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DESIGN AND SYNTHESIS OF SULFONYL-SUBSTITUTED 4,5-DIARYLTHIAZOLES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

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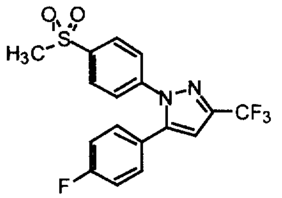
Abstract: A series of novel sulfone substituted 4,5-diarylthiazoles have been synthesized and evaluated for their inhibition of the two isoforms of human cyclooxygenase (COX-1 and COX-2). This series displays exceptionally selective COX-2 inhibition. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction: Elevated levels of prostaglandins have long been associated with inflammation.[1] Vane discovered that inhibition of the enzyme cyclooxygenase (COX-1) prevented the conversion of arachidonic acid to prostaglandins. Recently, COX-2, an inflammation-upregulated[2] isoform of the enzyme cyclooxygenase, has been discovered. Currently marketed nonselective COX inhibitors (nonsteroidal antiinflammatory drugs, NSAIDS) deplete gastrointestinal tissues of basal levels of prostaglandins needed for normal, healthy function and cause gastrointestinal irritation and ulceration.[3] Therefore, selective inhibition of COX-2 is the goal for development of gastric sparing, antiinflammatory agents.

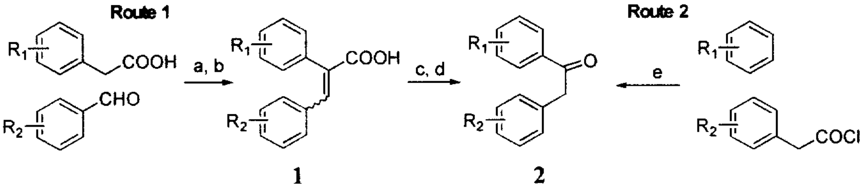
A variety of classes of COX-2 inhibitors have been described.[4] Exemplary of the diaryl-heterocycle class is SC-58125,[5] which requires a sulfonyl moiety for optimal selectivity. Recently reported research on diaryl thiazoles by Gauthier et al.[6] lead us to report our discoveries within this class.



SC-58125
hCOX-1 IC_{50} = >1000 μM
hCOX-2 IC_{50} = 0.10 μM

Chemistry: As shown in Scheme 1, the starting deoxybenzoins (**2**) were prepared via two routes. Route 1 consists of a Perkin condensation yielding acid **1**, Curtius rearrangement of the acylazide of 1 and subsequent hydrolytic treatment of the resulting enamine to yield **2**. Route 2 consists of Friedel-Crafts acylation of an aromatic substrate by a substituted phenacetyl chloride.

Scheme 1



Reaction Conditions: (a) Ac_2O, Et_3N, Δ; (b) H_2O; (c)DPPA, Et_3N, $Ph\text{-}CH_3$, 0 °C → reflux; (d)*t*-BuOH, HCl, RT → reflux; (e) $AlCl_3$, CH_2Cl_2

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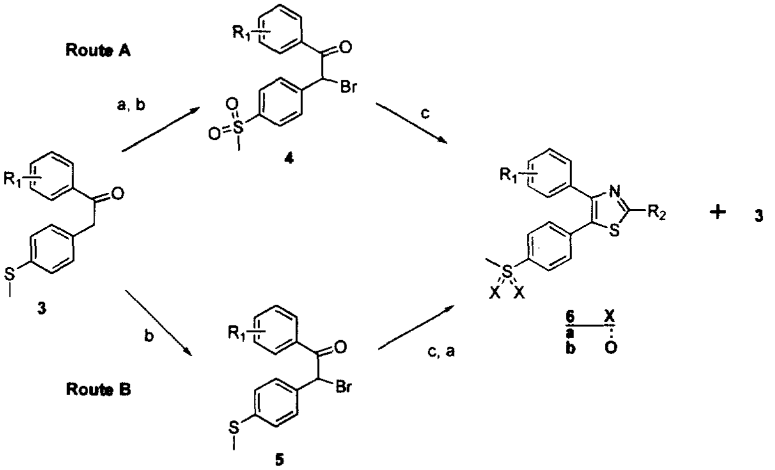
Our initial strategy for preparation of thiazole **6** is shown in Scheme 2, Route A. Although short, Route A frequently suffered low yields due to debromination of bromoketone **4**[7] during the Hantzch thiazole-forming reaction.[8] In general, the use of electron deficient thioamides[9] (e.g., ethyl thiooxamate) tended to exacerbate this side-reaction.

Scheme 2: Synthesis of 5-(*p*-methylsulfonylphenyl)thiazoles



Reaction Conditions: (a) *m*-CPBA or OXONE; (b) Br_2, HBr, HOAc (c) R-CS-NH_2, CH_3CN or EtOH, RT → reflux.

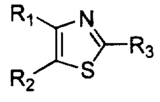
In addition, the rate of dehalogenation was more prominent with bromoketones bearing a sulfonyl-substituted phenyl proximal to the bromine. Use of thioether substituted bromo ketone **5** during the Hantzch synthesis provided thiazole **6a** in good yields with minimal dehalogenation. Oxidation of **6a** with *m*-CPBA or OXONE® yielded sulfone **6b**. This approach was also successful for the regioisomeric 4-(*p*-methylsulfonyl)thiazoles.

The subtle structural changes required to alter selectivity were most notable in the two regioisomeric thiazoles as shown in Table 1. Although sterically very similar, 2-trifluoromethyl analogs **7** and **10** show remarkably different COX-1 potency while being potent COX-2 inhibitors. Within the range of our enzyme assay,[2e] the 2-methyl analogs **8** and **11** have similar potencies (consistent with Gauthier et. al[6a]). Most striking however is the disparity in activity between regioisomeric 2-phenyl analogs **9** and **12**. The 5-*p*-methylsulfonylphenyl thiazole regioisomer series displayed potent and selective COX-2 inhibition and thus was studied further.

Lipophilic 2-position substituents, including the sterically bulky *t*-butyl analog **14**, are potent and selective. Analogs with polar substituents, such as 2-ethoxycarbonyl (**15**) and 2-cyanomethyl (**16**) exhibit decreased potency against COX-2. Tethered 2-aryl analogs display exceptional selectivity throughout the series. Interestingly, the decreased COX-2 potency noted for phenylpropyl derivative **19** was regained by incorporation of a *p*-bromo substituent on this terminal phenyl (**20**). The more lipophilic 2-aryl moieties displayed greater COX-2 potency while more polar pyridyl moieties (**25**, **26**) resulted in one to two orders of magnitude drop in COX-2 potency.

Thiazole **21** displayed excellent selectivity and potency in vitro and good activity in vivo in the carrageenan rat paw edema (CPE) model of inflammation (ED_{50} 20 mpk).[11] Maintaining the 2-(2-chlorophenyl) moiety, we varied the 4-substitutent. Interestingly, although any single fluorine substitution provided good potency and activity, the 2,5-difluorophenyl substitution of thiazole **31** displayed greatly diminished activity in vitro. Analogs **33** and **34** show that the thienyl moiety is a good replacement for a phenyl.

Table 1



Compd.	R_1	R_2	R_3	hCOX-1 (IC_{50} uM)	hCOX-2 (IC_{50} uM)
7	4-CH_3SO_2Ph	4-F-Ph	CF_3	1.07	0.006
8	4-CH_3SO_2Ph	4-F-Ph	CH_3	>100	0.12
9	4-CH_3SO_2Ph	4-F-Ph	Ph	>100	0.54
10	4-F-Ph	4-CH_3SO_2Ph	CF_3	>100	0.023
11	4-F-Ph	4-CH_3SO_2Ph	CH_3	>10	0.11
12	4-F-Ph	4-CH_3SO_2Ph	Ph	>100	>30
13	4-F-Ph	4-CH_3SO_2Ph	CH_2CH_3	19	0.023
14	4-F-Ph	4-CH_3SO_2Ph	*t*-Bu	>100	0.11
15	4-F-Ph	4-CH_3SO_2Ph	CO_2Et	>100	0.61
16	4-F-Ph	4-CH_3SO_2Ph	CH_2CN	>100	0.35
17	4-F-Ph	4-CH_3SO_2Ph	$PhCH_2$	>100	0.018
18	4-F-Ph	4-CH_3SO_2Ph	$Ph(CH_2)_2$	>100	0.032
19	4-F-Ph	4-CH_3SO_2Ph	$Ph(CH_2)_3$	>1000	0.52
20	4-F-Ph	4-CH_3SO_2Ph	*p*-Br-$Ph(CH_2)_3$	>10	0.007
21	4-F-Ph	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.05
22	4-F-Ph	4-CH_3SO_2Ph	4-Cl-Ph	>100	0.05
23	4-F-Ph	4-CH_3SO_2Ph	4-CH_3O-Ph	>10	0.27
24	4-F-Ph	4-CH_3SO_2Ph	2-thienyl	>100	0.021
25	4-F-Ph	4-CH_3SO_2Ph	3-Pyr	>1000	0.43
26	4-F-Ph	4-CH_3SO_2Ph	4-Pyr	>100	1.6
27	4-F-Ph	4-CH_3SO_2Ph	4-*t*-Bu	>100	>100
28	Ph	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.01
29	2-F-Ph	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.010
30	3-F-Ph	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.016
31	2,5-di-F-Ph	4-CH_3SO_2Ph	2-Cl-Ph	>100	>100
32	2,4-di-F-Ph	4-CH_3SO_2Ph	2-Cl-Ph	70	0.021
33	2-thienyl	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.057
34	3-thienyl	4-CH_3SO_2Ph	2-Cl-Ph	>100	0.079

Conclusion: This series of methylsulfonyl substituted diarythiazoles is comprised of very selective COX-2 inhibitors. The thiazole nucleus imparts exceptional selectivity for COX-2. More lipophilic 2-position substituents generally enhance COX-2 inhibitory potency. Exemplary is analog **21** which displayed good activity in the carrageenan paw edema model (Edema ED_{50} = 20 mpk, Hyperalgesia 27% inhibition at 20 mpk). However, the class of diarylthiazoles are generally less potent in vivo than their pyrazole congeners. In addition to their antiinflammatory activity, compounds of this class are highly fluorescent and have been used to probe their binding within the COX-2 enzyme active site.[11]

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