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Conformationally Restricted 3,4-Diarylfuranones (2,3a,4,5-Tetrahydronaphthofuranones) as Selective Cyclooxygenase-2 Inhibitors†

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Abstract—A number of naphthofuranones were synthesized and tested for COX-1 and COX-2 inhibition. Few of them were identified as selective COX-2 inhibitors. Structure–activity relationship studies within the series are discussed.

The vicinal diaryl heterocycle having an aminosulfonyl (SO_2NH_2) or a methanesulfone (SO_2Me) moiety attached to the *p*-position of one of the aryl ring is the most widely used chemical entity for the development of selective COX-2 inhibitors. Its simplest form is exemplified by DUP-697.[1] After the discovery of inducible isozyme (COX-2) in 1991, the first breakthrough came with the reports that NS398 and the diarylheterocycle DUP-697 were anti-inflammatory but not ulcerogenic (Fig. 1).[1,2] Subsequent research and rational drug design resulted in a number of potent and selective COX-2 inhibitors which validated the initial concept that a selective COX-2 inhibitor would illicit effective anti-inflammatory activity without the adverse ulcerogenic effect associated with the use of NSAIDs that inhibit both COX-1 and COX-2. Accordingly celecoxib[3] and rofecoxib[4] followed by valdecoxib[5] and etoricoxib[6] became the first and second generation selective COX-2 inhibitors (Fig. 1) to enter the market. These compounds are known to be useful for the treatment of inflammation and other related diseases with reduced gastrointestinal side effects of NSAIDs.

Among the various diaryl heterocycles exploited for the development of selective COX-2 inhibitors, 3,4-diarylfuranones received considerable attention due to their interesting pharmacological and pharmacokinetic properties. This is exemplified by the invention of rofecoxib, where methylsulfonyl-aryl group and a phenyl group were attached to the 3- and 4-position of the central furanone ring, respectively, followed by a number of reports that disclose the various possible modifications of 3,4-diarylfuranone, that is basic skeleton of rofecoxib **9** (**11**–**13**, Fig. 2).[7,8] Very recently replacement of phenyl group (adjacent to the methylsulfonyl-aryl group) of **9** by 4-acetoxyphenyl[9] or 6-(1-azolanyl)-3-pyridyl[10] group has been reported in order to provide furanone derivatives having encouraging COX-2

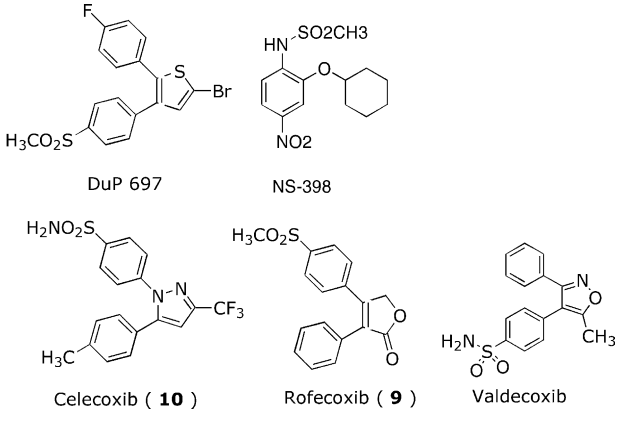

Figure 1. Some selective COX-2 inhibitors.

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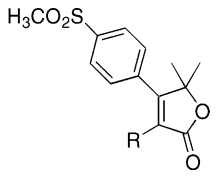


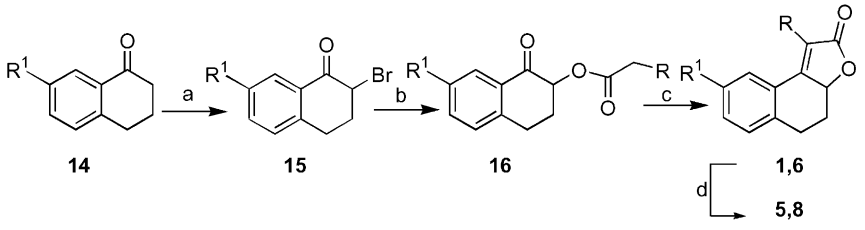
11; R = C_6H_5
12; R = OC_6H_5
13; R = OPr-i

Figure 2. Some furanone derivatives as selective COX-2 inhibitors.

selectivity. Indeed, some of these derivatives have been reported as more potent and selective than **9**. Interestingly, in all these cases the structure activity relationship (SAR) study was focused or restricted on the modification of the central furanone ring or 3-phenyl group individually.[11] In pursuance of our research on the development of various diarylfuranone derivatives as cyclooxygenase inhibitors,[12,13] we became interested in the synthesis of conformationally restricted 3,4-diarylfuranones. We now wish to report the development of naphthofuranones as cyclooxygenase inhibitors and to the best of our knowledge, the effect of linking furanone ring to the phenyl group of a diaryl furanone has not been reported in the literature.[14]

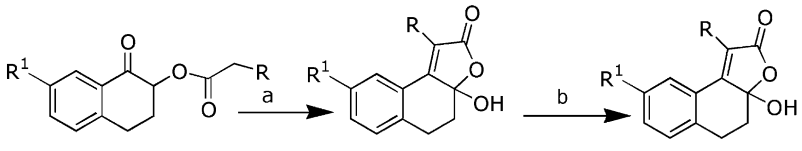
The naphthofuranone derivatives were efficiently prepared[13b,c] from phenacylester **16** generated from arylacetic acid [obtained from 1-(4-methylsulfanylphenyl)-1-ethanone via Willgerodt reaction] and appropriate bromoketone **15** (Scheme 1) obtained by bromination of α-tetralone 14.[13b] The ester **16** was then cyclized to the naphthofuranones **1** and **6** which was then oxidized to the corresponding sulfone derivatives **5** and **8**. All the cyclization reactions were performed strictly under inert atmosphere at 10 °C. However, temperature, concentration of DBU, along with the presence of oxygen in the cyclization step of Scheme 1 was found to be critical and hydroxy naphthofuranones **2** and **7** (Scheme 2) were obtained when the reaction was performed in the presence of three equivalents of DBU under oxygen atmosphere at 25–30 °C.[13c] Methyl sulfoxide **3** and methyl sulfone **4** was prepared via controlled oxidation[15] of **2**. Alternatively, **2**–**4** and **7** were also prepared from **15** via one pot procedure according to the procedure described earlier.[13b]

All the naphthofuranones synthesized were tested in initial screens for selectivity and potency against recombinant human COX-2 (expressed in sf9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme.[16] In vitro data for all the compounds is listed in Table 1. Fusion of the furanone ring to the phenyl group is well tolerated in terms of in vitro potency and COX-2 selectivity. Naphthofuranone 5 and 8 (Table 1) showed good in vitro potency with respect to COX-2 inhibition and were comparable to rofecoxib. Replacement of methylsulfone moiety of 5 and 8 by methylsulfanyl functionality led to the alteration of selectivity (compounds **1** and **6**, Table 1) with the retention of cyclooxygenase inhibitory activity. However, COX-2 selectivity over COX-1 was regained to some extent when the furanone ring was substituted further by a



R^1 = H, Me		R =	R^1 =
	1	C_6H_5SMe-p	H
	5	$C_6H_5SO_2Me$-p	H
	6	C_6H_5SMe-p	Me
	8	$C_6H_5SO_2Me$-p	Me

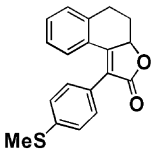
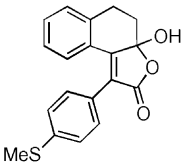
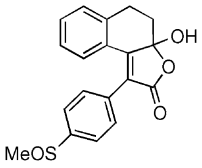
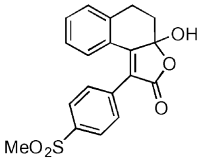
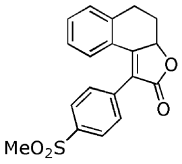
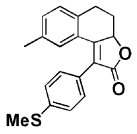
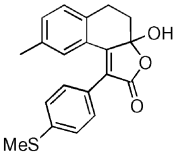
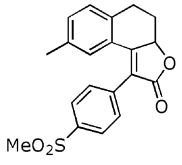
Scheme 1. Reagents and conditions: (a) Br_2, HBr, CH_3CO_2H; (b) DMF, KOH, RCH_2CO_2H, 10 °C –rt, 1.0 h; (c) DBU, CH_3CN, 10 °C, 30 min then dil HCl, 10 °C, 30 min; (d) oxone, acetone–H_2O (2:1), rt, 30 min.



R^1 = H, Me		R =	R^1 =		R =	R^1 =
	2	C_6H_5SMe-p	H	**3**	C_6H_5SOMe-p	H
	7	C_6H_5SMe-p	Me	**4**	$C_6H_5SO_2Me$-p	H

Scheme 2. Reagents and conditions: (a) O_2, DBU, CH_3CN, 25 °C, 6 h; (b) oxone, acetone–H_2O (2:1), rt.

Table 1. In vitro data for Diaryl furanones

Compd	Structure	% of inhibition (100 μM)[a]		IC_{50} (μM)[b]		IC_{50}(COX-1)/IC_{50}(COX-2)
		COX-1	COX-2	COX-1	COX-2	
1		100	100	0.053	0.827	0.06
2		80	71	16.70	0.85	19.64
3		11	0	n.d.	n.d.[c]	—
4		57	0	n.d.	n.d.	—
5		100	100	> 45	0.562	> 80.07
6		100	86	0.061	0.971	0.06
7		97	88	13.2	0.67	19.70
8		52	92	> 30	0.665	> 45.1
9	Rofecoxib			> 500	0.329	> 1519
10	Celecoxib			10.70	0.036	297.22

[a]Average of at least three determinations.
[b]The result is the mean value of two determinations, and the deviation from the mean is < 10% of the mean value.
[c]n.d., not determined.

hydroxyl group (**2** and **7**, Table 1). Interestingly, complete loss of activity was observed in the case of corresponding methylsulfinyl or methylsulfonyl analogue (**3** and **4**, Table 1). Based on their IC_{50} compound **5** and **8** was identified as potent COX-2 inhibitor (IC_{50} ~0.5–0.6 μM) with good selectivity (COX-1: IC_{50} >30–45 μM).

Structure–activity studies for the diaryl heterocyclic class of selective COX-2 inhibitors have shown that both methylsulfonyl and aminosulfonyl, which can dispose a pair of oxygen atoms, are well recognized to be important moieties for optimal COX-2 inhibition.[17] Removal of oxygen essentially altered the selectivity for COX-2 inhibition.[18] This phenomenon was also seen in our naphthafuranone derivatives **1** and **6** as shown in Table 1. However, the reason for the moderate selectivity shown by their hydroxyl analogues **2** and **7** is not clear at present. Among the methanesulfone derivatives the reason for inactivity of compound **4** is also unclear. Lack of required conformation for COX-2 inhibition seemed to be lost in such case. On the other hand, presence of hydrophilic hydroxy group clearly disfavored the cyclooxygenase inhibitory activities in terms of selectivity as well as potency (**4** vs **5**, Table 1) keeping the methylsulfonyl moiety intact. Nevertheless, compounds **5** and **8** which possess an additional ring that provide them a restricted conformational freedom showed good COX-2 inhibitory activity suggesting that they possess the required conformation for inhibiting COX-2. In order to gain further knowledge on the role of restricted conformation in COX-2 potency as well as selectivity in the present case freely rotating analogue (i.e., without fused cyclohexyl ring but with an alkyl group) of COX-2 inhibitor **5**, that is 5-ethyl-3-(4-methylsulfonylphenyl)-4-phenyl-2,5-dihydro-2-furanone (**17**) was synthesized[19] and tested in vitro. The diarylfuranone **17** was found to be less active than **5** in both the inhibition (COX-1: 20% inhibition @ 100 μM; COX-2: 14% inhibition @ 100 μM) confirming the restricted conformational freedom as an essential requirement for the inhibition of both the isoforms especially COX-2 in the case of methanesulfonyl derivatives. Their hydroxyl analogue, for example **4**, however, clearly shows deviation from this observed phenomenon.

Conclusion

In conclusion we have described synthesis and cyclooxygenase inhibiting properties of a number of 1-aryl substituted naphthofuranones having methylsulfanyl, methylsulfinyl or methanesulfone moiety attached to the *p*-position of the aryl ring. Initial SAR studies indicate that restricted conformation along with the presence of methanesulfone moiety is crucial for optimal COX-2 inhibition in this series, whereas methylsulfanyl derivatives having a hydroxyl group show moderate selectivity in COX-2 inhibition over COX-1. Some of the compounds synthesized are potent and selective COX-2 inhibitors in vitro and therefore provide a useful basis for the development of a novel anti-inflammatory agent without having the side effects of non-selective NSAIDs.

Acknowledgements

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17. (a) The SO_2Me and SO_2NH_2 moieties are believed to induce COX-2 selectivity by insertion into the secondary pocket of COX-2 which is absent in COX-1. The secondary pocket present in COX-2 has been attributed to the presence of isoleucine (Ile^{523}) in COX-1 relative to the smaller valine (Val^{523}) in COX-2. See: Loung, C.; Miller, A.; Barnett, J.; Chow, J.; Ramesha, C.; Browner, M. F. *Nat. Struct. Biol*. **1996**, *3*, 927. (b) These substituents usually confer optimal COX-2 inhibitory potency when one of them is present at the para position of one aryl ring. See: Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1619.
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19. The diarylfuranone **17** was prepared from phenylester[13b] generated from 2-(4-methylsulfanylphenyl)acetic acid and appropriate bromoketone (obtained by bromination of 1-phenyl-1-butanone) followed by oxidation of the methylsulfanyl moiety to methanesulfone.