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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis and anti-inflammatory evaluation of some pyrazolo[3,4-*b*]pyridines

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**Abstract** Novel series of pyrazolo[3,4-*b*]pyridines with basic skeleton different from the known COX inhibitors were synthesized from 5-amino-1-[4-(aminosulfonyl)phenyl]-3-phenyl-1*H*-pyrazole, which in turn was prepared by the condensation of (4-sulfamoylphenyl)hydrazine with α-cyanoacetophenone. All the newly synthesized compounds were tested for their in vivo anti-inflammatory activity by carrageenan-induced rat paw edema assay. Some of the most potent compounds were evaluated in different COX and LOX assays. Some of the new compounds were found to possess moderate anti-inflammatory activity.

**Keywords** COX · 5-LOX · Anti-inflammatory drug · Pyrazolopyridine · Fused pyrazole derivatives

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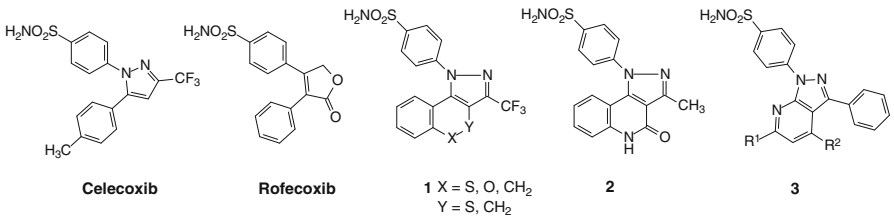
## Introduction

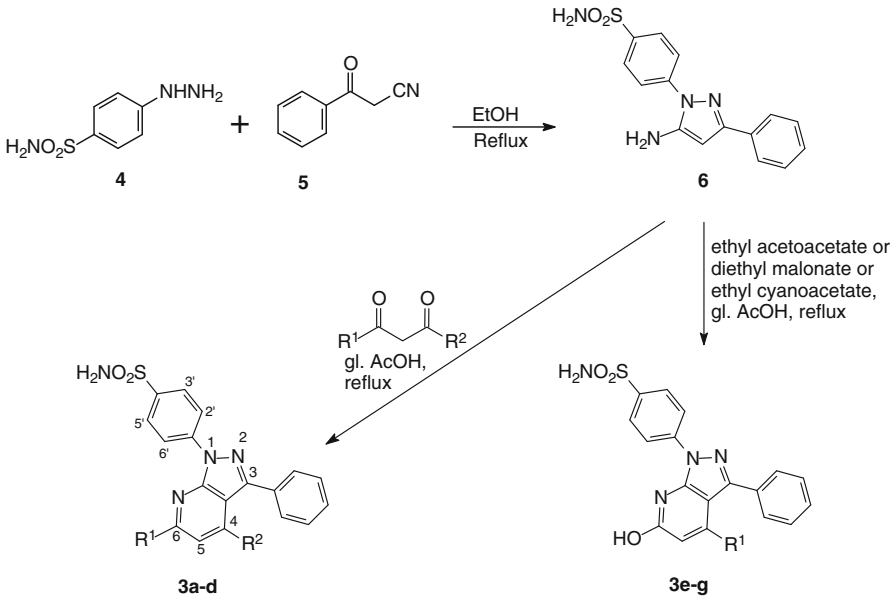
Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin, or ibuprofen are widely used in the treatment of acute or chronic inflammation and offer symptomatic pain relief (Reitz and Isakson, 1995; Lombardino, 1985). Conventional NSAIDs exert nonselective inhibition (Dannhardt and Kiefer, 2001) of cyclooxygenase (COX) enzymes, which catalyzes the rate-limiting step in the formation of prostanoids from arachidonic acid (Smith and Langenbach, 2001; Dennis, 2000; Marnett *et al.*, 1999; Jakobsson *et al.*, 1999; Tanioka *et al.*, 2000). Two isoforms of the COX enzyme (known as COX-1 and COX-2) have been identified (Xie *et al.*, 1991; Kujubu *et al.*, 1991). COX-1 is constitutively present in platelets and all tissues and produces prostaglandins (PGs) which exert cytoprotective effect in the gastrointestinal tract and control renal function in the kidneys (Ormrod *et al.*, 2002). Differently, COX-2 is activated by pro-inflammatory stimuli and facilitates the release of prostaglandins involved in inflammatory process (Kanapure and Letts, 2004). The development of multibillion dollar drugs, celecoxib (Penning *et al.*, 1997), and rofecoxib (Prasit *et al.*, 1999) (Chart 1) enthused the medicinal chemists all over the world to search for new structurally different anti-inflammatory drugs. A perusal of literature reveals that the synthesis of fused pyrazole derivatives containing the well-established pharmacophore, (4-aminosulfonyl)phenyl group, for evaluation as anti-inflammatory drug is still in its infancy. The limited studies performed indicate that fusion of pyrazole ring to other heterocycles such as in compounds **1** (Bertenshaw *et al.*, 1996; Seibert *et al.*, 1994) and **2** (Baruah *et al.*, 2004) (Chart 1) is well tolerated in terms of both in vitro and in vivo activities.

Appreciation of these findings coupled with our ongoing efforts toward the development of novel anti-inflammatory

**Chart 1** Motivation for the synthesis of pyrazolopyridines **3**




**Scheme 1** General synthetic pathways for the preparation of pyrazolo[3,4-*b*]pyridines




agents (Sharma and Sawhney, 1997; Sawhney and Sharma, 1993; Sawhney *et al.*, 1991, 1992, 1993), we thought it of interest to synthesize some fused pyrazolo[3,4-*b*]pyridines (**3**) (Chart 1) containing the well-established pharmacophore, (4-aminosulfony)phenyl, with a view to examine the effect of fusing the pyrazole ring to a pyridine ring. In this article, we report the synthesis and anti-inflammatory (AI) evaluation of a new series of pyrazolo[3,4-*b*]pyridines (**3**). Selected compounds showing good AI activity were also tested in different COX and LOX assays.

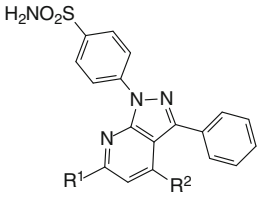
## Chemistry

Synthesis of various 4-(3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)benzenesulfonamides (**3**) is summarized in Scheme 1. The starting compound 3-oxo-3-phenylpropanenitrile (**5**) was readily prepared by the reaction of 2-bromo-1-phenyl-1-ethanone with potassium cyanide in aqueous ethanol at 50°C following literature procedure (Gakhar *et al.*, 1971). 4-Hydrazinobenzenesulfonamide (**4**) was prepared via diazotization of sulfanilamide followed by reduction of the corresponding diazonium salt with stannous chloride (Soliman, 1979). Reaction of **4** with **5** in refluxing ethanol gave 4-(5-amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**6**) following literature procedures (Vincenzo and Salvators, 1972; Singh *et al.*, 1979). The reaction of 5-aminopyrazoles with unsymmetrical 1,3-diketones has been a subject matter of intense investigation in the past. However, it has been unambiguously established that the reaction of 5-aminopyrazoles with (i) fluorinated $\beta$-diketones is initiated exclusively by the attack of the amino group on the carbonyl carbon adjoining the $CF_3$ group (Singh *et al.*, 2004) and (ii) $\beta$-ketoesters is initiated exclusively by the attack of the amino group on the ester carbonyl carbon (Tabak *et al.*, 1964). Thus, simple coupling of **6** with various 1,3-diketones, ethyl acetoacetate, diethyl malonate, or ethyl cyanoacetate in refluxing acetic acid afforded the desired pyrazolo[3,4-*b*]pyridines (**3a**–**g**) in moderate yields. The structures of all the new pyrazolopyridines **3a**–**g** were confirmed by their spectral data (IR, $^1$H NMR, and MS) and elemental analysis.

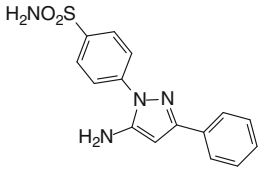
## Pharmacological results and discussion

The compounds synthesized were tested in vivo to evaluate their anti-inflammatory activity by the classic carrageenan-induced rat paw edema model at 20 mg kg$^{-1}$ by oral route (Table 1). Only two compounds, **3g** and **3e** showed appreciable anti-inflammatory activity of 70% inhibition

**Table 1** Anti-inflammatory activity and in vitro inhibitory potencies of compounds **3** and **6**




**3**




**6**

| Compounds | $R^1$ | $R^2$ | Inhibition paw edema (%) | | % Inhibition of COX-1 (10 μM)[a] | % Inhibition of COX-2 (10 μM)[b] | % Inhibition of 5-LOX (10 μM)[c] |
|---|---|---|---|---|---|---|---|
| | | | 0.5 h | 2.0 h | | | |
| **3a** | $CF_3$ | $CF_3$ | 28 | 55 | 0 | 0 | 0 |
| **3b** | $CF_3$ | Ph | 78 | 40 | NT | NT | NT |
| **3c** | $CF_3$ |  | 51 | 54 | 0 | 0 | 0 |
| **3d** | $CH_3$ | $CH_3$ | 51 | 35 | NT | NT | NT |
| **3e** | OH | $NH_2$ | 75 | 60 | 44 | 0 | 0 |
| **3f** | OH | OH | 25 | 30 | NT | NT | NT |
| **3 g** | OH | $CH_3$ | 30 | 70 | 0 | 0 | 0 |
| **6** | – | – | 48 | 44 | NT | NT | NT |
| Diclofenac sodium | – | – | 100 | 95 | 0.003 ($IC_{50}$ (μM)) | 42% (0.01 μM) | 16% |

[a,c] Dannhardt and Lehr (1992)

[b] Patrignani *et al.* (1996)

*NT* not tested

and 60% inhibition, respectively. Four compounds (**3a**, **3c**, **3e**, and **3g**) showing good level of AI activity were further evaluated for their inhibitory potency against COX-1/2 and 5-lipoxygenase (5-LOX) in an intact cell assay as described earlier (Dannhardt *et al.*, 1998). None of the compounds showed any significant inhibition of COX-1, COX-2, or 5-LOX. However, compound **3e** was found to be a weak inhibitor of COX-1 (44% inhibition) at 10-μmol concentration.

In conclusion, novel pyrazolo[3,4-*b*]pyridines were synthesized and screened for in vivo anti-inflammatory activity. Even though few compounds have shown good in vivo activity, this was not translated into in vitro activity. Investigations to explain these phenomena are ongoing.

## Experimental section

### Chemical synthesis

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument. $^1$H NMR spectra were recorded on a Bruker 300-MHz instrument. High-resolution mass spectra were measured in EI mode on a Kratos MS-50 spectrometer. All the newly synthesized compounds (**3a–g**, **6**) were subjected to microanalysis and gave satisfactory analytical results (within ±0.4% of the calculated values).

4-Hydrazinobenzenesulfonamide (**4**) (Soliman, 1979) and 3-oxo-3-phenylpropanenitrile (**5**) (Gakhar *et al.*, 1971) were synthesized according to known literature methods.

### *4-(5-Amino-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (**6**)*

α-Cyanoacetophenone (**5**, 1.45 g, 0.01 mol) was dissolved in 40-ml ethanol and 4-hydrazinobenzenesulfonamide (**4**, 1.87 g, 0.01 mol) was added. The reaction mixture was refluxed for 2 h. The contents were cooled and the crystalline solid which separated out was filtered, washed with cold ethanol, and crystallized from aqueous ethanol to give **6** (1.75 g, 56%). m.p. 136–138°C. IR $cm^{-1}$ 3378, 3279 $NH_2$ str., 1326, 1162 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$)

$\delta$ 5.99 (s, 1H, $C_4$–H), 6.93 (bs, 2H, $C_5$–$NH_2$), 7.30–7.41 (m, 3H, $C_{3''}$–H, $C_{4''}$–H, $C_{5''}$–H), 7.80 (d, 2H, $C_{2''}$–H, $C_{6''}$–H, $J = 6.9$ Hz), 7.88 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.6$ Hz), 8.03 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.6$ Hz); MS: $M^+$, *m/z* 314.

*4-[3-Phenyl-4,6-bis(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**3a**)*

A solution of 4-(5-amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**6**, 3.14 g, 0.01 mol) and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (1.41 ml, 0.01 mol) in glacial acetic acid (20 ml) was refluxed for 6 h. Excess of solvents was removed and the contents were cooled. The solid which separated out was filtered, washed with cold ethanol, and crystallized from ethanol to give **3a**. Yield 55%, m.p. 195–196°C. IR $cm^{-1}$ 3355, 3272 $NH_2$ str., 1325, 1142 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 4.87 (bs, 2H, $SO_2NH_2$), 7.52–7.60 (m, 5H, Ph–H), 7.92 (s, 1H, $C_5$–H), 8.14 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.8$ Hz), 8.63 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.8$ Hz); MS: $M^+$, *m/z* 486.0574 ($C_{20}H_{12}F_6N_4O_2S$ requires: 486.0585).

*4-[3,4-Diphenyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**3b**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**6**) and 4,4,4-trifluoro-1-phenylbutane-1,3-dione. Yield 53%, m.p. 200–201°C. IR $cm^{-1}$ 3335, 3240 $NH_2$ str., 1361, 1161 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 4.94 (bs, 2H, $SO_2NH_2$), 7.49–7.62 (m, 8H, Ph–H), 8.01 (s, 1H, $C_5$–H), 8.13 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.8$ Hz), 8.16–8.19 (m, 2H, Ph–H), 8.72 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.8$ Hz); MS: $M^+$, *m/z* 494.

*4-[3-Phenyl-4-(2-thienyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**3c**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (**6**) and 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione. Yield 50%, m.p. 180–181°C. IR $cm^{-1}$ 3374, 3268 $NH_2$ str., 1368, 1152 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 6.80 (bs, 2H, $SO_2NH_2$), 7.23 (dd, 1H, Th–4H, $J = 5.0$, 3.7 Hz), 7.48–7.61 (m, 6H, Ph–H, Th–5H), 7.87 (d, 1H, Th–3H, $J = 3.7$ Hz), 7.91 (s, 1H, $C_5$–H), 8.12 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.8$ Hz), 8.63 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.8$ Hz); MS: $M^+$, *m/z* 500.0589 ($C_{23}H_{15}F_3N_4O_2S_2$ requires: 500.0588).

*4-(4,6-Dimethyl-3-phenyl-1H-pyrazolo[3,4-b]pyridin-1-yl)benzenesulfonamide (**3d**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (**6**) and pentane-2,4-dione. Yield 53%, m.p. 220–221°C. IR $cm^{-1}$ 3366, 3260 $NH_2$ str., 1336, 1158 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 2.40 (s, 3H, $C_4$–$CH_3$), 2.69 (s, 3H, $C_6$–$CH_3$), 6.74 (bs, 2H, $SO_2NH_2$), 6.94 (s, 1H, $C_5$–H), 7.49–7.67 (m, 5H, Ph–H), 8.04 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.8$ Hz), 8.66 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.8$ Hz); MS: $M^+$, *m/z* 378.

*4-(4-Amino-6-hydroxy-3-phenyl-1H-pyrazolo[3,4-b]pyridin-1-yl)benzenesulfonamide (**3e**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (**6**) and ethyl cyanoacetate. Yield 58%, m.p. 231–232°C. IR $cm^{-1}$ 3367, 3306, 3242 OH and $NH_2$ str., 1706 C=O str., 1346, 1161 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 6.84 (bs, 5H, $C_5$–H, $SO_2NH_2$, $NH_2$), 7.32–7.43 (m, 3H, Ph–H), 7.77 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.0$ Hz), 7.84 (d, 2H, Ph–H, $J = 7.8$ Hz), 8.04 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.0$ Hz), 9.78 (s, 1H, OH); MS: $M^+$, *m/z* 381.

*4-(4,6-Dihydroxy-3-phenyl- 1H-pyrazolo[3,4-b]pyridin-1-yl)benzenesulfonamide (**3f**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**6**) and diethyl malonate. Yield 41%, m.p. 224–225°C. IR $cm^{-1}$ 3363, 3305, 3241 OH and $NH_2$ str., 1706 C=O str., 1345, 1161 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 6.80 (bs, 2H, $SO_2NH_2$), 6.87 (s, 1H, $C_5$–H), 7.32–7.43 (m, 3H, Ph–H), 7.59 (bs, 1H, $C_4$–OH), 7.78 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.5$ Hz), 7.85 (d, 2H, Ph–H, $J = 7.9$ Hz), 8.05 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.5$ Hz), 9.72 (s, 1H, $C_6$–OH); MS: $M^+$, *m/z* 382.0744 ($C_{18}H_{14}N_4O_4S$ requires: 382.0735).

*4-(6-Hydroxy-4-methyl-3-phenyl-1H-pyrazolo[3,4-b]pyridin-1-yl)benzenesulfonamide (**3g**)*

Synthesized from 4-(5-amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**6**) and ethyl acetoacetate. Yield 42%, m.p. 222–223°C. IR $cm^{-1}$ 3365, 3305, 3245 OH and $NH_2$ str., 1706 C=O str., 1346, 1161 $SO_2$ str.; $^1$H NMR (DMSO-$d_6$/$CDCl_3$) $\delta$ 2.13 (s, 3H, $C_4$-$CH_3$), 6.84 (s, 1H, $C_5$–H), 7.08 (bs, 2H, $SO_2NH_2$), 7.32–7.43 (m, 3H, Ph–H), 7.78 (d, 2H, $C_{2'}$–H, $C_{6'}$–H, $J = 8.5$ Hz), 7.83 (d, 2H, Ph–H, $J = 7.4$ Hz), 8.03 (d, 2H, $C_{3'}$–H, $C_{5'}$–H, $J = 8.5$ Hz), 9.92 (s, 1H, $C_6$–OH); MS: $M^+$, *m/z* 380.0945 ($C_{19}H_{16}N_4O_3S$ requires: 380.0943).

## Pharmacology

COX-1, COX-2, and 5-LOX assays

Selected compounds were tested in intact cell assays and whole blood assays as described earlier (Dannhardt and Lehr, 1992; Patrignani *et al.*, 1996).

Carrageenan-induced rat paw edema assay

Male/female Wistrar rats (120–140 g) were fasted with free access to water for 16 h prior to experiments. The rats were dosed orally with a 1-ml suspension of test compound in vehicle (0.5% carboxy methylcellulose). One group of six rats was kept as a control and was administered vehicle alone. Half an hour later edema was induced in rats by intradermal injection of 0.1 ml of a 1% solution of carrageenan in 0.5% carboxy methylcellulose into the plantar surface of the right hind paw (Winter *et al.*, 1962). The paw volume was measured before as well as 30 min and 2 h after carrageenan injection using plethysmometer. The mean increase in the paw volume in each group was calculated according to the formula:

$$\% \text{ Inhibition} = \left(1 - \frac{V_t}{V_c}\right) \times 100$$

where $V_c$ is the mean edema volume in control group and $V_t$ is the mean edema volume in group treated with test compounds.

Diclofenac sodium was used as standard drug for comparison.

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## References

Baruah B, Dasu K, Vaitilingam B, Vanguri A, Casturi SR, Yeleswarapu KR (2004) 1,2-diaryl-1-ethanone and pyraolo [4,3-c] quinoline-4-one as novel selective cyclooxygenase-inhibitors. Biorog Med Chem Lett 14:445–448

Bertenshaw SR, Talley JJ, Rogier DJ, Graneto MJ, Koboldt CM, Zhang Y (1996) Conformationally restricted 1,5-diarylpyrazoles are selective COX-2 inhibitors. Bioorg Med Chem Lett 6: 2827–2830

Dannhardt G, Kiefer W (2001) Cyclooxygenase inhibitors—current status and future prospects. Eur J Med Chem 36:109–115

Dannhardt G, Lehr M (1992) In Vitro evaluation of 5-lipoxygenase and cyclo-oxygenase inhibitors using bovine neutrophils and platelets and HPLC. J Pharm Pharmacol 44:419–424

Dannhardt G, Flemmer L, Hartmann RW, Kleber A, Schulze E (1998) Spectrofluorimetric quantification of malondialdehyde for evaluation of cyclooxygenase-1/thromboxane synthase inhibition. Arch Pharm Pharm Med Chem 331:359–364

Dennis EA (2000) Phospholipase $A_2$ in eicosanoid and glutathione metabolism (MAPEG). A widespread protein superfamily. Am J Respir Crit Care Med 161:S32–S35

Gakhar HK, Gill GS, Muthani JS (1971) Thiopegan derivatives. J Indian Chem Soc 48:953

Jakobsson PJ, Thoren S, Morgenstren R, Samuelsson B (1999) Identification of human prostaglandin E synthase: a microsomal glutathione-dependent, inducible enzymes, constituting a potential novel drug target. Proc Natl Acad Sci USA 96: 7220–7225

Kanapure SP, Letts LG (2004) The eicosanoids. Wiley, London, pp 131–162

Kujubu DA, Fletcher BS, Varnum BC, Lim RW, Herschman HR (1991) TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. J Biol Chem 266:12866–12872

Lombardino G (1985) Non steroidal antiinflammatory drugs. Wiley, New York

Marnett LJ, Rowlinson SW, Goodwin DC, Kalgutkar AS, Lanzo CA (1999) Arachidonic acid oxygenation by COX-1 and COX-2 mechanism of catalysis and inhibition. J Biol Chem 274:22903–22906

Ormrod D, Wellington K, Wagstaff AJ (2002) Valdecoxib. Drugs 62:2059

Patrignani P, Panara MR, Santini G, Sciulli MG, Padovano R, Cipollone F (1996) Differential inhibition of the cyclooxygenase activity of prostaglandin endoperoxidase synthase isozymes in vitro and *ex vivo* in man. Prostagland Leukot Essent Fatty Acids 55:115–119

Penning TD, Talley JJ, Bertneshaw SR, Carten JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (SC-58635, Celecoxib). J Med Chem 40:1347–1365

Prasit P, Wang Z, Brideau C, Chan CC, Charleson S, Cromlish W, Ethier D, Evans JF, Ford-Hutchinson AW, Gauthier JY, Gordon R, Guay J, Kargman S, Gresser M, Kennedy B, Leblanc Y, Leger S, Mancini J, O'Neill GP, Ouellet M, Percival MD, Perrier H, Riendeau D, Rogger I, Tagari P, Therien M, Vickers P, Wong E, Xu LJ, Young RN, Zamboni R, Boyce S, Rupniak N, Forrest M, Visco D, Patrick D (1999) The discovery of rofecoxib, [MK 966, 4-(4′-methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone], an orally active cyclooxygenase-2 inhibitor. Bioorg Med Chem Lett 9:1773

Reitz DB, Isakson PC (1995) Cyclooxygenase-2 inhibitors. Curr Pharm Des 1:211–220

Sawhney SN, Sharma PK (1993) Synthesis and anti-inflammatory activity of some 3-heterocycle-1,2-benzisothiazoles. Bioorg Med Chem Lett 3:1551–1554

Sawhney SN, Gupta A, Sharma PK (1991) Thiazole derivatives: part V-synthesis of some 2-(2-methylthiazol-4-yl)-3-mercapto-1,2,4-triazoles as potential anti-inflammatory agents. Indian J Chem 1:8–15

Sawhney SN, Sharma PK, Gupta A, Singh GB, Bani S (1992) Synthesis and anti-inflammatory activity of some 3-heterocyclyl-1,2-benzisothiazoles. Indian J Chem 31B:421–429

Sawhney SN, Sharma PK, Gupta A, Singh GB, Bani S (1993) Synthesis and anti-inflammatory activity of some 3-heterocyclyl-1,2-benzisothiazoles. Indian J Chem 32B:1190–1195

Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, Lee L, Isakson P (1994) Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci USA 91:12013

Sharma PK, Sawhney SN (1997) Potent anti-inflammatory 3-thiazole-4(5)-acetic acids of benzisothiazole. Bioorg Med Chem Lett 7:2427–2430

Singh SP, Sawhney SN, Tomar RK, Prakash O (1979) Mass spectra of some 2-(3′-Aryl-5′-aminopyrazol-1′-yl)benzothiazoles. Indian J Chem 17B:372–374

Singh SP, Naithani R, Aggarwal R, Prakash O (2004) Synthesis of some novel fluorinated pyrazolo[3,4-b]pyridines. Synth Commun 34:4359–4367

Smith WL, Langenbach RJ (2001) Why there are two cyclooxygenase isozymes. Clin Invest 12:1491–1495

Soliman R (1979) Preparation and antidiabetic activity of some sulfonylurea derivatives of 3,5-disubstituted pyrazoles. J Med Chem 22:321–325

Tabak SV, Grandberg A II, Kost AN (1964) Condensation of isomeric 1-phen-yl-x-aminopyrazoles with $\beta$-dicarbonyl compounds. J Gen Chem USSR 34:277

Tanioka T, Nakatani Y, Semmyo N, Murakami M, Kudo I (2000) Molecular identification of cytosolic prostaglandin $E_2$ synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin $E_2$ biosynthesis. J Biol Chem 275:32775–32782

Vincenzo S, Salvators P (1972) An unequivocal synthesis of 7-oxopyrazolo[1,5-a] pyrimidines. J Heterocycl Chem 9:951

Winter CA, Risley EA, Nuss GW (1962) Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Proc Soc Exp Biol Med 111:544

Xie WL, Chipman JG, Robertson DL, Errikson RL, Simmons DL (1991) Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci USA 88:2692–2696