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ANTIINFLAMMATORY 2-BENZYL-4-SULFONYL-4*H*-ISOQUINOLINE-1,3-DIONES: NOVEL INHIBITORS OF COX-2

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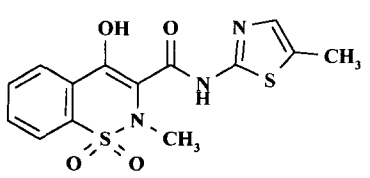
Abstract: A series of 2-benzyl-4-sulfonyl-4*H*-isoquinoline-1,3-diones was prepared. Members of this series are potent and selective inhibitors of cyclooxygenase-2 (COX-2) in both microsomal and cellular assays. Two representatives demonstrated activity in the carrageenan-induced paw edema model in rats upon oral administration.

The discovery of a new isoform of cyclooxygenase (COX-2) has stimulated a renewed interest in the field of non-steroidal antiinflammatory drugs (NSAIDs). In the early 1990's it was recognized that in addition to the constitutively expressed COX-1, there is a second isoform, COX-2. In contrast to the constitutive enzyme, levels of both COX-2 protein and mRNA are increased by inflammatory stimuli such as mitogens or certain cytokines, and decreased by glucocorticoids.[1] These findings led to the hypothesis that the gastrointestinal and renal toxicity often observed with NSAIDs is due to inhibition of COX-1, while the desired antiinflammatory activity is mediated by inhibition of COX-2. Therefore a selective inhibitor of COX-2 would have a superior safety profile.

Since this discovery, pharmaceutical companies have been searching for selective COX-2 inhibitors. Meloxicam[2] (**1**), an enol-carboxamide, is the first marketed selective inhibitor. Celecoxib[3] (**2**), is in Phase III clinical trials and is representative of the diarylheterocycle class of COX-2 inhibitors. A third class that has received much attention is the arylsulfonamides, represented by L-745,337[4] (**3**).



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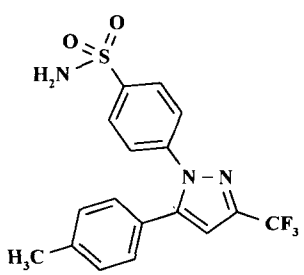

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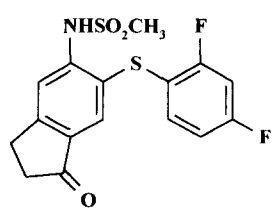

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We reported previously[5] on the SAR of enol-carboxamide type NSAIDs and concluded that further modification of this class was unlikely to improve the COX-2 selectivity exhibited by meloxicam. In the course of this work we noted that while the N-methyl was essential for activity in meloxicam-like enol-carboxamides, a benzyl substituent was tolerated in 1,3-dioxoisoquinoline-4-carboxamides. For example, compound **4** exhibits activity in a microsomal COX-2 assay although it is non-selective (Table 1). Further modification of these compounds led us into a new series of 2-benzyl-4-sulfonyl-4*H*-isoquinoline-1,3-diones, and some novel selective inhibitors of COX-2.

Sulfones **8-19** were prepared by reaction of homophthalimide **20** with the appropriate alkyl- or arylsulfonyl chloride in the presence of DBU (Scheme 1). Ketone **7** was prepared under the same conditions using benzoyl

Scheme 1

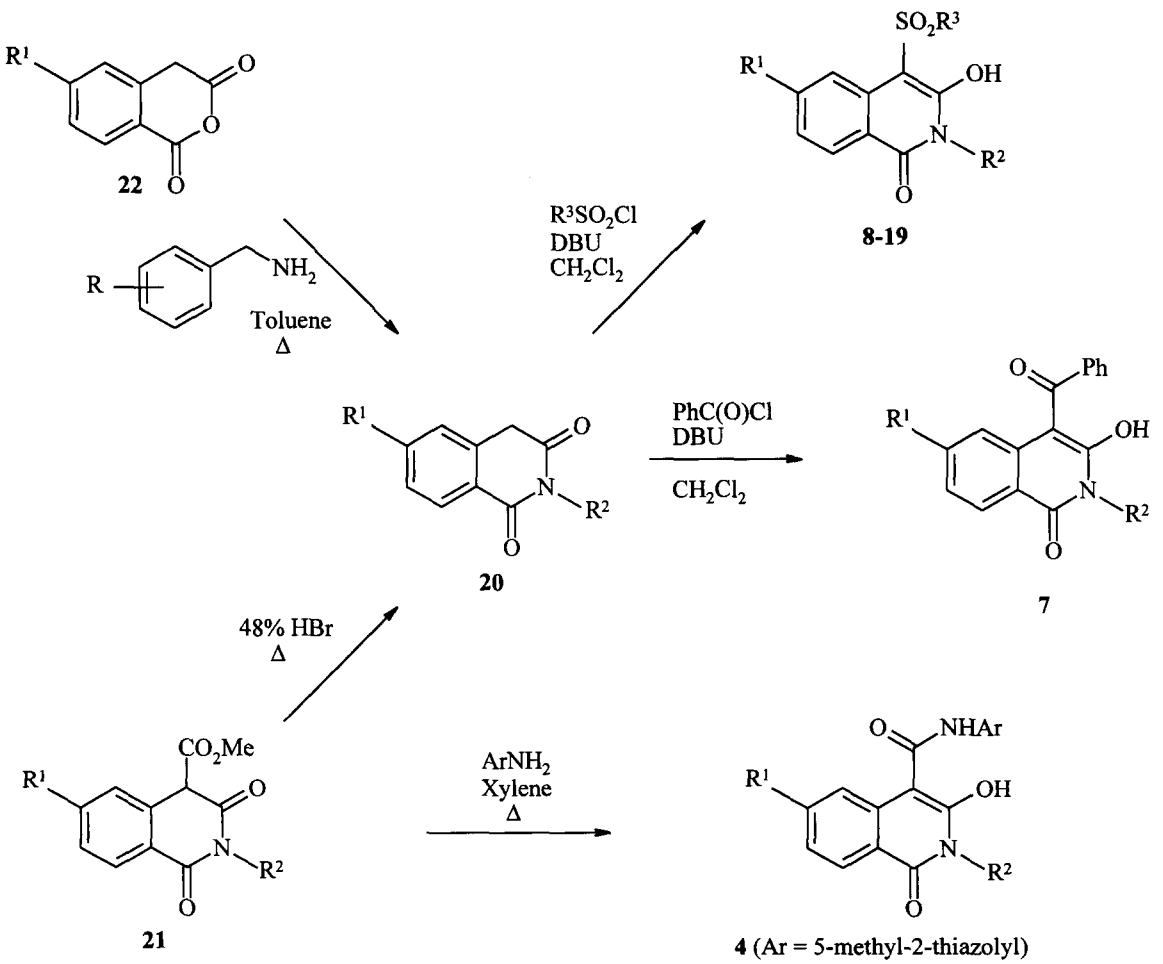
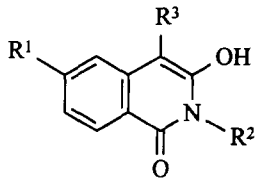


Table 1. Inhibition of COX-2 and COX-1 in Microsomal Assays

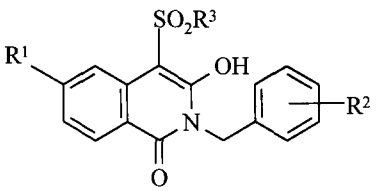


Cpd	R^1	R^2	R^3	% Inh. COX-2[a] 10	1 μg/mL	0.1	% Inh. COX-1[a] 10	1 μg/mL	0.1
1				77	72	24	39	-1	-7
4	Cl	CH_2Ph	C(O)NH(5Me2Thz)[b]	75	61	7	83	35	8
5	Cl	CH_3	CO_2Me	10	3	7	-9	10	9
6	Cl	CH_2Ph	CO_2Me	85	73	16	41	37	15
7	H	CH_2Ph	C(O)Ph	-3	-2	-2	23	-19	-18
8	H	CH_2Ph	SO_2Ph	72	58	22	74	59	17
9	H	CH_2Ph	SO_2Me	-9	1	5	7	12	9
10	H	CH_2Ph	SO_2*n*-Pr	27	15	-6	33	22	-9
11	H	CH_2Ph	SO_2*n*-Bu	20	30	0	15	15	4
12	H	CH_2Ph	SO_2*i*-Pr	58	56	27	23	11	-6
13	H	CH_2(4-ClPh)	SO_2*i*-Pr	67	62	3	36	4	-3
14	H	CH_2(4-FPh)	SO_2*i*-Pr	86	68	-1	47	28	11
15	H	CH_2(3,4-diFPh)	SO_2*i*-Pr	80	75	8	57	17	10
16	H	CH_2Ph	SO_2(4-BrPh)	100	92	28	100	74	44
17	H	CH_2Ph	SO_2(4-MeOPh)	97	74	21	93	81	33
18	Cl	CH_2Ph	SO_2*i*-Pr	97	87	34	57	34	10
19	Cl	CH_2(3,4-diFPh)	SO_2*i*-Pr	100	100	-3	96	40	13

[a]Each drug concentration (10, 1 or 0.1 μg/mL) was run in duplicate wells within the individual experiments. Results are expressed as the mean % inhibition of PGE_2 production. Detailed assay conditions are provided in reference 2. [b]5Me2Thz = 5-methyl-2-thiazolyl.

chloride. Amide **4** was prepared by heating ester **21** with 2-amino-5-methylthiazole. Intermediates **20** were prepared either by reaction of a homophthalic anhydride (**22**) with a benzyl amine (R_1 = H) or by hydrolysis and decarboxylation of **21** (R_1 = Cl). Intermediates **21** have been described in the literature.[6]

Table 2. Inhibition of COX-2 and COX-1 in Cell Assays



Cpd	R^1	R^2	R^3	% Inh COX-2[a] 10	1	0.1	IC_{50} (μM)	% Inh COX-1[a] 10	1	0.1	IC_{50} (μM)
1							0.16[b]				2.20
8	H	H	Ph	69	46	36	0.14[c]	93	54	21	0.73
12	H	H	*i*-Pr	65	49	37	0.29[c]	77	48	26	0.34[c]
13	H	4-Cl	*i*-Pr	64	51	9		69	44	-15	
14	H	4-F	*i*-Pr	82	72	50	0.09[b]	87	66	46	0.25
15	H	3,4-diF	*i*-Pr	76	54	37	0.2[b]	90	54	24	0.57
18	Cl	H	*i*-Pr	96	80	62	0.06	83	43	33	1.42
19	Cl	3,4-diF	*i*-Pr	92	71	64	0.1	81	49	18	1.36

[a]Each drug concentration (10, 1 or 0.1 μM) was run in triplicate wells within the individual experiments. Results are expressed as the mean % inhibition of PGE_2 production. The calculated IC_{50} value is the concentration that caused a 50% decrease in the maximal inhibition of cyclooxygenase activity as measured by PGE_2 production. Maximal inhibition (I_{max}) was 90%-100% unless noted. Detailed assay conditions are provided in reference 2. [b]I_{max} = 84%.

Compounds **5** and **6** showed that the amide functionality, which is critical to activity in enol-carboxamides such as **1**, could be changed to an ester with retention of COX-2 activity if a benzyl group is present at R_2 (Table 1). In an effort to improve activity and selectivity and to replace the metabolically unstable ester, we explored other functional groups at R_3. Ketone **7** was inactive while the phenyl sulfone **8** was active although not selective. We therefore began to explore other substituted sulfones.

Among the alkyl sulfones examined (**9-15**) an isopropyl sulfone was superior giving greater than 50% inhibition of COX-2 at both 10 and 1 μg/mL in a microsomal assay with less inhibition of COX-1. Aryl sulfones **16** and **17,** like **8**, were active but non-selective. A comparison of **18** and **19** with **12** and **15** indicates that a 6-Cl substituent enhances potency in the microsomal assay.

Several of these compounds were evaluated for COX-2 and COX-1 inhibition in cellular assays using stably transfected Cos-A2 cells (Table 2). IC_{50} values were determined for four of the most active compounds. Phenyl sulfone **8** was again active but non-selective. Isopropyl sulfones **12-15** were active but only slightly selective at best. Comparing **18** and **19** with **12** and **15** shows that as in the microsomal assay, a 6-Cl group improved activity in the COX-2 assay. More importantly it provided the most potent and selective compound **18**, with an IC_{50} of 0.06 μM in the cellular COX-2 assay and 1.4 μM for COX-1.

Compounds **18** and **19** were tested for antiinflammatory activity in the carrageenan paw edema model[7]. The results in Table 3 show that these compounds did demonstrate significant activity at 30 mg/kg p.o. In conclusion, we have described a novel series of cyclooxygenase inhibitors, in which COX-2 selectivity can be enhanced by structural modification and antiinflammatory activity can be demonstrated in vivo.

Table 3. Inhibition of Carrageenan-Induced Paw Edema

Cpd	Dose (mg/kg)[a]	% Inh.
1	30	56[b]
18	30	43[b]
19	30	39[b]

[a]Compounds dosed orally, 6 rats per test group.
[b]Significantly different from vehicle control group, $p < 0.05$.

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