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3,4-DIARYLPYRAZOLES: POTENT AND SELECTIVE INHIBITORS OF CYCLOOXYGENASE-2

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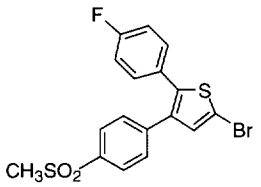
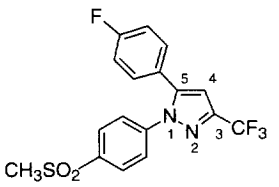
Abstract: A series of 3,4-diarylpyrazoles was synthesized and evaluated for their ability to selectively inhibit cyclooxygenase-2 (COX-2). A number of potent and selective inhibitors were identified and found to have oral anti-inflammatory activity in a rat carrageenan-induced foot pad edema assay. © 1997 Elsevier Science Ltd.

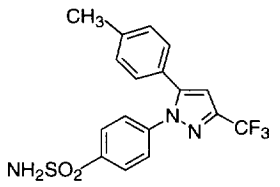
Nonsteroidal anti-inflammatory drugs (NSAIDs) block the formation of pro-inflammatory prostaglandins via inhibition of cyclooxygenase. It is the inhibition of this enzyme that accounts for the anti-inflammatory, analgesic and antipyretic effects of this class of drugs.[1] However, beneficial prostaglandin-regulated processes are also disrupted by chronic NSAID treatment, leading to potentially severe side-effects.[2] The recent discovery of a second, inducible form of cyclooxygenase (COX-2) that exists along with the constitutive form (COX-1) led to the hypothesis that selective inhibitors of COX-2 would be anti-inflammatory without causing the side effects associated with inhibition of COX-1. Recently, numerous selective inhibitors of COX-2 have been reported.



DuP 697



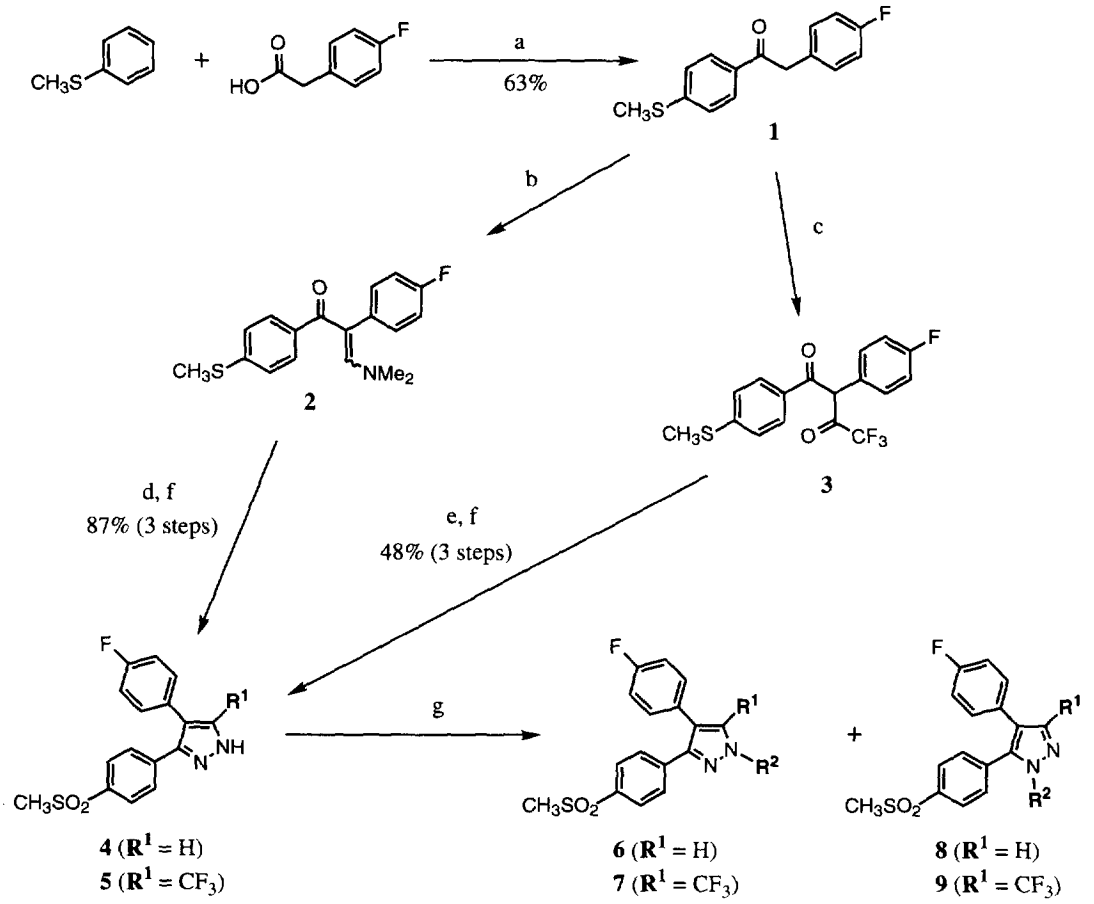
SC-58125



SC-58635
(celecoxib)

One major class of inhibitors is exemplified by DuP-697[3] and SC-581254 and encompasses a variety of methylsulfonyl- or sulfonamido-containing diarylheterocycles or carbocycles. We have recently reported our efforts in the 1,5-diarylpyrazole series of COX-2 inhibitors,[5] highlighted by the identification of SC-58635 (celecoxib), currently in Phase III clinical trials for rheumatoid and osteoarthritis. As part of our continuing efforts in this area, a series of 3,4-diarylpyrazoles was synthesized and evaluated for their ability to selectively inhibit COX-2. Several of these analogs not only selectively inhibited COX-2 in vitro, but also demonstrated potent oral anti-inflammatory efficacy in a rat carrageenan-induced foot pad edema model.

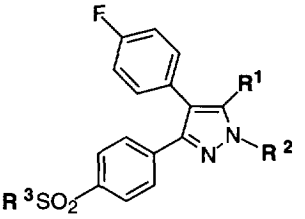
Scheme 1[a]



[a](a) PPA, 120 °C; (b) $Me_2NCH(OMe)_2$, DMF, 120 °C; (c) 1. LiHMDS, THF, -78 °C, 2. N-trifluoroacetylimidazole, -78 °C – 0 °C; (d) NH_2NH_2, MeOH/H_2O, reflux; (e) NH_2NH_2, AcOH, reflux; (f) Oxone®, MeOH, H_2O; (g) R^2X, K_2CO_3, DMF, 25 °C.

The 3,4-diarylpyrazole analogs were prepared as shown in Scheme 1. Friedel–Crafts acylation of thioanisole with 4-fluorophenylacetic acid in polyphosphoric acid (PPA), provided **1** in 63% yield. Condensation with DMF-dimethylacetal provided enaminoketone **2**, while acylation of the lithium enolate of **1** with N-trifluoroacetylimidazole gave diketone **3**. Treatment of **2** or **3** with hydrazine provided the respective pyrazole, which, upon Oxone® oxidation of the thioether, furnished pyrazole **4** or **5**. Alkylation with a variety of alkylating agents (X = Br or I) under K_2CO_3/DMF conditions, gave a mixture of two regioisomers, with the desired **6** or **7** as the major isomer. Purification either by recrystallization or chromatography provided pure **6** or **7** in yields ranging from 34 to 71%. Amide **7e** was synthesized from ester **7d** using standard Weinreb[6] conditions. Since sulfonamides have been a major emphasis of our previous pyrazole efforts,[5] a sulfonamide analog was also prepared. Sulfonamide **10** was synthesized from **7c** in 62% yield using the procedure recently described by Huang.[7]

Table 1. In Vitro COX-1 and COX-2 Enzyme Data.



compound	R^1	R^2	R^3	IC_{50} (μM)[a,b] COX-1	IC_{50} (μM)[a,b] COX-2
SC-58125				>100	0.10
4	H	H	CH_3	>100	>100
6a	H	$-CH_2CH{=}CH_2$	CH_3	>100	>100
6b	H	$-CH_2CH_2Ph$	CH_3	>100	0.53 ± 0.04
5	CF_3	H	CH_3	>100	>100
7a	CF_3	$-CH_2CH{=}CH_2$,	CH_3	>100	0.075 ± 0.035
7b	CF_3	$-CH_2CH_2Ph$	CH_3	>100	0.045 ± 0.03
7c	CF_3	$-CH_2CH_3$	CH_3	>100	0.13 ± 0.09
7d	CF_3	$-CH_2CO_2Et$	CH_3	>100	0.44 ± 0.19
7e	CF_3	$-CH_2CONHPh$	CH_3	>100	0.48 ± 0.28
10	CF_3	$-CH_2CH_3$	NH_2	1.36	0.033 ± 0.024

[a]Average of at least 3 determinations. [b]For assay conditions, see reference 8d.

The compounds were evaluated for their ability to inhibit recombinant human COX-1 and COX-2[8] and the data is shown in Table 1. The parent, unalkylated pyrazoles **4** and **5** had little COX-1 or COX-2 activity. Likewise, in all cases, regioisomers **8** and **9** had poor COX-1 and COX-2 activity (IC_{50} > 100 μM). In general, the CF_3-substituted analogs **7** were more potent COX-2 inhibitors than the trisubstituted analogs **6**, while neither series demonstrated any COX-1 inhibitory activity. For example, **7a** and **7b** were both very potent inhibitors of COX-2, while the analogous **6a** and **6b** were poor to moderate inhibitors of COX-2. Three of the CF_3- analogs, **7a**, **7b**, and **7c**, were all very potent inhibitors of COX-2, with potency greater than or equal to that of SC-58125. Analogs **7d** and **7e**, however, showed only moderate potency. From our previous experience with 1,5-diarylpyrazoles, we found that sulfonamide derivatives, although more potent inhibitors of both COX-1 and COX-2, exhibited an in vivo profile superior to the methylsulfonyl analogs. Although sulfonamide **10** was a 4-fold more potent inhibitor of COX-2 relative to the analogous sulfone **7c**, the COX-1 potency increased even more dramatically, resulting in a poor selectivity ratio for this compound.

Table 2. In Vivo Data for Selected Analogs.

compound	rat paw edema, % inhib.[a,b]
SC-58125	36% @ 10 mg/kg
7a	42% @ 10 mg/kg
7b	0% @ 10 mg/kg
7c	39% @ 10 mg/kg
7d	0% @ 30 mg/kg
10	15% @ 30 mg/kg

[a] 5 animals/group. [b] Maximum response is ~70%.

Some of the more potent COX-2 inhibitors in this series were tested in vivo in a rat carrageenan-induced foot pad edema assay[9] (Table 2). Two analogs, **7a** and **7c**, demonstrated good efficacy at a dose of 10 mg/kg (about equal to the potency of SC-58125). Surprisingly, the most potent COX-2 inhibitor of this series, **7b**, was not efficacious at this dose. Sulfonamide analog **10** also showed relatively poor efficacy at a dose of 30 mg/kg.

In summary, we have demonstrated that N-alkylated 3,4-diarylpyrazoles are potent and selective inhibitors of COX-2. In addition, several of these analogs were efficacious in a rat inflammation model. Further investigations into this series of selective COX-2 inhibitors are currently ongoing.

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