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Thiazole Analogues of the NSAID Indomethacin as Selective COX-2 Inhibitors

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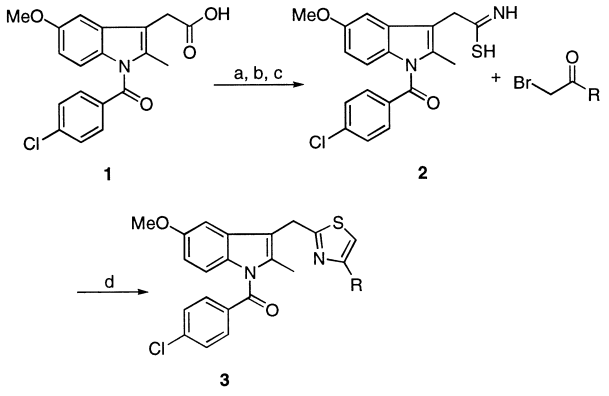
Abstract—The carboxyl group of the NSAID indomethacin was replaced with a variety of substituted thiazoles to obtain a series of potent, selective inhibitors of COX-2. Additional substitutions were made at the 1-position and 5-position of the indole of indomethacin.

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for the treatment of ailments such as pain, fever, and inflammation. Classical NSAIDs are nonselective inhibitors of both known isozymes of cyclooxygenase (COX-1 and COX-2). COX-1 is expressed constitutively in most cell types and plays a role in gastric cytoprotection and in maintaining normal renal function. The COX-2 pathway involves an induction mechanism resulting in elevated expression in inflamed tissues. These differences provide the rationale for the development of selective COX-2 inhibitors.[1] Two COX-2 inhibitors, celecoxib[2] and rofecoxib,[3] have been approved and are currently being marketed.

The typical side effects seen with the use of NSAIDs include ulcers and bleeding and incidence of renal problems with chronic therapy, presumably resulting from the inhibition of the COX-1 isozyme. Selective inhibition of COX-2 appears to provide an advantage for inflammation and pain relief without the negative side effects observed with traditional NSAIDs.[4]

Indomethacin (**1**) is a nonselective inhibitor of both COX-1 and COX-2.[5] A high throughput screening assay using recombinanat enzyme, however, showed the glycerol ester of indomethacin to be approximately 400 times selective for COX-2 (IC_{50} for COX-1 = 12.4 μM; IC_{50} for COX-2 = 30 nM).[6] Marnett and co-workers have recently reported ester and amide derivatives of indomethacin to be selective COX-2 inhibitors.[7] Previously, Merck reported that extending the acetic acid chain as well as replacing the *N*-benzoyl results in COX-2 selectivity.[8] We wish to report that replacement of the indomethacin carboxyl group with a variety of substituted thiazoles leads to a series of potent and selective inhibitors of COX-2.

A series of 4-substituted thiazoles was prepared as shown in Scheme 1. The indomethacin carboxyl group was activated with isobutylchloroformate then treated with ammonia gas to give the amide. The amide was allowed to react with phosphorus pentasulfide to form the thioamide. Reaction of the thioamide with a variety of α-bromoketones gave the 4-substituted thiazoles (**3**).



Scheme 1. Reagents and reaction conditions: (a) isobutylchloroformate; (b) NH_3 (g); (c) P_4S_{10}, THF/dioxane; (d) THF, rt, 24 h.

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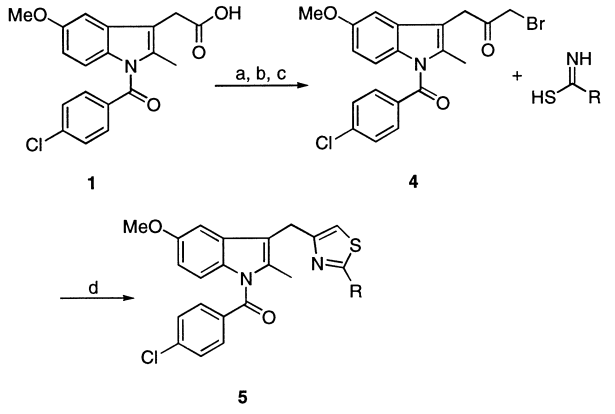
Treatment of indomethacin with thionyl chloride followed by trimethylsilyldiazomethane and HBr yielded the corresponding α-bromoketone **4** (Scheme 2). Subsequent reaction with selected thioamides gave the 2-substituted thiazole analogues (**5**).

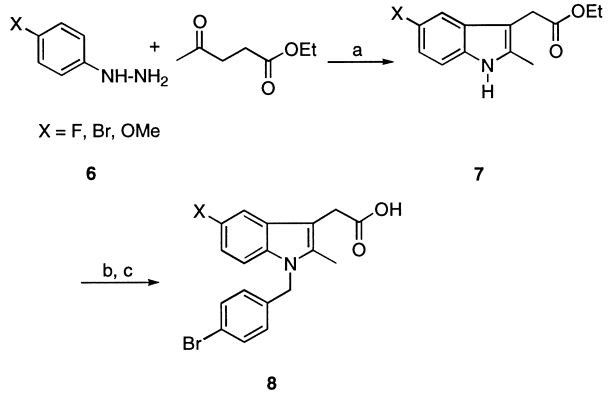
Replacement of the *p*-chlorobenzoyl group of indomethacin with *p*-bromobenzyl is reported to generate a COX-2 selective inhibitor.[8] Corresponding thiazole analogues with additional changes in the 5-position of indole (**8**) are prepared as shown in Scheme 3. Fischer indole synthesis is carried out between the appropriately substituted phenyl hydrazine and ethyl levulinate. Treatment with sodium hydride and 4-bromobenzyl bromide followed by ester hydrolysis gives the carboxylic acid which can be further elaborated as described in Scheme 1 or 2. The structures of all compounds were established by proton NMR and mass spectrometry.

A variety of thiazole analogues of indomethacin have been prepared and were tested for their inhibitions of human recombinant prostaglandin endoperoxidase H synthase-1 and -2 (PGHS-1 and PGHS-2, also referred to as COX-1 and COX-2, respectively).[6] These compounds were shown to be highly selective, potent inhibitors of COX-2. Little activity against COX-1 (<57% inhibition at 10 μM) was observed.



1 4 5

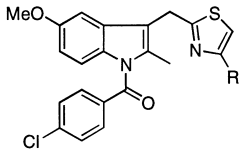
Scheme 2. Reagents and reaction conditions: (a) $SOCl_2$, CH_2Cl_2; (b) trimethylsilyldiazomethane, THF; (c) HBr, Et_2O; (d) THF, rt, 24 h.



6 7 8

Scheme 3. Reagents and reaction conditions: (a) NaOAc, HOAc, toluene; (b) NaH, 4-bromobenzyl bromide, DMF; (c) NaOH.

Table 1. Cyclooxygenase activity of thiazole analogues of indomethacin with substitutions in the 4-position of the thiazole[6]



3

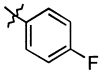
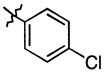
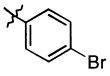
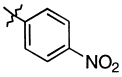
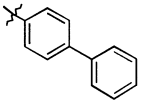
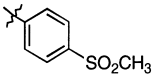
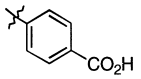
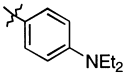
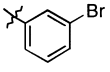
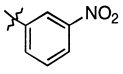
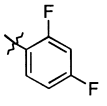
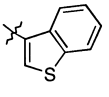
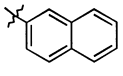
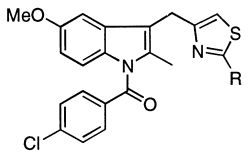
Compd	R	COX-2 IC_{50} (nM)	COX-1 (% inhibition @ 10 μM)
3a		12	28
3b		14	16
3c		0.3	27
3d		12	17
3e		21% @ 100 nM	13
3f		33% @ 100 nM	15
3g		120	35
3h		36% @ 100 nM	23
3i		8	18
3j		85% @ 100 nM	35
3k		75% @ 100 nM	12
3m	CO_2Et	40% @ 100 nM	1
3n	COOH	2% @ 100 nM	6
3p	*i*Pr	1% @ 100 nM	36
3q		1	20
3r		7	11
3s		6% @ 100 nM	13

Table 2. Cyclooxygenase activity of thiazole analogues of indomethacin with substitutions in the 2-position of the thiazole[6]



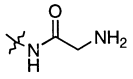
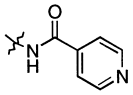
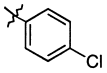
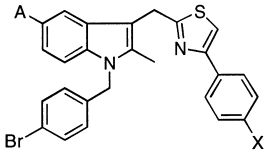
Compd	R	COX-2 IC_{50} (nM)	COX-1 (% inhibition @ 10 μM)
5a	NH_2	390	15.5 mM
5b		4% @ 100 nM	27
5c		45% @ 100 nM	0
5d		20	47
5e		75% @ 100 nM	57
5f		16% @ 100 nM	18
5g		42% @ 100 nM	24

Table 3. Cyclooxygenase activity of *N*-(*p*-bromophenyl)indole thiazole analogues with substitutions in the 5-position of the indole[6]



9

Compd	A	X	COX-2 IC_{50} (nM)	COX-1 (% inhibition @ 10 μM)
9a	OMe	Br	30	3
9b	OMe	Cl	7	2
9c	OMe	COOH	10% @ 100 nM	40
9d	OMe	NO_2	7	9
9e	Br	Br	7% @ 100 nM	13
9f	Br	Cl	9% @ 100 nM	4
9g	Br	NO_2	7% @ 100 nM	1
9h	F	Br	25% @ 100 nM	0
9i	F	Cl	37% @ 100 nM	7
9j	F	NO_2	40% @ 100 nM	1

The thiazole analogues with aromatic moieties were in general extremely potent inhibitors of COX-2. Halogen substitution on the phenyl ring resulted in good potency against COX-2 ($\leq$14 nM), with the *p*-bromophenyl analogue showing subnanomolar activity (ex. **3c**). The benzothiophene and naphthalene derivatives had single digit nanomolar activity (e.g., **3q** and **3r**, respectively). Aromatic substitutions in the 4-position of the thiazole (Table 1) were more active than the corresponding 2-substituted derivatives (Table 2).

Removal of the aromatic ring and substituting directly onto the thiazole ring resulted in decreased activity. The amine (**5a**), amide (**5b**), carboxylic acid (**3n**), ethyl ester (**3m**), and alkyl (**3p**) derivatives all showed minimal COX-2 activities.

Replacement of the *p*-chlorobenzoyl group of indomethacin with *p*-bromobenzyl is reported to generate a COX-2 selective inhibitor.[8] Replacing the *p*-chlorobenzoyl with *p*-bromobenzyl in the thiazole derivatives, however, resulted in decreased activity (Table 3). Comparison of the 4-(*p*-bromophenyl) analogues (**3c** and **9a**) shows the *N*-(*p*-chlorobenzoyl) compound to be 100 times more potent than the *N*-(*p*-bromobenzyl) derivative.

The 5-methoxy substitution on the indole appears to be important for activity as well (Table 3). The 5-bromo (**9e**, **9f**, and **9g**) and 5-fluoro (**9h**, **9i**, and **9j**) substitutions both resulted in significant losses of potencies.

We have demonstrated that potent and selective inhibitors of human recombinant COX-2 can be prepared by replacing the indomethacin carboxyl group with a variety of substituted thiazoles. Aromatic substitutions in the 4-position of the thiazole are preferred.

References and Notes

1. (a) Hawkey, C. J. *Lancet* **1999**, *353*, 307. (b) Masferrer, J. L.; Zweifel, B. S.; Manning, P. T. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3228.
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5. In our assay indomethacin showed 23 nM activity against COX-1 and 350 nM activity against COX-2.[6]
6. Human recombinant COX-1 and COX-2 were cloned and expressed in baculovirus (Sf9). Sf9 microsomes were pre-incubated with inhibitor for 60 min prior to the addition of arachidonic acid (10 μM). PGE_2 produced was analyzed by enzyme linked immunoassay.

7. (a) Kalgutkar, A. S.; Marnett, A. B.; Crews, B. C.; Remmel, R. P.; Marnett, L. J. *J. Med. Chem.* **2000**, *43*, 2860. (b) Kalgutkar, A. S.; Crews, B. C.; Rowlinson, S. W.; Marnett, A. B.; Kozak, K. R.; Remmel, R. P.; Marnett, L. J. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 925.
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