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Coumarins and bicoumarin from *Ferula sumbul*: anti-HIV activity and inhibition of cytokine release

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Abstract

The methanol extract of the dried roots of *Ferula sumbul* afforded two furanocoumarin esters, fesumtuorin A, B, one bicoumarin, fesumtuorin C, five spirobicoumarins, fesumtuorin D, E, F, G and H, along with nineteen known coumarins. Their structures were established on the basis of spectroscopic studies. Some of the isolated compounds showed anti-HIV activity and very weak inhibition of cytokine release.

Keywords: *Ferula sumbul*; Umbelliferae; Coumarin; Bicoumarin; Fesumtuorin

1. Introduction

The genus *Ferula* comprises 130 species distributed from the Mediterranean region to Central Asia. This genus is well documented as a good source of biologically active compounds such as coumarins, terpene alcohols, and sesquiterpene derivatives (Gonzalez & Barrera, 1995). Several species have been used in folk medicine (Uphof, 1968). As part of our ongoing studies of Turkish medicinal plants (Sezik et al., 1997), we investigated the constituents of *Ferula sumbul*, and describe herein the isolation and characterization of eight new coumarins (**1**–**8**), along with nineteen known coumarins (**9**–**27**) from this source, as well as their anti-HIV activities and inhibition of cytokine release.

2. Results and discussion

The IR spectrum of fesumtuorin A (**1**) indicated the presence of a hydroxyl group (3423 cm^{-1}), a lactone carbonyl (1728 cm^{-1}) and a furan ring (885 cm^{-1}). The UV spectrum had absorption maxima at 220, 250, 267 and 311 nm, very similar to those of linear furanocoumarins (Lee & Soine, 1969). The ^1H NMR spectrum in the downfield region showed two pairs of doublets, one at δ_H 6.26 and 8.15 ($J = 9.8$ Hz) attributed to the C-3 and C-4 protons of the coumarin nucleus while the second pair of signals at δ_H 7.79 and 7.21 ($J = 2.2$ Hz) confirmed the presence of the benzofuran moiety. The single aromatic proton signal at δ_H 7.14 was assigned to the C-8 proton. The upfield region contained two tertiary methyl groups (δ_H 1.29 and 1.32), one methyl group (δ_H 1.31, 3H, *d*, $J = 6.9$ Hz) which was coupled with one methine proton (δ_H 4.34, 1H, *q*, $J = 6.9$ Hz), two methylene protons (δ_H 4.66 and 4.91) and another methine proton (δ_H 5.38).

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The ^{13}C NMR spectrum (Table 2) displayed nineteen carbon atoms, among which were detected 11 sp^2 carbon atoms of a furanocoumarin nucleus and the eight carbons of a side chain which included three methyls (δ_C 26.9, 25.7, 20.6), one methylene attached to an oxygen function (δ_C 72.9), two methine carbons at δ_C 68.0 and 79.5, one carbonyl carbon at δ_C 176.0 and one quaternary carbon at δ_C 71.6. These data agreed with the molecular formula of **1** as $C_{19}H_{20}O_8$, which was supported by the HR mass spectral data. It was concluded that **1** is a linear furanocoumarin derived from the known oxypeucedanin hydrate (**11**) (Harkar, Razdan & Waight, 1984), previously isolated from this plant. From comparison of the ^{13}C NMR spectral data of compounds **1** and **11**, the structure of **1** was proposed to be a 12-hydroxy propionic ester of **11**. In the HMBC spectrum, the proton signals at δ_H 1.31 (H-18), 4.34 (H-17) and 5.38 (H-12) were correlated with the carbon signal at δ_C 176.0 (C-16). The proton signal at δ_H 4.66 (H-11) was correlated with the carbon signals at δ_C 79.5 (C-12) and 150.0 (C-5). Thus, the structure of fesumtuorin A (**1**) was elucidated as illustrated in Fig. 1.

Fesumtuorin B (**2**), $C_{19}H_{20}O_8$, had the same molecular formula as compound **1**. The ^{13}C NMR spectral data of **2** were similar to those of compound **1** except for the signals due to C-4, 4a, 5, 6, 7, 8 and 8a. The ^1H NMR spectral data of **2** were also similar to those of **1** except for the methine signals [**2**: δ_H 5.58 (1H, *s*); **1**: 7.14 (1H, *s*, H-8)]. From these results the structure of **2** was deduced to be a 5-substituted furanocoumarin. ^{13}C NMR spectral data of compounds **2** and helaclenol (**12**) (Harkar et al., 1984) were very similar except for the signals of compound **2** at δ_C 20.5, 68.0 and 176.0. These results suggested that compound **2** was a C-12 substituted helaclenol (**12**). The proton signals at δ_H 1.43 (H_3-18), 4.36 (H-17) and 5.30 (H-12) were correlated with the carbon signal at δ_C 176.0 (C-16) in the HMBC spectrum. The proton signal at δ_H 4.45 (H-11) was correlated with the carbon signals at δ_C 79.4 (C-12) and 132.4 (C-8). Thus, the main difference between compound **2** and **1** resulted from the different substitution positions on the furanocoumarin nucleus at C-8 and C-5, respectively.

Fesumtuorin C (**3**) was assigned as $C_{32}H_{30}O_{11}$ on the basis of its HR mass spectrum. The IR spectrum showed absorptions due to hydroxyl groups (3431 cm^{-1}), a lactone (1730 cm^{-1}) and a furan ring (877 cm^{-1}). ^1H NMR and H–H COSY spectra suggested the presence of two sets of protons for two furanocoumarin skeletons [δ_H 8.14 (*d*, $J = 9.7$ Hz), 6.00 (*d*, $J = 9.7$ Hz), 7.63 (*d*, $J = 2.2$ Hz), 7.11 (*d*, $J = 2.2$ Hz), 6.77 (*s*); 7.89 (*d*, $J = 9.6$ Hz), 6.27 (*d*, $J = 9.6$ Hz), 7.69 (*d*, $J = 2.1$ Hz), 6.84 (*d*, $J = 2.1$ Hz), 7.38 (*s*)]. Furthermore, the ^1H NMR spectrum exhibited the presence of two pairs of methylenes [δ_H 5.06 (*dd*, $J = 1.9$, 10.0 Hz), 4.48 (*br t*, $J = 9.4$ Hz); 4.55 (*dd*, $J = 2.6$, 10.2 Hz), 4.41 (*dd*, $J = 6.2$, 10.2 Hz)], two methines [δ_H 4.21 (*dd*, $J = 1.9$, 8.5 Hz), 3.95 (*dd*, $J = 2.6$, 6.2 Hz)] and four methyls (δ_H 1.50, 1.36, 1.29, 1.26). In the ^{13}C NMR spectrum data (Table 2), one furanocoumarin moiety was nearly identical to the corresponding part of compound **11**, the other corresponding very well to the carbon chemical shifts of compound **12**. It was assumed that **3** is a furanocoumarin dimer derived from compounds **11** and **12**. A difference in carbon chemical shifts was observed for the side chain carbons. The assignment of protons on the side chains was based on the ^1H–^1H COSY, ^{13}C–^1H COSY and HMBC spectra. In the HMBC spectrum, the proton signal at δ_H 4.48 (H-11) was correlated with the carbon signals at δ_C 150.4 (C-5), 77.0 (C-12) and 79.5 (C-13), while the proton signal at δ_H 4.41 (H-11′) was correlated with the carbon signal at δ_C 132.4 (C-8′), 79.5 (C-12′) and 73.1 (C-13′). In the NOESY spectrum, the proton signal at δ_H 3.95 (H-12′) was correlated with the methyl proton signals at δ_H 1.29 (H_3-14′) and 1.26 (H_3-15′), and the proton signal at δ_H 4.21 (H-12) was correlated with the methyl proton signals at δ_H 1.36 (H_3-14) and 1.50 (H_3-15). Significant correlation was observed between the proton signals at δ_H 3.95 (H-12′) and 1.50 (H_3-15); correlation between the methine proton signals at δ_H 3.95 (H-12′) and (H-12) was also observed. Acetylation of **3** with acetic anhydride and pyridine gave **3a**. The ^1H NMR spectrum of compound **3a** showed the presence of one acetyl methyl signal at δ_H 2.01, and the signal at δ_H 4.21 (H-12) in **3** was downfield shifted to δ_H 5.58 (H-12) in **3a**. On the basis of the above data, the structure of **3** was determined as shown.

Fesumtuorin D (**4**) was assigned the molecular formula as $C_{32}H_{28}O_{10}$ ($[M]^+$ m/z 572.1697) by HR–MS. The ^1H NMR spectrum of **4** indicated the presence of two 8-substituted linear furanocoumarin skeletons [δ_H 7.74 (*d*, $J = 9.6$ Hz), 6.36 (*d*, $J = 9.6$ Hz), 7.64 (*d*, $J = 2.2$ Hz), 6.76 (*d*, $J = 2.2$ Hz), 7.33 (*s*); 6.84 (*d*, $J = 9.8$ Hz), 5.76 (*d*, $J = 9.8$ Hz), 7.53 (*d*, $J = 2.1$ Hz), 6.69 (*d*, $J = 2.1$ Hz), 7.08 (*s*)] (Fisher & Nordby, 1966; Lee & Soine, 1969; Razdan, Karchroo, Harkar & Koul, 1982). The ^{13}C NMR spectrum of **4** also indicated the presence of two furanocoumarin units and two sets of side chain groups, but there was only one carbonyl carbon attributable to a lactone carbon (δ_C 160.4). One set of side chain carbon signals (δ_C 71.8, 61.3, 58.2, 24.6 and 18.9) was very similar to that of the side chain in helaclenin (**14**) (Adityachaudhury, Ghosh & Choudhuri, 1974), while another corresponding set of side chain carbon signals (δ_C 72.8, 83.1, 83.0, 28.4 and 22.7) was significantly different from the data of **14**, especially the downfield shift of the methine and quaternary carbons at δ_C 83.1 and 83.0. It was assumed that the lactone carbonyl carbon in one of the linear

furacoumarin moieties was condensed with the hydroxyl groups at the side chain of another furanocoumarin moiety and formed a spirobicoumarin structure similar to that of rivulobin D (**10**), which was recently isolated from *Pleurospermum rivulorum* (Taniguchi, Yabu, Hada, Baba, Xiao & Liu, 1998a, 1998b).

Based on analysis of 2D NMR spectra, the ^{1}H NMR and ^{13}C NMR data of compound **4** were assigned as shown in Tables 1 and 2. The methyl proton signal at δ_H 1.59 (H-14′) and the methine proton resonance at δ_H 4.53 (H-12′) were correlated with the proton signal at δ_H 5.76 (H-3) in the NOESY spectrum. The proton signal at δ_H 4.53 (H-12′) was correlated with the carbon signal at δ_C 118.3 (C-2) in the HMBC spectrum (Table 3). These facts indicated that this methine proton was adjacent to the proton H-3 and carbon C-2. Therefore, the structure of compound **4** was determined as shown.

Fesumtuorin E (**5**) had the same molecular ion peak and similar fragment ion peaks in the EI mass spectrum as compound **4**. The ^{1}H and ^{13}C NMR spectral data of compound **5** were also similar to those of compound **4**. The chemical shift of the methyl group at δ_C 22.6 (C-14′) was clearly different from that of the corresponding methyl signal [δ_C 28.4 (C-14′)] in **4**. In the NOESY spectrum, the methyl proton signal at δ_H 5.74 (H-3) was correlated with the proton signals at δ_H 4.84 (H-12′) and 1.46 (H-14′), and no correlation was observed between the methine proton signal at δ_H 4.84 (H-12′) and the proton signal at δ_H 5.74 (H-3), in contrast to compound **4**. These correlations indicated that the methylene protons (H-11′) were adjacent to H-3, and the structure of compound **5** was deduced as shown.

Fesumtuorin F (**6**) was assigned the molecular formula as $C_{32}H_{30}O_{11}$ ([M]$^+$ 590.1806) by HR–MS. Its ^{1}H NMR spectrum indicated the presence of two 5-substituted furanocoumarin skeletons (Steck & Mazurek, 1972; Harkar et al., 1984). The ^{13}C NMR spectrum of **6** also indicated the presence of two furanocoumarin units, but there was only one carbonyl carbon attributable to a lactone carbon (δ_C 163.0), as was observed for compounds **4** and **5**. One set of ^{13}C NMR spectral data of **6** corresponded well to the side chain of the oxypeucedanin hydrate (**8**) (Table 2) (Harkar et al., 1984). The proton and carbon NMR signals were assigned with the aid of 2D NMR analysis (Table 3). In the NOESY spectrum of **6**, the methyl proton signals at δ_H 1.40 (H-14′) and 4.39 (H-12′) were correlated with the proton signal at δ_H 5.58 (H-3), these correlations indicated the spiro-ring part in **6** was similar to that of **4**, as shown in Fig. 2.

Fesumtuorin G (**7**) had the same molecular formula and main fragment ion peaks in the EI mass spectra as did **6**. Its ^{1}H NMR spectrum indicated the presence of two sets of 5-substituted furanocoumarin units (Table 1). The ^{13}C NMR spectrum of **7** was also similar to those of **6**. In the NOESY spectrum, the methyl proton signals at δ_H 1.43 (H-14′) and 4.78 (H-11′) were correlated with the proton signal at δ_H 5.95 (H-3),

Table 1
^{1}H NMR spectral data of compounds **4**–**8**[a] (400 MHz, values with TMS as internal std.)

H	4	5	6	7	8
3	5.76 *d* (9.8)	5.74 *d* (9.8)	5.58 *d* (9.8)	5.95 *d* (9.8)	5.68 *d* (9.8)
4	6.84 *d* (9.8)	6.86 *d* (9.8)	7.70 *d* (9.8)	7.72 *d* (9.8)	7.24 *d* (9.8)
5	7.08 *s*	7.09 *s*	–	–	–
8	–	–	5.95 *s*	7.19 *s*	6.91 *s*
9	7.53 *d* (2.1)	7.55 *d* (2.1)	7.48 *d* (2.1)	7.66 *d* (2.1)	7.48 *d* (2.2)
10	6.69 *d* (2.1)	6.69 *d* (2.1)	6.87 *d* (2.1)	7.22 *d* (2.1)	6.80 *d* (2.2)
11	4.39 *dd* (11.2, 5.6)	4.51 *dd* (11.2, 5.7)	4.45 *dd* (9.8, 2.3)	5.07 *dd* (9.8, 2.1)	4.33 *d* (5.5)
	4.25 *dd* (11.2, 6.1)	4.38 *dd* (11.2, 5.7)	4.11 *t* (9.1)	4.70 *t* (9.0)	–
12	3.13 *t* (5.7)	3.28 *t* (5.7)	3.68 *dd* (8.2, 2.3)	4.35 *dd* (8.2, 2.1)	3.18 *t* (5.5)
14	1.07 *s*	1.18 *s*	1.13 *s*	1.58 *s*	1.44 *s*
15	1.19 *s*	1.30 *s*	1.19 *s*	1.62 *s*	1.74 *s*
3′	6.36 *d* (9.6)	6.35 *d* (9.6)	5.83 *d* (9.8)	6.28 *d* (9.8)	6.36 *d* (9.6)
4′	7.74 *d* (9.6)	7.74 *d* (9.6)	8.02 *d* (9.8)	8.21 *d* (9.8)	7.74 *d* (9.6)
5′	7.33 *s*	7.36 *s*			7.37 *s*
8′	–	–	7.10 *s*	7.30 *s*	–
9′	7.64 *d* (2.2)	7.66 *d* (2.2)	7.73 *d* (2.1)	7.88 *d* (2.1)	7.65 *d* (2.1)
10′	6.76 *d* (2.2)	6.79 *d* (2.2)	7.03 *d* (2.1)	7.26 *d* (2.1)	6.80 *d* (2.1)
11′	4.88 *dd* (10.4, 6.5)	4.77 *dd* (10.2, 5.7)	4.81 *dd* (10.0, 3.7)	4.84 *dd* (10.2, 3.9)	4.78 *dd* (9.6, 5.8)
	4.84 *dd* (10.4, 6.5)	4.53 *dd* (10.2, 5.7)	4.61 *t* (9.7)	4.78 *dd* (10.2, 3.9)	4.53 *dd* (9.6, 6.3)
12′	4.53 *t* (6.5)	4.84 *t* (5.7)	4.39 *dd* (9.4, 3.7)	5.04 *t* (3.9)	4.80 *dd* (6.3, 5.8)
14′	1.59 *s*	1.46 *s*	1.40 *s*	1.43 *s*	1.24 *s*
15′	1.77 *s*	1.78 *s*	1.45 *s*	1.74 *s*	1.36 *s*

[a] **4**, **5**, **8** measured in $CDCl_3$, **6** in CD_3OD, **7** in pyridine-d_5, values is parenthesis represents coupling constants in Hertz.

while no correlation was observed between H-12′ and H-3, indicating that the methylene proton was adjacent to proton H-3. The structure of compound **7** was thus determined as shown.

Fesumtuorin H (**8**) was assigned the molecular formula as $C_{32}H_{28}O_{10}$ ($[M]^+$ m/z 572.1699) by HR–MS. The ^1H NMR and ^{13}C NMR spectral data of **8** indicated the presence of two 5-substituted furanocoumarin skeletons. Based on analysis of 2D NMR spectra, the ^1H NMR and ^{13}C NMR data of **8** were assigned as shown in Tables 1 and 2. The methyl proton signal at δ_H 1.24 (H-14′) and the methylene proton signal at δ_H 4.78 (H-11′) were correlated with the proton signal at δ_H 5.68 (H-3) in the NOESY spectrum. The relative stereochemistry of **8** was deduced as illustrated (Fig. 1).

On the basis of detailed study of spectral data, the known compounds were identified as oxypeucedanin hydrate (**11**), heraclenol (**12**) and oxypeucedanin (**13**) (Harkar et al., 1984), heraclenin (**14**) (Adityachaudhury et al., 1974), oxypeucedanin methnolate (**15**) (Atkkinson, Boyd & Grundon, 1974), heraclenol 3′-me ester (**16**) (Bandopadhyay, Mailik & Seshadri, 1973), pranferol (**17**) (Grande, Maria, Balbino & Francisco, 1986), imperatorin (**18**) (Harkar et al., 1984), pabulenol (**19**) (Chatterjee, Banerji & Basa, 1972), xanthoxol (**20**) (Harkar et al., 1984), xanthotoxin (**21**), osthol (**22**), auraptenol (**23**) and meranzin hydrate (**24**) (Barik, Dey, Das, Chatterjee & Shoolery, 1983), feselol (**25**) (Miski, Ulubeloen, Lee & Mabry, 1985), conferol (**26**) (Perelson, Kiryanov, Bankovskii, Kiryalov & Bukreeva, 1976), and conferone (**27**) (Saidhodzhaev & Malikov, 1978). The ^{13}C NMR data of several compounds (**22**–**27**) were described in the literature, and are presented in the Section 3. In the case of compound feselol (**25**), the ^{13}C NMR data at C-13′ and C-12′ assignments were reversed, based on 2D NMR spectra.

Table 2
^{13}C NMR spectral data of compounds **1**–**8**[a] (100 MHz, values with TMS as internal std.)

C	1	2	3	4	5	6	7	8
2	163.1	162.8	163.2	118.3	117.5	120.1	118.2	118.4
3	113.2	115.1	112.4	119.4	119.1	119.2	118.4	118.0
4	141.2	146.7	141.4	129.3	130.0	125.5	125.4	124.3
4a	107.6	118.6	107.9	117.1	117.2	109.1	107.8	107.8
5	150.0	115.4	150.4	113.3	113.4	150.6	149.6	147.9
6	114.3	127.9	114.9	122.8	122.8	114.1	113.2	113.1
7	159.8	149.2	159.5	147.7	147.9	157.7	157.3	156.6
8	94.6	132.4	94.1	131.8	132.0	94.6	94.5	95.3
8a	153.8	144.4	153.3	141.7	141.7	151.4	151.3	150.5
9	146.9	148.6	146.5	144.9	145.0	145.1	144.1	143.6
10	106.2	108.0	106.3	106.9	106.8	105.8	105.7	104.2
11	72.9	73.6	75.7	71.8	72.0	75.4	76.1	72.2
12	79.5	79.4	77.0	61.3	61.5	78.3	77.8	61.3
13	71.6	71.8	79.5	58.2	58.3	72.8	71.9	58.3
14	26.9	26.9	23.3	24.5	24.6	27.0	27.6	24.6
15	25.7	25.8	24.0	18.6	18.7	25.0	25.6	18.9
16	176.0	176.0						
17	68.0	68.0						
18	20.6	20.5						
2′			162.6	160.4	160.2	163.0	160.6	160.2
3′			114.9	114.9	114.8	112.9	113.3	114.9
4′			146.7	144.3	144.3	141.3	139.2	144.2
4a′			117.8	116.5	116.5	108.6	107.4	116.5
5′			114.4	113.6	113.8	149.6	148.7	113.8
6′			128.0	126.1	126.1	114.1	114.3	126.0
7′			148.2	148.0	147.9	159.5	158.4	147.6
8′			132.4	131.6	131.3	95.5	94.7	131.3
8a′			143.4	143.4	143.2	153.5	153.1	143.3
9′			148.2	146.9	146.8	147.3	146.1	146.8
10′			107.9	106.7	106.8	105.8	105.4	106.8
11′			75.9	72.8	71.3	75.7	71.6	71.3
12′			79.5	83.1	80.9	83.9	82.0	80.8
13′			73.1	83.0	83.2	84.2	82.3	83.0
14′			27.1	28.4	22.6	29.0	22.8	22.6
15′			26.2	22.7	27.9	22.8	27.7	27.6

[a] **1**–**3**, **6** measured in CD_3OD, **4**, **5**, **8** in $CDCl_3$, **7** in pyridine-d_5.

Table 3
HMBC data of compounds **4** and **6**

4		**6**	
H	Correlated C	H	Correlated C
3	2, 4a	3	2, 4a
4	2, 8a	4	2, 8a
5	4, 7, 8a, 10	8	4a, 6, 7, 8a
9	6, 7, 10	9	6, 7, 10
10	6, 7, 9	10	6, 7, 9
11	8, 13	11	5, 12, 13
12	13	12	11
14	12, 13, 15	14	12, 13, 15
15	12, 13, 14	15	12, 13, 14
3′	2′, 4a′, 8a′	3′	2′, 4a′, 8a′
4′	2′, 8a′	4′	2′, 8a′
5′	4′, 7′, 8a′, 10′	8′	4a′, 6′, 7′, 8a′
9′	6′, 7′, 10′	9′	6′, 7′, 10′
10′	6′, 7′, 9′	10′	6′, 7′, 9′
11′	8′, 13′	11′	5′, 12′
12′	2, 11′, 14′	12′	2, 13′
14′	12′, 13′, 15′	14′	12′, 13′, 15′
15′	13′, 14′	15′	13′, 14′

Table 4
Anti-HIV activity of compounds **11**–**15**, **18** and **22**

Compound	IC_{50} (μg/ml)	EC_{50} (μg/ml)	TI
11	21.1	10	2.11
12	> 100	0.115	870
13	23.4	1.05	22.2
14	20.1	2.37	8.48
15	> 100	33.3	3.00
18	> 100	< 0.10	> 1000
22	11.7	0.155	75.5
AZT	500	0.032	15,625

Ferula sumbul is thus a rich source of coumarins derivatives. Oxypeucedanin methnolate (**15**), heraclenol 3′-me ester (**16**) and auraptenol (**23**) are isolated here for the first time from a *Ferula* species.

In searching for natural anti-AIDS agents, coumarins (Lee, Kashiwada, Huang, Snider, Cosentino & Lee, 1994), diterpenoids (Gustafson et al., 1992), and triterpenoids (Fujioka et al., 1994), and tannins (Kilkuskie, Kashiwada, Nonaka, Boder, Cheng & Lee, 1992), have been reported to have anti-HIV activity. In this paper, we report the activity of isolated compounds; their anti-HIV activity data are shown in Table 4. Compound **19** inhibited HIV replication in H9 lymphocytes with EC_{50} values of <0.10 μg/ml, and it inhibited uninfected H9 cell growth with IC_{50} values of >100 μg/ml, calculated therapeutic index (TI) value of >1000. In general, TI > 5.0 is considered to denote significant activity; compounds **11**, **12**, **13**, **17** and **21** showed potent anti-HIV activity with a TI value over 5.

Cytokines have various biological activities and are thought to be necessary for maintenance of homeosta-

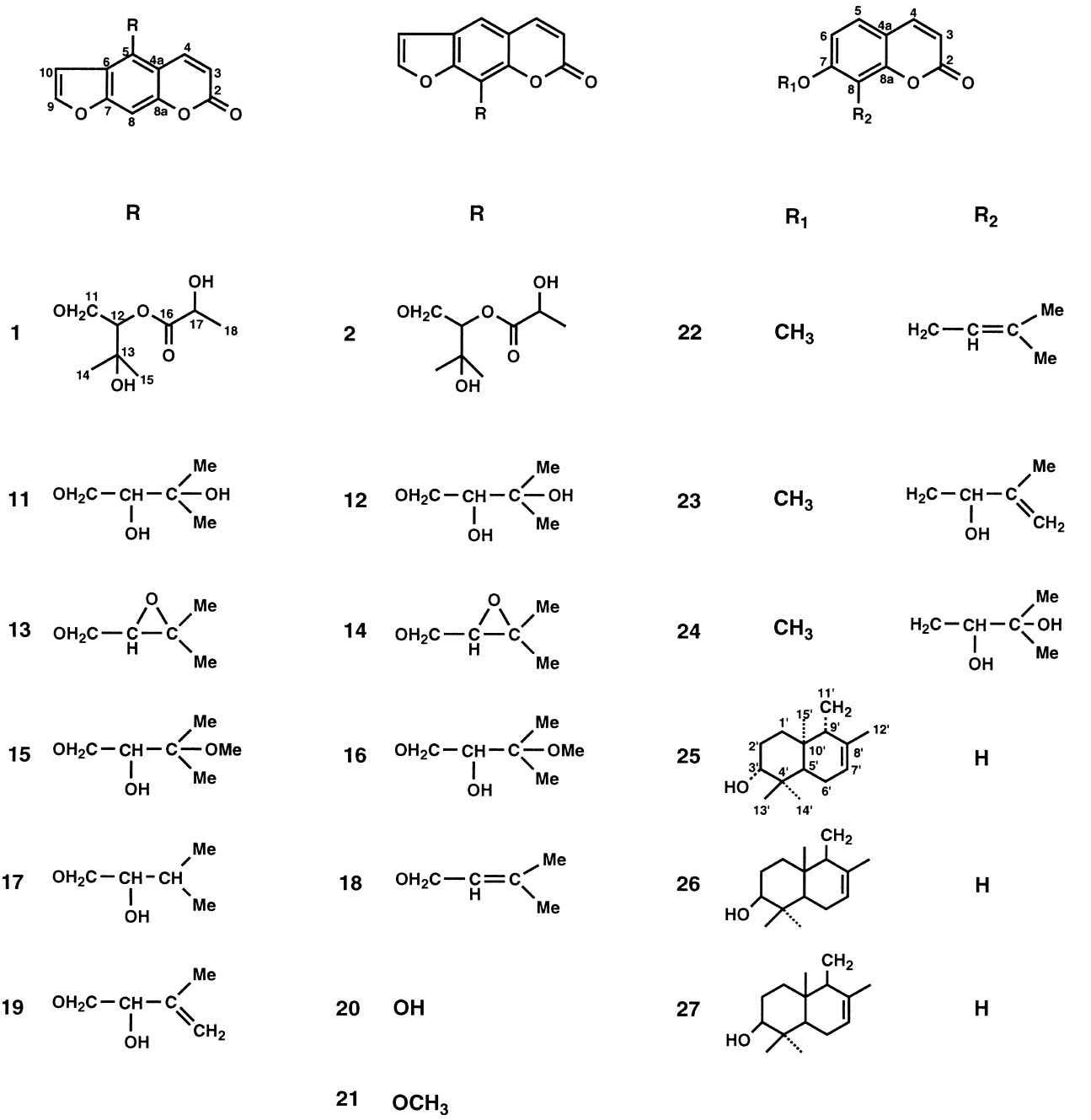

Fig. 1. Coumarins of *Ferula sumbul*.

sis of the human body. We examined the inhibitory effect (Ghezzi & Dinarello, 1988; Kita, Ohmoto, Hirai, Yamaguchi & Imanishi, 1992) on cytokine (IL-1α, β, TNFα, IL-2, IL-4, IL-8) production; data are given in Table 5. Tested compounds showed weak inhibitory effects on cytokine production (TNF α and IL-4) from liposaccharide-stimulated human peripheral mononuclear cells compared to the reference compound (prednisolone).

3. Experimental

3.1. General

NMR experiments were run on a Bruker ARX-400 instrument. ^{1}H NMR, 400 MHz, ^{13}C NMR, 100 MHz with TMS as int. standard; MS: JEOL JMSD-300 instrument; CC: silica gel, Sephadex LH-20, HPLC: GPC (Shodex packed column, GS-310, MeOH; Shodex H-2001, 2002, $CHCl_3$), silica gel (Si 60, Hibar RT 250-25).

3.2. Plant material

The roots of *Ferula sumbul* were collected in 1997 from Uzbekistan. Voucher specimens are deposited in the herbarium of the Institute of Botany, Academy of Sciences, Uzbekistan.

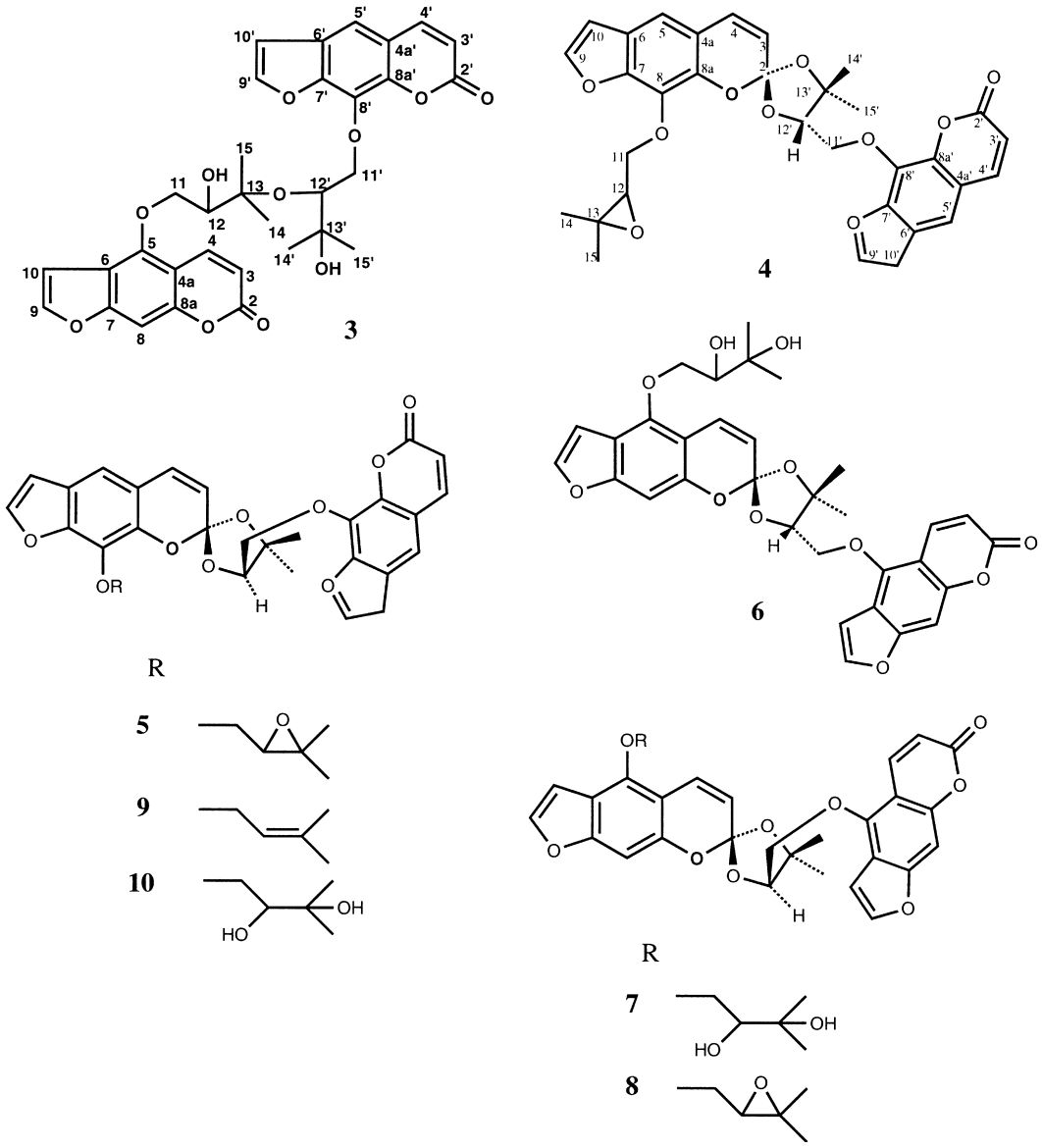

Fig. 2. Bicoumarins of *Ferula sumbul*.

3.3. Extraction and isolation

The roots of *F. sumbul* (500 g) were crushed and extracted three times with MeOH (50 l each) at 60°C for 6 h. The MeOH extracts were concertrated in vacuo to give a residue, which was partitioned between EtOAc and H_2O. The EtOAc layer was concertrated to give a residue (55 g), which was chromatographed on silica gel (800 g). The column was eluted with solvent of increasing polarity (hexane–EtOAc, EtOAc, EtOAc–MeOH and MeOH) to give 25 major frs (frs. 1–25). Fr. 16 (1.3 g) were chromatographed on silica gel with $CHCl_3$–MeOH (96:4, 90:10, 80:20) to give 8 frs. (frs. 16.1–16.8). Fr. 16.5 (390 mg) was chromatographed on Sephadex LH-20 with MeOH to give 4 frs. (frs. 16.5.1–16.5.4). Fr. 16.5.3 was chromatographed using HPLC (GPC, MeOH) to give 7.4 mg of **2** and 7.3 mg of **24**. Fr. 16.6 (323 mg) was also chromatographed on Sephadex LH-20 with MeOH to give 4 frs. (frs. 16.6.1–16.6.4). Fr. 16.6.3 was chromatographed using HPLC (Si 60, Hex:EtOAc:CH_3OH, 3:6.5:0.5) to give 16 frs. (frs. 16.6.3.1–16.6.3.16). 12 mg of **1** was separated using preparative TLC ($CHCl_3$:MeOH, 9:1) from 18.4 mg of fr. 16.6.3.4. Fr. 3 (11.0 g) gave **22** (5 g), fr. 4 (7.3 g) gave **18** (2 g), fr. 7 (13.4 g) was separated by silica gel, Sephadex LH-20 and HPLC to afford **11** (0.8 g), **12** (1.5 g), **15** (97 mg), **16** (348 mg), **23** (9.5 mg), **26** (8.5 mg), **17** (5 mg), **19** (33 mg), **20** (7 mg), **25** (28 mg). Fr. 6 (2.1 g) gave **21** (4.5 mg) and **27** (17 mg). Fr. 14 (9.5 g) gave **7** (1.27 g) and **13** (1 g). Fr. 10 (2.5 g) was chromatographed on silica gel with $CHCl_3$–MeOH (96:1, 97:3) to give 14 frs. (frs. 10.1–10.14). Fr. 10.5 (457 mg) was chromatographed on silica gel with $CHCl_3$ to give 5 frs. (frs. 10.5.1–10.5.5). Fr. 10.5.3 was chromatographed using HPLC (GPC, $CHCl_3$) to give 5 frs. (frs. 10.5.3.1–10.5.3.5). Fr. 10.5.3.2 (113 mg) was chromatographed using HPLC (Si 60, Hex:EtOAc, 1:1) to give 16 mg of **4** and 43 mg of **5**. Fr. 14 (9.5 g) was chromatographed on silica gel with $CHCl_3$–MeOH (98:2, 95:5, 80:20) to give 9 frs. (frs. 14.1–14.9). Fr. 14.3 (1.5 g) was chromatographed on Sephadex LH-20 with MeOH to give 5 frs. (frs. 14.3.1–14.3.5). Fr. 14.3.3 (930 mg) was chromatographed on silica gel with $CHCl_3$–MeOH (97:3) to give 6 frs. (frs. 14.3.3.1–14.3.3.6). Fr. 14.3.3.5 (129 mg) was chromatographed using HPLC (GPC, MeOH) to give 9.8 mg of **3** and 10 mg of **7** and 11 mg of fr. 14.3.3.5.7. The later was further purified by HPLC (Si 60, Hex:EtOAc, 1:2) to give 6.8 mg of **6**. Fr. 14.3.3.3 was separated by HPLC (GPC and then ODS) to give 7.2 mg of **10**. Fr. 7 was separated by silica gel, Sephadex LH-20 and HPLC (Si 60, Hex:EtOAc, 1:1) to afford 17.6 mg of **9**. Fr. 8 (2.9 g) was chromatographed on silica gel, Sephadex LH-20 and finally HPLC (Si 60 and then ODS) to give 9 mg of **7**.

Table 5
The inhibition of cytokine release by compounds **4**, **11**–**16**, **18**, **22** and prednisolone[a]

Compounds	Inhibition %	
	TNF-α	IL-4
4	61.3	42.8
11	80.1	34.4
12	80.8	42.1
13	81.3	41.8
14	83.9	47.3
15	83.9	38.6
16	79.4	42.1
18	63.1	42.8
22	85.4	50.7
Prednisolone	31.8	30.2

[a] Concentration (**4**, **11**–**16**, **18**, **22**: 1×10^{-5} g ml^{-1}, prednisolone: 3×10^{-8} g ml^{-1}). The inhibition by prednisolone for IL-2, 8, IL-1β and IFN-γ production are 36.6%, 36.6%, 21.1% and 1.8%, respectively; compounds **4**, **11**–**16**, **18**, **22** showed no significant inhibition of the production of these cytokines.

3.3.1. Fesumtuorin A (*1*)

$[\alpha]_D^{25}$: +17.4° (MeOH, *c* 1.1); UV λ_{max}^{MeOH} nm (log ε): 220 (4.24), 250 (4.07), 267 (4.01), 311 (3.92); IR ν_{max}^{KBr} cm^{-1}: 3423, 3406, 3106, 2965, 2926, 1728, 1625, 1610, 1579, 1459, 1356, 1261, 1208, 1134, 1103, 885, 865, 809. EIMS *m/z* (rel. int.): 376[M]$^+$ (96), 361 (14), 287 (17), 245 (8), 202 (65), 175 (92), 174 (36), 157 (19), 145 (27), 103 (93), 89 (19), 69 (31), 59 (86), 43 (80); HR–EIMS: *m/z*, 376.1147 (required for $C_{19}H_{20}O_8$, 376.1158); ^{1}H NMR spectral data (CD_3OD): δ 6.29 (*d*, *J* = 9.8 Hz, H-3), 8.15 (*d*, *J* = 9.8 Hz, H-4), 7.14 (*s*, H-8), 7.79 (*d*, *J* = 2.2 Hz, H-9), 7.21 (*d*, *J* = 2.2 Hz, H-10), 4.91 (*dd*, *J* = 10.4, 1.9 Hz, H-11), 4.66 (*t*, *J* = 9.6 Hz, H-11), 5.38 (*dd*, *J* = 8.8, 1.9 Hz, H-12), 1.32 (*s*, H-14), 1.29 (*s*, H-15), 4.34 (*q*, *J* = 6.9 Hz, H-17), 1.31 (*d*, *J* = 6.9 Hz, H-18); ^{13}C NMR spectral data: see Table 2.

3.3.2. Fesumtuorin B (*2*)

$[\alpha]_D^{25}$: +3.6° (MeOH, *c* 0.4); UV λ_{max}^{MeOH} nm (log ε): 217 (4.28), 248 (4.18), 299 (3.91), IR; ν_{max}^{KBr} cm^{-1}: 3447, 3425, 3136, 3075, 2971, 2928, 1729, 1713, 1623, 1614, 1589, 1538, 1403, 1334, 1212, 1129, 1101,1032, 874; EIMS *m/z* (rel. int.): 376 [M]$^+$ (16), 304 (1), 287 (4), 245 (5), 202 (97), 175 (58), 174 (37), 157 (9), 145 (11), 103 (38), 89 (23), 69 (4), 59 (26), 43 (39); HR–EIMS: *m/z* 376.1163 (required for $C_{19}H_{20}O_8$, 376.1158); ^{1}H NMR spectral data (CD_3OD): δ 6.38 (*d*, *J* = 9.6 Hz, H-3), 8.02 (*d*, *J* = 9.6 Hz, H-4), 5.58 (*s*, H-5), 7.89 (*d*, *J* = 1.9 Hz, H-9), 6.95 (*d*, *J* = 1.9 Hz, H-10), 5.03 (*d*, *J* = 11.1, 2.2 Hz, H-11), 4.45 (*t*, *J* = 9.7 Hz, H-11), 5.30 (*dd*, *J* = 8.6, 2.2 Hz, H-12), 1.28 (*s*, H-14), 1.24 (*s*, H-15), 4.36 (*q*, *J* = 7.0 Hz, H-17), 1.43 (*d*, *J* = 7.0 Hz, H-18); ^{13}C NMR spectral data: see Table 2.

*3.3.3. Fesumtuorin C (**3**)*

$[\alpha]_D^{25}$: 0° (pyridine, *c* 0.84); UV λ_{max}^{MeOH} nm (log ε): 204 (4.45), 217 (4.45), 248 (4.30), 305 (4.05); IR ν_{max}^{KBr} cm^{-1}: 3452, 3431, 3126, 3073, 2978, 2938, 1730, 1622, 1587, 1467, 1445, 1402, 1333, 1205, 1154, 1132, 1103, 1040, 1000, 877; EIMS, *m/z* (rel. int.): 590 $[M]^+$ (7), 572 (12), 488 (5), 368 (6), 287 (40), 202 (100), 174 (20), 145 (9), 103 (38), 69 (15), 59 (9), 43 (9); HR–EIMS, *m/z*, 590.1818 (requires for $C_{32}H_{30}O_{11}$, 590.1788); ^{1}H NMR spectral data (CD_3OD): δ 6.00 (*d*, *J* = 9.7 Hz, H-3), 8.14 (*d*, *J* = 9.7 Hz, H-4), 6.77 (*s*, H-8), 7.63 (*d*, *J* = 2.2 Hz, H-9), 7.11 (*d*, *J* = 2.2 Hz, H-10), 5.06 (*dd*, *J* = 10.0, 1.9 Hz, H-11), 4.48 (*t*, *J* = 9.4 Hz, H-11), 4.21 (*dd*, *J* = 8.5, 1.9 Hz, H-12), 1.36 (*s*, H-14), 1.50 (*s*, H-15), 6.27 (*d*, *J* = 9.6 Hz, H-3′), 7.89 (*d*, *J* = 9.6 Hz, H-4′), 7.38 (*s*, H-5′), 7.69 (*d*, *J* = 2.1 Hz, H-9′), 6.84 (*d*, *J* = 2.1 Hz, H-10′), 4.55 (*dd*, *J* = 2.6, 10.0 Hz, H-11′), 4.41 (*dd*, *J* = 10.2, 6.2 Hz, H-11′), 3.95 (*dd*, *J* = 6.2, 2.6 Hz, H-12′), 1.29 (*s*, H-14′), 1.26 (*s*, H-15′); ^{13}C NMR spectral data: see Table 2.

*3.3.4. Acetylation of fesumtuorin C (**3a**)*

A solution of **3** (2.5 mg) in pyridine (0.5 ml) and Ac_2O (0.5 ml) was allowed to stand overnight at room temperature. The reaction mixture was treated in usual way and purified by prep. TLC ($CHCl_3$: MeOH, 95:5) to give **3a** (2 mg). ^{1}H NMR spectral data (CD_3OD): δ 5.77 (*d*, *J* = 9.7 Hz, H-2), 7.70 (*d*, *J* = 9.7 Hz, H-3), 6.77 (*s*, H-8), 7.56 (*d*, *J* = 2.2 Hz, H-9), 7.03 (*d*, *J* = 2.2 Hz, H-10), 5.07 (*dd*, *J* = 10.0, 1.9 Hz, H-11), 4.64 (*t*, *J* = 9.4 Hz, H-11), 5.65 (*dd*, *J* = 8.5, 1.9 Hz, H-12), 2.01 (*s*, H-OAc), 1.33 (*s*, H_3-14), 1.38 (*s*, H_3-15), 6.15 (*d*, *J* = 9.6 Hz, H-2′), 7.76 (*d*, *J* = 9.6 Hz, H-3′), 7.24 (*s*, H-5′), 7.55 (*d*, *J* = 2.1 Hz, H-9′), 6.67 (*d*, *J* = 2.1 Hz, H-10′), 4.54 (*dd*, *J* = 10.2, 6.2 Hz, H-11′), 4.36 (*dd*, *J* = 10.2, 2.6 Hz, H-11′), 3.93 (*dd*, *J* = 6.2, 2.6 Hz, H-12′), 1.19 (*s*, H_3-14′), 1.14 (*s*, H_3-15′); EIMS *m/z* (rel. int.): 632 $[M]^+$ (15), 373 (30), 287 (43), 202 (100), 175 (23), 145 (12), 89 (29), 69 (20), 59 (38), 43 (85); HR–EIMS: *m/z* 632.1924 (required for $C_{34}H_{32}O_{12}$, 632.1894).

*3.3.5. Fesumtuorin D (**4**)*

$[\alpha]_D^{25}$: −4.8 ($CHCl_3$ *c* 1.0); UV λ_{max}^{MeOH} nm (log ε): 300 (4.27), 240 (4.99); IR ν_{max}^{KBr} cm^{-1}: 1732, 1625, 1590, 1403, 1333, 1220, 1133, 1101, 1029, 990, 874, 824, 756. EIMS *m/z* (rel. int.): 572 $[M]^+$ (62), 488 (9), 287 (18), 286 (81), 202 (65), 174 (65), 145 (20), 59 (82), 43 (31); HR–EIMS: *m/z* 572.1697 (required for $C_{32}H_{28}O_{10}$, 572.1682); ^{1}H NMR and ^{13}C NMR spectral data: see Tables 1 and 2.

*3.3.6. Fesumtuorin E (**5**)*

$[\alpha]_D^{25}$: +8.0° ($CHCl_3$ *c* 1.0); UV λ_{max}^{MeOH} nm (log ε): 300 (4.24), 240 (4.99); IR ν_{max}^{KBr} cm^{-1}: 1733, 1625, 1590, 1403, 1333, 1222, 1133, 1100, 1028, 990, 874, 824, 754; EIMS *m/z* (rel. int.): 572 $[M]^+$ (73), 488 (13), 287 (19), 286 (76), 202 (100), 174 (83), 145 (27), 69 (11), 59 (73), 43 (19); HR–EIMS: *m/z* 572.1705 (required for $C_{32}H_{28}O_{10}$, 572.1682); ^{1}H NMR and ^{13}C NMR spectral data: see Tables 1 and 2.

*3.3.7. Fesumtuorin F (**6**)*

UV λ_{max}^{MeOH} nm (log ε): 300 (4.23), 240 (4.97); IR ν_{max}^{KBr} cm^{-1}: 3417, 1728, 1626, 1580, 1461, 1128, 1098, 1032, 986, 877, 807, 750; EIMS *m/z* (rel. int.): 590 $[M]^+$ (54), 488 (18), 287 (9), 286 (21), 202 (100), 174 (40), 145 (11), 103 (38), 59 (35), 43 (19); HR–MS: *m/z* 590.1806 (required for $C_{32}H_{30}O_{11}$, 590.1788); ^{1}H NMR and ^{13}C NMR spectral data: see Tables 1 and 2.

*3.3.8. Fesumtuorin G (**7**)*

EIMS *m/z* (rel. int.): 590 $[M]^+$ (65), 487 (15), 304 (16), 287 (13), 286 (29), 202 (100), 174 (35), 145 (6), 69 (7), 59 (21), 43 (17); HR–EIMS: *m/z* 590.1803 (required for $C_{32}H_{30}O_{11}$, 590.1788); ^{1}H NMR and ^{13}C NMR spectral data: see Tables 1 and 2.

*3.3.9. Fesumtuorin H (**8**)*

UV λ_{max}^{MeOH} nm (log ε): 299 (4.10), 243 (4.83); IR ν_{max}^{KBr} cm^{-1}: 1730, 1626, 1588, 1458, 1401, 1333, 1216, 1148, 1100, 1028, 986, 876, 823, 756; EIMS *m/z* (rel. int.): 572 $[M]^+$ (52), 488 (7), 287 (16), 286 (39), 202 (82), 174 (35), 145 (18), 59 (59), 43 (67); HR–EIMS: *m/z* 572.1699 (required for $C_{32}H_{28}O_{10}$, 572.1682); ^{1}H NMR and ^{13}C NMR spectral data: see Tables 1 and 2.

*3.3.10. Osthol (**22**)*

^{13}C NMR spectral data ($CDCl_3$): δ 161.3 (C-2), 112.9 (C-3), 143.8 (C-4), 113.0 (C-4a), 126.2 (C-5), 107.4 (C-6), 160.2 (C-7), 117.9 (C-8), 152.8 (C-8a), 56.0 (C-OMe), 21.9 (C-1′), 121.2 (C-2′), 132.6 (C-3′), 25.8 (C-4′), 17.9 (C-5′).

*3.3.11. Auraptenol (**23**)*

^{13}C NMR spectral data (pyridine-d_5): δ 161.3 (C-2), 113.0 (C-3), 144.3 (C-4), 113.2 (C-4a), 127.3 (C-5), 107.8 (C-6), 161.0 (C-7), 115.8 (C-8), 154.1 (C-8a), 56.1 (C-OMe), 30.3 (C-1′), 74.9 (C-2′), 149.2 (C-3′), 110.2 (C-4′), 17.8 (C-5′).

*3.3.12. Meranzin hydrate (**24**)*

^{13}C NMR spectral data (CD_3OD): δ 163.8 (C-2), 113.0 (C-3), 146.4 (C-4), 114.4 (C-4a), 128.4 (C-5), 109.0 (C-6), 162.6 (C-7), 117.2 (C-8), 154.7 (C-8a), 56.7 (C-OMe), 26.3 (C-1′), 78.8 (C-2′), 74.1 (C-3′), 25.6 (C-4′), 25.5 (C-5′).

*3.3.13. Feselol (**25**)*

^{13}C NMR spectral data ($CDCl_3$): δ 161.2 (C-2), 113.1 (C-3), 143.4 (C-4), 112.6 (C-4a), 128.8 (C-5), 113.1 (C-6), 162.1 (C-7), 101.4 (C-8), 156.0 (C-8a), 37.9

(C-1′), 27.4 (C-2′), 78.9 (C-3′), 38.8 (C-4′), 49.5 (C-5′), 23.4 (C-6′), 123.8 (C-7′), 132.3 (C-8′), 53.9 (C-9′), 35.9 (C-10′), 67.1 (C-11′), 21.6 (C-12′), 28.1 (C-13′), 15.3 (C-14′), 14.9 (C-15′).

*3.3.14. Conferol (**26**)*

^{13}C NMR spectral data (pyridine-d_5): δ 160.9 (C-2), 113.2 (C-3), 143.9 (C-4), 112.9 (C-4a), 129.4 (C-5), 113.1 (C-6), 162.4 (C-7), 101.7 (C-8), 156.4 (C-8a), 32.2 (C-1′), 26.2 (C-2′), 74.8 (C-3′), 37.7 (C-4′), 43.7 (C-5′), 23.6 (C-6′), 124.3 (C-7′), 133.0 (C-8′), 54.1 (C-9′), 36.0 (C-10′), 67.6 (C-11′), 22.0 (C-12′), 22.6 (C-13′), 29.0 (C-14′), 15.1 (C-15′).

*3.3.15. Conferone (**27**)*

^{13}C NMR spectral data ($CDCl_3$): δ 161.2 (C-2), 113.2 (C-3), 143.4 (C-4), 112.7 (C-4a), 128.8 (C-5), 113.1 (C-6), 161.8 (C-7), 101.4 (C-8), 156.0 (C-8a), 38.5 (C-1′), 34.5 (C-2′), 216.1 (C-3′), 47.5 (C-4′), 51.2 (C-5′), 23.9 (C-6′), 123.7 (C-7′), 132.4 (C-8′), 53.1 (C-9′), 35.9 (C-10′), 66.7 (C-11′), 21.6 (C-12′), 22.4 (C-13′), 25.3 (C-14′), 14.6 (C-15′).

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