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# CHEMISTRY AND PHARMACOKINETICS OF DIARYLTHIOPHENES AND TERPHENYLS AS SELECTIVE COX-2 INHIBITORS[1]

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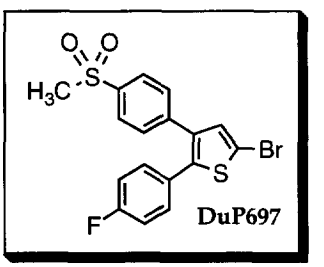
**Abstract**: DuP697, 2-bromo-4-(4'-sulfonylmethyl)phenyl-5-(4'-fluoro)phenylthiophene, is a selective type 2 cyclooxygenase (COX-2) inhibitor. Its relatively weak COX-2 selectivity coupled with a poor human pharmacokinetic profile led us to seek improvements on the in vitro selectivity while at the same time, addressing some of its pharmacokinetic liabilities. In this paper we discuss some strategies at solving the PK issue within a class of COX-2 inhibitors. The result of these efforts led to the discovery of a new class of COX-2 inhibitors the terphenyls, which prove to be superior alternatives to the diarylthiophenes.


**Introduction:** Cyclooxygenase (COX) is the first enzyme in the biosynthetic pathway to the prostaglandins (PGs). It was recently determined that mammalian cells contain two related but unique COX isozymes,[2] now commonly known as COX-1 and COX-2. COX-1 is constitutively expressed[3a,b] and is present in most tissues although the level of expression varies. Under normal physiological conditions COX-2 is nearly undetectable in most tissues, but its expression can be dramatically increased during inflammation or following exposure to mitogenic stimuli.[4a,b,5a-d] Based upon these findings, it is widely believed that a selective COX-2 inhibitor would offer advantages over current nonsteroidal antiinflammatory drug (NSAID) therapy by providing an improved safety profile. Indeed, in vivo antiinflammatory activities have been reported for selective COX-2 inhibitors[6a,b;7a-e,10a-b] which are devoid of any renal and gastrointestinal liabilities. Based on these findings, a major effort is now underway to identify and develop novel selective COX-2 inhibitors.




In our attempts to discover and develop novel safer compounds with potent antiinflammatory activity, 2-bromo-4-(4'-sulfonylmethyl)phenyl-5-(4'-fluoro)phenylthiophene DuP697[6a] was discovered, and entered into clinical trials. DuP697 was weakly active in vitro against bovine seminal cyclooxygenase (BSV COX-1), but was a potent inhibitor of prostaglandin production in cellular assays.[6a] In addition, DuP697 was orally active in the rat adjuvant arthritis (AA) and other inflammation models. Based on these data it was concluded that DuP697 was operating via a mechanism different from that known for common NSAIDs Since the discovery of the second cyclooxygenase isoform COX-2, we and other investigators have now

**Table 1:** Pharmacokinetic (PO) parameters of DuP697

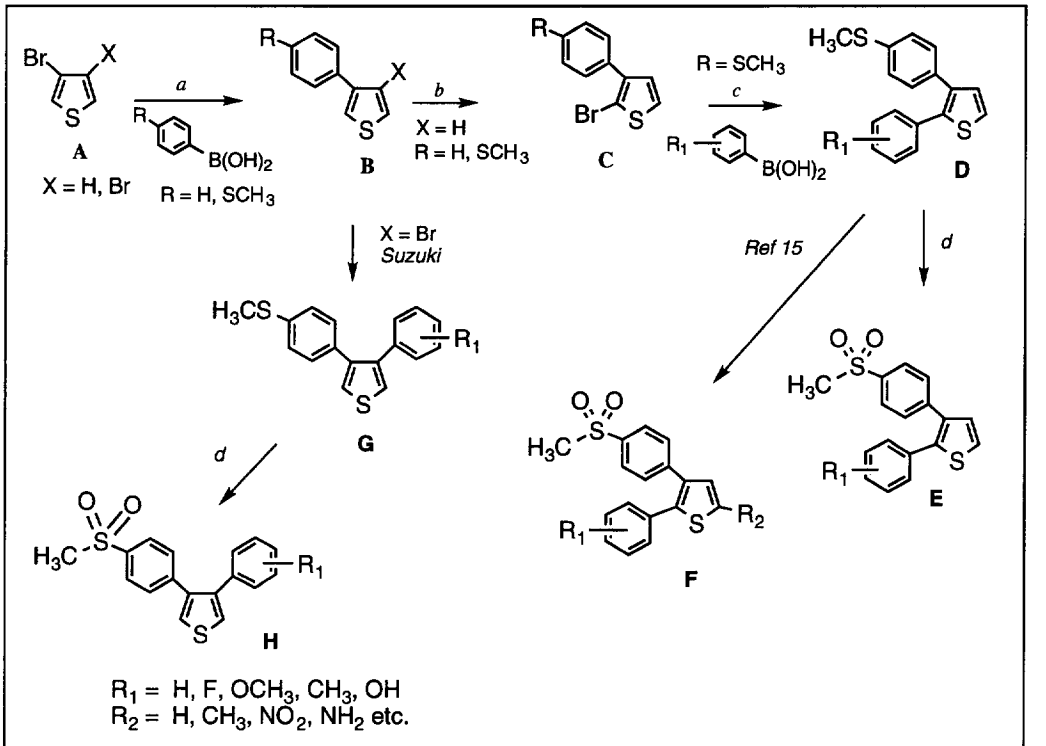
| **Parameter** | **Rat** (Sprague Dawley) | **Dog** (Beagle) | **Monkey** (Cynomolgus) | **Man** |
|---|---|---|---|---|
| Dose mg/kg | 15 | 15 | 15 | 10 |
| $C_{max}$, ng/mL | 2410 | 411 | 698 | 60.5 |
| $T_{max}$, hr | 8 | 1 | 24 | 3.0 |
| AUC, μg•h/mL | 51.6 | 1.5 | 56 | 3240 |
| $T_{1/2}$,h | 16.6 | 6.0 | 31.8 | 292 |
| F% | 75.1 | 4.4 | 30.4 | ND |

ND - not determined

shown[8a-c] that DuP697 is a selective, time dependent and essentially irreversible COX-2 inhibitor. Clinical development of DuP697 was curtailed for pharmacokinetic (PK) reasons (Table 1). The elimination profile of DuP697 in man and animals suggested that the compound distributed rapidly into tissues after absorption, followed by a much slower terminal elimination phase. Preliminary results using radio-labeled DuP697 indicated that enterohepatic recirculation played an important role in its long half-life. There was no evidence for any metabolite in man. Compound **2** was detected as the only metabolite in rats and dogs.[9] As a result, our focus, as well as the focus of several additional laboratories[7a-e,10] became the search for structurally related analogs of DuP697 with improved PK properties and enhanced COX-2 selectivity.

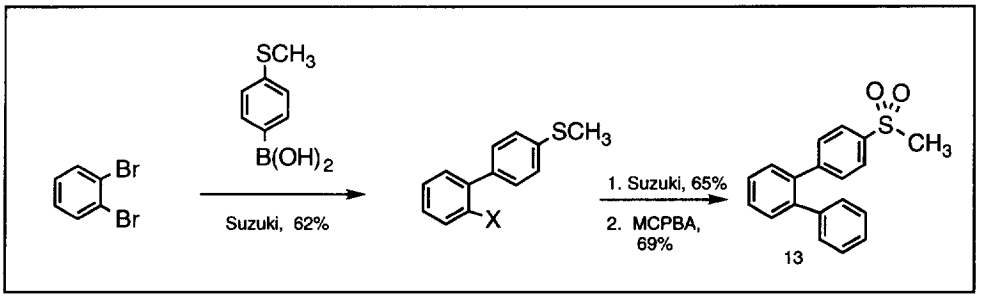
**Synthesis of diarylthiophenes:**[10] The 2,3-diarylthiophenes (Scheme 1) were prepared in a straightforward manner from commercial 3-bromothiophene. Palladium catalysed cross-coupling[11] of 3-bromothiophene **A** (X=H or Br) with a suitably substituted phenylboronic acid afforded compound **B**. Selective bromination[12] (NBS, $CH_2Cl_2$/AcOH) of **B** (X=H) afforded the 2-bromo intermediate **C**. Cross coupling of **C** with an appropriately substituted phenylboronic acid followed by oxidation (Oxone®/methanol)[13] gave the desired 2,3-diarylthiophene analogs. The Suzuki cross-coupling methodology was successfully applied to the synthesis of the 3,4-diarylthiophene analogs **G/H**, the diaryl tetrahydrobenzothiophene analog **12**, (from readily available 2-phenyl-3-bromo-benzothiophene[14]) and the terphenyl analog **13** (from 1,2-dibromobenzene, (Scheme 2, Table 3). The 2,3-diaryl-5-substituted thiophene **F** (Table 2, compounds **2-8**)

**Scheme 1**: General method for the preparation of 2,3 and 3,4-diarylthiophenes




*a. 4-methylthiophenylboronic, 2M $Na_2CO_3$, $Pd(PPh_3)_4$, toluene:EtOH 4:1, reflux, 80%; b. NBS, $CH_2Cl_2$, reflux, 1-2 h, 80%; c. arylboronic acid, Suzuki conditions,80%; d. Oxone/methanol, water, 75%.*

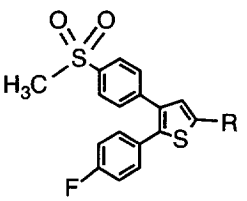
**Scheme 2:** Synthesis of the terphenyl analog **13**




were obtained from **D** via standard methods.[15] Compound **9** was obtained in three steps (NBS, AcOH; KCN, DMF and Oxone®, MeOH) fom 5-methyl-4-(4'-methylthiophenyl)-5-(4'-fluorophenyl) thiophene. Compound **10** was obtained by displacement of the 5-bromo substituent in DuP697 with the phenylthiolate anion.

**Biology - PK profile for diarylthiophenes:** The data shows (table 2 and table 3 ) that high levels (COX-1/COX-2 >100) of COX-2 selectivity are achieved. Modifications to the thiophene core (table 2) and the pendant phenyl (table 3) greatly affected the COX-2 selectivity. The critical pharmacophore for COX-2 selectivity has been reported by us[8a] and several other investigators[7a-e] to be the methylsulfone (compounds **1** verses **1e**). Removal of the 2-bromo substituent from DuP697 afforded **1,** a highly selective COX-2

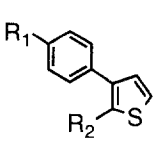
**Table 2.** In vitro COX activity for 5-substituted 2-(4'-fluoro)phenyl-3-(4'sulfonylmethyl)phenylthiophenes[a]




| Cmpd. | R | COX-1 (Ovine)[b] $IC_{50}$ μM[d] | COX-2 (Human)[c] $IC_{50}$ μM[d] | Selectivity COX-1/COX-2 |
|---|---|---|---|---|
| **1** | H | 490 | 8 | 61.2 |
| **DuP697** | Br | 38 | 7 | 5.42 |
| **2** | $SO_2CH_3$ | > 300 | 200 | > 1.52 |
| **3** | $NO_2$ | > 1000 | 14 | > 71.4 |
| **4** | $NH_2$.HCl | 6 | 3 | 2.00 |
| **5** | $CHCHCO_2C_2H_5$ | 100 | > 300 | < 0.34 |
| **6** | $CH_2CH_2CO_2C_2H_5$ | 200 | 130 | 1.52 |
| **7** | $CH_2CH_2CO_2H$ | 12 | > 300 | < 0.02 |
| **8** | $CH_3$ | 80 | 10 | 8.00 |
| **9** | $CH_2CN$ | > 300 | 49 | > 6.12 |
| **10** | $SC_6H_5$ | > 300 | 66 | < 0.02 |

[a]All compounds gave satisfactory $^1H$ NMR, mass spectra, and elemental analyses for C, H and N. [b]Obtained from Caymen pharmaceuticals. [c]Recombinant human enzyme obtained from baculovirus. [d]$IC_{50}$ represents inhibitor concentration required to reach 50% inhibition of enzymatic activity. The average standard deviation for these values was ± 15%. $IC_{50}$ values were determined using a 2 min. preincubation of the enzyme with inhibitor as previously described in ref 8a.

**Table 3.** In vitro COX activity for 1,2-diaryl analogs[a]



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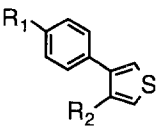
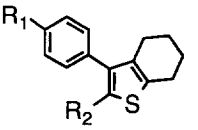
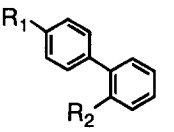


11



12



13

| Cmpd. | $R_1$ | $R_2$ | COX-1 (Ovine)[b] $IC_{50}$ μM[d] | COX-2 (Human)[c] $IC_{50}$ μM[d] | Selectivity COX-1/ COX-2 |
|---|---|---|---|---|---|
| 1 | 4-$SO_2CH_3$ | 4-$FC_6H_4$ | 490 | 8 | 61.2 |
| 1a | 4-$SO_2CH_3$ | $C_6H_5$ | > 1000 | 4 | > 250 |
| 1b | 4-$SO_2CH_3$ | 4-$CH_3C_6H_4$ | > 1000 | 13 | > 80 |
| 1c | 4-$SO_2CH_3$ | 4-$CH_3OC_6H_4$ | 48 | 5 | 9.6 |
| 1d | 4-$SO_2CH_3$ | 4-$HOC_6H_4$ | 293 | 86 | 3.4 |
| 1e | 4-H | $C_6H_5$ | 28 | >300 | <0.09 |
| 11 | 4-$SO_2CH_3$ | $C_6H_5$ | > 1000 | 4 | > 250 |
| 11a | 4-$SO_2CH_3$ | 4-$FC_6H_4$ | 674 | 8 | 84 |
| 11b | 4-$SO_2CH_3$ | 4-$CH_3C_6H_4$ | 438 | 4 | 110 |
| 11c | 4-$SO_2CH_3$ | 4-$CH_3OC_6H_4$ | > 1000 | 5 | > 200 |
| 11d | 4-$SCH_3$ | 4-$CH_3SC_6H_4$ | 15 | 101 | 0.15 |
| 11e | 4-$SCH_3$ | 4-$CH_3SO_2C_6H_4$ | 93 | 6 | 16 |
| 11f | 4-$SO_2CH_3$ | 4-$CH_3SO_2C_6H_4$ | > 300 | >300 | - |
| 12 | 4-$SO_2CH_3$ | $C_6H_5$ | > 1000 | 19 | > 52 |
| **13** | **4-$SO_2CH_3$** | **$C_6H_5$** | **> 1000** | **11** | **>100** |

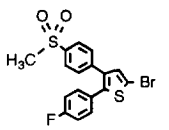
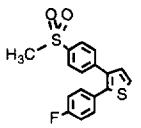
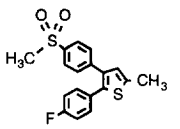
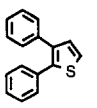
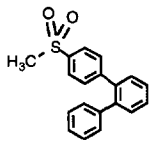
*a*, *b*, *c*, *d* refer to Table 2

inhibitor. This appears to be a common observation for compounds of the structural type **1**, **11**, **12** (table 3). Pendant para-phenyl substitutions also appear to affect the COX-2 selectivity (lipophilic para-phenyl substitutions appear to be the best). A second para-methylsulfone on the pendant phenyl (**11f**) led to an inactive analog.

The PK profile of representative compounds were determined to assess the clinical viability of the diarylthiophenes (table 4). The 2-bromo substituent in DuP697 that decreased the COX-2 selectivity (COX-1/COX-2 = 6) had a profound affect on the PK profile. DuP697 had good oral bioavailability (75%), due to its inertness to metabolism, extensive tissue distribution and long half-life ($T_{1/2}$). The des-bromo analog **1** gave greater COX-2 selectivity (COX-1/COX-2 = 61), but with a significantly poor PK profile. Its high clearance, high volume of distribution, long half-life ($T_{1/2}$) and poor oral bioavailability were undesirable. Also, in rats the methylsulfone metabolite **2** (Table 2) was formed from compound **1**. Similar PK characteristics were seen for the 3,4-diarylthiophene analogs.[16] The poor pharmacokinetics represented by compound **8** and **1e**, as well as their poor and non-selective profiles underscores the limitations of the diarylthiophenes as potential therapeutic agents.

Unable to overcome the PK liabilities of diarylthiophenes we shifted our focus to thiophene replacements. This led us to the terphenyl analog **13** (Table 3). The compound is at least 20 times (COX-1/COX-2 >100/6) more selective than DuP697. Preliminary PK evaluations showed **13** to be bioavailable (60%) with a resonable $C_{max}$, and a lower volume of distribution and half-life than some of the thiophene analogs. The terphenyl series thus offer an opportunity to manipulate the PK profile to acceptable levels.

**Table 4.** Rat (Sprague Dawley) pharmacokinetic parameters on COX inhibitors

| |  **DuP697** |  **1** |  **8** |  **1e** |  **13** |
|---|---|---|---|---|---|
| **COX-1/COX-2** | 6 | 61.2 | 8 | <0.09 | >100 |
| **Parameter** | | | | | |
| **IV** | | | | | |
| Dose, mg/kg | 15 | 15 | 15 | 15 | 15 |
| $T_{1/2}$, h | 22 | 14.3 | 19.4 | 4.94 | 1.7 |
| Cl, mL/h/kg | 218 | 3080 | 2150 | 9500 | 1690 |
| Vss, L/kg | 6.3 | 19.0 | 16.8 | 19.6 | 3.08 |
| **PO** | | | | | |
| Dose, mg/kg | 15 | 15 | 15 | 15 | 15 |
| Cmax, µg/mL | 2.4 | 0.008 | 0.020 | 0.100 | 1.43 |
| Tmax, h | 8.0 | 4.0 | 0.7 | 4.2 | 0.25 |
| $T_{1/2}$, h | 16.6 | 12.1 | NA | 2.5 | NA |
| F, % | 75 | 3.4 | 0.9 | 20 | 60 |

**NA - Not available**

In summary, while high levels of COX-2 selectivity were achieved within the diarylthiophene series, pharmacokinetic issues were not resolved. The terphenyl compound **13** represents an important lead having good COX-2 selectivity and an improved pharmacokinetic profile relative to DuP697. Details of the SAR will be published subsequently.[1]

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16. Unpublished results.

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