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NOVEL 1,2-DIARYLCYCLOBUTENES: SELECTIVE AND ORALLY ACTIVE COX-2 INHIBITORS

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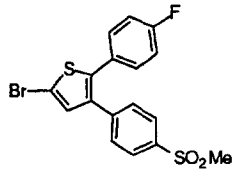
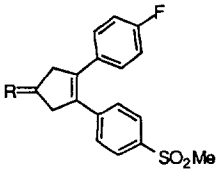
Abstract. A series of novel 2,3-diaryl-2-cyclobuten-1-ones have been synthesized and have been evaluated with respect to their ability to inhibit the isozymes of cyclooxygenase, COX-1 and COX-2. 4,4-Dimethyl-2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclobutenone **22** was found to be highly selective for inhibition of COX-2 and was orally active (ED_{50} = 2.4 mg/kg) in the rat paw edema model.

Several groups have described the preparation of selective inhibitors of cyclooxygenase II[1] (COX-2) that exhibit good oral activity.[2] The impetus behind such investigations is the potential that such a selective COX-2 inhibitor will greatly reduce the side-effect profile that is common with traditional nonsteroidal antiinflammatory drugs[3] (NSAIDs), since it has been hypothesized that inducible COX-2 mediates inflammation whereas constitutive COX-1 protects the gastrointestinal (GI) tract (in addition to other functions).[4] Several classes of selective COX-2 inhibitors that have been described to date are characterized by the presence of a bisaryl pharmacophore in which the aromatic moieties are attached to adjacent atoms in a bridging carbocyclic or heterocyclic 5-membered ring.[2] Both pentacyclic aromatic[5] (as in DuP 697[5a]) and non-aromatic[6] (as exemplified by SC-57666,[6a,b] SC-58451,[6c] or the cyclopentenone **1**[6d]) scaffolds have been investigated in this context. Herein, we describe the discovery and SAR of a series of potent and selective COX-2 inhibitors A in which the central 5-membered ring has been replaced by a cyclobutene.[7]

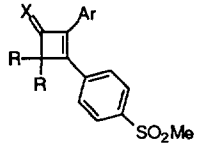


DuP-697



SC-57666 R = H
SC-58451 R = -CH_2CH_2-

1



A
22 R = Me, X = O Ar = Ph

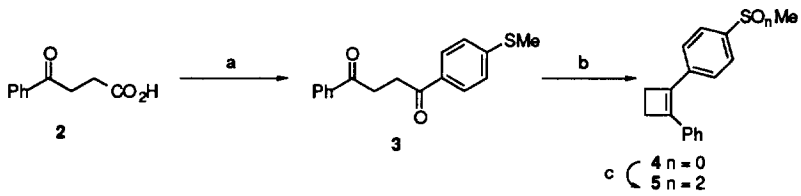
Chemistry

The cyclobutenes were prepared as depicted in Schemes 1-4. 1-Phenyl-2-[4-(methylsulfonyl)phenyl]cyclobutene **5** was prepared from 3-benzoylpropionic acid via Friedel-Crafts acylation with thioanisole followed by cyclization using the McMurry reagent[8] (Scheme 1).

The cyclobutenone **10** and cyclobutadiene **11** were prepared from phenyl acetylene and 4-bromothioanisole as outlined in Scheme 2. A [2+2] cycloaddition between **7** and the ketene derived from

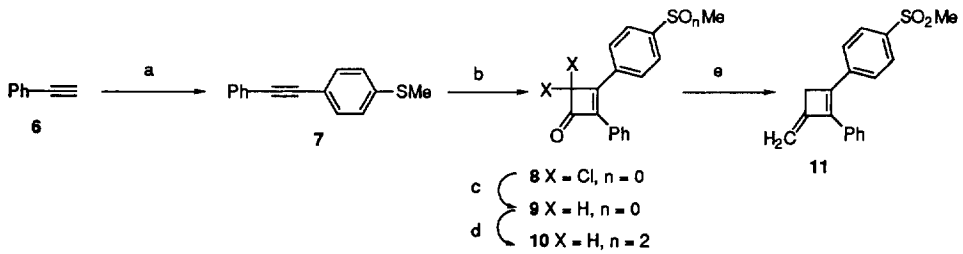
trichloroacetylchloride, in a procedure analogous to the one described by Hassner,[9] provided the intermediate dichlorocyclobutenone **8** as the major product. Reductive dechlorination of **8** with zinc[10] provided 2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclobutenone **9**, which could be oxidized to sulfone **10**[11] and homologated utilizing standard Wittig olefination procedures to provide diene **11**.

Scheme 1



Reagents: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; thioanisole, $AlCl_3$, $CHCl_3$, 0 °C (95%); (b) $TiCl_4$, -40 °C; Zn dust (50%); (c) oxone, MeOH, H_2O (21%).

Scheme 2



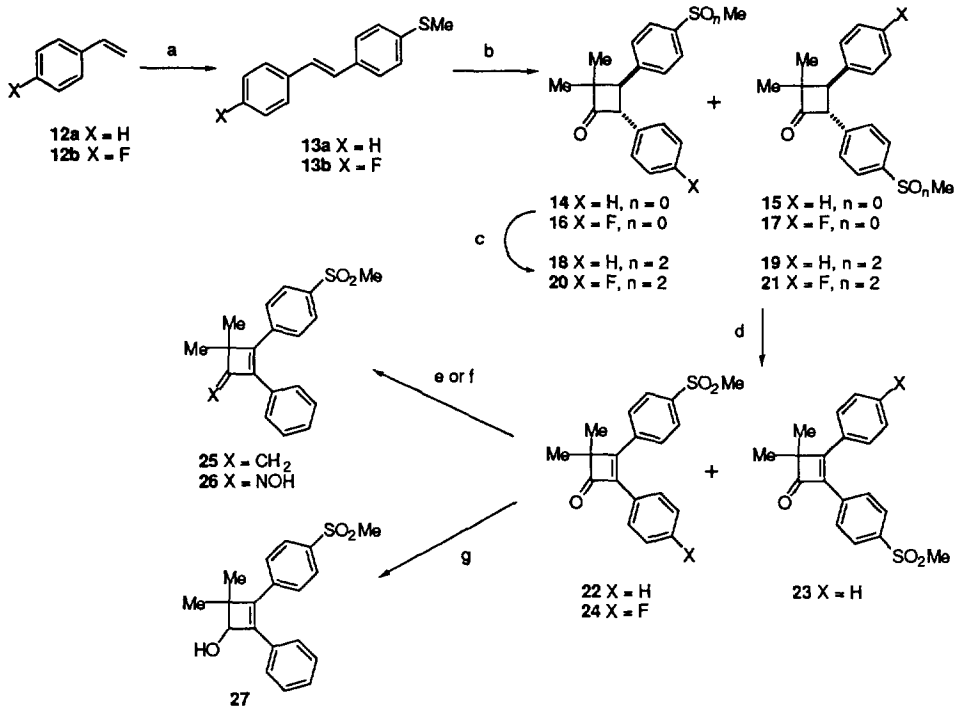
Reagents: (a) p-BrC_6H_4SMe, $Pd(Ph_3P)_2Br_2$, CuI, Et_3N, 75 °C (72%); (b) Cl_3CCOCl, $POCl_3$, Zn(Cu), Et_2O, 25 °C (23%); (c) Zn, HOAc, EtOH, TMEDA, 25 °C (27%); (d) oxone, CH_2Cl_2, MeOH, H_2O (62%); (e) Ph_3PCH_3Br, KO*t*-Bu, THF (60%).

The 4,4-dimethyl cyclobutenes **22-27** were synthesized according to the general procedure described by Ghosez[12] (Scheme 3) involving a [2+2] cycloaddition between the stilbenes **13** and the keteniminium salt derived from N,N-dimethylamide. Stilbenes **13** were prepared via Heck olefination of the requisite styrene with 4-bromothioanisole in excellent yield. Generation of the keteniminium salt from N,N-dimethyl-2-methylpropanamide using triflic anhydride and collidine, followed by reaction with stilbene **13a** provided a mixture of inseparable cyclobutanone regioisomers **14** and **15** in a 3:1 ratio[11] (85% combined isolated yield). Oxidation of the sulfide moiety using mCPBA provided the separable (silica gel chromatography) methyl sulfones **18** and **19**. The regioselectivity of the [2+2] cycloaddition reaction is strongly affected by the electronic nature of the reactants, as is demonstrated by comparing the reaction of the sulfone derivative of stilbene **13a** with that of the parent sulfide. In this case, cycloaddition with the same keteniminium salt generated the cyclobutenones **18** and **19** in a 1:4 ratio.[11] A one pot procedure involving bromination followed by dehydrohalogenation (NBS, hυ) furnished the regioisomeric cyclobutenones **22** and **23**. An analogous reaction sequence using the fluoro stilbene **13b** afforded the fluorinated cyclobutenone analog **24**. The cyclobutenes **25-27** were derived from cyclobutenone **22** via standard reactions as illustrated in Scheme

3. Thus, Wittig olefination provided diene **25**, reduction with $LiAlH_4$ afforded cyclobutenol **27** and reaction with hydroxylamine hydrochloride gave oxime **26**, all in acceptable yield.

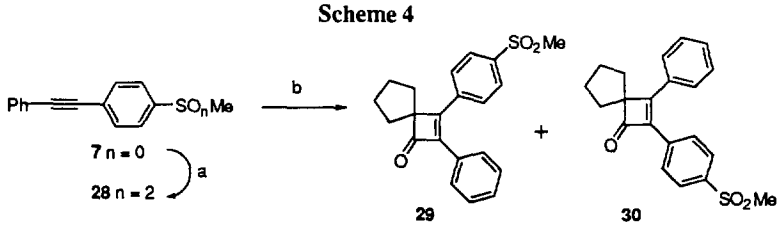
The spirocyclic sulfone **29** was prepared in analogy to the 4,4-dimethyl cyclobutenones as shown in Scheme 4. Thus, a [2+2] cycloaddition reaction according to Ghosez,[13] in this case with the keteniminium salt derived from N,N-dimethyl cyclopentylcarboxamide and the bis(aryl)acetylene **28** (obtained by oxidation of the aryl sulfide **7** (Scheme 2)), generated the corresponding spirocycles.

Scheme 3



Reagents: (a) p-BrC_6H_4SMe, $Pd(OAc)_2$, Bu_4NCl, LiOAc, LiCl, DMF, 115 °C (97-99%); (b) $Me_2NCOCHMe_2$, Tf_2O, 2,4,6-collidine, $ClCH_2CH_2Cl$, reflux (35-48%); (c) m-CPBA, CH_2CH_2, 0 °C (80%); (d) NBS, CCl_4, hυ, reflux (59-96%); (e) $HONH_2$-HCl, EtOH, pyr (36%); (f) Ph_3PBrCH_3, *t*-BuOK, THF (57%); (g) LAH, THF, 0 °C (99%).

Scheme 4



Reagents: (a) oxone, MeOH (54%); (b) $Me_2NCOCH(CH_2)_4$, Tf_2O, 2,4,6-collidine, $ClCH_2CH_2Cl$, reflux (42%).

Results and Discussion

In many of the series of selective COX-2 inhibitors that have been described to date,[2] the phenyl and 4-(methanesulfonyl)phenyl moieties comprise an important pharmacophore and the scaffold upon which this diaryl species has been arranged is typically a 5- or 6-membered ring.[14] We were interested in the possibility that modification of the dihedral angle between the aromatic moieties in a COX inhibitor may play a role in the selectivity of inhibition of COX-2 over COX-1. Decreasing the size of the scaffolding ring from a 6- or 5-membered ring to a 4-membered ring should have the effect of increasing the dihedral angle between the aromatic rings of the pharmacophore. Thus, a series of 1-phenyl-2-[4-(methylsulfonyl)phenyl]cyclobutenes were prepared as described above.

The in vitro inhibition of the COX-1 and COX-2 isozymes (CHO whole cell assay) by the cyclobutenes **10, 11, 22-27** and **29** is presented in Table 1, together with comparative data for indomethacin (**Indo**), DuP-697 and SC-58451. Also tabulated is the data generated from in vivo testing of a number of these compounds, namely the oral absorption in rats (as reflected by the maximal plasma concentration (C_{max})) and the efficacy in the rat paw edema assay upon oral administration.

Table 1. Cyclobutene Cyclooxygenase Inhibitors

Compound	COX-2 IC_{50} (μM)[a]	COX-1 IC_{50} (μM)[a]	Selectivity Ratio (COX-1/COX-2)	Plasma Concentration[b] C_{max} (μM), Time (h)	Rat Paw Edema ED_{50} (mg/kg)[c]
5	>5	nd	nd		
10	0.11	4.4	40		
11	0.0012	0.54	450	1, 1	5.5
22	0.0028	2	714	7.5, 1	2.4
23	0.096	2	21	8.5, 1	2.7
24	0.0050	0.37	74		
25	0.0022	0.12	55		
26	0.061	34	557	1.8, 1	4.2
27	0.53	45	85		
29	0.012	0.50	42		
Indo	0.049	0.039	0.8		2.0
DuP-697	0.0021	0.059	28	0.7, 2	1.3
SC-58451	0.0011	0.14	127		38%[d]

[a] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid-stimulated CHO cells stably expressing human COX-1 or COX-2 as described in ref 15. Each value is at least an average of duplicates. [b] Plasma concentration in rats when administered at 20 mg/kg in 1% methocel. [c] Ref 16. [d] % Inhibition at 30 mg/kg (Ref 6c).

While the 1,2-diarylcyclopentene SC-58451 displays good COX-2 activity and is selective, the analogous cyclobutene **1** is surprisingly inactive as a COX-2 inhibitor. However, the introduction of a

carbonyl moiety on the cyclobutene ring (cyclobutenone **10**) results in a moderately selective COX-2 inhibitor. The inhibitory potency against COX-2 and selectivity can be increased either by replacement of the carbonyl with an exocyclic methylene moiety (compare **10** and **11**) or by the introduction of a gem-dimethyl substituent on the cyclobutenone (compare **10** and **22**). This latter modification produces **22**, the most selective compound in the series. The relationship between the carbonyl group and the aromatic rings appears to be important for COX-2 activity as exemplified by **22** and its regioisomer **23**. Although both are equipotent against the COX-1 enzyme (IC_{50} = 2 μM), cyclobutenone **22**, in which the carbonyl group is conjugated with the phenyl moiety containing the methylsulfone, is 32 times more effective in inhibiting COX-2. The alcohol derivative of **22** (**27**) is 190 times less potent than the ketone **22** as an inhibitor of COX-2. Furthermore, the increase in selectivity that is observed upon addition of the gem-dimethyl substituent onto the cyclobutenone **10** is not a general trend. A similar modification of the cyclobutadiene **11** to **25** results in a decrease in selectivity, while the introduction of a spirocyclopentane in place of the gem-dimethyl group of **22** results in a less potent and less selective inhibitor of COX-2 (compare **22** and **29**). While replacement of the carbonyl moiety in **22** with an oxime (**26**) decreases the COX-2 activity approximately 20-fold, the COX-1 activity is likewise decreased such that the selectivity remains high. Finally, an apparently minor modification, such as the introduction of a fluorine atom in the para position on the phenyl substituent (**24**), results in a dramatic loss in selectivity even though **22** and **24** are of similar potency on the COX-2 enzyme. All these modifications illustrate the fact that the biaryl pharmacophore of selective and potent COX-2 inhibitors can be incorporated within a cyclobutene scaffold. However, the SAR is very tight in the cyclobutene portion of the molecule and subtle electronic and/or steric effects can dramatically alter the activity against COX-2 and/or the selectivity of inhibition of COX-2 over COX-1.

A number of these analogs were evaluated for their oral absorption and their efficacy in vivo as determined by the rat paw edema model.[16] The most promising compounds, **11**, **22**, **23** and **26** were all orally bioavailable and well behaved in rats and all showed good in vivo activity. Moreover, the in vivo activity of cyclobutenone **22** compares favourably with indomethacin and DuP-697 while being a more selective inhibitor of COX-2 than DuP-697 and SC-58451 in vitro (>700 fold in CHO cells (see Table 1) and 35 fold in human whole blood assays (IC_{50} for COX-2 and COX-1 are 0.06 and 2.1 μM, respectively)). The best compound in terms of combining intrinsic COX-2 activity, in vivo activity and pharmacokinetics, cyclobutenone **22**, was subjected to the highly stringent ^{51}Cr excretion model of ulcerogenicity[16] (100 mg/kg,[17] bid, 4 days) in order address the issue of GI toxicity. The rats treated with **22** exhibited ^{51}Cr leakage approximately twice that of the control rats, suggesting the formation of gastric lesions and/or erosions in the treated group at this high dose. However, the ^{51}Cr leakage caused by **22** was considerably less than that reported for the non-selective indomethacin and diclofenac when they were administered at a lower dose of 10 mg/kg (20-50 times increase in fecal ^{51}Cr excretion[16]). The high COX-2 selectivity of cyclobutenone **22** as determined in the in vitro assays is thus associated with an improved GI tolerability but the compound does not appear to be selective enough in vivo when its oral bioavailability and pharmacokinetic profile (C_{max} >3.5 times the IC_{50} for COX-1) are taken into account.

In summary, we have prepared a series of novel, potent and selective cyclobutenone COX-2 inhibitors from which **22** was identified as a very selective COX-2 inhibitor in vitro. Even with such an in vitro profile, the margin of safety of **22** with respect to GI toxicity is less than 40 times the efficacious dose in vivo.

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11. The regioisomers were readily assigned on the basis of NOE experiments. For example, irradiation at the resonance frequency of the methylene protons α to the carbonyl in **10** (δ 3.74, 1H, s; acetone-*d6*) resulted in enhancement of the aromatic protons on the aryl sulfone moiety, meta to the methyl sulfone (δ 8.05, 2H, d; acetone-*d6*). No enhancement of the proton resonances of the phenyl group (δ 7.40-7.50, 3H, m; δ 7.70, 2H, d) were observed. The other cyclobutenone regioisomers **14/15**, **18/19**, and **29/30** were assigned in a similar manner.
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17. Note that this dose is 40 times the efficacious dose based on the rat paw edema assay (ED_{50} = 2.4 mg/kg).

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