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DIARYL INDENES AND BENZOFURANS: NOVEL CLASSES OF POTENT AND SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

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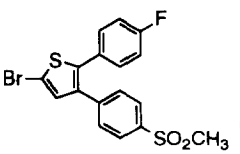
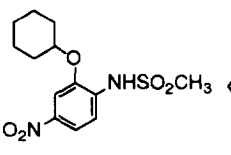
Abstract: Novel series of diaryl indenes and benzofurans have been shown to be potent and selective COX-2 inhibitors. A structure-activity relationship study suggests that the conversion of sulfones to sulfonamides affords potent, but slightly less selective COX-2 inhibitors, and that for benzofurans the 3-halo-4-methoxyphenyl sulfonamide analogs are more selective than the corresponding 4-fluorophenyl analog.

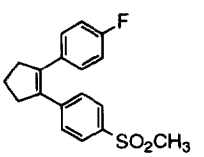
Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, have been widely used to treat chronic inflammation such as arthritis.[1] Major side effects, such as gastrointestinal (GI) hemorrhage and ulceration[1,2] have greatly limited the therapeutic potential of all the NSAIDs. It has been hypothesized that constitutive COX-1 protects the GI tract, whereas inducible COX-2 mediates inflammation.[3,4] Two structurally distinct compounds were reported to be selective COX-2 inhibitors (DuP 697 and NS-398).[5] Since then, several novel classes of potent and selective COX-2 inhibitors, such as SC-57666 (**1**)[6a] and SC-58451 (**2**),[6b] have been published.[6] Herein we now report the discovery of diaryl indenes and benzofurans as potent and selective COX-2 inhibitors.



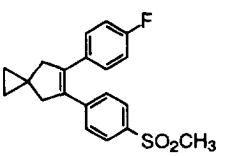
DuP 697



NS-398



SC-57666



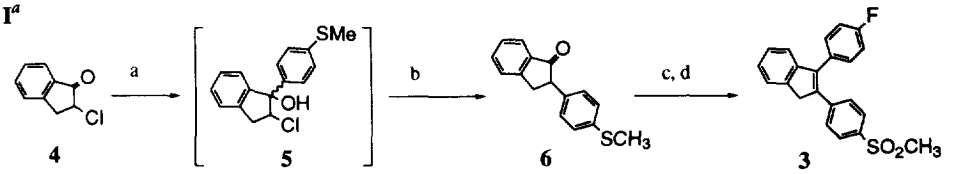
SC-58451

Chemistry

Diaryl indene **3** was prepared readily according to Scheme I. The starting chloroindanone **4** was obtained from the chlorination of the silyl enol ether of 1-indanone (TMSCl, Et_3N, and then NCS). The treatment of chloroindanone **4** with 4-methylthiophenyl magnesium bromide, followed by the rearrangement

of the resulting isomeric mixture of chlorohydrins **5**, yielded aryl indanone **6**.[7] Addition of 4-fluorophenyl magnesium bromide to indanone **6** and subsequent dehydration of the resulting alcohol yielded a diaryl indene methyl sulfide, which was treated with Oxone to give the desired sulfone **3**.

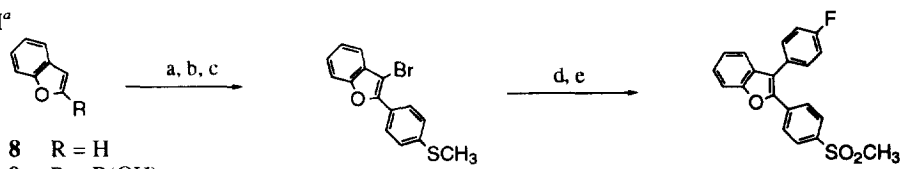
Scheme I[a]



[a] **Reagents:** (a) 4-methylthiophenyl magnesium bromide, 0 °C, THF; (b) reflux, 26%; (c) 4-fluorophenyl magnesium bromide; then 3 N HCl, 49%; (d) Oxone, THF/H_2O/EtOH, 71%

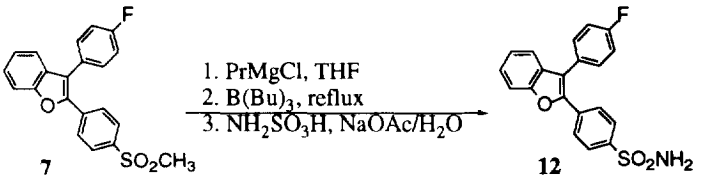
Preparation of diaryl benzofurans is exemplified in Scheme II for the synthesis of 4-fluorophenyl benzofuran **7**. Benzofuran **8** was successively treated with BuLi and trimethyl borate; hydrolytic work-up provided the corresponding boronic acid **9**. The Pd(0)-catalyzed Suzuki coupling of the boronic acid **9** with 4-bromothioanisole in toluene, EtOH, and sodium carbonate at reflux gave the monoaryl benzofuran **10**.[8] Bromination of benzofuran **10** with NBS in THF for 2 h gave bromide **11** in quantitative yield. Under Suzuki coupling conditions, bromide **11** was reacted with 4-fluorobenzene boronic acid (Lancaster) to give the diaryl benzofuran methyl sulfide, which was oxidized with Oxone to the final product, sulfone **7**. All benzofuran sulfones presented in this report were prepared in this manner, and all the required boronic acids used in step (d) were prepared following a similar procedure as in the preparation of **9**.

Scheme II[a]



[a] **Reagents**: (a) BuLi, $B(OMe)_3$; NaOH(aq); (b) 4-bromothioanisole, $Pd(Ph_3P)_4$, toluene, reflux; (c) NBS, THF; (d) 4-fluorobenzene boronic acid, $Pd(Ph_3P)_4$, toluene, reflux; (e) Oxone, THF/H_2O, 92%.

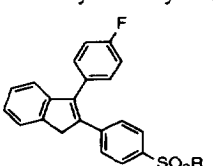
Sulfonamides were prepared from methyl sulfones using a convenient one-pot procedure recently published.[9] For example, a THF solution of methyl sulfone **7** at 0 °C was successively treated with 1.5 equivalents of propylmagnesium chloride and 2.5 equivalents of tributyl borane solution. The resulting anionic borate was thermally rearranged, with the expulsion of the corresponding homologated trialkyl borane, to give the corresponding sulfinate; oxidative amination with hydroxylamino sulfonic acid gave the corresponding sulfonamide **12**.



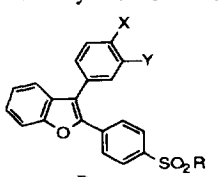
Results and Discussion

Based on the favorable pharmacological profile of diaryl cyclopentenes **1**[6a] and **2**,[6b] we initially focused our research efforts on diaryl systems which have a non-heterocyclic central ring. Diaryl indene **3** (Table 1) displayed an IC_{50} value of 11 nM for COX-2, and a selectivity ratio of 9000. On the other hand, the corresponding sulfonamide **13** (IC_{50} COX-1/COX-2 = 0.005/0.007 μM) was found to be a highly potent, but non-selective COX inhibitor. We were concerned that the benzylic group in the indene moiety might be enzymatically oxidized to give inactive metabolites. To circumvent this potential first-pass clearance process, the indene moiety was replaced by a benzofuran group. Diaryl benzofuran **7** was a very selective COX-2 inhibitor, displaying IC_{50} values of 20 nM, >100 μM for COX-2 and COX-1, respectively. The corresponding sulfonamide **12** was somewhat more potent than **7**, but only showed moderate selectivity toward COX-2 (IC_{50} COX-1/COX-2 = 75). A structure-activity study was initiated in which the sulfonamide moiety was retained and the 4-fluorophenyl group was varied in order to obtain a higher degree of selectivity. Some selected 3-halo-4-methoxyphenyl diaryl benzofurans (**14** - **17**) were prepared (Table 1).[10]

Table 1. In Vitro Activity of Diaryl indenes[a] and Diaryl Benzofurans[a]



A



B

no.	X	Y	R	Class	IC_{50} μM[b] COX-2	IC_{50} μM[b] COX-1	Selectivity (IC_{50} COX-1/COX-2)
3	F	H	CH_3	A	0.011	>100	>9000
13	F	H	NH2	A	0.005	0.007	1.4
7	F	H	CH_3	B	0.020	>100	>5000
12	F	H	NH2	B	0.007	0.49	70
14	MeO	F	CH_3	B	0.093	>100	>1075
15	MeO	F	NH2	B	0.005	1.13	226
16	MeO	Cl	CH_3	B	0.100	>100	>1000
17	MeO	Cl	NH2	B	0.020	5.74	287

[a]All new compounds were fully characterized. [b]Human recombinant enzymes, for its expression and assay, see reference 11.

The 3-halo-4-methoxyphenyl sulfones **14** and **16** were not as selective or as potent as the 4-fluorophenyl sulfone **7** (Table 1). Conversion of the sulfonyl moiety to a sulfonamide group yielded analogs **15** and **17** (IC_{50} for COX-2 = 5 nM and 20 nM, respectively) which were more potent, but less selective (selectivity ratio = 226, and 287, respectively) than the corresponding sulfones **14** and **16**. When compared with the 4-fluorophenyl sulfonamide **12**, 3-chloro-4-methoxyphenyl sulfonamide **17** showed weaker potency, but greater selectivity. On the other hand, 3-fluoro-4-methoxyphenyl sulfonamide **15** displayed both improved potency and greater selectivity than 4-fluorophenyl sulfonamide **12**. Thus, sulfonamides **15** and **17** exhibit very favorable overall *in vitro* pharmacological properties as highly potent and selective COX-2 inhibitors.

In summary, we have designed and synthesized novel, potent diaryl indenes and benzofurans as selective COX-2 inhibitors. An initial structure-activity relationship study suggests that the conversion of sulfones to sulfonamides affords potent, but slightly less selective COX-2 inhibitors, and that for benzofurans the 3-halo-4-methoxyphenyl sulfonamides are more selective than the corresponding 4-fluorophenyl sulfonamide. Our studies thus have successfully identified two novel classes of potent and selective COX-2 inhibitors, which may contribute to the development of a new generation of potent anti-inflammatory agents without the toxic side effects associated with the current NSAIDs.

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