Synthesis of 4-Alkyl-1,2-diphenyl-3,5-dioxopyrazolidines Possessing Aryl Methylsulfonyl and Sulfonamide Pharmacophores for Evaluation as Selective Cyclooxygenase-2 (COX-2) Inhibitors

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A group of 1,2-diphenyl-3,5-dioxopyrazolidines possessing a methylsulfonyl (**11**) or sulfonamide (**15**) substituent at the *para* position of the N^1-phenyl ring, in conjunction with a hydrogen, methyl or fluoro substituent at the *para* position of the N^2-phenyl ring, and a C-4 *n*-butyl, methyl or spiro-cyclopropyl substituent were synthesized for evaluation as potential cyclooxygenase-2 (COX-2) selective inhibitor antiinflammatory agents. The title compounds **11** and **15** were synthesized using a four-step and a three-step reaction sequence, respectively. Thus, the acetic acid promoted condensation of a nitrosobenzene **5** with an aniline derivative (**6**, **12**) gave the corresponding azobenzene product (**8**, **13**) which was reduced with zinc dust in the presence of ammonium chloride to yield the corresponding hydrazobenzene (**9**, **14**). Base-catalyzed condensation of **9** and **14** with a malonyl dichloride (**10**) afforded the target 3,5-dioxopyrazolidine product (**11**, **15**). 4-*n*-Butyl-1-(4-methylsulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine (**11a**) was a selective COX-1 inhibitor (COX-1 IC_{50} = 8.48 μM). In contrast, 4-*n*-butyl-1-(4-methylsulfonylphenyl)-2-(4-tolyl)-3,5-dioxopyrazolidine (**11b**, COX-2 IC_{50} = 11.45 μM) and 4-*n*-butyl-1-(4-methylsulfonylphenyl)-2-(4-fluorophenyl)-3,5-dioxopyrazolidine (**11c**, COX-2 IC_{50} = 9.86 μM) were about 46-fold and 20-fold less selective COX-2 inhibitors respectively, relative to the reference drug celecoxib.

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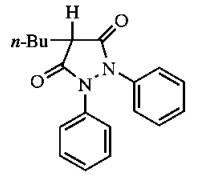
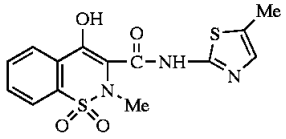
Introduction.

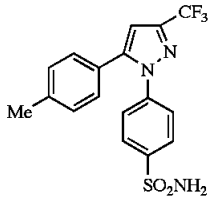
The design of agents to relieve pain and inflammation associated with arthritic diseases has undergone continual evolution resulting in the development of more efficacious classes of drugs that exhibit fewer adverse side effects. In this regard, structure-activity data for a 1,3-dicarbonyl class of compounds illustrated by the discontinued drug phenylbutazone **1** was used for the subsequent design of a new enolic class of drugs called "oxicams" represented by meloxicam **2** with reduced gastrointestinal ulcerogenic effects [1]. A single cyclooxygenase (COX) enzyme, which catalyzed the bioconversion of arachidonic acid to prostaglandins and thromboxanes, was originally believed to be responsible for both the therapeutic and adverse gastric ulceration effects associated with the use of non-steroidal antiinflammatory drugs (NSAIDs) prior to the discovery that there are two COX isozymes currently called COX-1 and COX-2 [2,3]. Thus, the synthesis of COX-2 is induced by mitogenic and proinflammatory stimulants [4] that leads to inflammatory processes [5] whereas, the constitutively expressed COX-1 isozyme is implicated in important physiological processes that include gastroprotection and vascular homeostasis [6]. These observations suggested that a drug which selectively inhibits the COX-2 isozyme would retain the desired clinical antiinflammatory effect, but be devoid of the ulcerogenic side effects associated with inhibition of COX-1, by non-selective NSAIDs that inhibit both COX-1 and COX-2. This drug design concept has been validated by post-market clinical studies that attest to the efficacy and improved safety of the selective COX-2 inhibitors celecoxib **3** and rofecoxib **4** [7,8]. The COX-2 selectivity indices (COX-1/COX-2 isozyme inhibition ratio) for meloxicam, celecoxib and rofecoxib are 2.0, 6.6 and 35.5, respectively [1]. The sulfonamido and methylsulfonyl pharmacophores present in celecoxib and rofecoxib are believed to induce COX-2 selectivity by insertion into the secondary pocket present in the COX-2 binding site that is absent in COX-1. This secondary pocket present in COX-2 is formed by a conformational change attributed to the presence of isoleucine (Ile^{523}) in COX-1 relative to the smaller valine (Val^{523}) in COX-2 [9]. It was anticipated that incorporation of a methylsulfonyl or sulfonamido substituent at the *para*-position of one of the phenyl rings of phenylbutazone may confer COX-2 selectivity and reduce the adverse gastrointestinal effects of phenylbutazone. We now report the synthesis, *in vitro* COX-1/COX-2 enzyme inhibition data and some *in vivo* antiinflammatory and



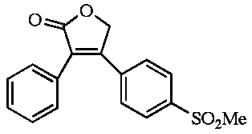
Phenylbutazone **1**



Meloxicam **2**
(Mobec®)



Celecoxib **3**
(Celebrex®)



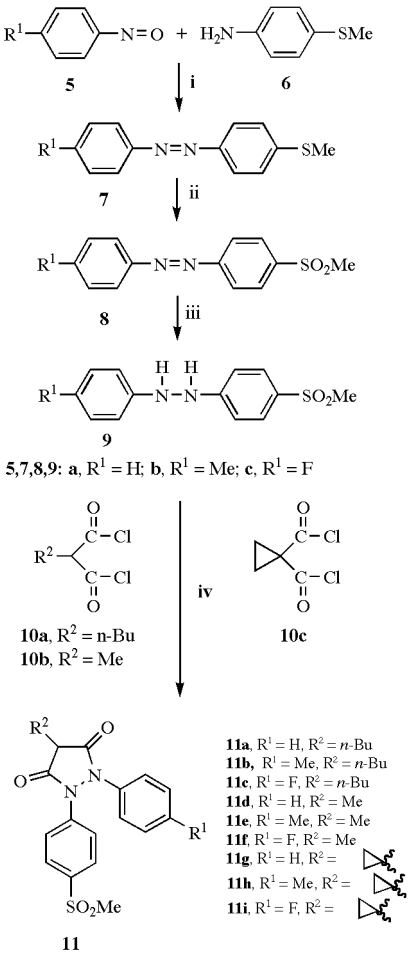
Rofecoxib **4**
(Vioxx®)

analgesic activity data for a class of 1,2-diphenyl-3,5-dioxopyrazolidines possessing a C-4 methyl, *n*-butyl or spirocyclopropyl substituent in conjunction with either a *para*-methylsulfonyl or sulfonamido substituent on one phenyl ring and either a *para*-hydrogen, methyl or fluoro substituent on the other phenyl ring.

Chemistry.

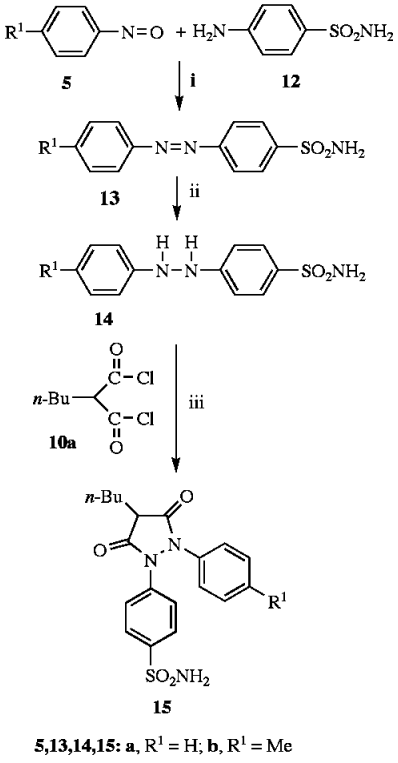
A group of 1-(4-methylsulfonylphenyl)-2-phenyl-4-alkyl-3,5-dioxopyrazolidines were synthesized using a modification of literature procedures [10-12] by the reaction sequence illustrated in Scheme 1. Accordingly, the acid catalyzed condensation of the nitrosobenzene compounds **5a-c** with 4-(methylthio)aniline (**6**) afforded the respective 4-methylthioazobenzene products **7a-c**. Oxidation of the methylthio group (**7a-c**) using potassium peroxymonosulfate gave the corresponding methylsulfonyl derivatives (**8a-c**). Subsequent reduction of the azo moiety (**8a**-c) using zinc dust in the presence of ammonium chloride afforded the corresponding 4-methylsulfonylhydrazobenzene products **9a-c**. Condensation of the 4-methylsulfonylhydrazobenzene compounds **9a-c** (R^1 = H, Me, F) with either 2-*n*-butylmalonyl dichloride (**10a**), or 2-methylmalonyl dichloride (**10b**), in the presence of pyridine afforded the respective 4-alkyl-1-(4-methylsulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine products **11a-f** (32-61 % range). In contrast, the related compounds **11g-i** possessing a C-4 spiro-cyclopropyl ring system could not be prepared using pyridine as a base for the condensation-cyclization reaction. Alternatively, reaction of the 4-methylsulfonylhydrazobenzenes **9a-c** with 1,1-cyclopropanedicarbonyl chloride (**10c**) using solid potassium carbonate as a base afforded the target products **11g-i** in moderate yields (15-20 % range).

Scheme 1[a]



[a] Reagents and conditions: (i) AcOH, 100 °C, 20 minutes; (ii) Oxone® (potassium peroxymonosulfate), MeOH, H_2O, 25 °C, 16 hours; (iii) zinc dust, saturated aqueous NH_4Cl, acetone:MeOH (1:1, v/v); (iv) pyridine, benzene, reflux, 2 hours (**11a-f**), K_2CO_3, benzene, reflux, 2 hours (**11g-i**).

Scheme 2[a]



[a] Reagents and conditions: (i) AcOH, 100 °C, 20 minutes; (ii) zinc dust, saturated aqueous NH_4Cl, acetone:MeOH (1:1, v/v); (iii) pyridine, benzene, reflux, 2 hours.

The structurally related 1-(4-aminosulfonylphenyl)-2-phenyl-3,5-dioxo-4-*n*-butylpyrazolidines **15a-b**, that possess a sulfonamide COX-2 pharmacophore, were prepared using the reaction sequence illustrated in Scheme 2 where sulfanilamide (**12**) was used to prepare the 4-aminosulfonylazobenzene intermediates **13a-b**.

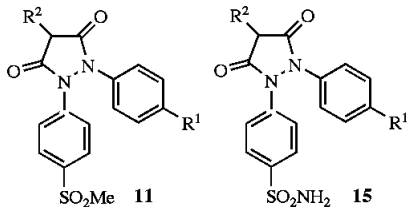
Biological Results.

A group of 1,2-diphenyl-3,5-dioxopyrazolidines were prepared to investigate the effect of methylsulfonyl (**11**) and sulfonamido (**15**) substitution at the *para*-position of the N^1-phenyl ring, in conjunction with a hydrogen, methyl or fluoro substituent (R^1) at the *para*-position of the N^2-phenyl ring and a C-4 *n*-butyl, methyl or spiro-cyclopropyl substituent (R^2), on *in vitro* COX-1 and COX-2 inhibitory activities and COX-2 selectivity (see Table 1), and *in vivo* antiinflammatory and analgesic activities.

Structure-activity relationships acquired for the methylsulfonyl group of compounds showed that a C-4 *n*-butyl substituent (**11a-c**) was required for inhibition of COX-1 or COX-2 since compounds possessing a C-4 methyl (**11d-f**), or spiro-cyclopropyl (**11g-i**), did not inhibit the COX-1 or COX-2 isozyme at a test compound concentration of 100 μM (see data in Table 1). The 3,5-dioxopyrazolidine ring system, which has a single alkyl substituent at C-4 (R^2 = *n*-butyl, methyl) also possesses an acidic C-4H which could give rise to an enolic tautomer, may resemble the enolic moiety in meloxicam (**2**). In this regard, one could rationalize the inability of the C-4 spiro-cyclopropyl compounds **11g-i**, which cannot form an enolic tautomer, to inhibit COX-1 or COX-2. However, the requirement of an enolizable C-4H is unclear since the C-4 butyl compounds **11a-c** inhibit the COX enzyme, but the C-4 methyl compounds **11d-f** are inactive COX inhibitors. The *para* N^2-phenyl substituent (R^1 = hydrogen, methyl, fluoro) was a determinant of COX-1 or COX-2 selectivity when one of the COX isozymes was inhibited. For example, in the methylsulfonyl group of compounds, compound **11a** having a N^2-phenyl substituent (R^1 = hydrogen) was a selective COX-1 inhibitor whereas, compounds **11b-c** (R^1 = methyl, fluoro) were selective COX-2 inhibitors. The nature of the *para* N^1-phenyl substituent was also a determinant of COX selectivity since the methylsulfonyl compound **11b** was a selective COX-2 inhibitor while the corresponding sulfonamide compound **15b** was an inactive COX-2 inhibitor (IC_{50} > 100 μM).

Table 1

In Vitro COX-1 and COX-2 Enzyme Inhibition Data



Compound	R^1	R^2	IC_{50}, μM [a] COX-1	IC_{50}, μM [a] COX-2	COX-2 S.I.[b]
11a	H	*n*-Bu	8.48	> 100	¾
11b	Me	*n*-Bu	> 100	11.45	> 8.73
11c	F	*n*-Bu	> 200	9.86	> 20.27
11d	H	Me	> 100	> 100	¾
11e	Me	Me	> 100	> 100	¾
11f	F	Me	> 100	> 100	¾
11g	H	CP[c]	> 100	> 100	¾
11h	Me	CP	> 100	> 100	¾
11i	F	CP	> 100	> 100	¾
15a	H	*n*-Bu	> 100	> 100	¾
15b	Me	*n*-Bu	> 10.73	> 100	¾
Celecoxib			22.9	0.0567	404

[a] Values are mean values of two determinations where the deviation from the mean is < 10% of the mean value; [b] *In vitro* COX-2 selectivity index (IC_{50} COX-1/COX-2); [c] CP = spiro-cyclopropyl.

The two selective COX-2 inhibitors 4-*n*-butyl-1-(4-methylsulfonylphenyl)-2-(4-tolyl)-3,5-dioxopyrazolidine (**11b**, COX-2 selectivity index > 8.73) and 4-*n*-butyl-1-(4-methylsulfonylphenyl)-2-(4-fluorophenyl)-3,5-dioxopyrazolidine (**11c**, COX-2 selectivity index > 20.27) were evaluated as antiinflammatory agents at three and five hours post drug administration using a carrageenan-induced rat paw edema assay. Compound **11b** exhibited moderate antiinflammatory activity where inflammation was inhibited by 11.1 ± 0.1% and 19.9 ± 3.8% at 3 and 5 hours post drug administration respectively, relative to the reference drug celecoxib (79.9 ± 1.9 and 58.2 ± 1.8 % inhibition at 3 and 5 hours post drug administration, respectively) for a 50 mg/kg oral dose. In contrast, the more selective COX-2 inhibitor **11c** did not exhibit oral antiinflammatory activity. However, 4-*n*-butyl-1-(4-methylsulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine (**11a**, COX-1 selectivity index = 8.48) enhanced inflammation by 7.0 ± 1.0 and 19.0 ± 2.5% at 3 and 5 hours post drug administration, respectively. This induction of inflammation by **11a** could be attributed to oxidative damage caused by the generation of phenylbutazone radicals formed *via* the peroxidase action of the COX enzyme. This explanation is consistent with the observation that factors not involved in the COX pathway are involved in aggravating inflammatory conditions [13]. Compounds **15a-b** having a N^1-(4-aminosulfonylphenyl) substituent were also inactive antiinflammatory agents in this assay.

Compounds **11b** and **11c** were also evaluated as analgesic agents using a rat 4% sodium chloride-induced abdominal constriction assay employing a 50 mg/kg intraperitoneal dose. Compound **11b** was an active analgesic agent where abdominal constriction was inhibited by 68.6 ± 7.0 and 16.2 ± 6.9% at 30 and 60 minutes post drug administration, respectively relative to the reference drug celecoxib (31.7 ± 9.6 and 62.0 ± 7.3% inhibition at 30 and 60 minutes post drug administration, respectively). Compound **11c** was a less potent analgesic agent (22.2 ± 9.0 and 18.9 ± 9.5% inhibition at 30 and 60 minutes, respectively).

EXPERIMENTAL

Melting points were determined using a Buchi capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Nicolet 550 Series II Magna FT-IR spectrometer. Nuclear magnetic resonance (^{1}H nmr, ^{13}C nmr) spectra were recorded on a Bruker AM-300 spectrometer. ^{13}C nmr was acquired using the J modulated spin echo technique where methyl and methine carbons appear as positive peaks and methylene and quaternary carbon resonances appear as negative peaks. Elemental analyses were performed for C, H, and N (Micro Analytical Service Laboratory, Department of Chemistry, University of Alberta). Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). 4-(Methyl)nitrosobenzene (**5b**) and 4-(fluoro)nitrosobenzene (**5c**) were prepared according to a literature procedure [14]. 2-*n*-Butylmalonyl dichloride (**10a**), 2-methylmalonyl dichloride (**10b**) and 1,1-cyclopropanedicarbonyl chloride (**10c**) were prepared according to a literature procedure [15]. All other reagents were purchased from Aldrich Chemical (Milwaukee, WI). *In vitro* COX-1 and COX-2 inhibition assays were performed using enzyme immunoassay (EIA) kits purchased from Cayman Chemical, Ann Arbor, MI. Male Sprague-Dawley rats, used in the anti-inflammatory and analgesic screens, were supplied by Animal Health Services, University of Alberta. All experiments involving animals were carried out using protocols approved by the Animal Welfare Committee, University of Alberta.

4-Methylthioazobenzene (**7a**).

Nitrosobenzene (1.07 g, 10.0 mmole) was dissolved in glacial acetic acid (10.0 ml) with slight warming and this solution was added to 4-(methylthio)aniline (1.39 g, 10.0 mmole) in glacial acetic acid (4.0 ml). The reaction was allowed to proceed with gentle heating on a steam bath for 20 minutes, the reaction mixture was poured into water (50 ml), the solid was collected by filtration after 5 minutes and washed with water (15 ml), Recrystallization from aqueous ethanol gave **7a** (1.72 g, 75%); mp 81-82 ºC, Lit mp 83-84 ºC [16]; ir (potassium bromide): 1488 (N=N) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.69 (s, 3H, SC*H*$_3$), 7.39 (d, J = 8.9 Hz, 2H, Harom), 7.49-7.57 (m, 3H, Harom), 7.89-7.95 (m, 4H, Harom).

4-Methylsulfonylhydrazobenzene (**9a**).

A solution of oxone (6.15 g, 10.0 mmole) in water (30 ml) was added slowly to a solution of **7a** (1.14 g, 5.0 mmole) in methanol (10 ml) at 0 °C, and the reaction mixture was stirred for 16 hours at room temperature. Removal of the solvent *in vacuo,* dissolution of the residue in water (20 ml), extraction with ethyl acetate (30 ml), washing the organic layer consecutively with water (30 ml) and brine (30 ml), drying the ethyl acetate fraction (sodium sulfate), and removal of the solvent *in vacuo* gave 4-methylsulfonylazobenzene (**8a**) as a light brown solid (1.04 g, 80%) which was used without further purification in the next step. Compound **8a** (0.80 g, 3.0 mmole) was dissolved in a minimum volume of acetone-methanol (1:1, v/v), a saturated aqueous solution of ammonium chloride (2.0 ml) was added, and additional acetone-methanol (1:1, v/v) was added to dissolve compound **8a** that had precipitated. A sufficient quantity of zinc dust was added with stirring to produce a colorless solution, the reaction mixture was filtered, and the filtrate was poured into ice-water (50 ml). The white solid that precipitated was collected by filtration under nitrogen, washed with water (50 ml), and dried under a stream of nitrogen to yield **9a** (0.59 g, 75%); mp 180-181 °C, Lit mp 179 °C [10]; ir (potassium bromide): 3325 (NH), 1300, 1142 (SO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.02 (s, 3H, SO_2CH_3), 5.76 (s, 1H, N*H*), 6.05 (s, 1H, N*H*), 6.81 (d, J = 8.6 Hz, 2H, H_{arom}), 6.90 (dd, J = 6.1 Hz, 6.1 Hz, 1H, H_{arom}), 6.96 (d, J = 8.9 Hz, 2H, H_{arom}), 7.22-7.27 (m, 2H, H_{arom}), 7.76 (d, J = 8.6 Hz, 2H, H_{arom}).

The physical and spectral data for compounds **9b-c**, which were prepared according to the procedure described above for the synthesis of **9a** except that 4-(methyl)nitrosobenzene (**5b**) and 4-(fluoro)nitrosobenzene (**5c**) were used in place of nitrosobenzene (**5a**), are listed below.

4-Methylsulfonyl-4'-methylhydrazobenzene (**9b**).

Compound **9b** was obtained by reduction of **8b** in 77% yield; mp 150-151 °C, Lit mp 147 °C [10]; ir (potassium bromide): 3490 (NH), 1293, 1145 (SO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 2.19 (s, 3H, C*H*$_3$), 2.93 (s, 3H, SO_2CH_3), 5.98 (s, 1H, N*H*), 6.65 (d, J = 8.5 Hz, 2H, H_{arom}), 6.83 (s, 1H, N*H*), 6.87 (d, J = 8.9 Hz, 2H, H_{arom}), 6.95 (d, J = 8.5 Hz, 2H, H_{arom}), 7.63 (d, J = 8.9 Hz, 2H, H_{arom}). Compound **9b** was used immediately for the preparation of **11b**, **11e** or **11h** as it decomposes slowly on standing.

4-Methylsulfonyl-4'-fluorohydrazobenzene (**9c**).

Compound **9c** was obtained by reduction of **8c** in 69% yield; mp 159-160 °C; ir (potassium bromide): 3342 (NH), 1300, 1146 (SO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.02 (s, 3H, SO_2CH_3), 5.72 (s, 1H, N*H*), 6.07 (s, 1H, N*H*), 6.74-6.80 (m, 2H, H_{arom}), 6.90-6.98 (m, 4H, H_{arom}), 7.76 (d, J = 8.9 Hz, 2H, H_{arom}). Compound **9c** was used immediately for the preparation of **11c**, **11f** or **11i** as it decomposes slowly on standing.

4-*n*-Butyl-1-(4-methylsulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine (**11a**).

Pyridine (0.5 ml), and then 2-*n*-butylmalonyl dichloride (0.45 g, 2.3 mmole), was added consecutively to a solution of **9a** (0.50 g, 1.9 mmole) in benzene (10 ml) with stirring. The reaction was allowed to proceed for 30 minutes at room temperature, and then at reflux for 4 hours. The cold reaction mixture was washed with 1 *N* HCl (10 ml) and extracted with saturated $NaHCO_3$ solution (3 x 20 ml). This aqueous extract was then acidified with 2 *N* hydrochloric acid to afford a solid precipitate which was recrystallized from ethanol to yield **11a** (0.31 g, 42%); mp 159-160 °C; ir (potassium bromide): 1728 (CO), 1304, 1147 (SO_2) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.35-1.41 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.05-2.09 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.02 (s, 3H, SO_2CH_3), 3.45 (t, J = 5.8 Hz, 1H, H-4), 7.22–7.40 (m, 5H, H_{arom}), 7.54 (d, J = 9.1 Hz, 2H, H_{arom}), 7.90 (d, J = 9.1 Hz, 2H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 13.68 (CH_2CH_3), 22.43, 27.96 (CH_2), 44.48 (SO_2CH_3), 46.15 (*C*-4), 121.80, 122.00, 127.22, 128.38, 129.31 (C_{arom}-H), 135.84 (C_{arom}-SO_2CH_3), 137.82, 140.13 (C_{arom}-N), 170.05, 170.37 (*C*O).

Anal. Calcd. for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.08; H, 5.71; N, 7.26.

Compounds **11b-f**, for which physical and spectral data are listed below, were prepared by reaction of a 4-(methylsulfonylphenyl)hydrazobenzene (**9a-c**) with a malonyl dichloride (**10a-c**) using a procedure similar to that described above for the synthesis of **11a**.

4-*n*-Butyl-1-(4-methylsulfonylphenyl)-2-(4-tolyl)-3,5-dioxopyrazolidine (**11b**).

Compound **11b** was obtained by the reaction of **9b** with 2-*n*-butylmalonyl dichloride in 51% yield; mp 144-145 °C; ir (potassium bromide): 1727 (CO), 1296, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.90 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.26-1.46 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.06-2.13 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.31 (s, 3H, tolyl-CH_3), 3.02 (s, 3H, SO_2CH_3), 3.43 (t, J= 5.8 Hz, 1H, H-4), 7.13-7.19 (m, 4H, H_{arom}), 7.53 (d, J = 8.9 Hz, 2H, H_{arom}), 7.89 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99. Found: C, 63.26; H, 6.10; N, 7.01.

4-*n*-Butyl-1-(4-methylsulfonylphenyl)-2-(4-fluorophenyl)-3,5-dioxopyrazolidine (**11c**).

The title compound **11c** was synthesized by the reaction of **9c** with 2-*n*-butylmalonyl dichloride in 61% yield; mp 75-76 °C; ir (potassium bromide): 1732 (CO), 1300, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.31-1.51 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.07-2.14 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.04 (s, 3H, SO_2CH_3), 3.45 (t, J = 5.8 Hz, 1H, H-4), 7.04-7.10 (m, 2H, H_{arom}), 7.27-7.33 (m, 2H, H_{arom}), 7.53 (d, J = 8.9 Hz, 2H, H_{arom}), 7.92 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{20}H_{21}FN_2O_4S•1/2H_2O$: C, 58.09; H, 5.32; N, 6.77. Found: C, 58.05; H, 5.02; N, 6.69.

4-Methyl-1-(4-methylsulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine (**11d**).

Compound **11d** was obtained by reaction of **9a** with 2-methylmalonyl dichloride in 46% yield; mp 104-105 °C; ir (potassium bromide): 1721 (CO), 1320, 1162 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62 (d, J = 7.6 Hz, 3H, C-4 CH_3), 3.02 (s, 3H, SO_2CH_3), 3.48 (q, J = 7.6 Hz, 1H, H-4), 7.22-7.40 (m, 5H, H_{arom}), 7.54 (d, J = 8.9 Hz, 2H, H_{arom}), 7.90 (d, J = 8.9 Hz, 2H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 11.94 (C-4 CH_3), 41.07 (SO_2CH_3), 44.32 (C-4), 121.76, 121.96, 127.10, 128.21, 129.19 (C_{arom}-H), 135.85 (C_{arom}-SO_2CH_3), 137.79, 140.09 (C_{arom}-N), 170.30, 170.67 (*C*O).

Anal. Calcd. for $C_{17}H_{16}N_2O_4S.3/4H_2O$: C, 57.04; H, 4.89; N, 7.82. Found: C, 57.16; H, 4.55; N, 7.41.

4-Methyl-1-(4-methylsulfonylphenyl)-2-(4-tolyl)-3,5-dioxopyrazolidine (**11e**).

Compound **11e** was obtained by reaction of **9b** with methylmalonyl dichloride in 32% yield; mp 198-199 °C; ir (potassium bromide): 1720 (CO), 1304, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.61 (d, J = 7.6 Hz, 3H, C-4 CH_3), 2.32 (s, 3H, tolyl-CH_3), 3.02 (s, 3H, SO_2CH_3), 3.45 (q, J = 7.6 Hz, 1H, H-4), 7.12-7.20 (m, 4H, H_{arom}), 7.54 (d, J = 8.9 Hz, 2H, H_{arom}), 7.90 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.48; H, 4.94; N, 7.82.

4-Methyl-1-(4-methylsulfonylphenyl)-2-(4-fluorophenyl)-3,5-dioxopyrazolidine (**11f**).

The title compound **11f** was synthesized by the reaction of **9c** with methylmalonyl dichloride in 35% yield; mp 110-112 °C; ir (potassium bromide): 1731 (CO), 1300, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.63 (d, J = 7.6 Hz, 3H, C-4 CH_3), 3.03 (s, 3H, SO_2CH_3), 3.47 (q, J = 7.6 Hz, 1H, H-4), 7.04-7.08 (m, 2H, H_{arom}), 7.27-7.32 (m, 2H, H_{arom}), 7.53 (d, J = 8.9 Hz, 2H, H_{arom}), 7.92 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{17}H_{15}FN_2O_4S.H_2O$: C, 53.67; H, 4.51; N, 7.36. Found: C, 53.72; H, 4.39; N, 7.10.

5-(4-Methylsulfonylphenyl)-6-phenyl-5,6-diazaspiro[2.4]heptane-4,7-dione (**11g**).

Potassium carbonate (1.0 g), and then cyclopropane-1,1-dicarbonyl dichloride (**10c**, 0.77 g, 4.6 mmole), was added to a solution of **9a** (1.0 g, 3.8 mmole) in benzene (20 ml) with stirring, and the reaction was allowed to proceed for 4 hours at reflux. The cooled mixture was quenched with water (20 ml), extracted with ethyl acetate (50 ml), the organic layer was washed with brine (20 ml), the organic fraction was dried (sodium sulfate), filtered, and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate:hexane (1:1, v/v) as eluant to afford **11g** as a colorless solid (0.27 g, 20 % yield); mp 101-103 °C; ir (potassium bromide): 1728 (CO), 1304, 1154 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.98 (s, 4H, CH_2), 3.02 (s, 3H, SO_2CH_3), 7.21-7.28 (m, 2H, H_{arom}), 7.34-7.41 (m, 3H, H_{arom}), 7.59 (d, J = 8.9 Hz, 2H, H_{arom}), 7.91 (d, J = 8.9 Hz, 2H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 22.63 (CH_2), 26.91 (C-4), 44.50 (SO_2CH_3), 121.60, 121.80, 126.94, 128.37, 129.25 (C_{arom}-H), 136.40 (C_{arom}-SO_2CH_3), 137.51, 140.70 (C_{arom}-N), 170.82, 171.20 (*C*O).

Anal. Calcd. for $C_{18}H_{16}N_2O_4S•1/2H_2O$: C, 59.16; H, 4.65; N, 7.67. Found: C, 59.17; H, 4.22; N, 7.48.

Compounds **11h-i**, for which physical and spectral data are listed below, were prepared by reaction of a 4-(methylsulfonylphenyl)hydrazobenzene (**9b-c**) with cyclopropane-1,1-dicarbonyl dichloride (**10c**) using a procedure similar to that described for the synthesis of **11g** above.

5-(4-Methylsulfonylphenyl)-6-(4-tolyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**11h**).

The title compound was synthesized by reaction of **9b** with **10c** in 15% yield; mp 98-100 °C; ir (potassium bromide): 1732 (CO), 1300, 1171 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.97 (s, 4H, CH_2), 2.32 (s, 3H, tolyl-CH_3), 3.02 (s, 3H, SO_2CH_3), 7.16 (d, J = 8.6 Hz, 2H, H_{arom}), 7.23 (d, J = 8.6 Hz, 2H, H_{arom}), 7.58 (d, J = 8.5 Hz, 2H, H_{arom}), 7.90 (d, J = 8.5 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{19}H_{18}N_2O_4S.2/3H_2O$: C, 59.67; H, 4.50; N, 7.32. Found: C, 59.30; H, 4.84; N, 6.84.

5-(4-Methylsulfonylphenyl)-6-(4-fluorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**11i**).

Compound **11i** was obtained by reaction of **9c** with **10c** in 19% yield; mp 105-107 °C; ir (potassium bromide): 1732 (CO), 1300, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.99 (s, 4H, CH_2), 3.03 (s, 3H, SO_2CH_3), 7.05-7.10 (m, 2H, H_{arom}), 7.23-7.58 (m, 2H, H_{arom}), 7.57 (d, J = 8.6 Hz, 2H, H_{arom}), 7.92 (d, J = 8.6 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{18}H_{15}N_2O_4$: C, 57.75; H, 4.04; N, 7.48. Found: C, 57.60; H, 4.36; N, 7.25.

4-Aminosulfonylazobenzene (**13a**).

Nitrosobenzene (2.14 g, 20.0 mmole) was dissolved in glacial acetic acid (20 ml) with slight warming, this solution was added to 4-aminobenzenesulfonamide (**12**, 3.44 g, 20.0 mmole) in glacial acetic acid (8.0 ml), the reaction was allowed to proceed with gentle heating on a steam bath for 20 minutes, and the cool reaction mixture was poured into water (100 ml). After standing for 5 minutes, the solid was collected by filtration, washed with water, and

recrystallized from aqueous ethanol to afford **13a** (3.92 g, 75%); mp 219-220 °C, Lit mp 220-221 °C [17]; ir (potassium bromide): 3325, 3280 (NH), 1307, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 6.57 (s, 2H, NH_2), 7.34-7.43 (m, 3H, H_{arom}), 7.78-7.82 (m, 2H, H_{arom}), 7.84 (d, J = 8.6, 2H, H_{arom}), 7.93 (*d*, J = 8.6 Hz, 2H, H_{arom}); ^{13}C nmr (deuteriochloroform + DMSO-d_6): δ 110.10, 111.60, 118.00, 127.07, 128.50 (C_{arom}–H), 131.94 (C_{arom}-SO_2NH_2), 148.83, 152.50 (C_{arom}-N).

4-*n*-Butyl-1-(4-aminosulfonylphenyl)-2-phenyl-3,5-dioxopyrazolidine (**15a**).

4-Aminosulfonylazobenzene (**13a**, 3.13 g, 12.0 mmole) was dissolved in a minimum quantity of acetone-methanol (1:1, v/v), and a saturated solution of ammonium chloride (1.2 ml) was added with stirring. Additional acetone-methanol (1:1, v/v) was added to dissolve **13a** that had precipitated. Zinc dust was added to this solution with stirring until the solution turned colorless, and the reaction mixture was filtered into ice-water. The white precipitate was collected by filtration under nitrogen, washed with water and dried to yield **14a** (2.81 g, 89%), which was used without further purification in the next reaction. Pyridine (1.0 ml), and then 2-*n*-butylmalonyl dichloride (1.0 g, 5.0 mmole), was added to a solution of **14a** (1.0 g, 3.8 mmole) in benzene (20.0 ml), and the reaction mixture was heated at reflux for 2 hours. The cooled reaction mixture was quenched with water (20 ml), extracted with ethyl acetate (50 ml), the organic layer was washed with brine (20 ml), the organic layer was dried (sodium sulfate), filtered, and the solvent was removed *in vacuo*. The residue obtained was purified by silica gel column chromatography using ethyl acetate:hexane (1:1, v/v) as eluant to afford **15a** as a colorless solid (0.77 g, 52% yield); mp 98-99 °C; ir (potassium bromide): 3356, 3253 (NH), 1721 (CO), 1320, 1162 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.27-1.41 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.98-2.05 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.35 (t, J = 5.8 Hz, 1H, H-4), 4.69 (s, 2H, SO_2NH_2), 7.12-7.30 (m, 5H, H_{arom}), 7.57 (d, J = 8.9 Hz, 2H, H_{arom}), 7.79 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.74; H, 5.48; N, 10.46.

The physical and spectral data for compound **15b**, which was prepared using the same procedure described above for the preparation of **15a** except that 4-methylnitrosobenzene (**5b**) was used in place of nitrosobenzene (**5a**), is listed below.

4-*n*-Butyl-1-(4-aminosulfonylphenyl)-2-(4-tolyl)-3,5-dioxopyrazolidine (**15b**).

Compound **15b** was obtained by reaction of **14b** with **10a** in 38 % yield; mp 172-173 °C; ir (potassium bromide): 3363, 3261 (NH), 1721 (CO), 1328, 1155 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.31-1.51 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.05-2.13 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.31 (s, 3H, tolyl-CH_3), 3.43 (t, J = 5.8 Hz, 1H, H-4), 4.80 (s, 2H, SO_2NH_2), 7.13-7.20 (m, 4H, H_{arom}), 7.48 (d, J = 8.9 Hz, 2H, H_{arom}), 7.87 (d, J = 8.9 Hz, 2H, H_{arom}).

Anal. Calcd. for $C_{20}H_{23}N_3O_4S$: C, 59.83; H, 5.77; N, 10.47. Found: C, 59.63; H, 5.76; N, 10.14.

Cyclooxygenase (COX) Inhibition Assays.

The *in vitro* ability of the test compounds to inhibit COX-1 and COX-2 was determined using a COX-(ovine) inhibitor screening kit (catalog no. 560101, Cayman Chemical, Ann Arbor, MI) according to the method previously reported [18].

Antiinflammatory Assay.

The test compounds were evaluated using the *in vivo* rat carrageenan-induced foot paw edema model reported previously [19].

Analgesic Assay.

Analgesic activity was determined using the 4% sodium chloride-induced writhing (abdominal constriction) assay as described previously [20].

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