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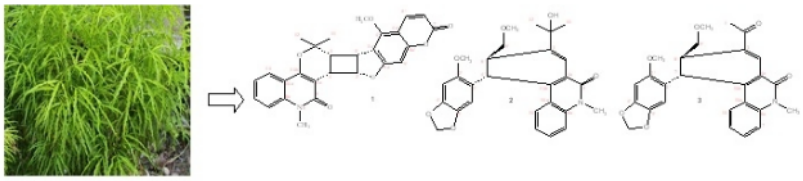

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Three novel quinolinone alkaloids from the leaves of *Melicope denhamii*

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Three previously unreported quinolinone alkaloids: melicodenines J-L (**1-3**) and six known compounds (**4-9**), were isolated from the leaves of *Melicope denhamii* (Seem) T.G. Hartley. The structures of three quinolinone alkaloids were identified based on HRESIMS and NMR spectra. Compounds **1-9** were assayed in three cancer cells (MCF-7, HeLa, and P-388). Compounds **1** and **5** showed high cytotoxic activity against HeLa cells with IC_{50} values of 1.8 and 0.8 µM, respectively.

Keywords: *Melicope denhamii*, melicodenines J-L, quinolinone adduct, cytotoxic

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1. Introduction

M. denhamii (Seem) T.G. Hartley (Rutaceae) is one small tree indigenous to Java Islands, Indonesia. The *Melicope* genus produces alkaloids (Chen et al. 2003; Nakashima et al. 2011), flavonoids (Saputri et al. 2018), and phenylpropanoids (Nakashima et al. 2012), with terpenyl side chain in the aromatic ring. Many alkaloids from *Melicope* show biological activities as cytotoxic agents (Chen et al. 2003; Nakashima et al. 2012), and antimalaria (Rasamison et al. 2016). Recently studies on *Melicope* resulted in the hybrid

compound by [2+2] cycloaddition and a Diels-Alder adduct from incorporated phenylpropanoid-phenylpropanoid, alkaloid-alkaloid, alkaloid-benzopyran, and alkaloid-phenylpropanoid derivatives (George et al. 2016; Nakashima et al. 2012; 2011; Saputri et al. 2019). Three new compounds, melicodenine J (**1**) is a [2+2] cycloaddition, melicodenines K (**2**), and L (**3**) are Diels-Alder adduct derivatives were isolated from *M. denhamii* leaves. The cytotoxic activities of their isolates (**1**-**9**) against MCF-7, HeLa, and P-388 cancer cell lines were reported in this study.

2. Result and Discussion

Melicodenine J (**1**) was isolated as a yellow amorphous solid and showed a positive ion peak $[M+H]^+$ at *m/z* 458.1613, consistent with the molecular composition $C_{27}H_{23}NO_6$. The UV exhibited maximum absorption (λ_{max} 219, 259, 292, 320, and 334 nm), indicating a typical quinolinone alkaloid-coumarin (Nakashima et al. 2012). The IR measurement showed absorption bands for conjugated carbonyl at 1627 cm^{-1}, aromatic ring at 1595 cm^{-1}, and ether at 1128 cm^{-1}. The ^1H NMR spectrum of **1** showed four protons [δ_H 5.41 (1H, *dd*, *J* = 6.7, 2.6 Hz, H-2′), δ_H 4.75 (1H, *t*, *J* = 6.7 Hz, H-3′), δ_H 4.08 (1H, *t*, *J* = 9.5 Hz, H-4), δ_H 3.10 (1H, *dd*, *J* = 9.5, 6.7 Hz, H-3)] were characteristics of a 1,2,3,4-tetrasubstituted cyclobutane ring. A signal at δ_H 5.41 indicates an oxymethine attached to the cyclobutane ring (Holla et al. 2012; Nakashima et al. 2012). Four signals of a 1,2-disubstituted benzene [δ_H 7.90 (1H, *dd*, *J* = 8.0, 1.2 Hz, H-10), δ_H 7.43 (1H, *dt*, *J* = 8.5, 1.2 Hz, H-8), δ_H 7.15 (1H, *t*, *J* = 8.0 Hz, H-9), δ_H 7.08 (1H, *d*, *J* = 8.5 Hz, H-7)], two methyls [δ_H 1.73 (3H, *s*, H-11), δ_H 1.20 (3H, *s*, H-12)] along with a N-methyl signal at δ_H 3.38 suggested that the partial structure of **1** as a N-methylflindersin moiety (Kamperdick et al. 1999). A signal of aromatic at δ_H 5.94 (1H, *s*, H-9′), two signals of *cis* vinylic [δ_H 7.85 (1H, *d*, *J* = 9.6 Hz, H-5′), δ_H 5.95 (1H, *d*, *J* = 9.6 Hz, H-6′)], and a methoxyl at δ_H 4.25 (3H, *s*, 4′-OCH_3) recommended that the other partial structure of **1** as a bergapten moiety (Saputri et al. 2021). Based on the ^1H NMR data suggested that the structure of **1** is a [2+2] cycloaddition product between N-methylflindersin with bergapten (Nakashima et al. 2012). The ^{13}C NMR and HMQC spectra of **1** exhibited the signals of 27 carbons were completely separated, including four methyls [δ_C 25.4, 25.5, 29.0, 58.4], 11 methines [δ_C 35.5, 43.2, 45.0, 85.1, 90.5, 109.5, 113.5, 121.6, 123.1,

130.7, 139.5], five quaternary carbons [δ_C 104.4, 105.2, 107.3, 116.2, 138.5], one oxycarbon [δ_C 75.5], two carbonyls [δ_C 161.8, 162.2], and four oxyaryls [δ_C 152.6, 156.5, 156.6, 168.6]. The HMBC spectrum, an N-methyl signal at δ_H 3.38, showed a correlation with a carbonyl [δ_C 162.2 (C-5)] and a quaternary carbon [δ_C 138.5 (C-6a)]. An aromatic signal at δ_H 7.90 (H-10) correlated to C-6a and a methine carbon [δ_C 130.7 (C-8)]. Two methyl signals at δ_H 1.73 (H-11) and δ_H 1.20 (H-12) correlated to an oxycarbon [δ_C 75.5 (C-2)], and a methine carbon [δ_C 45.0 (C-3)] proved that a part of the structure of N-methylflindersin. A signal of vinylic at δ_H 7.85 (H-5′) showed correlation with a lactone carbonyl [δ_C 161.8 (C-7′)], two oxyaryls [(δ_C 152.6 (C-4′), and (δ_C 156.5, C-8a′)]. A methoxyl at δ_H 4.25 (4′-OCH_3) correlated to C-4′ verified the location of the methoxyl group at C-4′. One proton of aromatic at δ_H 5.94 (H-9′) showed correlation with two oxyaryls [(δ_C 168.6, C-9a′), C-8a′)], two quaternary carbons [(δ_C 104.4, C-3a′), and (δ_C 107.3, C-4a′)] and carbonyl carbon (δ_C 161.8, C-7′) reinforced the other partial structure of **1** as a bergapten (Saputri et al. 2021). An oxymethine proton at δ_H 5.41 (H-2′) correlated to a methine carbon δ_C 35.5 (C-4). A signal at δ_H 4.75 (H-3′) correlated to C-3a′, C-4a′, C-4′, and C-9a′ (a part of bergapten), C-3, and C-4 (a part of N-methylflindersin). A methine signal of a cyclobutane ring at δ_H 3.10 (H-3) correlated to C-4, C-3a′, and a methine, δ_C 85.1 (C-2′). A methine signal of a cyclobutane ring at δ_H 4.08 (H-4) correlated to C-4a and C-2′. In the NOESY spectrum, an oxymethine (H-2′) correlated to H-3 and H-3′, and a methine proton (H-3) correlated to H-4 and H-3′ revealed the signal that a 1,2,3,4-tetrasubstituted cyclobutane ring is a *cis* orientation. Consequently, the structure of melicodenine J is shown in Fig. 1.

Melicodenine K (**2**) was isolated as colorless oil in which showed an ion peak $[M+H]^+$ at *m/z* 464.2080 correspondings for a molecular composition $C_{27}H_{30}NO_6$ by the combination of HRESIMS spectra and NMR data. The IR spectrum showed bands of conjugated carbonyl (1639 cm^{-1}), aromatic (1502 and 1485 cm^{-1}), and ether (1112 cm^{-1}) groups. The ^1H NMR spectrum of **2**, showing four aromatic signals [δ_H 7.52 (1H, *dd*, *J* = 8.6, 1.2 Hz, H-10), δ_H 7.46 (1H, *t*, *J* = 7.7 Hz, H-8), δ_H 7.35 (1H, *d*, *J* = 8.6 Hz, H-7), δ_H 7.15 (1H, *t*, *J* = 7.7 Hz, H-9)], an N-methyl signal at δ_H 3.80, a vinylic at δ_H 6.97 (1H, *s*, H-4), and two methyls [δ_H 1.49 (3H, *s*, H-11), δ_H 0.88 (3H, *s*, H-12)] indicating for a 3-isoprenyl-1-methyl 2-quinolinone moiety (Chen et al. 2003). The ^1H NMR spectrum

of **2** also exhibited two protons of aromatic [δ_H 6.57 (1H, s, H-3′), δ_H 6.13 (1H, s, H-6′)], two methines [δ_H 4.82 (1H, *s*, H-7′), δ_H 3.19 (1H, *dd*, *J* = 9.8, 6.0 Hz, H-8′)], splitting two signals of a methylene [δ_H 3.51 (1H, *dd*, *J* = 8.3, 6.0 Hz, H-9a′, δ_H 3.38 (1H, *t*, *J* = 9.8 Hz, H-9b′)], two methoxyls [δ_H 3.95 (3H, *s*, 2′-OCH_3), δ_H 3.30 (3H, *s*, 9′-OCH_3)], and splitting two signals of a methylenedioxy [δ_H 5.79 (1H, *d*, *J* = 1.2 Hz), δ_H 5.75 (1H, *d*, *J* = 1.2 Hz)] characteristics for a melicodin A moiety (Nakashima et al. 2012). Compound **2** indicated that 27 carbon signals were utterly separated in the ^{13}C NMR spectra, including five methyl carbons, two methylene carbons, nine methine carbons, one carbonyl carbon, and ten quaternary carbons. From the NMR (^1H, ^{13}C) NMR spectrum exhibited that the structure of **2** is a Diels-Alder adduct moiety and was confirmed by HMBC spectrum (George et al. 2016; Nakashima et al., 2012). The HMBC correlation, an N-methyl at δ_H 3.80, and an aromatic at δ_H 7.46 (H-8) very similar to **1**. A vinylic signal at δ_H 6.97 (H-4) correlated to δ_C 71.6 (C-2), δ_C 139.7 (C-3), δ_C 39.1 (C-8′), and δ_C 160.6 (C-5). Two methyls at δ_H 0.88 (H-12) and δ_H 1.49 (H-11) correlated to C-2, indicating the 3-isoprenyl 1-methyl 2-quinolinone moiety. Two signals of aromatic at δ_H 6.57 (H-3′), and δ_H 6.13 (H-6′) correlated to δ_C 150.8 (C-2′), δ_C 147.0 (C-4′), and δ_C 140.7 (C-5′). A methylenedioxy signal [δ_H 5.79 and δ_H 5.75] correlated to C-4′, C-5′ indicated fused at C-4′ and C-5′, a methoxyl at δ_H 3.95 (2′-OCH_3) correlated to C-2′. A methoxyl signal at δ_H 3.30 (9′-OCH_3) correlated to δ_C 76.2 (C-9′). Two signals of an aromatic, a methylenedioxy, two methoxyls are the signal of a melicodin A moiety. A methine at δ_H 4.82 (H-7′) correlated to δ_C 149.3 (C-10b), δ_C 124.9 (C-4a), δ_C 119.2 (C-1′), δ_C 108.5 (C-6′), C-8′, and C-9′. A methine signal at δ_H 3.19 (H-8′) correlated to C-3, δ_C 115.6 (C-4), C-10b, C-1′, δ_C 34.7 (C-7′), and C-9′. The correlation of three methines [(δ_H 4.82 (H-7′), δ_H 3.19 (H-8′), and δ_H 6.97 (H-4)], indicating the structure of **2** are Diels–Alder adduct. The NOE spectrum, the proton signal at H-3′ correlated with H-8′ and 2′-OCH_3 exhibited that the proton signal at H-7′ and H-8′ revealed *trans* orientation, and the relative configuration of **2** was similar to melicodenine H (Nakashima et al. 2012). The structure of melicodenine K (**2**) is shown in the Fig. 1.

Melicodenine L (**3**) was obtained as a yellowish oil, showing an ion peak $[M+H]^+$ at *m/z* 448.1752, conforms for a molecular composition $C_{26}H_{25}NO_6$ through HRESIMS spectra. The UV (λ_{max} 226, 246, 259, 265, 309 nm), IR (1636, 1600, 1552, and 1119), and

NMR (^{1}H and ^{13}C) of **3** had very identical with **2**. The significant difference in the 1D and 2D NMR, compound **3** showed an acetyl group at δ_H 2.45 (H-1), δ_C 25.8 (C-1), and δ_C 198.2 (C-2). The HMBC and HMQC experiments assigned the acetyl group at C-1 and C-2. The methyl proton at δ_H 2.45 correlated with a carbonyl [δ_C 198.2 (C-2)] in the HMBC spectrum. A signal of α,β-unsaturated ketone at δ_H 8.09 (H-4) correlated to C-2, δ_C 146.2 (C-10b), δ_C 135.9 (C-3), δ_C 160.2 (C-5), and δ_C 37.3 (C-8′). The NOE spectrum of **3**, showing the relative configurations very similar to melicodenine K. Therefore, the structure of melicodenine L (**3**) in Fig. 1. In conclusion, melicodenine L (**3**) is demethylation and is followed by an oxidation reaction of **2**.

Six known compounds, melicodenine E (**4**), F (**5**), melicobisquinolinone B (**6**), N-methylflindersin (**7**), melicodin A (**8**), and bergapten (**9**), elucidating by comparing their NMR spectra based on the chemical shift that reported (Johns et al. 1968; Kamperdick et al., 1999; Nakashima et al. 2012; 2011).

In vitro evaluation against MCF-7, HeLa, and P-388 for their activities in accord with the MTT method (Table 1) uses artonin E and doxorubicin as a positive control. The cells without active compound as a negative control (Tanjung et al. 2018, Tjahjandarie et al. 2021). Melicodenines J (**1**) and F (**5**) exhibited very high activity against HeLa. A type Diels-Alder adduct (**2**, **3**, **6**), a type monomer, was inactive (**7-9**). However, compounds **1-9** were inactive on MCF-7 and P-388 cancer cells (Table 1). A type [2 + 2] cycloaddition adduct (**1**, **4**, **5**) plays a key role for the cytotoxic effect. The effect of the bond angle of the cyclobutane ring more than active the cyclohexene ring inhibiting the growth of HeLa cells.

Experimental

3.1. Plant material

The collecting of the fresh leaves of *M. denhamii* came from Tanah Merah, Bangkalan, Madura Island, East Java, Indonesia, in Feb 2016. The plant was identified by a senior botanist (I. Rachman) from the Bogoriense Herbarium, Indonesia. A specimen (MD 20171207) was deposited as a reference.

3.2. Extraction and isolation

The dried leaves of *M. denhamii* (3.1 kg), extracted with MeOH two times (10 L, each for three days) at room temperature, and the MeOH extract (100 g) treated with 5% aqueous H_2SO_4 (pH 3-4) and then partitioned with *n*-hexane (18 g), and EtOAc (15 g), respectively. The acid layer was treated with NH_4OH (pH 8-9) and extracted with EtOAc to give alkaloid extract (1 g). The alkaloid extract (4.8 g), fractionated by radial planar chromatography on silica gel, using a gradient of n-hexane-EtOAc (from 9:1 to 1:1 v/v) to afford two significant fractions, A (188 mg) and B (450 mg). Purification of fraction A by radial planar chromatography, eluted with n-hexane-acetone (from 9:1 to 4:1 v/v), gave compound **7** (88 mg). Fraction B (450 mg), further separated by CC chromatography on Sephadex LH-20, eluted with methanol, gave two subfractions, B_1 (253 mg) and B_2 (75 mg). Subfraction B_1 separated with radial planar chromatography, eluted with *n*-hexane-EtOAc (from 9:1 to 7:3 v/v), gave compounds **1** (9.8 mg), **6** (25 mg), and **2** (6.2 mg). Similarly, subfraction B_2 separated by the same method, eluted with *n*-hexane-$CHCl_3$ (from 7:3 to 3:7 v/v), afforded compound **3** (4.8 mg), compound **4** (5 mg), and compound **5** (6 mg). The EtOAc extract (14 g), fractionated by VLC on silica gel, using a gradient of *n*-hexane-EtOAc (from 9:1 to 3:7 v/v), gave four significant fractions, C-F. Fraction C (800 mg) further separated by radial planar chromatography on silica gel, eluted with *n*-hexane-$CHCl_3$ (4:1 to 1:1 v/v), afforded compound **8** (27 mg). Fraction E (205 mg) by the same method, eluted with *n*-hexane-diisopropyl ether (7:3 to 3:7 v/v), afforded compound **9** (16 mg).

3.4. Spectral Data

Melicodenine J (**1**): yellow solid, m.p. 224-225° C, $[\alpha]^{20}_D$ = + 6° (*c* 0.0005, MeOH): UV (MeOH) λ_{max} (log ε) 219 (4.48), 259 (3.83), 292 (3.83), 320 (4.06), and 334 nm (4.03). IR (KBr) γ_{max} (cm^{-1}) 1627, 1595, 1461, and 1128. ^{1}H-NMR ($CDCl_3$, 4100 MHz), δ_H ppm: 7.90 (1H, *dd*, *J* = 8.0, 1.2 Hz, H-10), 7.85 (1H, *d*, *J* = 9.6 Hz, H-5′), 7.43 (1H, *dt*, *J* = 8.5, 1.2 Hz, H-8), 7.15 (1H, *t*, *J* = 8.0 Hz, H-9), 7.08 (1H, *d*, *J* = 8.5 Hz, H-7), 5.95 (1H, *d*, *J* = 9.6 Hz, H-6′), 5.94 (1H, *s*, H-9′), 5.41 (1H, *dd*, *J* = 6.7, 2.6 Hz, H-2′), 4.75 (1H, *t*, *J* = 6.7 Hz, H-3′), 4.25 (3H, *s*, 4′-OCH_3), 4.08 (1H, *t*, *J* = 9.5 Hz, H-4), 3.38 (3H, *s*, N-CH_3), 3.10 (1H, *dd*, *J* = 9.5, 6.7 Hz, H-3), 1.73 (3H, *s*, H-11), 1.20 (3H, *s*, H-12). ^{13}C-NMR ($CDCl_3$,

100 MHz), δ_C ppm: 168.6 (C-9a′), 162.2 (C-5), 161.8 (C-7′), 156.6 (C-10b), 156.5 (C-8a′), 152.6 (C-4′), 139.5 (C-5′), 138.5 (C-6a), 130.7 (C-8), 123.1 (C-10), 121.6 (C-9), 116.2 (C-10a), 113.5 (C-7), 109.5 (C-6′), 107.3 (C-4a′), 105.2 (C-4a), 104.4 (C-3a′), 90.5 (C-9′), 85.1 (C-2′), 75.5 (C-2), 45.0 (C-3), 43.2 (C-3′), 35.5 (C-4), 29.0 (6-NCH_3), 25.5 (C-11), 25.4 (C-12). HRESIMS *m/z* 458.1613 $[M+H]^+$ calculated for $C_{27}H_{23}NO_6$ *m/z* 458.1604.

Melicodenine K (**2**): colorless oil, $[\alpha]^{20}_D = +8^o$ (*c* 0.0005, MeOH): UV (MeOH) λ_{max} (log ε) 229 (3.99), 259 (3.60), 308 (3.51), 325 (3.46), 359 (3.56) and 377 nm (4.41). IR (KBr) γ_{max} (cm^{-1}) 1639, 1502, 1485, and 1112. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ_H ppm: 7.52 (1H, *dd*, *J* = 8.6, 1.2, H-10), 7.46 (1H, *t*, *J* = 7.7Hz, H-8), 7.35 (1H, *d*, *J* = 8.6 Hz, H-7), 7,15 (1H, *t*, *J* = 7.7 Hz, H-9), 6.97 (1H, *s*, H-4), 6.57 (1H, *s*, H-3′), 6.13 (1H, *s*, H-6′), 5.79 and 5.75 (2H, *d*, *J* = 1.2 Hz, 4′-O-CH_2-O-5′), 4.82 (1H, *s*, H-7′), 3.95 (3H, *s*, 2′-OCH_3), 3.80 (3H, *s*, N-CH_3), 3.51 (1H, *dd*, *J* = 8.3, 6.0 Hz, H-9′a), 3.38 (1H, *t*, *J* = 9.8 Hz, H-9′b), 3.30 (3H, *s*, 9′-OCH_3), 3.19 (1H, *dd*, *J* = 9.8, 6.0 Hz, H-8′), 1.49 (3H, *s*, H-11), 0.88 (3H, *s*, H-12). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ_C ppm: 160.6 (C-5), 150.8 (C-2′), 149.3 (C-10b), 147.0 (C-4′), 140.7 (C-5′), 139.7 (C-3), 139.3 (C-6a), 129.8 (C-8), 124.9 (C-4a/C-10), 122.5 (C-9), 120.2 (C-10a), 119.2 (C-1′), 115.6 (C-4), 114.5 (C-7), 108.5 (C-6′), 101.1 (4′-O-CH_2-O-5′), 94.4 (C-3′), 76.2 (C-9′), 71.6 (C-2), 59.0 (9′-OCH_3), 56.6 (2′-OCH_3), 39.1 (C-8′), 34.7 (C-7′), 30.0 (C-11), 29.9 (6-NCH_3), 29.2 (C-12), HRESIMS *m/z* 464.2080 $[M+H]^+$ calculated for $C_{27}H_{30}NO_6$ *m/z* 464.2073.

Melicodenine K (**3**): yellowish oil, $[\alpha]^{20}_D = -8^o$ (*c* 0.0005, MeOH): UV (MeOH) λ_{max} (log ε) 226 (4.38), 246 (4.20), 259 (4.07), 265 (3.65), and 309 nm (3.96). IR (KBr) γ_{max} (cm^{-1}) 1636, 1600, 1552, and 1119. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ_H ppm: 8.09 (1H, *s*, H-4), 7.68 (1H, *d*, *J* = 8.1 Hz, H-10), 7.52 (1H, *t*, *J* = 7.8 Hz, H-8), 7.36 (1H, *d*, *J* = 8.6 Hz, H-7), 7,15 (1H, *t*, *J* = 7.8 Hz, H-9), 6.56 (1H, *s*, H-3′), 6.10 (1H, *s*, H-6′), 5.79 and 5.75 (2H, *s*, 4′-O-CH_2-O-5′), 5.36 (1H, *s*, H-7′), 3.96 (3H, *s*, 2′-OCH_3), 3.81 (3H, *s*, 6-NCH_3), 3.51 (1H, *dd*, *J* = 9.7, 4.4 Hz, H-8′), 3.38 (1H, *t*, *J* = 9.8 Hz, H-9′b), 3.25 (1H, *dd*, *J* = 10.1, 4.4 Hz, H-9′a), 3.16 (1H, *t*, *J* = 10.1 Hz, H-9′b), 2.45 (3H, *s*, H-1). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ_C ppm: 198.2 (C-2), 160.2 (C-5), 150.6 (C-2′), 147.1 (C-4′), 146.2 (C-10b), 140.9 (C-5′), 140.4 (C-6a), 135.9 (C-3), 133.1 (C-4), 131.5 (C-8), 126.3 (C-10), 123.7 (C-4a), 123.0 (C-9), 120.5 (C-1′), 120.0 (C-10a), 114.7 (C-7), 107.8

(C-6′), 101.1 (4′-O-CH_2-O-5′), 95.0 (C-3′), 72.5 (C-9′), 58.2 (9′-OCH_3), 56.7 (2′-OCH_3), 37.3 (C-8′), 33.0 (C-7′), 30.0 (6-NCH_3), 25.8 (C-1). HRESIMS *m/z* 448.1752 $[M+H]^+$ calculated for $C_{26}H_{25}NO_6$ *m/z* 448.1760.

4. Conclusions

In summary, three unreported quinolinone alkaloids: melicodenines J-L (**1-3**), along with six known compounds (**4-9**), were isolated from *Melicope denhamii* leaves. The cytotoxicity activity of compounds (**1-9**) was evaluated against MCF-7, HeLa, and P-388 cells. Compounds **1** and **5** showed high activity against HeLa cells.

Supplementary material

HRESIMS and NMR spectra are available online in the supplementary materials as Fig. S1–S18.

Acknowledgments

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Disclosure statement

No contravention of interest that reveal in the team researcher.

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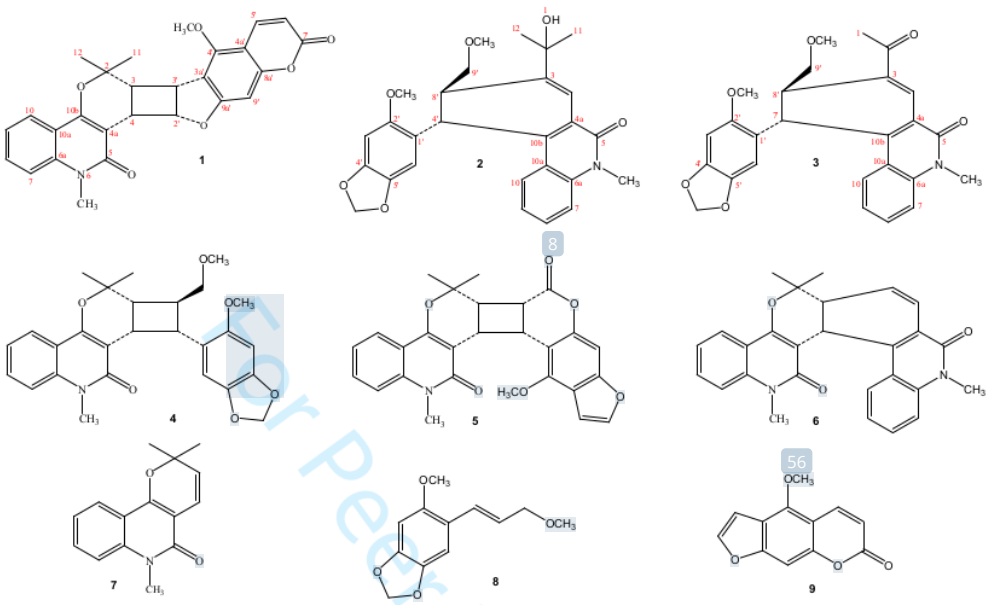

Figure 1: Structures of compounds **1-9** from *M. denhamii*

Table 1. Cytotoxic activities of the isolated compounds from *M. denhamii*

Compounds	μM		
	MCF-7	HeLa	P-388
Melicodenine J (**1**)	> 100	1.8 ± 0.02	> 100
Melicodenine K (**2**)	> 100	62.9 ± 1.45	29.1 ± 1.10
Melicodenine L (**3**)	> 100	40.9 ± 1.13	> 100
Melicodenine E (**4**)	> 100	> 100	11.9 ± 0.87
Melicodenine F (**5**)	> 100	0.8 ± 0.15	38.3 ± 1.42
Melicobisquinolinone B (**6**)	> 100	> 100	13.9 ± 0.65
N-methylflindersin (**7**)	> 100	> 100	87.2 ± 0.30
Melicodin A (**8**)	15.0 ± 0.15	> 100	> 100
Bergapten (**9**)	> 100	> 100	> 100
Doxorubicin	0.8 ± 0.02	0.9 ± 0.04	-
Artonin E	-	-	1.3 ± 0.07

SUPPLEMENTARY INFORMATION

Three novel quinolinone alkaloids from the leaves of *Melicope denhamii*

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Three previously unreported quinolinone alkaloids: melicodenines J-L (**1-3**), and six known compounds (**4-9**) were isolated from the leaves of *Melicope denhamii* (Seem) T.G. Hartley. The chemical structures of **1-3** were identified by combination of HRESIMS, 1D, and 2D NMR spectra. Compounds **1-9** were assayed in three cancer cells (MCF-7, HeLa, and P-388). Compounds **1** and **5** showed high cytotoxic activity against HeLa cells with an IC_{50} value of 1.8 and 0.8 µM, respectively.

Keywords: *Melicope denhamii*, melicodenines J-L, quinolinone adduct, cytotoxic

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3. Experimental

3.1. General experimental procedures

UV spectra measured using a Shimadzu series 1800 UV-VIS spectrophotometer with MeOH. The IR spectra and mass spectra recorded on a spectrum two FT-IR spectrometer in KBr and an ESI-TOF Waters LCT Premier XE, respectively. NMR spectra measured on a JEOL JNM ECA-400 at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ using TMS as the internal standard. Column chromatography and radial chromatography carried out using silica gel 60 and silica gel 60 PF_{254}. Optical rotations determined with a Perkin Elmer Polarimeter Model 341.

3.5. Cytotoxicity assay

The MCF-7, HeLa, and P-388 cancer cell lines were cultured in 96-well at a density of 3 × 10^4 cells/cm^3. The cells were incubated at 37° C for 24 h for growth. The isolates (**1-9**) with different concentrations (100, 30, 10, 3, 1, 0.3, and 0.1 µM) with triplicate were added to each well and incubated at 37° C for 48 h. After incubation, the MTT reagent was added into culture cells and let for four hours. The inhibition of cells by each of compounds **1-9** was recorded with a microplate reader spectrometer at λ 540 nm. IC_{50} values of the compounds **1-9** calculated by regression analysis (Saputri et al. 2018; Tanjung et al. 2021, Tjahjandarie et al. 2020).

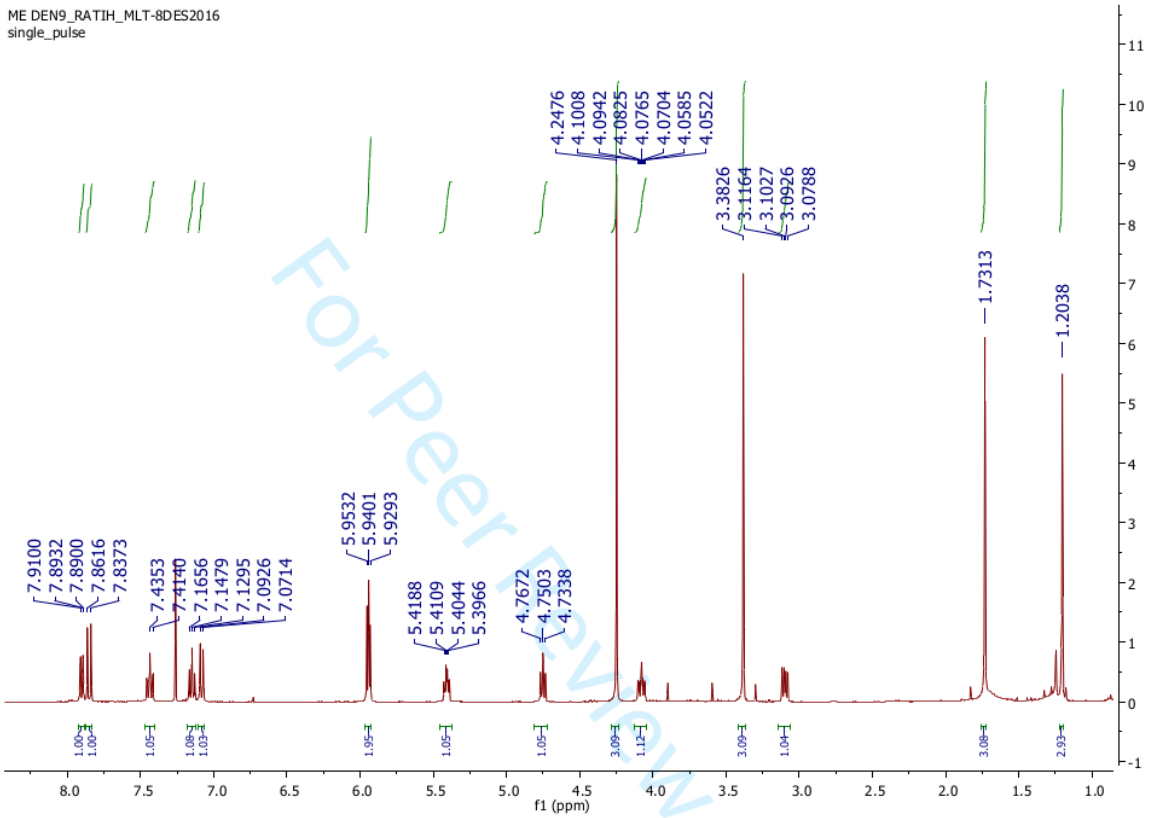

Figure S1. ^{1}H NMR spectrum of melicodenine J (**1**)

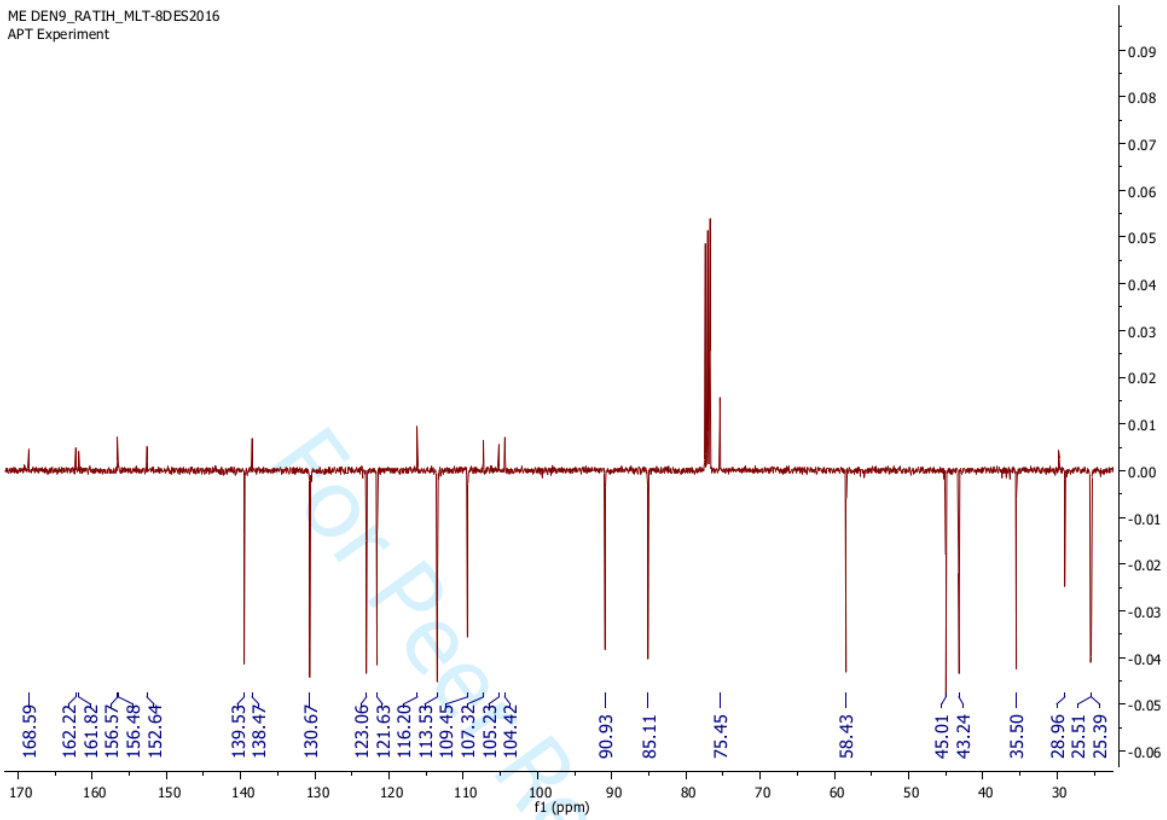

Figure S2. ^{13}C NMR (APT experiment) spectrum of melicodenine J (**1**)

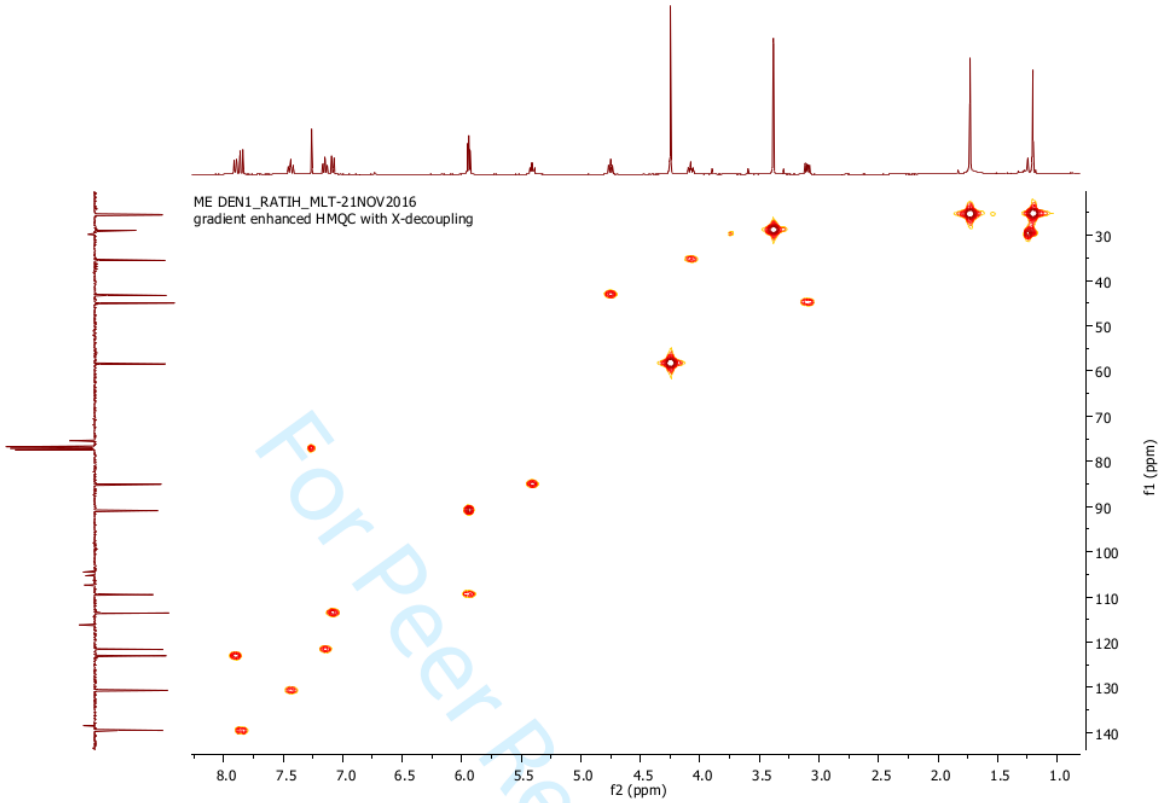

Figure S3. HMQC spectrum of melicodenine J (**1**)

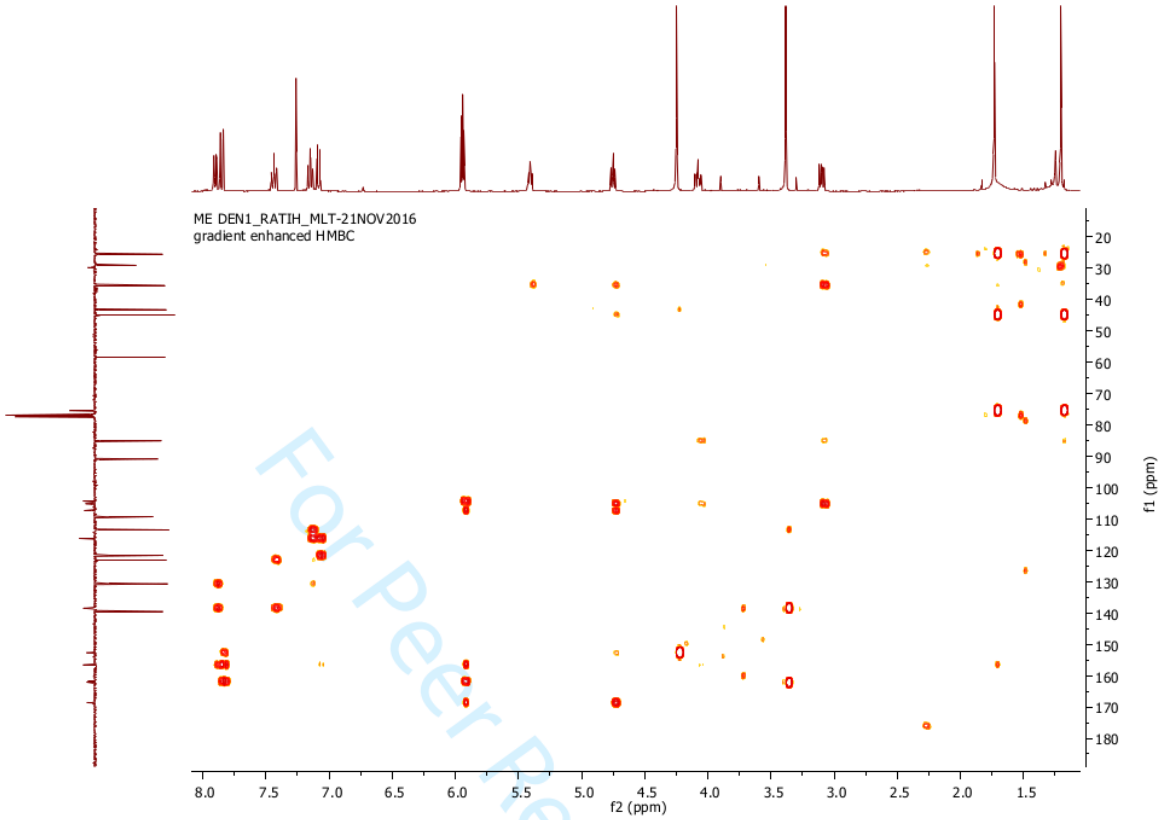

Figure S4. HMBC spectrum of melicodenine J (**1**)

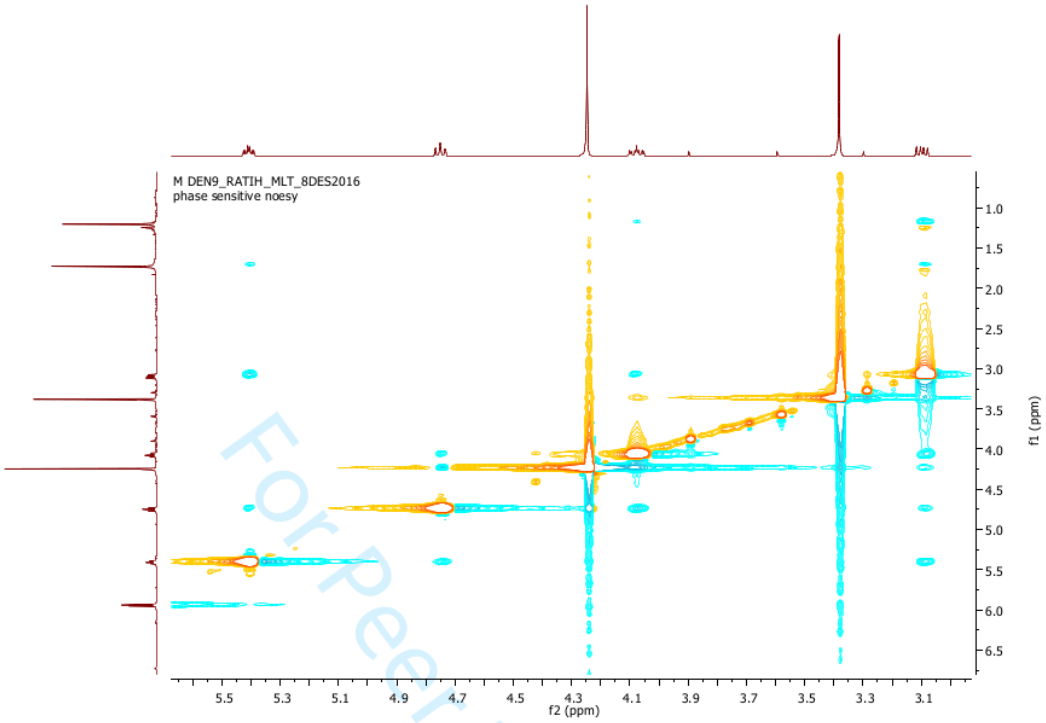

Figure S5. NOESY spectrum of melicodenine J (**1**)

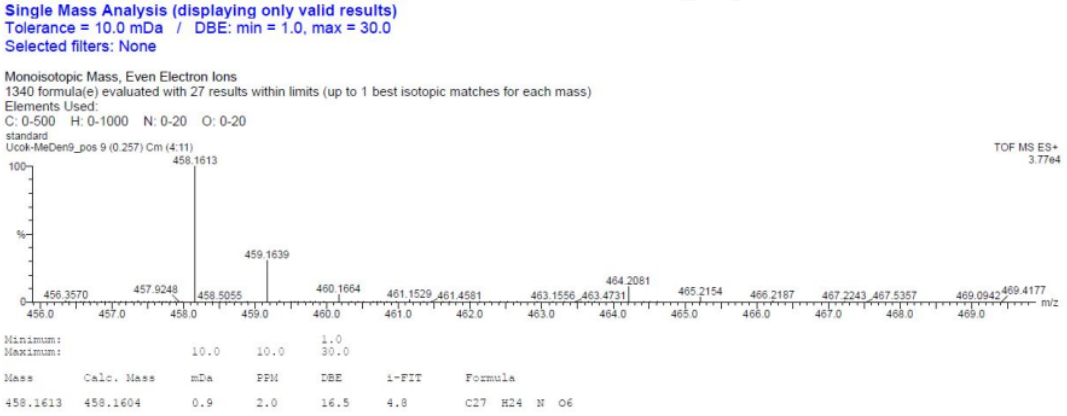

Figure S6. HRESIMS spectrum of melicodenine J (**1**)

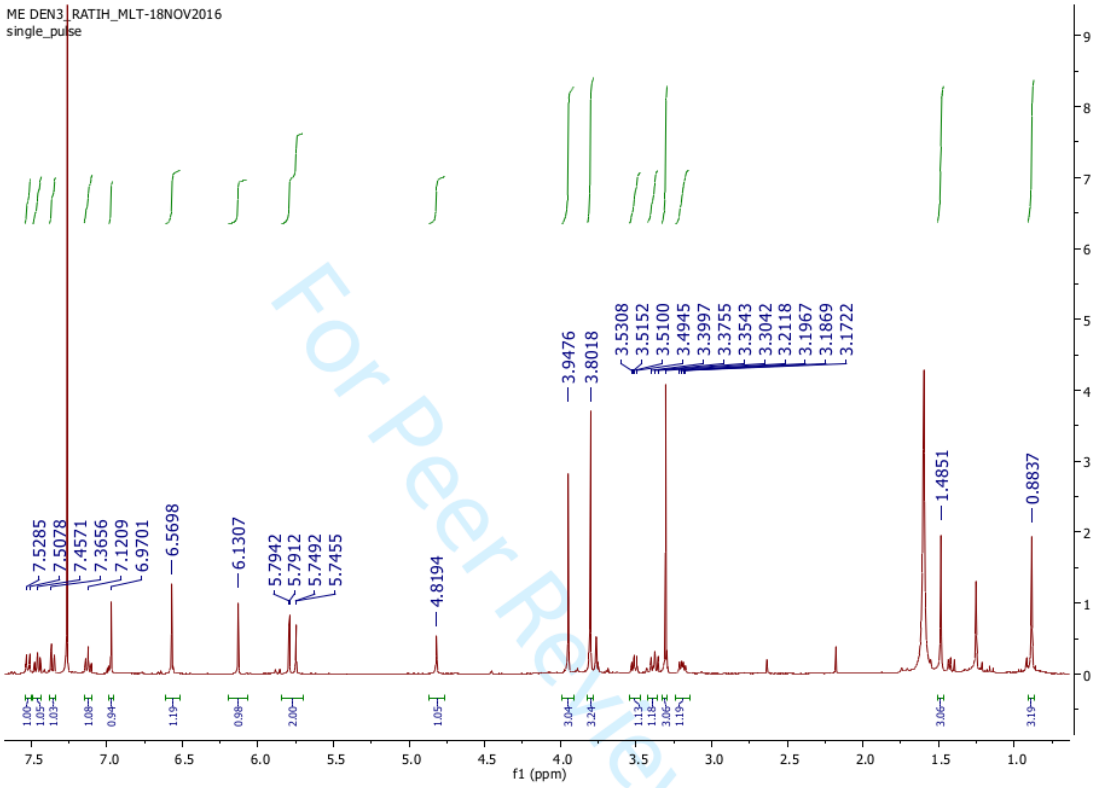

Figure S7. ^{1}H NMR spectrum of melicodenine K (**2**)

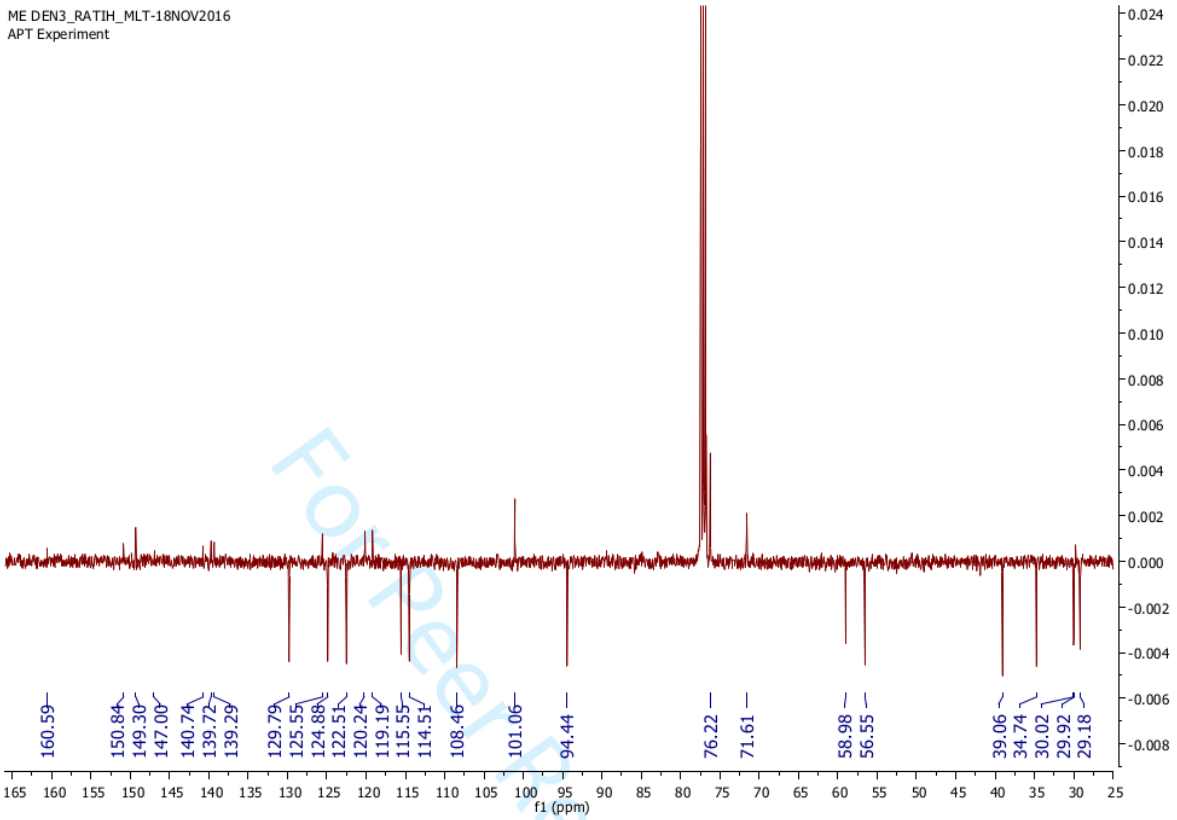

Figure S8. ^{13}C NMR (APT experiment) spectrum of melicodenine K (**2**)

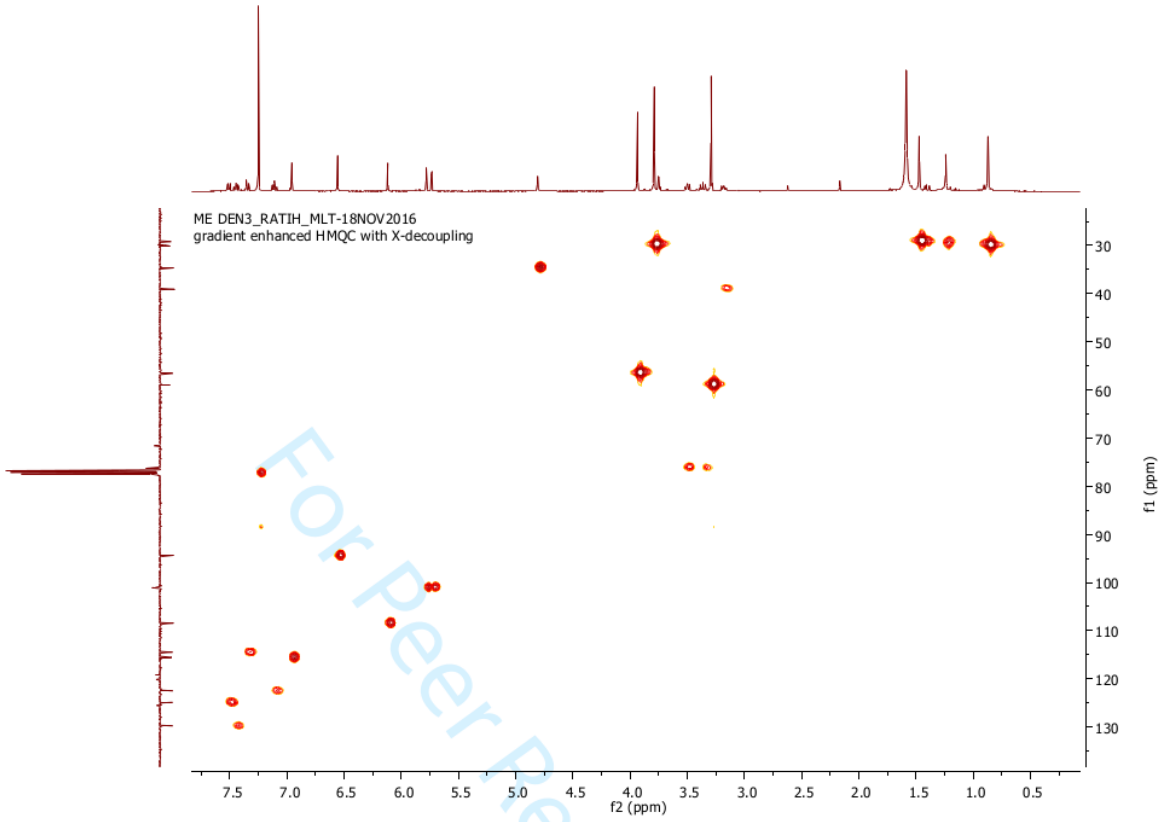

Figure S9. HMQC spectrum of melicodenine K (**2**)

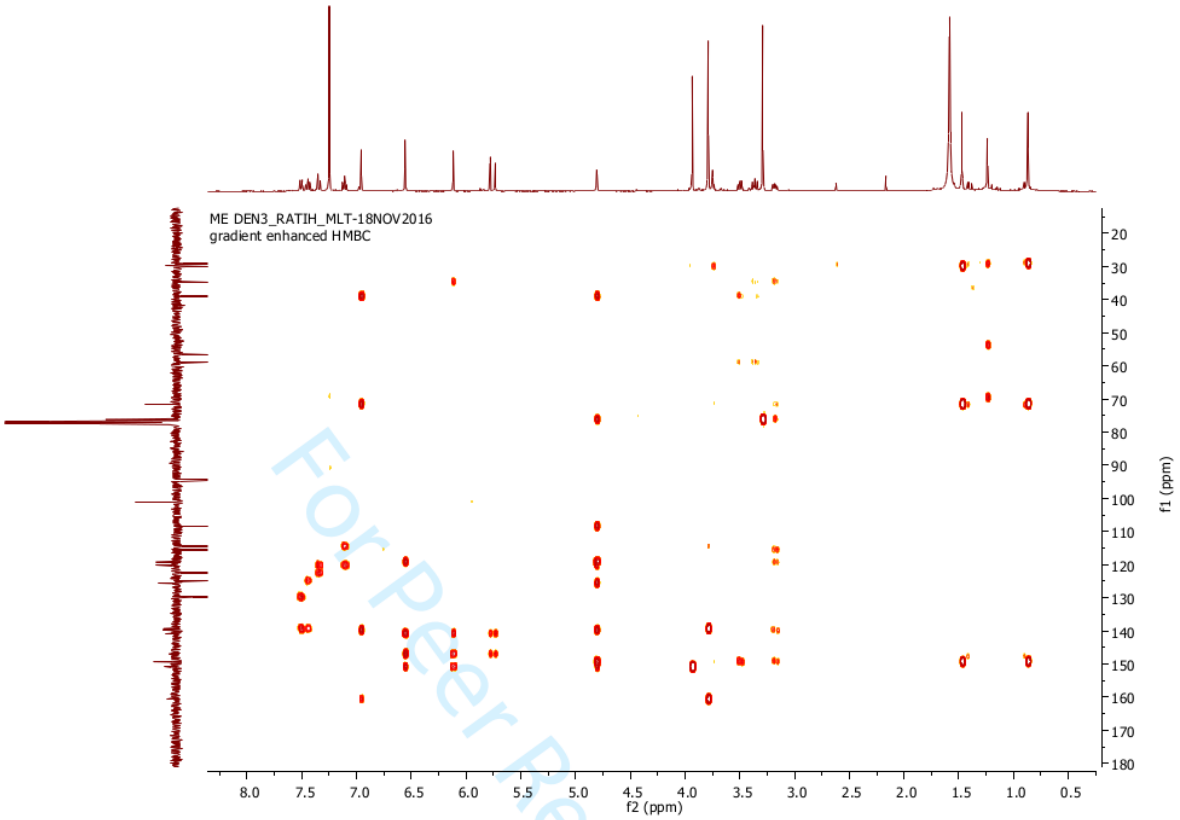

Figure S10. HMBC spectrum of melicodenine K (**2**)

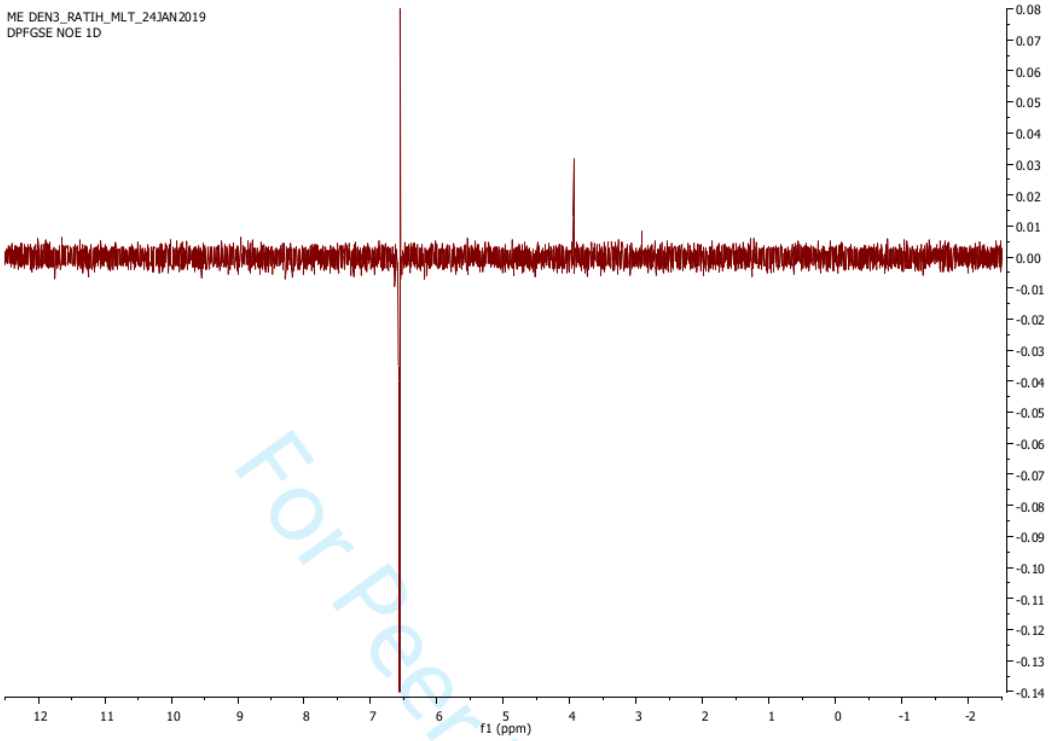

Figure S11. NOE spectrum of melicodenine K (**2**)

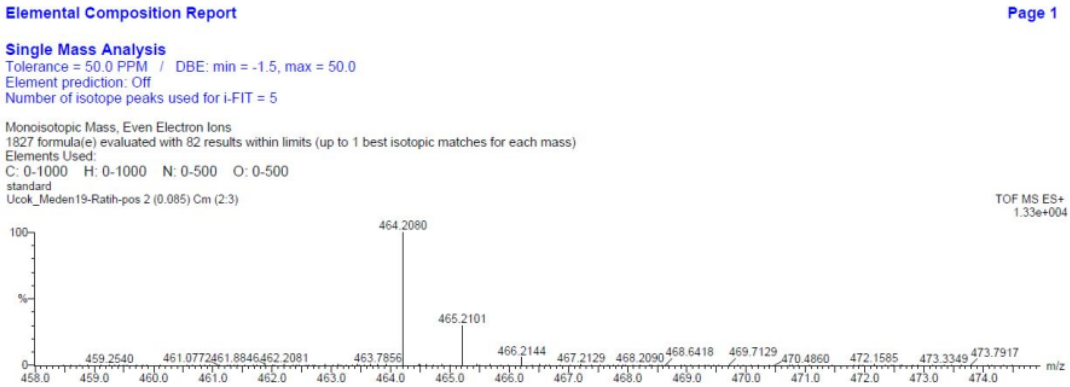

Figure S12. HRESIMS spectrum of melicodenine K (**2**)

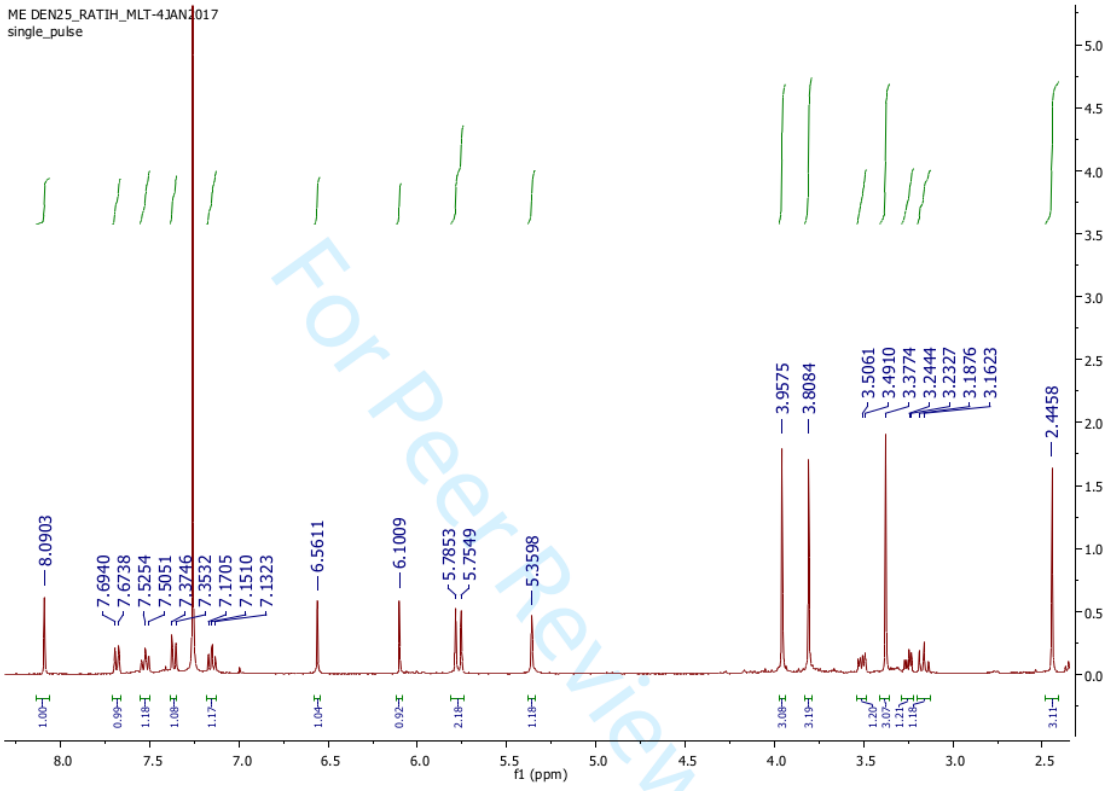

Figure S13. ^{1}H NMR spectrum of melicodenine L (**3**)

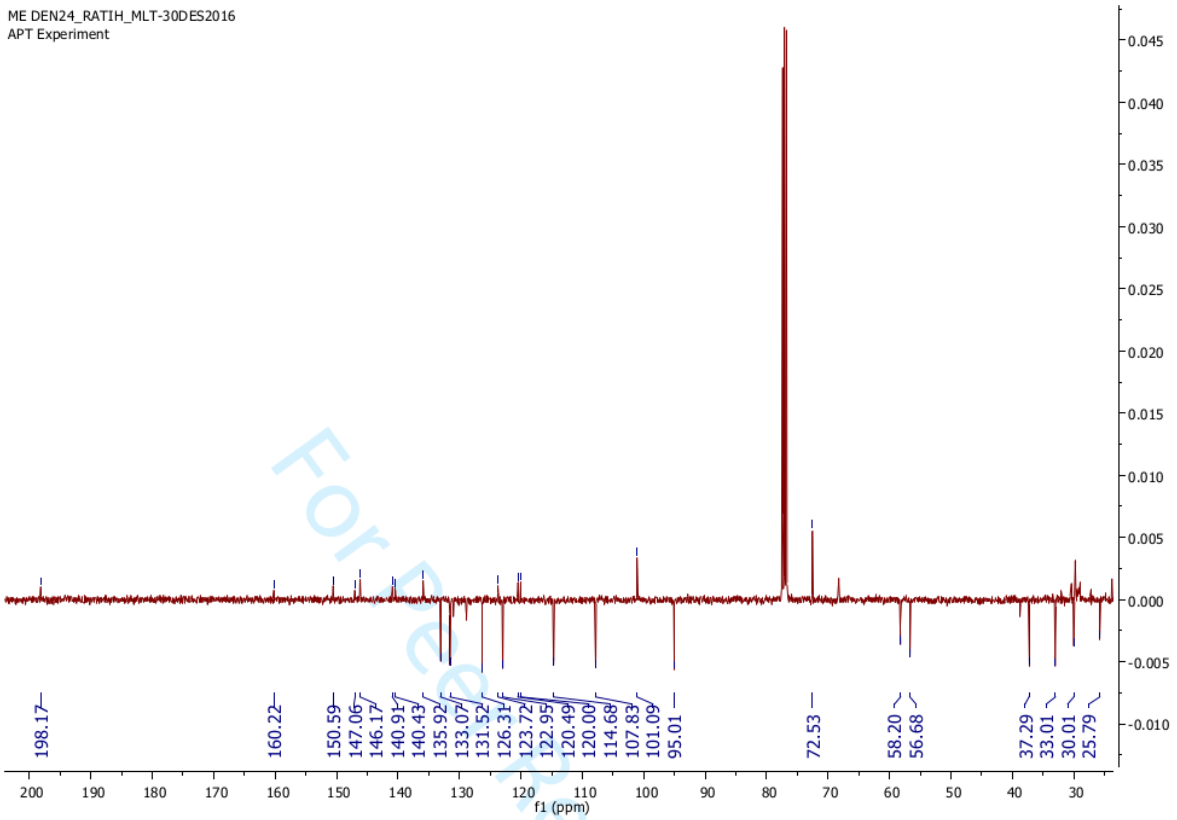

Figure S14. ^{13}C NMR (APT experiment) spectrum of melicodenine L (**3**)

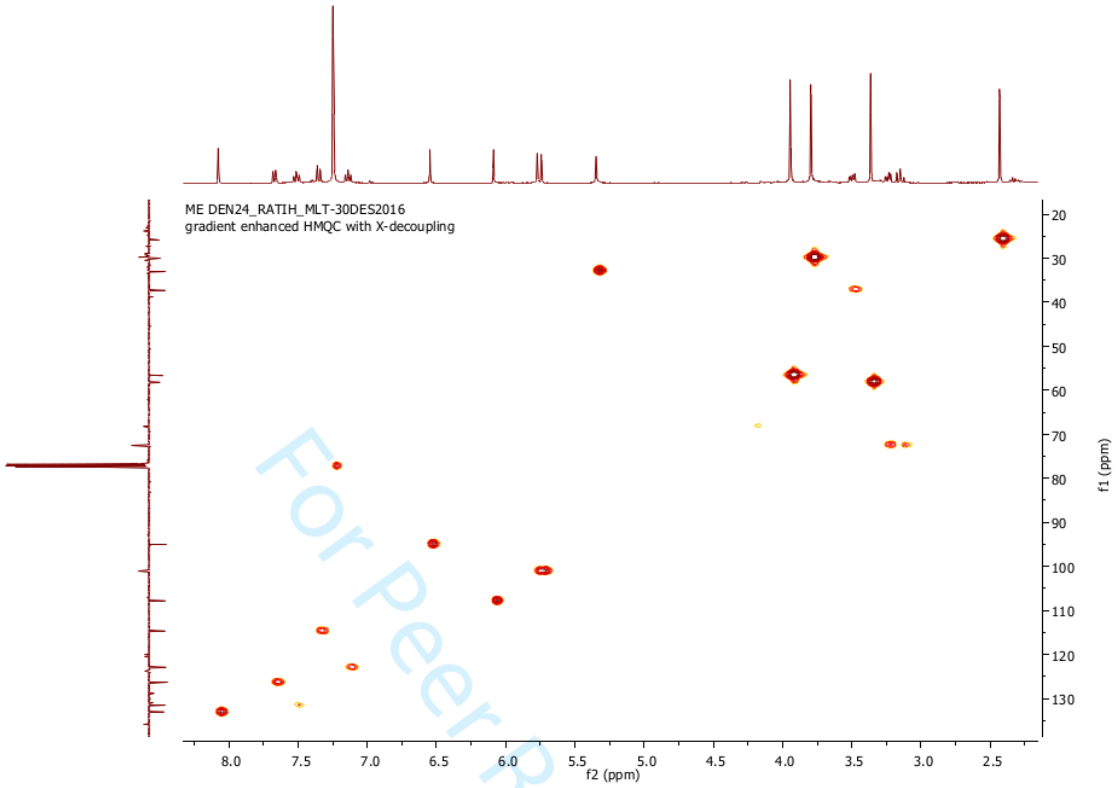

Figure S15. HMQC spectrum of melicodenine L (**3**)

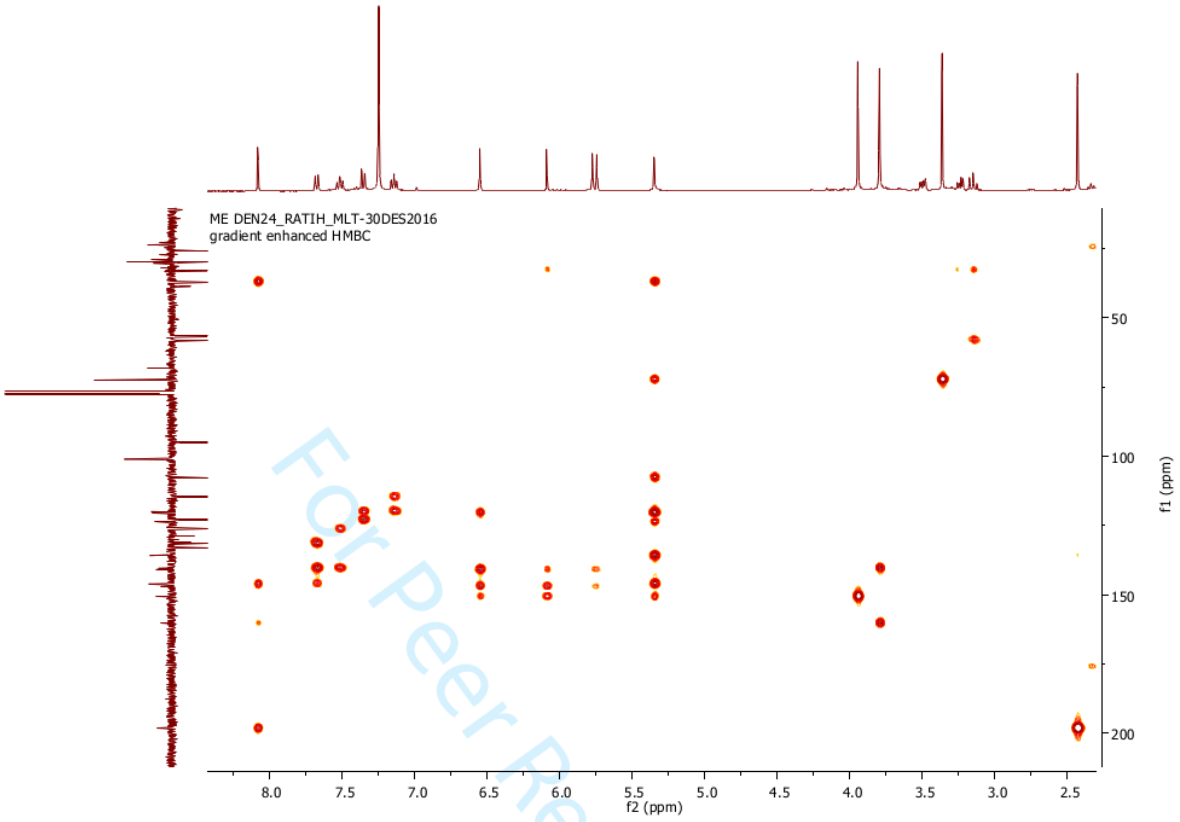

Figure S16. HMBC spectrum of melicodenine L (**3**)

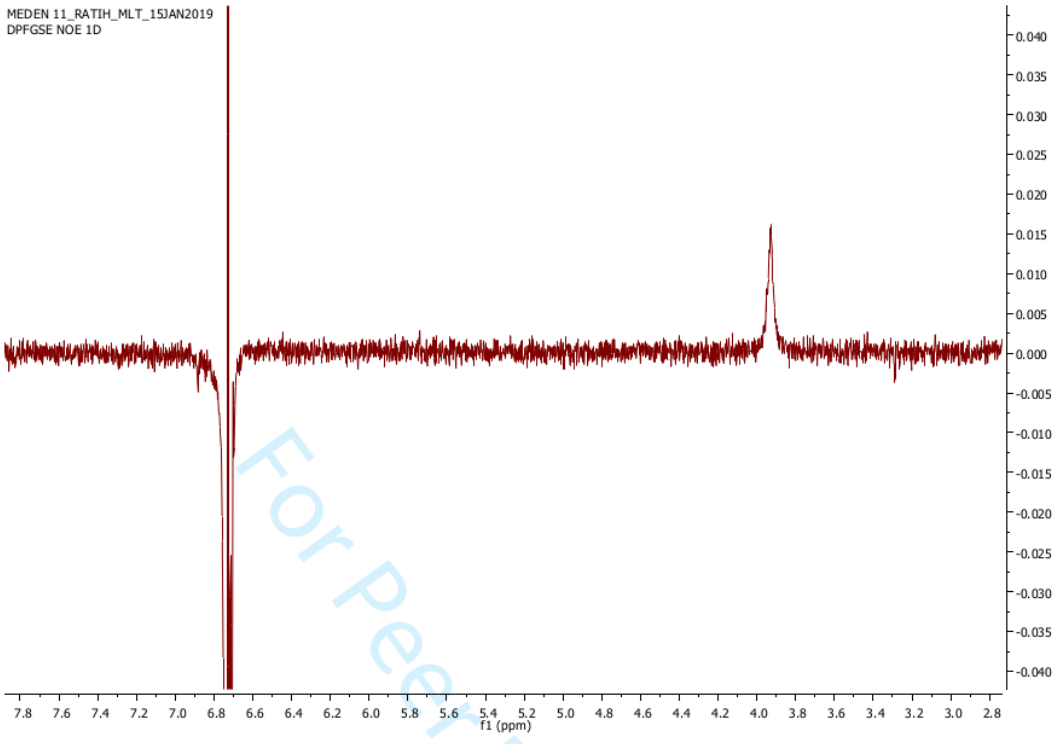

Figure S17. NOE spectrum of melicodenine L (**3**)

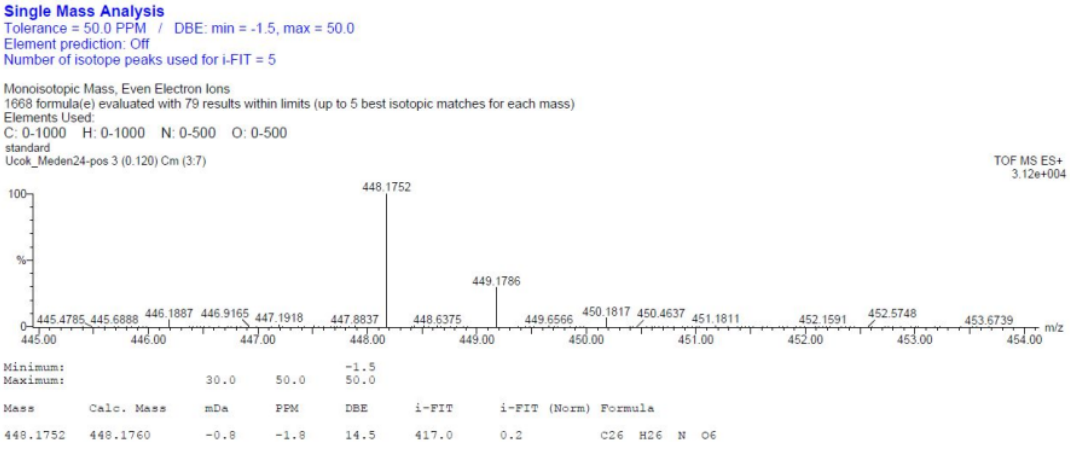

Figure S18. HRESIMS spectrum of melicodenine L (**3**)

REVISION GNPL-2021-1069 R2

Thank you for the comments and suggestions. We have revised the manuscript to make it more concise and made some revisions in term of the English issues according to your valuable suggestion. The spot-to-spot response is following.

No	Editorial Office:	RESPONS
1	Table 1 should be moved in supplementary material.	Thanks for your suggestion. Table 1 was moved in supplementary material.

No	REVIEWER 1	RESPONS
1	The manuscript needs extensive english revision.	Thanks for your suggestion. The sentence has been revised to be clearly.

No	REVIEWER 2	RESPONS
1	Whether the peak shape of compound 1 H-3' ; H-4 and compound 2 H-8 is correct in spectral data	Thanks for your suggestion. The peak shape of compound **1** was changed H-4: δ_H 4.08 (1H, *t*, *J* = 9.5 Hz, H-4), H-3': δ_H 4.75 (1H, *t*, *J* = 6.7 Hz, H-3′) The peak shape of compound **2** was changed H-8: δ_H 7.46 (1H, *t*, *J* = 7.7Hz, H-8)
2	It is recommended that table and the title of the table in the article be centered	Thanks for your suggestion. **Table 1.** Cytotoxic activities of the isolated compounds from *M. denhamii*
3	P4 L29 Whether the chemical shift values marked in front of the carbon can be unified before and after.	The sentence has been revised to be clearly. A signal at δ_H 4.75 (H-3′) correlated to C-3a′, C-4a′, C-4′, and C-9a′ (a part of bergapten), C-3, and C-4 (a part of N-methylflindersin).
4	P6 L13 Statement components lack predicates, please check .	The sentence has been revised to be clearly. The NOE spectrum of **3**, showing the relative configurations very similar to melicodenine K.
5	P15 L8 Suspected grammatical error, please check	The sentence has been revised to be clearly. After incubation, the MTT reagent was added into culture cells and let for four hours
6	Whether the results and discussion can be put later.	The format of result and discussion in the Natural Product Research written then introduction .
7	Lack of negative control in vitro activity test. If a negative control is	Thanks for your suggestion. *In vitro* evaluation against MCF-7, HeLa,

	missing, please add it	and P-388 for their activities in accord with the MTT method (Table 1) uses artonin E and doxorubicin as a positive control. The cells without active compound as a negative control (Tanjung et al. 2018, Tjahjandarie et al. 2021).
8	In the conclusion of the in vitro activity experiment, the inhibitory activities of the nine compounds against the three cancer cells were not clearly expressed, and whether they could be expressed in detail	Thanks for your suggestion. *In vitro* evaluation against MCF-7, HeLa, and P-388 for their activities in accord with the MTT method (Table 1) uses artonin E and doxorubicin as a positive control. The cells without active compound as a negative control (Tanjung et al. 2018, Tjahjandarie et al. 2021). Melicodenines J (**1**) and F (**5**) exhibited very high activity against HeLa. A type Diels-Alder adduct (**2**, **3**, **6**), a type monomer, was inactive (**7-9**). However, compounds **1-9** were inactive on MCF-7 and P-388 cancer cells (Table 1). A type [2 + 2] cycloaddition adduct (**1**, **4**, **5**) plays a key role for the cytotoxic effect. The effect of the bond angle of the cyclobutane ring more than active the cyclohexene ring inhibiting the growth of HeLa cells.
9	In the fourth conclusion part of the paper, WiDr cancer cells appeared, which was inconsistent with P-388 cells in other relevant contents of the paper. Please check	The sentence has been revised to be clearly. In summary, three unreported quinolinone alkaloids: melicodenines J-L (**1-3**), along with six known compounds (**4-9**), were isolated from *Melicope denhamii* leaves. The cytotoxicity activity of compounds (**1-9**) was evaluated against MCF-7, HeLa, and P-388 cells. Compounds **1** and **5** showed high activity against HeLa cells.

Three novel quinolinone alkaloids from the leaves of Melicope denhamii

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