Effect of Structural Modification of Enol−Carboxamide-Type Nonsteroidal Antiinflammatory Drugs on COX-2/COX-1 Selectivity

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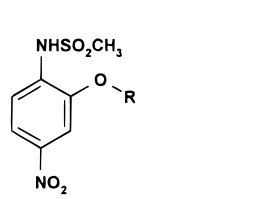
Meloxicam (**5**), an NSAID in the enol−carboxamide class, was developed on the basis of its antiinflammatory activity and relative safety in animal models. In subsequent screening in microsomal assays using human COX-1 and COX-2, we discovered that it possessed a selectivity profile for COX-2 superior to piroxicam and other marketed NSAIDs. We therefore embarked on a study of enol−carboxamide type compounds to determine if COX-2 selectivity and potency could be dramatically improved by structural modification. Substitution at the 6- and 7-positions of the 4-oxo-1,2-benzothiazine-3-carboxamide, alteration of the *N*-methyl substituent, and amide modification were all examined. In addition we explored several related systems including the isomeric 3-oxo-1,2-benzothiazine-4-carboxamides, thienothiazines, indolothiazines, benzothienothiazines, naphthothiazines, and 1,3- and 1,4-dioxoisoquinolines. While a few examples were found with greater potency in the COX-2 assay, no compound tested had a better COX-2/COX-1 selectivity profile than that of **5**.

Introduction

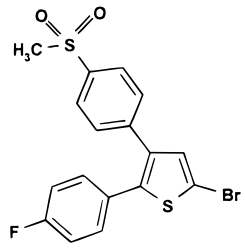
The discovery of a new isoform of cyclooxygenase (COX-2) has stimulated renewed interest in the field of nonsteroidal antiinflammatory drugs (NSAIDs). The antiinflammatory properties of these drugs have been attributed to their ability to inhibit the enzyme cyclooxygenase, which catalyzes the transformation of arachidonic acid to prostaglandin H_2 (PGH_2), the key step in the biosynthesis of prostaglandins (PGs).[1]

In the early 1990s, it was recognized that there were two isoforms of this enzyme. In addition to the constitutively expressed enzyme (COX-1) there is an inducible isoform (COX-2). In contrast to the constitutive enzyme, levels of both COX-2 mRNA and protein are increased by inflammatory stimuli such as mitogens or certain cytokines. In addition, glucocorticoids have been shown to block the expression of COX-2 mRNA and protein whereas the level of COX-1 activity is not affected.[2] Since glucocorticoids do not cause gastrointestinal distress, 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, it was proposed that a selective inhibitor of COX-2 would have a superior safety profile.[3] A number of currently marketed NSAIDs developed prior to the discovery of COX-2 have now been evaluated for inhibition of both enzymes. Not surprisingly, most studies have found that they are either nonselective or selective for COX-1.[4]

Screening of known antiinflammatory compounds for inhibition of the two isoforms soon led to the discovery of selective leads. Compounds such as NS-398 (**1a**)[5] and DuP 697 (**2**)[6] provided leads for the first two major classes of selective COX-2 inhibitors reported thus far, arylsulfonamides such as nimesulide (**1b**), an older compound[7a] found selective in some assay systems and the newer compound L-745,337 (**3**),[7b] and diaryl heterocycles and related compounds such as SC-58125 (**4**).[8] The latter two, representative of compounds in their respective classes, are reported to be highly selective for COX-2. In cell-based assays, **3** is reported to be over 200-fold selective for COX-2 (IC_{50} 0.05 μM versus >10 μM)[7b] while in enzyme assays **4** is reported to be over 1000-fold selective for human recombinant COX-2 (IC_{50} 0.09 μM) over COX-1 (IC_{50} > 100 μM).[8b]



1a R = cyclohexyl
1b R = phenyl



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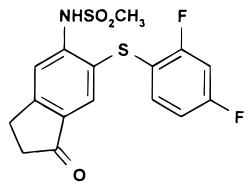

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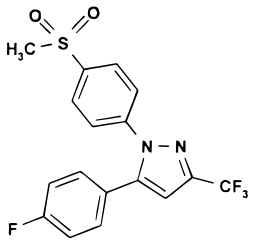

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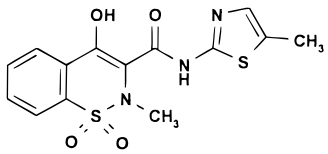

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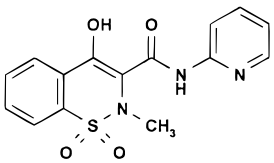

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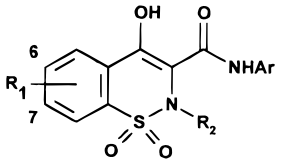
Table 1. Inhibition of COX-2 and COX-1 by Meloxicam Analogs



				% inh COX-2[a]				% inh COX-1			
compd	R_1	R_2	Ar	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)
1[b]							9.4^{+}				50[c]
5	H	Me	5-Me-2-thiazolyl	77	72	24	0.49^{++}	39	−1	−7	36.6^{++}
6	H	Me	2-pyridyl	62	58	25	59%/100 μM	35	10	−7	1.3^{++}
7	H	Me	2-thiazolyl	35	23	3		51	17	−32	
8	H	Me	4-Me-2-thiazolyl	71	67	37	0.83^{+++}	80	30	9	6.76^{+}
9	H	Me	5-Et-2-thiazolyl	1	20	9		30	23	−4	
10	H	Me	4,5-diMe-2-thiazolyl	74	66	30		66	22	1	
11	H	Me	4-Pr-2-thiazolyl	20	17	1		44	1	−3	
12	H	Me	5-Ph-2-thiazolyl	19	0	−22		97	55	6	
13	H	Me	4-CF_3-2-thiazolyl	−52	−49	−39		72	19	8	
14	H	Me	2-benzothiazolyl	57	45	30		95	49	13	
15	H	Me	5-Me-2-thiadiazolyl	23	14	0		2	18	0	
16	H	H	5-Me-2-thiazolyl	31	31	19		41	18	14	
17	H	Et	5-Me-2-thiazolyl	30	14	3		27	−6	−2	
18	H	CH2Ph	5-Me-2-thiazolyl	22	−3	0		42	10	3	
19	H	Me	4-Me-2-oxazolyl	−7	4	13		−7	5	5	
20	H	Me	5-Me-3-isoxazolyl	9	10	9		10	7	−2	
21	H	Me	Ph	−18	−19	−1		26	16	−8	
22	6-OMe	Me	5-Me-2-thiazolyl	40	33	22		−36	−13	−1	
23	6-OMe	Me	2-pyridyl	26	19	19		−18	−14	−18	
24	6-OMe	Me	Ph	24	19	25		−3	−5	−6	
25	6-OMe	Me	4-ClPh	5	−9	14		14	13	9	
26	6-Me	Me	5-Me-2-thiazolyl	50	42	5		24	14	0	
27	6-Me	Me	2-pyridyl	29	16	7		−20	5	−9	
28	6-Me	Me	Ph	3	14	37		−1	−8	−1	
29	6-Me	Me	4-ClPh	−12	6	9		21	−1	0	
30	6-Cl	Me	5-Me-2-thiazolyl	76	74	41		62	26	11	
31	6-Cl	Me	2-pyridyl	39	42	7		43	14	3	
32	6-Cl	Me	Ph	−6	−6	4		17	16	15	
33	6-Cl	Me	4-ClPh	−34	−33	−6		18	23	6	
34	6-F	Me	5-Me-2-thiazolyl	72	65	27		56	21	2	
35	6-F	Me	2-pyridyl	58	46	20		27	11	0	
36	6-F	Me	Ph	−39	−43	−13		61	38	9	
37	6-F	Me	4-ClPh	−42	−28	6		40	16	6	
38	7-OMe	Me	5-Me-2-thiazolyl	70	60	30		50	16	6	
39	7-OMe	Me	2-pyridyl	51	37	14		44	9	−2	
40	7-OMe	Me	Ph	1	0	6		3	15	−8	
41	7-Me	Me	5-Me-2-thiazolyl	68	62	35		69	31	8	
42	7-Me	Me	2-pyridyl	39	33	8		45	29	18	
43	7-Me	Me	Ph	−6	31	38		28	28	2	
44	7-Cl	Me	5-Me-2-thiazolyl	66	67	46		85	36	−9	
45	7-Cl	Me	2-pyridyl	72	59	18		77	38	−7	
46	7-F	Me	5-Me-2-thiazolyl	72	70	39		82	36	−4	
47	7-F	Me	2-pyridyl	62	56	16		74	26	3	

[a] Each dose was run in duplicate wells within the individual experiments. Results are expressed as the mean percent inhibition of control PGE_2 production. Dose−response curves ($n \geq 2$) were analyzed by nonlinear regression using the Hill equation using SAS Software System (SAS Institute, Inc., Cary, NC).[28,29] The calculated IC_{50} value is the concentration of the drug that causes a 50% decrease in the maximal inhibition of cyclooxygenase activity as measured by PGE_2 production. Highest percent inhibition observed on IC_{50} curve (I_{max}): + 90−110%, ++ 80−90%, +++ 70−80%, ++++ 60−70%. [b] Purchased from Sigma Chemical Co. [c] Estimated IC_{50} value. Nonlinear regression analysis did not converge.

Meloxicam (**5**),[9] an NSAID in the enol−carboxamide class, was developed on the basis of its antiinflammatory activity and relative safety in animal models. This favorable therapeutic index has been confirmed in clinical trials.[10] In subsequent studies we and others discovered that it possessed a selectivity profile for COX-2 superior to several other marketed NSAIDs.[11] A comparison of **5** with piroxicam (**6**) revealed different inhibitory profiles for the two enzymes. While **6** showed some selectivity for COX-2 in a microsomal assay, COX-2 inhibition plateaued at 60%. In contrast, **5** achieved about 80% inhibition and had 75-fold selectivity for COX-2 at the IC_{50}. Given the different profiles observed for **5** and **6,** and the fact that this group of NSAIDs was developed prior to the discovery of COX-2, we decided to explore the SAR of this class to determine if COX-2 selectivity could be improved.

Chemistry

The syntheses of most of the enol−carboxamide and related compounds found in Tables 1−4 were carried out using established methods. 1,2-Benzothiazine-3-carboxamides (Table 1) were prepared as described by Lombardino[12,13] (Scheme 1, method A). Other aromatic 1,2-thiazine-3-carboxamides[14] are shown in Table 2 and were prepared in an analogous fashion.

The synthetic approach to the isomeric 1,2-benzothiazine-4-carboxamides and related compounds found in

Scheme 1

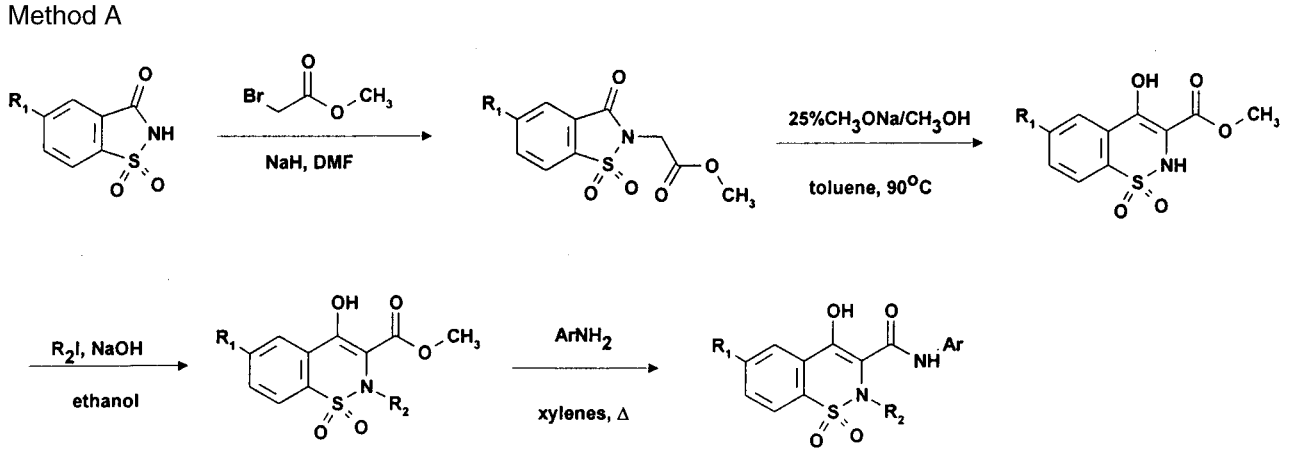
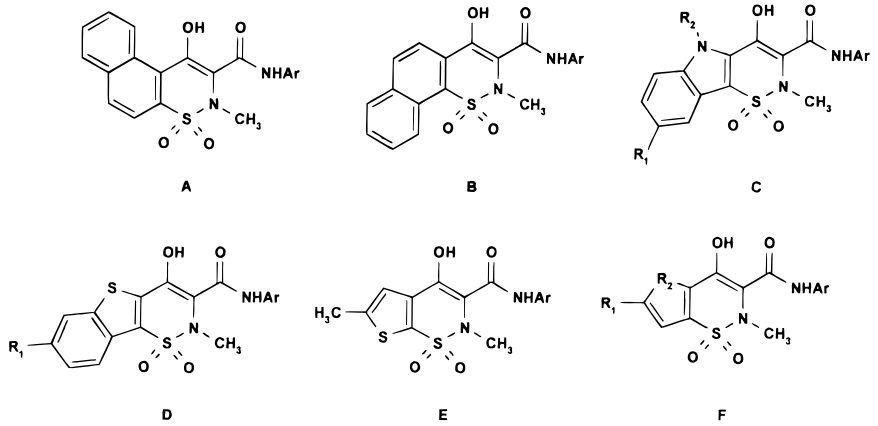


Table 2. Inhibition of COX-1 and COX-2 by Miscellaneous Oxicams

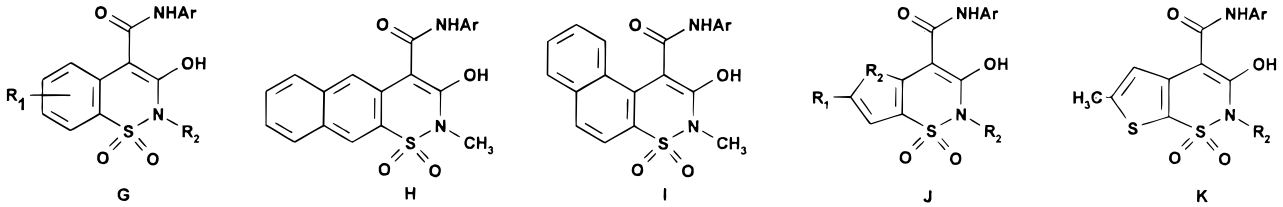


					% inh COX-2				% inh COX-1			
compd	type	Ar	R_1	R_2	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)[a]	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)[a]
48	A	2-thiazolyl			1	−3	−28		69	15	−10	
49	A	2-pyridyl			−3	1	−14		25	−10	−35	
50	A	Ph			−5	4	16		18	−5	−14	
51	B	2-thiazolyl			43	23	8		100	100	75	
65	B	5-Me-2-thiazolyl			67	60	44		100	100	80	
53	B	2-pyridyl			16	22	30		100	78	29	
54	B	Ph			−29	−33	−17		88	64	4	
55	B	4-ClPh			−10	−9	−5		38	34	15	
56	C	2-thiazolyl	H	Me	−1	−18	−7		97	44	−2	
57	C	5-Me-2-thiazolyl	H	Me	23	8	−3		97	32	1	
58	C	2-pyridly	H	Me	−11	−4	1		90	14	0	
59	C	Ph	H	Me	4	−7	8		93	31	9	
60	C	2-thiazolyl	H	Et	17	13	10		81	−1	−41	
61	C	2-pyridyl	H	Et	−3	9	23		25	−1	−4	
62	C	Ph	H	Et	9	4	5		5	0	−9	
63	C	2-thiazolyl	OMe	Me	1	−5	−1		86	33	3	
64	C	2-pyridyl	OMe	Me	7	6	11		88	35	1	
65	C	Ph	OMe	Me	35	3	−1		79	23	6	
66	C	2-thiazolyl	Cl	Me	3	−12	−13		95	80	16	
67	C	2-pyridyl	Cl	Me	4	−20	−14		90	28	−11	
68	C	Ph	Cl	Me	−8	2	−3		−12	10	1	
69	D	2-thiazolyl	Cl		37	8	−9		100	100	99	
70	D	5-Me-2-thiazolyl	Cl		75	41	46		100	100	58	
71	D	2-pyridyl	Cl		−17	6	6		93	100	69	
72	E	2-thiazolyl			−7	−9	−7		−24	5	1	
73	E	5-Me-2-thiazolyl			−10	−15	3		14	6	9	
74	E	2-FPh			70	37	25		100	96	78	
75	F	5-Me-2-thiazolyl	Me	S	58	43	3		93	68	31	
76	F	5-Me-2-thiazolyl	Me	O	−12	3	−11		1	−7	−8	
77	F	5-Me-2-thiazolyl	H	S	77	73	27	0.51^{++}	41	6	−7	19.8^{+}

[a] See footnote *a* in Table 1.

Table 3 is shown in Scheme 2 (method B). The starting material in Scheme 2, **145**, was prepared in two steps by carboxylation of an appropriately substituted *N*-methyl-*o*-toluenesulfonamide followed by cyclodehydration.[15] Reaction with 2-chlorophenyl isocyanate provided the 2-chlorophenyl amide **146** which was readily

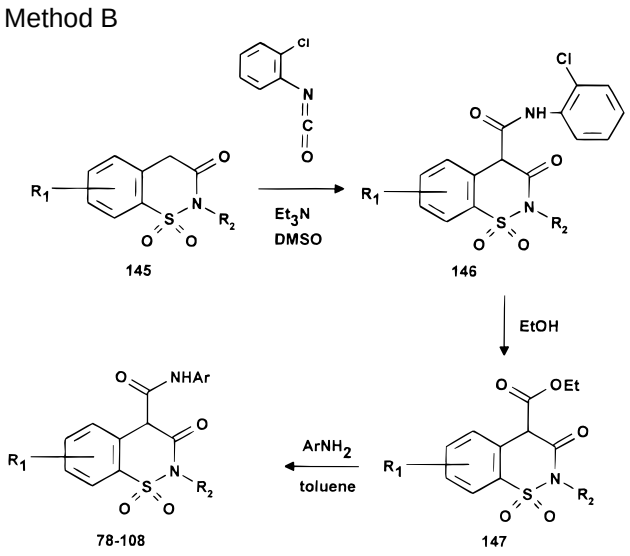
Table 3. Inhibition of COX-2 and COX-1 by Isomeric Oxicam Derivatives



					% inh COX-2				% inh COX-1			
compd	type	R_1	R_2	Ar	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)[a]	10 (μg/mL)	1 (μg/mL)	0.1 (μg/mL)	IC_{50} (μM)[a]
78	G	H	Me	Ph	23	31	10		100	92	65	
79	G	H	Me	4-BrPh	41	2	−9		100	88	54	
80	G	H	Me	5-Me-2-thiazolyl	10	5	−5		66	18	3	
81	G	H	Me	2-pyridyl	1	8	−11		53	17	10	
82	G	6-Cl	Me	4-BrPh	100	100	87		97	97	33	
83	G	6-Cl	Me	4-ClPh	100	95	82	0.064^+	99	100	60	0.39^+
84	G	6-Cl	Me	2,4-diFPh	99	82	61	0.3^+	100	100	67	0.24^+
85	G	6-Cl	Me	2,4-diClPh	100	100	96	0.009^+	100	100	89	0.08^+
86	G	6-Cl	Me	2-ClPh	100	94	83	0.008^+	100	100	94	0.041^+
87	G	6-Cl	Me	2,4-diBrPh	97	97	90	0.007^+	99	99	59	0.14^+
88	G	6-Cl	Me	5-Me-2-thiazolyl	73	9	−2		95	44	23	
89	G	6-Cl	Me	2-thiazolyl	88	42	18		98	76	18	
90	G	6-Cl	Me	2-pyridyl	42	13	−13		96	53	−13	
91	G	7-Cl	Me	4-BrPh	100	56	1		100	89	27	
92	G	7-Cl	Me	5-Me-2-thiazolyl	52	−22	2		94	66	10	
93	G	7-Cl	Me	2-thiazolyl	37	−14	−49		99	66	−8	
94	G	7-Cl	Me	2-pyridyl	−12	−19	−17		45	41	7	
95	G	6-F	Me	2-ClPh	85	38	20		100	96	32	
96	G	6-F	Me	2,4-diFPh	56	−2	−40		97	73	22	
97	G	6-F	Me	2,4-diClPh	95	72	62		100	94	40	
98	G	7-Me	Me	2-ClPh	−2	17	33		97	98	63	
99	G	5,6-diCl	Me	2,4-diClPh	68	39	28		98	55	19	
100	G	6,7-diCl	Me	2-ClPh	99	58	15		100	97	28	
101	G	6-F	CH2Ph	2,4-diClPh	85	23	−9		98	39	3	
102	G	6-Cl	CH2Ph	2,4-diClPh	92	22	−15		100	54	4	
103	G	6-Cl	Et	2,4-diClPh	100	66	37		99	85	36	
104	G	6-Cl	cyclopropyl	2,4-diClPh	100	76	59		100	65	24	
105	H			2-thiazolyl	6	0	13		64	11	−3	
106	H			4-ClPh	93	30	−44		100	100	57	
107	I			2-thiazolyl	−3	0	−18		93	57	24	
108	I			Ph	13	39	13		72	54	18	
109	J	Me	S	2-pyridyl	25	31	5		82	53	15	
110	J	Me	S	4-ClPh	57	31	−5		98	80	40	
111	J	Cl	S	2,4-diClPh	74	18	−5		91	57	32	
112	J	Me	O	4-ClPh	33	51	24		93	73	52	
113	K			4-ClPh	96	42	8		100	90	58	

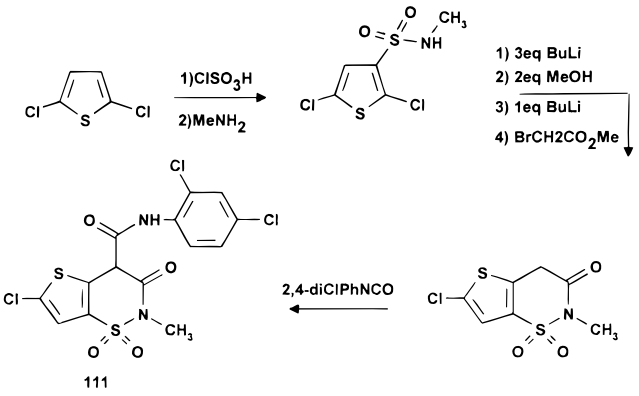
[a] See footnote *a* in Table 1.

Scheme 2



converted to the ester **147**.[16] Reaction with the appropriate aryl amine gave **78**−**108**. Heterocycle-fused

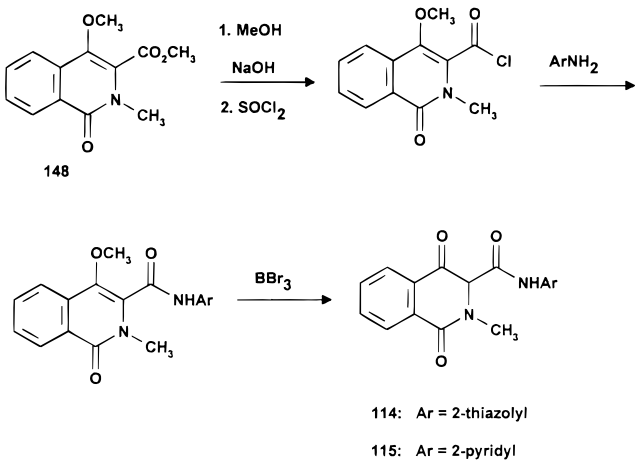
Scheme 3



compounds (type J) were obtained as shown for **111** in Scheme 3. The isomeric **113** was prepared from the aryl isocyanate and appropriate thienothiazine.[17]

Compounds **114** and **115** were prepared from ester **148**[18] as described in Scheme 4. Compounds **116** and **117** were prepared according to a published procedure.[19] The remaining type M compounds **118**−**126** were pre-

Scheme 4



pared by refluxing the corresponding esters[20] with the appropriate amines as in method A. The preparations of the remaining compounds in Table 4 are illustrated in Scheme 5. Type N compounds with $R_1 = R_2 = H$ are known,[21] and compounds **127**, **128**, **135**−**138**, **140**, and **141** were prepared by reaction of the heteroarylamine with the appropriate 4-oxothiochromane-3-carboxylic acid ester. Compounds **129**, **132**, **139**, and **142** were prepared by reaction of 3-chlorophenyl isocyanate with the appropriate enamine followed by acid workup. Sulfoxides **130** and **133** were prepared by oxidation of **129** and **132**, respectively, with oxone. Oxidation of sulfoxides with H_2O_2 gave sulfones **131** and **134**. Substituted thiochroman-4-ones required as intermediates were prepared by known methods.[22]

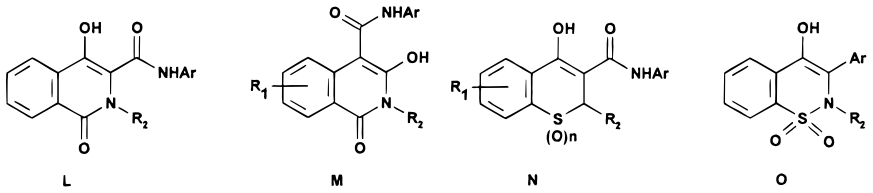
The indolyl ketone **143** was prepared by reaction of the zinc salt of indole with enamine acid chloride **149**[23] followed by hydrolysis of the enamine. Benzimidazole derivative **144** was prepared by refluxing amide **150** (prepared from *o*-phenylenediamine by method A) in HOAc.

Results and Discussion

The enol−carboxamides are a well-established class of NSAIDs with several marketed representatives. The SAR for these compounds has been extensively explored for optimization of antiinflammatory activity. The selectivity profiles that we found for **5** and **6** indicated that different members of this class can distinguish the COX isoforms to varying degrees. Since no previous attempt to optimize this class for COX-2 selectivity had been reported, we embarked on an extensive survey to determine if a new lead would emerge that could be further modified to yield a more selective compound.

Results from this effort are reported in Tables 1−4. We examined a large number of previously reported compounds as well as new ones. Screening data at 10,

Table 4. Miscellaneous Systems



compd	type	R_1	R_2	*n*	Ar	% inh COX-2 10 (μg/mL)	% inh COX-2 1 (μg/mL)	% inh COX-2 0.1 (μg/mL)	IC_{50} (μM)[a]	% inh COX-1 10 (μg/mL)	% inh COX-1 1 (μg/mL)	% inh COX-1 0.1 (μg/mL)	IC_{50} (μM)[a]
114	L		Me		2-thiazolyl	−5	3	−15		37	11	2	
115	L		Me		2-pyridyl	60	−4	−15		19	−3	−19	
116	M	H	Me		Ph	75	93	68	0.17+	80	65	31	0.37+
117	M	H	Me		4-ClPh	60	79	76	0.046+	96	77	57	0.12+
118	M	6-Cl	Me		5-Me-2-thiazolyl	13	2	4		76	35	5	
119	M	6-Cl	Me		Ph	11	7	11		78	42	13	
120	M	6-Cl	Me		2,4-diClPh	100	100	77	0.2+	97	93	36	0.6+
121	M	6-Cl	CH_2Ph		5-Me-2-thiazolyl	75	61	7		83	35	8	
122	M	6-Cl	CH_2Ph		2,4-diClPh	96	60	0		100	84	6	
123	M	6-Me	Me		5-Me-2-thiazolyl	−10	3	5		51	52	30	
124	M	6-Me	Me		Ph	2	37	6		90	72	40	
125	M	6-Me	Me		2-pyridyl	28	38	9		73	62	22	
126	M	6-Me	Me		2,4-diClPh	100	89	46		100	100	79	
127	N	H	H	0	5-Me-2-thiazolyl	7	23	15		35	29	16	
128	N	H	H	0	2-pyridyl	63	22	−9		83	34	−1	
129	N	H	H	0	3-ClPh	81	79	36		83	75	19	
130	N	H	H	1	3-ClPh	17	15	29		38	−2	−2	
131	N	H	H	2	3-ClPh	28	19	15		84	41	6	
132	N	6-Cl	H	0	3-ClPh	52	51	38		54	26	31	
133	N	6-Cl	H	1	3-ClPh	−40	−9	−7		76	17	0	
134	N	6-Cl	H	2	3-ClPh	56	24	0		94	64	−10	
135	N	6-Cl	H	0	5-Me-2-thiazolyl	−7	16	6		18	21	11	
136	N	6-Cl	H	0	2-pyridyl	66	39	20		92	58	27	
137	N	6-Cl	Me	0	5-Me-2-thiazolyl	60	56	19		30	20	12	
138	N	6-Cl	Me	0	2-pyridyl	0	−13	−11		30	25	14	
139	N	6-Cl	Me	0	3-ClPh	23	21	28		12	10	15	
140	N	H	diMe	0	5-Me-2-thiazolyl	28	20	10		16	11	−25	
141	N	H	diMe	0	2-pyridyl	26	23	20		−48	−28	−14	
142	N	H	diMe	0	3-ClPh	33	29	28		29	20	3	
143	O	H	Me		3-indoloyl	11	16	36		24	3	13	
144	O	H	Me		2-benzimidazolyl	22	0	−5		16	4	−4	

[a] See footnote *a* in Table 1.

Table 5. Physical Constants and Method of Synthesis for Compounds **5**−**144**

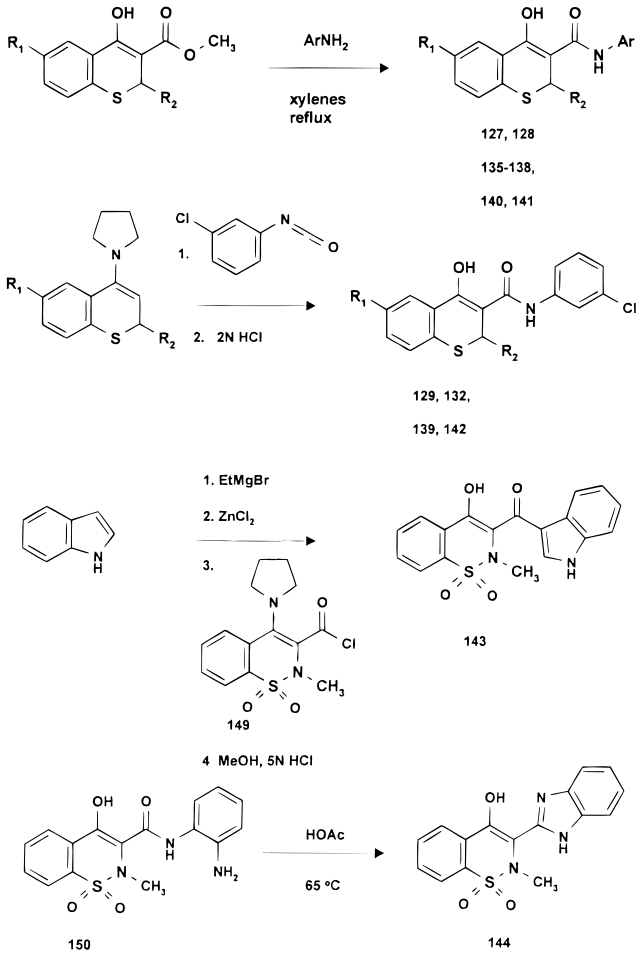
compd	method	mp (°C)	formula	anal[a]	compd	method	mp (°C)	formula	anal[a]
5	A	254−255	$C_{14}H_{13}N_3O_4S_2$	C, H, N	**75**	A	243−244	$C_{13}H_{13}N_3O_4S_3$	C, H, N
6	*b*	198−200	$C_{15}H_{13}N_3O_4S$		**76**	A	237−238	$C_{13}H_{13}N_3O_5S_2$	C, H, N
7	A	248	$C_{13}H_{11}N_3O_4S_2$	C, H, N	**77**	A	226−227	$C_{12}H_{11}N_3O_4S_3$	C, H, N
8	A	238	$C_{14}H_{13}N_3O_4S_2$	C, H, N	**78**	B	163−165	$C_{16}H_{14}N_2O_4S$	C, H, N
9	A	258−260	$C_{15}H_{15}N_3O_4S_2$	C, H, N	**79**	B	166−167	$C_{16}H_{13}BrN_2O_4S$	C, H, N
10	A	230−232	$C_{15}H_{15}N_3O_4S_2$	C, H, N	**80**	B	168−170	$C_{14}H_{13}N_3O_4S_2 \cdot H_2O$	C, H, N
11	A	231−233	$C_{16}H_{17}N_3O_4S_2$	C, H, N[c]	**81**	B	215−216	$C_{15}H_{13}N_3O_4S$	C, H, N
12	A	283−285	$C_{19}H_{15}N_3O_4S_2$	C, H, N	**82**	B	204−205	$C_{16}H_{12}BrClN_2O_4S$	C, H, N
13	A	280−281	$C_{14}H_{10}F_3N_3O_4S_2$	HRMS	**83**	B	184−186	$C_{16}H_{12}Cl_2N_2O_4S$	C, H, N
14	A	242−244[d]	$C_{17}H_{13}N_3O_4S_2 \cdot 0.5H_2O$	C, H, N	**84**	B	170−172	$C_{16}H_{11}ClF_2N_2O_4S$	C, H, N
15	A	274[e]	$C_{13}H_{12}N_4O_4S_2$	C, H, N	**85**	B	188−189	$C_{16}H_{11}Cl_3N_2O_4S$	C, H, N
16	A	155	$C_{14}H_{14}N_3O_5S$	C, H, N	**86**	B	153−155	$C_{16}H_{12}Cl_2N_2O_4S$	C, H, N
17	A	259−261	$C_{14}H_{13}N_3O_5S$	HRMS	**87**	B	181−183	$C_{16}H_{11}Br_2ClN_2O_4S$	C, H, N
18	A	227−228	$C_{13}H_{11}N_3O_4S_2$	C, H, N	**88**	B	207−209	$C_{14}H_{12}ClN_3O_4S_2$	C, H, N
19	A	242	$C_{15}H_{15}N_3O_4S_2$	C, H, N	**89**	B	219−220	$C_{13}H_{10}ClN_3O_4S_2$	C, H, N
20	A	204−207	$C_{20}H_{17}N_3O_4S_2 \cdot 0.5H_2O$	C, H, N	**90**	B	238−239	$C_{15}H_{12}ClN_3O_4S$	C, H, N
21	A	211−213	$C_{16}H_{14}N_2O_4S$	C, H, N	**91**	B	104−106	$C_{16}H_{12}BrClN_2O_4S$	C, H, N
22	A	260−263[f]	$C_{15}H_{15}N_3O_5S_2$	C, H, N	**92**	B	222−223	$C_{14}H_{12}ClN_3O_4S_2$	C, H, N
23	A	214−216	$C_{16}H_{15}N_3O_5S$	C, H, N	**93**	B	218−219	$C_{13}H_{10}ClN_3O_4S_2$	C, H, N
24	A	245−247	$C_{17}H_{16}N_2O_5S$	C, H, N	**94**	B	266−267	$C_{15}H_{12}ClN_3O_4S$	C, H, N
25	A	284−285	$C_{17}H_{15}ClN_2O_5S$	C, H, N	**95**	B	147−148	$C_{16}H_{12}ClFN_2O_4S$	C, H, N
26	A	274−276	$C_{15}H_{15}N_3O_4S_2$	C, H, N	**96**	B	180−181	$C_{16}H_{11}F_3N_2O_4S$	C, H, N
27	A	238−240	$C_{16}H_{15}N_3O_4S$	C, H, N	**97**	B	214−215	$C_{16}H_{11}Cl_2FN_2O_4S$	C, H, N
28	A	260−261	$C_{17}H_{16}N_2O_4S$	C, H, N	**98**	B	164−165	$C_{17}H_{15}ClN_2O_4S$	C, H, N
29	A	295−296	$C_{17}H_{15}ClN_2O_4S$	C, H, N	**99**	B	192−193	$C_{16}H_{10}Cl_4N_2O_4S$	C, H, N
30	A	288−290[g]	$C_{14}H_{12}ClN_3O_4S_2$	C, H, N	**100**	B	170−172	$C_{16}H_{11}Cl_3N_2O_4S$	C, H, N
31	A	243−245	$C_{15}H_{12}ClN_3O_4S$	C, H, N	**101**	B	188−190	$C_{22}H_{15}Cl_2FN_2O_4S$	C, H, N
32	A	288−290	$C_{16}H_{13}ClN_2O_4S$	C, H, N	**102**	B	188−189	$C_{22}H_{15}Cl_3N_2O_4S$	C, H, N
33	A	>300	$C_{16}H_{12}Cl_2N_2O_4S$	C, H, N	**103**	B	164−165	$C_{17}H_{13}Cl_3N_2O_4S$	C, H, N
34	A	284−286	$C_{14}H_{12}FN_3O_4S_2$	C, H, N	**104**	B	163−164	$C_{18}H_{13}ClN_2O_4S$	C, H, N
35	A	243−245	$C_{15}H_{12}FN_3O_4S$	C, H, N	**105**	B	267	$C_{17}H_{13}N_3O_4S_2$	C, H, N
36	A	259−261	$C_{16}H_{13}FN_2O_4S$	C, H, N	**106**	B	231−233	$C_{20}H_{15}ClN_2O_4S$	C, H, N
37	A	275−277	$C_{16}H_{12}FClN_2O_4S$	C, H, N	**107**	B	106−108	$C_{20}H_{19}ClN_2O_4S$	C, H, N[k]
38	A	221−224	$C_{15}H_{15}N_3O_5S_2$	C, H, N	**108**	B	169−170	$C_{21}H_{22}N_2O_4S$	C, H, N
39	A	200−202	$C_{16}H_{15}N_3O_5S$	C, H, N	**109**	*l*	259−260	$C_{14}H_{13}N_3O_4S_2$	C, H, N
40	A	252−254	$C_{17}H_{16}N_2O_5S$	C, H, N	**110**	*l*	155−157	$C_{15}H_{13}ClN_2O_4S_2$	C, H, N
41	A	219−225	$C_{15}H_{15}N_3O_4S_2$	C, H, N	**111**	*l*	229−230	$C_{14}H_9Cl_3N_2O_4S_2$	C, H, N
42	A	226−227	$C_{16}H_{15}N_3O_4S \cdot 0.25H_2O$	C, H, N	**112**	*l*	205−207	$C_{15}H_{13}ClN_2O_5S$	C, H, N
43	A	269−271	$C_{17}H_{16}N_2O_4S \cdot 0.25H_2O$	C, H, N	**113**	B	178	$C_{15}H_{13}ClN_2O_4S_2$	C, H, N
44	A	260−261	$C_{14}H_{12}ClN_3O_4S_2$	C, H, N	**114**	*m*	206	$C_{14}H_{11}N_3O_3S \cdot 0.25H_2O$	C, H, N
45	A	225−226	$C_{15}H_{12}ClN_3O_4S$	C, H, N	**115**	*m*	178−180	$C_{16}H_{13}N_3O_3S$	HRMS
46	A	266−270	$C_{14}H_{12}FN_3O_4S_2$	C, H, N	**116**	A	237	$C_{17}H_{14}N_2O_3$	C, H, N
47	A	249−251	$C_{15}H_{12}FN_3O_4S$	C, H, N	**117**	A	208−210	$C_{17}H_{13}ClN_2O_3 \cdot 0.25H_2O$	C, H, N
48	A	244−245	$C_{17}H_{13}N_3O_4S_2$	C, H, N	**118**	A	259−260	$C_{15}H_{12}ClN_3O_3S \cdot 025H_2O$	C, H, N
49	A	255−256	$C_{19}H_{15}N_3O_4S$	C, H, N	**119**	A	254−257	$C_{16}H_{12}ClN_3O_3 \cdot 0.5C_2H_4O_2$	C, H, N
50	A	240−241	$C_{20}H_{16}N_2O_4S$	C, H, N[h]	**120**	A	178−180	$C_{17}H_{11}Cl_3N_2O_3$	C, H, N
51	A	248	$C_{17}H_{13}N_3O_4S_2$	C, H, N	**121**	A	250−253	$C_{21}H_{16}ClN_3O_3S \cdot 0.25H_2O$	C, H, N
52	A	219−220	$C_{18}H_{15}N_3O_4S_2$	HRMS	**122**	A	180−184	$C_{23}H_{15}Cl_3N_2O_3$	C, H, N
53	A	237−238	$C_{19}H_{15}N_3O_4S$	C, H, N	**123**	A	241−244	$C_{16}H_{15}N_3O_3S \cdot 0.3C_2H_4O_2$	C, H, N
54	A	273−274	$C_{20}H_{16}N_2O_4S$	C, H, N	**124**	A	189−193	$C_{18}H_{16}N_2O_3 \cdot 0.2H_2O$	C, H, N
55	A	259	$C_{20}H_{15}ClN_2O_4S$	C, H, N	**125**	A	215−219	$C_{16}H_{15}N_3O_3S \cdot 0.25H_2O$	C, H, N
56	A	260	$C_{16}H_{17}N_4O_4S_2$	C, H, N	**126**	A	189−193	$C_{18}H_{14}Cl_2N_2O_3$	C, H, N
57	A	250	$C_{17}H_{16}N_4O_4S_2$	HRMS	**127**	*n*	246−248	$C_{14}H_{12}N_2O_2S_2$	C, H, N
58	A	252−253	$C_{18}H_{16}N_4O_4S$	C, H, N	**128**	*n*	resin	$C_{15}H_{12}N_2O_2S \cdot 0.25H_2O$	C, H, N
59	A	258−260	$C_{19}H_{17}N_3O_4S$	C, H, N	**129**	*n*	140−146	$C_{16}H_{12}ClNO_2S$	C, H, N
60	A	229−230	$C_{17}H_{16}N_4O_4S_2$	C, H, N	**130**	*n*	191−194	$C_{16}H_{12}ClNO_3S$	C, H, N
61	A	230	$C_{19}H_{18}N_4O_4S$	C, H, N	**131**	*n*	198−200	$C_{16}H_{12}ClNO_4S \cdot 0.5H_2O$	C, H, N
62	A	268	$C_{20}H_{19}N_3O_4S$	C, H, N	**132**	*n*	178−182	$C_{16}H_{11}Cl_2NO_2S$	C, H, N
63	A	248−249	$C_{17}H_{16}N_4O_5S_2$	C, H, N	**133**	*n*	208−211	$C_{16}H_{11}Cl_2NO_3S \cdot 0.25H_2O$	C, H, N
64	A	247−248	$C_{19}H_{18}N_4O_5S$	C, H, N	**134**	*n*	233−236	$C_{16}H_{11}Cl_2NO_4S \cdot 0.25H_2O$	C, H, N
65	A	245−246	$C_{20}H_{19}N_3O_5S$	C, H, N[i]	**135**	*n*	267−269	$C_{14}H_{11}ClN_2O_2S_2$	C, H, N
66	A	282	$C_{16}H_{13}ClN_4O_4S_2$	C, H, N	**136**	*n*	134−138	$C_{15}H_{11}ClN_2O_2S \cdot 0.25H_2O$	C, H, N
67	A	245	$C_{18}H_{15}ClN_4O_4S$	C, H, N	**137**	*n*	233−236	$C_{15}H_{13}ClN_2O_2S_2 \cdot 0.5H_2O$	C, H, N
68	A	285	$C_{19}H_{16}ClN_3O_4S$	C, H, N[j]	**138**	*n*	195−198	$C_{16}H_{13}ClN_2O_2S$	C, H, N
69	A	259−260	$C_{15}H_{10}ClN_3O_4S_3$	C, H, N	**139**	*n*	209−213	$C_{17}H_{13}Cl_2NO_2S$	C, H, N
70	A	260−261	$C_{16}H_{12}ClN_3O_4S_3$	C, H, N	**140**	*n*	206−210	$C_{16}H_{16}N_2O_2S_2 \cdot 0.25H_2O$	C, H, N
71	A	231−232	$C_{17}H_{12}ClN_3O_4S_2$	C, H, N	**141**	*n*	resin	$C_{17}H_{16}N_2O_2S$	C, H, N
72	A	229	$C_{12}H_{11}N_3O_4S_3$	C, H, N	**142**	*n*	195−198	$C_{18}H_{16}ClNO_2S$	C, H, N
73	A	240−241	$C_{13}H_{13}N_3O_4S_3$	C, H, N	**143**	*n*	281−283	$C_{18}H_{14}N_2O_4S$	C, H, N
74	A	159−160	$C_{15}H_{13}FN_2O_4S_2$	C, H, N	**144**	*n*	279−281	$C_{16}H_{13}N_3O_3S$	C, H, N

[a] Unless otherwise noted, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 5 ppm of theoretical. [b] Purchased from Sigma Chemical Co. [c] N: calcd, 11.07; found, 10.43. [d] Lit.[15b] 237. [e] Lit.[15b] 276. [f] Lit.[11a] 260. [g] Lit.[11a] 285. [h] C: calcd, 63.15; found, 62.71. [i] N: calcd, 10.16; found, 10.64. [j] N: calcd, 10.06; found, 9.28. [k] C: calcd, 57.34; found, 57.80. [l] Scheme 3. [m] Scheme 4. [n] Scheme 5.

1, and 0.1 μg/mL were obtained for all compounds, and IC_{50} values (μM) were generated for several that showed particularly interesting activity or selectivity.

Table 1 shows data for the 4-hydroxy-1,2-benzothiazine-3-carboxamides, which include **5** and **6**. The screening results suggest that the potency of **5** (IC_{50} 0.49

Scheme 5



μM) and its 75-fold selectivity for COX-2 are not improved by structural modification. The importance of the position of the 5-methyl group is illustrated by comparing **5** with **7** and **8**. Increasing the size of the methyl group greatly diminished activity for COX-2 (**9**) and in the case of **12** enhanced COX-1 activity. No other heterocyclic amide examined (**14**, **15**, **19**, and **20**) gave a compound superior to **5**.

Removing the *N*-methyl group (**16**) or replacing it with an ethyl (**17**) or benzyl (**18**) decreased both selectivity and potency. Various substituents on the benzothiazine ring were evaluated (**22**−**47**). Examination of the results indicates that the 7-substituted compounds generally retain more activity than their 6-substituted counterparts but offer no substantive advantage over the unsubstituted compounds. In this series of compounds, the phenyl or substituted phenyl amides (**21**, **24**, **25**, **28**, **29**, **32**, **33**, **36**, **37**, **40**, and **43**) exhibited relatively poor activity against both COX-2 and COX-1.

Results for various aromatic oxicam systems are shown in Table 2. Most of these compounds had poor COX-2 inhibitory activity, with the exception of **77** with an IC_{50} of 0.51 μM and about 40-fold selectivity for COX-2. Once again, increasing the size of the molecule did not enhance COX-2 selectivity. In fact, compounds with naphthothiazine (B) and benzothienothiazine (D) nuclei were particularly good inhibitors of COX-1.

Various 1,2-benzothiazine-4-carboxamides are described in Table 3. The effect of structural modification in this series differs from the isomeric carboxamides in Tables 1 and 2 in two ways. First, phenyl or substituted phenyl amides exhibit quite good COX inhibitory activity. Compounds **85**−**87** were the most potent COX-2 inhibitors we tested, with IC_{50}s of 0.007−0.009 μM. However they were also good COX-1 inhibitors, thus selectivities for COX-2 ranged from about 5- to 20-fold. Also, ethyl, cyclopropyl, and benzyl substitutents on the nitrogen retained activity (**101**−**104**) whereas as mentioned earlier this was not the case with the 3-carboxamides.

Results for other miscellaneous systems are shown in Table 4. The 1,4- and 1,3-dioxoisoquinoline systems L and M have been described and preceded the commercially successful benzothiazines.[14,18,19] The 1,4-dioxoisoquinolines tested (**114** and **115**) were weak or inactive. The 1,3-dioxoisoquinolines **116**, **117**, and **120** had good activity but poor selectivity. Like the 4-carboxamides (type G) in Table 3, the (substituted) phenyl amides had better activity than that of the heteroarylamides and a benzyl group is tolerated on the nitrogen (**121** and **122**).

We also examined several 4-hydroxy-2*H*-1-benzothiopyran-3-carboxamides (type N). Some members of this series had also been previously described as having antiinflammatory activity.[21] In general, these compounds had weak to moderate activity at best. Interestingly, compounds with unoxidized sulfur (**129** and **132**) were about as good as or better than their sulfoxide or sulfone counterparts.

Finally, several potential amide bioisosteres and replacements were examined, none of which had any activity. Two examples shown are a 3-indolyl group (**143**) which had been reported to be an amide bioisostere[24] and a 2-benzimidazolyl group (**144**).

In summary, different COX-2/COX-1 inhibitory profiles for **5** and **6** prompted us to undertake an extensive study of the effect of structural modification of enol−carboxamide antiinflammatory compounds on COX-2/COX-1 selectivity. We were encouraged by reports that the active site of COX-2 is slightly larger than that of COX-1,[25,26] supporting the concept of transforming a known NSAID into a selective COX-2 inhibitor by structural modification. Recent disclosure of the crystal structure of murine COX-2 bound to an analog of **4** revealed pockets in COX-2 not present in COX-1 that accommodated the inhibitor.[26] Other researchers recently exploited the difference in the two enzymes to convert indomethacin, a COX-1 selective NSAID, into a highly selective COX-2 inhibitor.[27]

We examined the effect of modification of both the steric and electronic nature of substituents on various portions of the molecule in enol−carboxamide-type NSAIDs. Substituents were added to the 6- and 7-positions of the benzothiazine, and the size of the carboxamide and N-substituent was modified. We observed some differences in the effect of certain substituents in the isomeric 3- and 4-carboxamide series and some compounds, notably **83** and **85**−**87** had greater potency. However there was no indication from the compounds we examined that further modification of this class of NSAID would yield an appreciably more selective inhibitor than **5**. Although no definite conclusion can be made at the present time, one possibility is that this class of NSAID binds in a region or manner where greater structural modification than was undertaken here is necessary for further discrimination between the enzymes.

Experimental Section

Melting points were taken on a Buchi 510 melting point apparatus and are uncorrected. ^{1}H NMR were all consistent with molecular structures and were recorded on a Bruker AC-270 spectrometer. Elemental analyses were performed at Midwest Microlab, Indianapolis, IN, and were within 0.4% of the calculated values unless otherwise indicated. High-resolution mass spectra were run on a VG Autospec mass spectrometer run at 10 000 resolution EI.

Method A. 6-Chloro-*N*-(4-chlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (33). 5-Chloro-1,2-benzoisothiazolin-3-one 1,1-dioxide (20 g, 92 mmol) was dissolved in DMF (500 mL) and was treated portionwise with NaH (60% wt, 5.16 g, 129 mmol). The mixture became lighter in color and was stirred for 30 min at 50 °C. Methyl bromoacetate (10.5 mL, 110 mmol) was then added, and the resulting mixture was stirred for 4 h. The solution was poured into ice/water (2 L), and the resulting solid was collected and dried *in vacuo* to give 5-chloro-3-oxo-1,2-benzoisothiazoline-2-acetic acid methyl ester 1,1-dioxide (15.05 g, 56%).

This ester (15.00 g, 52 mmol) was dissolved in anhydrous toluene (200 mL) and was treated with sodium methoxide (25% wt in methanol, 30 mL, 130 mmol). The mixture was warmed to 80 °C and stirred for 4 h. The resulting orange/brown suspension was poured into ice/water (200 mL) and acidified with concentrated HCl (30 mL) with vigorous stirring. The resulting grayish solid was filtered off and dried *in vacuo* to give methyl 6-choro-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (11.25 g, 75%).

The above compound (5.3 g, 18 mmol) was dissolved in ethanol (50 mL) and was treated with 1 M aqueous NaOH (20 mL, 20 mmol) followed by MeI (3.4 mL, 55 mmol) and was stirred at room temperature for 24 h. The resulting suspension was filtered, and the solid was washed with H_2O and dried *in vacuo* to yield methyl 6-choro-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (4 g, 72%).

Methyl 6-chloro-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (0.20 g, 0.71 mmol) and 4-chloroaniline (90 mg, 0.70 mmol) were combined in xylenes (3 mL) and heated to reflux for 2 days. The mixture was cooled to room temperature, and the resulting solid was filtered off to give **33** (220 mg, 85%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 13.91 (br s, 1H), 10.52 (br s, 1H), 8.01 (s, 1H), 7.96 (m, 2H), 7.79 (d, 2H), 7.47 (d, 2H), 2.89 (s, 3H). Anal. ($C_{16}H_{12}Cl_2N_2O_4S$) C, H, N.

Method B. 3,4-Dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-4-(5-methylthiazolyl)carboxanilide (80). To a solution of 2.32 g (10.98 mmol) of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine 1,2-dioxide (**145**, R = H) in 25 mL of DMSO were added under N_2 1.11 g (10.98 mmol) of Et_3N and 1.69 g (10.98 mmol) of *o*-chlorophenyl isocyanate. After 2 h, the reaction was quenched with 20 mL of 2 N HCl. Solid precipitated from the reaction mixture. This solid was filtered, washed well with EtOH, and recrystallized from CH_2Cl_2/petroleum ether to give 2.9 g (72.5%) of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-4-(*o*-chlorophenyl)carboxanilide 1,1-dioxide (**146**, R = H), mp 145−147 °C.

A solution of 2.65 g (7.26 mmol) of **146** (R = H) in 50 mL of EtOH was refluxed overnight under N_2. Solvent was removed on a rotary evaporator, the residue dissolved in Et_2O, and the Et_2O solution washed with 2 N HCl and brine. The Et_2O phase was dried and concentrated to give 1.8 g of crude product. Flash column chromatography starting with petroleum ether, followed by 25% CH_2Cl_2 to 50% CH_2Cl_2 in petroleum ether, gave 1.6 g of the desired product as a thick oil. The oil was triturated with petroleum ether/CH_2Cl_2 to give 1.1 g (50%) of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxylic acid ethyl ester 1,1-dioxide (**147**, R = H), mp 67−69 °C.

A mixture of the above ester (445 mg, 1.57 mmol) and 2-amino-5-methylthiazole (197 mg, 1.73 mmol) in 75 mL of toluene was refluxed under N_2 for 2 h. The EtOH and toluene collected in a Dean−Stark trap were drained at 20 min intervals. The remaining toluene was removed on rotary evaporator. The residue was treated with CH_2Cl_2, and the resulting solid was filtered and recrystallized from DMSO/H_2O to give 260 mg (47%) of **80**: mp 168−170 °C; ^{1}H NMR (DMSO-d_6) δ 8.57 (d, 1H), 7.68 (d, 1H), 7.5 (t, 1H), 7.43 (s, 1H), 7.14 (t, 1H), 3.16 (s, 3H), 2.35 (s, 3H). Anal. ($C_{14}H_{13}N_3O_4S_2\cdot H_2O$) C, H, N.

6-Chloro-3,4-dihydro-2-methyl-3-oxo-2*H*-thieno[2,3-*e*]-1,2-thiazine-4-(2,4-dichlorophenyl)carboxanilide 1,1-Dioxide (111). To a mixture of 19 g (163 mmol) of chlorosulfonic acid and 1.54 g (12.97 mmol) of thionyl chloride at 0 °C was added slowly 10 g (65.35 mmol) of 2,5-dichlorothiophene. After 2 h at room temperature, the reddish solution was slowly poured onto ice. The ice-cold aqueous solution was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were washed with brine, dried, and concentrated to give an oily material which crystallized upon standing in the freezer. The 2,5-dichlorothiophene-3-sulfonic acid chloride was washed with petroleum ether (small amount) and was used directly in the next step.

To a solution of 2.4 g (9.5 mmol) of 2,5-dichlorothiophene-3-sulfonic acid chloride in 50 mL of THF at 0 °C was added 1.6 mL (19 mmol) of a solution of 40% $MeNH_2$ in H_2O followed by 1.92 g (19 mmol) of Et_3N. The resulting mixture was stirred at 0 °C and allowed to come to room temperature over a period of 2 h. The reaction mixture was concentrated and the residue taken up in CH_2Cl_2. The CH_2Cl_2 solution was washed with dilute HCl and brine, dried, and concentrated to give a crude product. A crystalline product was obtained upon treatment with CH_2Cl_2/petroleum ether. A total of 1.6 g (68%) of 2,5-dichlorothiophene-3-sulfonic acid methylamide was obtained, mp 58−59 °C.

To a solution of 1.23 g (5 mmol) of 2,5-dichlorothiophene-3-sulfonic acid methylamide in 20 mL of THF was added 6 mL (15 mmol) of 2.5 M BuLi in hexane at −78 °C. After 0.5 h, 0.4 mL (10 mmol) of MeOH was added to quench the trianion to give *in situ* the monochlorothiophene monoanion. After 5 min, another 2 mL (5 mmol) of 2.5 M BuLi in hexane was added, forming regiospecifically the desired dianion. The resulting mixture was stirred for 10 min, and 841 mg (5.5 mmol) of methyl bromoactate was added. After 1 h at −78 °C, the reaction mixture was quenched with saturated NH_4Cl and the aqueous phase pH was adjusted to 3. The aqeuous phase was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were washed with brine, dried, and concentrated to give 1.4 g of crude product. Flash column chromatography starting with petroleum ether, followed by 20% CH_2Cl_2/petroleum ether and 30% CH_2Cl_2/petroleum ether gave 240 mg of 6-chloro-3,4-dihydro-2-methyl-3-oxo-2*H*-thieno[2,3-*e*]-1,2-thiazine 1,1-dioxide.

To a solution of 340 mg (1.35 mmol) of the above thieno-[2,3-*e*]-1,2-thiazine 1,1-dioxide and 254 mg (1.35 mmol) of 2,4-dichlorophenyl isocyanate in 10 mL of DMSO at room temperature was added 137 mg (1.35 mmol) of Et_3N. After 1 h, the reaction was quenched with dilute HCl in an ice bath and then extracted with Et_2O (3×). The combined Et_2O extracts were washed with brine, dried, and concentrated to give 285 mg of crude product. This material was recrystallized from CH_2Cl_2/petroleum ether (3×) to give 22 mg of **111**: mp 229−230 °C; NMR ($CDCl_3$) δ 8.7 (br, 1H), 8.28 (d, 1H), 7.46 (s, 1H), 7.3 (m, 2H), 3.07 (s, 3H). Anal. ($C_{14}H_9Cl_3N_2S_2O_4$) C, H, N.

4-Hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic Acid Pyridin-2-ylamide (115). A mixture of 5 g (20.2 mmol) of **148**, 12 mL of 10% NaOH solution, and 30 mL of EtOH was stirred at 60 °C for 38 h. The EtOH was removed *in vacuo* and the product precipitated by adding HCl to the remaining reaction mixture. The product was filtered, rinsed with water, and recrystallized from MeOH, giving 3 g (12.8 mmol, 63%) of carboxylic acid, mp 183−185 °C.

The carboxylic acid (34 g, 145 mmol), prepared as described above, was suspended in 50 mL of thionyl chloride and heated in a water bath at 45 °C for 30 min. The thionyl chloride was removed *in vacuo*, and the product was triturated and rinsed with petroleum ether and dried, giving 30 g (119 mmol, 82%) of acid chloride, mp 66−67 °C.

2-Aminopyridine (13.5 g, 144 mmol) in 200 mL of benzene was added to 18.1 g (72 mmol) of the acid chloride. The resulting orange emulsion was heated at 60 °C for 2 h. After two-thirds of the benzene was removed *in vacuo*, the mixture was cooled and filtered, and the solid was rinsed with water,

5% HCl, and more water and then recrystallized from MeOH, giving 12 g (39 mmol, 54%) of the enol−ether amide, mp 209−211 °C.

BBr_3 (11.8 g, 47 mmol) was added to 7 g (23 mmol) of the enol−ether amide in 100 mL of 1,2-dichloroethane cooled to 0−10 °C. After 15 h of refluxing, the 1,2-dichloroethane was removed *in vacuo*, 40 mL of EtOH was added (exothermic) and after 15 min of refluxing, 20 mL of water was added. After the mixture was heated for another 15 min, more EtOH was added to the cooled reaction, and as the product began to precipitate, 200 mL of water was added. The product was filtered, dissolved in hot Na_2CO_3 solution, filtered, and reprecipitated with HOAc. After filtering, rinsing with water, and drying, 4 g (13.6 mmol, 58%) of **115** was obtained: mp 178−180 °C; NMR (DMSO-d_6) δ 12.15 (br s, 1H), 9.0 (br s, 1H), 8.32 (s, 1H), 8.22 (m, 2H), 8.05 (m, 1H), 7.75 (m, 2H), 7.60 (m, 1H), 7.09 (m, 1H), 3.50 (s, 3H); HRMS ($C_{16}H_{13}N_3O_3$) calcd 295.0957, found 295.0969.

6-Chloro-4-hydroxy-*N*-(3-chlorophenyl)-2*H*-1-benzothiopyran-3-carboxamide (132). Titanium tetrachloride (1.67 mL, 15.2 mmol) was added dropwise to an ice-cooled solution of 5.50 g (27.7 mmol) of 6-chlorothiochroman-4-one and 11.81 g (0.166 mol) of pyrrolidine in a mixture of 20 mL of dry toluene and 20 mL of dry petroleum ether. The resulting brown suspension was stirred 15 min in the cold and then at room temperature overnight. The reaction mixture was filtered, washed with 50% toluene/petroleum ether, and concentrated *in vacuo* to an oil. To remove a little insoluble residue, the oil was dissolved in ether, $MgSO_4$ was added, and the mixture was filtered, washing with ether and CH_2Cl_2. The filtrate was concentrated to give 6.44 g (92%) of enamine as a brown semisolid.

A solution of 1.00 g (3.97 mmol) of the preceding enamine and 0.58 mL (4.77 mmol) of 3-chlorophenyl isocyanate in 10 mL of $CHCl_3$ was refluxed 2.5 h under Ar. Then, 10 mL of 2 N HCl was added, and refluxing continued for 15 min. The reaction mixture was cooled to room temperature and stirred 1 h. Ether was added, and the crystals were filtered, washed with water and ether, and dried to give 0.91 g. The filtrate was extracted with EtOAc to give an oil which was crystallized from EtOH/petroleum ether to obtain an additional 0.13 g which was combined with the first crop, giving 1.04 g (2.94 mmol, 74%). A portion (250 mg) of the crude product was recrystallized from MeOH/CH_2Cl_2/ether and dried *in vacuo* at 65 °C to give 215 mg of **132**: mp 178−182 °C; NMR (DMSO-d_6) δ 10.45 (br s, 1H), 7.95−7.2 (m, 7H), 4.0 (m, 1H) 3.68 (m, 2H) (also peaks at 14.50 (s), 9.85 (s), and 4.0 (m), attributed to presence of 15% enol form). Anal. ($C_{16}H_{11}Cl_2NO_2S$) C, H, N.

6-Chloro-4-hydroxy-1-oxo-*N*-(3-chlorophenyl)-2*H*-1-benzothiopyran-3-carboxamide (133). A suspension of 800 mg (2.27 mmol) of **132** and 1.47 g (2.38 mmol) of oxone in 10 mL of water and 20 mL of acetone was stirred 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was diluted with water and filtered, and the resulting solid was washed with water, EtOH, and ether and allowed to dry to give 760 mg (2.07 mmol, 91%). A portion (250 mg) was recrystallized from DMF/ether and dried *in vacuo* at 65 °C to obtain 158 mg of light yellow crystals: mp 208−211 °C dec; IR (KBr) sulfoxide 1030 cm^{-1}; NMR (DMSO-d_6) δ 10.15 (s, 1H), 8.05−7.2 (m, 7H), 4.38 (d, 2H); also 10.75 (s), 4.70 (m), and 3.95 (m) attributed to 20% keto form. Anal. ($C_{16}H_{11}Cl_2NO_3S\cdot0.25H_2O$) C, H, N.

6-Chloro-1,1-dioxo-4-hydroxy-*N*-(3-chlorophenyl)-2*H*-1-benzothiopyran-3-carboxamide (134). A suspension of 450 mg (1.22 mmol) of **133** in 10 mL of glacial HOAc and 1 mL of 30% H_2O_2 was refluxed for 10 min and then poured into water. After standing, the precipitated product was filtered and washed with water to give 300 mg. This was triturated in MeOH and filtered to give 50 mg. The filtrate was flash chromatographed on silica gel, eluting with 2% and 5% MeOH/CH_2Cl_2 to obtain another 20 mg. The combined product was recrystallized from acetone/ether to give two crops which were combined and dried *in vacuo* at 65 °C to give 57 mg (0.15 mmol, 12%): mp 233−236 °C dec; IR (KBr) sulfone 1160, 1305 cm^{-1}; NMR (DMSO-d_6) δ 10.20 (s, 1H), 8.10−7.25 (m, 7H), 4.80 (s, 2H); also 10.60 (s) and 4.50 (m) attributed to 20% keto form. Anal. ($C_{16}H_{11}Cl_2NO_4S\cdot0.25H_2O$) C, H, N.

6-Chloro-4-hydroxy-*N*-(5-methyl-2-thiazolyl)-2*H*-1-benzothiopyran-3-carboxamide (135). To a solution of 840 mg (4.23 mmol) of 6-chlorothiochroman-4-one in 8.5 mL of dry THF at −70 °C under Ar was added 3.17 mL (5.07 mmol) of 1.6 M lithium diisopropylamide solution. This was warmed to 0 °C for 30 min and recooled to −70 °C, and 0.74 mL (4.23 mmol) of HMPA followed by 0.40 mL (5.07 mmol) of methyl cyanoformate was added. The reaction was stirred for 15 min at −70 °C, 30 min at 0 °C, and 30 min at room temperature and then quenched with saturated NH_4Cl solution. This was extracted with ether, and the organic phases were washed with aqueous NH_4Cl and Na_2CO_3, dried (Na_2SO_4), and concentrated *in vacuo* to give 1.46 g of a dark oil. Flash chromatography on silica gel eluting with 1% EtOAc/petroleum ether afforded 660 mg (2.58 mmol, 61%) of ester as an oil which crystallized.

The preceding ester (250 mg, 0.974 mmol) and 170 mg (1.46 mmol) of 2-amino-5-methylthiazole in 2.5 mL of xylene was refluxed under Ar, 4.5 h. The reaction mixture was concentrated *in vacuo*, triturated in alcohol, and filtered. The resulting solid was recrystallized from DMF/ether to give yellow crystals which were boiled in MeOH, concentrated, filtered, and dried *in vacuo* at 65 °C to obtain 168 mg (0.5 mmol, 51%) of **135**: mp 267−269 °C; NMR (DMSO-d_6) (consistent with 55:45 keto:enol forms) δ 12.15 (s, 0.45H), 7.90−7.20 (m, 5H), 4.15 (d, 0.55H), 3.85 (s, 0.9H), 3.75 (m, 0.55H), 3.6 (d, 0.55H), 2.3 (s, 3H). Anal. $C_{14}H_{11}ClN_2O_2S_2$ (C, H, N).

4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-1-benzo[*e*]-[1,2]thiazinyl Indol-3-yl Ketone (143). A solution of 3 M EtMgBr in ether (2.5 mL, 7.6 mmol) was added via syringe to 0.89 g of indole (7.6 mmol) in 24 mL of THF under Ar. The reaction mixture was stirred at ambient temperature for 15 min, and 15 mL of 0.5 M $ZnCl_2$ in THF (7.6 mmol) was then added. After 30 min the enamine acid chloride (**149**) reaction mixture[25] (3.78 mmol theoretical) was added. After 2 h the reaction mixture was poured into 150 mL of saturated NH_4-Cl. The aqueous phase was extracted with ether, neutralized with $NaHCO_3$ solution, and extracted again. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The major product was purified by flash chromatography on silica gel, eluting with 1% MeOH in CH_2Cl_2, giving 632 mg of enamine ketone (1.55 mmol, 41%): mp 203−206 °C; NMR ($CDCl_3$) δ 8.7 (s, 1H) 8.5 (m, 2H), 7.85 (m, 1H), 7.75 (m, 1H), 7.6 (m, 2H), 7.42 (m, 1H), 7.3 (m, 2H), 3.3 (m, 4H), 2.68 (s, 3H), 1.82 (m, 4H).

A 162 mg (0.4 mmol) portion of the above enamine ketone was combined with 10 mL of MeOH and 2 mL of 5 N HCl and heated to reflux. After 3 h the reaction mixture was stirred on ice and the resulting precipitate filtered and recrystallized from EtOH, giving 40 mg of **143** (11 mmol, 28%): mp 282−284 °C; NMR (DMSO-d_6) δ 12.4 (s, 1H), 8.75 (s, H), 8.34 (m, 1H), 8.20 (m, 1H), 7.95 (m, 4H), 7.60 (m, 1H), 7.30 (m, 2H), 2.88 (s, 3H). Anal. ($C_{18}H_{14}N_2O_4S$) C, H, N.

3-(Benzimidazol-2-yl)-4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-1-benzo[*e*][1,2]thiazine (144). A solution of 100 mg of **150** (0.29 mmol) in 5 mL of HOAc was heated on an oil bath at 65 °C for 17 h. The HOAc was removed *in vacuo* and the residue suspended in water and extracted into CH_2-Cl_2. The extracts were washed with water and brine, dried ($NaSO_4$), and concentrated. The residue was recrystallized from EtOH, giving 16 mg of **144** (0.049 mmol, 17%): mp 279−281 °C; NMR (DMSO-d_6) δ 12.71 (s, 1H), 8.07 (d, 1H), 7.8 (m, 3H), 7.62 (m, 1H), 7.4 (m, 1H), 7.22 (m, 2H), 2.89 (s, 3H). Anal. ($C_{16}H_{13}N_3O_3S$) C, H, N.

Biological Methods. Microsomal COX-1 and COX-2 Assays. The expression of human COX-1 and COX-2 genes in a baculovirus system, preparation of microsomes from High Five insect cells, and microsomal assays are described in ref 12.

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