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Natural Product Sciences
29(1) : 38-41 (2023)
https://doi.org/10.20307/nps.2023.29.1.38

Xanthones and 4-Phenylcoumarins from the Twigs of *Mesua beccariana* (Baill.) Kosterm

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Abstract – Two xanthones and 4-phenylcoumarins were isolated from the twigs of *Mesua beccariana* (Baill.) Kosterm. Among them, one new xanthone, beccarianin A (**1**), along with 7-isoprenyl-jacareubin (**2**), mammea A/AA cyclo F (**3**), and mammea A/BA cyclo F (**4**). These structures were determined by spectrometric and spectroscopic methods, HRESIMS data, NMR, and UV spectra. Two xanthones (**1-2**) and two 4-phenylcoumarins (**3-4**) were evaluated for their cytotoxic effect on the HeLa cells. Compound **1** showed active activity (IC_{50} = 8.2 μM), and compounds **3-4** showed moderate activity (IC_{50} = 12.3 and 15.6 μM, respectively).
Keywords – *Mesua beccariana*, beccarianin A, xanthone, 4-phenylcoumarin, cytotoxic

Introduction

Mesua beccariana (Baill.) Kosterm (Calophyllaceae) is a flowering plant found in tropical rainforest Southeast Asia and is commonly called ironwood tree and is used as herbal medicinal. The aqueous decoction of roots or leaves of *M. beccariana* was used to treat fever, wound medicine, and inflammation.[1] The *Mesua* plants produce diverse phenolic compounds, including chromanone acids, 4-phenyl and 4-propyl coumarins, and xanthone derivatives. The phenolic compounds showed biological activities as an antioxidant, anti-inflammatory, acetylcholinesterase inhibition, and anti-cancer.[2-10]

Beccarianin A (**1**) is a new geranylated xanthone along with 7-isoprenyl-jacareubin (**2**), mammea A/AA cyclo F (**3**), and mammea A/BA cyclo F (**4**) were isolated from *M. beccariana* twigs (Fig. 1). Two xanthones (**1-2**) and 4-phenylcoumarins (**3-4**) from *M. beccariana* were also reported about the anticancer activity against HeLa cells.

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Experimental

General experimental procedures – The wavelength maxima in methanol of compounds **1-4** were measured using a UV spectrophotometer (Shimadzu series 2600i). The chemical formula of the phenolic compounds was recorded using an ESI-TOF mass spectrometer (Waters Corporation - LCT Premier XE). The chemical structure of xanthones was measured by an NMR spectrometer (JEOL ECA-400) operating at 400 MHz (^{1}H NMR spectrum) and 100 MHz (^{13}C NMR spectrum) using TMS as the internal standard and $CDCl_3$ (δ_H 7.26 and δ_C 77.1, respectively) as reference standards. Silica gel 60 and PF_{254} were employed as state phases for gravity column and radial chromatography.

Plant material – The fresh twigs of *M. beccariana* were collected in Muara Tiga Village, Batu Ampar, Kubu Raya, West Kalimantan, on June 2019. Indonesia. The specimen of plants (MBS 20190617) was identified at the Bogoriense Herbarium, Indonesia, and compared with the same specimen as a reference.

Extraction and isolation – The dried twigs of *M. beccariana* (0.9 kg) were extracted with 90% methanol for two days (two times) and then partitioned with *n*-hexane and ethyl acetate. The *n*-hexane extract (3 g) was separated with column chromatography (CC), using a

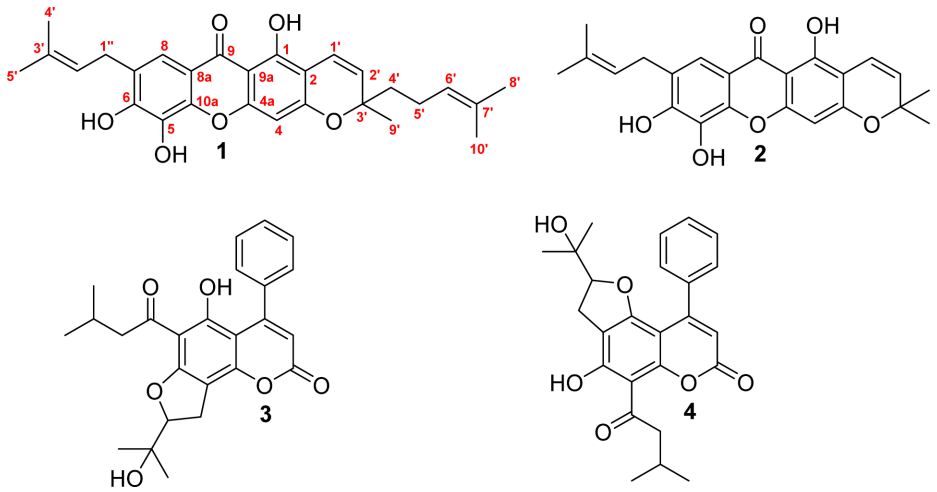

Fig. 1. Xanthones and 4-phenylcoumarins from *M. beccariana* twigs.

mixture of *n*-hexane-ethyl acetate as mobile phase (from 39:1 to 19:1 v/v) to yield compounds 1 (4 mg) and 2 (12 mg). The ethyl acetate extract (10 g) was separated on silica gel by CC, using an *n*-hexane-acetone gradient (from 19:1 to 4:1 v/v) to yield five fractions A–E. Compounds 3 (16 mg) and 4 (8 mg) were yielded from fraction C after separation by radial chromatography, eluting with *n*-hexane-diisopropyl ether gradient (from 9:1 to 1:1 v/v).

Beccarianin A (**1**) – yellowish solid, $[\alpha]^{20}_{D} = +0.1°$ (*c* 0.01, MeOH): UV (MeOH) λ_{max} (log ε) 253 (4.53); 279 (4.47) and 332 (4.12) nm. The NMR data of **1** is shown in Table 1. HRESIMS *m/z* 463.2126 $[M+H]^+$ (calculated for $C_{28}H_{31}O_6$ for 463.2121).

7-Isoprenyl-jacareubin (**2**) – yellow solid, UV (MeOH) λ_{max} (log ε) 252 (4.60); 281 (4.61) and 335 nm (4.31). The chemical shift of **3** in the NMR data was compared to the 7-isoprenyl-jacareubin.[11]

Mammea A/AA cyclo F (**3**) – yellowish oil, UV (MeOH) λ_{max} (log ε) 234 (4.47); 295 (4.35) and 339 nm (4.30). The NMR data of **3** is very identic to the literature data.[12]

Mammea A/BA cyclo F (**4**) – yellowish oil, UV (MeOH) λ_{max} (log ε) 236 (4.42); 298 (4.30) and 338 nm (4.32). The (^{1}H, ^{13}C) NMR spectrum of **4** shows an identical chemical shift to the literature data.[8]

Cytotoxic assay – The cervical cancer cells (HeLa) were cultivated in RPMI 1640 with 10% fetal bovine serum and 1% penicillin/streptomycin seed in 96-well plates at a density of 5×10^4 cells/cm^3. Culture cells were incubated with 5% CO_2 at 37 ºC for 24 hours. All of the isolates (**1-4**) in well with triplicate of diverse concentrations (100, 50, 10, 5, 1, 0.5, and 0.1 µM) before being incubated for 48 hours at 37 ºC. After incubation the MTT reagent was added to the culture cells and left on for four hours. The inhibition of cells by the isolates (**1-4**) was assessed using a microplate reader set to λ 540 nm.[13-16] To determine the IC_{50} values for the isolates (**1-4**), regression analysis was utilized.

Results and Discussion

Beccarianin A (**1**) was isolated as a yellowish solid, showing the $[M+H]^+$ ion, with chemical formula $C_{28}H_{31}O_6$, was identified by the HRESIMS at *m/z* 463.2126 (calcd 463.2121). The UV spectrum of beccarianin A (**1**) in MeOH (λ_{max} 253, 279, and 332 nm) indicates the chromophore of a xanthone core.[17] Two aromatic protons of **1** [δ_H 6.25 (1H, *s*, H-4), δ_C 99.4 (C-4) and 7.60 (1H, *s*, H-8), δ_C 117.4 (C-8)], which are indicative of xanthone 1,2,3,5,6,7-hexasubstitued were observed in the NMR data and verified by HMQC and HMBC spectrum. Beccarianin A (**1**) also showed one hydroxy proton at δ_H 13.14 (1H, *s*, 1-OH) and one isoprenyl chain, including a vinyl proton [δ_H 5.35 (1H, *t*, J = 7.3 Hz, H-2"), δ_C 121.0 (C-2")], a methylene proton [δ_H 3.43 (2H, *d*, J = 7.3 Hz, H-1"), δ_C 28.7 (C-1")], and two methyl protons [δ_H 1.78 (3H, *s*, H-4",), δ_C 25.9 (C-4"), 1.77 (3H, *s*, H-5"),), δ_C 18.0 (C-5")]. Compound **1**, also attributed to the 3'-methyl-5'-isoprenyl-$\Delta^{1'}$-pyran ring consists of three types of vinyl [δ_H 6.83 (1H, *d*, J = 10.2 Hz, H-1', δ_C 115.4 (C-1'), 5.54 (1H, *d*, J = 10.2 Hz, H-2', δ_C 126.4 (C-2'), 5.09 (1H, *t*, J = 7.2 Hz, H-6', δ_C 123.7 (C-6')], two methylenes [δ_H 2.09 (2H, *m*, H-5', δ_C 22.7 (C-5'), 1.80 (1H, *m*, H-4'a), 1.69 (1H, *m*, H-4'b, δ_C 41.7 (C-4')], and three methyls [δ_H 1.66 (3H, *s*, H-8'), δ_C 25.8 (C-8'), 1.57 (3H, *s*, H-10'), 1.45 (3H, *s*, H-9'), δ_C 27.1 (C-9')]. The ^{13}C NMR spectrum of bec-

Table 1. ^{1}H and ^{13}C NMR (100 MHz) NMR spectral data of **1** in $CDCl_3$

No.C	δ_H (mult, *J* Hz)	δ_C	HMBC
1	-	160.8	-
2	-	101.6	-
3	-	162.8	-
4	6.25 (*s*)	99.4	C-2, C-3, C-4a, C-9a
4a	-	158.9	-
5	-	133.9	-
6	-	148.4	-
7	-	126.4	-
8	7.60 (*s*)	117.4	C-7, C-9, C-10a
8a	-	110.3	-
9	-	180.4	-
9a	-	102.5	-
10a	-	143.9	-
1'	6.83 (*d*, 10.2)	115.4	C-1, C-3'
2'	5.54 (*d*, 10.2)	126.4	C-2, C-3'
3'	-	80.7	-
4'	1.68 (*m*) 1.80 (*m*)	41.7	C-4', C-6', C-7'
5'	2.09 (*m*)	22.7	C-4'
6'	5.09 (*t*, 7.2)	123.7	C-8', C-10
7'	-	131.9	-
8'	1.66 (*s*)	25.8	C-6', C-7', C-10'
9'	1.45 (*s*)	27.1	C-2', C-3', C-4'
10'	1.57 (*s*)	17.7	C-6', C-7', C-8'
1"	3.43 (*d*, 7.3)	28.7	C-6, C-7, C-8, C-2", C-3"
2"	5.35 (*t*, 7.3)	121.0	C-4", C-5"
3"	-	133.7	-
4"	1.78 (*s*)	25.9	C-2", C-3", C-5"
5"	1.77 (*s*)	18.0	C-2", C-3", C-4"
1-OH	13.14 (*s*)	-	-

carianin A showed 28 carbon signals that separated, including six oxyaryl carbons [δ_C 162.8 (C-3), 160.8 (C-1), 158.9 (C-3), 148.4 (C-6), 143.9 (C-10a), 133.9 (C-5)], two methine carbons [δ_C 117.4 (C-8), 99.4 (C-4)], four carbons [δ_C 126.4 (C-7), 110.3 (C-8a), 102.5 (C-9a), 101.6 (C-2)], and one carbonyl carbon at δ_C 180.4 (C-9), indicating that the xanthone 1,2,3,5,6,7-hexasubstitued derivative.

The 3'-methyl-5'-isoprenyl-$\Delta^{1'}$-pyran ring, isoprenyl chain, and hydroxy groups in the xanthone structure were identified by the HMBC spectrum (Fig. 2). An aromatic proton at δ_H 7.60 (H-8) correlated to a carbon C-7 (δ_C 126.4), a carbonyl at C-9 (δ_C 180.4), and an oxyaryl at C-10a (δ_C 143.9). A methylene proton at δ_H 3.43 (H-1") correlated to C-7, an oxyaryl at C-6 (δ_C 148.4), a carbon at C-3" (δ_C 133.7), and two methine carbons at C-8 (δ_C 117.4) and C-2" (δ_C 121.0), supporting the isoprenyl at C-7. An aromatic proton at δ_H 6.25 (H-5) correlated to two carbons [δ_C 102.5 (C-9a), 101.6 (C-2)], and two oxyaryls [δ_C 162.8 (C-3), 158.9 (C-4a)], indicating the 3'-methyl-5'-isoprenyl-$\Delta^{1'}$-pyran ring fused at C-2 and C-3.[2] A set vinyl proton supported the 3'-methyl-5'-isoprenyl-$\Delta^{1'}$-pyran linkages in C-2 and C-3 of the xanthone structure. A vinyl proton at δ_H 6.83 (H-1') correlated to C-1, and an oxycarbon at δ_C 80.7 (C-3'), a second vinyl proton at δ_H

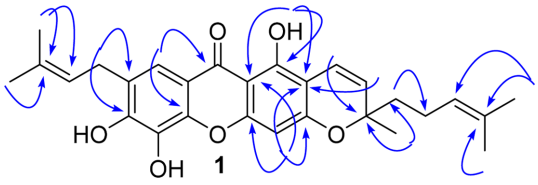

Fig. 2. HMBC significant of beccarianin A (**1**).

5.54 (H-2') corresponded to C-1, and C-3'. The methyl proton at δ_H 1.45 (H-9') is linked to C-3', a methine carbon at C-2' (δ_C 126.4), and a methylene carbon at C-4' (δ_C 41.7). Two methyl protons [δ_H 1.66 (H-8'), 1.57 (H-10')] correlated to a methine carbon at C-6' (δ_C 123.7) and carbon signal at C-7' (δ_C 131.9), supporting the 3'-methyl-5'-isoprenyl-$\Delta^{1'}$-pyran ring in the HMBC spectrum. The structure of **1** was established to be beccarianin A. The name beccarianin A was given based on the name of the plant origin.

The cytotoxic activity of beccarianin A (**1**), 7-isoprenyl-jacareubin (**2**), mammea A/AA cyclo F (**3**), and mammea A/BA cyclo F (**4**) were assayed against cervical cancer cells (HeLa) by MTT methods. Compounds (**1-4**) exhibited IC_{50} values of 8.2 ± 0.2, 60.1 ± 1.2, 12.3 ± 0.4, and 15.6 ± 0.3 μM, respectively. The cells not exposed to the active compound were negative controls, and doxorubicin was a positive control.[18-19] The cytotoxic activity suggested that beccarianin A (**1**) showed active activity, and 7-isoprenyl-jacareubin (**2**) was inactive. Two 4-phenylcoumarins (**3-4**) are isomers that showed moderate activity, and compound **3** tends to be more active than **4**. The placement of 3-methyl-butanoyl at C-6, furan ring fused at C-7 and C-8 of **3** was slightly more than 3-methyl-butanoyl at C-8, furan ring fused at C-6 and C-7 of **4**.

In conclusion, two xanthones (**1**–**2**) and 4-phenylcoumarins (**3-4**) were isolated from the twigs of *M. beccariana*. Beccarianin A (**1**) showed active activity against HeLa cells, and compounds (**3-4)** were moderate.

Acknowledgments

The research was provided financial assistance by Penelitian Dasar Kompetitif Nasional, No. 922/UN3.15/PT/2022, Universitas Airlangga.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Received December 7, 2022
Revised March 7, 2023
Accepted March 9, 2023

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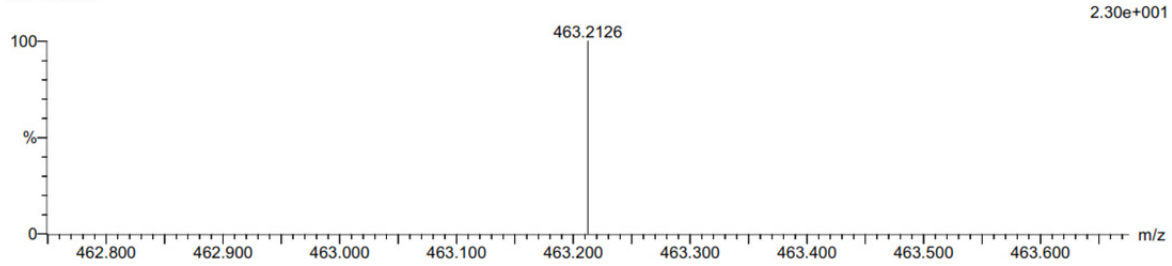
Keywords – *Mesua beccariana*, beccarianin A, xanthone, 4-phenylcoumarin, cytotoxic

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
114 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-200
MESUA H KB4 3 (0.068)
TOF MS ES+



Minimum:				-1.5			
Maximum:		10.0	3.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
463.2126	463.2121	0.5	1.1	13.5	17.9	1.7	C28 H31 O6

Figure S1. HRESIMS spectrum of beccarianin A (**1**)

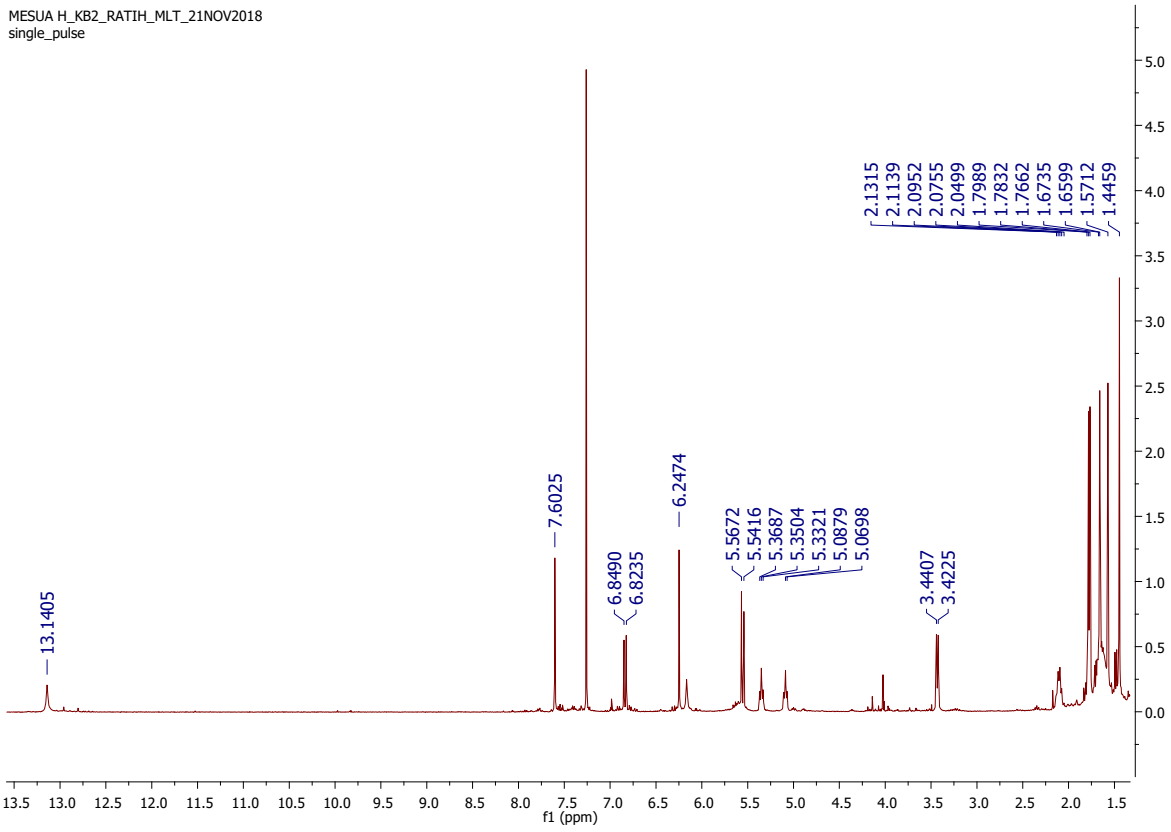


Figure S2. ^{1}H NMR spectrum of beccarianin A (**1**)

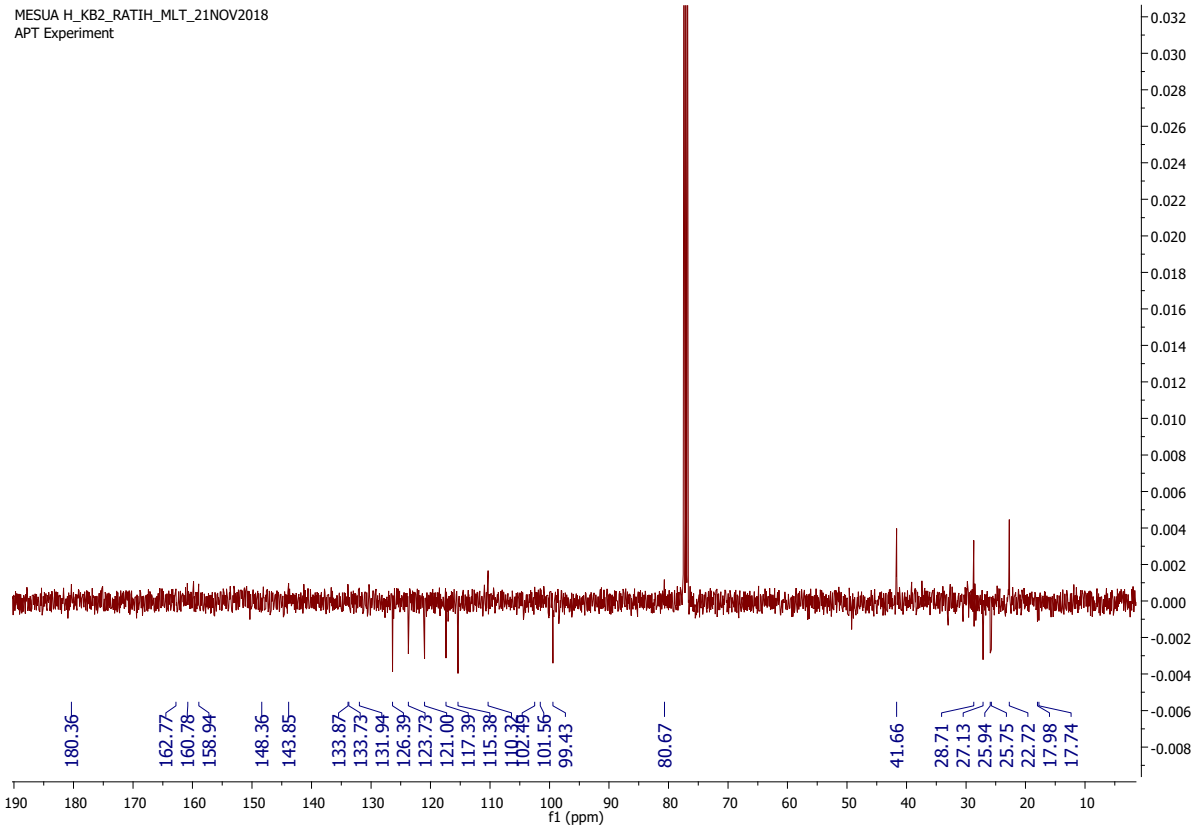


Figure S3. ^{13}C NMR (APT experiment) spectrum of beccarianin A (**1**)

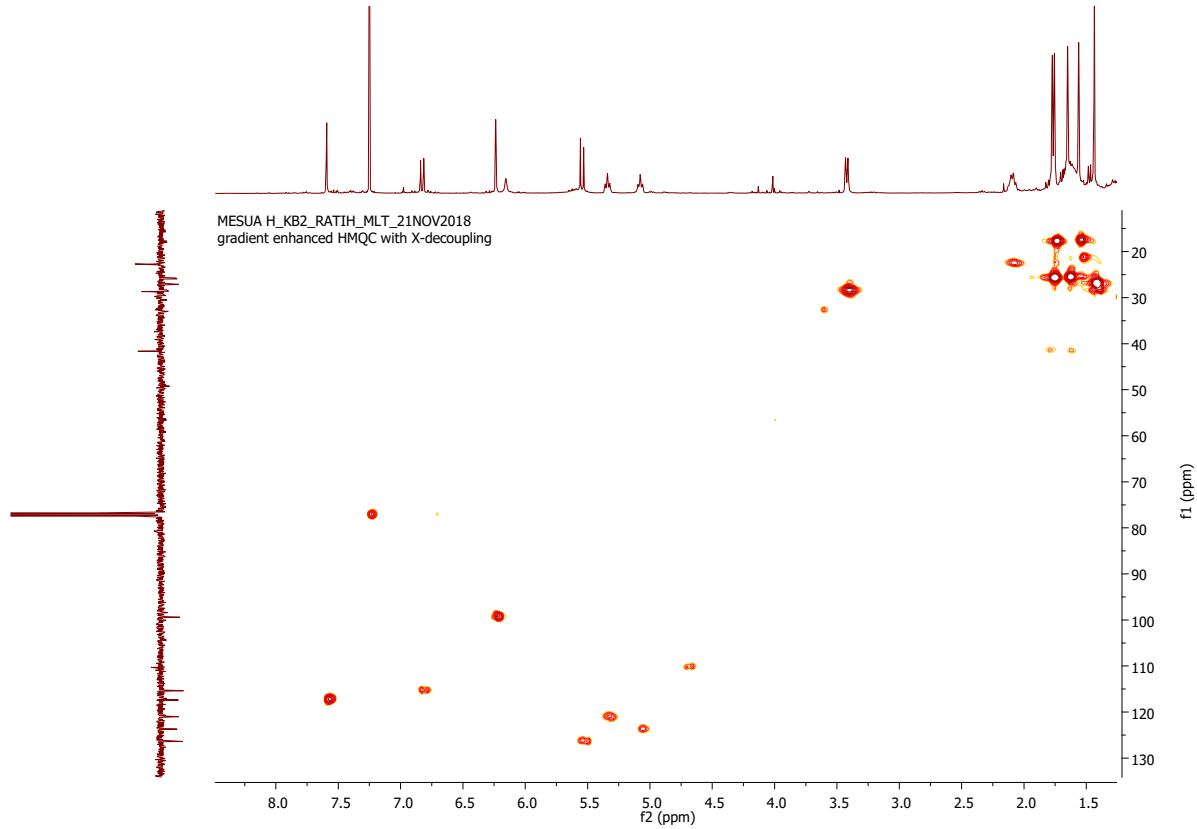


Figure S4. HMQC spectrum of beccarianin A (**1**)

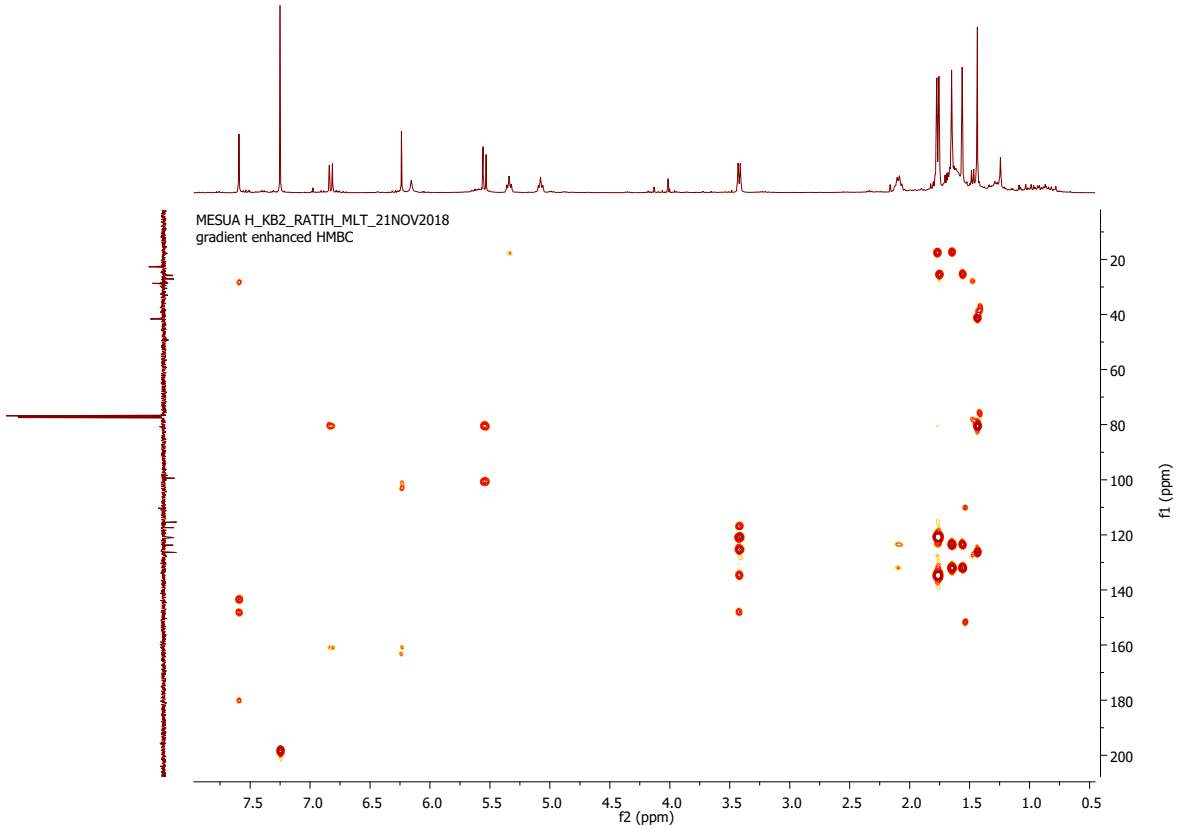


Figure S5. HMBC spectrum of beccarianin A (**1**)

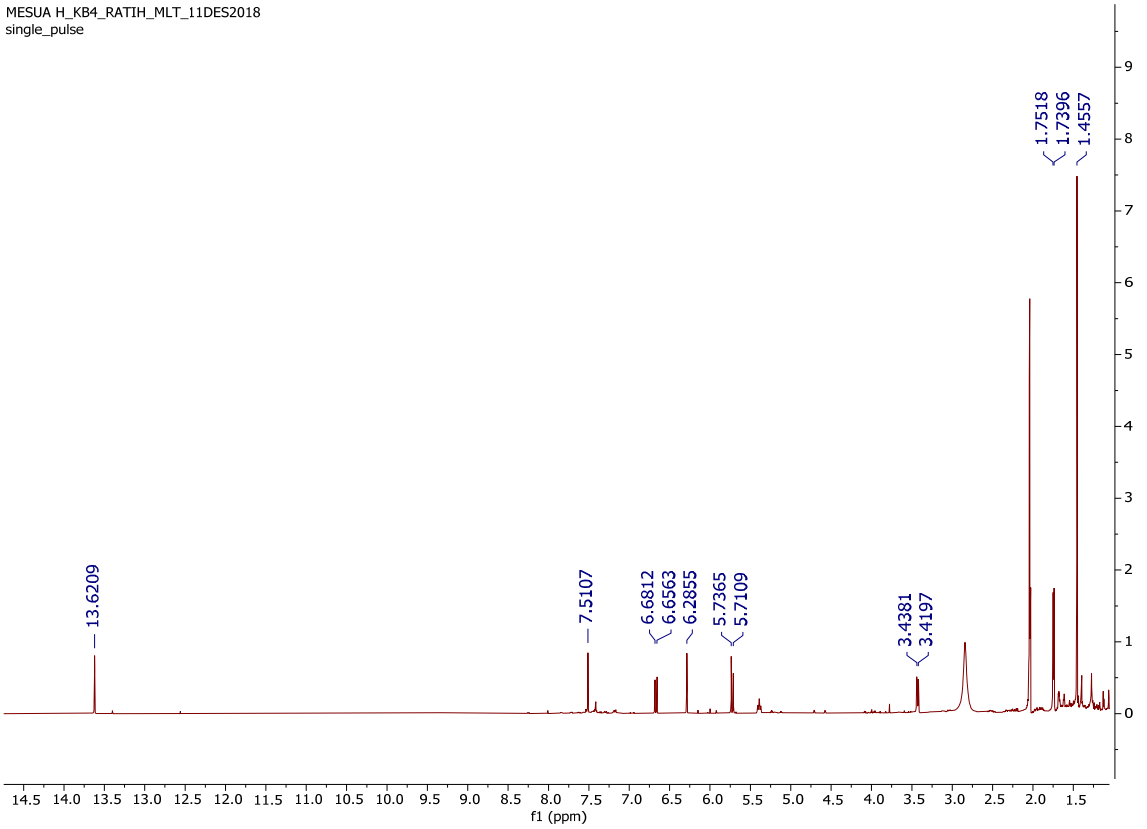


Figure S6. ^{1}H NMR spectrum of 7-isoprenyl-jacareubin (**2**)

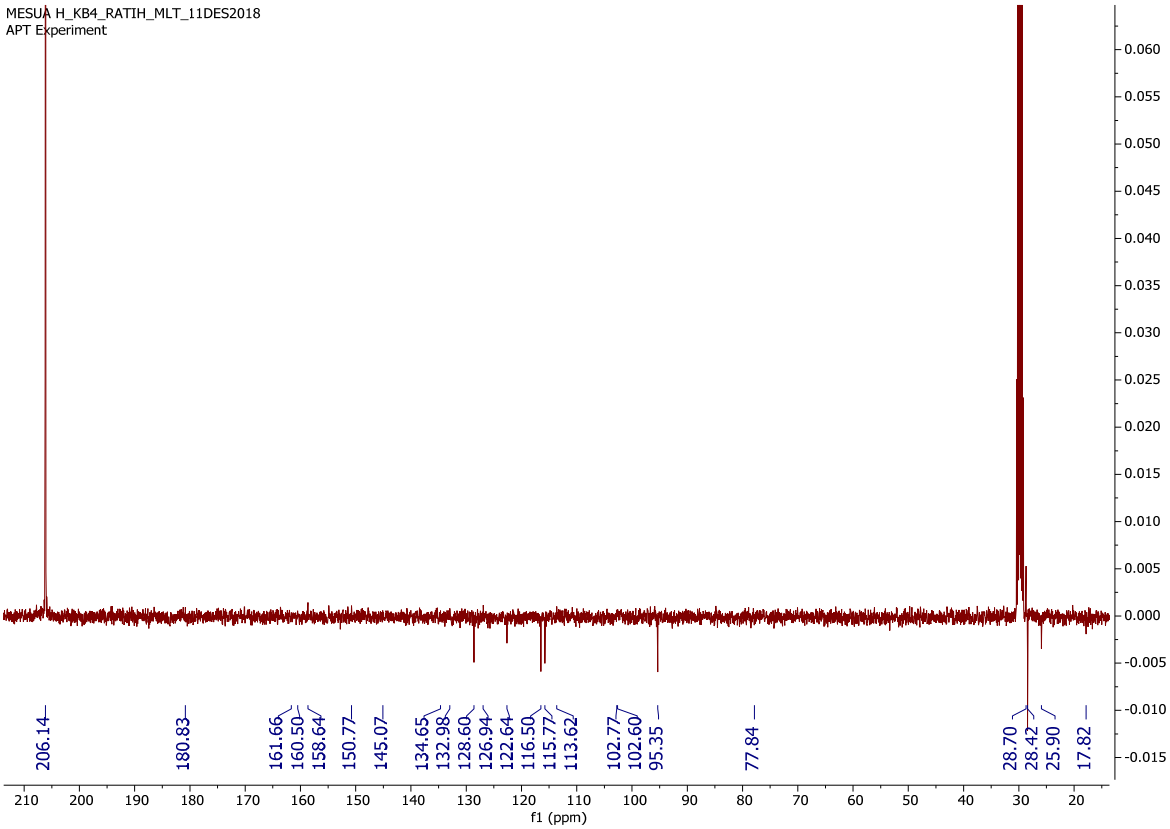


Figure S7. ^{13}C NMR (APT experiment) spectrum of 7-isoprenyl-jacareubin (**2**)

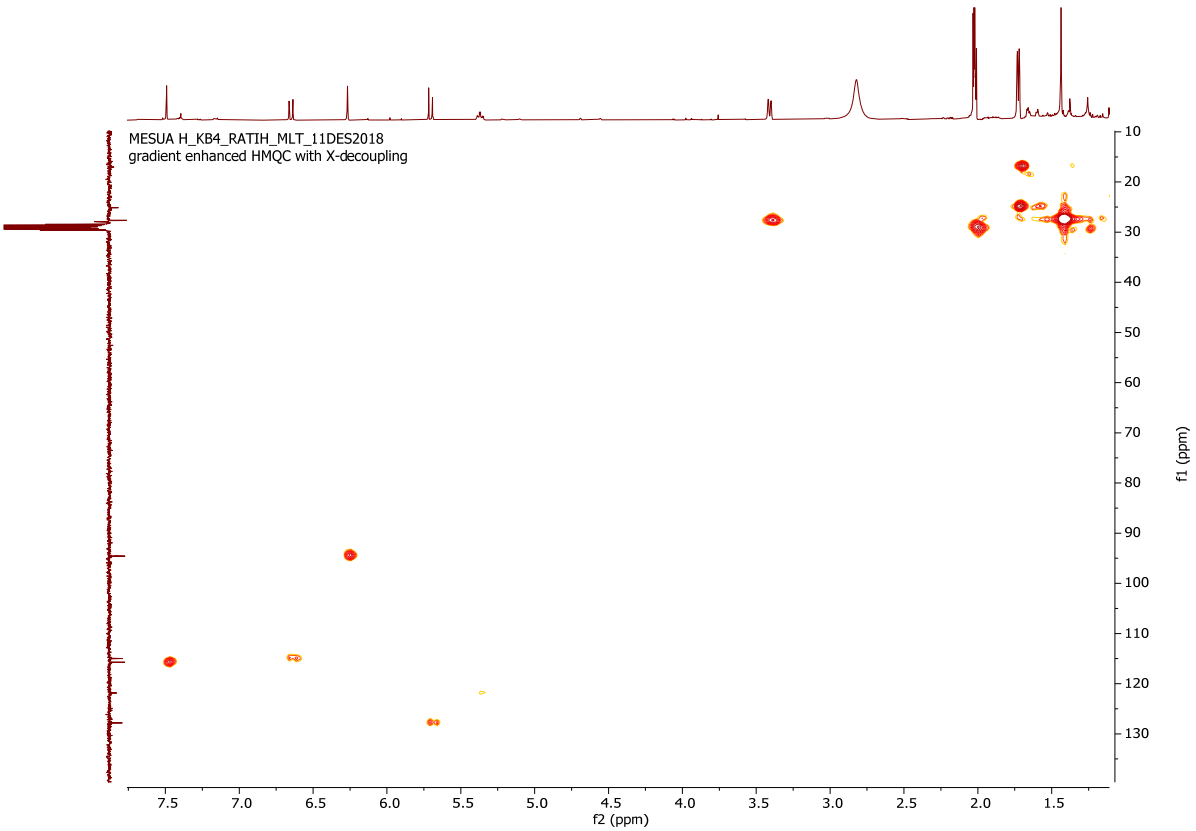


Figure S8. HMQC spectrum of 7-isoprenyl-jacareubin (**2**)

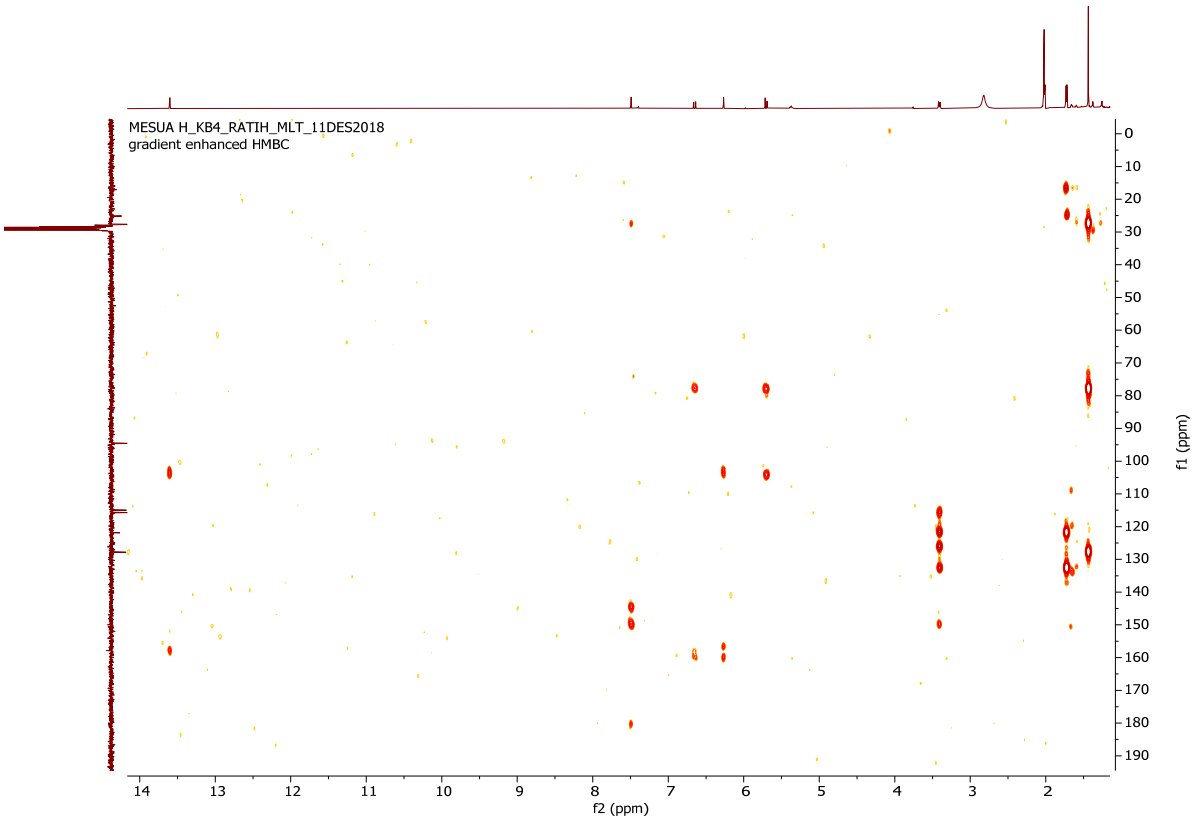


Figure S9. HMBC spectrum of 7-isoprenyl-jacareubin (**2**)