Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 18, pp. 2123-2128, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00359-2

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2,3-DIARYLTHIOPHENES AS SELECTIVE COX-2 AND COX-1 INHIBITORS

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Abstract. A series of 2,3-diarylthiophene compounds was prepared and their biological activities were evaluated against human Cox-1 and Cox-2 enzymes. It appears that the methylsulfone group is essential for both the activity and selectivity for the Cox-2 enzyme. Removal of the methylsulfone group gave relatively selective Cox-1 inhibitors.

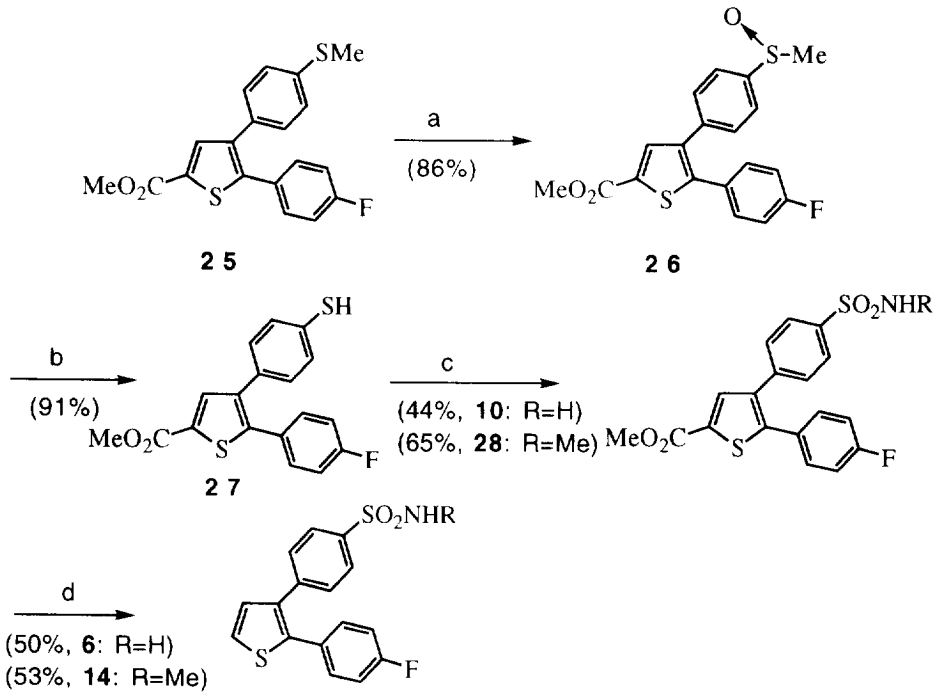
Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for the relief of pain and swelling associated with inflammation. The therapeutic effect of NSAIDs is related to their capacity to inhibit the formation of prostaglandins (PGs) via the cyclooxygenase (Cox) pathway.[1] However, all of these molecules, in spite of their beneficial effects, suffer from the same drawback, namely gastric complications such as ulceration, perforation and hemorrhage. These side effects may be attributable to the inhibition of the constitutively expressed Cox-1 enzyme.[2] Recently a new cyclooxygenase enzyme (Cox-2) which is induced under inflammatory conditions, has been reported.[3] The discovery of drugs that could selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme is obviously of significant therapeutic interest. Notable progress has been made in this field by the discovery of Cox-2 selective inhibitors such as SC-58125 and SC-57666 which are structurally related to DU697[4] and L-745,337 which is structurally related to Flosulide.[5]

We and others have shown that the antiinflammatory agent DuP 697 (**1**),[4] a member of the "tricyclic" class, is a moderately selective Cox-2 inhibitor (see Table 1). This compound does not cause gastrointestinal lesions at a dose of 400 mg/kg p.o. which is the expected profile for a selective Cox-2 inhibitor. To understand what features of the molecule control the activity and selectivity, the structure activity relationship (SAR) around the thiophene template was explored. The information obtained from this study will be useful in the development of new Cox-2 inhibitors.

Synthesis: Compounds **1** to **4** (Table 1) were prepared according to the literature.[6] The sulfonamide analogues could be efficiently obtained as described in Scheme 1 and 2. The sulfoxide **26** was prepared in 86% yield by treatment of the thioether **25** with mCPBA in CH_2Cl_2 at 0 °C. Pummerer rearrangement of sulfoxide **26** with TFAA afforded the thiol **27** after co-evaporation with MeOH/Et_3N.[7] The sulfonamide group was then formed using the method of Kharasch; Cl_2 in AcOH followed by aminolysis to give **10** and **28** in 44 and 65% yields respectively.[8] After hydrolysis and decarboxylation, the analogues **6** and **14** were

obtained. The positional isomer **7** could be prepared via the cyanohydrin route as shown in Scheme 2. 4-Bromobenzaldehyde **29** was treated with TMSCN in the presence of ZnI_2 in 1,2-dichloroethane to give the

Scheme 1



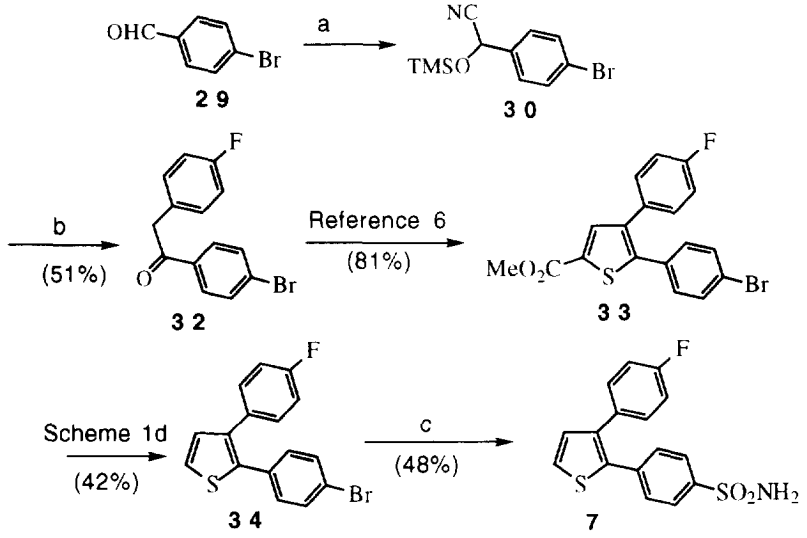
Reagents: (a) mCPBA, CH_2Cl_2,0 °C; (b)i. TFAA, reflux; ii. Et_3N/MeOH; iii. coevaporation; (c)i. Cl_2, HOAc, 0 °C to rt; ii. NH_2R, THF, 0 °C to rt; (d)i. NaOH, MeOH, THF; ii. Cu, quinoline, 140 °C.

cyanohydrin **30**. The anion derived from **30** (LDA/THF) was condensed with 4-fluorobenzyl bromide **31** to provide the ketone **32** in 51% yield which was converted to the thiophene **34** using the method described in the literature.[6] Finally, the sulfonamide group was introduced by lithiation of **34** (tBuLi/-100 °C), condensation on SO_2 in THF at -100 °C followed by sequential treatment with SO_2Cl_2 and NH_3 afforded **7** in 48% yield.

For the synthesis of the corresponding selenone, the thiophene **37** was prepared as outlined in Scheme 3. Following lithiation and trapping of the anion with Se then MeI the selenide **38** was obtained (26% yield). The oxidation to the selenone **16** was performed as described by Krief (mCPBA, CH_2Cl_2, 0 °C) in 80% yield.[9]

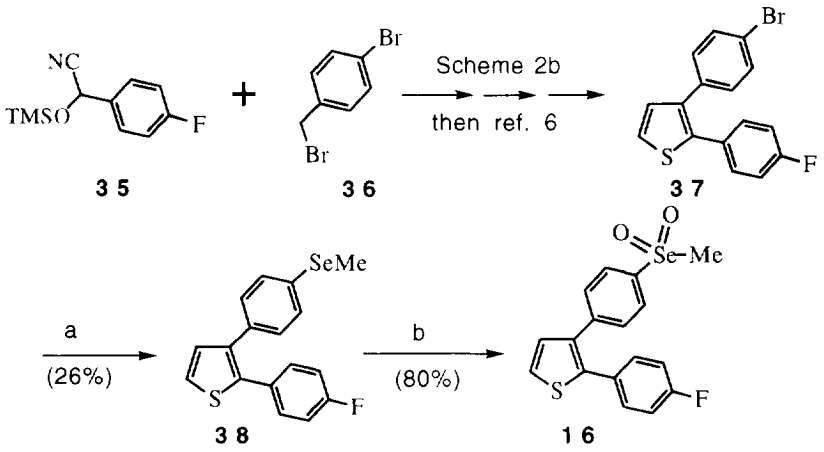
Scheme 4 describes the synthesis of the thiophene ester **42** which was employed in preparation of the analogues **17-24** using standard chemistry.

Scheme 2



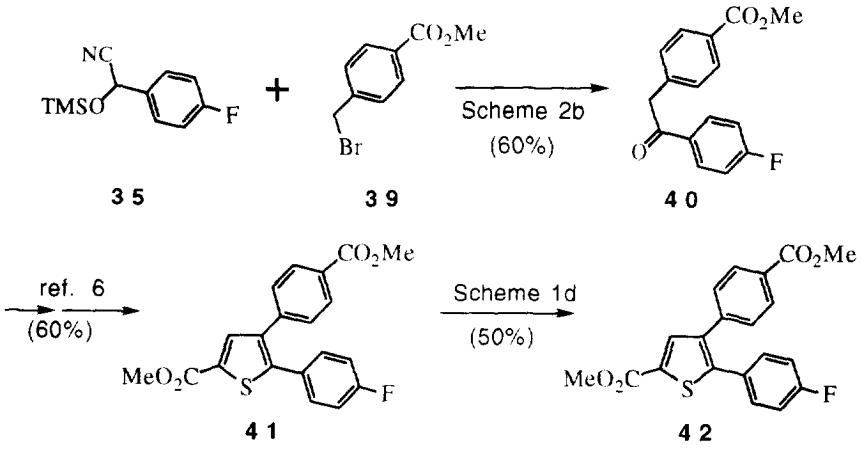
Reagents: (a) TMSCN, ZnI_2, $ClCH_2CH_2Cl$, rt; (b) LDA, -78 °C to 5 °C, 4-fluorobenzyl bromide follow by TBAF; (c)i. nBuLi, THF, -100 °C to rt; ii. SO_2, THF, -100°C to rt then coevaporate with hexane; iii. SO_2Cl_2 0 °C to rt; iv. NH_3, THF, 0 °C to rt

Scheme 3



Reagents: a)i. tBuLi, THF, -100 ° to -78 °C, 5 min; ii. Se, rt; iii. MeI, -78 °C to rt; b) mCPBA, CH_2Cl_2,0 °C to rt.

Scheme 4



Discussion: Compounds **1-24** (Table 1) were tested *in vitro* for their ability to inhibit the Cox-2 and Cox-1 enzymes. DuP 697 (**1**) shows high activity against both Cox-isoforms with a Cox-1/Cox-2 IC_{50} ratio of 120. The positional isomer **2** is slightly less active and selective than **1** (Cox-1/Cox-2 = 55). On the other hand, the desbromo analog (**3**) of DuP 697, although less potent in Cox-2 (0.25 μM), is inactive at 100 μM against the Cox-1 enzyme under our assay conditions. This absence of the bromine atom dramatically improved the selectivity of the compound (Cox-1/Cox-2 > 400) while at the same time maintaining a reasonable potency in Cox-2.

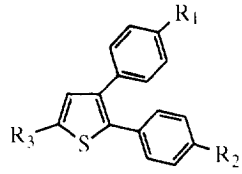
The methylsulfone group proved to be critical for both the activity and selectivity of the series. The methyl sulfide (**43**) and methylfulfoxide (**44**) were found inactive against the Cox-2 enzyme. The ethylsulfone (e.g., **5**) and other functionalities (see Table 1) gave a substantial loss of activity. However, the sulfonamide **6** remained active against the Cox-2. In general, the sulfonamides are more active against Cox-2 enzymes than the corresponding methylsulfone (**6** vs. **3**). However, the sulfonamides are less selective than the methylsulfones, as observed by the Searle group in the cyclopentene series.[10] In addition, the sulfonamide analogs tolerate substitution at C5 as exemplified by compounds **9** to **12**.[11] As observed with the methylsulfones, the positional isomers in the sulfonamide cases are less potent against Cox-2 and Cox-1 enzymes. For compound **13** complete loss of activity against both Cox-isoforms was observed. The selenone compound **16** remains potent against the Cox-2 enzyme but is less selective than the desbromo analog (**3**) of DuP 697.

Interestingly, replacement of the methylsulfone moiety by other functionalities such as in compounds **17-24** gave compounds that are inactive in Cox-2 at 30 μM. Some of these compounds such as **23** and **24** turned out to be quite selective for the Cox-1 enzyme.

In conclusion, the methyl sulfone group is optimum for both the activity and selectivity for Cox-2. The SAR is extremely tight. Cox-1 selective compound could be obtained by replacing the methylsulfone group by a number of functionalities.

Table 1. IC_{50} values (μM) against Cox-2 and Cox-1 enzymes.

Microsomes from baculovirus infected SF9 [12]cells expressing either recombinant human Cox-2 or Cox-1 were used as enzyme source. Cox-1 (25 μg/mL) or Cox-2 (4 μg/mL) enzymes containing microsomal membrane proteins were preincubated for 15 min with the inhibitor followed by a 15 min incubation with arachidonic acid at 1 μM.[2c] PGE_2 was measured by EIA.



Compound	R1	R2	R3	Cox-2	Cox-1	Cox-1/Cox-2
1 (DuP 697)	SO_2Me	F	Br	0.005	0.60	120
2	F	SO_2Me	Br	0.02	1.1	55
3	SO_2Me	F	H	0.25	>100	>400
4	F	SO_2Me	H	4.3	>50	>12
5	SO_2Et	F	H	>30	>50	-
6	SO_2NH_2	F	H	0.03	1.3	43
7	F	SO_2NH_2	H	0.67	2.7	4.0
8	SO_2NH_2	$C(Me)_2OH$	H	>30	>50	-
9	SO_2NH_2	F	$CH(Me)_2$	0.01	0.23	23
10	SO_2NH_2	F	CO_2Me	0.07	1.0	14
11	SO_2NH_2	F	$C(Me)_2OH$	0.41	5.4	13
12	F	SO_2NH_2	$C(Me)_2OH$	1.6	>50	>31
13	F	SO_2NH_2	CO_2Me	>30	>50	-
14	SO_2NHMe	F	H	7.2	>50	>6.9
15	SO_2NHAc	F	H	5.4	>50	>9.2
16	SeO_2Me	F	H	0.55	32	58
17	$CONH_2$	F	H	>30	3.2	<0.11
18	COMe	F	H	>30	0.75	<0.02
19	CO_2H	F	H	>30	>50	-
20	CO_2Me	F	H	>30	17	<0.57
21	CH_2CO_2H	F	H	>30	-	-
22	CHO	F	H	>30	0.98	<0.03
23	CN	F	H	>30	0.21	<0.01
24	CH_2OH	F	H	>30	0.35	<0.01
43	SMe	F	H	>30	0.34	<0.01
44	SOMe	F	H	>30	15	<0.50

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(*Received in USA* 14 *July* 1995; *accepted* 14 *August* 1995)