16.6 mmol) of NaOH. After stirring at ambient temperature for 3 days, the reaction mixture was quenched with water (200 mL) and then was extracted into ether. The ethereal extracts were dried over K2CO3 and then concentrated to give 9.78 g (98% yield) of cis-3,4-epoxy-3,4-dihydro-2,2-dimethyl-6-iodo-2H-1-benzopyran as a yellow oil which was used without further purification: 1H-NMR (DMSO-d6; 300 MHz) δ 7.83 (d, 1 H), 7.54 (dd, 1 H), 6.59 (d, 1 H), 4.04 (d, 1 H), 3.70 (d, 1 H), 1.45 (s, 3 H), and 1.18 ppm (s, 3 H).

To a solution of 5.18 g (17.2 mmol) of the epoxide prepared above in ethanol (155 mL) was added 155 mL of ammonium hydroxide. After stirring for 8 h at ambient temperature, another 155 mL of ammonium hydroxide was added. The reaction mixture was stirred at ambient temperature for 3 days. The reaction mixture was diluted with saturated NaCl solution and then was extracted into 20% THF / CH2Cl2. The organic extracts were dried over K2CO3 and concentrated to give 5.48 g
of the title compound which was used without further purification: $^1$H-NMR (DMSO-d$_6$; 300 MHz) δ 7.84 (d, 1 H), 7.37 (dd, 1 H), 6.53 (d, 1 H), 5.44 (br d, 1 H), 3.49 (d, 1 H), 3.32 (br s, 1 H), 3.16 (dd, 1 H), 2.5 (br s, 2 H), 1.35 (s, 3 H), and 1.07 ppm (s, 3 H).

**Example 2**

*trans*-2-[(2,3-Dihydro-2,2-dimethyl-3-hydroxy-6-iodo-4H-1-benzopyran-4-yl)-2,3-dihydro-1H-isooindol-1-one.*

To a solution of 5.48 g (17.2 mmol) of *trans*-4-amino-3,4-dihydro-2,2-dimethyl-6-iodo-2H-1-benzopyran-3-ol as prepared in Example 1 in methanol (34 mL) containing 3.38 g (20.6 mmol) of 2-carbomethoxybenzaldehyde was added 68.7 mL (34.4 mmol) of 0.5 M zinc chloride-modified sodium cyanoborohydride in methanol, prepared according to the method of Kim et al. *J. Org. Chem.* 50 (11), 1927 (1985). The reaction mixture was refluxed for 3 h, cooled to room temperature and quenched with water (375 mL). The reaction mixture was extracted into 20% THF / CH$_2$Cl$_2$, and the extracts were dried over MgSO$_4$. Purification was achieved by flash chromatography (CH$_2$Cl$_2$ : MeOH : NH$_4$OH (94.75 : 3.5 : 1.75) to give 7.07 g of the title compound as a white solid. An analytical sample, mp 224 - 228 °C, was obtained by additional flash chromatography using (25% Et$_2$O-CH$_2$Cl$_2$): $^1$H-NMR (DMSO-d$_6$; 300 MHz) δ 7.79 (d, 1 H), 7.53 - 7.68 (m, 3 H), 7.46 (dd, 1 H), 7.02 (s, 1 H), 6.67 (d, 1 H), 5.75 (d, 1 H), 5.1 (bs, 1 H), 4.5 (br d, 1 H), 4.1 (br, d 1 H), 3.89 (br, 1 H), 1.45 (s, 3 H), and 1.22 ppm (s, 3 H); mass spectrum (Cl), m/e 436, 435, 417, 402.

Anal. Calcd. for C$_{19}$H$_{18}$INO$_3$ · 1 H$_2$O: C, 51.36; H, 4.31; N, 3.15

Found: C, 51.62; H, 4.04; N, 2.95.

**EXAMPLE 3**

3-[(*trans*-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl)-4-isopropoxy-cyclobut-3-ene]-1,2-dione.

To a solution of 217 mg (0.50 mmol) of *trans*-2-[2,3-dihydro-2,2-dimethyl-3-hydroxy-6-iodo-4H-1-benzopyran-4-yl]-2,3-dihydro-1H-isoindol-1-one, prepared in Example 2, and 235 mg (0.55 mmol) of 3-(1-methylethoxy)-4-((tri-n-butylstannyl)-3-cyclobutene-1,2-dione, as prepared by Liebeskind et al. (*J. Org. Chem.* 55, 5359 (1990)), in DMF (620 µL) was added 23 mg (0.03 mmol) of *trans*-benzyl(chloro)bis(trisphenyl-phosphine) palladium (II) and 8.5 mg (0.04 mmol) of copper (I) chloride. After stirring at ambient temperature for 1.5 h, the reaction mixture
was dissolved in hot CH₃CN (200 mL) and was washed with hexane. The acetonitrile phase was dried over MgSO₄ and was concentrated to a solid, which was then dissolved in hot THF / CH₂Cl₂ and absorbed onto silica gel. Purification by flash chromatography (65% EtOAc / 35% hexane) gave 36 mg (16% yield) of the title compound. Additional compound was prepared in a repeat reaction in 52% yield by purifying with a short flash chromatography column using (CH₃CN elution). Repeated crystallizations from CH₃CN / Et₂O / hexane provided an analytically pure sample, mp > 250 °C: ¹H-NMR (DMSO-d₆; 400 MHz) δ 7.83 (d, 1 H), 7.78 (dd, 1 H), 7.54 - 7.66 (m, 3 H), 7.38 (s, 1 H), 7.05 (d, 1 H), 5.86 (d, 1 H), 5.32 (br d, 1 H), 5.24 (septet, 1 H), 4.47 - 4.48 (br d, 1 H), 3.9 - 4.1 (br, 2 H), 1.51 (s, 3 H), 1.29 (s, 3 H), 1.25 (d, 3 H), and 1.02 ppm (d, 3 H); mass spectrum (DEI) m/e 447, 429, 414. Anal. Calcd. for C₂₅H₂₅NO₆: 0.5 H₂O: C, 68.41; H, 5.74; N, 3.07
Found: C, 68.31; H, 5.56; N, 3.08.

EXAMPLE 4

4-Amino-3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoidol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione.

To a solution of 154 mg (0.344 mmol) of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoidol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione as prepared in Example 3 in CH₃CN was bubbled ammonia gas for 30 min. The reaction mixture was then sealed and stirred for 16 h. The reaction mixture was concentrated. Flash chromatography (CH₂Cl₂ : MeOH : NH₄OH (94.75 / 3.5 / 1.75)) followed by crystallization from THF and petroleum ether gave 136 mg of the title compound as a white solid, mp > 250 °C: ¹H-NMR (DMSO-d₆; 400 MHz) δ 8.90 (br s, 1 H), 8.76 (br s, 1 H), 7.7 - 7.8 (m, 3 H), 7.51 - 7.63 (m, 3 H), 6.98 (d, 1 H), 1.48 (s, 3 H), and 1.27 ppm (s, 3 H); IR (KBr) 1780, 1730, 1670, and 1640 cm⁻¹; mass spectrum (+ Cl), m/e 405.

Anal. Calcd. for C₂₃H₂₅NO₅: C, 68.31; H, 4.98; N, 6.93
Found: C, 67.91; H, 5.12; N, 6.78.

EXAMPLE 5

3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoidol-2-yl)-chroman-6-yl]-4-(2-hydroxy-ethylamino)-cyclobut-3-ene-1,2-dione.

A solution of 529 mg (1.18 mmol) of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoidol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione as prepared in Example 3 in CH₃CN (20 mL) and ethanolamine (716 µL; 11.8 mmol) was stirred at room temperature for 4 days. The reaction mixture was heated at 50 °C for 1
h, cooled to room temperature, diluted with H₂O, and extracted into 20% THF / CH₂Cl₂. The organic extracts were dried over MgSO₄ and purified by flash chromatography (CH₂Cl₂ : MeOH : NH₄OH (93.25 ; 4.5 ; 2.25)) followed by trituration from MeOH / ether to give 124 mg of the title compound as a tan solid, mp 205 - 215 °C: ¹H-NMR (DMSO-d₆; 400 MHz) δ 8.93 (t, 1 H), 7.79 (dd, 1 H), 7.74 (s, 1 H), 7.69 (dd, 1 H), 7.5 - 7.64 (m, 3 H), 7.00 (d, 1 H), 5.75 (d, 1 H), 5.2 - 5.5 (br, 1 H), 4.86 (s, 1 H), 4.4 - 4.5 (br d, 1 H), 3.67 (m, 2 H), 3.53 (q, 2 H), 1.48 (s, 3 H), and 1.27 ppm (s, 3 H); IR (KBr) 1780, 1710, 1660, and 1600 cm⁻¹; mass spectrum (+FAB), m/z 449 (M + H), and 471 (M + Na).

Anal. Calcd. for C₂₅H₂₄N₂O₆·1 H₂O: C, 64.37; H, 5.62; N, 6.01. Found: C, 64.32; H, 5.83; N, 6.18.

EXAMPLE 6

3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-pyrrolidin-1-yl-cyclobut-3-ene-1,2-dione.

A solution of 413 mg (0.922 mmol) of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione as prepared in Example 3 in CH₃CN (9 mL) and 385 µL (4.61 mmol) of pyrrolidine was stirred at room temperature for 16 h. The reaction mixture was diluted with pH 7 buffer and was extracted into 20% THF / CH₂Cl₂. The organic extracts were dried (MgSO₄) and combined with the crude product from an identical run using 205 mg of starting material. The combined crude products were dissolved in 50% THF / MeOH, absorbed onto silica gel, and purified by flash chromatography (CH₂Cl₂ : MeOH : NH₄OH (93.25 / 4.5 / 2.25)) and then re-chromatographed (85% EtOAc / hexane) to give 323 mg of the title compound. An analytical sample, mp >250 °C, was obtained by recrystallization from THF / petroleum ether to give 278 mg of product: ¹H-NMR (DMSO-d₆; 400 MHz) δ 7.80 (dd, 1 H), 7.71 (dd, 1 H), 7.54 - 7.67 (m, 3 H), 7.09 (br s, 1 H), 6.97 (d, 1 H), 5.80 (d, 1 H), 5.3 (br s, 1 H), 3.75 (t, 2H), 3.14 - 3.19 (m, 1 H), 3.02 - 3.05 (m, 1 H), 1.62 - 1.76 (m, 2 H), 1.49 (s, 3 H), 1.41 - 1.44 (m, 1 H), 1.27 (s, 3 H), and 1.17 - 1.19 ppm (m, 1 H); IR (KBr) 1770, 1720, 1665, and 1595 cm⁻¹; mass spectrum (-FAB), m/z 457 (M - H), 324, and 132.

Anal. Calcd. for C₂₇H₂₆N₂O₅·0.25 H₂O: C, 70.04; H, 5.77; N, 6.05. Found: C, 69.95; H, 5.84; N, 5.85.
EXAMPLE 7

3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-methylamino-cyclobut-3-ene-1,2-dione.

A solution of 408 mg (0.911 mmol) of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione as prepared in Example 3 in CH$_3$CN (9 mL) and 569 µL (4.55 mmol) of 8.0 M methanol in ethanol was stirred at room temperature for 6 h. The reaction mixture was diluted with pH 7 buffer and then extracted into 20% THF / CH$_2$Cl$_2$. The crude product was dissolved in a little MeOH, absorbed onto silica gel, and purified by flash chromatography (CH$_2$Cl$_2$ : MeOH : NH$_4$OH (92.5 / 5 / 2.5)) to give 296 mg of pure product. Recrystallization from THF / petroleum ether gave 187 mg of the title compound as a white solid, mp >250 °C: $^1$H-NMR (DMSO-d$_6$; 400 MHz) δ 8.84 (q, 1 H), 7.79 (d, 1 H), 7.71 (s, 1 H), 7.51 - 7.67 (m, 3 H), 6.99 (d, 1 H), 5.75 (d, 1 H), 3.22 (d, 3 H), 1.48 (s, 3 H), and 1.27 ppm (s, 3 H); IR (KBr) 1770, 1720, 1670, and 1605 cm$^{-1}$; mass spectrum (+FAB), m/e 419 (M + H), 441 (M + Na).

Anal. Calcd. for C$_{24}$H$_{22}$N$_2$O$_5$ · 0.25 H$_2$O: C, 68.16; H, 5.36; N, 6.62

Found: C, 68.22; H, 5.33; N, 6.54.

EXAMPLE 8:

3-Hydroxy-4-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione.

A solution of 303 mg (0.676 mmol) of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione in THF (5 mL) containing 1.13 mL (6 N HCl) was heated at 50 °C for 48 h. The reaction mixture was diluted with 2 N HCl and extracted into 20% THF-CH$_2$Cl$_2$. The combined organic extracts were dried (MgSO$_4$), concentrated, and recrystallized from THF to give 112 mg of the title compound as a tan solid, mp >250 °C: $^1$H-NMR (DMSO-d$_6$; 400 MHz) δ 7.84 (dd, 1 H), 7.81 (d, 1 H), 7.52 - 7.64 (m, 3 H), 7.51 (s, 1 H), 6.93 (d, 1 H), 5.3 (br s, 1 H), 4.4 - 4.5 (br d, 1 H), 3.8 - 4.1 (br, 2 H), 1.47 (s, 3 H), and 1.26 ppm (s, 3 H); IR (KBr) 3400, 1785, 1720, 1670, and 1600 cm$^{-1}$; mass spectrum (DCI+), m/e 406 (M + H).

Anal. Calcd. for C$_{23}$H$_{19}$NO$_6$ · 0.5 H$_2$O: C, 66.66; H, 4.86; N, 3.38

Found: C, 66.67; H, 4.60; N, 3.34.
EXAMPLE 9

3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydro-isooindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione.

A solution of 275 mg (0.631 mmol) of trans-2-[2,3-dihydro-2,2-dimethyl-3-hydroxy-6-iodo-4H-1-benzopyran-4-yl]-2,3-dihydro-1H-isooindol-1-one as prepared in Example 1 in DMF 800 µL containing 10.8 mg (0.056 mmol) of copper (I) iodide, 28.7 mg (0.038 mmol) of trans-benzyl(chloro)bis(triphenylphosphine) palladium (II), and 325 mg (0.758 mmol) of 3-(tri-n-butylstannyl)-4-methyl-3-cyclobutene-1,2-dione 2-(ethylene acetal), as prepared by Liebeskind et. al. (J. Org. Chem. 55, 5359 (1990), was purged with N₂, and then stirred at room temperature for 16 h. The reaction mixture was diluted with 20% THF-CH₂Cl₂ (50 mL), washed with sat. aq. NH₄Cl, and then 10% KF. The organic phase was dried over Na₂SO₄, concentrated, and purified by flash chromatography (CH₂Cl₂ : MeOH : NH₄OH (94.75 / 3.5 / 1.75)) to give 298 mg of 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydro-isooindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione 2-(ethylene acetal) which was used directly in the next reaction: partial ¹H-NMR (DMSO-d₆; 300 MHz) δ 7.83 (d, 1 H), 7.53 - 7.66 (m, 5 H), 5.89 (d, 1 H), 5.2 - 5.4 (br d, 1 H), 4.4 - 4.6 (br d, 1 H), 1.89 (s, 3 H), 1.52 (s, 3 H), and 1.30 ppm (s, 3 H).

To a solution of 276 mg (0.616 mmol) of 3-[trans-3-hydroxy-[2,2-dimethyl-4-(1-oxo-1,3-dihydro-isooindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione-2-(ethylene acetal) in THF (12 mL) was added 9.2 mL of 50% aqueous H₂SO₄. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 50 mL of H₂O and then extracted into 20% THF-CH₂Cl₂. The organic extract was dried (Na₂SO₄), concentrated, and combined with the crude product from a similar run using 264 mg of 3-[trans-3-hydroxy-[2,2-dimethyl-4-(1-oxo-1,3-dihydro-isooindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione 2-(ethylene acetal). Purification by flash chromatography (CH₂Cl₂ : MeOH : NH₄OH (95.5 / 3 / 1.5)) and crystallization from THF / petroleum ether gave 268 mg of the title compound as a pale yellow solid, mp >250 °C: 7.81 - 7.84 (two doublets, 2 H), 7.53 - 7.66 (m, 4 H), 7.09 (d, 1 H), 5.87 (d, 1 H), 5.3 - 5.4 (br s, 1 H), 4.5 (br d, 1 H), 2.36 (s, 3 H), 1.52 (s, 3 H), and 1.29 ppm (s, 3 H); IR (KBr) 1775, 1760, 1660, and 1610 cm⁻¹; mass spectrum (DCI+) m/e 404 (M + H).

Anal. Calcd. for C₂₄H₂₁NO₅:  C, 71.45; H, 5.25; N, 3.47
Pharmacology

Bladder smooth muscle relaxing activity of the compounds of this invention was established in accordance with standard pharmaceutically accepted test procedures in representative compounds as follows:

Sprague-Dawley rats (150-200 g) are rendered unconscious by CO₂ asphyxiation and then euthanized by cervical dislocation. The bladder is removed into warm (37 deg.C) physiological salt solution (PSS) of the following composition (mM): NaCl, 118.4; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 4.7; H₂O, 1.2; NaHCO₃, 24.9; KH₂PO₄, 1.2; glucose, 11.1; EDTA, 0.023; gassed with 95% O₂; 5% CO₂; pH 7.4. The bladder is opened and then cut into strips 1-2 mm in width and 7-10 mm in length. The strips are subsequently suspended in a 10 ml tissue bath under an initial resting tension of 1.5 g. The strips are held in place by two surgical clips one of which is attached to fixed hook while the other is attached to an isometric force transducer. The preparations, which usually exhibit small spontaneous contractions, are allowed to recover for a period of 1 hour prior to a challenge with 0.1 µM carbachol. The carbachol is then washed out and the tissue allowed to relax to its resting level of activity. Following 1 further 30 min period of recovery an additional 15 mM KCl are introduced into the tissue bath. This increase in KCl concentration results in a large increase in the amplitude of spontaneous contractions (and initiation of contractions in previously quiescent strips) superimposed upon a small increase in basal tone. Following stabilization of this enhanced level of contractile activity, incremental increases in the concentration of test compound or vehicle are introduced into the tissue bath. Contractile activity is measured for each compound or vehicle concentration during the last min of a 30 min challenge.

Isometric force developed by the bladder strips is measured using a concentration required to elicit 50% inhibition of pre-drug contractile activity (IC₅₀ concentration) is calculated from this concentration-response curve. The maximum percentage inhibition of contractile activity evoked by a test compound is also recorded for concentrations of test compound < or equal to 30 µM.

Aortic smooth muscle relaxing activity of the compounds of this invention was established in accordance with standard pharmaceutically accepted test procedures in representative compounds as follows:

Sprague-Dawley rats (150-200 g) are rendered unconscious by CO₂ asphyxiation and then euthanized by cervical dislocation. The thoracic aorta is removed into warm
(37 deg.C) Krebs-Henseleit solution. The aorta is cleaned of fat and loose adventitia and cut into rings 3-4 mm in width. The rings are subsequently suspended between two stainless steel wire tissue holders in a 10 ml tissue bath. One wire tissue holder is attached to fixed hook while the other is attached to an isometric force transducer. Resting tension is set at 1.0 g. The tissues are allowed to recover for a period of 60 mins prior to beginning the experiment. The tissues are challenged with 25 mM KCl to elicit a contracture. The tissue are then washed repeatedly with fresh Krebs-Henseleit solution over a period of 30 mins and allowed to recover to baseline tension. 25 mM KCl is then introduced into the tissue bath to evoke a contracture that is allowed to stabilize for not less than 45 mins. Increasing concentrations of test compound or vehicle are then added to the tissue bath in a cumulative fashion.

Isometric force developed by the aortic rings is measured using force transducer and recorded on a polygraph. The percentage inhibition of contractile force evoked by each concentration of a given test compound is used to generate a concentration-response curve. The concentration required to elicit 50% inhibition of pre-drug contractile activity ($IC_{50}$ concentration) is calculated from this concentration-response curve. The maximum percentage inhibition of contractile activity evoked by a test compound is also recorded for concentrations of test compound < or equal to 30 uM.

Pharmacological test data are presented in Table I.
### Table I

**Inhibition of Contractions in Isolated Rat Bladder and Aortic Tissue**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ or (% Inhibition of Bladder Contraction at 30 μM)</th>
<th>IC$_{50}$ or (% Inhibition of Aorta Contraction at 30 μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 3</td>
<td>10.1 ± 0.39 μM</td>
<td>1.16 ± 0.21 μM</td>
</tr>
<tr>
<td>Example 4</td>
<td>0.19 ± 0.02 μM</td>
<td>0.17 ± 0.04 μM</td>
</tr>
<tr>
<td>Example 5</td>
<td>(14%)</td>
<td>N.D.</td>
</tr>
<tr>
<td>Example 6</td>
<td>(33%)</td>
<td>N.D.</td>
</tr>
<tr>
<td>Example 7</td>
<td>1.62 μM</td>
<td>0.83 ± 0.24 μM</td>
</tr>
<tr>
<td>Example 8</td>
<td>21.9 μM</td>
<td>N.D.</td>
</tr>
<tr>
<td>Example 9</td>
<td>0.11 μM</td>
<td>0.015 ± 0.007 μM</td>
</tr>
</tbody>
</table>

N.D.: not determined.

Hence, the compounds of this invention have a pronounced effect on smooth muscle contractility and are useful in the treatment of hypertension, urinary incontinence, irritable bladder and bowel disease, asthma, stroke and similar disease states as mentioned above, which are amenable to treatment with compounds by administration, orally, parenterally, or by aspiration to a patient in need thereof.

### Pharmaceutical Composition

When the compounds of the invention are employed in the treatment of diseases or disorders associated with smooth muscle contractions, they can be formulated into oral dosage forms such as tablets, capsules and the like. The compounds can be administered alone or by combining them with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting wax, cocoa butter and the like. Diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The compounds may also be injected intravenously or parenterally, in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic. For administration by inhalation or insufflation, the compounds may be formulated into an aqueous or partially aqueous
solution, which can then be utilized in the form of an aerosol. The compounds may also be formulated into dry aerosol inhalation formulations.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Treatment will generally be initiated with small dosages, less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.
What is claimed is:
1. A compound according to the formula:

\[
\text{Structure Image}
\]

wherein:

R₁ is C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₃-₁₀ cycloalkyl, C₂-₆ alkenyl, C₆-₁₀ aryl, H, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxy carbonyl, amino, pyrrolidine, piperidine, morpholine, C₁-₁₂ mono or di-alkylamino optionally substituted with hydroxy or C₁-₆ alkoxy, or mono or bicyclic heteroaryl selected from quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoazole, and benzothiophene;

a and b together form an -O- linkage, C=O, or a direct bond;

R₂ and R₃, independent from each other, are H or C₁-₆ alkyl, optionally substituted by fluorine;

either R₄ is hydrogen, hydroxy, C₁-₆ alkanoyloxy, C₇-₁₁ aroyloxy, carbamoyloxy, C₁-₆ alkoxy carbonyloxy, mono or di C₁-₁₂ alkyl carbamoyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are selected from the group consisting of C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxy carbonyl, nitro, cyano, halogeno, C₁-₆ alkyl sulfonamido, C₁-₆ perfluoroalkyl sulfonamido, amino, C₁-₆ acylamino, C₁-₆ perfluoroacylamino, C₁-₁₂ mono or di-alkylamino, C₁-₆ alkyl sulfonyl, C₆-₁₀ aryl sulfonyl, carboxy, C₁-₁₂ mono or dialkylaminocarbonyl, and hydrogen;

and n is 1 to 3.
2. A compound according to claim 1 wherein:
   \( R_1 \) is hydrogen, \( C_{1-6} \) perfluoroalkoxy, \( C_{1-6} \) perfluoroalkyl, \( C_{1-6} \) alkyl, \( C_{6-10} \) aryl, \( C_{1-6} \) alkoxy; hydroxy, \( C_{1-6} \) alkoxy carbonyl, amino, pyrrolidine, piperidine, morpholine, \( C_{1-12} \) mono or di-alkylamino optionally substituted with hydroxy or \( C_{1-6} \) alkoxy, or mono or bicyclic heteroaryl selected from quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoazole, and benzothiophene;

   a and b together form an -O- linkage;

   \( R_2 \) and \( R_3 \), independent from each other, are hydrogen or \( C_{1-6} \) alkyl, optionally substituted by fluorine;

   either \( R_4 \) is hydrogen, hydroxy, \( C_{1-6} \) alkanoyloxy, or \( C_{7-11} \) aroyloxy, and \( R_5 \) is hydrogen; or \( R_4 \) and \( R_5 \) together are a bond;

   \( R_6 \) and \( R_7 \), independent from each other, are trifluoromethoxy, methoxy, chloro, bromo, fluoro, methyl, trifluoromethyl or H;

   and

   \( n = 1 \).

3. A compound according to claim 2 wherein:
   \( R_1 \) is isopropoxy, amino, hydroxyethylamino, pyrrolidinyl, methylamino, hydroxy, or methyl;

   \( R_2 \) and \( R_3 \) are methyl;

   \( R_4 \) is OH;

   \( R_5 \) is H;

   \( R_6 \) and \( R_7 \) are H;

   \( n \) is 1; and
a and b together form an -O- linkage.

4. A compound according to claim 3 which is 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,2-dihydroisoindol-2-yl)-chroman-6-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione.

5. A compound according to claim 3 which is 4-amino-3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroiso-indol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione.

6. A compound according to claim 3 which is 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-(2-hydroxy-ethylamino)cyclobut-3-ene-1,2-dione.

7. A compound according to claim 3 which is 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-pyrrolindin-1-yl-cyclobut-3-ene-1,2-dione.

8. A compound according to claim 3 which is 3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-methylamino-cyclobut-3-ene-1,2-dione.

9. A compound according to claim 3 which is 3-hydroxy-4-[trans-3-hydroxy-2,2-dimethyl-4(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione.

10. A compound according to claim 3 which is 3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione.

11. A method of treating a disease associated with the regulation of smooth muscle contractions in the cardiovascular, respiratory, gastrointestinal, or urinary systems which comprises administration to a mammal in need thereof of a therapeutically effective amount of a compound represented by the formula:

![Chemical Structure](image)
wherein:

R₁ is C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₃-₁₀ cycloalkyl, C₂-₆ alkenyl, C₆-₁₀ aryl, H, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxycarbonyl, amino, pyrrolidine, piperidine, morpholine, C₁-₁₂ mono or di-alkylamino optionally substituted with hydroxy or C₁-₆ alkoxy, or mono or bicyclic heteroaryl selected from quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoxazole, and benzothiophene;

R₂ and R₃, independent from each other, are hydrogen or C₁-₆ alkyl, optionally substituted by fluorine;

either R₄ is hydrogen, hydroxy, C₁-₆ alkanoyloxy, C₇-₁₁ aroyloxy, carbamoyloxy, C₁-₆ alkoxy carbonyloxy, mono or di C₁-₁₂ alkylcarbamoyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are selected from the group consisting of C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxycarbonyl, nitro, cyano, halogeno, C₁-₆ alkylsulfonamido, C₁-₆ perfluoroalkylsulfonamido, amino, C₁-₆ acylamino, C₁-₆ perfluoroacylamino, C₁-₁₂ mono or di-alkylamino, C₁-₆ alkylsulfonyl, C₆-₁₀ arylsulfonyl, carboxy, C₁-₁₂ mono or dialkylaminocarbonyl, or hydrogen;

and

n = 1-3.

12. A method according to claim 11 wherein the therapeutically effective compound used is selected from those having the formula:
wherein:
R₁ is hydrogen, C₁-6 perfluoralkoxy, C₁-6 perfluoroalkyl, C₁-6 alkyl, C₆-10 aryl, C₁-6 alkoxy, hydroxy, C₁-6 alkoxy carbonyl, amino, pyrrolidine, piperidine, morpholine, C₁-12 mono or di-alkylamino optionally substituted with hydroxy or C₁-6 alkoxy, or mono or bicyclic heteroaryl selected from quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoazole, and benzothiophene;

a and b together form an -O- linkage;

R₂ and R₃, independent from each other, are hydrogen or C₁-6 alkyl, optionally substituted by fluorine;

either R₄ is hydrogen, hydroxy, C₁-6 alkanoyloxy, or C₆-12 aroyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are trifluoromethoxy, methoxy, chloro, bromo, fluoro, methyl, trifluoromethyl or H; and

n = 1

13. The method according to claim 12 wherein the therapeutically effective compound used is selected from those having the formula

![Chemical Structure](image)

wherein R₁ is isopropoxy, amino, hydroxyethylamino, pyrrolidinyl, methylamino, hydroxy or methyl;
R₂ and R₃ is methyl;

R₄ is OH;

R₅ is H;

R₆ and R₇ is H;

n is 1; and

a and b together form an -O- linkage.

14. A method of treatment according to claim 13 wherein the compound used is selected from:

3-[trans-3-hydroxy-2,2-dimethyl-4-(oxo-1,2-dihydroisoindol-2-yl)-chroman-6-yl]-4-isoproxy-cyclobut-3-ene-1,2-dione,
4-amino-3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroiso-indol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione,
3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-(2-hydroxy-ethylamino)-cyclobut-3-ene-1,2-dione,
3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-pyrrolindin-1-yl-cyclobut-3-ene-1,2-dione,
3-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-methylamino-cyclobut-3-ene-1,2-dione,
3-hydroxy-4-[trans-3-hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-cyclobut-3-ene-1,2-dione, and
3-[trans-3-Hydroxy-2,2-dimethyl-4-(1-oxo-1,3-dihydroisoindol-2-yl)-chroman-6-yl]-4-methyl-cyclobut-3-ene-1,2-dione.

15. A pharmaceutical composition for the treatment of a disease or disorder attributed to smooth muscle contraction which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula
wherein:

R₁ is C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₃-₁₀ cycloalkyl, C₂-₆ alkenyl, C₆-₁₀ aryl, H, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxycarbonyl, amino, pyrrolidine, piperidine, morpholine, or C₁-₁₂ mono or di-alkylamino optionally substituted with hydroxy or C₁-₆ alkoxy, or mono or bicyclic heteroaryl selected from quinoline, pyridine, indole, pyrrole, quinazoline, pyrazine, pyrimidine, thiophene, furan, benzofuran, benzimidazole, pyrazole, benzoxazole, and benzothiophene;

a and b together form an -O- linkage, C=O, or a direct bond;

R₂ and R₃, independent from each other, are hydrogen or C₁-₆ alkyl, optionally substituted by fluorine;

either R₄ is hydrogen, hydroxy, C₁-₆ alkanoyloxy, C₇-₁₁ aroyloxy carbamoyloxy, C₁-₆ alkoxycarbonyloxy, mono or di C₁-₁₂ alkylcarbamoyloxy, and R₅ is hydrogen; or R₄ and R₅ together are a bond;

R₆ and R₇, independent from each other, are selected from the group consisting of C₁-₆ perfluoroalkoxy, C₁-₆ perfluoroalkyl, C₁-₆ alkyl, C₁-₆ alkoxy, hydroxy, C₁-₆ alkoxycarbonyl, nitro, cyano, halogeno, C₁-₆ alkylsulfonamido, C₁-₆ perfluoroalkylsulfonamido, amino, C₁-₆ acylamino, C₁-₆ perfluoroacylamino, C₁-₁₂ mono or di-alkylamino, C₁-₆ alkylsulfonyl, C₆-₁₀ arylsulfonyl, carboxy, C₁-₁₂ mono or dialkylaminocarbonyl, or hydrogen;

and

n = 1-₃.
A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/04 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Date of the actual completion of the international search
6 July 1995

Date of mailing of the international search report
21.07.95

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HN Rijswijk
Tel. ( +31-70) 340-2040, Tx. 31 651 epo nl,
Fax ( +31-70) 340-3016

Authorized officer
Van Bijlen, H

Form PCT/ISA/310 (second sheet) (July 1992)
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 12-14 are directed to a method of treatment of (diagnostic
   method practised on) the human/animal body, the search has been carried out
   and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
   searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment
   of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
   covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
   restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest  ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
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