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3,4-DIARYLTHIOPHENES ARE SELECTIVE COX-2 INHIBITORS

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Abstract: A group of 3,4-diarylthiophenes containing either a sulfone or sulfonamide moiety were synthesized and tested for COX-1 and COX-2 inhibition. They are selective inhibitors of COX-2 and possess antiinflammatory activity *in vivo.*

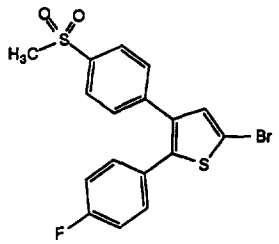
Introduction

Inhibition of prostaglandin production with non-steroidal antiinflammatory drugs (NSAIDs) has been widely used for the treatment of both acute and chronic inflammatory diseases.[1] These compounds have had significant side effects which potentially limit their use in a large proportion of the potential patient population.[2]

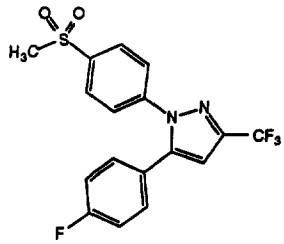
Arachidonic acid is converted to prostaglandins by at least two isoforms of the enzyme cyclooxygenase.[3,4] The constitutive form of this enzyme (COX-1) is responsible for the normal production of prostaglandins. An inducible form of cyclooxygenase (COX-2) is primarily responsible for the production of prostaglandins at sites of inflammation. Currently marketed NSAIDs inhibit both enzymes and consequently function as antiinflammatory agents with concomitant gastric and renal toxicity. The goal of our project is to discover selective inhibitors of COX-2 which should possess antiinflammatory activity without toxic side effects.

There have been a few reports of selective COX-2 inhibitors which are active in animal models of inflammation without the normal toxicity associated with cyclooxygenase inhibition.[5-9] Our attention was directed toward the studies of Gans et. al.[8] which described a 2,3-diarylthiophene (DuP-697), Figure 1.

Figure 1



DuP-697



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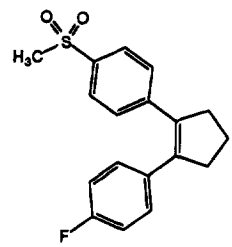

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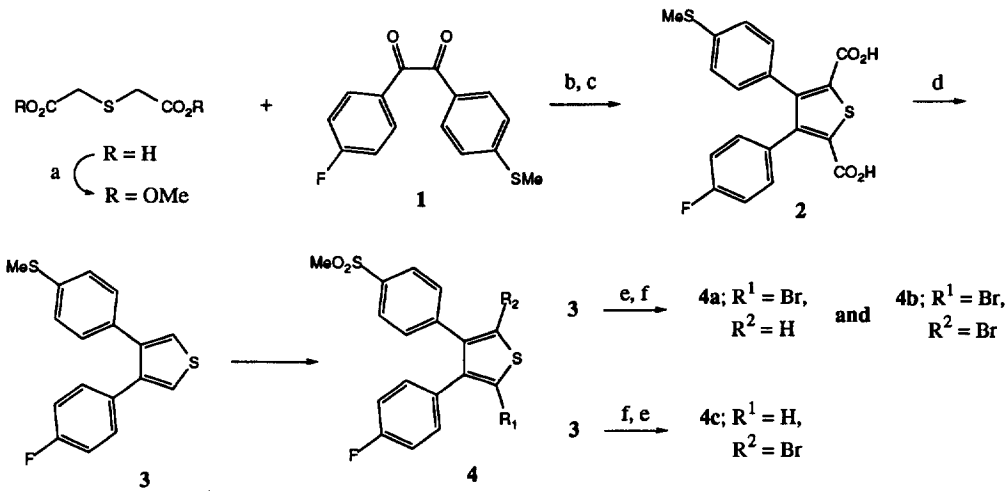
The structure of DuP-697 along with that of other diaryl heterocycle NSAISDs suggested that the nature of the substituents on the benzene rings may be important for the selective inhibition of COX-2. Since many diaryl substituted heterocycles are claimed to possess antiinflammatory properties, it was not clear what effect changes to the central ring would have. Simply isomerizing DuP-697 to its 3,4-diaryl isomer would provide insight to the importance of various structural features. This modification also provides a novel template to be investigated as a

possible NSAID having improved therapeutic properties compared with currently marketed drugs. The present study describes a series of 3,4-diarylthiophenes which are selective COX-2 inhibitors.

Chemistry

Synthesis of 3,4-diarylthiophenes has been previously described.[10,11] Condensation of a substituted benzil with dimethyl thiodiglycolate, the Hinsberg thiophene synthesis, seemed most appropriate for our needs, Scheme 1. Dimethyl thiodiglycolate is readily prepared from thiodiglycolic acid under acidic conditions.[12] Condensation of a substituted benzil with the diester in the presence of sodium methoxide yields a mixture of 2-carbomethoxy -5-carboxy thiophenes.[11] This mixture is then treated with sodium hydroxide solution in ethanol[13] to yield the 2,5-dicarboxythiophene, **2**. Decarboxylation to the 2,5-dihydro-3,4-diarylthiophene **3** is accomplished by heating in freshly distilled quinoline with copper powder as a catalyst[14], Scheme 1.

Scheme 1[a]



[a] Reaction conditions: (a) saturated HCl in MeOH; (b) NaOMe, THF, MeOH; (c) NaOH, EtOH, H_2O; (d) freshly distilled quinoline, Cu powder; (e) MCPBA, CH_2Cl_2; (f) Br_2, HOAc, 90°C.

Oxidation of the methyl sulfide to methyl sulfonyl by MCPBA in methylene chloride at 0 °C[15] followed by treatment with one equivalent of bromine in acetic acid[16] at 90°C yields a 9:1 mixture of 2-bromo-3-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)thiophene[17], **4a** and 2,5-dibromo-3-(4-methylsulfonyl phenyl)-4-(4-fluorophenyl) thiophene, **4b**, Scheme 1. Bromination of the 2,5-dihydro thiophene (sulfide oxidation state for sulfur) yields the 2-bromo-3-(4-methylthiophenyl)-4-(4-fluorophenyl) thiophene. Subsequent oxidation gives excellent yields of the sulfone, **4c**. The methyl sulfonyl moiety in **5** is conveniently transformed into a sulfonamide by the procedure of Huang et. al.[18] to yield **6**. In the case of the thiophenes, it was necessary to use 1.6M nBuLi as base to effect this transformation.[19]

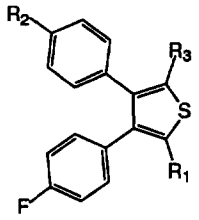
Certain symmetrically substituted benzils are commercially available. For our purposes, synthesis of unsymmetrically substituted benzils via Bi_2O_3 oxidation[20] of the corresponding benzoins[21] was ultimately necessary for the synthesis of selective COX-2 inhibitors. 4-methylthio-4'-fluoro benzoin and 4-methylthio-3'-

fluoro-4'-methoxy benzoin result from the condensation of 4-methylthiophenyl magnesium bromide with 4-fluorophenyl trimethylsilyl cyanohydrin and 3-fluoro-4-methoxyphenyl trimethylsilyl cyanohydrin respectively. 4-methylthiophenyl trimethylsilyl cyanohydrin is treated with commercially available p-methoxyphenyl magnesium bromide to yield 4-methoxy-4'-methylthio benzoin. The crude product can generally be crystallized from ethyl acetate and hexane to give good yields of analytically pure product. Benzoins are cleanly and selectively oxidized to benzils (α-diketone) by Bi_2O_3 in a mixture of glacial acetic acid and 2-ethoxy ethanol at 110 °C. Oxidation of the sulfide to a sulfone does not occur under these conditions.

Results and Discussion

The 3,4-diarylthiophene **4a** had similar activity, selectivity for COX-2[22] and in vivo potency[23] when compared to DuP-697, Table 1. The regioisomer in which the bromine is adjacent to the methylsulfonylphenyl ring, **4c**, was inactive as a COX-1 or COX-2 inhibitor. It is interesting to note that the loss of *in vitro* activity which accompanied the incorporation of a bromine atom adjacent to the 4-methylsulfonylphenyl ring was somewhat reversed by addition of a second bromine atom, **4b**, Table 1.

Table 1



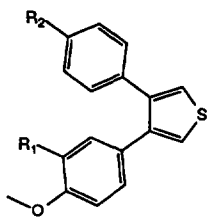
Compound	R_1	R_2	R_3	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-1/ COX-2	Carrageenan % inhib. @ 10 mpk
4a	Br	SO_2Me	H	5.2	0.015	347	30 ± 10
4b	Br	SO_2Me	Br	>1000	0.7 ± 1.4	>1,428	
4c	H	SO_2Me	Br	>100	>100		
5	H	SO_2Me	H	>1000	0.08	>12,500	33 ± 16
6	H	SO_2NH_2	H	1.8 ± 0.5	0.008 ± 0.007	225	46.5 ± 9[a]
DuP-697				0.81	0.014	58	57 ± 14

[a] % inhibiton @ 30 mpk

The des-bromo analog, **5**, was also active *in vitro* as a selective COX-2 inhibitor, and had *in vivo* activity similar to **4a**.[24] Owing to its inactivity as a COX-1 inhibitor, the 2,5-dihydrothiophene **5**, has selectivity for COX-2 over COX-1 of greater than four log units. Increased selectivity is a major goal of this project and was therefore thought to be a great advantage to this series. Thiophene **5** showed no incidence of gastric lesions when tested at 600 mpk in either mice or rats.[25]

Conversion of the methyl sulfonyl group in **5** to a sulfonamide leads to **6** which is less selective *in vitro* . Substitution of the 4-fluoro substituent by 4-methoxy in compound **7** gives rise to significant COX-1 activity, Table 2. Introduction of a 4-methoxy substituent has generally increased the COX-1 activity for the diaryl

Table 2



Compound	R1	R2	IC_{50} (μM) COX1	IC_{50} (μM) COX2	COX-1/ COX-2
7	H	SO_2Me	0.9	0.05	18
8	F	SO_2Me	>100	0.03 ± 0.005	>3,333
9	F	SO_2NH_2	10 ± 1	0.009 ± 0.006	>1,111

heterocyclic inhibitors that we have studied. Closely related to this structure is **8** which contains a 3-fluoro-4-methoxy phenyl. Addition of the 3-fluoro substituent actually increases COX-2 activity slightly while decreasing COX-1 activity by more than 2 orders of magnitude. Interconversion of the sulfonyl moiety in **8** to a sulfonamide, **9**, increases both the COX-1 and COX-2 activity *in vitro*, Table 2.

Conclusion

Initial studies for a variety of 3,4-diaryl thiophenes indicate that they are both selective COX-2 inhibitors *in vitro* and antiinflammatory agents *in vivo*. These compounds have similar potency in acute animal models of inflammation to the related 2,3-diaryl thiophenes [8]. In addition, they appear to be more selective inhibitors of the inducible form of cyclooxygenase. These initial results are promising for the development of an NSAID without gastric or renal toxicity. Further investigation into this series should result in improved activity and selectivity.

References and Notes

(1) Vane, J. R. *Nature (New Biol.)* **1971**, *231*, 232.
(2) Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. *N. Engl. J. Med.* **1992**, *327*, 749.
(3) Maier, J. A.; Hla, T.; Maciag, T. *J. Biol. Chem.* **1990**, *265*, 10805.
(4) O'Banion, M. K.; Winn, V. D.; Young, D. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 4888.
(5) Special Issue On Cyclooxygenase, *Med. Chem. Res.* **1995**, *5*, 319.
(6) Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S. A . ; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1994**, *37*, 3878.
(7) Isakson, P.; Seibert, K.; Masferrer, J.; Salvemini, D.; Lee, L.; Needleman, P. Discovery of a Better Aspirin. Presented at the Ninth International Conference on Prostaglandins and Related Compounds, Florence Italy, June 1994.
(8) Gans, K. R.; Galbraith, W.; Roman, R. J.; Haber, S. B.; Kerr, J. S.; Schmidt, W. K.; Smith, C.; Hewes, W. E.; Ackerman, N. R.*J. Pharmacol. Exp. Ther.* **1990**, *254*, 180.
(9) Futaki, N.; Takahashi, S.; Yokoyama, M.; Arai, I.; Higuchi, S.; Otomo, S. *Prostaglandins* **1994**, *47*, 55.
(10) Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* **1985**, *26* 1981.
(11) Hinsberg, O. *Ber.* **1910**, *43*, 901.
(12) Tanner, D. D.; Osman, S. A. A. *J. Org. Chem.* **1987**, *52*, 4689.
(13) Bryant, W. M. D.; Smith D. M. *J. Amer Chem Soc.* **1936**, *58*, 1014.
(14) Overberger, C. G.; Mallon, H. J.; Fine, R. *J. Amer. Chem. Soc.* **1950**, *72*, 4958.
(15) Block, H. In Reactions of Organosulfur Compounds, Blomquist, A. T. and Wasserman, H. H. Eds.; Academic: New York, 1978; p 16.
(16) Wriede, U.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 4485.
(17) The crystal structure for **4a** was determined by Nigam P. Rath, University of Missouri, St. Louis.
(18) Huang, H. C.; Reinhard, E. J.; Reitz, D. B. *Tetrahedron Lett.* **1994**, *35*, 7201.
(19) Bertenshaw, S. R.; Collins, P. W.; Penning, T. D.; Reitz, D. B.; Rogers, S. World Patent application no. 9415932.
(20) Rigby, W. *J. Chem. Soc.* **1951**, 793.
(21) Krepski, L. R.; Heilmann, S. M.; Rasmussen, J. K. *Tetrahedron Lett.* **1983**, *24*, 4075.
(22) Human recombinant enzyme preparations were used for both enzymes. See supplementary material for reference 5.
(23) Reference (18) and Winter, C. A.; Risely, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
(24) Compound **5** showed dose response behavior when tested from 0.5-20 mpk in the carrageenan rat foot edema model. The 10 mpk dose is reported for comparison to other compounds.
(25) Compound **5** was tested for gastric lesions at multiple doses (6-10 animals per dose); 600 mpk being the highest dose tested. Blood levels were determined for a 100 mpk dose in rats (Cmax = 0.95 μg/ml). For experimental details, see supplemental material for reference 5.

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