Two New Triterpenes from Fern Adiantum incisum

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Adiantum incisum, Fern, Adininaneone, Adininaonol

Two new triterpenes, adininaneone (1) and adininaonol (2) were isolated from *Adiantum incisum*. Three known triterpenes, adiantone (3), isoadiantone (4) and 23-hydroxyfernene (5) were also isolated for the first time from the methanolic extracts of *A. insicum*. The structures were elucidated with the help of modern spectroscopic techniques.

Introduction

The genus Adiantum (Adianthaceae) syn A. caudatum L. is a Fern used in Ayurvredic medicine and is well known for its antibacterial, antiviral, antifungul and other biological activities [1,2]. In recent years several new bioactive compounds have been isolated from this genus. Despite recent progress, the Adiantum of the western Himalayan region have been little explored, and this stimulated us to chemically investigate the biologically active constituents of these plants. A. incisum Forsk. [3] grows abundantly in the Hilly area of Pakistan near the city of Mangora. Here we report the isolation of two new compounds, adininaneone (1) and adininaonol (2) along with three known compounds, adiantone (3), isoadiantone (4) and 23-hydroxyfernene (5) which have been isolated for the first time from this plant.

Results and Discussion

The ethyl acetate extract of *A. incisum* was subjected to repeated column chromatography on silica gel and preparative thin layer chromatography to afford the new compounds, 1-2. The HREI MS of compound 1 showed the [M]⁺ at m/z 440.3587 in agreement with the molecular formula $C_{30}H_{48}O_2$ (calcd. 440.3559) indicating seven double-bond equivalents, five for the pentacyclic terpenic nucleus, one for the olefinic and one for the carbonyl. The base peak at m/z 95.0823 was due to the fragment C_7H_{11} . The overall mass fragmentation

pattern of 1 was similar to that found in pentacyclic triterpene skeleton [4]. The IR spectrum of 1 showed broad absorption at 3405 (OH), 1645 (α , β unsaturated carbonyl), 1341 (C=C) and 1011 (C-O) cm⁻¹. The UV spectrum of 1 displayed only terminal absorption at 201.8 nm.

The ¹H NMR spectrum of 1 showed signals for eight methyls, one olefinic proton and several methylene protons, indicating the triterpenic nature of this compound. A one-proton singlet at δ 5.71 was assigned to the olefinic H-16 [4]. Multiplets centered at δ 2.32 and 2.02 were due to H₂-20 and H₂-19, respectively. Two doublets, integrating for three protons each, resonated at δ 0.80 (*d*, J_{29,22} = 6.5 Hz, H₃-29) and 0.82 (*d*, J_{30,22} = 6.5 Hz, H₃-30) [4]. The tertiary methyls H₃-23, H₃-24, H₃-25, H₃-26, H₃-27 and H₃-28 resonated as singlets at δ 0.89, 0.83, 0.84, 0.90, 1.16 and 0.69, respectively.

The COSY-45⁰ spectrum of 1 exhibited coupling between the two methylene protons which resonated at δ 2.32 (H₂-20) and 2.02 (H₂-19).

The ¹³C-NMR spectrum of **1** showed resonances for all thirty cabon atoms in the molecule. The DEPT spectra revealed the presence of eight methyl, nine methylene, five methine carbons, and of eight quaternary carbon atoms. The three downfield carbons at δ 123.5 (C-16), 172.0 (C-17) and 200.0 (C-15) indicated the presence of an α , β unsaturated ketonic functionality, while the signal at δ 77.2 (C-21) indicated that a hydroxy group was present in the molecule. In the HMBC experi-

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ment (Table 3) H_3 -29 (δ 0.80) and H_3 -30 (δ 0.82) were coupled with quarternary C-21 (δ 77.2), suggesting that the hydroxy group should be placed at C-21 [5]. The coupling of protons at δ 2.32 (H_2 -20), 2.02 (H_2 -19) and 0.69 (H_3 -28) with C-17 (δ 172.0) and C-21 (δ 77.2) and of H-16 (δ 5.71) showed coupling with C-14 (δ 49.2), C-18 (δ 42.0) and C-21 (δ 77.2) indicated that there was a double bond between C-17 and C-16 [4]. H_3 -27 (δ 1.16) was found to be coupled with C-15 (δ 200.0), C-8 (δ 41.8) and C-13 (δ 49.7) indicating the presence of a ketonic group at C-15 [6].

The stereochemistry of compound 1, particularly the β configuration of the hydroxyl function, was ascertained by NOE difference measurements at certain points in the molecule. Irradiation at δ 1.89 (H-22 α) resulted in 5.67% nOe at δ 0.69 (H₃-28) and 2.94% nOe at δ 2.32 (H₂-20). Irradiation at δ 1.16 (H₃-27) resulted in 11.01% nOe at δ 0.69 (H₃-28), 9.82% nOe at δ 1.29 (H-9 α) and 7.88% nOe at δ 1.53 (H₂-12). Irradiation at δ 0.90 (H₃-26) resulted in 6.98% nOe at δ 1.59 (H-13B) and 8.54% nOe at δ 0.84 (H₃-25). Finally, irradiation at δ 0.84 (H₃-25) resulted in 7.98% nOe at δ 0.90 (H₃-26) and 5.27% nOe at δ 0.83 (H₃-24). These NOE interactions are summarized in Table 3. On the basis of this evidence, compound 1 was identified as 21β -hydroxy-15-oxo-hop-16-ene.

The HREI MS of compound **2** showed the [M]⁺ at m/z 428.3674 in agreement with the molecular formula C₂₉H₄₈O₂ (calcd. 428.3664) indicating six double-bond equivalents, five for the pentacyclic terpenic nucleus and one for the carbonyl. The base peak at m/z 191.1797 was agreement with the fragment C₁₄H₂₃. The IR spectrum of **2** showed broad absorptions at 3495 (O-H), 2815 (C-H) and 1704 (C=O) cm⁻¹ [7]. The UV spectrum of **2** displayed only terminal absorption at 202.0 nm indicating the absence of any chromophore in the molecule.

The ¹H NMR spectrum of 2 showed signals for seven methyl and methylene protons in the range of δ 0.89–2.68. The 1H doublet of double doublets resonating at δ 2.68 (*ddd*, *J*_{gem} = 15.5 Hz, *J*_{21B, 22a} = 5.5 Hz, *J*_{21B, 22B} = 3.0 Hz) and 2.35 (*ddd*, *J*_{gem} = 15.5 Hz, *J*_{21a, 22B} = 5.5 Hz, *J*_{212, 22a} = 3.0 Hz) were assigned to the H-21/H-21', while 1H resonating at δ 2.04 (*ddd*, *J*_{gem} = 15.5 Hz, *J*_{22B, 21a} = 5.5 Hz, *J*_{22B, 21B} = 3.0 Hz) was due to H-22. The H-18 resonated as a doublet at δ 1.76 (*d*, *J*_{18, 13} = 6.0 Hz). The seven methyl singlets, integrating for three protons each, resonated at δ 1.26 (H₃-29), 1.04 (H₃-25), 1.00 (H₃-26), 0.93 (H₃-27), 0.84 (H₃-23), 0.79 (H₃-24) and 0.78 (H₃-28).

In the COSY-45⁰ spectrum of **2**, the downfield C-21 methylene protons at δ 2.68 and 2.35 showed coupling with H-22 resonating at δ 2.04. Coupling between H-13 (δ 1.56) with H-18 (δ 1.76) was also appeared in the spectrum.

The ¹³C NMR spectrum of 2 showed resonances for all twenty nine carbon atoms in the molecule. The DEPT spectra revealed the presence of seven methyl, eleven methylene, four methine and seven quaternary carbon atoms. The two downfield quaternary carbon signals at δ 217.0 (C-19) and 77.9 (C-20) showed the presence of one ketonic and one hydroxyl functionality in the molecule. In the HMBC experiment (Table 3) H_3 -29 (δ 1.26) was found to be coupled with C-20 (δ 77.9), C-19 (δ 217.0) and C-21 (δ 33.7). H-18 (δ 1.76) showed couplings with C-28 (δ 22.1), C-19 (δ 217.0) and C-20 (δ 77.9). The couplings of H-13 (δ 1.56) with C-18 (& 58.8), C-27 (& 16.4), C-17 (& 37.3) and C-19 (δ 217.0), indicated that the hydroxyl group should be positioned at C-20 [8] and carbonyl group at C-19 [9]. H₃-28 (δ 0.78) showed couplings with C-16 (\$\delta\$ 20.9), C-18 (\$\delta\$ 58.8), C-22 (\$\delta\$ 41.1) and C-19 (δ 217.0) which further indicate of the presence of the carbonyl group at C-19.

The stereochemistry of compound 2, particularly the β configuration of the hydroxyl function, was ascertained by NOE difference measurements at certain points in the molecule. Irradiation at δ 1.26 (H₃-29) resulted in 11.91% nOe at δ 2.35 (H-21 α) and 3.84% nOe at δ 1.89 (H-22 α). Irradiation at δ 0.93 (H₃-27) resulted in 9.86% nOe at δ 1.32 (H-9 α), 7.98% nOe at δ 1.52 (H₂-12) and 9.07% nOe at δ 1.41 (H₂-16). Irradiation at δ 0.78 (H₃-28) resulted in 5.21% nOe at δ 2.04 (H-22B), 4.27% nOe at δ 2.68 (H-21ß), 9.76% nOe at δ 1.76 (H-18ß) and 6.98% nOe at δ 1.56 (H-13ß). Finally, irradiation at δ 1.00 (H₃-26) resulted in 6.87% nOe at δ 1.56 (H-13 β) and 8.94% nOe at δ 1.04 (H₃-25). These NOE interactions are summarized in Table 3. On the basis of these findings, compound **2** was identified as 20β -hydroxy-19-Oxolean.

Compounds 3-5 isolated here for the first time from the *Adiantum incisum* had been previously isolated from other natural sources. These structures were determind by camparision of their spectral data with the literature values [10-12].

Experimental Section

General

The IR spectra were recorded on a JASCO A-302 spectrophotometer. The UV spectra were measured on a Hitachi U-3200 spectrophotometer. The melting point was measured on a BUCHI-535 apparatus. Optical rotation was measured in MeOH on a JASCO-DIP-360 digital polarimeter. The EI, FD and HREI MS were recorded on JMS HX 110 with the data system DA 5000 and on MAT 112S mass spectrometer. The ¹H NMR spectra were recorded on Bruker AM 300, AM 400 and AMX 500 spectrometers using UNIX data system at 300, 400 and 500 MHz, respectively, while ¹³C NMR spectra were recorded at 125 MHz on the same instruments. The 2D COSY-45⁰ spectra was recorded on Bruker AM 300 spectrometer using UNIX data system at 300 MHz. Precoated silica gel 60F₂₅₄ aluminum sheets (Merck, Art. No. 1.05554) were used to check the

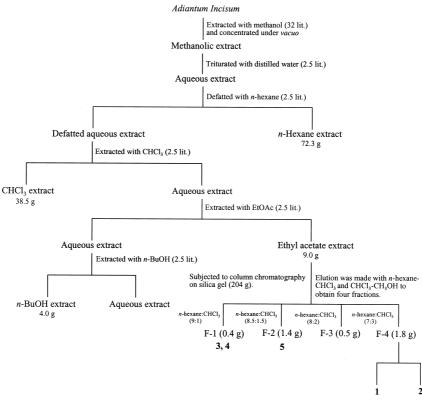
purity. Spots were visualized by spraying with ceric sulphate in 10% H₂SO₄ followed by heating.

Plant material

A. incisum (14 Kg, fresh weight) was collected during mid August 1996 from the Kalam area near the city of Mangora (Swat) and identified at the NARC (National Agriculture Research Council) and the voucher speciman number was 369-B.

Extraction and isolation

The whole, fresh plant (~ 14 kg/collection) were washed, ground immediately after collection with methanol, and extracted exhaustively with methanol (4 × 8 lit., minimum 72 h/extraction). After filtration the solvent was removed in *vacuo* to provide the crude methanol extract (900 g). The methanolic extract was dissolved in distilled water (2.5 lit.) and successively fractionated using *n*-hexane, CHCl₃, EtOAc and *n*-BuOH. The EtOAc extract (9.0 gm) was loaded onto a silica gel (204 g) column and subjected to the gradient elution with mixtures of *n*-hexane : CHCl₃ (1.5 lit. each) and



Scheme 1.

finally with CHCl₃ : MeOH (1.5 lit. each) as the solvent-system which yielded four fractions, F-1 (0.4 g), F-2 (1.4 g), F-3 (0.5 g) and F-4 (1.8 g). The fraction F-4 (1.8 g) which was obtained by elution with *n*-hexane-CHCl₃ (7:3) was subjected to preparative TLC using *n*-hexane-CHCl₃-EtOAc (6:3:1) which afforded the new compounds 1 ($R_f = 0.41$) and 2 ($R_f = 0.53$) (Scheme I).

Final purification of compounds 1 and 2 was accomplished by reversed-phase C_{18} HPLC (Microsorb C_{18} , 10×250 mm, 5μ m) of fraction (F-4): 1 (retention time 36.8 min.) and 2 (46.4 min.) using H₂O/CH₃OH/*i*-PrOH/CH₃CN (7:1:1:1), flow rate 2.0 ml/min.

Adininaneone (1): Colorless compound (11.2 mg, $1.2 \times 10^{-3}\%$, yield). – M. p. 223 °C. – $[\alpha]_D^{25}$ –40.2° (2 × 10⁻³% gm/ml, CHCl₃). – UV/ vis (CHCl₃) λ_{max} (lg ε) = 202 nm (3.60). – IR (KBr): ν_{max} = 3405 (O-H), 2813 (C-H), 1645 (C= O), 1341 (C=C), 1011 (C-O) cm⁻¹. – ¹H and ¹³C NMR (Table 1). – MS (EI, 70 eV): m/z = 440, 425, 397, 318, 299, 273, 205, 142, 122, 95. – MS (HREI): m/z = 440.3587 [C₃₀H₄₈O₂, calcd. 440.3559], 397.3209 [M⁺-C₃H₇], 273.2325 [M⁺-C₁₀H₁₅O₂],

Table 1. 1 H and 13 C NMR (500 and 125 MHz, CDCl₃) data of compound 1.

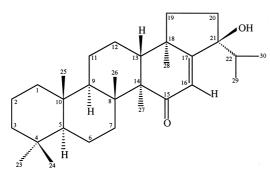
Carbon atom	Connectivity	¹³ C NMR [δ/ppm]	¹ H NMR (HMQC) [δ/ppm]
1	CH ₂	40.3	1.93 (m)
2	CH_2	18.6	1.37 (m)
3	CH_2	42.1	1.46 (m)
4	С	33.2	_
5	CH	56.1	1.67 (t, $J_{5, 6} = 6.6$ Hz, α -H)
6	CH ₂	18.3	1.26 (m)
7	CH ₂	33.1	1.73 (m)
8	С	41.8	_
9	CH	50.2	1.29 (t, $J_{9, 11} = 6.4$ Hz, α -H)
10	С	37.0	_
11	CH_2	21.7	1.63 (m)
12	CH_2	29.6	1.53 (m)
13	CH	49.7	1.59 (t, $J_{13, 12} = 6.3$ Hz, β -H)
14	С	49.2	_
15	С	200.0	_
16	CH	123.5	5.71 (s)
17	С	172.0	_
18	С	42.0	-
19	CH_2	41.1	2.02 (m)
20	CH_2	33.7	2.32 (m)
21	С	77.2	_
22	CH	37.3	1.89 (m, α-H)
23	CH_3	33.4	0.89 (s, α-H)
24	CH_3	21.5	0.83 (s, β-H)
25	CH_3	16.4	0.84 (s, β-H)
26	CH_3	14.7	0.90 (s, β-H)
27	CH_3	15.9	1.16 (s, α-H)
28	CH_3	16.5	0.69 (s, α-H)
29	CH_3	22.0	0.80 (d, $J_{29, 22} = 6.5$ Hz)
30	CH_3	22.0	0.82 (d, $J_{30, 22} = 6.5$ Hz)

Adininaonol (2): Colorless compound (11.0 mg, 1.2 × 10⁻³%, yield). – M. p 227 °C. – $[a]_{D}^{25}$ – 29.4° (1.16 × 10⁻³% gm/ml, CHCl₃). – UV/vis (CHCl₃) λ_{max} (lg ε) = 202 nm (3.60). – IR (KBr): ν_{max} = 3395 (O-H), 2815 (C-H), 1704 (C=O), 1141 (C-O) cm⁻¹. – ¹H and ¹³C NMR (Table 2). – MS (EI, 70 eV): m/z = 428, 410, 191, 137, 123, 95. – MS (HREI): m/z = 428.3674 [C₂₉H₄₈O₂, calcd. 428.3664], 191.1794 [M⁺-C₁₅H₂₅O₂], 137.1301 [M⁺-C₁₉H₃₁O₂] 123.1098 [M⁺-C₂₀H₃₃O₂], 95.086 [M⁺-C₂₂H₃₇O₂].

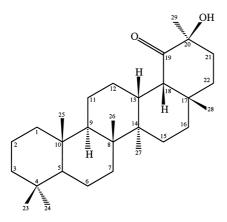
Table 2. 1 H and 13 C NMR (500 and 125 MHz, CDCl₃) data of compound **2**.

Carbon atom	Connectivity	¹³ C NMR δ/ppm]	¹ H NMR (HMQC) $[\delta/ppm]$
1	CH ₂	40.3	1.89 (m)
2	CH_2	18.2	1.43 (m)
3	CH_2	42.1	1.58 (m)
4	С	33.2	_
5	СН	56.1	1.61 (t, $J_{5, 6} = 6.7$ Hz, α -H)
6	CH_2	18.2	1.28 (m)
7	CH ₂	32.2	1.71 (m)
8	C	41.8	_
9	СН	50.3	1.32 (t, $J_{9, 11} = 6.2$ Hz, α -H)
10	С	37.1	_
11	CH ₂	21.6	1.66 (m)
12	CH ₂	29.6	1.52 (m)
13	Сн	49.7	1.56 (t, $J_{13, 12} = 6.1$ Hz, β -H)
14	С	42.0	_
15	CH ₂	41.9	1.97 (m)
16	CH ₂	20.9	1.41 (m)
17	C	37.3	_
18	СН	58.8	1.76 (d, $J_{18, 13} = 6.0$ Hz)
19	С	217.0	_
20	C	77.9	-
21	CH ₂	33.7	2.68 (ddd, $J = 15.5, 5.5, 3.0$
			Hz, β-H)
			2.35 (ddd, $J = 15.5, 5.5, 3.0$
			Hz, <i>a</i> -H)
22	CH ₂	41.1	2.04 (ddd, J = 15.5, 5.5, 3.0
			Hz, β-H)
23	CH ₃	33.3	0.84 (s, β -H)
24	CH ₃	21.5	0.79 (s, α-H)
25	CH ₃	14.5	1.04 (s, β -H)
26	CH ₃	16.5	1.00 (s, β -H)
27	CH ₃	16.4	0.93 (s, α -H)
28	CH ₃	22.1	0.78 (s, β -H)
29	CH ₃	22.5	1.26 (s, α -H)

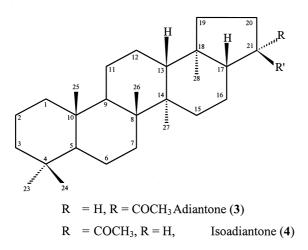
Adiantone (3): Colorless compound (16.5 mg, 1.8×10^{-3} %, yield). – M. p 224 °C. – $[\alpha]_D^{25}$ +81.1° (CHCl₃). –IR (KBr): ν_{max} = 2812 (C-H), 1698 (C= O) cm⁻¹. – ¹H NMR (400 MHz, CDCl₃): δ = 0.68 (s, 3 H, 28-H₃), 0.79 (s, 3 H, 24-H₃), 0.81 (s, 3 H, 25-H₃), 0.84 (s, 3 H, 23-H₃), 0.94 (s, 3 H, 26-H₃),



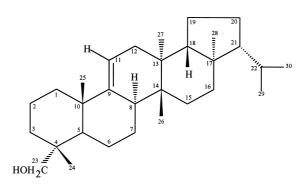




Adininaonol (2)



0.96 (s, 3 H, 27-H₃), 2.13 (s, 3 H, MeCO-). - MS



23-Hydroxyferene (5)

(EI, 70 eV): m/z = 412, 397, 367, 313, 231, 191, 137, 95. – MS (HREI): m/z = 412.3730 [C₂₉H₄₈O, calcd. 412.3704].

Isoadiantone (4): Colorless compound (26.3 mg, 2.8×10^{-3} %, yield). – M. p 236 °C. – $[\alpha]_D^{25}$ +2.3° (CHCl₃). – IR (KBr): $\nu_{max} = 2805$ (C-H), 1705 (C=O) cm⁻¹. – ¹H NMR (300 MHz, CDCl₃): $\delta = 0.68$ (s, 3 H, 28-H₃), 0.79 (s, 3 H, 24-H₃), 0.82 (s, 3 H, 25-H₃), 0.83 (s, 3 H, 23-H₃), 0.93 (s, 3 H, 26-H₃), 0.95 (s, 3 H, 27-H₃), 2.14 (s, 3 H, *Me*CO-). – MS (EI, 70 eV): m/z = 412, 397, 369, 313, 231, 191,123, 69. – MS (HREI): m/z = 412.3694 [C₂₉H₄₈O, calcd. 412.3704].

23-Hydroxyfernene (5): Colorless compound (8.0 mg, 0.8×10^{-3} %, yield). – M.p. 190 °C. – $[\alpha]_D^{25}$ –12.4° (CHCl₃). -IR (KBr): $\nu_{max} = 3412$ (O-H), 2804 (C-H), 1339 (C=C) cm⁻¹. – ¹H NMR (300 MHz, CDCl₃): $\delta = 0.76$ (s, 3 H, 28-H₃), 0.81 (d, $J_{30, 22} = 6.5$ Hz, 3 H, 30-H₃), 0.85 (s, 3 H, 24-H₃), 0.87 (d, $J_{29, 22} = 6.5$ Hz, 3 H, 29-H₃), 0.91 (s, 3 H, 27-H₃), 0.93 (s, 3 H, 26-H₃), 1.05 (s, 3 H, 25-H₃), 3.70 (d, J = 11.0 Hz, 1 H, 23a-H), 3.82 (d, J = 11.0 Hz, 23b-H), 5.21 (t, $J_{11, 12} = 3.0$ Hz, 1 H, 11-H). – MS (EI, 70 eV): m/z = 426, 411, 395, 341, 273, 259, 243, 177, 107, 95. – MS (HREI): m/z = 426.3813 [C₃₀H₅₀O, calcd. 426.3861].

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Compound 1		Compound 2		
NOE's	HMBC Correlations	NOE's	HMBC Correlations	
_	16-H C-14, C-15, C-17, C-18, C-21	_	13-H C-12, C-14, C-18, C-27	
_	19-H C-17, C-18, C-20, C-21, C-28	-	21β-H C-19, C-20, C-22, C-29	
_	20-H C-17, C-18, C-19, C-21, C-22	_	21 <i>a</i> -H C-19, C-20, C-22, C-29	
22 <i>a</i> -H: 20-H ₂ , 28 <i>a</i> -H ₃	22-H C-17, C-20, C-21	_	22β-H C-17, C-18, C-20, C-21	
	23-H C-4, C-5, C-24	_	23-H C-4, C-5, C-24	
_	24-H C-4, C-5, C-23	_	24-H C-4, C-5, C-23	
25β-H ₃ : 24β-H ₃ , 26β-H ₃	25-H C-1, C-9, C-10	25β-H ₃ : 23β-H ₃ , 26β-H ₃	25-H C-1, C-5, C-9, C-10	
$26\beta - H_3 : 13\beta - H, 25\beta - H_3$	26-H C-8, C-9, C-14	$26\beta - H_3 : 13\beta - H, 25\beta - H_3$	26-H C-7, C-8, C-9, C-14	
27a-H ₃ : 9a-H, 12-H ₂ , 28a-H ₃	27-H C-8, C-13, C-14, C-15	27a-H ₃ : 9a-H, 12-H ₂ , 16-H ₂	27-H C-8, C-13, C-14, C-15	
28 <i>a</i> -H ₃ : 22 <i>a</i> -H, 27 <i>a</i> -H ₃	28-H C-13, C-17, C-18	28β-H ₃ : 13β-H, 18β-H, 21α-H, 22β-H	28-H C-16, C-17, C-18, C-22	
_	29-H C-21, C-22, C-30	29 [′] a-H ₃ : 21 <i>a</i> -H, 22 <i>a</i> -H	29-H C-19, C-20, C-21	
_	30-H C-21, C-22, C-29	_	_	

Table 3. Diagnostic NOE's and HMBC correlations of 1 and 2.

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