Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 5539–5544

BIOORGANIC & MEDICINAL CHEMISTRY

Discovery of 2-Phenyl-3-sulfonylphenyl-indole Derivatives as a New Class of Selective COX-2 Inhibitors

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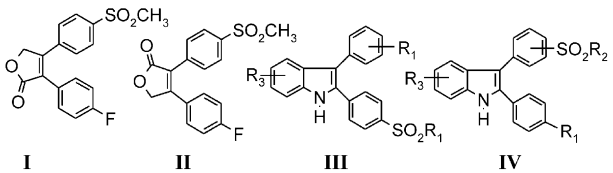
Received 9 May 2003; revised 29 August 2003; accepted 4 September 2003

Abstract—2-Sulfonylphenyl-3-phenyl-indole derivatives have been reported to be highly potent and selective COX-2 inhibitors previously. In this paper, the regio-isomeric analogues-2-phenyl-3-sulfonylphenyl-indoles were identified as potent and selective COX-2 inhibitors. This work led to the discovery of compounds **4a** and **8a** possessing higher activity than Celecoxib on cellular assay.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain among the most widely prescribed drugs worldwide for the treatment of inflammation including pain-releasing, anti-pyretic and rheumatoild arthritis. The mechanism of action was through their inhibition of prostaglandin biosynthesis via the enzyme cyclooxygenase-2 (COX-2).[1] COX-2 and COX-1 are two similar but distinct isoforms of cyclooxygenase (COX).[2–5] COX-2 is induced upon inflammatory stimuli and is responsible for progression of inflammation, whereas COX-1 is a constitutively expressed isoform and is responsible for the maintenance of physiological homestasis, such as gastrointestinal integrity and renal function. Thus selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities when compared with the traditional NSAIDs.

Current research has focused on developing safer NSAIDs- selective COX-2 inhibitors. Several selective COX-2 inhibitors such as Celecoxib,[6] Rofecoxib[7,8] and Valdecoxib[9] have been marketed as a new generation of NSAIDs, structurally featuring with vicinal diarylheterocycles inhibitors.[10–32] The other two categories of selective COX-2 inhibitors[33,34] are sulfonanilide inhibitors,[35–37] and modifications of classical NSAIDs.[38–41] The pharmacophore of diarylheterocycles inhibitors is characterized by a central carbocyclic or heterocyclic ring system bearing two vicinal aryl moieties and one benzene ring being substituted with a methylsulfonyl or aminosulfonyl group at the para position. The regio-isomeric analogues deriving from the alteration of the position of sulfonylphenyl group on the central ring exhibited different activity for COX-2, for instance, the lactone **I** ($IC_{50} = 0.01$ μM) have significant inhibitory activity for COX-2 whereas its isomeric analogue **II** was found to be essentially inactive against the same enzyme on cellular assay.[7] Previously,[42] we have reported 2-sulfonylphenyl-3-phenyl-indole derivatives (**III**) to be highly potent and selective COX-2 inhibitors. We herein synthesized and evaluated the regio-isomeric analogues (**IV**)—2-phenyl-3-sulfonylphenyl-indole derivatives as a new class of selective COX-2 inhibitors.



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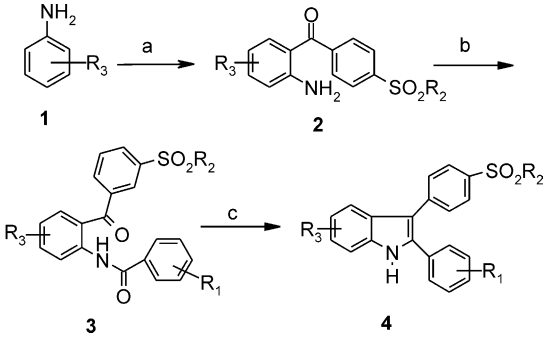
doi:10.1016/j.bmc.2003.09.008

Chemistry

All the compounds **4** and **8** described herein were synthesized by using the general routes outlined in Scheme 1 and 2. In method A (outlined in Scheme 1), McMurry coupling reaction[43–45] was employed in the key step of the route to construct an indole skeleton. The commercially available starting material **1** was taken Friedel–Crafts reaction with 4-methylsulfonyl or 4-aminosulfonyl benzoyl chloride, and then hydrolyzed by concentrated H_2SO_4 to give the substituted 2-aminobenzophenone **2**, which was then acylated with substituted benzoyl chloride to provide compound **3.** The intermediate **3** was cyclized to form the final compound **4** by the McMurry condensation.

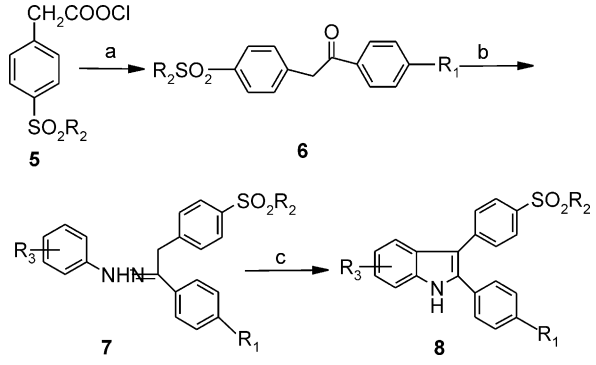
Method A:



Scheme 1. Reagent: (a) (i) $R_2C_6H_4COCl$, $ZnCl_2$, 205 °C; (ii) H_2SO_4, 120 °C; (b) 4-$R_1SO_2C_6H_4COCl$, THF, Et_3N, rt; (c) Zn, $TiCl_4$, THF, reflux.

Fischer indole synthesis method was carried out in method B (outlined in Scheme 2). 4-Methyl(amino)-sulfonyl- phenylacetyl chloride **5** was taken Friedel–Crafts reaction with substituted benzene to give rise to the corresponding substituted phenylacetophenone **6**, which was condensed with substituted phenylhydrazine to give arylhydrazone **7**. Finally the arylhydrazone **7** was cyclized to the target compound **8** in the presence of acetic acid and BF_3.

Method B:



Scheme 2. Reagent: (a) $AlCl_3$, $C_6H_5R_1$, 80 °C; (b) $R_3C_6H_4NHNH_2$·HCl, 130 °C; (c) BF_3·Et_2O, AcOH, reflux.

All the target compounds were identified by spectroscopic data and confirmed by elemental analyses.

Results and Discussion

For the ease of synthesis compounds **4** were prepared as 5-chloro-indole derivatives, except for **4i** with 5-methyl substitution. Compound **8** were prepared as both the methyl sulfone **8a** and the sulfonamide **8b**. All the compounds synthesized in this work were evaluated for their ability to inhibit COX-2 and COX-1 by cellular assay using freshly harvested mouse peritoneal macrophages as described in the literature.[46] The details of these assays were described in the Experimental. The IC_{50} values for COX-1 inhibition by the compounds were not able to determine due to the low inhibitory activity at the concentration of 10 μM of the tested compounds. The results reported in Table 1 showed that all the compounds exhibited high inhibition against COX-2 compared to the inhibition for COX-1 ($IC_{50} > 10$ μM). Compounds **4a** ($IC_{50} = 0.27$ nM) and **8b** ($IC_{50} = 0.22$ nM) were found to be more potent and selective than Celecoxib ($IC_{50} = 0.52$ nM) against COX-2.

The sulfonylphenyl group is necessary for the diaryl-heterocycles inhibitors to exert selective inhibition against COX-2. When the indole ring possesses two methylsulfonylphenyl groups such as compounds **4h** and **4i**, there were two possible binding modes: 2-methylsulfonylphenyl or 3-methylsulfonylphenyl binding to the hydrogen bond pocket. Though it was uncertain of the binding mode methylsulfonyl group was identified as a poor group to enter into the nonselective pocket by the activity of **4h** ($IC_{50} = 1.48$ nM) and **4i** ($IC_{50} = 3.57$ nM) which were less than that of Celecoxib. The sulfonamide **8a** ($IC_{50} = 0.22$ nM) is more active than the corresponding methylsulfone **8b** ($IC_{50} = 2.55$ nM).

The comparison between the regio-isomeric analogues showed that compound **8a** ($IC_{50} = 0.22$ nM) is 2 times more active than its regio-isomer 2-methylsulfonylphenyl-3-phenyl-indole[42] ($IC_{50} = 0.60$ nM), whereas **8b** ($IC_{50} = 2.55$ nM) is about 25 times less potent than its

Table 1. In vitro[a] inhibitory results

No.	Structure			IC_{50} (nM)[b] COX-2	IC_{50} (μM)[b] COX-1
	R_1	R_2	R_3		
4a	H	CH_3	5-Cl	0.27	>10
4b	2-F	CH_3	5-Cl	1.76	>10
4c	4-Cl	CH_3	5-Cl	3.54	>10
4d	4-CH_3	CH_3	5-Cl	1.68	>10
4e	4-OCH_3	CH_3	5-Cl	2.81	>10
4f	2-$OCOCH_3$	CH_3	5-Cl	7.16	>10
4g	4-$OCOCH_3$	CH_3	5-Cl	6.0	>10
4h	4-SO_2CH_3	CH_3	5-Cl	1.48	>10
4i	4-SO_2CH_3	CH_3	5-CH_3	3.57	>10
8a	H	CH_3	H	0.22	>10
8b	H	NH_2	H	2.55	>10
Celecoxib				0.52	>10

[a]Cell level. For details, see Experimental.
[b]All IC_{50} determinations including Celecoxib were carried out in triplicate and have less than 10% error.

isomeric one 2-aminosulfonylphenyl-3-phenyl-indole[42] ($IC_{50}=0.09$ nM). The influence of the regio-isomeric analogues for methylsulfone compounds on the inhibitive activity is different from those for sulfonamide series. However, compound **4a** ($IC_{50}=0.27$ nM) was found to be comparable to its isomeric compound 2-methylsulfonylphenyl-3-phenyl-5-chloro-indole ($IC_{50}=0.36$ nM). It seems that no correlation between the regio-isomers and the inhibitory activity exists because of the limit of the sample number.

Conclusions

The series of 2-phenyl-3-sulfonylphenyl-indole derivatives described in this paper were proved to be potent and selective inhibitors of COX-2. The indole ring was proved to be an effective scaffold that derived two classes of COX-2 inhibitors. This work led to the discovery of compounds **4a** and **8a** possessing higher activity than Celecoxib on cellular assay.

Experimental

Biological methods

In vitro test of inhibitory activity for cyclooxygenase-1 and cyclooxygenase-2.

Cell culture

Adherent macrophages were harvested from the peritoneal cells of male mice (C57BL-6J, Level 2, from Experiment Animal Center, Academy of Military Medical Science) after the injection (ip) of brewer thioglycollate medium (5 mL/100 g body weight) for 3 days. Shortly, peritoneal cells obtained from 3∼4 mice were mixed and seeded in 48 well cell culture cluster (Costar) at a cell density of 1×10^9 cell/L in RPMI-1640 supplemented with 5% (v/v) newborn calf serum, 100 ku/L penicillin and 100 g/L streptomycin. After settlement for 2∼3 h, non-adherent cells were washed by D-Hanks' balanced salt solution. Then macrophages were cultured in RPMI-1640 without serum. Almost all of adherent cells were macrophages as assessed by Giemsa staining. Cell viability was examined by trypan blue dye exclusion. All incubation procedures were performed with 5% CO_2 in humidified air at 37 °C.

COX-1 assay

Macrophages were incubated with test compound at different concentrations or solvent (Me_2SO) for 1 h and were stimulated with calcimycin 1 μmol L^{-1} for 1 h. The amount of 6-keto-$PGF_{1\alpha}$ (a stable metabolite of PGI_2) in supernatants was measured by RIA according to manufacturer's guide. The inhibitory ratio was calculated as

$$IR=\frac{(C_s-C_t)}{(C_s-C_c)}$$

C_s, C_t, C_c refer to 6-keto-$PGF_{1\alpha}$ concentration in supernatants of calcimycin, test compound, and control groups, respectively.

COX-2 assay

Macrophages were incubated with test compound at different concentrations or solvent (Me_2SO) for 1 h and were stimulated with LPS 1 mg/L for 9 h. The amount of PGE_2 in supernatants was measured by RIA. The inhibitory ratio was calculated using the same formula as in **COX-1 assay** section. Cs, Ct, Cc refer to PGE_2 concentration in supernatants of LPS, test compound, and control groups, respectively.

Statistical analysis data were expressed as the mean ± SD of more than three independent experiments. Dose–inhibitory effect curves were fit through 'uphill dose response curves, variable slope' using Prism, GraphPad version 3.00:

$$Y=\frac{1}{1+10^{[(\log IC_{50}-X)\times \mathrm{Hillslope}]}}$$

Chemistry

All solvents were used dried and freshly distilled. Melting points were determined using Yanaco melting point apparatus and are uncorrected. ^1H NMR were recorded on a Bruker AM-300 (300 MHz) spectrometer. Elemental analyses were performed at analytical division of Institute of Material Medica and were within 0.4% of the calculated values.

Method A

The general procedure for the preparation of substituted 2-phenyl-3-sulfonylphenyl-indoles (**4a**–**4i**) is illustrated below in the synthesis of 2-phenyl-3-(4-methylsulfonylphenyl)-5-chloro-indole (**4a**).

2-Phenyl-3-(4-methylsulfonylphenyl)-5-chloro-indole (4a). Step 1: 2-amino-5-chloro-4′-methylsulfonylbenzophenone (2). A mixture of 20.0 g (0.1 mol) of *p*-methylsulfonylbenzoic acid and 20 mL of thionyl chloride was heated under reflux to give a clear solution. Removal of the excess of thionyl chloride under reduced pressure obtained white solid and immediately used for the next reaction. To the *p*-methylsulfonylbenzoyl chloride at 140 °C was added in portions with stirring 5.1 g (0.04 mol) of 4-chloroaniline. The mixture was heated to 180 °C and 6.8 g (0.05 mol) of $ZnCl_2$ was added. The temperature was gradually increased to about 205 °C and kept for 2 h. After cooling to 120 °C, 60 mL of 3 N HCl was added and the mixture stirred and heated under reflux. The hot acid layer was decanted and this procedure repeated three times. The water-insoluble residue was dissolved in 80 mL of 70% sulfuric acid and refluxed for 8 h, after cooling poured into a large amount of ice water. The reaction mixture was neutralized with aqueous ammonia and extracted with ethyl acetate, dried over Na_2SO_4. The solvent was removed

and the residue was crystallized from 95% ethanol to give the title compound 5.1 g as yellow needle crystals, yield 40.9%, mp 176–177 °C.

Step 2: 2-*N*-(benzoyl)-amido-5-chloro-4′-methylsulfonyl-benzophenone (3a). To a solution of 3.1g, 0.010 mol of 2-amino-4′-methylsulfonylbenzophenone **2**, 1.6 mL 0.011 mol of triethylamine in 20 mL of dry THF under nitrogen was added a solution of 1.4 g (0.010 mol) of benzoyl chloride in 10 mL of dry THF. The reaction mixture was stirred at room temperature for 2 h, and filtered. The filtrate was concentrated and the residue was purified by column chromatograph on silica gel (eluant: petroleum ether/ethyl acetate, 3/1) to give the title compound 3.0 g as light yellow needle crystals, yield 74.8%, mp 203–205 °C.

Step 3: 2-phenyl-3-(4-methylsulfonylphenyl)-5-chloro-indole (4a). To a suspension of 1.14 g (3 mmol) of 2-*N*-(benzoyl)-amido-5-chloro-4′-methylsulfonyl-benzophenone (**3a**) and 0.87 g (12 mmol) of 90% Zn in 20 mL dry THF was added dropwise 0.7 mL (6.2 mmol) of $TiCl_4$ and heated under reflux for 1.5 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (3/1) as eluant. The title compound (0.45 g) was obtained as white crystals, yield 54.2%, mp 273–275 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.25 (s, 3H, SO_2CH_3), 7.20–7.94 (m, 12H, Ar–H), 12.05 (s, 1H, N–H). Anal. calcd for: $C_{21}H_{16}NO_2SCl$: C 66.05, H 4.22, N 3.67; Found: C 65.98, H 4.47, N 3.75.

The following compounds (**4b–4i**) were prepared according to the general procedure described above.

2-(2-Fluorophenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4b). The title compound was obtained as white crystals, yield 60.0%, mp 246–248 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.21 (s, 3H, SO_2CH_3), 7.21–7.88 (m, 11H, Ar–H), 12.04(s, 1H, N–H). Anal. calcd for: $C_{21}H_{15}FNO_2SCl$: C 63.07, H 3.78, N 3.50; Found: C 63.30, H 3.93, N 3.27.

2-(4-Chlorophenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4c). The title compound was obtained as white crystals, yield 79.9%, mp 269–271 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.25 (s, 3H, SO_2CH_3), 7.20–7.94 (m, 11H, Ar–H), 12.05 (s, 1H, N–H). Anal. calcd for: $C_{21}H_{15}NO_2SCl_2$: C 60.58, H 3.63, N 3.36; Found: C 60.58, H 3.68, N 3.07.

2-(4-Methylphenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4d). The title compound was obtained as white crystals, yield 69.2%, mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.32 (s, 3H, CH_3), 3.24 (s, 3H, SO_2CH_3), 7.16–7.92 (m, 11H, Ar–H), 11.92 (s, 1H, N–H). Anal. calcd for: $C_{22}H_{18}NO_2SCl$: C 66.74, H 4.58, N 3.54; Found: C 66.81, H 4.58, N 3.54.

2-(4-Methoxyphenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4e). The title compound was obtained as white crystals, yield 66.6%, mp 246–248 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.23 (s, 3H, SO_2CH_3), 3.74 (s, 3H, CH_3), 6.97–7.92 (m, 11H, Ar–H), 11.87 (s, 1H, N–H). Anal. calcd for: $C_{22}H_{18}NO_3SCl$: C 64.15, H 4.40, N 3.40; Found: C 63.93, H 4.40, N 3.13.

2-(2-Acetyloxyphenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4f). The title compound was obtained as white crystals, yield 67.0%, mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO) δ 1.85 (s, 3H, CH_3), 3.20 (s, 3H, SO_2CH_3), 7.19–7.86 (m, 11H, Ar–H), 11.93 (s, 1H, N–H). Anal. calcd for: $C_{23}H_{18}NO_4SCl$: C 62.80, H 4.12, N 3.18; Found: C 62.56, H 4.31, N 2.82.

2-(4-Acetyloxyphenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4g). The title compound was obtained as white crystals, yield 70.0%, mp 248–250 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.28 (s, 3H, CH_3), 3.26 (s, 3H, SO_2CH_3), 7.19–7.95(m, 11H, Ar–H), 12.02 (s, 1H, N–H). Anal. calcd for: $C_{23}H_{18}NO_4SCl$: C 62.80, H 4.12, N 3.18; Found: C 62.83, H 4.08, N 2.96.

2-(4-Methylsulfonylphenyl)-3-(4-methylsulfonylphenyl)-5-chloro-indole (4h). The title compound was obtained as white crystals, yield 46.8%, mp 173–175 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.25 (s, 3H, SO_2CH_3), 3.27 (s, 3H, SO_2CH_3), 7.23–7.96 (m, 11H, Ar–H), 12.16 (s, 1H, N–H). Anal. calcd for: $C_{22}H_{18}NO_4S_2Cl$: C 57.45, H 3.94, N 3.05; Found: C 57.74, H 4.30, N 3.10.

2-(4-Methylsulfonylphenyl)-3-(4-methylsulfonylphenyl)-5-methyl-indole (4i). The title compound was obtained as light yellow crystals, yield 43.5%, mp 299–301 °C; ^{1}H NMR (300 MHz, DMSO) δ 2.37 (s, 3H, CH_3), 3.25 (s, 3H, SO_2CH_3), 3.26 (s, 3H, SO_2CH_3), 7.05–7.96 (m, 11H, Ar–H), 11.83 (s, 1H, N–H). Anal. calcd for: $C_{23}H_{21}NO_4S_2$: C 62.85, H 4.82, N 3.19; Found: C 62.88, H 4.98, N 2.83.

Method B

2-phenyl-3-(4-methylsulfonylphenyl)-indole (8a). Step 1: 4-methylsulfonylphenylacetonphenone (6a). A mixture of 5.0 g (0.023 mol) of 4-methylsulfonylphenyl-acetic acid and 10 mL of thionyl chloride was heated under reflux to give a clear solution. Removal of the excess of thionyl chloride under reduced pressure to give a light yellow solid and without purification put into the next reaction. To the solution of the solid obtained above in 30 mL of dry benzene was added in portions 4.7 g (0.035 mol) of anhydrous aluminum chloride at 20–25 °C. When addition was complete, the mixture was heated to reflux for 2 h, then cooled and poured into a mixture of ice and 10 mL of 1 N hydrochloric acid. The benzene was removed in vacuo and the crude product was collected by filtration and washed with sodium carbonate and water. The filter cake was sucked to dryness and recrystallized from 95% ethanol to give 3.9 g of the title compound as light yellow crystals, yield 60.9%, mp 190–192 °C. Anal. calcd for: $C_{15}H_{14}O_3S$: C 65.67, H 5.14; Found: C 65.56, H 5.03.

Step 2: 2-phenyl-3-(4-methylsulfonylphenyl)-indole (8a). A mixture of 0.9 g (3.3 mmol) of 4-methylsulfonylphenyl-acetophenone **6a** and 0.5 g (3.3 mmol) of phenylhydrazine hydrochloride was heated at 130 °C for 0.5 h to

give the arylhydrazone **7a** and without purification put into the next reaction. To the solution of **7a** in 20 mL of acetic acid was added 0.2 g of $BF_3{\cdot}Et_2O$ and heated to reflux for 1 h. Acetic acid was removed in vacuo and the resulting residue was suspended in water, filtered and purified by column chromatography using petroleum ether/ethyl acetate 3:1 as eluant, 0.45 g of the title compound was obtained as white crystals, yield, 39.5%, mp 239–241 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.24 (s, 3H, SO_2CH_3), 7.05–7.90 (m, 13H, Ar–H), 11.77 (s, 1H, N–H). Anal. calcd for: $C_{21}H_{17}NO_2S$: C 72.60, H 4.93, N 4.03; Found: C 72.35, H 5.03, N 4.25.

2-Phenyl-3-(4-aminosulfonylphenyl)-indole (8b). The procedure is according to the general procedure described in method B. The title compound was obtained as light yellow needle crystals, yield 29.5%, mp 223–225 °C. ^{1}H NMR (300 MHz, DMSO) δ 3.32 (s, 2H, SO_2NH_2), 7.04–7.82 (m, 13H, Ar–H), 11.71 (s, 1H, N–H). Anal. calcd for: $C_{20}H_{16}N_2O_2S$: C 68.94, H 4.63, N 8.04; Found: C 68.95, H 4.71, N 7.78.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (No. 20072057). We thank the analytical division of Institute of Material Medica for the spectroscopic data and elementary analyses.

References and Notes

1. Vane, J. R. *Nature* **1971**, *231*, 232.
2. Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. *N. Engl. J. Med.* **1992**, *327*, 749.
3. O'Banion, M. K.; Sadowski, H. B.; Winn, V.; Young, D. A. *J. Biol. Chem.* **1991**, *266*, 23261.
4. Kujubu, D. A.; Herschmann, H. R. *J. Biol. Chem.* **1992**, *267*, 7991.
5. De Brum-Fernandez, A. J. *J. Rheumatol.* **1997**, *24*, 246.
6. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
7. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
8. Nicoll Griffith, D. A.; Yergey, J. A.; Trimble, L. A.; Silva, J. M.; Li, C.; Chauret, N.; Gauthier, J. Y.; Grimm, E.; Leger, S.; Roy, P.; Therien, M.; Wang, Z. Y.; Prasit, P.; Zamboni, R.; Young, R. N.; Brideau, C.; Chan, C.-C.; Mancini, J.; Riendeau, D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2683.
9. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
10. Friesen, R. W.; Dubé, D.; Fortin, R.; Frenette, R.; Prescott, S.; Cromlish, W.; Greig, G. M.; Kargman, S.; Wong, E.; Chan, C. C.; Gordon, R.; Xu, L.; Riendeau, D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2677.
11. Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhart, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1994**, *37*, 3878.
12. Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H. C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y.; Reitz, D. B. *J. Med. Chem.* **1995**, *38*, 4570.
13. Black, W. C.; Brideau, C.; Chan, C. C.; Charleson, S.; Chauret, N.; Claveau, D.; Ethier, D.; Gordon, R.; Greig, G.; Guay, J.; Hughes, G.; Jolicoeur, P.; Leblanc, Y.; Nicoll-Griffith, D.; Ouimet, N.; Riendeau, D.; Visco, D.; Wang, Z.; Xu, L.; Prasit, P. *J. Med. Chem.* **1999**, *42*, 1274.
14. Huang, H. C.; Li, J. J.; Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; Manning, R. E.; Seibert, K.; Koboldt, C. M.; Gregory, S. A.; Anderson, G. D.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E.; Burton, E. G.; Cogburn, J. N.; Isakson, P. C.; Reitz, D. B. *J. Med. Chem.* **1996**, *39*, 253.
15. Palomer, A.; Cabre, F.; Pascual, J.; Campos, J.; Trujillo, M. A.; Entrena, A.; Gallo, M. A.; Garcia, L.; Mauleon, D.; Espinosa, A. *J. Med. Chem.* **2002**, *45*, 1402.
16. Leblanc, Y.; Gauthier, J. Y.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2123.
17. Gauthier, J. Y.; Leblanc, Y.; Black, W. C.; Chan, C. C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, P. K.; Leger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87.
18. Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619.
19. Leblanc, Y.; Roy, P.; Boyce, S.; Brideau, C.; Chan, C. C.; Charleson, S.; Gordon, R.; Grimm, E.; Guay, J.; Leger, S.; Li, C. S.; Riendeau, D.; Visco, D.; Wang, Z.; Webb, J.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2207.
20. Lau, C. K.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Kargman, S.; Li, C. S.; Prasit, P.; Riendeau, D.; Therien, M.; Visco, D.; Xu, L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3187.
21. Shin, S. S.; Noh, M. S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J. Y.; Kim, J. K.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165.
22. Bai, A. P.; Guo, Z. R.; Hu, W. H.; Shen, F.; Cheng, G. F. *Chin. Chem. Lett.* **2001**, *12* (9), 775.
23. Khanna, I. K.; Weier, R. M.; Yu, Y.; Xu, X. D.; Koszyk, F. J.; Collins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Perkins, W. E.; Casler, J. J.; Masferrer, J. L.; Zhang, Y. Y.; Gregory, S. A.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1634.
24. Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X.; Koszyk, F. J.; Collins, P. W.; Cogburn, J. N.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Yuan, J.; Yang, D. C.; Zhang, Y. Y. *J. Med. Chem.* **2000**, *43*, 3168.
25. Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. *J. Med. Chem.* **2002**, *45*, 1511.
26. Puig, C.; Crespo, M. I.; Godessart, N.; Feixas, J.; Ibarzo, J.; Jimenez, J.-M.; Soca, L.; Cardelus, I.; Heredia, A.; Miralpeix, M.; Puig, J.; Beleta, J.; Huerta, J. M.; Lopez, M.; Segarra, V.; Ryder, H.; Palacios, J. M. *J. Med. Chem.* **2000**, *43*, 214.
27. Li, J. J.; Norton, M. B.; Reinhard, E. J.; Anderson, G. D.; Gregory, S. A.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Zhang, Y.; Zweifel, B. S.; Reitz, D. B. *J. Med. Chem.* **1996**, *39*, 1846.
28. Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschenes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.;

Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777.
29. Dubé, D.; Brideau, C.; Deschênes, D.; Fortin, R.; Friesen, R. W.; Gordon, R.; Girard, Y.; Riendeau, D.; Savoie, C.; Chan, C. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1715.
30. Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350.
31. Michel, T.; Brideau, C.; Chan, C. C.; Cromlish, W. A.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Kargman, S.; Lau, C. K.; Leblanc, Y.; Li, C. S.; Oneill, G. P.; Riendeau, D.; Roy, P.; Wang, Z.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 47.
32. Roy, P.; Leblanc, Y.; Ball, R. G.; Brideau, C.; Chan, C. C.; Chauret, N.; Cromlish, W.; Ethier, D.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Guay, J.; Kargman, S.; Lau, C. K.; Oneill, G. P.; Silva, J.; Therien, M.; van Staden, M.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 57.
33. Laval, X.; Delarge, J.; Somers, F.; Tullio, P.; Henrotin, Y.; Pirotte, B.; Dogne, J. M. *Curr. Med. Chem.* **2000**, *7*, 1041.
34. Dannhardt, G.; Kiefe, W. *Eur. J. Med. Chem.* **2001**, *36*, 109.
35. Futaki, N.; Takahashi, S.; Yokoyama, I.; Arai, I.; Higuchi, S.; Otomo, S. *Prostaglandins* **1994**, *47*, 55.
36. Li, C. S.; Black, W. C.; Chan, C. C.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C. K.; Mancini, J.; Ouimet, N.; Roy, P.; Vickers, P.; Wong, E.; Young, R. N.; Zamboni, R.; Prasit, P. *J. Med. Chem.* **1995**, *38*, 4897.
37. Ouimet, N.; Chan, C. C.; Charleson, S.; Claveau, D.; Gordon, R.; Guay, D.; Li, C. S.; Ouellet, M.; Percival, D.; Riendeau, D.; Wong, E.; Zamboni, R.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 151.
38. Kalgutkar, A. S.; Crews, B. C.; Rowlinson, S. W.; Garner, C.; Seibert, K.; Lawrence, J.; Marnett, L. J. *Science* **1998**, *280*, 1268.
39. Kalgutkar, A. S.; Marnett, A. B.; Crews, B. C.; Remmel, R. P.; Marnett, L. J. *J. Med. Chem.* **2000**, *43*, 2860.
40. Black, W. C.; Bayly, C.; Belley, M.; Chan, C. C.; Charleson, S.; Denis, D.; Gauthier, J. Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C. K.; Leblanc, Y.; Mancini, J.; Ouellet, M.; Percival, D.; Roy, P.; Skorey, K.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 725.
41. Bayly, C. I.; Black, W. C.; Leger, S.; Ouimet, N.; Ouellet, M.; Percival, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 307.
42. Hu, W. H.; Guo, Z. R.; Chu, F. M.; Bai, A. P.; Yi, X.; Cheng, G. F.; Li, J. *Bioorg. Med. Chem.* **2003**, *11*, 1153.
43. Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
44. Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.
45. Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991.
46. Hu, Y. F.; Cheng, G. F. *Acta Pharmaceutica Sinica* **2000**, *35*, 343.