Rapid Communication

Synthesis and cyclooxygenase (COX-1/COX-2) inhibiting property of 3,4-diarylfuranones†

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A series of diarylfuranone including some 5-hydroxy derivatives and naphthofuranones have been synthesized as a unique class of COX-1/COX-2 inhibitors. In contrast to the earlier report of structurally similar rofecoxib, these compounds have been characterized as nonselective but highly potent COX inhibitors. Structure Activity Relationship study confirmed that methoxy and methyl sulfanyl moieties are essential for COX activity and replacement or removal of any of this group affect COX-2 potency drastically rather than COX-1 efficacy. Studies on in vitro, in vivo screens and pharmacokinetics are discussed.

Sulfonyl-substituted diary heterocycle is the most widely used pharmacophore motif for the development of selective COX-2 inhibitors and its simplest form is represented by DUP-697. The pharmacophore for this series include either a methanesulfonamide (SO₂NH₂) or a methanesulfone (SO₂Me), which is attached to the p-position of the phenyl ring. This phenyl moiety and a lipophilic moiety are attached to the adjacent positions of the template. The template may consist of a carbocycle, heterocycle or even acyclic structure, which may adopt favourable geometry. After the discovery of inducible isozyme (COX-2) in 1991, the first breakthrough came with the reports that the diaryheterocycle DUP-697 and NS398 were anti-inflammatory but not ulcerogenic. This observation generated interest and subsequently, enormous efforts were paid by the pharmaceutical research laboratories to convert them into structurally related but clinically better candidates. This rational and scientific approach in this series resulted in celecoxib and rofecoxib as first generation selective COX-2 inhibitors (Figure 1) to enter the market.

Rofecoxib, a selective COX-2 inhibitor, belongs to a tricyclic class of compounds having furanone ring as a template (Figure 1). Design of rofecoxib involved two way modification of DUP-697: (i) replacement of thiophene ring by a five membered lactone along with the C-2 substituent by lone pairs of electron of the lactone oxygen to enhance bioavailability and COX-2 selectivity, (ii) retention of methanesulfone rather than sulfonamide moiety to maximize COX-2 selectivity. Although the Structure Activity Relationship (SAR) study revealed that interchange of 4-methylsulfonyl phenyl with the other phenyl ring led to essentially inactive isomorphic compound, however, various possible modifications of basic skeleton of rofecoxib 31 have been reported (Figure 2) as is exemplified by 32-34. Indeed some of these derivatives are more potent and selective than 31. All these reports confirmed that the presence of 4-(methylsulfonyl)phenyl moiety and its position of attachment to the central ring are critical for optimal COX selectivity and potency. However, we have observed that replacement of methylsulfonyl moiety

![DuP697](image1)

![NS398](image2)

![Celecoxib (35)](image3)

![Rofecoxib (31)](image4)

Figure 1 — Some selective COX-2 inhibitors.

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of rofecoxib analogues by methylsulfonyl group\textsuperscript{7} led to little change in COX efficacy but produces dramatic change in selectivity. This observation intrigued and prompted us to carry on a detailed study on such type of rofecoxib analogues that would explore a deeper insight on their synthesis and pharmacological profile as COX inhibitors. In this communication, we describe the synthesis and the SAR study of a unique series of furanone derivatives, which are non-selective in COX-1 and COX-2 inhibition contrary to the earlier reported structurally similar rofecoxib.

In recent years, a number of methods have been developed for the synthesis of 3,4-disubstituted furanones\textsuperscript{8} due to their enormous medicinal interest as well as synthetic utility. We however adopted the aldol-type cyclization of phenylacylester\textsuperscript{8a-d} for our purpose due to the simple yet versatile nature of this protocol. Accordingly, the majority of the diarylfuranones listed in Table I were synthesized according to the Schemes I and II.

Synthesis of diarylfuranones 1-5 was carried out following the procedure described in the literature\textsuperscript{8d}. Similarly, the diarylfuranones 6-20 and 23-25 were efficiently prepared from phenacylester 36 generated from arylacetic acid [obtained from 1-(4-methylsulfonylphenyl)-1-ethanone via Willgerodt reaction] and appropriate bromoketone (Scheme I, path-b).

![Diagram](chart.png)

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

![Diagram](chart.png)

**Scheme I**

Reagents and conditions: (a) DBU, CH\textsubscript{3}CN, 10 °C, 30 min. (b) O\textsubscript{2}, DBU, CH\textsubscript{3}CN, 25 °C, 6 hrs.
Table I—*In vitro* data for diarylfuranones

<table>
<thead>
<tr>
<th>Compd</th>
<th>% of inhibition (100 µM)*</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COX-1</td>
<td>COX-2</td>
</tr>
<tr>
<td>1  4-Methoxyphenyl</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>2  Phenyl</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>3  3,4-Difluorophenyl</td>
<td>99</td>
<td>47</td>
</tr>
<tr>
<td>4  4-Bromophenyl</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>5  4-Trifluoromethyl phenyl</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>6  4-Methoxyphenyl</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>7  4-Ethoxyphenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>8  3-Fluoro-4-methoxy phenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>9  4-Benzoxyp phenyl</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>10 5-Indanyl</td>
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<tr>
<td>11 4-Isobutylphenyl</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>12 3-Methoxyphenyl</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>13 3,4-Dimethoxyphenyl</td>
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<td>14 2,4-Difluorophenyl</td>
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<td>15 4-Chlorophenyl</td>
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<td>0</td>
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<tr>
<td>16 3-Chlorophenyl</td>
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<td>17 4-Trifluoromethyl phenyl</td>
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<td>18 4-Bromophenyl</td>
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<td>19 4-Hydroxyphenyl</td>
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<td>20 4-Thiomethylphenyl</td>
<td>99, 100(1)</td>
<td>100, 66(1)</td>
</tr>
<tr>
<td>21 4-Methoxyphenyl</td>
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<td>23 Phenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24 4-Fluorophenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>25 4-Methoxyp phenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>26 Phenyl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>27 4-Fluorophenyl</td>
<td>100,100(1)</td>
<td>100,55(1)</td>
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—Contd
Table I—In vitro data for diarylfuranones (—Contd)

<table>
<thead>
<tr>
<th>Compd</th>
<th>% of inhibition (100 μM)*</th>
<th>IC₅₀ (μM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COX-1</td>
<td>COX-2</td>
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<tr>
<td>28</td>
<td>96, 63(1)</td>
<td>100, 56(1)</td>
</tr>
<tr>
<td>29</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>100, 100(1)</td>
<td>86, 68 (1)</td>
</tr>
<tr>
<td>31</td>
<td>Rofecoxib</td>
<td>&gt;500</td>
</tr>
<tr>
<td>35</td>
<td>Celecoxib</td>
<td>10.70</td>
</tr>
</tbody>
</table>

*Figures in the brackets indicate concentration in μM. *Average of at least three determinations.

The result is the mean value of two determinations, and the deviation from the mean is <10% of the mean value.

nd = not determined.

Scheme I and II were used.

All the cyclization reactions were performed strictly under inert atmosphere at 10 °C. Interestingly, temperature, concentration of DBU, along with the presence of oxygen in the cyclization step of Schemes I and II was found to be critical. A side product was isolated, sometimes even as a major product, when the reaction was performed in the presence of three equivalents of DBU under oxygen atmosphere at 25-30 °C. Depending on the nature of the esters used (36; R' = H or alkyl), these products were identified as either 3,4-diaryl-substituted maleic anhydride or 5-hydroxyfuranones 26-28, respectively (Scheme I, path-b)*.

Mechanistically, the cyclization of ester proceeds through the usual aldol-type condensation reaction in the presence of DBU leading to the formation of furanones. However, isolation of 5-hydroxyfuranones could be accounted for by its further reaction with
oxygen in the presence of DBU. This involves facile generation of carbanion that may subsequently react with molecular oxygen followed by the cleavage of O-O bonds. To confirm this mechanistic sequence, furanone 23 was treated with DBU in acetonitrile under the oxygen atmosphere where 26 was isolated in good yield. Thus, the oxidative cyclization reaction proceeds through the stepwise formation of furanone followed by its oxidation to the corresponding 5-hydroxy derivative.

Compounds synthesized were tested in initial screens for selectivity and potency in in vitro against recombinant human COX-2 (expressed in sf9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme. Selected compounds were subsequently tested in human whole blood assay for both COX-1 and COX-2 activity. In vivo activity was evaluated using carrageenan-induced rat paw edema model.

The first compound synthesized in this series i.e., 3-(4-methoxyphenyl)-4-(4-methylsulfanyl phenyl)-2,5-dihydro-2-furanone 1 was characterized as a nonselective but highly potent COX inhibitor (compd 1, Table I). Interchange of position of aryl moieties with each other did not affect the activity pattern (compd 6, Table I).

Replacement of methoxy by ethoxy group (compd 7, Table I) or attachment of a fluorine atom at ortho-position of methoxy group (compd 8, Table I) had no significant effect on COX inhibiting activity. However, a larger group such as benzylxy (compd 9, Table I) in place of methoxy led to complete decrease in COX activity suggesting that the latter binds in an enzyme pocket that is more restricted for a bulky group. In order to understand the role of methylsulfanyl and methoxy group in COX activity, this series was investigated further. It was observed that removal of methylsulfanyl moiety (compd 21, Table I) led to decrease in COX-2 inhibition without affecting COX-1, whereas removal of both the groups (compd 22, Table I) resulted in complete decrease in COX-2 but moderate decrease in COX-1 inhibition. Change in position of methoxy group (compd 12, Table I) also resulted in complete decrease in COX-2 potency. These observations indicate that both methoxy and methylsulfanyl moiety are essential for COX activity and replacement or removal of any of this group affects COX-2 potency drastically rather than COX-1 efficacy. This was further supported by the data presented in Table I (compds 2-5 and 13-20).

Interestingly, removal of methoxy group was compensated by the attachment of an ethyl substituent at the C-5 position of the lactone ring (compds 23 and 24, Table I). Extension of the C-5 attachment to the adjacent phenyl ring (compd 29, Table I) led to moderate decrease in COX-2 potency. However, presence of another substituent e.g., hydroxy group at C-5 position led to significant decrease in COX-2 potency (compds 26 and 27, Table I). Thus, the ethyl chain at the C-5 position imparted the required conformation that was perhaps needed for the COX-2 inhibition. COX-1 potency was not affected drastically except where neither methoxy nor methylsulfanyl moiety was present as pharmacophore (compd 28, Table I).

Some of these furanone derivatives selected based on their impressive IC50 values, were tested in vivo at a dose of 30 mg/kg p.o. and the percentage of inhibition of paw edema was calculated. Compound 1 (compd 1, Table I), which exhibited maximum inhibition at 30 mg/kg p.o., was selected for further study. The COX-1 and COX-2 potency of 1 was measured by human whole blood assay and compared with celecoxib, rofecoxib and indomethacin (see Table II). IC50 values for COX-1 was determined by measuring TXB-2 production in human whole blood

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd</th>
<th>IC50s, µM</th>
<th>Log p8</th>
<th>ED50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>COX-1</td>
<td>COX-2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.005</td>
<td>0.186</td>
<td>3.74±0.41</td>
</tr>
<tr>
<td>2</td>
<td>Rofecoxib</td>
<td>5.4</td>
<td>0.580</td>
<td>1.54±0.43</td>
</tr>
<tr>
<td>3</td>
<td>Celecoxib</td>
<td>10.0</td>
<td>0.187</td>
<td>3.01±0.86</td>
</tr>
<tr>
<td>4</td>
<td>Indomethacin</td>
<td>0.213</td>
<td>0.247</td>
<td></td>
</tr>
</tbody>
</table>

*The result is the mean value of two determinations, and the deviation from the mean is < 10% of the mean value.
*Calculated using the ACDLabs program developed by Advanced Chemistry Development Inc., Canada.
*ED50 values were determined using a minimum of four dose points, 6 animals/group.
and for COX-2 inhibition was determined by measuring lipopolysaccharide induced PGE\textsubscript{2} production in human whole blood.

As can be seen from Table II, compound 1 is comparable to celecoxib, rofecoxib and indomethacin with respect to COX-2 inhibition. However, its abnormally low IC\textsubscript{50} value for COX-1 inhibition prompted further investigation. The inhibition of COX-2 by rofecoxib is reported to be occurring via a two-step time-dependent mechanism\textsuperscript{13} (leading to a tightly bound inhibited complex), whereas weak inhibition of COX-1 is non-time dependent. Inhibition of both the isoforms by non-selective COX inhibitors such as indomethacin and flurbiprofen is time dependent\textsuperscript{12}. Since a large number of furanone derivatives, as described above, exhibited non-selective inhibition of COX enzymes, their mechanism of action therefore, could be different from that of rofecoxib.

According to the pharmacokinetic study compound 1 (C\textsubscript{max} 0.12±0.01\textmu M) and rofecoxib (C\textsubscript{max} 5.61±1.10\textmu M) displayed substantially different pharmacokinetics in male rats when dosed orally at 100 mg/kg. Thus, the furanone derivative 1 exhibited discouraging oral pharmacokinetics\textsuperscript{13} when compared to rofecoxib. Although the purpose of incorporation of lactone moiety into DUP-697 in the design of rofecoxib was to address the oral absorption issue, this was however, not achieved in 1.\textsuperscript{4} Theoretically, the logP value, as calculated for 1 was found to be higher than rofecoxib (Table II), which supports the pharmacokinetic data and could be the reason for poor absorption associated with 1. Surprisingly, in spite of poor pharmacokinetics, compound 1 exhibited substantial inhibition of rat paw edema and the ED\textsubscript{50} value for 1 was noted as 1.17±0.33 mg/kg, fairly comparable to rofecoxib (Table II). Experimental evidences suggest\textsuperscript{13} that COX-1 has significant contribution to PG synthesis in inflammation and thus inhibition of COX-1 might be a required process for anti-inflammatory activity. This was further supported by the clinical efficacy of piroxicam, a relatively COX-1 selective inhibitor. So the high potency of 1 perhaps could be justified by its low IC\textsubscript{50} values for both COX-1/COX-2 inhibitions. We anticipated that metabolism of furanone 1 may lead to the generation of corresponding sulfoxide and/or sulfone along with the other related metabolites as reported in the case of rofecoxib.\textsuperscript{46} Accordingly, we have synthesized\textsuperscript{46} and found that they are less or moderately active in \textit{in vitro} (COX-1 & COX-2 is 63 & 15 for sulfoxide at 1\textmu M) and more importantly in \textit{in vivo} (5% for sulfoxide and 27% for sulfone at 30 mg/kg). These observations rule out the possibility that 1 may act as a prodrug of either sulfoxide or sulfone \textit{in vivo}. Further study on pharmacodynamics of 1 is however, needed to confirm this conclusion.

In summary, we have described the synthesis of 4,5-diaryl furanones via aldol type condensation or oxidative cyclization of phenacetyl ester including the first synthesis of naphthofuranones along with the novel synthesis of 5-hydroxydiaryl furanones as well. These furanones are structurally similar to highly selective rofecoxib and other furanones\textsuperscript{15}, but exhibit non-selective nature of NSAIDs. Methylsulfanyl and methoxy groups have been proved to be the key features in regulating the COX inhibitory activity of this series. Compound 1 exhibited excellent anti-inflammatory activity in the carrageenan-induced rat paw edema assay following oral administration. Because of their impressive IC\textsubscript{50} values for COX inhibition, these compounds could be useful for the treatment of pain and inflammation like piroxicam or in other therapeutic areas.\textsuperscript{16} To summarize, diaryl furanone 1 has been identified as a potent inhibitor of COX isoenzymes with interesting pharmacological properties.

**Experimental Section**

**General methods.** All the solvents used were commercially available and distilled before use. Reactions were monitored by TLC on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on a silica gel (SRL 230-400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded in CDCl\textsubscript{3} solution on Varian Gemini 200 and 50 MHz spectrometers respectively using TMS as internal standard (chemical shift in \textepsilon; ppm), infrared spectra on a Perkin-Elmer 1650 FT-IR spectrometer; UV spectra on a Shimadzu UV 2100S UV-VIS recording spectrophotometer; and MS spectra were obtained on a HP-5989A mass spectrometer. Melting points were determined using Buchi melting point B-540 apparatus and are uncorrected. Microanalyses were performed using Perkin-Elmer 2400 CHN S/O analyzer.

**Typical experimental procedures for the preparation of furanone**

Preparation of 7-methyl-a-tetralone 37 (R\textsuperscript{l} = CH\textsubscript{3}). To a mixture of toluene (25 mL) and butyrolac-
chloride (5 mL, 61.39 mmoles) was added aluminium
over anhydrous
concentrated
EtOAc
(3 × 50 mL) washed with water (2 × 100 mL), dried
over anhydrous Na₂SO₄ and concentrated. The result-
ning liquid isolated was purified by column chroma-
tography over silica gel using 5% EtOAc-petroleum ether
(60-80 °C) to give 8 g (81%) of the title compound as
pale yellow oil. 1H NMR (200 MHz, CDCl₃): δ 7.93
(1H, d, J = 7.88 Hz, 1H), 7.26-7.50 (m, 4H), 3.50-3.89
(m, 2H), 2.7-2.75 (m, 2H); IR (KBr, cm⁻¹): 1684, 1599;
MS (Ms, 30): m/z 226 (M+, 28), 177 (60), 164 (100).

Preparation of 2-bromo-a-tetralone 38 (R²=H,
CH₃). To a solution of 37 (R²= H, CH₃) (6.25
mmoles) in acetic acid (10 mL) was added 40% aqueous
solution of HBr (1 mL) followed by the addition of
bromine (6.18 mmoles) solution in acetic acid
(2 mL) at 25°C. The solution was stirred for 3 hr at 25
°C and then poured into water (10 mL) followed by
extraction with EtOAc (2 × 30 mL). Combined
organic layer was washed with water (3 × 50 mL), dried
over anhydrous Na₂SO₄ and concentrated to give the
desired bromo ketone.

2-Bromo-a-tetralone 38 (R²=H): yield 76%;
1H NMR (200 MHz, CDCl₃); δ 8.2-8.0 (m, 1H), 7.6-
7.8 (m, 3H), 4.7 (3H), 3.4-3.3 (m, 1H), 3.0-2.9
(m, 1H), 2.7-2.4 (m, 2H); IR (KBr, cm⁻¹): 1684, 1599;
MS (Cl, i-Butane): m/z 226 (M⁺, 25), 144 (60), 118 (100).

2-Bromo-7-methyl-a-tetralone 38 (R²=CH₃):
yield 30%; 1H NMR (200 MHz, CDCl₃): δ 8.04-8.00
(m, 1H), 7.4-7.0 (m, 1H), 4.7 (m, 1H), 3.4-3.2 (m,
2H), 3.0-2.8 (m, 2H), 2.6-2.3 (m, 5H); IR (KBr, cm⁻¹):
1682, 1610; MS (Cl, i-Butane): m/z 240 (M⁺, 9), 132
(100).

Preparation of an ester 39. To a solution of ary-
lactic acid (21.9 mmoles) in DMF (50 mL) was added
slowly a solution of potassium hydroxide (26.3
mmoles) in water (10 mL) and concentrated. The mix-
ture was stirred for 0.5 hr at 10-15°C. A solution of 38
(26.3 mmoles) in DMF (50 mL) was added to this mixture and
stirring was continued for 3 hr at 25°C. The mixture
was then poured into water (250 mL) and extracted with
EtOAc (2 × 150 mL). Combined organic layer was washed
with water, dried over anhydrous Na₂SO₄ and
concentrated in vacuo. The resulting residue was
purified over silica gel using 10% EtOAc-petroleum ether
(60-80 °C) (500 mL) to give the required ester 39.

1-Oxo-1,2,3,4-tetrahydro-2-naphthalenyl-2-(4-
methylsulfanylphenyl)acetate 39 (R = H, R¹ =
C₆H₃SMe-p): low melting solid; yield 41%; 1H NMR
(200 MHz, CDCl₃): δ 8.00 (d, J = 7.88 Hz, 1H), 7.51-
7.70 (m, 7H), 5.55 (m, 1H), 3.76 (s, 2H), 3.19-3.11
(m, 2H), 2.46 (s, 3H), 2.36-2.28 (m, 2H); IR (KBr,
cm⁻¹): 1743, 1701, 1603; MS (Cl, i-Butane): m/z 326
(M⁺, 10), 164 (100). Anal. Found: C, 70.92; H, 5.56.
C₉H₁₀O₂S requires C, 70.66; H, 5.52%.

7-Methyl-1-oxo-1,2,3,4-tetrahydro-2-naphthalen-
yl-2-(4-methylsulfanylphenyl)acetate 39 (R = Me,
R¹ = C₆H₃SMe-p): low melting solid; yield 55%;
1H NMR (200 MHz, CDCl₃): δ 7.91 (d, J = 8.21 Hz,
1H), 7.28-7.40 (m, 6H), 5.52 (m, 1H), 3.75 (s, 2H),
3.11-3.01 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 2.31-
2.25 (m, 2H); IR (KBr, cm⁻¹): 1741, 1697, 1608; MS
(Cl, i-Butane): m/z 341 (M⁺, 28), 177 (70), 164 (100).
Anal. Found: C, 70.46; H, 5.93. C₁₀H₁₀O₂S requires
C, 70.56; H, 5.92%.

Preparation of furanones 29, 30, 26 and 28
General procedure. To a solution of 39 (7.6
mmoles) in acetonitrile (50 mL) was added slowly
diazobicyclo[4.4.0]undec-7ene (11.5 mmoles) under
nitrogen atmosphere at 10-15°C. The mixture was
stirred for 0.5 hr at 10-15°C followed by the addition
of water (50 mL) and 2N HCl (50 mL). The mixture
was extracted with EtOAc (3 × 50 mL). Combined
organic layer was washed with water (2 × 100 mL) and
dried over anhydrous Na₂SO₄. After removal of solvent under vacuum the crude product was purified
by column chromatography over silica gel using 10%
EtOAc-petroleum ether (60-80 °C) (400 mL) to give the
desired product.

1-(4-Methylsulfanylphenyl)-2,3a,4,5-tetrahydro-
naphtho[2,1-b]furan-2-one 29: yield 13%; mp 112-
124 °C; 1H NMR (200 MHz, CDCl₃): δ 7.6-7.0 (m,
8H), 5.11 (dd, J = 4.95 Hz, 1H), 3.19 (m, 2H), 2.6 (m,
1H), 2.5 (m, 3H), 2.0 (s, 1H); IR (KBr, cm⁻¹): 1742, 1657,
1597; MS (Cl, i-Butane): m/z 309 (M⁺, 30), 308
(100). Anal. Found: C, 74.21; H, 5.13. C₁₀H₁₀O₂S requires
C, 74.00; H, 5.23%.

8-Methyl-1-(4-methylsulfanylphenyl)-2,3a,4,5-tet-
araftadronaphtho[2,1-b]furan-2-one 20: yield 32%;
mp 144-45 °C; 1H NMR (200 MHz, CDCl₃): δ 7.9 (d,
J = 8.3 Hz, 2H), 7.68 (d, J = 8.07 Hz, 2H), 7.3-7.1
(m, 2H), 7.0 (d, J = 8.3 Hz, 1H), 5.11 (dd, J = 4.99 Hz,
1H), 3.18 (m, 2H), 3.09 (s, 3H), 2.76-2.7 (m, 1H),
2.34 (s, 3H), 2.06 (m, 1H); 13C NMR (50 MHz,
CDCl₃): δ 172.48 (C=O), 159.42, 142.38, 138.55,
136.71, 132.64, 131.56, 130.31, 130.03, 129.52,
129.38, 127.66, 127.61, 126.50, 123.89, 78.74, 29.73,
27.38, 21.48, 15.90; IR (KBr, cm⁻¹): 1739; MS (Cl, i-Butane): m/z 322 (M⁺, 100), 246 (40), 218 (42), 203 (51). Anal. Found: C, 74.58; H, 5.61. C₁₈H₁₆O₃ requires C, 74.51; H, 5.63%.

5-Ethyl-5-hydroxy-3-(4-methylsulfanylphenyl)-4-phenyl-2,5-dihydro-2-furanone 26: yield 35%; ¹H NMR (200 MHz, CDCl₃): δ 7.52-7.13 (m, 9H), 3.86 (bs, 1H, D₂O exchangeable), 2.47 (s, 3H), 2.11 (mIH), 1.92 (mIH), 0.89 (t, J = 7.47 Hz, 3H); IR (KBr, cm⁻¹): 3319, 1739;

Furanone 28: yield 89%; mp 93-94°C; IH NMR (500 MHz, CDCl₃): δ 5.79-5.23 (m, 9H), 3.55 (bs, 1H, D₂O exchangeable), 2.09-2.02 (m, 2H), 0.91-0.83 (t, J = 4.75 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 172.46 (C═O), 159.64, 139.36, 131.25, 129.87, 129.71, 129.45, 128.92, 128.68, 125.84, 125.61, 125.03, 115.73, 25.48 (CH₂), 8.05 (CH₃); IR (KBr, cm⁻¹): 3319, 1739; MS (Cl, i-Butane): m/z 280 (M⁺, 11), 262 (93), 178 (100). Anal. Found: C, 77.21; H, 5.66. C₁₈H₁₆O₃ requires C, 77.13; H, 5.75%.

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References and Notes


The reaction of 2-bromo-a-tetralone with arylacetic acid was affected by the concentration of alkali. The bromo compound participated in elimination reaction in the presence of excess alkali leading to the formation of α,β-unsaturated ketone rather than the required ester. A detailed report on the reaction mechanism and studies will be published elsewhere. For a preliminary account see Patil and Veeramaneni V R, Padakani P S, Veeramaneni V R, Pal M & Yeleswarapu K R, Synlett, 2002, 947.


9. (a) The reaction of 2-bromo-a-tetralone with arylacetic acid was affected by the concentration of alkali. The bromo compound participated in elimination reaction in the presence of excess alkali leading to the formation of α,β-unsaturated ketone rather than the required ester. A detailed report on the reaction mechanism and studies will be published elsewhere. For a preliminary account see Patil and Veeramaneni V R, Padakani P S, Veeramaneni V R, Pal M & Yeleswarapu K R, Synlett, 2002, 947.


(b) We have synthesized all the possible major metabolites of 1, the details of which along with their pharmacological properties will be communicated soon.


16 It has been shown that COX-1 selective inhibitors such as Resveratrol could be useful as anticancer agent, for example see, *Drug Data Rep*, 19(4), 1997, 372.