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Isolation and synthesis of analgesic and anti-inflammatory compounds from *Ochna squarrosa* L.

V. Anuradha,[a] Pullela V. Srinivas,[a] R. Ranga Rao,[a] K. Manjulatha,[b] Muralidhar G. Purohit[b] and J. Madhusudana Rao[a,*]

[a]*Natural Products Laboratory, Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Department of Chemistry, University of Gulbarga, Gulbarga, India*

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Abstract—Two new furanoflavonoids (**1**, **2**), one new chalcone dimer (**3**) along with six known compounds, chrysophanol, 5-*O*-methyl squarrosin, 5-methoxy furano[4″,5″,6,7]flavone, calodenone, lophirone A and lophirone H were isolated from the ethyl acetate-soluble fraction of methanol extract of root bark of *Ochna squarrosa*. Chrysophanol, calodenone, lophirone A and lophirone H were isolated from this plant for the first time. The structures of all the isolated compounds were confirmed by 1D and 2D spectroscopic data. These compounds were tested for analgesic and anti-inflammatory activity. All the new compounds showed good analgesic and anti-inflammatory activity. A simple and facile method for the cleavage of benzyl ethers using I_2 in trigol is also reported.

1. Introduction

Ochna squarrosa commonly known as 'sunari' or 'yerra juvvi' belongs to the family Ochnaceae. It is a small shrub, grows up to 50 cm tall with thin, dark brown stem.[1] In traditional systems of medicine, it is considered as one of the important drug used in the treatment of various conditions like constipation, ulcers, sores and cancers. Its root bark is used as a digestive tonic.[2] Boiled leaves of *O. squarrosa* are used in the treatment of lumbago and ulcers. Decoction of its root is used in the treatment of menstrual complaints and asthma.

In this paper, we report isolation of two new furanoflavonoids and one new chalcone dimer together with six other known compounds, chrysophanol,[3] 5-*O*-methyl squarrosin,[4] 5-methoxy furano[4″,5″,6,7]flavone,[5] calodenone,[6] lophirone A[7] and lophirone H.[8] Synthesis of two new furanoflavonoids is also reported. The synthesis of furanoflavonoids began with resacetophenone. During the cyclization of furanochalcone to furanoflavone, a simple and facile method for the cleavage of benzyl ethers was also observed. The scope and generality of the method was extended to many other compounds with different functionalities. Analgesic and anti-inflammatory activity of the isolated compounds has been investigated.

2. Chemistry

2.1. Isolation and structure elucidation

Compound **1** was obtained as a pale yellow amorphous solid, mp 272 °C and was analyzed for $C_{18}H_{12}O_5$ by HRESIMS and ^{13}C NMR data. In the IR spectrum absorption bands at 3426 cm^{-1} and 1623 cm^{-1} suggested the presence of a hydroxyl group and an α,β-unsaturated carbonyl group. The 200 MHz ^1H NMR spectrum in Me_2CO-d_6 displayed a singlet at δ 3.96 integrating for three protons indicating the presence of a methoxyl group attached to an aromatic ring. The position of methoxyl group on the aromatic ring was established from NOE experiment. Irradiation of methoxyl group at δ 3.96 resulted in an enhancement of H-2′ signal indicating that the methoxyl group is attached at C-3′ of ring C.

Keywords: Ochna squarrosa; Furanoflavanoid; Chalcone dimer; Analgesic activity; Anti-inflammatory activity.
* Corresponding author. E-mail: janaswamy@iict.res.in

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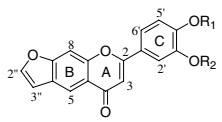
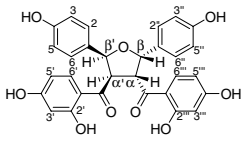


1. R_1 = H, R_2 = Me
2. R_1 = H, R_2 = H



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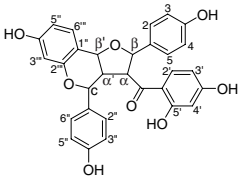


4. Lophirone H

^{1}H NMR spectrum further has a singlet at δ 6.96 integrating for one proton, attributed to an olefinic proton, which is adjacent to the carbonyl group. Two doublets at δ 7.06 (J = 8.8 Hz), 7.56 (J = 2.4 Hz) and a double doublet at δ 7.66 (J = 8.4 Hz, 2.4 Hz) each integrating for one proton suggested the presence of a 1,3,4-trisubstituted aromatic ring. A doublet at δ 8.20 (J = 2.0 Hz) and a double doublet at δ 7.12 (J = 1.2 Hz, 2.4 Hz) integrating for one proton each indicated the H-2″, H-3″ of the furan ring. A doublet at δ 8.10 (J = 1.2 Hz) and a singlet at δ 8.40 each integrating for one proton indicated the presence of a 1,2,4,5-tetrasubstituted aromatic ring. A singlet at δ 9.98 is due to the presence of a hydroxyl group. The explanation is further supported by the disappearance of a peak at δ 9.98 in a heavy water exchange condition.

The appearance of H-5 proton as a singlet indicated the annellation of furan ring to be at C-6/C-7 positions. Further confirmation of the annellation of furan ring at C-6/C-7 came from the long-range correlation of H-3″ proton at δ 7.12 with the H-5 proton at δ 8.40 in ^{1}H–^{1}H COSY experiment.

The ^{13}C NMR spectrum in Me_2CO-d_6 of compound **1** exhibits the presence of 18 carbon atoms whose multiplicity is explained using DEPT and HMBC correlations. The DEPT experiment revealed the presence of one methyl, eight methines and nine quaternary carbons. In the HMBC spectrum, absence of correlation between H-3″ proton and C-9 and correlations of H-3″ with C-5, C-6 and C-10 clearly suggested the linear fusion of the furan ring with the aromatic ring. Hence, the structure of compound **1** was identified as 4′-hydroxy-3′-methoxyfurano[4″,5″,6,7] flavone.

Compound **2** was isolated as a pale yellow amorphous solid, mp 282 °C. The molecular formula is analyzed as $C_{17}H_{10}O_5$ using HRESIMS and ^{13}C NMR data. The spectral data of compound **2** were similar to those obtained for compound **1**. The significant difference in the ^{1}H NMR spectrum is the absence of a peak at δ 3.96 suggesting the absence of methoxyl group in compound **2**. The disappearance of two signals at δ 9.86 and δ 9.88 in deuterium exchange conditions indicated the presence of two phenolic hydroxyl groups. The absence of a signal at δ 56.4 in the ^{13}C NMR spectrum of compound **2** confirmed the absence of methoxyl group. Thus, the structure of compound **2** was confirmed as 3′, 4′-dihydroxyfurano[4″,5″,6,7]flavone. The structures of compound **1** and compound **2** were further confirmed by their synthesis.

Compound **3** was isolated as a pale yellow amorphous solid, with mp 262 °C analyzed for $C_{30}H_{24}O_9$ using HRESIMS and ^{13}C NMR spectral data. A combination of HRESIMS (M^+-1; 527) and ^{13}C NMR results indicated that compound **3** has a symmetrical structure. IR spectrum of compound **3** displayed absorption bands at 3384 cm^{-1} and 1633 cm^{-1} suggesting the presence of a hydroxyl group and a chelated carbonyl group, respectively.

The ^{1}H NMR spectrum of compound **3** in Me_2CO-d_6 showed signals for 12 protons. Two doublets at δ 6.80 and δ 7.40 each integrating for two protons suggested the presence of a 1,4-disubstituted aromatic ring. Two doublets at δ 6.08 (J = 2 Hz) and δ 7.38 (J = 8 Hz) each integrating for one proton and a double doublet at δ 6.10 (J = 8 Hz, 2 Hz) integrating for one proton suggested the presence of a 1,2,4-trisubstituted aromatic ring. A double doublet at δ 5.42 (J = 8 Hz, 1.2 Hz) integrating for one proton indicated the presence of a methine proton attached to an oxygen atom. Another double doublet at δ 4.72 (J = 8 Hz, 2 Hz) integrating for one proton indicated the presence of a methine proton attached to the carbonyl group. A singlet at δ 12.50 integrating for one proton indicated the presence of a chelated hydroxyl group. The presence of hydroxyl group was confirmed by deuterium exchange experiment.

The ^{13}C NMR spectrum of compound **3** showed only 15 signals whose multiplicity was explained using DEPT and HMBC correlations. DEPT experiment showed that there are no methylene carbons. Two signals at δ 58.7 and δ 83.8 indicated the presence of two aliphatic methine carbons of tetrahydrofuran ring. The ^{1}H–^{1}H COSY long-range spectrum showed a weak correlation between H-6′ of ring A′ and β proton of the furan ring indicating that the benzoyl ring is attached to the α carbon and the phenyl group to the β carbon of the furan ring.

The spectral data of compound **3** (^{1}H and ^{13}C) resembled with those of lophirone G[8] with slight variations, but its optical rotation and melting point were found to be different. This indicated that compound 3 has similar structural framework as lophirone G with a difference in its absolute configuration.

The relative stereochemistry of the furan ring was established with the help of NOESY experiment. The NOESY spectrum of compound **3** showed a long-range coupling between α and β protons of the furan ring indicating a *cis*-stereochemistry between them. The relative stereochemistry of the two protons at α and α′ was explained on the basis of optical activity. If all the substituents on the furan ring of compound **3** were to be arranged in a *cis* configuration with respect to each other, it would generate a plane of symmetry resulting it to be

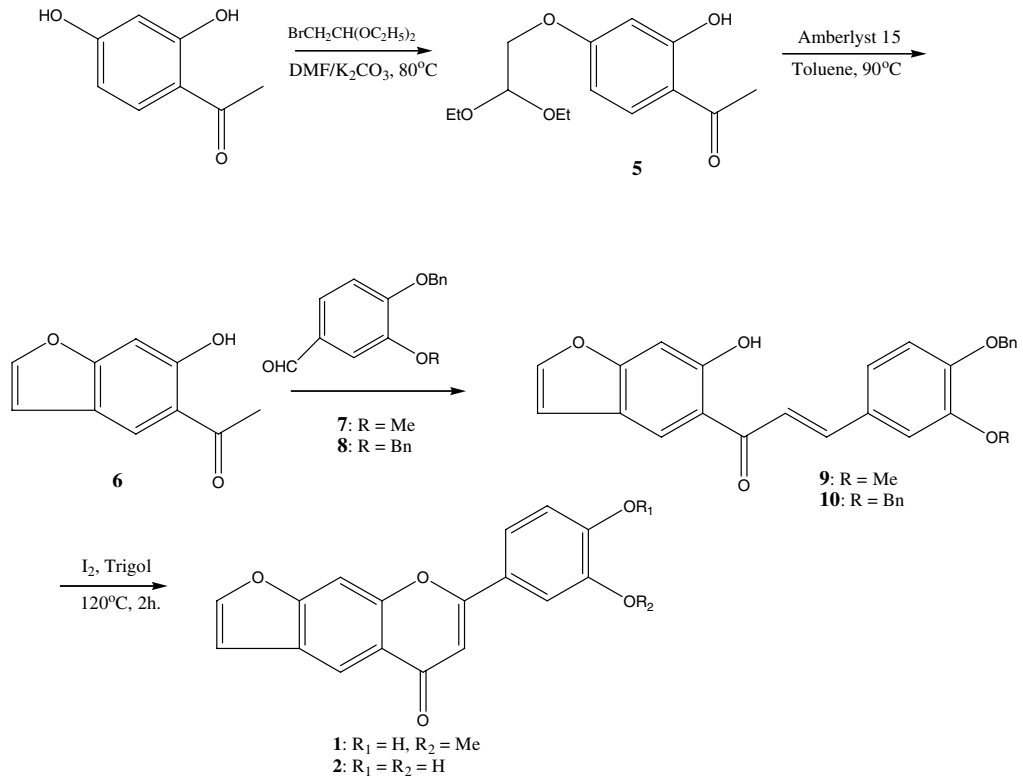
optically inactive. But, compound **3** is optically active with an optical rotation of −6.4°. This indicates that compound **3** has a *cis–trans–cis* relative stereochemistry at the furan ring. This was further confirmed by its NOE spectrum. Irradiation of α proton at δ 4.72 resulted in an enhancement of β proton at δ 5.42 indicating that the two protons are in *cis* relative stereochemistry with each other.

2.2. Synthesis

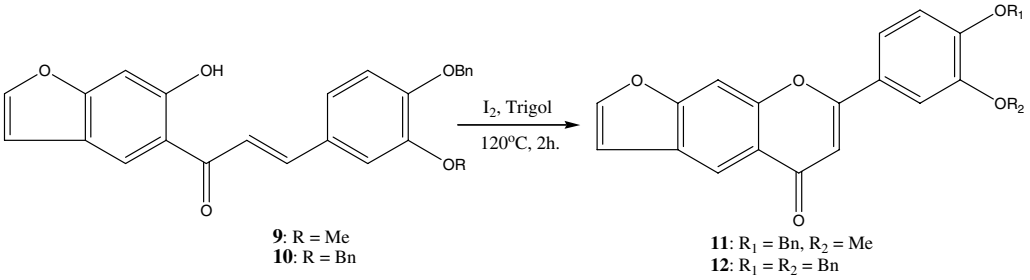
The synthesis began with resacetophenone. Resacetophenone was treated with bromoacetaldehyde diethyl acetal in the presence of potassium carbonate in anhydrous DMF to give compound **5**, which on treatment with acidic Amberlyst 15 in toluene at 90 °C yielded 5-acetyl-6-hydroxycoumarone[9] (**6**). 5-Acetyl-6-hydroxy coumarone was condensed with aldehyde **7** or **8** in the presence of KOH in anhydrous ethanol to give chalcone **9** or **10** which was cyclized using I_2 in trigol[10] at 120 °C to afford 4′-hydroxy-3′-methoxyfurano[4″,5″,6,7]flavone (**1**) or 3′,4′-dihydroxyfurano[4″,5″,6,7]flavone (**2**) (Scheme 1).

During the course of our studies towards the synthesis of furanoflavonoids, compound **1** and compound **2**, we needed to synthesize furanoflavones **11** and **12** from chalcones **9** and **10**, respectively, using I_2 in trigol[7] (Scheme 2).

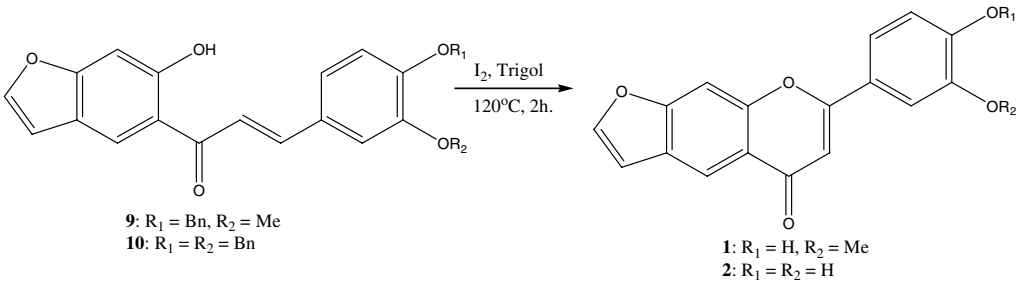
Interestingly, the ^{1}H NMR spectrum of the resultant product showed the absence of characteristic benzyl ether protons at their respective positions. The ESIMS spectrum of the compounds obtained also revealed the absence of benzyl ether group. Based on this, it was concluded that benzyl ether in compounds **9** and **10** has



Scheme 1.



Scheme 2.



Scheme 3.

been cleaved to give compounds **1** and **2** along with the cyclization of chalcone to its corresponding flavone (Scheme 3).

An extensive literature survey revealed that though different methods are available for selective cleavage of benzyl ethers, most of them suffer from certain drawbacks such as lack of selectivity, reduction of double bonds, etc. Prompted by this discovery, we decided to extend our investigation to other substrates and establish its wider[11,12] applicability. The scope and generality of this procedure is illustrated with several examples and the results are summarized in Table 1.

3. Conclusion

Two new anti-inflammatory and analgesic furanoflavones along with a new chalcone dimer were isolated from *O. squarrosa*. The newly isolated furanoflavones were also synthesized involving a new methodology of benzyl deprotection. I_2 in trigol was demonstrated to be a simple and convenient reagent to cleave benzyl ethers. The advantages of this method are inexpensive, co-reagent not needed, simple reaction conditions, high selectivity, retention of unsaturation, etc. These advantages are very useful in complex multiple synthesis which requires sequential protection and deprotection of various functionalities.

4. Biological assay

The crude extract and isolated compounds were tested for analgesic (tail-flick method) and anti-inflammatory (carrageenan-induced paw oedema method) activity, diclofenac sodium was taken as reference standard. The crude ethyl acetate-soluble fraction of the methanol extract of root bark showed very promising analgesic and anti-inflammatory activity. The paw oedema percent protection values are shown in Table 2. Among the tested samples crude extract has exhibited promising percent protection at 25 mg/kg and is comparable to standard at 20 mg/kg. The isolated molecules also could protect but they are comparable at higher dose level than standard drug used in preset investigation.

The percent analgesia are recorded at different time intervals as shown in Table 3. The results of analgesic activity indicate that all the test compounds have exhibited significant activity at 25 mg/kg when compared with the control, 1% Tween 80. The crude extract and compound 1 have promising protection at early reaction time and potent than at standard reaction time. The potent analgesic and anti-inflammatory activity of the crude extract may be probably due to the synergistic effect of the mixture of compounds in natural proportion.

5. Experimental

5.1. Isolation procedures

The shade-dried root bark of *O. squarrosa* (8 kg) was extracted with methanol to give 120 g of extract, which was partitioned between ethyl acetate and water. The ethyl acetate-soluble fraction (15 g) was subjected to column chromatography over silica gel (60–120 mesh, 300 g) and eluted with hexane/ethyl acetate in the increasing order of polarities to afford five fractions. Fraction 3 (hexane/ethyl acetate 90:10) was further subjected to column chromatography and eluted with hexane/ethyl acetate 95:5 to give compound **1** (0.040 g) and compound **2** (0.020 g) upon elution with hexane/ethyl acetate 90:10. Fraction 5 was further subjected to column chromatography and eluted with hexane/ethyl acetate 75:25 to give compound **3** (0.012 g) and compound **4** (0.010 g) upon elution with hexane/ethyl acetate 70:30.

Compound **1**: [4′-hydroxy-3′-methoxyfurano[4″,5″,6,7]-flavone]. Mp 272 °C. IR (KBr) ν_{max} 3426, 1623, 1298, 1109, 831, 569 cm^{-1}. ^1H NMR (300 MHz, Me_2CO-d_6) δ 3.96 (3H, s, –OMe), 6.96 (1H, s, H-3), 7.06 (1H, d, J = 8.8 Hz, H-5′), 7.12 (1H, dd, J = 1.2 Hz, 2.4 Hz, H-3″), 7.56 (1H, d, J = 2.4 Hz, H-2′), 7.66 (1H, dd, J = 8.4 Hz, 2.4 Hz, H-6′), 8.10 (1H, d, J = 1.2 Hz, H-8), 8.20 (1H, d, J = 2 Hz, H-2″), 8.40 (1H, s, H-5). ^{13}C NMR (75 MHz, Me_2CO-d_6) δ 56.4 (C–OMe), 101.6 (C-8), 105.2 (C-3), 108.0 (C-3″), 110.2 (C-10), 112.4 (C-2′), 118.0 (C-5), 120.4 (C-6′), 124.0 (C-5′), 124.0 (C-1′), 126.8 (C-6), 149.6 (C-3′), 149.8 (C-2″), 152.4 (C-4′), 154.0 (C-9), 157.6 (C-7), 163.8 (C-2), 178.0 (C=O). HRESIMS m/z [M^++H] 309.0767, calcd 309.0763.

Table 1. Selective cleavage of benzyl ethers using I_2/trigol

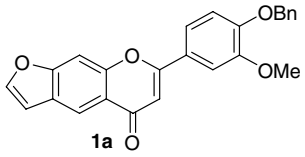
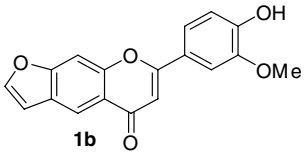
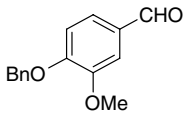
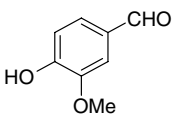
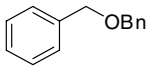
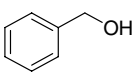
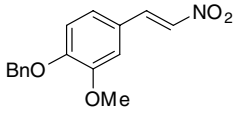
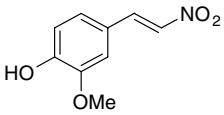
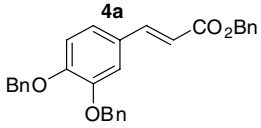
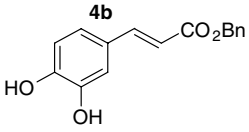
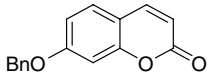
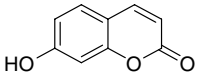
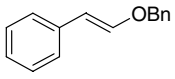
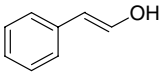
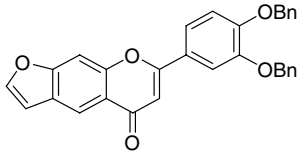
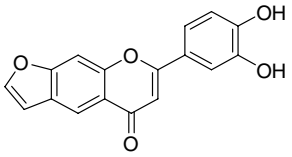
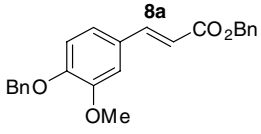
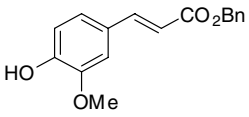
Entry	Substrate	Product	Time (h)	Isolated yield (%)
1	 **1a**	 **1b**	3	60
2	 **2a**	 **2b**	3	65
3	 **3a**	 **3b**	2	65
4	 **4a**	 **4b**	3	60
5	 **5a**	 **5b**	3	70
6	 **6a**	 **6b**	2	70
7	 **7a**	 **7b**	3	65
8	 **8a**	 **8b**	3	70
9	 **9a**	 **9b**	3	70

Table 2. Anti-inflammatory activity of *Ochna squarrosa* crude extract and compounds on the carrageenan-induced paw oedema of Albino rats

Treatment	Dose (mg/kg)	Paw oedema percent protection (h)				
		1/2	1	2	3	4
Control	Tween 80, 1%	4.15 (±0.37)	4.19 (±0.21)	3.31 (±0.01)	2.47 (±0.02)	2.3 (±0.05)
Diclofenac sodium	20	29* (±0.04)	37 (±0.08)	50** (±0.03)	46.5** (±0.05)	33.5** (±0.03)
1	25	10.9* (±0.005)	43** (±0.015)	30** (±0.02)	21.74* (±0.016)	18.5* (±0.015)
2	25	30** (±0.004).	40** (±0.06)	47** (±0.02)	42** (±0.084)	34** (±0.055)
3	25	20* (±0.017)	34.7 (±0.008)	37** (±0.057)	33.4** (±0.027)	16.7* (±0.008)
Crude extract	25	43.7** (±0.001)	48** (±0.008)	52.3** (±0.004)	43.7** (±0.026)	36.9** (±0.055)

Significance levels *$p < 0.05$, **$p < 0.01$ compared with respective control (ANOVA followed by Dunnett's test). Each value represents ± SE ($n = 6$).

Table 3. Analgesic activity effect of *Ochna squarrosa* crude extract and compounds in Swiss mice by tail-flick method

Treatment	Dose (mg/kg)	Percent analgesia (min)					
		30	60	90	120	150	180
Control	Tween 80, 1%	3.03 (±0.03)	5.79 (±0.03)	9.09 (±0.03)	7.5 (±0.05)	5.3 (±0.02)	2.2 (±0.02)
Diclofenac sodium	20	28.00 (±0.07)	39.5** (±0.13)	51.5** (±0.09)	71.36** (±0.13)	51.36** (±0.11)	24.77** (±0.05)
1	25	57.49** (±0.98)	75.39** (±0.65)	73.15** (±1.68)	72.7** (±1.57)	24.16** (±0.79)	3.8 (±0.58)
2	25	18.91** (±0.90)	30.88** (±0.33)	57.52** (±0.09)	69.11** (±1.09)	22.77 (±1.04)	15.05 (±0.34)
3	25	24.65** (±1.38)	31.35 (±0.41)	66.02** (±0.73)	57.53** (±0.85)	40.41** (±0.73)	16.57** (±0.78)
Crude extract	25	77.92** (±0.07)	73.12** (±0.07)	74.88** (±01.0)	45.6 (±0.03)	44.45** (±0.30)	21.76** (±0.32)

Significance levels $^{**}p < 0.01$ compared with respective control Tween 80, 1% (ANOVA followed by Dunnett's test). Each value represents ± SE ($n = 6$).

Compound **2**: [3′,4′-dihydroxyfurano[4″,5″,6,7]flavone]. Mp 282 °C. IR (KBr) ν_{max} 3414, 2924, 618, 1149, 1024, 770, 604 cm^{-1}. ^1H NMR (300 MHz, Me_2CO-d_6) δ 6.70 (1H, s, H-3), 6.88 (1H, d, $J = 8.8$ Hz, H-5′), 7.12 (1H, dd, $J = 1.2$ Hz, 2.7 Hz, H-3″), 7.42 (1H, d, $J = 2.4$ Hz, H-2′), 7.44 (1H, dd, $J = 8.4$ Hz, 2.4 Hz, H-6′), 8.00 (1H, d, $J = 1.2$ Hz, H-8), 8.12 (1H, d, $J = 2$ Hz, H-2″), 8.30 (1H, s, H-5). ^{13}C NMR (75 MHz, Me_2CO-d_6) δ 101.0 (C-8), 104.3 (C-3), 107.8 (C-3″), 113.9 (C-10), 116.6 (C-2′), 117.9 (C-5), 119.5 (C-6′), 120.7 (C-5′), 122.2 (C-1′), 126.4 (C-6), 147.6 (C-3′), 149.3 (C-2″), 150.4 (C-4′), 154.1 (C-9), 157.4 (C-7), 164.1 (C-2), 177.7(C=O). HRESIMS *m/z* [M^++H] 295.0602, calcd 295.0606.

Compound **3**: [Lophirone L] mp 262 °C $[\alpha]_D$ −6.4° (*c* 1; EtOH) IR (KBr) ν_{max} 3384, 2949, 1632, 1454, 1022, 631 cm^{-1}. ^1H NMR (200 MHz, Me_2CO-d_6) δ 4.72 (1H, dd, $J = 8$ Hz, 2 Hz, H-α), 5.42 (1H, d, $J = 8$ Hz, 1.2 Hz, H-β), 6.08 (1H, d, $J = 2$ Hz, H-3′), 6.10 (1H, dd, $J = 8$ Hz, 2 Hz, H-5′), 6.80 (2H, d, $J = 8$ Hz, H-3, 5), 7.38 (1H, d, $J = 8$ Hz, H-6′), 7.40 (2H, d, $J = 8$ Hz, H-2, 6), 12.50 (1H, s, –OH) ^{13}C NMR (75 MHz, Me_2CO-d_6) δ 58.7 (C-α), 83.8 (C-β), 103.1 (C-3′), 108.0 (C-5′), 113.9 (C-1′), 115.6 (C-3, 5), 128.6 (C-2, 6), 131.4 (C-1), 132.4 (C-6′), 157.3 (C-4), 164.9 (C-2′), 165.7 (C-4′), 201.4 (C=O). HRESIMS *m/z* [M^+−H] 527.1341, calcd 527.1342.

5.2. Synthetic procedures

General procedure for the debenzylation of benzyl ethers: To a solution of benzyl ether (1.0 g, 2.5 mmol) in trigol was added iodine (0.46 g, 3.75 mmol) and refluxed for 2 h at 120 °C. After completion of the reaction, the reaction mixture was treated with hypo solution and extracted with ethyl acetate (3×50 ml), dried and concentrated. The product obtained was purified using column chromatography. The fractions eluted at 30% ethyl acetate in petroleum ether contained pure hydroxy compound.

5.3. Biological assay procedures

5.3.1. Animals. The animals were procured from the National Institute of Nutrition, Hyderabad, India, and were maintained in colony cages at 25 ± 2 °C; they were fed standard animal feed.

5.3.2. Anti-inflammatory activity. Anti-inflammatory activity was evaluated by carrageenan-induced paw oedema test in rats.[13] Diclofenac sodium 20 mg/kg was administered as a standard for comparison and test compounds, extract at dose level of 25 mg/kg were administered orally. The paw volume was measured using the mercury displacement technique with the help of plethysmograph immediately before and 30 min, 1, 2, 3 and 4 h after carrageenan injection. The percent inhibition of paw oedema was calculated.

5.3.3. Analgesic activity. Test for analgesic activity was performed by tail-flick technique[14,15] using Wistar albino mice (25–30 g) of either sex selected by random sampling technique. Diclofenac sodium 20 mg/kg was administered as a standard for comparison and test compounds, extract at dose level of 25 mg/kg were administered orally. The reaction time was recorded at 30, 60, 90, 120, 150 and 180 min after treatment, cut-off time was 10 s. The percent analgesic activity was calculated.

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