

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 November 2008 (20.11.2008)

PCT

(10) International Publication Number
WO 2008/140251 A2

(51) International Patent Classification:
C07D 207/444 (2006.01) **A61P 37/00** (2006.01)
A61P 29/00 (2006.01)

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(21) International Application Number:
PCT/KR2008/002677

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(22) International Filing Date: 14 May 2008 (14.05.2008)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
10-2007-0046489 14 May 2007 (14.05.2007) KR
10-2008-0014364 18 February 2008 (18.02.2008) KR

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (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*

(54) Title: CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract: The present invention relates to *1H*-pyrrole or furan-2,5dione derivatives and a pharmaceutical composition for inhibiting cyclooxygenase-2(COX-2), more specifically for treating or preventing inflammation, an allergic disorder, inflammatory dermatosis, an immunologic disorder, a neurodegenerative disorder, arthritis, pain or fever comprising the same.

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Description

Cyclooxygenase-2 Inhibitors

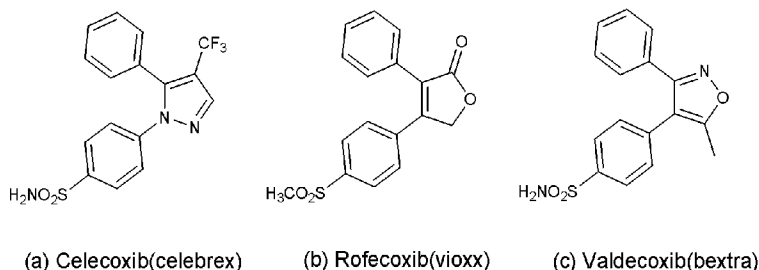
Technical Field

- [1] The present invention relates to 1*H*-pyrrole or furan-2,5-dione derivatives and a pharmaceutical composition for inhibiting cyclooxygenase-2(COX-2), more specifically for treating or preventing inflammation, an allergic disorder, inflammatory dermatosis, an immunologic disorder, a neurodegenerative disorder, arthritis, pain or fever comprising the same.

[2]

Background Art

- [3] A human body produces cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX-2) as hormones which are associated with inflammation process. Cyclooxygenase-1 is also called prostaglandin H₁ synthase and expressed in most of tissues. Prostaglandin H₁ produced by cyclooxygenase-1 is involved in the synthesis and supply of arachidonic acid metabolites to regulate physiological processes such as protection of gastrointestinal cells, kidney function and platelet aggregation. Meanwhile, cyclooxygenase-2 is also known as prostaglandin H₂ synthase, which produces prostaglandin H₂ to induce inflammation and pain. Cyclooxygenase-2 is expressed only by stimulation differently from cyclooxygenase-1.
- [4] Non-steroidal anti-inflammation drugs (NSAIDs) such as aspirin and ibuprofen exhibit their medicinal effects through inhibiting the activity of cyclooxygenases and suppressing the biosynthesis of prostaglandins. However, the non-steroidal anti-inflammation drugs not only inhibit the activity of cyclooxygenase-2 to reduce inflammation but also inhibit the activity of cyclooxygenase-1 to cause adverse effects such as renal toxicity and gastrointestinal ulceration. Therefore, there has been a need in the art for the development of an anti-inflammation drug selectively inhibiting cyclooxygenase-2 over cyclooxygenase-1.
- [5] Cyclooxygenase-2 inhibitors which have been commercialized until now include celecoxib (Celebrex) and valdecoxib (Bextra) developed by Pfizer, and rofecoxib (Vioxx) developed by Merck. Celecoxib (Celebrex) (a) can be used for the treatment of arthritis and severe pain, and rofecoxib (Vioxx) (b) can be used for the treatment of pain and inflammation. Meanwhile, valdecoxib (Bextra) (c) can be extensively used for the treatment of rheumatism and arthritis.

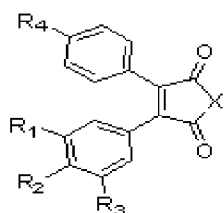


[8]

Technical Problem

[12]

[14]



(I)

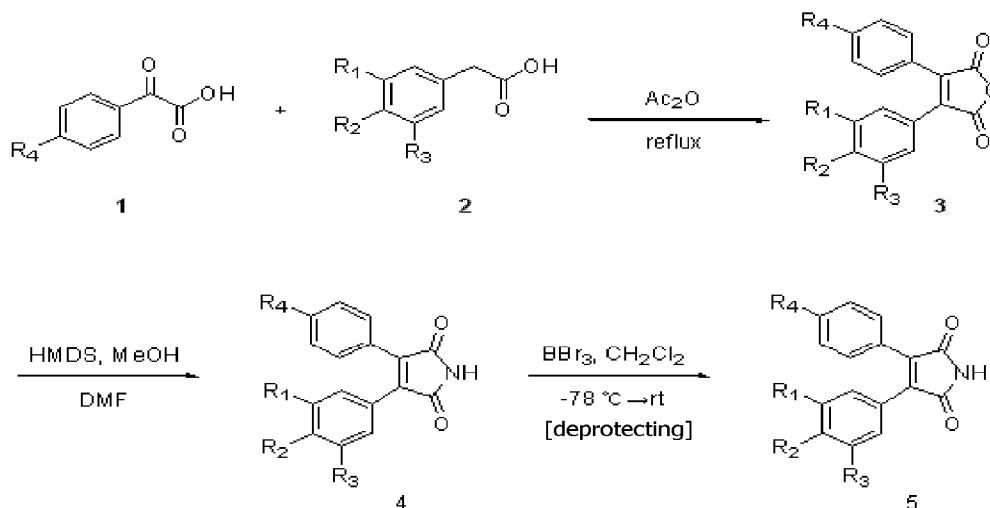
- [15] wherein,
- [16] R_1 , R_2 and R_3 are each independently hydrogen, hydroxy, C_1-C_5 lower alkoxy, $R_5C(=O)O$, R_5S , $R_5S(=O)$, $R_5S(=O)_2$, $NH_2S(=O)_2$, $R_5C(=O)NH$, or $(R_5C(=O))_2N$; or R_2 and R_3 taken together with the carbon atoms to which they are attached form a heterocycle;
- [17] R_4 is hydrogen, R_5S , $R_5S(=O)$ or $R_5S(=O)_2$;
- [18] R_5 is C_1-C_5 lower alkyl; and
- [19] X is O or NH.
- [20] In the above formula (I), R_1 , R_2 and R_3 are, preferably, each independently hydrogen, hydroxy, C_1-C_5 lower alkoxy, $R_5C(=O)O$, R_5S , $R_5S(=O)_2$, $NH_2S(=O)_2$, or $R_5C(=O)NH$; the heterocycle is, preferably, dioxolane or dioxane; and R_5 is, most preferably, methyl.
- [21]
- [22] The term " C_1-C_5 lower alkoxy" as used herein means a straight or branched alkoxy group having 1 to 5 carbon atoms, which includes methoxy, ethoxy, propanoxy, etc. but is not limited thereto.
- [23] The term "Heterocycle" as used herein means a 4 to 7-membered ring having 1 to 3 heteroatom(s) selected from the group consisting of oxygen, sulfur and nitrogen, which includes dioxolane, dioxane, etc. but is not limited thereto.
- [24] The term " C_1-C_5 lower alkyl" as used herein means a straight or branched hydrocarbon having 1 to 5 carbon atoms, which includes methyl, ethyl, propyl, butyl, pentyl, hexyl, etc. but is not limited thereto.
- [25] The most preferable compound among the compounds of the present invention is selected from the following group.
- [26] 3-(3-methoxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [27] 3-benzo[1,3]dioxol-5-yl-4-phenylfuran-2,5-dione;
- [28] 3-benzo[1,3]dioxol-5-yl-4-phenyl-1*H*-pyrrole-2,5-dione;
- [29] 3-(3,4-dihydroxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [30] 3-(3,4,5-trihydroxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [31] 3-(4-thiomethoxyphenyl)-4-phenylfuran-2,5-dione;
- [32] 3-(4-thiomethoxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [33] 3-(4-methanesulfonylphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [34] 3-(4-aminosulfonylphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
- [35] 3-(4-acetoxyphenyl)-4-(4-methanesulfonylphenyl)furan-2,5-dione;
- [36] 3-(4-hydroxyphenyl)-4-(4-thiomethoxyphenyl)-1*H*-pyrrole-2,5-dione; and
- [37] 3-(4-acetaminophenyl)-4-(4-thiomethoxyphenyl)furan-2,5-dione.

[38]

[39] The compounds of the present invention can be prepared according to the processes depicted in the following Reaction Schemes 1, 2 and 3. However, those illustrated in the following Reaction Schemes represent only typical processes used in the present invention. The manipulation order, reagents, reaction conditions, etc. may be changed without limit.

[40] [Reaction Scheme 1]

[41]



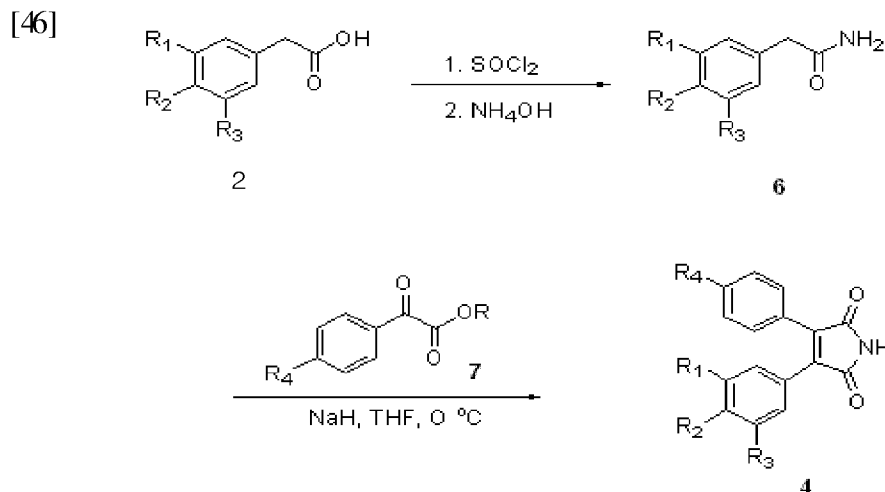
[42] As shown in the above Reaction Scheme 1, a furan-2,5-dione derivative(3) according to the present invention can be prepared by reacting phenylglyoxalic acid (1) and phenylacetic acid (2) in acetic anhydride. The acetic anhydride is used as a reactant as well as solvent. The reaction temperature is preferably from room temperature to 130°C , most preferably about 100°C . The reaction time is preferably 2-10 hours, most preferably about 3 hours. As a catalyst, an acid catalyst can be used, which includes titanium chloride(TiCl_4), $\text{BF}_3(\text{OEt})_2$, thionyl chloride (SOCl_2), etc. but is not limited thereto.

[43] Meanwhile, a 1H-pyrrole-2,5-dione derivative(4) according to the present invention can be prepared by treating a furan-2,5-dione derivative (3) with methanol, dimethylformamide (DMF) and hexamethyldisilazane (HMDS). The reaction temperature is most preferably room temperature, and the reaction time is preferably 10-36 hours, most preferably 12 hours. Alternatively, ammonia gas can be used in a solvent such as acetonitrile and lower alcohol including methanol.

[44] A 1H-pyrrole-2,5-dione derivative(5) wherein R_1 , R_2 and/or R_3 are hydroxy can be prepared by dealkylating a 1H-pyrrole-2,5-dione derivative(4) wherein R_1 , R_2 and/or R_3 are alkoxy or taken together with the carbon atoms to which they are attached form

dioxolane or dioxane. The dealkylating agent includes boron tribromide (BBr_3), trimethylsilane iodide (TMSI), aluminium chloride (AlCl_3), etc. but is not limited thereto.

[45] [Reaction Scheme 2]

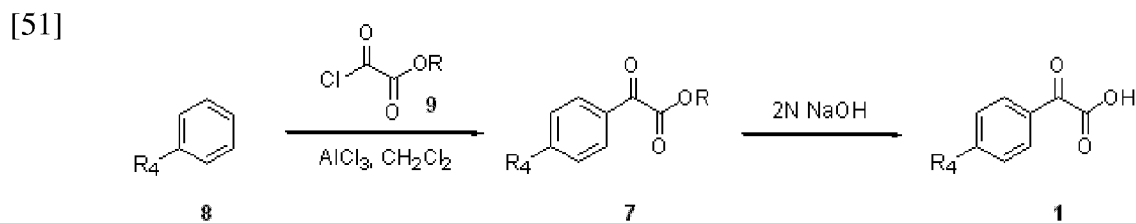


[47] As shown in the above Reaction Scheme 2, a 1*H*-pyrrole-2,5-dione derivative (4) according to the present invention can be prepared by converting phenylacetic acid (2) to acyl chloride, and then treating the acyl chloride with ammonia water to give phenylacetamide (6), followed by the condensation of the phenylacetamide (6) with an ester compound (7).

[48]

[49] Meanwhile, the phenylglyoxalic acid (1) and ester compound (7) used in the above Reaction Schemes 1 and 2 can be prepared according to a known process as shown in the following Reaction Scheme 3.

[50] [Reaction Scheme 3]



[52]

[53] Another aspect of the present invention relates to a pharmaceutical composition for inhibiting cyclooxygenase-2 comprising the compound of the above formula (I) or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier. In particular, the pharmaceutical composition of the present invention can be used for treating or preventing inflammation, an allergic disorder, inflammatory

dermatosis, an immunologic disorder, a neurodegenerative disorder, arthritis, pain or fever.

[54]

[55] The pharmaceutical composition according to the present invention can be administered orally, e.g., ingestion or inhalation; or parenterally, e.g., injection, deposition, implantation or suppositories. The injection can be, for example, intravenous, intradermal, subcutaneous, intramuscular or intraperitoneal. Depending on the route of administration, the pharmaceutical composition of the present invention may be formulated as tablets, capsules, granules, fine subitiae, powders, sublingual tablets, suppositories, ointments, injection solutions, emulsions, suspensions, syrups, aerosols, etc. The above various forms of the pharmaceutical composition of the present invention can be prepared in a manner well known in the art using a pharmaceutically acceptable carrier(s) which are usually used for each form. Examples of the pharmaceutically acceptable carriers include excipient, filler, expander, binder, disintegrator, lubricant, preservative, antioxidant, isotonic agent, buffer, coating agent, sweetening agent, dissolvent, base, dispersing agent, wetting agent, suspending agent, stabilizer, colorant, aromatic, etc.

[56] The pharmaceutical composition of the present invention contains 0.01 to 100 wt% of the compound according to the present invention or pharmaceutically acceptable salt thereof depending on the form thereof.

[57] The specific dosage of the present pharmaceutical composition can be varied with species of mammals including a human-being, route of administration, body weight, gender, age, severity of disease, judgment of doctor, etc. It is preferable that 0.01 to 50 mg of the active ingredient is administered per kg of body weight a day for oral use, while 0.01 to 10 mg of the active ingredient is administered per kg of body weight a day for parenteral use. The total daily dosage can be administered once or over several times depending on the severity of disease, judgment of doctor, etc.

[58]

Advantageous Effects

[59] The compounds of the present invention have excellent cyclooxygenase-2 inhibitory activity and low cytotoxicity. Therefore, the compounds of the present invention can be used for preparing pharmaceutical compositions for treating or preventing inflammation, an allergic disorder, inflammatory dermatosis, an immunologic disorder, a neurodegenerative disorder, arthritis, pain or fever.

[60]

Best Mode for Carrying Out the Invention

[61] The present invention is further illustrated by the following examples, which are not to be construed to limit the scope of the invention.

[62]

[63] Example 1: Preparation of 3-benzo[1,3]dioxol-5-yl-4-phenylfuran-2,5-dione (MCR-3004)

[64] Benzoylformic acid (1.67 g) and 3,4-(methylenedioxy)phenylacetic acid (2 g) were dissolved in acetic anhydride (20 ml) and refluxed for 3 hours. After the reaction was completed, the reaction mixture was allowed to cool to room temperature and treated with excessive water. Then, the reaction mixture was neutralized with a saturated NaHCO_3 aqueous solution, extracted with ethyl acetate three times, and washed with a saline solution. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was recrystallized with ethanol and methanol to give the target compound as a yellow solid (2.93 g, 90 %).

[65] ^1H NMR(400 MHz, DMSO-d_6) δ 7.50-7.44(5H, m, Ph), 7.06-7.00(2H, m, PhOCH_2 O), 6.89(1H, m, PhOCH_2 O), 6.10(2H, s, PhOCH_2 O)

[66] ^{13}C NMR(100 MHz, DMSO-d_6) δ 165.6, 149.9, 147.9, 138.4, 137.2, 130.9, 129.8, 129.3, 128.2, 125.3, 121.4, 109.5, 109.3, 102.3.

[67]

[68] Example 2: Preparation of 3-benzo[1,3]dioxol-5-yl-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3005)

[69] To a solution of the compound (0.68 g, 2.311 mmol) obtained in Example 1 dissolved in DMF (5 ml) were added HMDS (4.88 ml, 23.11 mmol) and methanol (0.47 ml, 11.555 mmol) in sequence, and the reaction mixture was stirred at room temperature for 16 hours. After the reaction was completed, the reaction mixture was extracted with ethyl acetate three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was subjected to silica gel column chromatography (n-hexane:EtOAc = 3:1) and recrystallized with ethanol and methanol to give the target compound as a yellow solid(0.61 g, 89 %).

[70] ^1H NMR(400 MHz, DMSO-d_6) δ 11.19(1H, s, -NH), 7.42-7.36(5H, m, Ph), 6.94(2H, s, PhOCH_2 O), 6.85(1H, s, PhOCH_2 O), 6.05(2H, s, PhOCH_2 O)

[71] ^{13}C NMR(100 MHz, DMSO-d_6) δ 171.5, 148.3, 147.1, 135.3, 129.5, 128.4, 124.4, 122.1, 109.3, 108.4, 101.4.

[72]

[73] Example 3: Preparation of 3-(3,4-dihydroxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3006)

[74] To a solution of the compound (0.06 g, 0.190 mmol) obtained in Example 2 dissolved in CH_2Cl_2 was dropped BBr_3 (1.14 ml, 1.142 mmol) at -78°C under nitrogen atmosphere, and the reaction mixture was stirred for 16 hours. After the reaction was completed, the reaction mixture was slowly neutralized with a saturated NaHCO_3 aqueous solution and extracted with ethyl acetate three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was subjected to silica gel column chromatography (n-hexane:EtOAc = 3:1) to give the target compound as a yellow solid (0.01 g, 16 %).

[75] ^1H NMR (400 MHz, DMSO-d_6) δ 7.42-7.36 (5H, m, Ph), 6.88 (1H, d, $J = 2.0$ Hz, Ph (OH)), 6.73 (1H, dd, $J = 2.0$ Hz, $J = 8.4$ Hz, Ph(OH)), 6.68 (1H, d, $J = 8.4$ Hz, Ph(OH))

[76] ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 171.8, 147.3, 145.0, 136.5, 133.8, 129.5, 116.9, 115.5.

[77]

[78] Example 4: Preparation of 2-phenylacetamide

[79] To phenylacetic acid (4.25 g, 31.216 mmol) was dropped thionyl chloride (10 ml) at room temperature, and the reaction mixture was stirred for 6 hours. One drop of DMF was added and refluxed for 1 hour. After the reaction was completed, the solvent was evaporated under reduced pressure and the resulting residue was diluted with CH_2Cl_2 . Then, NH_4OH (100 ml) was slowly added and stirred at room temperature for 12 hours. After the reaction was completed, the reaction mixture was extracted with CH_2Cl_2 three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was recrystallized with CH_2Cl_2 to give the target compound as a white solid (3.8 g, 90 %).

[80] ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (1H, s, $-\text{CONH}_2$), 7.30-7.20 (5H, m, Ph), 6.87 (1H, s, $-\text{CONH}_2$)

[81] ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 136.5, 129.0, 128.1, 126.2, 42.2.

[82]

[83] Example 5: Preparation of ethyl (4-thiomethoxyphenyl)oxoacetate

[84] To anhydrous CH_2Cl_2 was dropped anhydrous AlCl_3 (2.73 g, 21.97 mmol) and ethyl chlorooxoacetate (3.5 ml, 31.33 mmol) at -5°C . Afterwards, thioanisole (2.58 ml, 21.97 mmol) was dropped and stirred for 3 hours. After the reaction was completed,

the reaction mixture was extracted with CH_2Cl_2 three times, and the organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was subjected to silica gel column chromatography (n-hexane:EtOAc = 3:1) to give the target compound as a pale yellow oil (3.58 g, 73 %).

[85] ^1H NMR (400 MHz, DMSO-d_6) δ 7.91(2H, d, J = 7.8 Hz, Ph), 7.45(2H, d, J = 7.8 Hz, Ph), 4.45(2H, q, J = 7.2 Hz, OCH_2CH_3), 2.60(3H, s, PhSCH_3), 1.37(3H, t, J = 7.2 Hz, OCH_2CH_3)

[86] ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.3, 164.2, 136.0, 132.2, 130.2, 130.0, 62.8, 14.3.

[87]

[88] Example 6 Preparation of 3-(4-thiomethoxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3011)

[89] To a solution of ethyl (4-thiomethoxyphenyl)oxoacetate (0.5 g, 2.229 mmol) obtained in Example 5 and 2-phenylacetamide (0.25 g, 1.850 mmol) obtained in Example 4 dissolved in anhydrous THF at 0 °C was added NaH (0.2 g, 8.333 mmol), and the reaction mixture was stirred for 24 hours. Concentrated HCl (3 ml) was slowly added at 0 °C, and the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was recrystallized with ethanol to give the target compound as a yellow solid (0.37 g, 68 %).

[90] ^1H NMR (400 MHz, DMSO-d_6) δ 11.2(1H, s, -NH), 7.42-7.37(5H, m, Ph), 7.35(2H, d, J = 8.3 Hz, PhSCH_3), 7.24(2H, d, J = 8.3 Hz, PhSCH_3), 2.47(3H, s, PhSCH_3)

[91] ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 141.3, 136.5, 136.3, 130.5, 129.9, 129.4, 128.9, 125.6, 125.2, 14.5.

[92]

[93] Example 7: Preparation of 3-(4-methanesulfonylphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3014)

[94] The compound (0.1 g, 0.339 mmol) obtained in Example 6 was dissolved in CH_2Cl_2 and cooled to 0 °C. m-CPBA (meta-chloroperoxybenzoic acid) (0.15 g, 0.677 mmol) was dropped and stirred at 0 °C for 2 hours. The reaction was quenched by adding 10 % Na_2SO_3 and the reaction mixture was extracted with ethyl acetate and a saturated NaHCO_3 aqueous solution. The organic phase was washed with distilled water and a saline solution, dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was subjected to silica gel column chro-

matography (n-hexane:EtOAc = 1:1) to give the target compound as a pale yellow solid (0.09 g, 81 %).

[95] ^1H NMR (400 MHz, DMSO- d_6) δ 11.40 (1H, s, -N H), 7.95 (2H, d, $J=8.4$ Hz, Ph SOCH₃), 7.61 (2H, d, $J=8.4$ Hz, PhSOCH₃), 7.44-7.37 (5H, m, Ph), 3.25 (3H, s, -SCH₃)

[96] ^{13}C NMR (100 MHz, DMSO- d_6) δ 171.7, 171.6, 141.7, 138.9, 134.5, 131.1, 130.4, 130.2, 129.0, 128.7, 127.4, 43.7.

[97]

[98] Example 8: Preparation of 4-chlorosulfonylphenylacetic acid

[99] To chlorosulfonic acid (35 ml) was dropped phenylacetic acid (5 g, 36.724 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 hour and then at room temperature for 12 hours. After the reaction was completed, the reaction mixture was slowly cooled to 0 °C and further stirred for 20 minutes. The resulting solid was filtered to give the target compound (7.8 g, 91 %).

[100] ^1H NMR (400 MHz, DMSO- d_6) δ 7.55-7.47 (2H, m, Ph), 7.29-7.20 (2H, m, Ph), 3.58 (1H, s, -CH₂ COOH) 3.56 (1H, s, -CH₂ COOH)

[101] ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.5, 172.4, 147.6, 146.0, 135.6, 134.6, 129.7, 128.8, 127.7, 126.4, 125.4, 123.8.

[102]

[103] Example 9: Preparation of aminosulfonylphenylacetamide

[104] To a solution of the compound (3 g, 12.784 mmol) obtained in Example 8 dissolved in SOCl₂ (30 ml) was dropped 6 drops of DMF. Afterwards, the reaction mixture was stirred at room temperature for 16 hours, and SOCl₂ was evaporated under reduced pressure. The resulting residue was dissolved in acetonitrile and bubbled with NH₃ gas at 0 °C. Then, the reaction mixture was stirred at 0 °C for 10 minutes and at room temperature for 3 hours in sequence. The resulting solid was filtered and the filtrate was distilled under reduced pressure. Then, distilled water was added and kept in a refrigerator. The resulting solid was filtered and the filtrate was saturated with a saline solution and extracted with ethyl acetate three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO₄) and distilled under reduced pressure to give a solid product. The solid product combined with the previously obtained solid was recrystallized with acetone to give the target compound as a white solid (0.9 g, 33 %).

[105] ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (2H, d, $J=7.4$ Hz, Ph), 7.55 (1H, br, -CONH₂), 7.42 (2H, d, $J=7.4$, Ph), 7.30 (2H, br, -SO₂ NH₂), 6.95 (1H, br, -CONH₂), 3.46 (2H, s, -CH₂ -)

[106] ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 142.1, 140.5, 129.5, 125.5, 41.8.

[107]

[108] Example 10: Preparation of 3-(4-aminosulfonylphenyl)-4-phenyl-1H-pyrrole-2,5-dione (MCR-3015)

[109] To a solution of ethyl phenyloxoacetate (463 mg) and aminosulfonylphenylacetamide (355 mg) obtained in Example 9 dissolved in anhydrous THF (10 ml) at 0 °C was added NaH (60%, 133 mg), and the reaction mixture was stirred for 24 hours. Concentrated HCl (5 ml) was slowly added at 0 °C, and the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was recrystallized with ethanol to give the target compound as a yellow solid (0.37 g, 68 %).

[110] ^1H NMR (400 MHz, DMSO-d_6) δ 11.3 (1H, s, -NH), 7.82 (2H, d, $J = 8.2$ Hz, PhSO_2NH_2), 7.53 (2H, d, $J = 8.2$ Hz, PhSO_2NH_2), 7.44 (1H, s, PhSO_2NH_2), 7.44-7.36 (5H, m, Ph)

[111] ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 172.0, 144.5, 137.9, 135.4, 132.2, 130.2, 129.8, 129.7, 129.6, 128.5, 128.3, 128.0, 125.9, 125.6, 62.0

[112]

[113] Example 11: Preparation of (4-thiomethoxyphenyl)oxoacetic acid

[114] To the compound (4 g, 17.835 mmol) obtained in Example 5 was dropped 2N NaOH (8.9 ml) at room temperature, and the reaction mixture was stirred at room temperature for 3 hours. After the reaction was completed, the reaction mixture was acidified with concentrated HCl to pH 2 and extracted with CH_2Cl_2 three times. The organic phase was dried with anhydrous magnesium sulfate (MgSO_4) and distilled under reduced pressure. The resulting residue was recrystallized with CH_2Cl_2 and hexane to give the target compound as a pale yellow solid (3.04 g, 87 %).

[115] ^1H NMR (400 MHz, CDCl_3) δ 8.23 (2H, d, $J = 8.6$ Hz, Ph), 7.30 (2H, d, $J = 8.6$ Hz, Ph), 2.54 (3H, s, $-\text{SCH}_3$)

[116] ^{13}C NMR (100 MHz, CDCl_3) δ 183.6, 162.1, 150.2, 131.5, 128.0, 124.9, 14.5.

[117]

[118] Example 12: Preparation of 3-(4-thiomethoxyphenyl)-4-phenylfuran-2,5-dione (MCR-3010)

[119] The compound obtained in Example 11 and phenylacetic acid were used according to the same procedure as Example 1 to give the target compound (69 %).

[120] ^1H NMR (400 MHz, DMSO-d_6) δ 7.50-7.45 (5H, m, Ph), 7.34 (2H, d, $J = 8.5$ Hz, Ph -

- SCH₃), 7.31(2H, d, $J = 8.5$ Hz, Ph-SCH₃), 2.50(3H, s, -SCH₃)
- [121] ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 142.5, 137.7, 137.0, 130.4, 129.7, 129.2, 128.7, 127.7, 125.1, 123.3, 13.8.
- [122]
- [123] Example 13: Preparation of 3-(3,4,5-trimethoxyphenyl)-4-phenylfuran-2,5-dione (MCR-3007)
- [124] 3,4,5-trimethoxyphenylacetic acid was used according to the same procedure as Example 1 to give the target compound(69 %).
- [125] ¹H NMR (400 MHz, DMSO-d₆) δ 7.50 (s, 5H, aromatic-C₆H₅), 6.79 (s, 2H, C₆H₂), 3.72(s, 3H, -OCH₃), 3.58(s, 3H, -OCH₃)
- [126] ¹³C NMR (100 MHz, DMSO-d₆) δ 164.9, 152.6, 139.5, 137.8, 137.6, 130.4, 129.3, 128.7, 127.7, 122.4, 107.1, 60.1, 55.6.
- [127]
- [128] Example 14: Preparation of 3-(3-methoxyphenyl)-4-phenyl-1 H-pyrrole-2,5-dione (MCR-3002)
- [129] To a solution of 3-(3-methoxyphenyl)-4-phenylfuran-2,5-dione(1.022 g, 3.646 mmol) dissolved in methanol were added hexamethyldisilazane(5.885 g, 36.46 mmol) and DMF(5 ml), and the reaction mixture was stirred at room temperature for 24 hours. Then, the reaction mixture was neutralized with a saturated NaHCO₃ aqueous solution and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried with anhydrous magnesium sulfate(MgSO₄) and distilled under reduced pressure. The resulting solid was washed with petroleum ether and diethyl ether, and filtered to give the target compound as a yellow solid(0.468 g, 46 %).
- [130] ¹H NMR (400 MHz, CDCl₃ +DMSO-d₆) δ 10.38 (s, 1H, -NH), 7.46-7.24 (m, 5H, aromatic-C₆H₅), 7.04~6.89 (m, 4H, aromatic-C₆H₄-OCH₃), 3.67 (s, 3H, -OCH₃)
- [131] ¹³C NMR (100 MHz, CDCl₃ +DMSO-d₆) δ 171.5, 159.2, 136.9, 136.5, 129.8, 129.5, 128.6, 128.3, 122.1, 115.7, 114.7, 55.0
- [132]
- [133] Example 15: Preparation of 3,4-diphenyl-1 H-pyrrole-2,5-dione (MCR-3001)
- [134] 3,4-diphenylfuran-2,5-dione was used according to the same procedure as Example 14 to give the target compound(37 %).
- [135] ¹H NMR (400 MHz, CDCl₃ +DMSO-d₆) δ 10.88 (s, 1H, -NH), 7.50-7.33 (m, 10H, aromatic-C₆H₅)
- [136] ¹³C NMR (100 MHz, CDCl₃ +DMSO-d₆) δ 170.9, 135.9, 129.0, 128.8, 128.0, 127.7.
- [137]

[138] Example 16: Preparation of 3-(3,4,5-trimethoxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3008)

[139] 3-(3,4,5-trimethoxyphenyl)-4-phenylfuran-2,5-dione obtained in Example 13 was used according to the same procedure as Example 14 to give the target compound(97 %).

[140] ^1H NMR (400 MHz, DMSO- d_6) δ 11.27 (br, 1H, -NH), 7.42 (s, 5H, aromatic-C $_6$ H $_5$), 6.72 (q, 2H, aromatic-C $_6$ H $_2$), 3.69-3.67 (q, 3H, -OCH $_3$), 3.56 (s, 6H, -OCH $_3$)

[141] ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.1, 171.9, 152.9, 139.1, 136.7, 136.5, 130.1, 129.8, 129.4, 128.8, 124.3, 107.7, 60.6, 56.1.

[142]

[143] Example 17: Preparation of 3-(3-hydroxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3003)

[144] To a solution of 3-(3-methoxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione(0.2 g, 0.716 mmol) obtained in Example 14 dissolved in CH $_2$ Cl $_2$ (24 ml) was slowly added BBr $_3$ (0.179 g, 0.716 mmol) at -78 °C, and the reaction mixture was left to room temperature and stirred for 12 hours. After the reaction was completed, the reaction mixture was neutralized with a saturated NaHCO $_3$ aqueous solution and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried with anhydrous magnesium sulfate(MgSO $_4$) and distilled under reduced pressure to give the target compound as a yellow solid(100 mg, 50%).

[145] ^1H NMR (400 MHz, CDCl $_3$) δ 10.8 (s, 1H, -NH), 7.46~7.43 (m, 5H, aromatic-C $_6$ H $_5$), 6.92~6.81 (m, 4H, aromatic -C $_6$ H $_4$ OH)

[146] ^{13}C NMR (100 MHz, CDCl $_3$) δ 171.1, 171.6, 129.8, 129.3 128.9 128.2 120.5 116.5 60.1.

[147]

[148] Example 18: Preparation of 3-(3,4,5-trihydroxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione (MCR-3009)

[149] 3-(3,4,5-trimethoxyphenyl)-4-phenyl-1 H -pyrrole-2,5-dione obtained in Example 16 was used according to the same procedure as Example 17 to give the target compound(88 %).

[150] ^1H NMR (400 MHz, DMSO- d_6) δ 11.02 (1H, s, -NH), 9.00 (2H, s, OH), 8.61 (1H, s, OH), 7.39 (5H, s, Ph), 6.42 (2H, s, Ph(OH) $_2$)

[151] ^{13}C NMR (100 MHz, DMSO- d_6) δ 172.4, 172.3, 146.2, 137.2, 135.9, 134.2, 130.1, 129.9, 129.5, 128.8, 119.0, 109.5.

[152]

[153] Example 19: Preparation of

3-(4-acetoxyphenyl)-4-(4-methanesulfonylphenyl)furan-2,5-dione (MCR-3018)

[154] (4-Thiomethoxyphenyl)oxoacetic acid obtained in Example 11 and (4-acetoxyphenyl)acetic acid were used according to the same procedure as Example 1 to provide 3-(4-acetoxyphenyl)-4-(4-thiomethoxyphenyl)furan-2,5-dione, which was used according to the same procedure as Example 7 to give the target compound (26 %).

[155] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 8.04(2H, d, $J = 8.8$ Hz, aromatic- C_6H_2), 7.69(2H, d, $J = 8.8$ Hz, aromatic- C_6H_2), 7.50(2H, d, $J = 8.6$ Hz, aromatic- C_6H_2), 7.27(2H, d, $J = 8.6$ Hz, aromatic- C_6H_2), 3.28(3H, s, PhSO_2CH_3), 2.28(3H, s, PhOCOCH_3).

[156]

[157] Example 20: Preparation of 3-(4-hydroxyphenyl)-4-(4-thiomethoxyphenyl)-1H-pyrrole-2,5-dione (MCR-3019)

[158] (4-Thiomethoxyphenyl)oxoacetic acid obtained in Example 11 and (4-acetoxyphenyl)acetic acid were used according to the same procedure as Example 1 to provide 3-(4-acetoxyphenyl)-4-(4-thiomethoxyphenyl)furan-2,5-dione, which was used according to the same procedure as Example 2 to give the target compound (30 %).

[159] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 11.08(1H, s, OH), 7.33(2H, d, $J = 6.8$ Hz, aromatic- C_6H_2), 7.32-7.24(4H, m, aromatic- C_6H_4), 6.68-6.74(2H, m, aromatic- C_6H_2), 2.48(3H, s, $\text{C}_3\text{H}_3\text{S}$).

[160]

[161] Example 21: Preparation of

3-(4-acetaminophenyl)-4-(4-thiomethoxyphenyl)furan-2,5-dione (MCR-3026)

[162] (4-Thiomethoxyphenyl)oxoacetic acid obtained in Example 11 and (4-acetaminophenyl)acetic acid were used according to the same procedure as Example 1 to give the target compound (59 %).

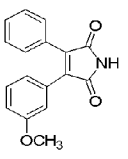
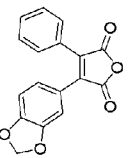
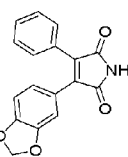
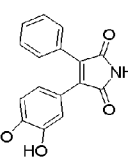
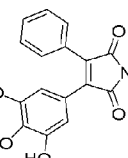
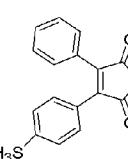
[163] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 10.21(1H, s, NH), 7.65(2H, d, $J = 8.8$ Hz, aromatic- C_6H_2), 7.42(4H, t, $J = 8.0$ Hz, aromatic- C_6H_4), 7.33(2H, d, $J = 8.8$ Hz, aromatic- C_6H_2), 2.50(3H, s, SCH_3), 2.07(3H, s, PhNHCOCH_3).

[164]

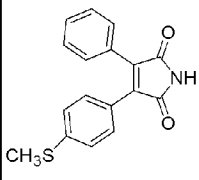
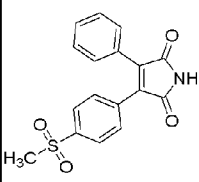
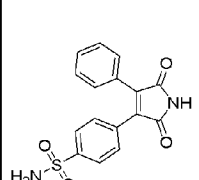
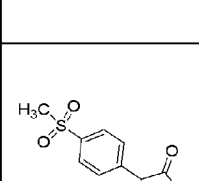
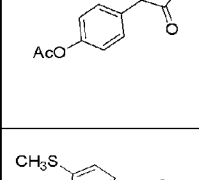
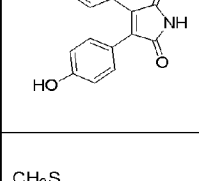
[165] The chemical structures and spectroscopic data of the representative compounds of the present invention which were prepared in the above Examples are summarized in Table 1.

[166] Table 1

[167]

No.	Compound Code	Chemical Structure	Spectroscopic Data
1	MCR3002		^1H NMR (400 MHz, CDCl_3 + $\text{DMSO}-d_6$) δ 10.38 (1H, br, -NH), 7.46–7.24 (5H, m, Ph), 7.04–6.89 (4H, m, PhOCH_3), 3.67 (3H, s, OCH_3); ^{13}C NMR (100 MHz, CDCl_3 + $\text{DMSO}-d_6$) δ 171.5, 159.2, 136.9, 136.5, 129.8, 129.5, 128.6, 128.3, 122.1, 115.7, 114.7, 55.0.
2	MCR3004		^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.50–7.44 (5H, m, Ph), 7.06–7.00 (2H, m, PhOCH_2O), 6.89 (1H, m, PhOCH_2O), 6.10 (2H, s, PhOCH_2O); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 165.6, 149.9, 147.9, 138.4, 137.2, 130.9, 129.8, 129.3, 128.2, 125.3, 121.4, 109.5, 109.3, 102.3.
3	MCR3005		^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.19 (1H, s, -NH), 7.42–7.36 (5H, m, Ph), 6.94 (2H, s, PhOCH_2O), 6.85 (1H, s, PhOCH_2O), 6.05 (2H, s, PhOCH_2O); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 171.5, 148.3, 147.1, 135.3, 129.5, 128.4, 124.4, 122.1, 109.3, 108.4, 101.4.
4	MCR3006		^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.42–7.36 (5H, m, Ph), 6.88 (1H, d, $J = 2.0$ Hz, $\text{Ph}(\text{OH})_2$), 6.73 (1H, dd, $J = 2.0$ Hz, $J = 8.4$ Hz, $\text{Ph}(\text{OH})_2$), 6.68 (1H, d, $J = 8.4$ Hz, $\text{Ph}(\text{OH})_2$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 172.0, 171.8, 147.3, 145.0, 136.5, 133.8, 129.5, 116.9, 115.5.
5	MCR3009		^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.02 (1H, s, -NH), 9.00 (2H, s, OH), 8.61 (1H, s, OH), 7.39 (5H, s, Ph), 6.42 (2H, s, $\text{Ph}(\text{OH})_2$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 172.4, 172.3, 146.2, 137.2, 135.9, 134.2, 130.1, 129.9, 129.5, 128.8, 119.0, 109.5.
6	MCR3010		^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.50–7.45 (5H, m, Ph), 7.34 (2H, d, $J = 8.5$ Hz, $\text{Ph}-\text{SCH}_3$), 7.31 (2H, d, $J = 8.5$ Hz, $\text{Ph}-\text{SCH}_3$), 2.50 (3H, s, $-\text{SCH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 142.5, 137.7, 137.0, 130.4, 129.7, 129.2, 128.7, 127.7, 125.1, 123.3, 13.8.

[168]

7	MCR3011		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.2 (1H, s, -NH), 7.42-7.37 (5H, m, Ph), 7.35 (2H, d, J = 8.3 Hz, PhSCH ₃), 7.24 (2H, d, J = 8.3 Hz, PhSCH ₃), 2.47 (3H, s, PhSCH ₃); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 172.1, 141.3, 136.5, 136.3, 130.5, 129.9, 129.4, 128.9, 125.6, 125.2, 14.5.
8	MCR3014		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.40 (1H, s, -NH), 7.95 (2H, d, J = 8.40 Hz, PhSOCH ₃), 7.61 (2H, d, J = 8.40 Hz, PhSOCH ₃), 7.44-7.37 (5H, m, Ph), 3.25 (3H, s, -SCH ₃); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 171.7, 171.6, 141.7, 138.9, 134.5, 131.1, 130.4, 130.2, 129.0, 128.7, 127.4, 43.7.
9	MCR3015		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.3 (1H, s, -NH), 7.82 (2H, d, J = 8.2 Hz, PhSO ₂ NH ₂), 7.53 (2H, d, J = 8.2 Hz, PhSO ₂ NH ₂), 7.44 (1H, s, PhSO ₂ NH ₂), 7.44-7.36 (5H, m, Ph); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 171.3, 172.0, 144.5, 137.9, 135.4, 132.2, 130.2, 129.8, 129.7, 129.6, 128.5, 128.3, 128.0, 125.9, 125.6, 62.0.
10	MCR3018		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.04 (2H, d, J = 8.8 Hz, PhSO ₂ CH ₃), 7.69 (2H, d, J = 8.8 Hz, PhSO ₂ CH ₃), 7.50 (2H, d, J = 8.6 Hz, PhOCOCH ₃), 7.27 (2H, d, J = 8.6 Hz, PhOCOCH ₃), 3.28 (3H, s, PhSO ₂ CH ₃), 2.28 (3H, s, PhOCOCH ₃); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 169.4, 165.3, 165.1, 152.8, 142.6, 139.8, 137.2, 133.0, 131.6, 130.9, 127.9, 124.9, 123.1, 122.0, 43.7, 21.3.
11	MCR3019		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.08 (1H, s, PhOH), 7.33 (2H, d, J = 6.8 Hz, Ph), 7.32-7.24 (4H, m, Ph), 6.68-6.74 (2H, m, Ph), 2.48 (3H, s, CH ₃ S); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 172.0, 171.8, 158.82, 140.2, 135.7, 133.4, 131.3, 129.9, 125.3, 125.1, 119.3, 115.4, 14.0.
12	MCR3026		¹ H NMR (400 MHz, DMSO-d ₆) δ 10.21 (1H, s, PhNHCOCH ₃), 7.65 (2H, d, J = 8.8 Hz, PhSCH ₃), 7.42 (4H, t, J = 8.0 Hz, PhNHCOCH ₃), 7.33 (2H, d, J = 8.8 Hz, PhSCH ₃), 2.50 (3H, s, PhSCH ₃), 2.07 (3H, s, PhNHCOCH ₃); ¹³ C NMR (100 MHz, DMSO-d ₆) δ 169.3, 165.8, 142.7, 141.9, 137.1, 136.6, 130.7, 130.2, 125.7, 124.2, 122.4, 119.2, 24.6, 14.4.

[169]

[170] Biological Activity Test

[171] For the biological activities of the compounds of the present invention, the concentration to inhibit the production of prostaglandin E₂ (PGE₂) by 50% in Raw264.7 murine macrophage cell line treated with lipopolysaccharide (LPS) (IC₅₀) was analyzed, and for the compounds showing less than 10 μM of IC₅₀ in the above test, the concentration to inhibit the activity of COX-2 enzyme which is associated with the

production of PGE₂ by 50% (IC₅₀) was tested. Also, for the cytotoxicities of the compounds according to the present invention, cell viability (IC₅₀) was measured according to a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

[172]

[173] Experiment 1: Inhibition of LPS-induced PGE₂ production

[174] Raw264.7 cells (murine macrophage cell line), which were obtained from Korean Cell Line Bank (KCLB), were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS), penicillin (100 units/mL) and streptomycin sulfate (100 µg/mL) at 37 °C in a humidified atmosphere with 5% CO₂. 1 mL of Raw264.7 cells in DMEM (5 × 10⁵ cells/mL) was seeded into each well of 24-well plates, left overnight and replaced with a fresh medium. Various concentrations of compounds were added and then incubated for 1 hour. Lipopolysaccharide (LPS) was added at 1 µg/mL and incubated for 24 hours (or appropriate time). The obtained supernatant was diluted five fold. 150 µL of analysis buffer was added to non specific binding (NSB) wells and 100 µL of analysis buffer was added to zero standard (BO) wells. 100 µL of standard samples were added to the other wells. 50 µL of PGE₂ conjugates were added (except for NSB). Then, 50 µL of PGE₂ antibody solution was added and shaken for 2 hours. Each well was subject to suction and washed with washing buffer five times. 200 µL of para-nitrophenyl phosphate (pNPP) substrate was added to each well and left at room temperature for 1 hour in bench, and then 50 µL of stop solution was added. The absorbance was measured at 405 nm. The production of PGE₂ was evaluated using the measured absorbance and standard curve, and the concentration to inhibit by 50% (IC₅₀) compared to the group treated with only LPS was analyzed. The results are summarized in Table 2, where the values were obtained from three independent experiments.

[175]

[176] Experiment 2: Inhibition of COX-2 activity

[177] To a background tube were added 970 µL of reaction buffer and 10 µL of heme, and then 10 µL of COX-2 protein inactivated by boiling for 3 minutes. To a COX-2 100% initial activity tube were added 970 µL of reaction buffer and 10 µL of heme, and then 10 µL of COX-2 protein. To a COX-2 inhibition tube were added 950 µL of reaction buffer and 10 µL of heme, and then 10 µL of COX-2 protein and 20 µL of standard sample. All tubes were left at 37 °C for 10 minutes. 10 µL of arachidonic acid was added and vortexed, and then left at 37 °C for 2 minutes. 50 µL of 1M HCl and 100 µL

of saturated tin chloride solution were added in sequence and vortexed, and then left at room temperature for 5 minutes. 100 μ L of Enzyme ImmunoAssay(EIA) buffer was added to non specific binding wells and 50 μ L of EIA buffer was added to zero standard(BO) wells. Background sample, COX-2 100% initial activity sample diluted 4000:1 and COX-2 inhibition sample were added in 50 μ L aliquots to the other wells. Prostaglandin screening tracer was added in 50 μ L aliquots except for total activity(TA) and Bik-like killer(Blk). PG screening antiserum was added in 50 μ L aliquots except for TA, NSB and Blk, and left at room temperature for 18 hours. Each well was subject to suction and washed with washing buffer 5 times. Ellman's reagent was added in 200 μ L aliquots and tracer was added in 5 μ L aliquots to only TA wells. The plates were shaken for 60-90 minutes with shielding the light and the absorbance was measured at 405 nm. The inhibition of COX-2 activity was evaluated using the measured absorbance and standard curve, and the concentration to inhibit by 50%(IC₅₀) compared to the group of COX-2 100% initial activity samples was analyzed. The results are summarized in Table 2, where the values were obtained from three independent experiments.

[178]

[179] Experiment 3: Cytotoxicities

[180] Raw264.7 cells(murine macrophage cell line) were cultured in Dulbecco's modified Eagle's medium(DMEM) containing 10% fetal bovine serum(FBS), penicillin(100 units/mL) and streptomycin sulfate(100 μ g/mL) at 37 °C in a humidified atmosphere with 5% CO₂. The cells were collected by centrifugation and scraper, and added in 1x10⁵ cells/well to 96-well plates having 100 μ L of Roswell Park Memorial Institute(RPMI) 1640 medium containing 10% FBS.

3-beta,4-beta-epoxy-8-alpha-isobutyryloxyguaia-1(10),11,(13)-diene-12,6-olide was dissolved in dimethylsulfoxide(DMSO) and the concentration of DMSO did not exceed 0.1% for all tests. After overnight, samples and LPS(1 μ g/mL) were added and the plates were incubated for 24 hours. The cells were washed once and 50 μ L of medium without FBS containing 5 mg/mL of

3-(4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide(MTT) was added. Then, the plates were incubated at 37 °C for 4 hours. Afterwards, the medium was removed and formazan blue formed in the cells was dissolved in 100 μ L of DMSO. The absorbance was measured at 540 nm to analyze the cytotoxicities in IC₅₀ values. IC₅₀ means the concentration to exhibit 50% reduction in the number of cells compared to the group which was not treated with compounds. The results are summarized in Table

2, where the values were obtained from three independent experiments.

[181]

[182]

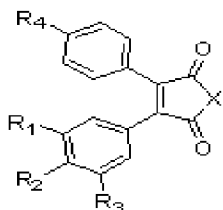
Table 2

[183]

Compound Code	Cell Viability IC ₅₀ (μ M)	PGE2 Production Inhibition IC ₅₀ (μ M)	COX-2 Activity Inhibition IC ₅₀ (μ M)	Compound Code	Cell Viability IC ₅₀ (μ M)	PGE2 Production Inhibition IC ₅₀ (μ M)	COX-2 Activity Inhibition IC ₅₀ (μ M)
MCR3001	269.90	27.94	ND	MCR3016	333.94	30.46	ND
MCR3002	259.63	9.95	ND	MCR3017	261.90	68.75	ND
MCR3003	158.01	13.83	ND	MCR3018	261.82	4.41	16.63
MCR3004	328.68	7.13	18.52	MCR3019	124.74	0.84	21.01
MCR3005	195.36	7.96	ND	MCR3020	266.08	12.6	ND
MCR3006	206.59	2.69	16.04	MCR3021	283.66	23.75	ND
MCR3007	312.56	37.1	ND	MCR3022	271.24	—	ND
MCR3008	150.55	25.08	ND	MCR3023	121.22	25.5	ND
MCR3009	261.45	8.19	17.51	MCR3024	242.04	45.2	ND
MCR3010	194.77	3.58	18.45	MCR3025	260.76	10.76	ND
MCR3011	151.88	4.73	16.34	MCR3026	249.75	5.71	20.11
MCR3012	303.22	21.52	ND	MCR3027	276.61	78.48	ND
MCR3013	265.89	15.42	ND	MCR3028	257.40	71.29	ND
MCR3014	268.74	2.71	17.5	MCR3029	305.41	131.53	ND
MCR3015	158.18	0.61	15.62				

Claims

- [1] A compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

wherein,

R₁, R₂ and R₃ are each independently hydrogen, hydroxy, C₁-C₅ lower alkoxy, R₅ C(=O)O, R₅ S, R₅ S(=O), R₅ S(=O)₂, NH S(=O)₂, R₂ C(=O)NH, or (R₅ C(=O))₂ N; or R₂ and R₃ taken together with the carbon atoms to which they are attached form a heterocycle;

R₄ is hydrogen, R₅ S, R₅ S(=O) or R₅ S(=O)₂;

R₅ is C₁-C₅ lower alkyl; and

X is O or NH.

- [2] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein R₁, R₂ and R₃ are each independently hydrogen, hydroxy, C₁-C₅ lower alkoxy, R₅ C(=O)O, R₅ S, R₅ S(=O)₂, NH S(=O)₂, or R₅ C(=O)NH.
- [3] The compound according to claim 2 or pharmaceutically acceptable salt thereof, wherein R₅ is methyl.
- [4] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein R₁ is hydrogen; R₂ and R₃ taken together with the carbon atoms to which they are attached form dioxolane or dioxane.
- [5] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein R₁, R₂ and R₃ are each independently hydrogen, hydroxy, or C₁-C₅ lower alkoxy; or R₂ and R₃ taken together with the carbon atoms to which they are attached form dioxolane or dioxane; and R₄ is hydrogen.
- [6] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein R₁ and R₃ are hydrogen; R₂ is hydroxy, C₁-C₅ lower alkoxy, R₅ C(=O)O, R₅ S, R₅ S(=O), R₅ S(=O)₂, NH S(=O)₂, R₂ C(=O)NH, or (R₅ C(=O))₂ N; and R₄ is hydrogen.
- [7] The compound according to claim 6 or pharmaceutically acceptable salt thereof, wherein R₅ is methyl.

- [8] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein R_1 and R_3 are hydrogen; R_2 is hydrogen, hydroxy, C_1-C_5 lower alkoxy, $R_5C(=O)O$, R_5S , $R_5S(=O)$, $R_5S(=O)_2$, $NH_2S(=O)_2$, $R_5C(=O)NH$, or $(R_5C(=O))_2N$; and R_4 is R_5S , $R_5S(=O)$ or $R_5S(=O)_2$.
- [9] The compound according to claim 8 or pharmaceutically acceptable salt thereof, wherein R_5 is methyl.
- [10] The compound according to claim 1 or pharmaceutically acceptable salt thereof, wherein the compound is selected from the following group:
 3-(3-methoxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-benzo[1,3]dioxol-5-yl-4-phenylfuran-2,5-dione;
 3-benzo[1,3]dioxol-5-yl-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(3,4-dihydroxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(3,4,5-trihydroxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(4-thiomethoxyphenyl)-4-phenylfuran-2,5-dione;
 3-(4-thiomethoxyphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(4-methanesulfonylphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(4-aminosulfonylphenyl)-4-phenyl-1*H*-pyrrole-2,5-dione;
 3-(4-acetoxyphenyl)-4-(4-methanesulfonylphenyl)furan-2,5-dione;
 3-(4-hydroxyphenyl)-4-(4-thiomethoxyphenyl)-1*H*-pyrrole-2,5-dione; and
 3-(4-acetaminophenyl)-4-(4-thiomethoxyphenyl)furan-2,5-dione.
- [11] A pharmaceutical composition for inhibiting cyclooxygenase-2(COX-2) comprising the compound of formula (I) according to any one of claims 1 to 10 or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.
- [12] The pharmaceutical composition according to claim 11 for treating or preventing inflammation, an allergic disorder, inflammatory dermatosis, an immunologic disorder, a neurodegenerative disorder, arthritis, pain or fever.