DOI 10.1007/s10600-023-03976-y
Chemistry of Natural Compounds, Vol. 59, No. 2, March, 2023

CADABATONE, A NEW SESQUITERPENE LACTONE FROM *Cadaba fruticosa*

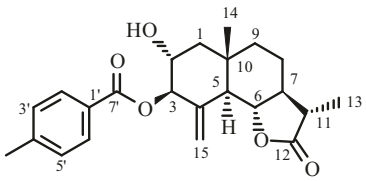
Ayesha Abdul Jabbar,[1] Sadia Khan,[1]
Mehdi Hassan Kazmi,[1] Abdul Malik,[2]*
Itrat Fatima,[2] Farah Inamullah,[1]
Sadia Farheen,[3] and Beena Naqvi[3]

*Cadabatone (**1**), a new eudesmanolide-type sesquiterpene lactone, has been isolated from the EtOAc soluble subfraction of the methanolic extract of* Cadaba fruticosa *(L.) Druce, along with known compounds, 3-epierivanin (**2**), 3,5,7,4-tetrahydroxyflavone (**3**), esculetin (**4**), rosmarinic acid (**5**),* α*-amyrin (**6**), and* β*-amyrin (**7**), isolated for the first time from this species. The structures of these compounds were elucidated by spectroscopic studies including MS, IR, 1D and 2D NMR spectroscopy.*

Keywords: *Cadaba fruticosa*, Capparidaceae, cadabatone, eudesmanolide-type sesquiterpene, spectroscopic studies.

The genus *Cadaba*, belonging to the family Capparidaceae comprises 30 species of shrubs growing in Africa, Arabia and the Indo-Pakistan subcontinent. In Pakistan, the genus is represented by only two species, namely *Cadaba fruticosa* and *Cadaba heterotricha*. *C. fruticosa* (L.) Druce (syn. *C. farinosa*) is a multibranched shrub that is commonly found in Karachi and other parts of the Sindh province of Pakistan. Its leaves and roots have purgative, antihelmintic, antispasmodic, amenagogue, and aperient properties [1–3] and the fruits are commonly used to treat worm infection. The plant also possesses antimicrobial, antioxidant, antidiabetic, antipyretic, and anti-inflammatory activities [4]. A literature survey of the genus *Cadaba* revealed the presence of alkaloids [5–7], terpenoids [8, 9], and flavonoids [10–12]; however, only two compounds have so far been reported from *C. fruticosa* [13, 14]. The ethnopharmacological and chemotaxonomic importance of this genus prompted us to undertake further phytochemical studies on *C. fruticosa*. Herein we report the isolation and structural elucidation of a new sesquiterpene lactone, named cadabatone (**1**), along with known 3-epierivanin (**2**) [15], 3,5,7,4-tetrahydroxyflavone (**3**) [16], esculetin (**4**) [17], rosmarinic acid (**5**) [18], α-amyrin (**6**), and β-amyrin (**7**) [19], isolated from the species for the first time.

Cadabatone (**1**) was obtained as a colorless gummy solid. The HR-EI-MS showed $[M]^+$ peak at *m/z* 384.1936 corresponding to the molecular formula $C_{23}H_{28}O_5$. The IR spectrum showed absorption bands for hydroxyl groups (3422 cm^{-1}), a γ-lactone moiety (1760 cm^{-1}), an ester carbonyl (1718 cm^{-1}), an aromatic ring (1620, 1508 cm^{-1}), and an exocyclic double bond (1650, 865 cm^{-1}).



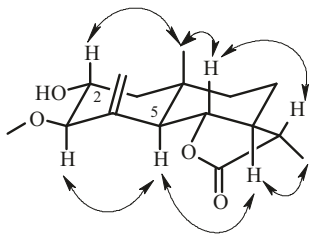
1

1) Department of Applied Chemistry, University of Karachi, 75270, Karachi, Pakistan; 2) International Centre for Chemical and Biological Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, 75270, Karachi, Pakistan, e-mail: abdulmalik.hej@gmail.com; 3) Pharmaceutical Research Centre, PCSIR Laboratories Complex Karachi, 75270, Karachi, Pakistan. Published in *Khimiya Prirodnykh Soedinenii*, No. 2, March–April, 2023, pp. 236–238. Original article submitted February 22, 2022.

 0009-3130/23/5902-0278 ©2023 Springer Science+Business Media, LLC

TABLE 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data and HMBC Correlations of **1** ($CDCl_3$, δ, ppm, J/Hz)

C atom	δ_H	δ_C	HMBC
1α/β	1.30 (m); 2.44 (m)	48.2	C-2, 3, 5, 10
2	3.79 (ddd, J = 9.5, 9.0, 3.5)	70.1	C-1, 3, 4, 10
3	3.85 (d, J = 9.5)	81.9	C-1, 2, 4, 5, 7′
4	–	145.0	
5	2.75 (d, J = 11.0)	45.1	C-3, 4, 6, 7, 10
6	3.98 (t, J = 11.0)	78.5	C-4, 5, 7, 8
7	1.69 (m)	52.7	C-6, 8, 9, 11, 12, 13
8α/β	1.89 (m); 1.49 (m)	24.0	C-6, 7, 9, 10, 11
9α/β	2.04 (m); 1.52 (m)	35.1	C-7, 8, 10, 14
10	–	40.8	
11	2.32 (dq, J = 11.5, 6.5)	42.0	C-6, 7, 8, 12, 13
12	–	178.6	
13	1.26 (d, J = 6.5)	12.2	C-7, 11, 12
14	1.19 (s)	18.0	C-1, 9, 10
15	5.19 (s); 4.97 (s)	109.5	C-3, 4, 5
1′	–	131.1	
2′/6′	8.18 (d, J = 7.5)	127.2	C-1′, 3′, 4′, 7′
3′/5′	7.82 (d, J = 7.5)	130.6	C-1′, 2′, 4′
4′	–	139.4	
7′	–	166.2	
Me-4′	2.48 (s)	21.0	C-3′, 4′



1

Fig. 1. Important NOESY correlations of **1**.

The ^{13}C NMR (BB and DEPT) spectra of **1** showed 21 signals comprising three methyls, four methylene, eight methine, and six quaternary carbons (Table 1). The downfield signals at δ 166.2 and 178.6 could respectively be assigned to the carbonyls of ester and γ-lactone moieties. The olefinic carbons resonated at δ 145.0 and 109.5, while the signals at δ 70.1, 81.9, and 78.5 could be ascribed to the oxymethine carbons, respectively. Additionally, an aromatic methyl resonated at δ 21.0 while the signal of another tertiary methyl was observed at δ 18.0. The signals ranging from δ 127.2–139.4 were due to aromatic carbons. The ^{1}H NMR data showed the signals of a tertiary angular methyl and a secondary lactonic methyl at δ 1.19 (s, H_3-14) and 1.26 (d, J = 6.5 Hz, H_3-13), respectively, which are characteristic of eudesmanolides [20]. The exomethylene protons resonated as singlets at δ 5.19 and 4.97. Two oxymethine protons resonated at δ 3.79 (ddd, J = 9.5, 9.0, 3.5 Hz, H-2) and 3.85 (d, J = 9.5 Hz, H-3). The lactonic protons resonated at δ 3.98 (t, J = 11 Hz), 1.69 (m), and 2.32 (dq, J = 11.5, 6.5 Hz), being assigned to H-6, H-7, and H-11, respectively, which are consistent with the *trans*-fusion of the lactonic ring. The presence of 4-methylbenzoyl moiety was also inferred by the aromatic protons providing an AA′BB′ pattern with resonances at δ 8.18 (2H, d, J = 7.5 Hz) and 7.82 (2H, d, J = 7.5 Hz) and the singlet of aromatic methyl at δ 2.48. The presence of 4-methylbenzoyl moiety was also supported by the fragment ion peak in EI-MS at *m/z* 266 ($C_{15}H_{22}O_4$). It further showed diagnostic fragments at *m/z* 222 $[266 - CO_2]^+$, 210 $[266 - C_3H_4O]^+$, 193 $[266 - C_3H_4O_2]^+$, and 169 $[266 - C_5H_5O_2]^+$. These data indicated that compound **1** has eudesmanolide-type sesquiterpene lactone skeleton [15], including 4-methylbenzoyl moiety. The oxymethine proton at δ 3.85 showed ^{1}H–^{1}H-COSY correlation to another oxymethine proton at δ 3.79, which in turn showed further correlations with methylene protons at δ 1.30 and 2.44, permitting us to assign the position of the hydroxyl group at C-2. The larger coupling constant between H-2 and H-3 allowed us to assign the equatorial configuration to the

hydroxyl moiety. It was further confirmed by HMBC correlations (Table 1); the oxymethine proton at δ 3.79 showed ^{2}J correlations with C-1 (δ 48.2) and C-3 (δ 81.9) and ^{3}J correlations with C-4 (δ 145.0) and C-10 (δ 40.8). The oxymethine proton at δ 3.85 showed ^{2}J correlations with C-2 (δ 70.1) and C-4 (δ 145.0) as well as ^{3}J correlations with C-1 (δ 48.2), C-5 (δ 45.1), C-15 (δ 109.5), and C-7′ (δ 166.2), confirming the position of 4-methylbenzoyl moiety and the exocyclic methylene group at C-3 and C-4, respectively. The 6,12-eudesmanolide moiety was further confirmed by ^{2}J correlations of H-6 at δ 3.98 with C-5 (δ 45.1), C-7 (δ 52.7) as well as ^{3}J correlations with C-4 (δ 145.0), C-8 (δ 24.0), and C-11 (δ 42.0). The close similarity of NMR chemical shifts to those of known eudesmanolides [15], allowed us to assign the same relative configuration of **1**. The larger coupling constants of H-6 and H-7 as well as H-7 and H-11 suggested H-7 to be α-oriented which could further be authenticated by the NOESY spectrum. NOESY correlations (Fig. 1) were observed between β-oriented Me-14 with H-2 and H-6 as well as H-6 with H-11. Similarly, α-oriented H-5 showed correlations with H-3 and H-7 as well as H-7 with Me-13. All these pieces of evidence were in complete agreement with the assigned structure of **1** as 2α-hydroxy-3β-4-methylbenzoyl-5,7α,6,11β(*H*)-eudesm-4,15-en-6,12-olide.

EXPERIMENTAL

General Procedures. Optical rotations were measured on a JASCO DIP-360 polarimeter. UV spectra were recorded on a Hitachi UV-3200 spectrophotometer. IR spectra were recorded on a JASCO 302-A spectrophotometer in KBr, whereas NMR data were recorded on a Bruker AV-500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) in $CDCl_3$ with tetramethylsilane as an internal standard. EI- and HR-EI-MS were recorded on Finnigan MAT 12 and MAT 312 spectrometers Aluminum sheets precoated with silica-gel 60 F_{254} (E. Merck, Darmstadt, Germany) were used for thin-layer chromatography (TLC), while silica gel (250–400 mesh, E. Merck) was used for column chromatography.

Plant Material. The whole plants of *C. fruticosa* (L.) Druce were collected from Karachi, Sindh, Pakistan, in 2020 and identified by Prof. Dr. Beena Naqvi Plant Taxonomist, Pharmaceutical Research Centre, PCSIR Laboratories Complex Karachi, Pakistan, where a voucher specimen (No. CF-136/173-2021) was deposited in the Herbarium.

Extraction and Isolation. The whole plants of *C. fruticosa* (9 kg) were shade-dried, ground, and extracted with MeOH (3 × 25 L). The combined MeOH extract was evaporated under reduced pressure to yield the crude extract (200 g), which was divided into subfractions soluble in *n*-hexane (50 g), $CHCl_3$ (18 g), EtOAc (25 g), *n*-BuOH (40 g), and H_2O (38 g), respectively. The EtOAc-soluble fraction was subjected to column chromatography over silica gel, eluting with mixtures of *n*-hexane–EtOAc in increasing order of polarity to obtain six fractions F_1–F_6. Fraction F_3, eluted with *n*-hexane–EtOAc (5.0:5.0), was chromatographed over silica gel and eluted with mixtures of *n*-hexane–EtOAc in increasing order of polarity. The subfractions, eluted with *n*-hexane–EtOAc (6.5:3.5), (6.0:4.0), and (4.5:5.5), furnished compounds **4** (18 mg), **6** (22 mg), and **7** (20 mg), respectively. Fraction F_4, eluted with *n*-hexane–EtOAc (4.0:6.0), showed two major spots on TLC and was again chromatographed over silica gel using *n*-hexane–EtOAc (6.0:4.0) as an eluent to provide compounds **2** (15 mg) and cadabatone (**1**) (6 mg) from the top and tail fractions, respectively. Fraction F_5, eluted with *n*-hexane–EtOAc (3.0:7.0), was further purified by column chromatography to afford two successive subfractions F_{5A} and F_{5B}, eluted with *n*-hexane–EtOAc (5.5:4.5) and (7.0:3.0) to afford compounds **3** (20 mg) and **5** (16 mg), respectively.

Cadabatone (1), colorless gummy solid, $[\alpha]_D$ –26° (*c* 0.3, $CHCl_3$). UV (MeOH, λ_{max} nm) (log ε): 204 (3.78). IR (KBr, ν_{max}, cm^{-1}): 865, 1508, 1620, 1650, 1718, 1760, 3422. EI-MS (*m/z*, $I_{rel.}$, %): 384 (9), 369 (30), 366 (52), 266 (50), 222 (65), 210 (77), 193 (68), 169 (80), 119 (100), 97 (85), 73 (35), 55 (75), 44 (90). HR-EI-MS *m/z* 384.1936 (calcd for $C_{23}H_{28}O_5$, 384.1940). For ^{1}H, ^{13}C NMR, and HMBC data, see Table 1.

The authors declare no conflict of interest.

REFERENCES

1. S. M. H. Jafri, *Flora of West Pakistan*, S. I. Ali and E. Nasir, eds., Department of Botany, University of Karachi, Pakistan, 1973, No. 34, p. 35.
2. S. M. H. Jafri, *Pak. J. For*., **8**, 204 (1958).
3. S. R. Baquer and M. Tasnif, *Medicinal Plants of Southern West Pakistan*, PCSIR Bulletin/Monograph, 1967, No. 3, p. 5.

4. S. Saboo, *J. Pharmacogn. Phytochem.*, **9**, 2331 (2020).
5. V. U. Ahmad, A. R. Amber, S. Arif, M. H. M. Chen, and J. Clardy, *Phytochemistry*, **24**, 2709 (1985).
6. V. U. Ahmad, K. Fizza, A. R. Amber, and S. Arif, *J. Nat. Prod*., **50**, 1186 (1987).
7. G. Yousif, G. M. Iskander, and E. B. Eisa, *Fitoterapia*, **55**, 117 (1984).
8. V. U. Ahmad, A. R. Amber, K. Fizza, and A. Kamal, *Z. Naturforsch*., **45b**, 1100 (1990).
9. N. M. Al-Musayeib, G. A. Mohamed, S. R. M. Ibrahim, and S. A. Ross, *Med. Chem. Res*., **22**, 5297 (2013).
10. A. A. Gohar, *Z. Naturforsch*., **57C**, 216 (2002).
11. G. A. Mohamed, S. R. M. Ibrahim, N. M. Al-Musayeib, and S. A. Ross, *Arch. Pharm. Res*., **37**, 459 (2014).
12. G. A. Al-Hamoud, R. S. Orfali, S. Sugimoto, Y. Yamano, N. Alothyqi, A. M. Alzahrani, and K. Matsunami, *Molecules*, **24**, 2167 (2019).
13. V. U. Ahmad, A. Basha, and Atta-ur-Rahman, *Phytochemistry*, **14**, 292 (1975).
14. S. P. Garg, R. Bhushan, and R. C. Kapoor, *Planta Med*., **43**, 293 (1981).
15. J. F. Sanz, E. Falco, and J. A. Marco, *J. Nat. Prod.*, **53**, 940 (1990).
16. G. R. Nagarajan and V. S. Parmar, *Planta Med*., **31**, 146 (1977).
17. H. Tsukamoto, S. Hisada, S. Nishibe, D. G. Roux, and J. P. Rourke, *Phytochemistry*, **23**, 699 (1984).
18. W. Eun-Rhan and S. P. Mei, *Arch. Pharm. Res.*, **27**, 173 (2004).
19. S. B. Mahato and A. P. Kundu, *Phytochemistry*, **37**, 1517 (1994).
20. Atta-Ur-Rahman, *Studies in Natural Products Chemistry*, Elsevier Publishing Co., Amsterdam, 1990, p. 212.