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CONFORMATIONALLY RESTRICTED 1,5-DIARYLPYRAZOLES ARE SELECTIVE COX-2 INHIBITORS

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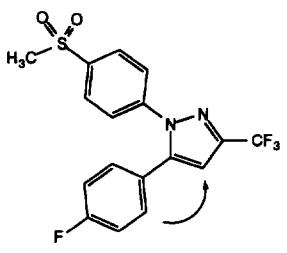
Abstract: Benzothiopyranopyrazoles and benzopyranopyrazoles containing either a sulfone or sulfonamide moiety were synthesized and tested for COX-1 and COX-2 inhibition. This new class of COX-2 selective inhibitors possess antiinflammatory activity in vivo.

Introduction

Nonsteroidal antiinflammatory drugs (NSAID's) are widely used for the treatment of acute and chronic inflammatory conditions.[1] NSAID's function by blocking the conversion of arachidonic acid to prostaglandins by the enzyme cyclooxygenase.[2] The constitutive form of cyclooxygenase (COX-1) produces prostaglandins that are important for normal platelet, gastrointestinal, and kidney function. Recently a second isoform of cyclooxygenase, COX-2, was identified that is induced during inflammatory states.[3] Currently marketed NSAIDs inhibit both COX isoforms. As a class NSAIDs are antiinflammatory but show anti platelet activity and frequently have significant gastric and renal side effects.[4] The goal of our research is to identifiy selective inhibitors of COX-2 that should be antiinflammatory without conventional NSAID side effects.

Several papers have described selective COX-2 inhibitors that are active in animal models of inflammation without the normal toxicity associated with nonselective cyclooxygenase inhibition.[5-10] In our search for novel, selective COX-2 inhibitors, diarylpyrazoles were found to posses excellent overall properties. This study examines the effect of linking the pyrazole ring to a benzene ring in a diaryl pyrazole, Figure 1.

Figure 1



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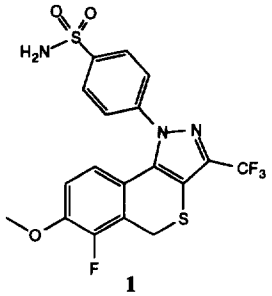

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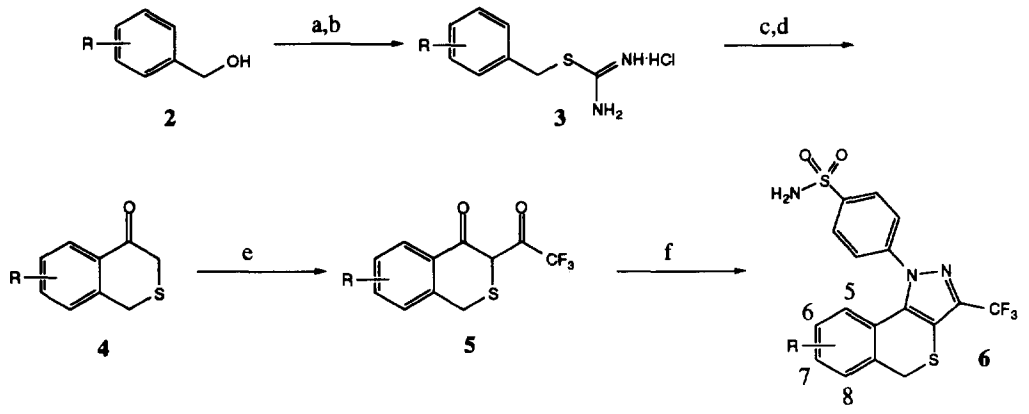
Chemistry

The conformationally restricted pyrazoles were conveniently prepared via acylation of an appropriate ketone followed by reaction with a substituted phenylhydrazine in ethanol, Scheme 1. Tetralone, chromanone and thiochromanone are commercially available. Isothiochromanones were prepared by the procedure of Lumma and Berchtold[11] starting from the appropriately substituted benzyl alcohol[12] or benzyl halide. 3-Fluoro-4-methoxybenzyl alcohol (starting material for **1**) was synthesized by borane-dimethyl sulfide reduction[13] of the

corresponding benzoic acid. 2-Fluoro-3-methoxybenzoic acid was synthesized in high yield by the procedure of Schlosser et. al.[14] using n-BuLi and potassium *tert*-butoxide as base.

Scheme 1[a]



[a] Reaction conditions: (a) conc. HCl; (b) thiourea, MeOH; (c) $NaOCOCH_2Cl$, NaOH, EtOH, H_2O; (d) TFA, TFAA; (e) CF_3CO_2Et, NaOMe, MeOH, Et_2O; (f) 4-sulfonamidophenylhydrazine hydrochloride, EtOH.

Cyclization to an isothiochromanone was accomplished using trifluoroacetic anhydride (TFAA) in trifluoroacetic acid (TFA). Typically, the acid (10 mmol) in TFA (50 mL) and TFAA (20 mL) was stirred at room temperature or reflux. For benzene rings containing an electron donating substituent (methoxy or methyl), the reaction was complete in less than 1 h at room temperature. When the benzene ring was substituted with fluorine or chlorine, the reaction was heated to reflux for 12-16 h to effect complete reaction. Upon completion, the reaction was carefully poured into $K_2CO_{3(aq)}$ solution and extracted with Et_2O. The Et_2O was then washed with 1 N HCl, $NaHCO_3$, and brine. The crude product was then chromatographed on SiO_2 eluting with 20% Et_2O in hexanes to yield a pure product in 50-85% yield.

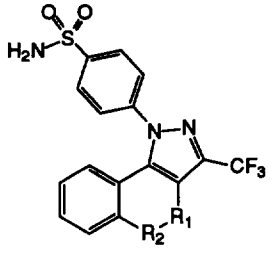
The general procedure for acylation of ketones is as follows: an isothiochromanone (10 mmol) and ethyl trifluoroacetate (10 mmol) were dissolved in Et_2O (50 mL), NaOMe (25% in MeOH, 10.5 mmol) was then added and the reaction stirred for 16 h. The reaction was acidified with 1 N HCl (150 mL) and Et_2O (200 mL) was added. The organics were washed with $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4 and the solvent removed in vacuo to afford a solid which was used without further purification. Formation of the pyrazoles was accomplished by dissolving the above diketone (10 mmol) and 4-sulfonamidophenylhydrazine hydrochloride (11 mmol) in EtOH (150 mL) and heating to reflux for 4 to 12 h. Upon cooling the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (200 mL) and washed with 1 N HCl (150 mL), $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and the solvent removed in vacuo . The solid was then recrystallized from warm $EtOH/H_2O$ or ethyl acetate/hexanes. Yields for the last two steps were typically 80-95%.

Results and Discussion

Fusion of the pyrazole ring to the non-sulfonamide containing benzene ring is well tolerated in terms of

both in vitro and in vivo activity. Isothiochromanone **6** and thiochromanone **8** derived inhibitors had slightly better selectivity for COX-2 than the chromanone and tetralone containing inhibitors, Table 1. Compound **6** was also found to be a potent inhibitor of COX-2 in vivo in the air-pouch model of inflammation.[15] We chose to pursue the isothiochromanone derived inhibitors because of their selectivity for the inducible enzyme and the variety of reagents available for analog synthesis.

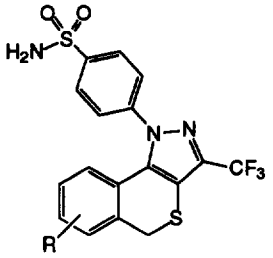
Table 1



Compound	R_1	R_2	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-1/ COX-2	Air-Pouch % inhibition @ 2mpk
6	S	CH_2	0.4 ± 0.3	0.02 ± 0.01	20	99
7	CH_2	CH_2	13.6 ± 5.6	1.1 ± 0.06	12.4	
8	CH_2	S	9.7 ± 3.3	0.46 ± 0.08	21	
9	CH_2	O	7.1 ± 2.8	1.33 ± 0	5.3	

Our previous work[10] suggested that additional selectivity could be gained by varying the substituents on the non-sulfonamide containing benzene ring. Accordingly, various analogs were synthesized and tested for cyclooxygenase inhibition. As expected, introduction of a 7-methoxy or 7-fluoro substituent did not enhance the selectivity for COX-2, while a 7-methoxy-8-fluoro decreased COX-1 potency without affecting COX-2 inhibition, Table 2. The selectivity enhancing effect of the 8-fluoro substituent seemed to be a general phenomenon for this series as seen in compounds **13-15**. The 7-methoxy-8-fluoro (**1**) and 7-methyl-8-fluoro (**13**) substituted inhibitors were tested in the carrageenan rat foot edema assay[16] and had ED_{50}'s of 17.7 and 15.0 mpk respectively.

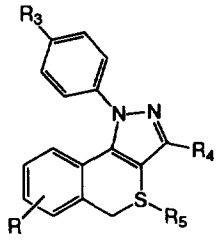
Table 2



Compound	R	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-1/ COX-2	Air-Pouch % inhibition @ 2mpk
10	7-CH_3	0.79 ± 0.4	0.022 ± 0.002	36	75
11	7-OCH_3	0.3 ± 0.06	0.013 ± 0.003	23	
1	7-OCH_3, 8-F	2.73 ± 0.1	0.009 ± 0.003	303	74
12	7-F	0.27 ± 0.2	0.04 ± 0.001	7	
13	7-CH_3, 8-F	11.1 ± 1.3	0.016 ± 0.005	693	63
14	8-F	6.24 ± 1.9	0.021 ± 0.02	297	
15	7,8-diF	2.67 ± 0.9	0.006 ± 0.007	381	80

Substitution of the CF_3 group in **1** by CF_2H increases selectivity tenfold, Table 3, in addition, replacement of the sulfonamide by methyl sulfone leads to a fourfold increase in selectivity. Unfortunately, both of these substitutions lead to reduced potency in vivo. Oxidation of the sulfide in **1**, an attempt to increase aqueous solubility, also lead to a dramatic loss of in vitro and in vivo activity. Substitution of the trifluoromethyl group in **12** by nitrile reduced COX-2 potency and selectivity.

Table 3



Compound	R_3	R_4	R	R_5	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-1/ COX-2	Air-Pouch % inhibition @ 2mpk
16	SO_2NH_2	CF_2H	7-OCH_3, 8-F		>100	0.032 ± 0.012	>3125	21
17	SO_2CH_3	CF_3	7-OCH_3, 8-F		>100	0.075 ± 0.013	>1333	37
18	SO_2NH_2	CF_3	7-OCH_3, 8-F	O	>100	1.5 ± 0.51	>67	0
19	SO_2NH_2	CN	7-F		0.76 ± 0.02	0.14	5	

Conclusion

Initial studies on a series of benzothiopyranopyrazoles indicate that they are both selective COX-2 inhibitors in vitro and antiinflammatory agents in vivo. These compounds have similar potency in acute animal models of inflammation to the related 1,5-diaryl pyrazoles.[17] Initial results are promising for the development of a novel NSAID without gastric or renal toxicity.

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