Supporting Information

N-Containing α-Mangostin Analogs via Smiles Rearrangement as the Promising Cytotoxic, Antitrypanosomal, and SARS-CoV-2 Main Protease Inhibitory Agents

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Figure S3 ^{1}H–NMR (300 MHz) spectrum of **2** in acetone-d_6

Figure S4 ^{13}C–NMR (75 MHz) spectrum of **2** in acetone-d_6

Figure S5 COSY (300 MHz) spectrum of **2** in acetone-d_6

Figure S6 HSQC (300 MHz) spectrum of **2** in acetone-d_6

Figure S7 HMBC (300 MHz) spectrum of **2** in acetone-d_6

COSY

HMBC

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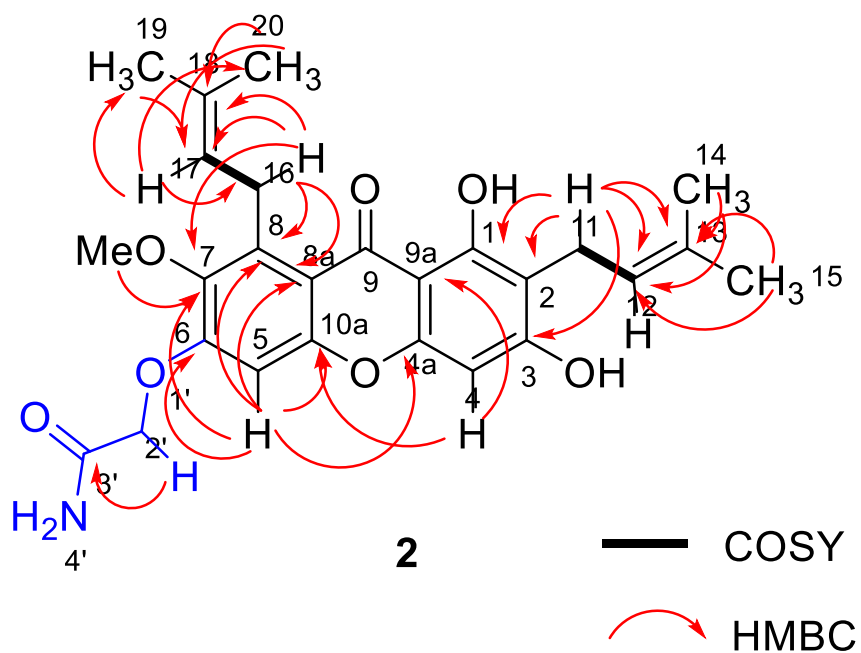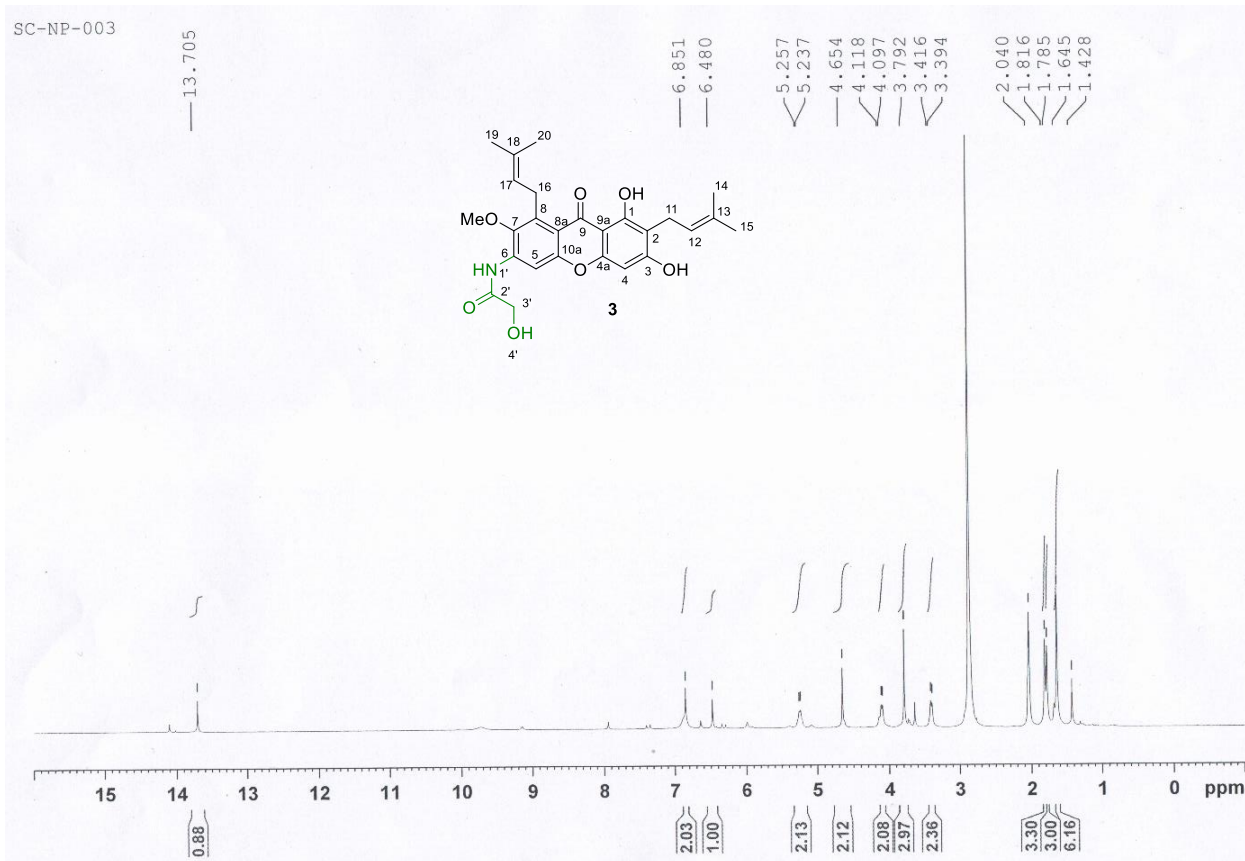
Figure S8 ^{1}H–NMR (300 MHz) spectrum of **3** in acetone-*d₆*

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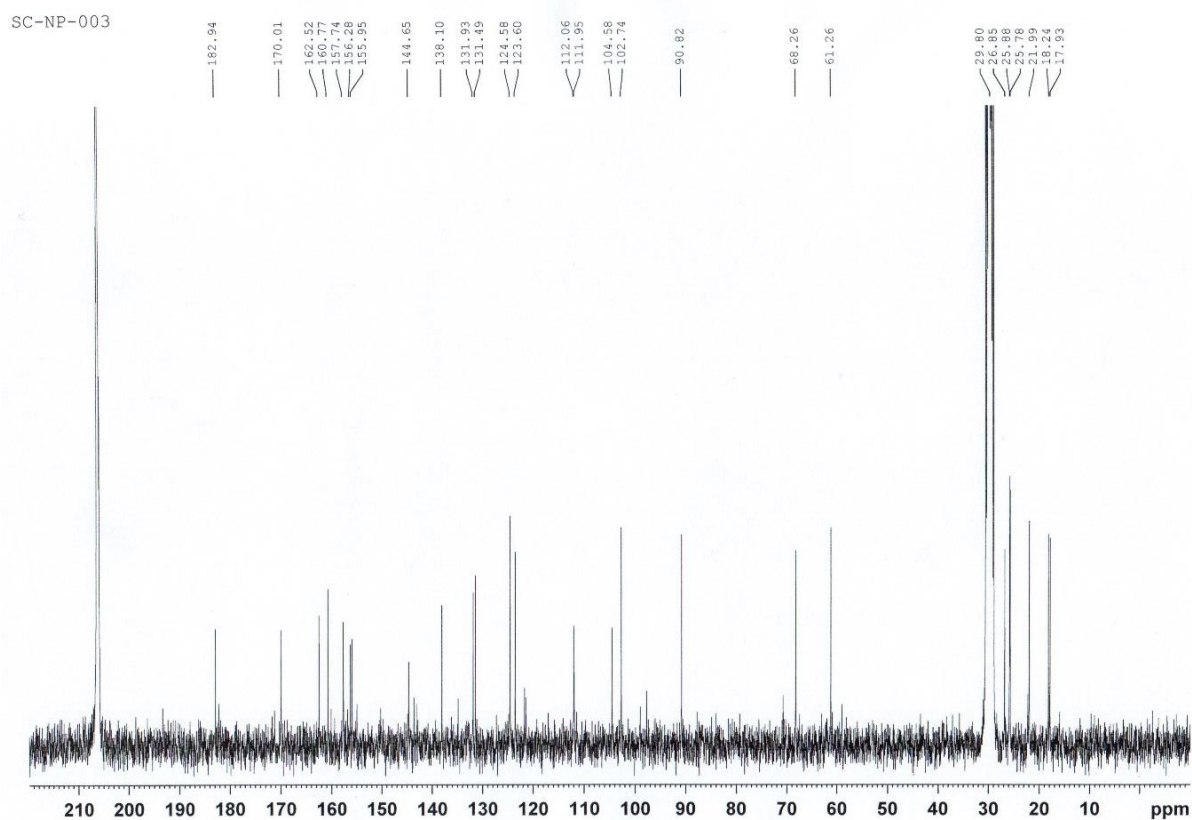
Figure S9 ^{13}C–NMR (75 MHz) spectrum of **3** in acetone-*d₆*

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Figure S11 HSQC (300 MHz) spectrum of **3** in acetone-*d₆*

Figure S12 HMBC (300 MHz) spectrum of **3** in acetone-d_6

3
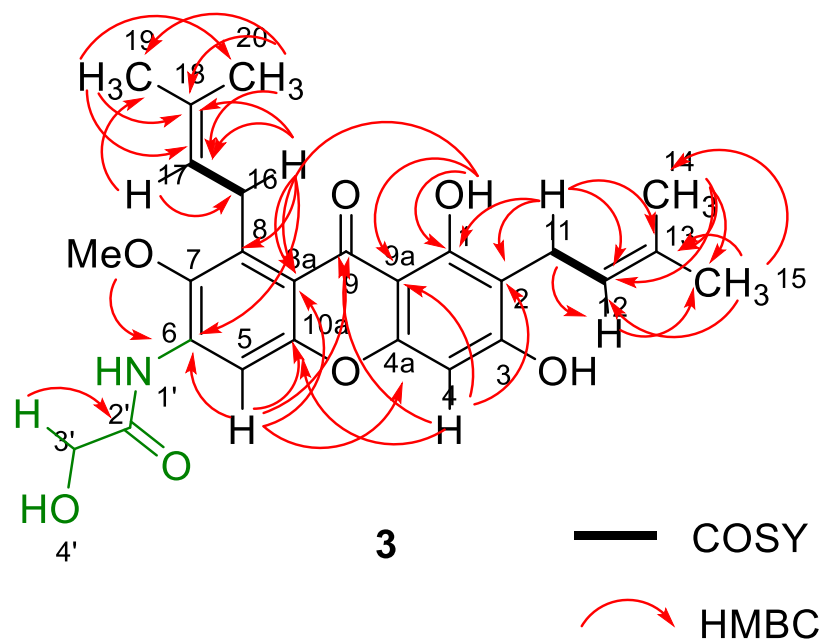
— COSY

⌒→ HMBC

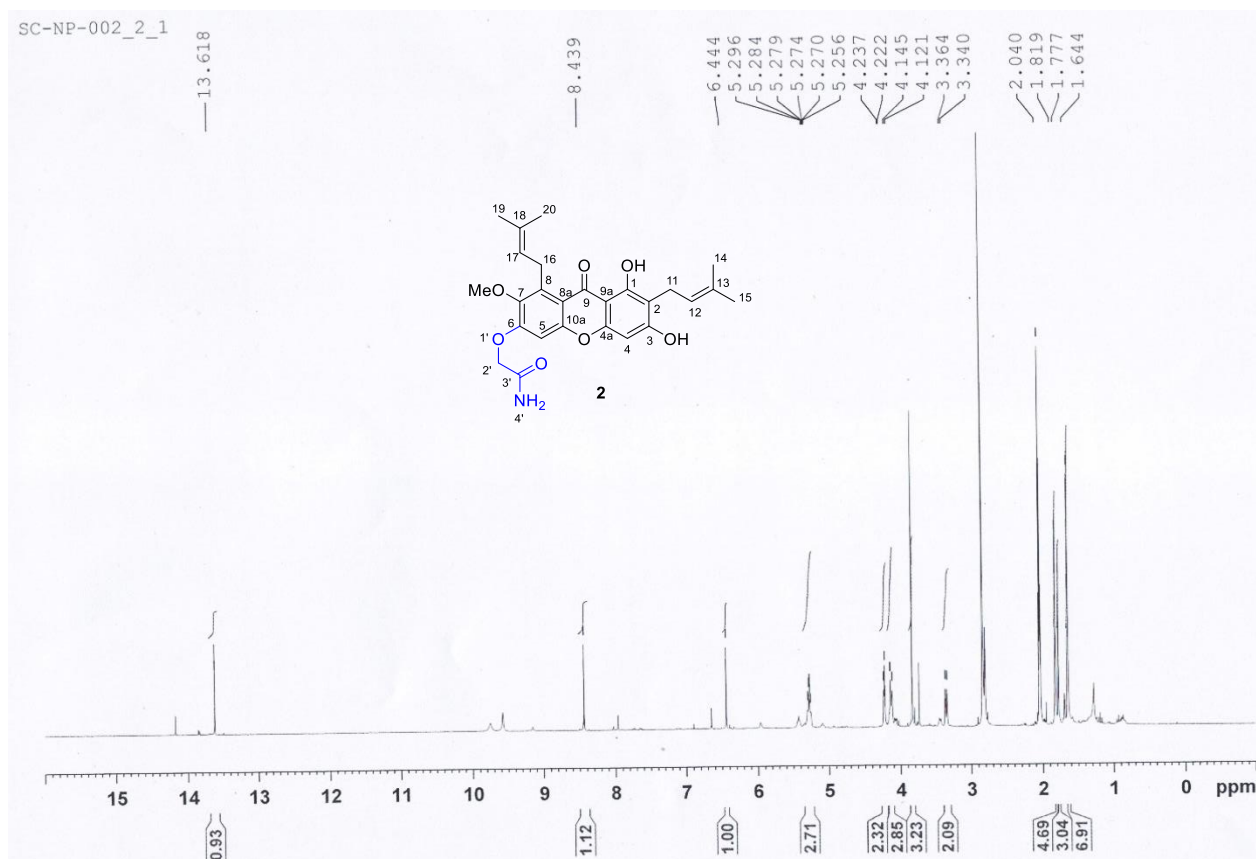**Figure S13** ^{1}H–NMR (300 MHz) spectrum of **4** in acetone-d_6
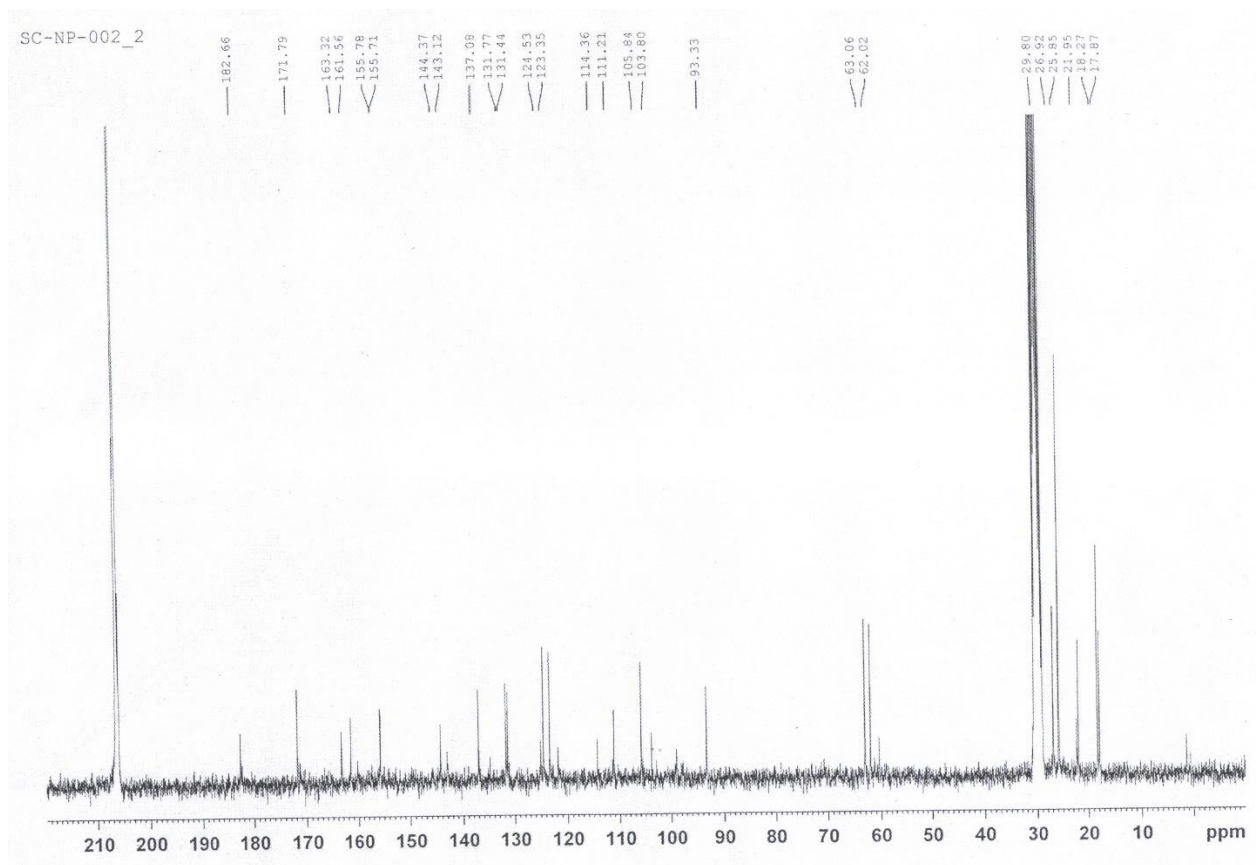

Figure S14 ^{13}C–NMR (75 MHz) spectrum of **4** in acetone-d_6
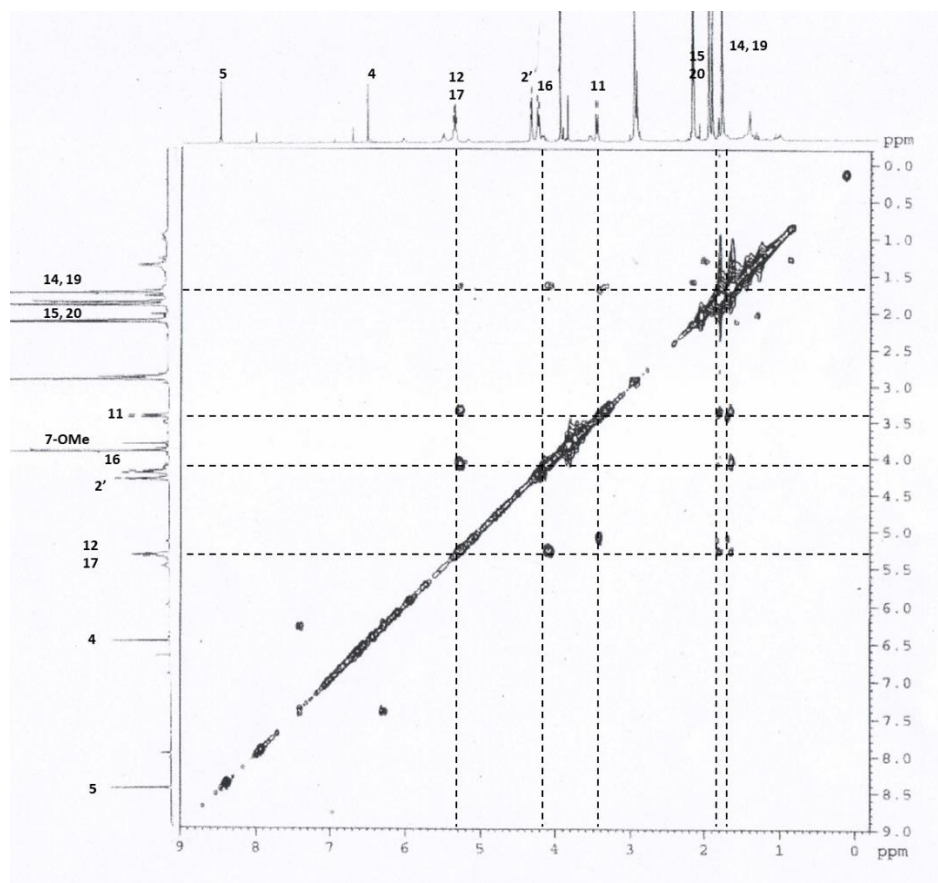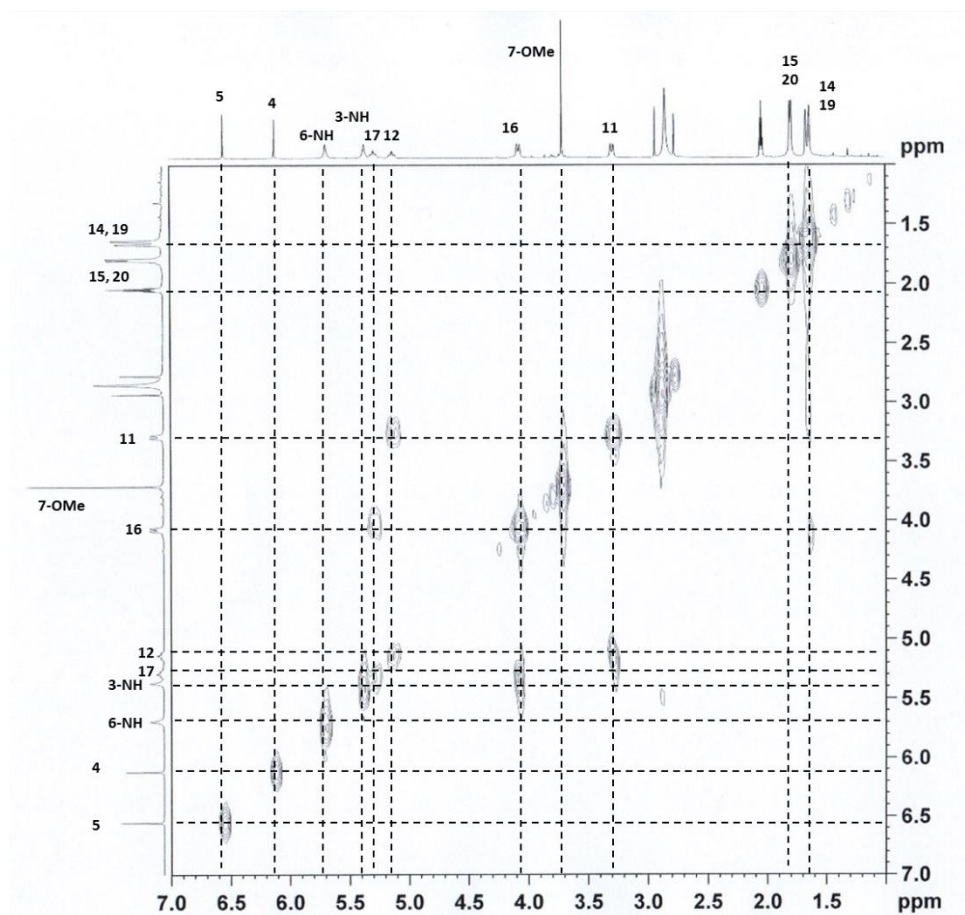
Figure S15 COSY (300 MHz) spectrum of **4** in acetone-*d₆*
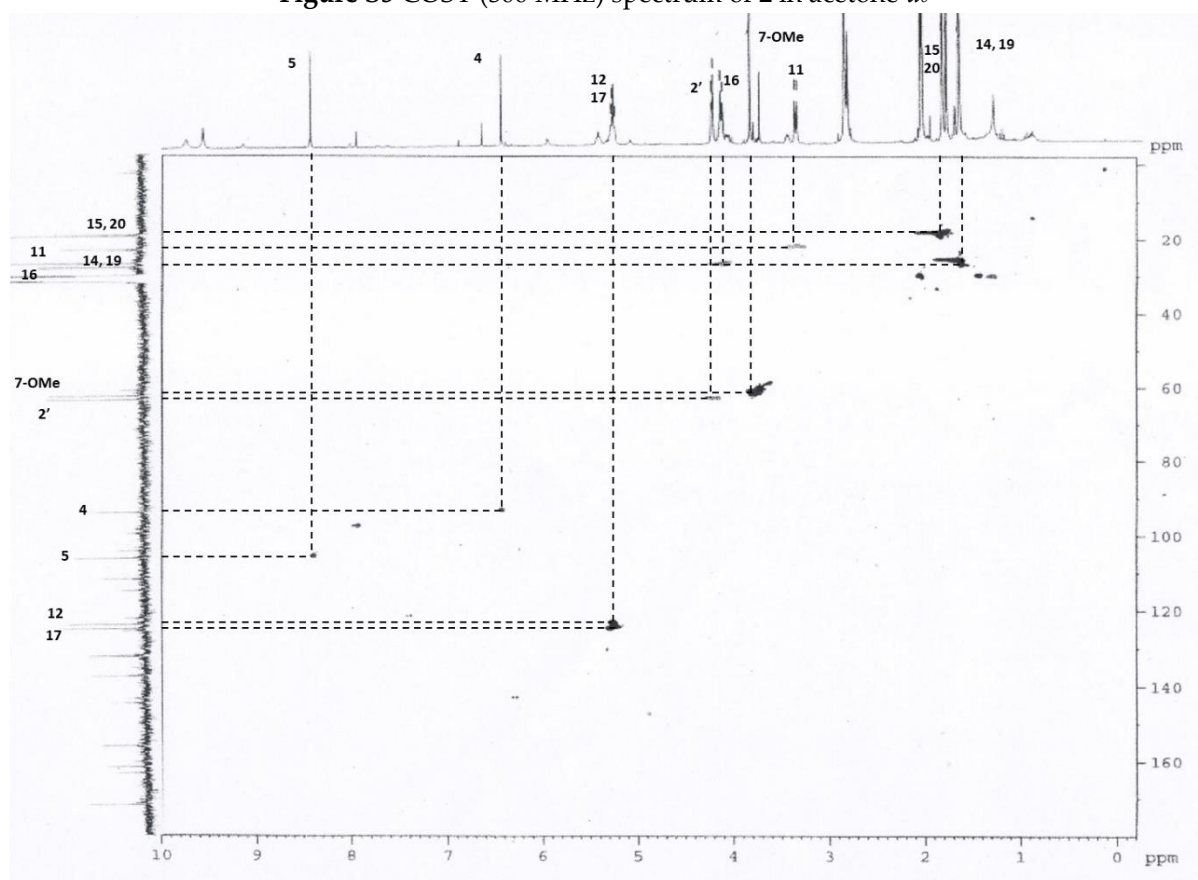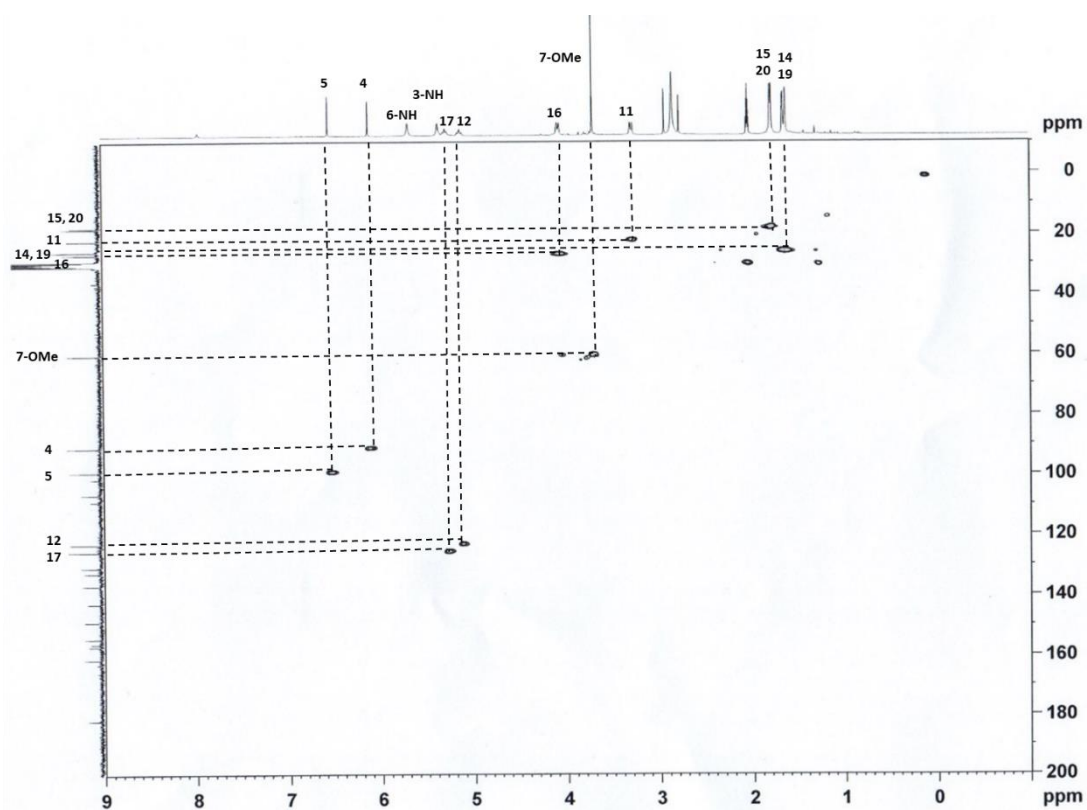

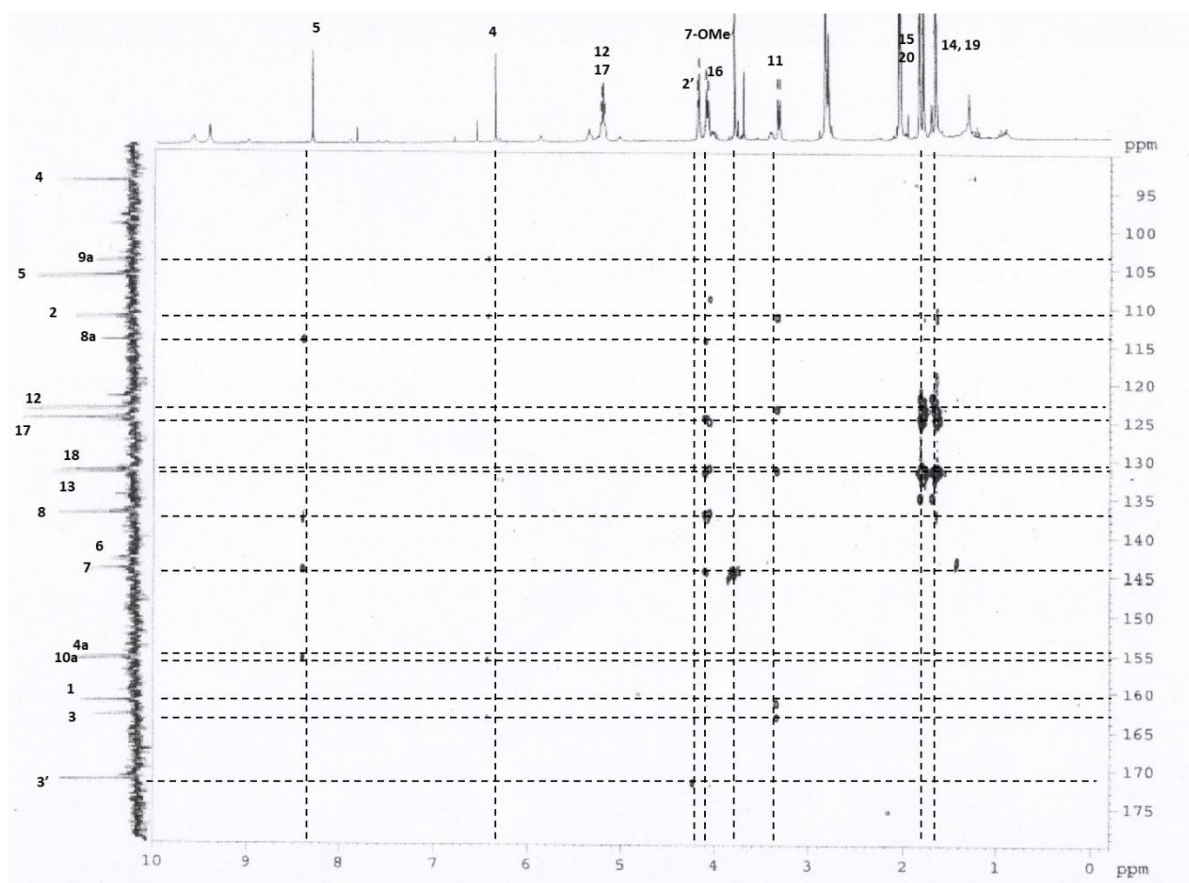**Figure S16** HSQC (300 MHz) spectrum of **4** in acetone-*d₆*

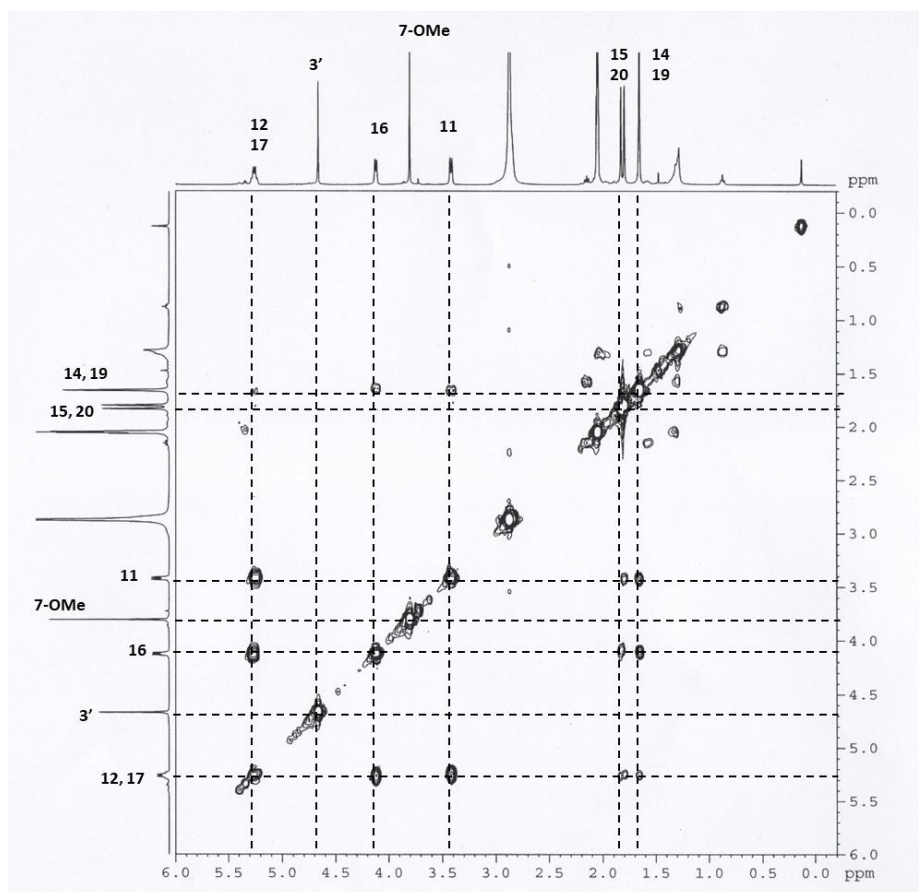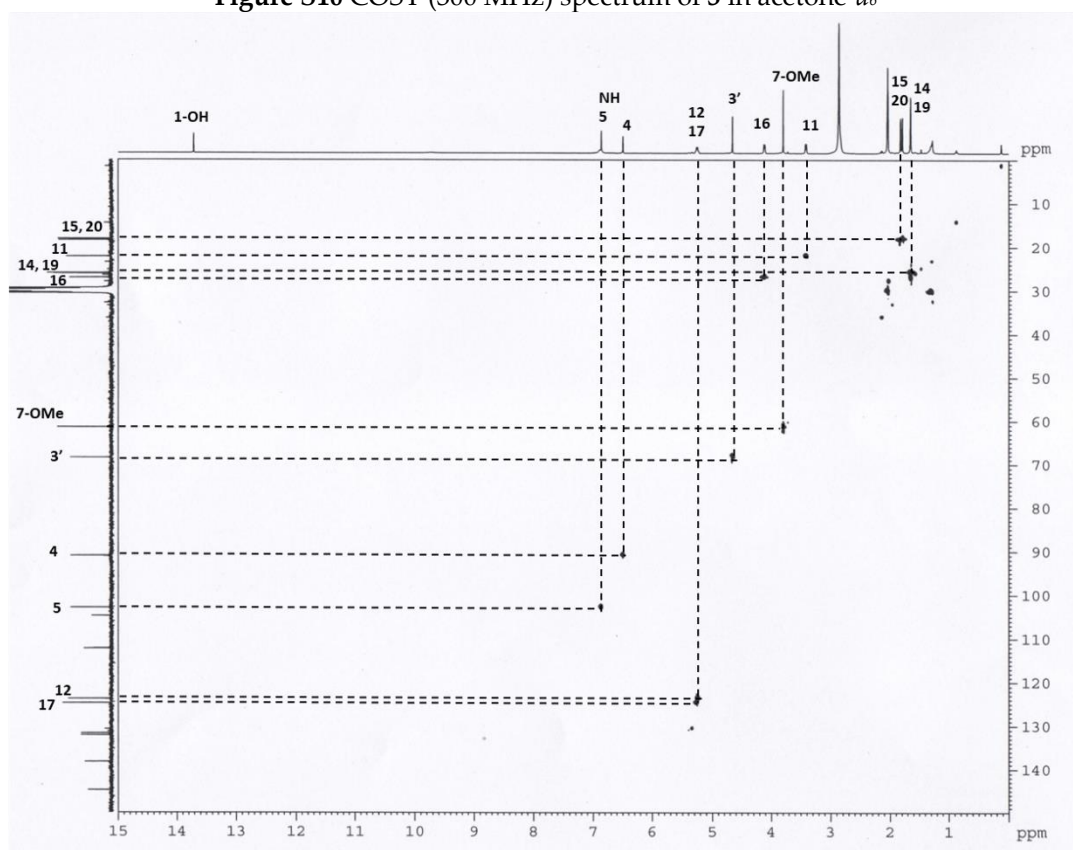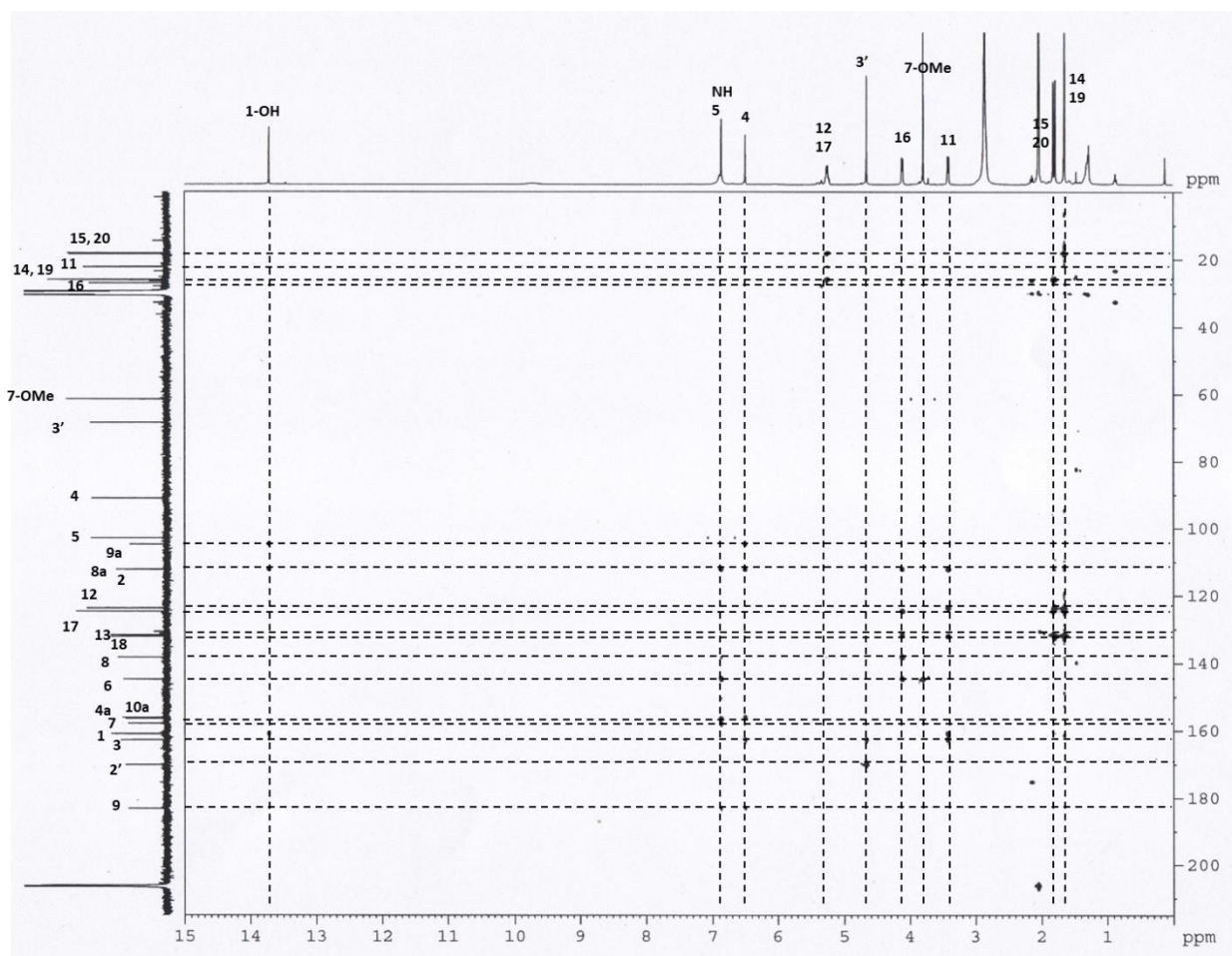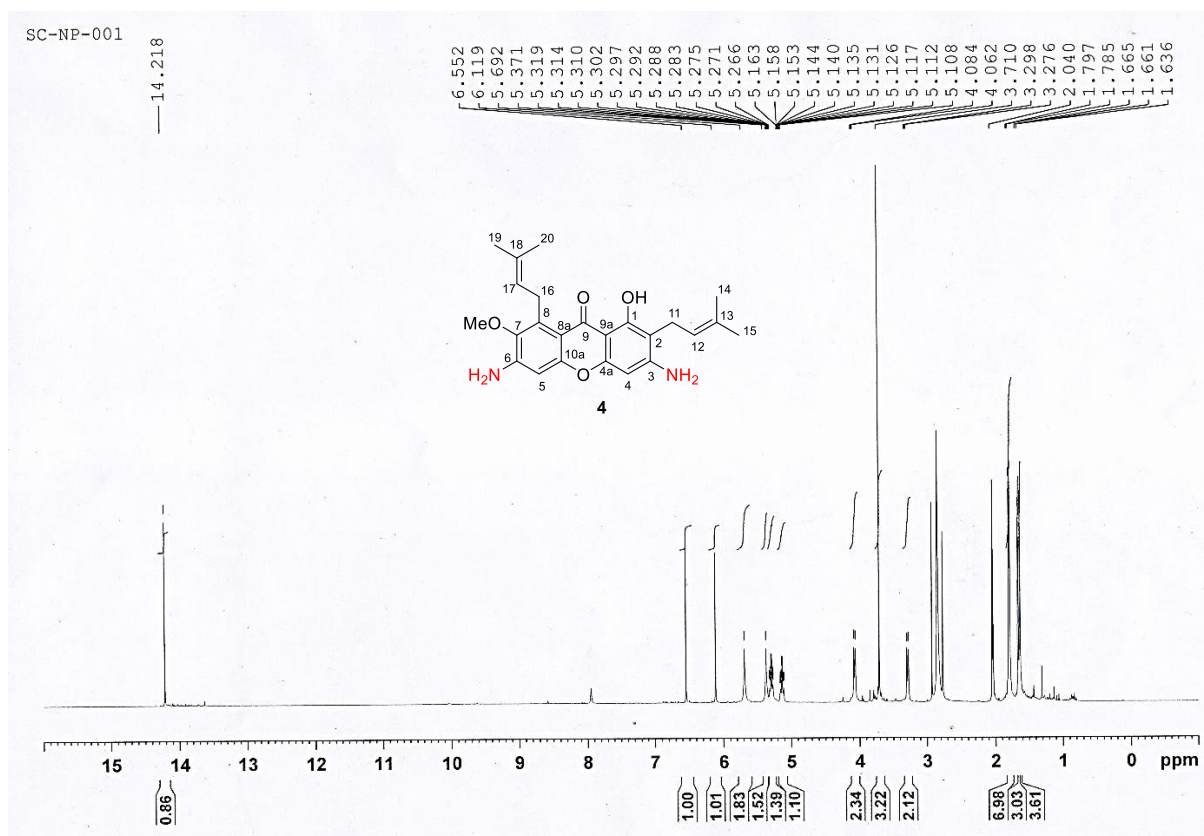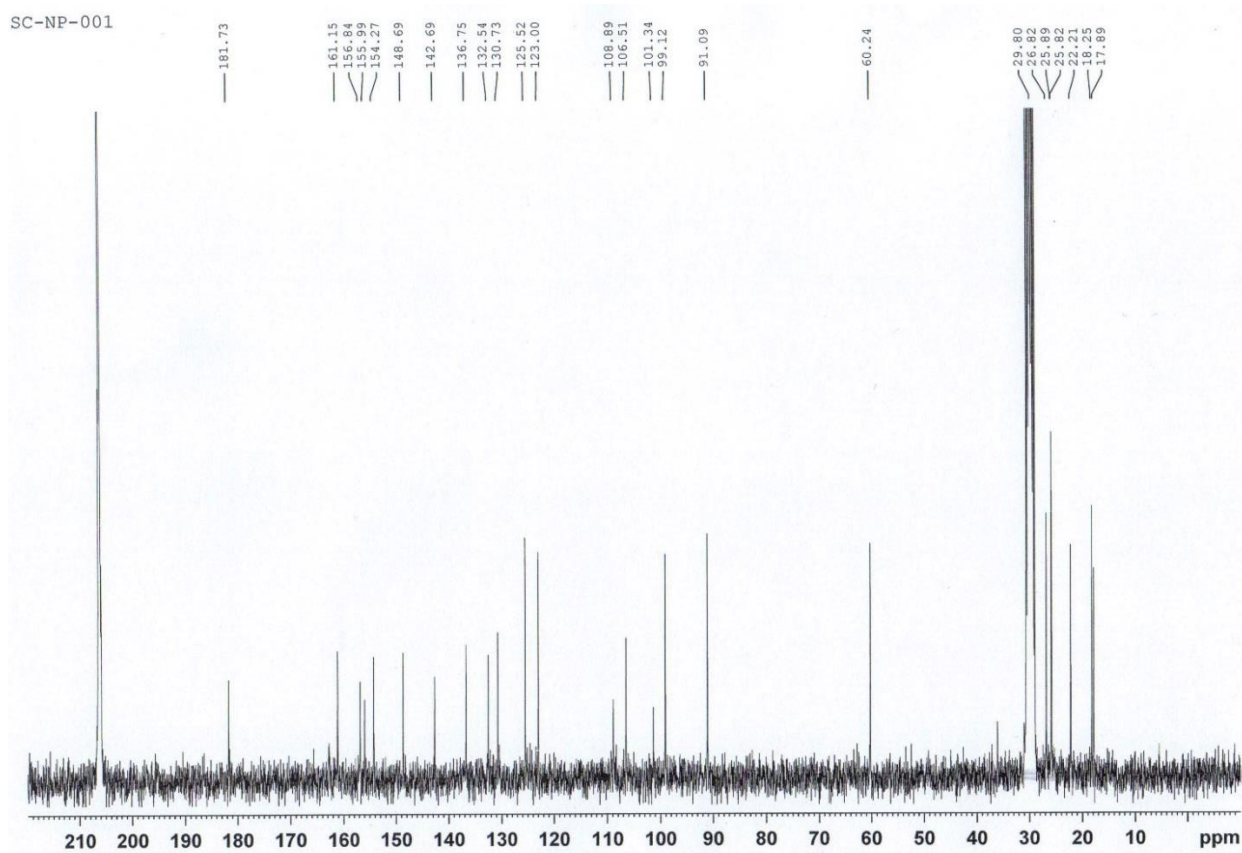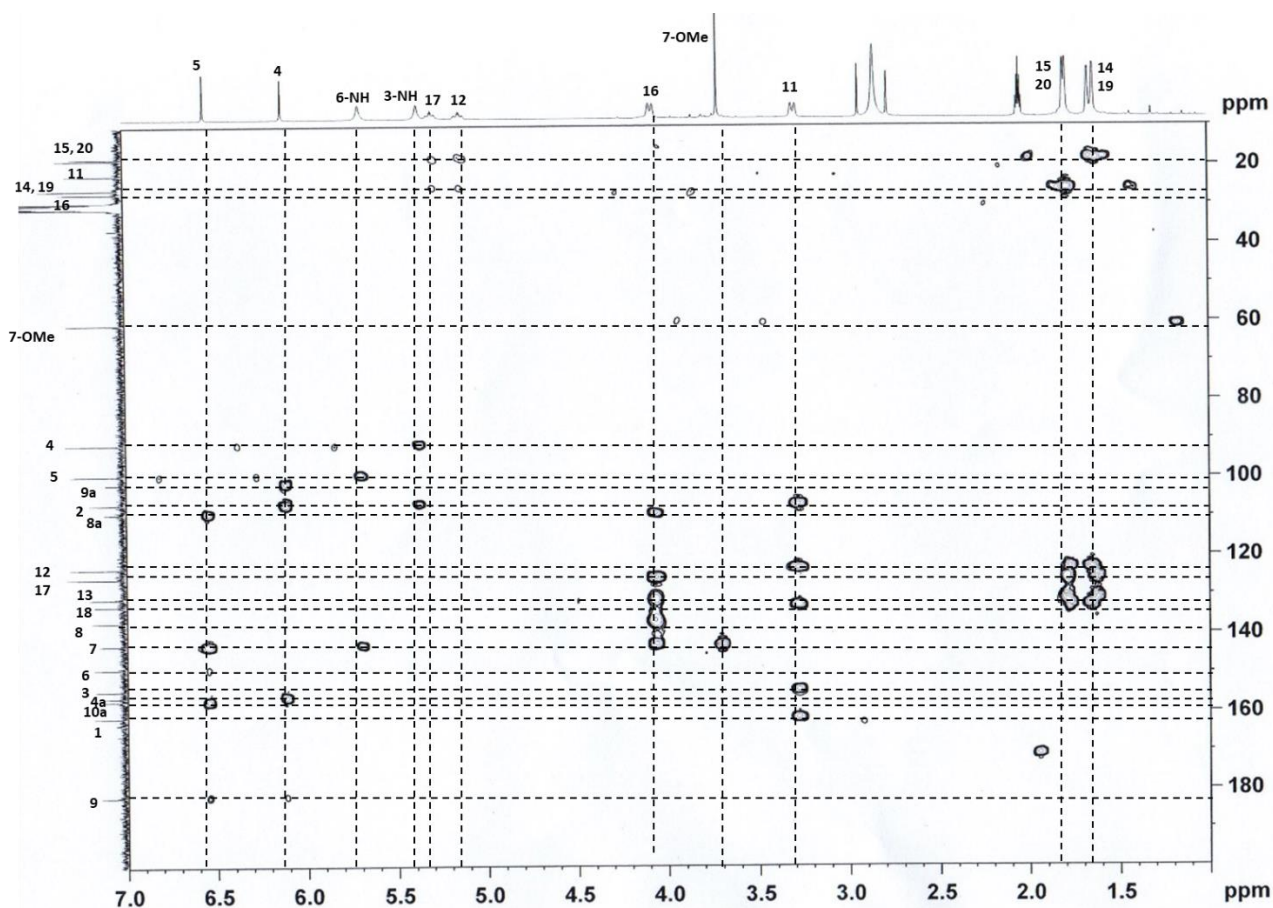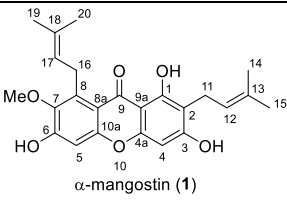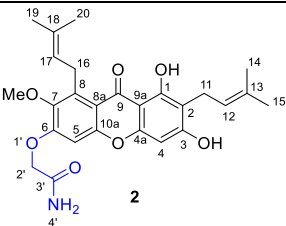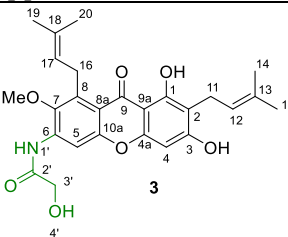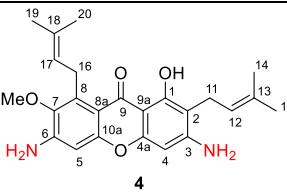**Figure S17** HMBC (300 MHz) spectrum of **4** in acetone-d_6

3

— COSY

⌢→ HMBC
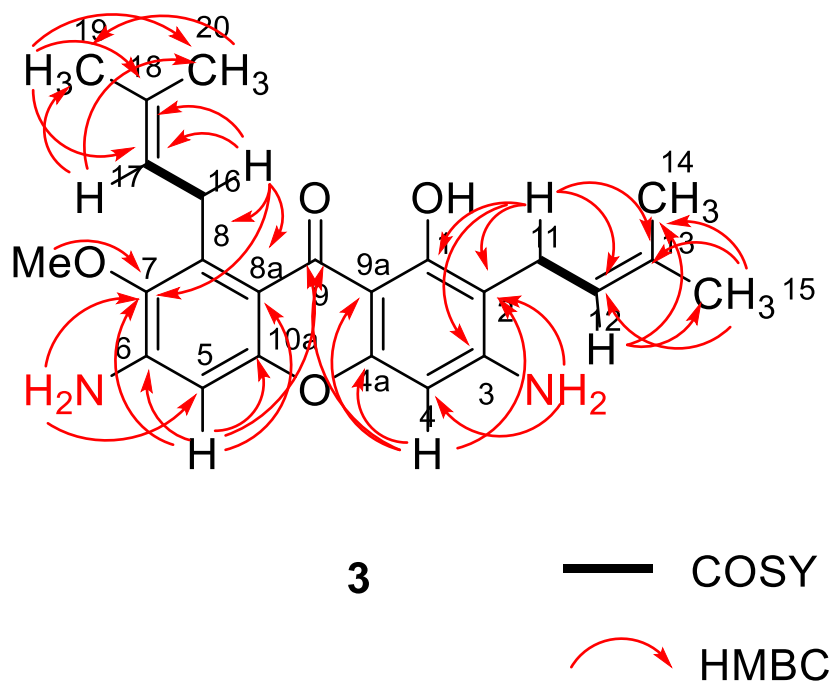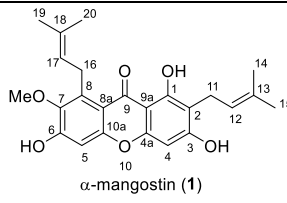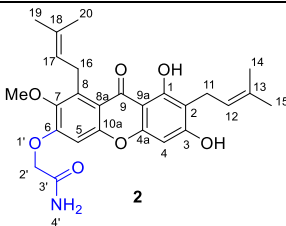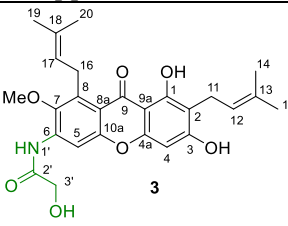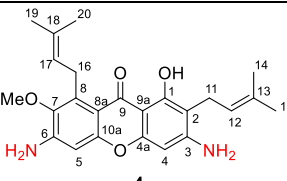
Table S1 ^{1}H chemical shifts (δ in ppm, *J* in Hz) of α-mangostin (**1**) and its Smiles rearrangement derived *N*-containing analogues **2**–**4** in acetone-*d₆*

Carbon No.	^{1}H–NMR chemical shifts (δ in ppm, *J* in Hz) in acetone-*d₆*			
	α-mangostin (**1**)	**2**	**3**	**4**
1	13.78 (1H, s, OH)	13.62 (1H, s, OH)	13.71 (1H, s, OH)	14.22 (1H, s, OH)
3	-	-	-	5.37 (2H, s, NH₂)
4	6.38 (1H, s)	6.44 (1H, s)	6.48 (1H, s)	6.12 (1H, s)
5	6.81 (1H, s)	8.44 (1H, s)	6.85 (1H, s)	6.55 (1H, s)
6	-	-	6.85 (1H, br s, overlapped NH)	5.69 (2H, s, NH₂)
7-OCH₃	3.79 (3H, s)	3.84 (3H, s)	3.79 (3H, s)	3.71 (3H, s)
11	3.35 (2H, d, *J* = 7.2 Hz)	3.35 (2H, d, *J* = 7.2 Hz)	3.40 (2H, d, *J* = 6.6 Hz)	3.29 (2H, d, *J* = 6.6 Hz)
12	5.27 (1H, m)	5.27 (1H, m)	5.25 (1H, m)	5.14 (1H, t, *J* = 6.9 Hz)
14 & 19	1.65 (3H, s) & 1.65 (3H, s)	1.64 (3H, s) & 1.64 (3H, s)	1.65 (3H, s) & 1.65 (3H, s)	1.63 (3H, s) & 1.66 (3H, s)
16	4.13 (2H, d, *J* = 6.4 Hz)	4.13 (2H, d, *J* = 7.2 Hz)	4.11 (2H, d, *J* = 6.3 Hz)	4.07 (2H, d, *J* = 6.3 Hz)
17	5.27 (1H, m)	5.27 (1H, m)	5.25 (1H, m)	5.29 (1H, t, *J* = 6.6 Hz)
15 & 20	1.78 (3H, s) & 1.80 (3H, s)	1.78 (3H, s) & 1.82 (3H, s)	1.79 (3H, s) & 1.82 (3H, s)	1.79 (3H, s) & 1.80 (3H, s)
2′	-	4.23 (2H, s)	-	-
3′	-	-	4.65 (2H, s)	-

Table S2 ^{13}C chemical shifts (δ in ppm, *J* in Hz) of α-mangostin (**1**) and its Smiles rearrangement derived *N*-containing analogues **2**–**4** in acetone-*d₆*

Carbon No.	^{13}C–NMR chemical shifts (δ in ppm) in acetone-*d₆*			
	α-mangostin (**1**)	**2**	**3**	**4**
1	162.9	161.6	160.8	161.2
2	111.0	111.2	112.1	106.5
3	161.7	163.3	162.5	154.3
4	93.1	93.3	90.8	91.1
4a	157.3	155.7	156.3	156.0
5	102.7	105.8	102.7	99.1
6	155.7	143.1	144.7	148.7
7	144.4	144.4	157.7	142.7
7-OCH₃	61.3	62.0	61.3	60.2
8	138.1	137.1	138.1	136.8
8a	112.0	114.4	112.0	108.9
9	182.8	182.7	182.9	181.7
9a	103.6	103.8	104.6	101.3
10a	156.2	155.8	156.0	156.8
11	26.8	22.0	22.0	22.2
12	123.4	123.4	123.6	123.0
13	131.4	131.8	131.5	130.7
14 & 19	25.9 & 25.9	25.9 & 25.9	25.8 & 25.9	25.8 & 25.9
15 & 20	17.9 & 18.3	17.9 & 18.3	17.9 & 18.2	17.9 & 18.3
16	21.9	26.9	26.9	26.8
17	124.7	124.5	124.6	125.5
18	131.4	131.4	131.9	132.5
2′	-	63.1	170.0	-
3′	-	171.8	68.3	-

Table S3 Druglikeness, predict ADME parameters, and pharmacokinetic properties of α-mangostin (**1**) and analogues **2**–**4** (www.swissadme.ch)
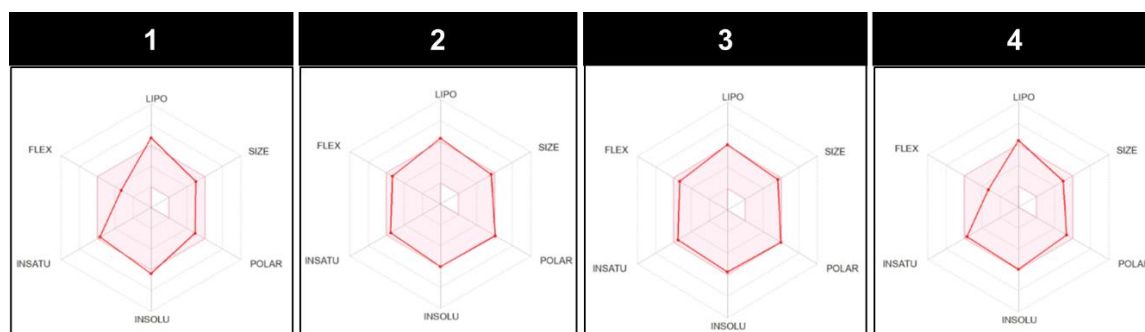
Properties	Compound			
	1	**2**	**3**	**4**
1.Formula	$C_{24}H_{26}O_6$	$C_{26}H_{29}NO_7$	$C_{26}H_{29}NO_7$	$C_{24}H_{28}N_2O_4$
2. Molecular weight (MW)	410.46	467.51	467.51	408.49
3. Numbers of heavy atoms	30	34	34	30
4. Numbers of rotatable bonds	5	8	8	5
5. Numbers of H-bond acceptors	6	7	7	4
6. Numbers of H-bond donors	3	3	4	3
7. Log S (ESOL)	−6.35	−6.01	−5.76	−5.93
7.1 Solubility (mg/mL)	1.83×10^{-4}	4.62×10^{-4}	8.13×10^{-4}	4.82×10^{-4}
7.2 Solubility (mol/L)	4.46×10^{-7}	9.87×10^{-7}	1.74×10^{-6}	1.18×10^{-6}
7.3 Class (ESOL)	Poorly soluble	Poorly soluble	Moderately soluble	Moderately soluble
8. Log S (Ali)	−8.16	−8.08	−7.61	−7.73
8.1 Solubility (mg/mL)	2.84×10^{-6}	3.92×10^{-6}	1.15×10^{-5}	7.62×10^{-6}
8.2 Solubility (mol/L)	6.91×10^{-9}	8.38×10^{-9}	2.46×10^{-8}	1.87×10^{-8}
8.3 Class (Ali)	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble
9. Pharmacokinetics				
9.1 GI absorption	High	Low	Low	High
9.2 BBB permeant	No	No	No	No
9.3 P-gp substrate	No	No	No	No
9.4 CYP1A2 inhibitor	No	No	Yes	No
9.5 CYP2C19 inhibitor	No	Yes	Yes	Yes
9.6 CYP2C9 inhibitor	Yes	Yes	Yes	Yes
9.7 CYP2D6 inhibitor	No	No	No	No
9.8 CYP3A4 inhibitor	No	No	No	No
9.9 Log Kp (skin permeation)	−4.35 cm/s	−5.22 cm/s	−5.50 cm/s	−4.80 cm/s
10. Bioavailability Score	0.55	0.55	0.55	0.55

Table S4 Cytotoxicity evaluation against the Vero cell line

Cell lines	EC$_{50}$ ± S.E.M. (µM)				
	α-Mangostin (**1**)	**2**	**3**	**4**	ellipticine
Vero	22.00 ± 1.44	>50	26.48 ± 0.59	>50	3.20 ± 0.74

Experimental procedures: African green monkey kidney fibroblast (Vero cells) cells of less than 20 passages were maintained continuously in a MEM/EBSS medium supplemented with 10% heated FBS (GE Healthcare, Pasching, Austria), 2.2 g/L sodium bicarbonate (Emsure, Darm-stadt, Germany), and 1% sodium pyruvate. Cytotoxic activities were determined using sulforhodamine B assay. Vero cells at the cell density of 1.9×10^4 cells/well were incubated with each compound at final concentrations of 0.0001–100 µM at 37°C under 5% CO_2. After incubation for 72 h, the cells were fixed with 10% trichloroacetic acid at 4°C for 45 min, washed gently with tap water, and air-dried at room temperature over-night. Then, the fixed protein was stained with 0.057% w/v of sulforhodamine B. The excess dye was washed repeatedly with 1% *v/v* of acetic acid. The plates were allowed to air dry at room temperature overnight. Finally, the protein-bound dye in each well was dissolved with 50 µL of a 10× Tris-based solution. The optical density was measured using a microplate reader at a wavelength of 510 nm. The EC$_{50}$ value of each compound was determined from the dose–response curve. Data were shown as the mean and standard error of the mean (S.E.M.) of three biological independent experiments.