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TERPHENYL CYCLOOXYGENASE-2 (COX-2) INHIBITORS:[1] OPTIMIZATION OF THE CENTRAL RING AND o-BIPHENYL ANALOGS

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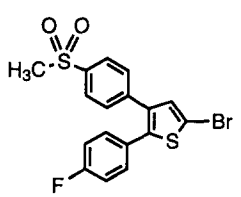
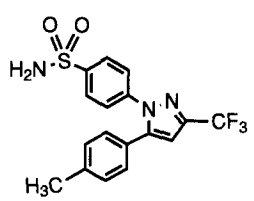
Abstract: The discovery of terphenyl derivatives as highly selective COX-2 inhibitors resulted from our efforts to overcome poor pharmacokinetics demonstrated by the COX-2 selective diarylthiophene DuP 697 [2-bromo-4-(4′-sulfonylmethyl)phenyl-5-(4′-fluoro)phenylthiophene]. Detailed SAR related to the ortho-biphenyls and variants of the central ring are described herein.

Introduction: The discovery of cyclooxygenase-2 (COX-2) as the enzyme responsible for the generation of COX products in inflammation[2] lead to a flurry of activity to identify agents that selectively block its effects.[3] Several years ago, we had identified DuP 697 as a selective and time-dependent inhibitor of COX-2.[4a–d] DuP 697 entered phase I clinical trials but was withdrawn due to an unacceptably long half life.[5] Several investigators have used the DuP 697 template and focused their attention on replacing the thiophene core with other cyclic and heterocyclic core structures.[6a–g] These efforts have lead to the discovery of Celebrex and MK966, which are now in late phase III clinical trials.[7]



DuP 697



Celebrex

Previously, we had shown that structural changes to the thiophene core afforded compounds that were highly (>100-fold) selective for the COX-2 isoform;[4a–d] however, these compounds exhibited poor oral activity. In contrast, a terphenyl analog was found to be orally bioavailable.[1,5] Since this disclosure we and others[8] have shown that the terphenyls are superior to the corresponding thiophene analogs in their selectivity for the COX-2 isoform. Like the DuP 697 class of compounds, the terphenyls also demonstrate a quasi-irreversible time-dependent inhibition of COX-2.[4b,c] Herein we wish to discuss our efforts at replacing the central phenyl to include six-membered heterocyclic moieties as well as COX-2 SAR refinements to the ortho position of the biaryl-4-methylsulfone moiety.

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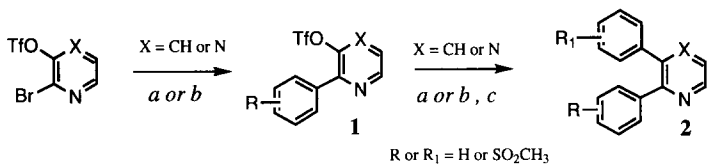
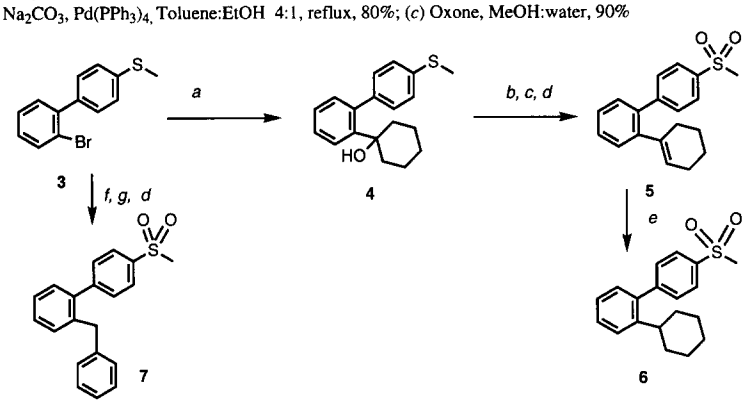
Synthesis: The six-membered heterocyclic analogs (pyridyl and piperazinyl, Scheme 1) were synthesized via a sequential Suzuki cross-coupling technique[9] followed by oxidation as discussed by us previously.[5] Heterocyclic biphenyl analogs were prepared in a similar manner from appropriate heterocyclic boronic acids although in some cases the 4-thiomethyl-2′-biphenyl boronic acid was coupled to the 2′-bromobiphenyl moiety. The cycloalkyl analogs **4–6** and the benzyl analog **7** were synthesized from the bromo-biphenyl analog **3** via the routes outlined in Scheme 2. Suzuki cross coupling of 4-methylthiophenyl boronic acid with 2-bromophenol afforded the 4-methylthiobiphenyl-2′-hydroxy intermediate. This served as a versatile intermediate towards the synthesis of the phenoxy analog **9** (Scheme 3). Condensation of the 2′-amino-4-methylsulfonylbiphenyl intermediate (obtained via the Suzuki cross-coupling of 2-bromoaniline with 4-methylthiophenyl boronic acid) with 1,5-dibromopentane under basic conditions and oxidation afforded the desired 1-piperidyl compound **10** (Scheme 4). The 1-N-methyl-tetrahydropiperidin-4-yl compound **11** was prepared in good yields via the reduction of the N-methylpyridinum salt with sodium borohydride in methanol.

Scheme 1



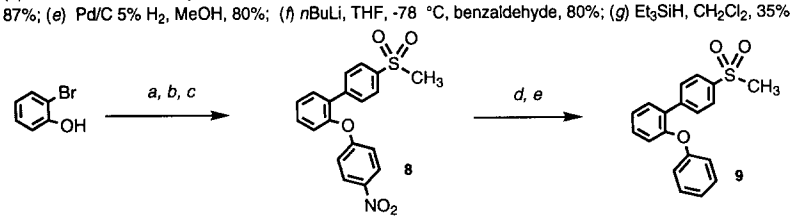
(*a*) Phenylboronic acid, 2 M Na_2CO_3, $Pd(PPh_3)_4$, Toluene:EtOH 4:1 reflux, 30%; (*b*) 4-thiomethylboronic acid, 2 M Na_2CO_3, $Pd(PPh_3)_4$, Toluene:EtOH 4:1, reflux, 80%; (*c*) Oxone, MeOH:water, 90%

Scheme 2



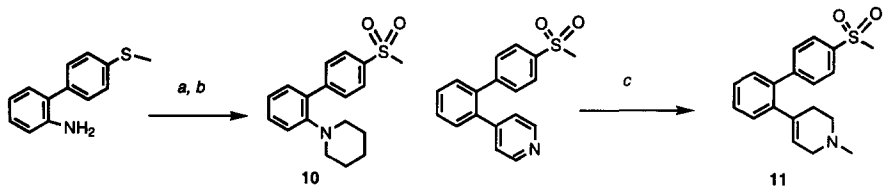
(*a*) *n*BuLi, THF, -78 °C, cyclohexanone ,77%; (*b*) *p*TsOH, toluene,6 5%; (*c*) Oxone, MeOH:water, 53%; (*d*) MCPBA 87%; (*e*) Pd/C 5% H_2, MeOH, 80%; (*f*) *n*BuLi, THF, -78 °C, benzaldehyde, 80%; (*g*) Et_3SiH, CH_2Cl_2, 35%

Scheme 3



(*a*) 4-thiomethylphenylboronic acid, 2 M Na_2CO_3, $Pd(PPh_3)_4$, Toluene:EtOH 4:1 reflux, 50%; (*b*) NaH, 1-fluoro-4-nitrobenzene, DMF , rt, 96%; (*c*) Oxone, MeOH:water 85%; (*d*) Fe, AcOH reflux 70%; (*e*) Isoamyl nitrite, THF, 61%

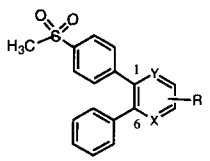
Scheme 4

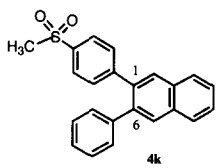


(*a*)1,5-dibromopentane, Et_3N, EtOH 38%; (*b*) Oxone , MeOH:water, 77%; (*c*) MeI, $NaBH_4$, MeOH, 90%

Discussion: It is now widely accepted that the arylmethylsulfonyl, or in some cases the arylsulfonamide functionality, coupled with an adjacent aryl group in a 1,2 substitution relationship on the central core are crucial for COX-2 inhibition. Much has been reported on the effect of COX-2 selectivity on variants of the five membered central heterocyclic core and substitutions on the respective phenyl groups. Recently we discussed our efforts at identifying the terphenyls as highly selective and bioavailable COX-2 inhibitors. We now expand the SAR of the terphenyls and also include heterocyclic biaryl moieties as well as expand the scope of the ortho-biaryl substitution.

Table 1. In vitro COX activity: central ring modifications





4k

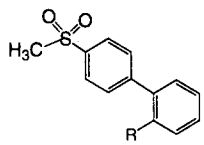
Compd	R[a]	X/Y	COX-1 (Ovine)[b] IC_{50} μM[d]	COX-2 (Human)[c] IC_{50} μM[d]	Sel. COX-1/ COX-2
2	H	CH	>1000	11	>100
4a	3-OH	CH	404	147	3
4b	3-NH_2	CH	35	194	0.18
4c	4-NH_2	CH	17	254	0.07
4d	3-NO_2	CH	>300	38	>8
4e	4-NO_2	CH	>100	44	>23
4f	3-CO_2CH_3	CH	>300	48	>6
4g	3-CO_2H	CH	232	>300	<0.77
4h	-	X = N, Y = CH	>1000	39	>26
4i	-	X = CH, Y = N	>300	>300	-
4j[e]	-	X, Y = N	>300	>300	-
4k[e]	-	-	>300	41	>7

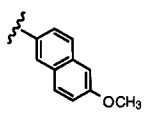
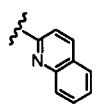
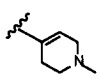
[a]All compounds gave satisfactory ^1H NMR, mass spectra, and elemental analyses for C, H and N. [b]Obtained from Caymen Pharmaceuticals. [c]Recombinant human enzyme obtained from baculovirus.[10] [d]IC_{50} represents inhibitor concentration required to reach 50% inhibition of enzymatic activity. The average standard deviation for these values was ± 15%. IC_{50} values were determined using a 2 min preincubation of the enzyme with the inhibitor as previously described.[4b]

The COX SAR around the central ring is shown in Table 1. While a number of investigators[8] have shown that COX-2 selectivity varies with the substitutions on the central phenyl ring, our efforts in this region of the molecule included other functionalities. For example, electron-withdrawing substitutions like the nitro and ester analogs **4d–4f** favor COX-2 inhibition and are about three to fourfold weaker than the unsubstituted analog **2b**. Interestingly however, the carboxylic acid analog **4g** is inactive against COX-2 and shows weak activity against COX-1. The amino compounds **4b–4c** are selective towards COX-1 whereas the phenol analog **4a** shows

selectivity towards COX-2 albeit weak in potency. Expansion of the central ring size to include the naphthyl analog **4k** affords a selective COX-2 inhibitor (COX-1/COX-2 > 7). The terphenyls as a class, were fairly insoluble and the need to include hydrophilic functionalities without compromising the COX-2 inhibition became one of our priorities. Towards this end we investigated the replacement of the central phenyl with heterocyclic six membered cores. In the pyridyl series only analog **4h** was potent and selective against COX-2. The other pyridyl isomer **4i** and the pyridazine analog **4j** were inactive against the COX isozymes.

Table 2. In vitro COX activity: 2-biphenyl substitutions



Compd	R[a]	COX-1 (Ovine)[b] IC_{50} μM[d]	COX-2 (Human)[c] IC_{50} μM[d]	Sel. COX-1/ COX-2
2	Phenyl	>1000	11	>100
2a		>1000	30	>33
2b		>1000	57	>18
2c		>300	>300	-
2d		>300	87	>6
2e		>300	>300	-
2f		>300	>300	-
6		>1000	31	>32
10		43	14	3
5		>1000	33	>31
11		>300	>300	-
7	$C_6H_5CH_2$	>300	>300	-
9	C_6H_5O	>1000	33	>30

[a,b,c,d]Refer to Table 1.

We next focused our attention at probing the lipophilicity and or hydophilicity requirements at the ortho-position of the biphenyl; a number of diverse substitutions were investigated (Table 2). The naphthyl analog **2a** and the quinoline analog **2b** while less potent appear to be selective for COX-2. In the pyridyl series (**2c–e**) only the 3-pyridyl analog **2d** shows COX-2 activity and selectivity. Introduction of another nitrogen, as in the case of the pyrimidine analog **2e** results in a loss of activity. Loss of COX-2 selectivity is observed going from the cyclohexyl analog **6** (COX-1/COX-2 >32) to the 1-piperidine analog **10** (COX-1/COX-2 = 3). Such fluctuations in COX activity are seen for the cyclohexene analog **5** (COX-2 active and selective) and its heterocyclic counterpart the N-methyl-tetrahydro-piperidin-1-yl analog **11** (COX inactive). Such subtleties were also evident for the benzyl analog **7**, which was inactive while the phenoxy analog **9** showed good potency and selectivity for COX-2. Although these data confirm a preference for lipophilic substitution for COX-2 activity, it is not clear why compounds **7** and **9** vary in their COX profiles. While we had optimized the SAR around the terphenyl and the heterocyclic biaryl moieties we did not pursue these further for strategic reasons. It should be noted however, that the Merck group has recently shown that the central pyridyl analogs can be optimized to afford highly potent, selective and orally bioavailable COX-2 inhibitors.[11]

In summary, we have demonstrated that the terphenyl and the 2-pyridyl series of analogs are potent alternatives to some of the diaryl-5-membered heterocyclic COX-2 inhibitors. COX-2 activity is dictated by the size and lipophilicity of the substitutions at the ortho-position of the biphenyl bearing the critical COX-2 pharmacophore. Hydrophilic substitutions confer less activity and their selectivity profile consequently varies.

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