ISSN 2462-2052 | eISSN 2600-8718 *Journal of Science and Mathematics Letters*
DOI: https://doi.org/10.37134/jsml.vol12.1.5.2024 *Volume 12, Issue 1, 34-42, 2024*

Research Article

Semi-synthesis of *N*-substituted Mahanimbine *via* Alkylation

Nurliana Mohd Yunos[1], Siti Mariam Mohd Nor[1]* and Mohd Azlan Nafiah[2]

[1]Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[2]Department of Chemistry, Faculty of Science and Mathematics, Universiti Pendidikan Sultan Idris, 35900 Tanjong Malim, Perak, Malaysia
*Corresponding author: smariam@upm.edu.my

Received: 6 September 2023; **Accepted:** 19 November 2023; **Published:** 5 January 2024

ABSTRACT

Mahanimbine, a prenylated carbazole found primarily in the Rutaceae family, has remarkable biological features such as anticancer, antidiabetic and antioxidant. Therefore, it is intriguing to tweak the mahanimbine structure with the aim of adding extra value to their activity. Three new derivatives were semi-synthesised by *N*-alkylation of naturally isolated mahanimbine using alkyl bromides, yielding *N*-butylmahanimbine, *N*-(3-methylbutyl) mahanimbine, and *N*-benzylmahanimbine. The structures of *N*-alkylated mahanimbines were elucidated using different spectroscopic techniques (FTIR, GCMS, and NMR).

Keywords: mahanimbine, alkylation, *N*-terminal, derivative, *Murraya*

1. INTRODUCTION

Prenylated pyranocarbazoles are naturally occurring compounds with valuable pharmacophores found in a wide range of biologically active chemicals. The Rutaceae family has yielded numerous compounds in this class. Some isolated prenylated pyranocarbazoles are mahanine from *Micromelum minutum* leaves (Nakahara et al., 2002), pyrayafoline D from *Murraya koenigii* leaves (Ito et al., 2006), murrayamine J from *M. Koenigii* barks (Tan et al., 2014), dimeric bisisomahanine from *Glycosmis stenocarpa* roots (Cuong et al., 2004), and microphyldine E from *M. microphylla* leaves (Ma et al., 2021).

Among the various prenylated pyranocarbazoles discovered in *M. koenigii* (Sim and Teh, 2011), mahanimbine (**1**) is the most frequent isolated together with girinimbine. In addition, mahanimbine (**1**) is also found in *M. euchrestifolia* (Ma et al., 2021), *M. paniculate* (Bhati'acharyya et al., 1978), *M. euchrestifolia* (Wu et al., 1996), *M. siamensis* (Meragelman et al., 2000), *Clausena cambodiana* (Sakunpak et al., 2021), and *C. excavata* (Ito et al., 1997). Mahanimbine (**1**) has been shown to have anticancer (Pei et al., 2018; Mondal et al., 2022; Hobani, 2022; Xie et al., 2020), antiobesity (Birari et al., 2010), antifungal (Chowdhury et al., 2001), antidiabetic (Dineshkumar et al., 2010), antimicrobial (Ramsewak et al., 1999), antioxidant (Rao et al., 2006; Rou et al., 2018), antianxiety (Dahiya et al., 2016), antiaging (Mani et al., 2021), and larvicidal (Sukari et al., 2013) activities. This compound **1** is also known to inhibit acetylcholinesterase. The structure of mahanimbine (**1**) has previously been modified through intramolecular cyclisation (Tan and Nafiah, 2021; Chakraborty, 2020; Yedukondalu et

al., 2017), epoxidation (Chakraborty, 2020), and nitration (Chakraborty, 2018) reaction on its prenyl side chain. On the *N*-terminal of mahanimbine (**1**), short-chain alkylation (Joshi et al., 1970) and formylation (Yedukondalu et al., 2016) reactions have also been documented (Figure 1).

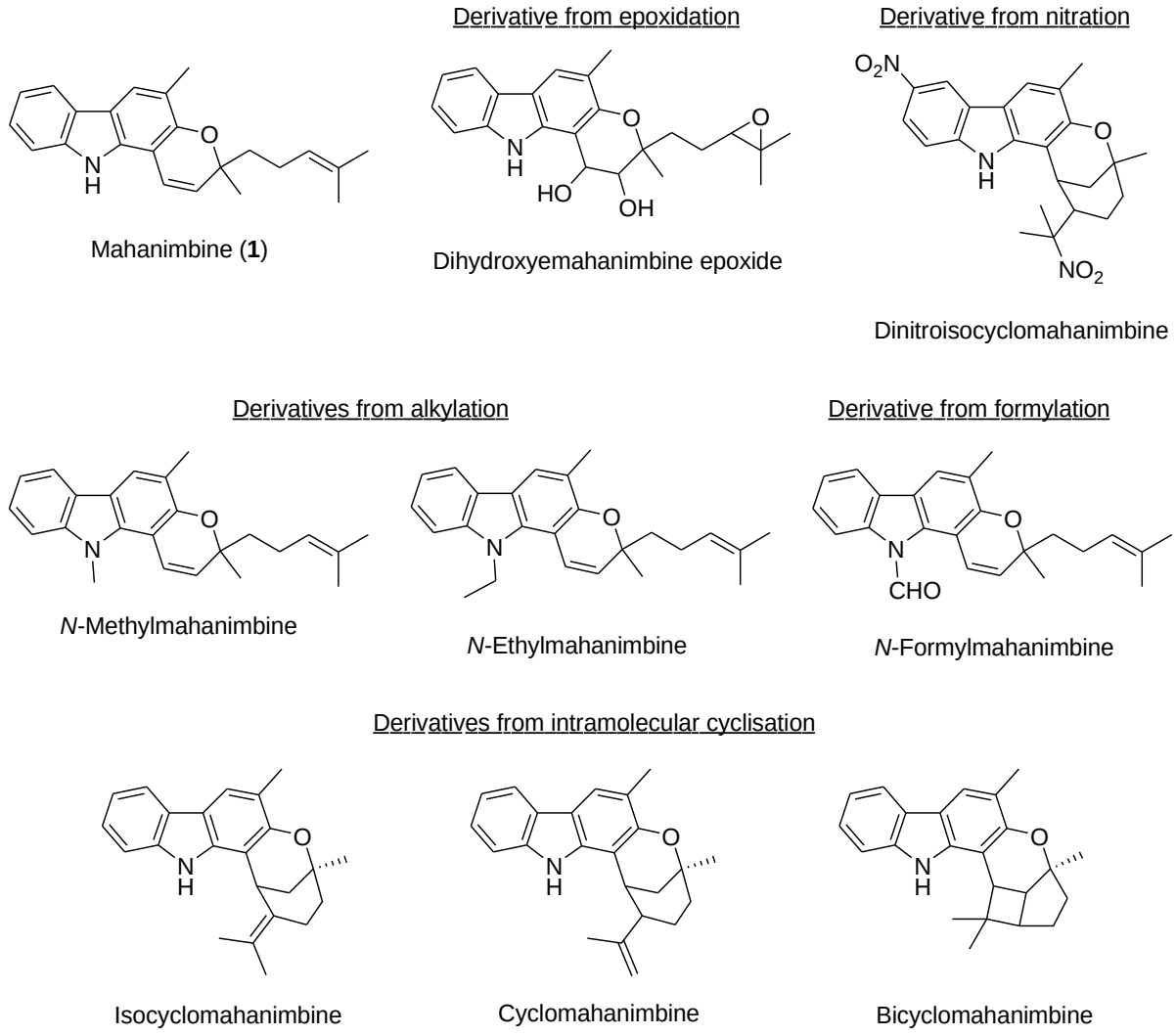


Figure 1. Derivatives of mahanimbine (**1**)

Several research have been conducted to provide reliable evidence of mahanimbine's biological characteristics. Despite this, there has been no update on the clinical trial until recently. However, the specific treatment and side effects, if any, should be investigated further. Future research will also help to improve mahanimbine solubility and absorption, as well as delivery techniques. In view of the biological features of mahanimbine (**1**), it was believed useful to modify its structure with the aim of producing a variety of derivatives that may enhance the property or be accountable for the activity for drug development. Therefore, the goal of this research was to synthesise an *N*-alkylated derivative of mahanimbines, which have a somewhat longer aliphatic carbon chain and an aromatic ring. Alkyl and benzyl substituents have been proven to enhance the biological activities of the derivatives (Bashir et al., 2015; Liu et al., 2021). It was also proven by the cytotoxic of girinimbine and its *N*-alkylkated girinimbines (Osman et al., 2021).

2. MATERIALS AND METHODS

2.1. General

All chemicals and solvents were acquired from commercial providers and used as received. Thin-layer chromatography (silica gel 60 F245 (Merck KGaA) precoated aluminium-backed plates) was used to monitor all reactions, which were subsequently visualised under ultraviolet light (UV Lamp UVGL-58) and dipped in $KMnO_4$ solution. The solvents were removed under vacuum by an EYELA rotary evaporator N-100 or a Buchi rotavapor R-215. The organic phases were dried under Na_2SO_4 and filtered. The stationary phase employed in column chromatography was silica gel 60 (100-150 mesh, 0.040-0.063 mm). The melting point was measured using Electrothermal IA9000 Series, and the measurement was repeated at least three times. The IR spectra were acquired using UATR methods on a Perkin-Elmer FT-IR Model Spectrum 100 series spectrophotometer. The MS spectra were collected using a Shimadzu QP5050A spectrometer. 1D and 2D NMR spectra were recorded with on JEOL FT-NMR 500 MHz spectrophotometer using $CDCl_3$. The chemical shifts (δ) were recorded in ppm described with an appropriate abbreviation for multiplicities as s (singlet), d (doublet), t (triplet), m (multiplet), and br. (broad), whereas the coupling constants *J* are given in Hz.

2.2. Mahanimbine

Isolated mahanimbine (**1**) of Malaysian dried bark of *M. koenigii* from Pahang was obtained from the Natural Products Laboratory of the co-researcher at Universiti Pendidikan Sultan Idris, Malaysia. The structure of this mahanimbine (**1**) was re-analysed by spectroscopic techniques in the Department of Chemistry, Universiti Putra Malaysia, and the data was compared with reported literatures (Dahiya et al., 2016; Ahmad et al., 2014). This isolated mahanimbine (**1**) was further used for the semi-synthesis of mahanimbine derivatives (**2**-**4**).

2.3. Semi-synthesis of Mahanimbine derivatives

The method used was adapted from Mohd Nor et al. (2017). Mahanimbine (**1**) (0.10 g, 1 eq) and K_2CO_3 (0.32 g, 7.5 eq) were dissolved in CH_3CN (2 mL) and allowed to cool to 0°C. 1-Bromobutane (0.66 mL, 10 eq) was added and stirred for 3 days at 60°C. The reaction solution was mixed with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was dried and evaporated. The crude product was separated using column chromatography with EtOAc:hexane (1:9) as the solvent to yield **2**. A similar reaction was carried out with 1-bromo-3-methylbutane to prepare **3**. Column chromatography using $CHCl_3$:*n*-hexane (1:9) was used to purify the crude product.

N-Butylmahanimbine (**2**): Yellow oil (9.1 mg, 18%); IR (UATR) 2924, 2864, 1635, 1595, 1456, 1349, 1182, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.91 (1H, d, J = 8.0 Hz, H5), 7.69 (1H, s, H4), 7.34 (1H, t, J = 6.9 Hz, H8), 7.32 (1H, d, J = 6.9 Hz, H7), 7.16 (1H, t, J = 8.0 Hz, H6), 7.00 (1H, d, J = 9.8 Hz, H1'), 5.67 (1H, d, J = 9.8 Hz, H2'), 5.12 (1H, t, J = 8.3 Hz, H7'), 4.37 (2H, t, J = 8.3 Hz, H10), 2.32 (3H, s, H9), 2.21 (2H, m, H6'), 1.89 (2H, m, H11), 1.78 (2H, t, J = 9.2 Hz, H5'), 1.65 (3H, s, H9'), 1.57 (3H, s, H10'), 1.46 (2H, m, H12), 1.44 (3H, s, H4'), 0.98 (3H, t, J = 6.9 Hz, H13); δ_C (125 MHz, $CDCl_3$) 150.7 (C2), 141.2 (C8a), 135.1 (C1a), 131.7 (C8'), 128.1 (C2'), 124.3 (C7), 124.1 (C7'), 123.1 (C5a), 121.4 (C4), 119.1 (C5), 119.0 (C6), 118.9 (C3), 118.3 (C4a), 117.1 (C1'), 108.4 (C8), 105.5 (C1), 78.0 (C3'), 45.0 (C10), 40.2 (C5'), 32.1 (C11), 25.7 (C9'), 25.1 (C4'), 22.9 (C6'), 20.3 (C12), 17.6 (C10'), 16.3 (C9), 14.0 (C13); m/z (EIMS) 387 (M^+, $C_{27}H_{33}NO$).

N-(3-Methylbutyl)mahanimbine (**3**): Yellow oil (38.9 mg, 32%); IR (UATR) 2954, 2868, 1635, 1587, 1461, 1353, 1126, 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.90 (1H, d, J = 6.8 Hz, H5), 7.68 (1H, s, H4), 7.34 (1H, t, J = 6.8 Hz, H8), 7.29 (1H, d, J = 8.0 Hz, H7), 7.15 (1H, t, J = 6.8 Hz, H6), 7.00 (1H, d, J = 9.7 Hz, H1'), 5.67 (1H, d, J = 9.7 Hz, H2'), 5.12 (1H, t, J = 8.0 Hz, H7'), 4.37 (2H, t, J = 6.9 Hz, H10), 2.32 (3H, s, H9), 2.23 (3H, m, H12, H6'), 1.80 (2H, m, H11), 1.78 (2H, t, J = 8.0 Hz, H5'), 1.64 (3H, s, H9'), 1.57 (3H, s, H10'), 1.44 (3H, s, H4'), 1.02 (6H, d, J = 5.5 Hz, H13, H14); δ_C (125 MHz, $CDCl_3$) 150.9 (C2), 141.3 (C8a), 135.3 (C1a), 131.8 (C8'), 128.2 (C2'), 124.4 (C7), 124.2 (C7'), 123.4 (C5a), 121.5 (C4), 119.3 (C6), 119.2 (C5), 119.0 (C3), 118.4 (C4a), 117.3 (C1'), 108.4 (C8), 105.6 (C1), 78.1 (C3'), 43.9 (C10), 40.3 (C5'), 38.6 (C11), 26.6 (C12), 25.8 (C9'), 25.2 (C4'), 23.0 (C13, C14), 22.8 (C6'), 17.7 (C10'), 16.4 (C9); m/z (EIMS) 401 (M^+, $C_{28}H_{35}NO$).

The method used was adapted from Mohd Nor et al. (2017). Mahanimbine (**1**) (0.10 g, 1 eq) and K_2CO_3 (0.32 g, 7.5 eq) were dissolved in CH_3CN (2 mL) and allowed to cool to 0°C. Benzyl bromide (0.72 mL, 20 eq) was added dropwise over 15 min and stirred for 4 days at room temperature. The reaction mixture was added to water (10 mL) and extracted with EtOAc (3×10 mL). The organic phase was dried and evaporated. Column chromatography was employed to purify the crude product (EtOAc:Hexane, 1:9).

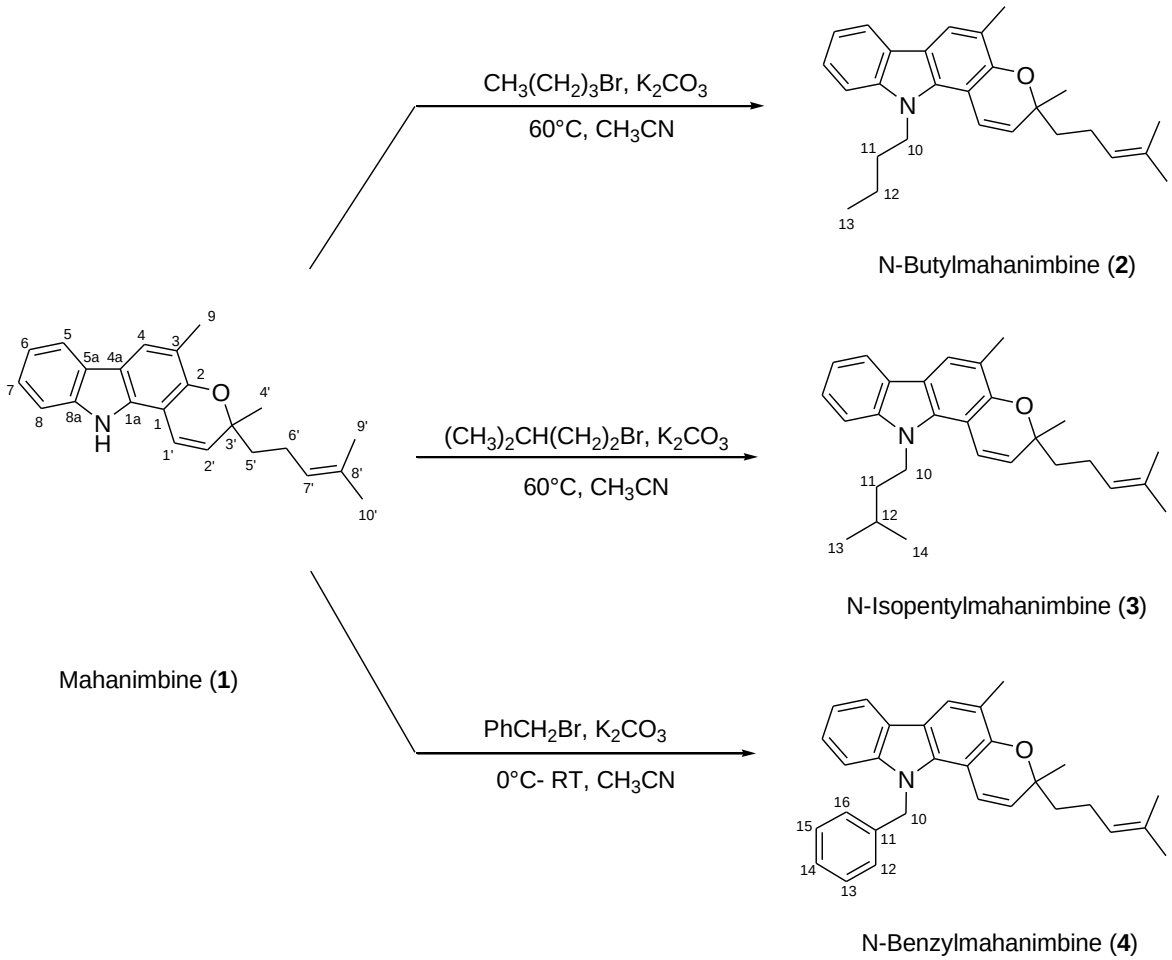
N-Benzylmahanimbine (**4**): White solid (92.5 mg, 72%); m.p.: 138-139°C; IR (UATR) 2920, 1600, 1443, 1342, 1174, 730 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.95 (1H, d, *J* = 6.9 Hz, H5), 7.73 (1H, s, H4), 7.30 (1H, d, *J* = 5.7 Hz, H13, H15), 7.29 (1H, t, *J* = 6.9 Hz, H7), 7.25 (1H, t, *J* = 6.9 Hz, H8), 7.19 (1H, d, *J* = 8.0 Hz, H6), 7.18 (1H, t, *J* = 8.0 Hz, H14), 7.14 (1H, d, *J* = 5.7 Hz, H12, H16), 6.69 (1H, d, *J* = 9.2 Hz, H1'), 5.60 (2H, s, H10), 5.47 (1H, d, *J* = 9.2 Hz, H2'), 5.09 (1H, t, J = 6.9 Hz, H7'), 2.35 (3H, s, H9), 2.16 (2H, m, H6'), 1.73 (2H, t, J = 3.7 Hz, H5'), 1.64 (3H, s, H9'), 1.55 (3H, s, H10'), 1.39 (3H, s, H4'); δ_C (125 MHz, $CDCl_3$) 150.9 (C2), 141.7 (C8a), 138.0 (C11), 136.0 (C1a), 131.7 (C8'), 129.0 (C13, C15), 127.9 (C2'), 127.4 (C14), 125.8 (C12, C16), 124.4 (C7'), 124.3 (C7), 123.4 (C5a), 121.4 (C4), 119.5 (C5), 119.0 (C6), 118.9 (C3), 118.7 (C4a), 117.1 (C1'), 108.6 (C8), 105.7 (C1), 78.0 (C3'), 49.0 (C10), 40.1 (C5'), 25.7 (C9'), 25.0 (C4'), 22.7 (C6'), 17.6 (C10'), 16.3 (C9); m/z (EIMS) 421 (M^+, $C_{30}H_{31}NO$).

3. RESULTS AND DISCUSSION

Three *N*-substituted mahanimbine derivatives (**2**-**4**) were semi-synthesised by alkylation of the amine terminal with corresponding alkyl bromides (Scheme 1). All derivatives (**2**-**4**) displayed absorption at 1635, 1635, and 1600 cm^{-1}, suggesting the existence of C=C groups. Meanwhile, the presence of a C-N was revealed by absorption at 1349, 1353, and 1342 cm^{-1}. The presence of C-O was detected at 1182, 1126, and 1174 cm^{-1}. *N*-Butylmahanimbine (**2**) and *N*-(3-methylbutyl) mahanimbine (**3**) were obtained as yellow oil. The EIMS spectra revealed [M^+] at m/z 387 and 401, respectively, which correspond to the chemical formulas $C_{27}H_{33}NO$ and $C_{28}H_{35}NO$. *N*-Benzylmahanimbine (**4**) was synthesised as a white solid with a melting point of 138-139°C. The EIMS spectrum revealed the peak of a [M^+] at m/z 421, confirming the chemical formula $C_{30}H_{31}NO$.

In the ^1H NMR spectra of all *N*-alkylated mahanimbines (**2**-**4**), the characteristic of a broad singlet of the amine's proton at δ 7.84 in (**1**) disappeared. This demonstrated that the nucleophilic substitution reaction of (**1**) with alkyl bromides was successful. The ^1H NMR spectra of all derivatives (**2**-**4**) displayed similar pattern of signals for the core prenylated pyranocarbazole structures. A singlet signal at δ 7.69 (**2**), 7.68 (**3**) and 7.73 (**4**) which was assigned to one isolated aromatic protons at positions H4. Another singlet signal appeared at δ 2.32, 2.32, and 2.35 (H9) and δ 1.44, 1.44, and 1.39 (H4'), which indicated the existence of two methyl groups attached to the pyranocarbazole ring. The doublet signals belong to olefinic

protons H1' and H2' were observed for each derivatives as follows: δ 7.00 (d, J=9.8 Hz) and 5.67 (d, *J* = 9.8 Hz) for **2**; δ 7.00 (d, *J* = 9.7 Hz) and 5.67 (d, *J* = 9.7 Hz) for **3**; and δ 6.69 (d, *J* = 9.2 Hz) and 5.47 (d, *J* = 9.2 Hz) for **4** which confirmed the pyran ring. The presence of a prenyl fragment in **4** was characterised by the presence of two triplet signals at δ 1.73 (*J* = 6.9 Hz) and 5.09 (*J* = 6.9 Hz) assigned to the methylene and methyne groups H5' and H7', respectively; a multiplet at δ 2.16 was due to the methylene proton H6'; and two singlets at δ 1.55 and 1.64 were assigned to H10 and H9.

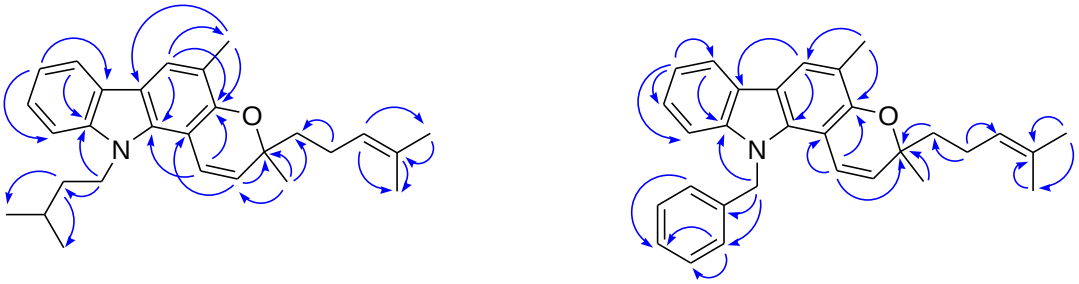


Scheme 1. Alkylation reaction at *N*-terminal of mahanimbine (**1**).

The COSY spectra for **2** and **3** revealed couplings between H10 and H11, suggesting the presence of an alkyl moiety in the structure. Meanwhile, the existence of a prenyl group was revealed by the coupling between H5' and H6' (**3**) and H9' and H10' (**4**). Compounds **2** and **3** showed one signal in the extremely upfield area at δ 0.98 (H13, t, *J* = 6.9 Hz) and 1.02 (H13 and H14, d, *J* = 6.9 Hz), indicating the methyl protons of alkyls. Meanwhile, methylene protons H10 were identified as a triplet signal at δ 4.37 for both compounds with coupling constants *J* = 8.3 and *J* = 6.9 Hz. The presence of benzyl groups in **4** was confirmed by two doublet signals at δ 7.14 (*J* = 5.7 Hz) and 7.30 (*J* = 5.7 Hz), which were assigned to the aromatic protons H12, H16, and H13, H15, respectively. A singlet signal at δ 5.60 was linked to the benzylic methylene H10, while a triplet signal at δ 7.18 was attributed to the aromatic proton H14.

The ^{13}C NMR analysis revealed a total of twenty-seven, twenty-eight, and thirty carbons, which verified the molecular formulas for **2**-**4**. The signals recorded at δ 25.1, 25.2, and 25.0 were ascribed to the methyl carbon C4' attached to the pyran ring of **2**, **3**, and **4**, respectively. The highly downfield signal at δ 150.7, 150.9, and 150.9 corresponded to the quaternary carbon

C2 for **2**, **3**, and **4**. Meanwhile, the presence of five, four, and three methylene carbons was identified in the DEPT spectrum for **2**, **3**, and **4**, respectively, validating the structure of the compounds. The HMQC analysis allocated all protonated carbons in mahanimbine derivatives (**2**-**4**). The site for alkyl moieties was discovered to be directly connected to the nitrogen of carbazole at C10 positions in the HMBC analysis of all mahanimbine derivatives (**2**-**4**). This is proven by the correlations between the methylene proton signals of the alkyl moiety at δ 4.37, 4.37, and 5.60 (H10) and the carbon signals at δ 141.2, 141.3, and 141.7 (C8a). Figure 2 depicts some further associations for compounds **3** and **4**.



N-(3-Methylbutyl)mahanimbine (**3**) *N*-Benzylmahanimbine (**4**)

Figure 2. Selected HBMC correlation of *N*-alkylated mahanimbines (**3** and **4**)

Furthermore, NMR data comparisons with our analysis mahanimbine (**1**) and literatures data (Dahiya et al., 2016; Ahmad et al., 2014) validated the core structure of prenylated pyranocarbazole in all derivatives (**2**-**4**), with additional peaks for alkyl substituents connected to the core structures (Table 1 and Table 2).

Table 1. Comparison of ^{1}H NMR (500 MHz) data for mahanimbines (**1**-**4**)

H	**δ_H ($CDCl_3$, ppm, *J* in Hz)**			
	1	**2**	**3**	**4**
4	7.67 (1H, s)	7.69 (1H, s)	7.68 (1H, s)	7.73 (1H, s)
5	7.91 (1H, d, 8.0)	7.91 (1H, d, 8.0)	7.90 (1H, d, 8.0)	7.95 (1H, d, 6.9)
6	7.18 (1H, t, 8.0)	7.16 (1H, t, 8.0)	7.15 (1H, t, 6.8)	7.19 (1H, d, 8.0)
7	7.30 (1H, t, 8.1)	7.32 (1H, d, 6.9)	7.29 (1H, d, 8.0)	7.30 (1H, t, 6.9)
8	7.36 (1H, d, 8.1)	7.34 (1H, t, 6.9)	7.34 (1H, t, 6.8)	7.25 (1H, t, 6.9)
9	2.34 (3H, s)	2.32 (3H, s)	2.32 (3H, s)	2.35 (3H, s)
10	-	4.37 (2H, t, 8.3)	4.37 (2H, t, 6.9)	5.60 (2H, s)
11	-	1.89 (2H, m)	1.80 (2H, m)	-
12	-	1.46 (2H, m)	2.23 (1H, m)	7.14 (1H, d, 5.7)
13	-	0.98 (3H, t, 6.9)	1.02 (3H, d, 5.5)	7.30 (1H, d, 5.7)
14	-	-	1.02 (3H, d, 5.5)	7.18 (1H, t, 8.0)
15	-	-	-	7.30 (1H, d, 5.7)
16	-	-	-	7.14 (1H, d, 5.7)
1’	6.63 (1H, d, 10.3)	7.00 (1H, d, 9.8)	7.00 (1H, d, 9.7)	6.69 (1H, d, 9.2)
2’	5.65 (1H, d, 10.3)	5.67 (1H, d, 9.8)	5.67 (1H, d, 9.7)	5.47 (1H, d, 9.2)
4’	1.46 (3H, s)	1.44 (3H, s)	1.44 (3H, s)	1.39 (3H, s)
5’	1.77 (2H, t, 8.0)	1.78 (2H, t, 9.2)	1.78 (2H, t, 8.0)	1.73 (2H, t, 6.9)
6’	2.17 (2H, m)	2.21 (2H, m)	2.23 (2H, m)	2.16 (2H, m)
7’	5.12 (1H, t, 6.9)	5.12 (1H, t, 8.3)	5.12 (1H, t, 8.0)	5.09 (1H, t, 6.9)
9’	1.67 (3H, s)	1.65 (3H, s)	1.64 (3H, s)	1.64 (3H, s)
10’	1.59 (3H, s)	1.57 (3H, s)	1.57 (3H, s)	1.55 (3H, s)
NH	7.85 (1H, br. s)	-	-	-

Table 2. Comparison of ^{13}C NMR (125 MHz) data for mahanimbines (**1**-**4**)

C	δ_C ($CDCl_3$, ppm)			
	1	**2**	**3**	**4**
1	104.3	105.5	105.6	105.7
1a	135.0	135.1	135.3	136.0
2	150.0	150.7	150.9	150.9
3	116.7	118.9	119.0	118.9
4	121.3	121.4	121.5	121.4
4a	118.5	118.3	118.4	118.7
5	119.4	119.1	119.2	119.5
5a	124.0	123.1	123.4	123.4
6	119.4	119.0	119.3	119.0
7	124.3	124.3	124.4	124.3
8	110.5	108.4	108.4	108.6
8a	136.6	141.2	141.3	141.7
9	16.2	16.3	16.4	16.3
10	-	45.0	43.9	49.0
11	-	32.1	38.6	138.0
12	-	20.3	26.6	125.8
13	-	14.0	23.0	129.0
14	-	-	23.0	127.4
15	-	-	-	129.0
16	-	-	-	125.8
1’	117.6	117.1	117.3	117.1
2’	128.6	128.1	128.2	127.9
3’	78.3	78.0	78.1	78.0
4’	25.9	25.1	25.2	25.0
5’	40.9	40.2	40.3	40.1
6’	22.8	22.9	22.8	22.7
7’	124.2	124.1	124.2	124.4
8’	131.8	131.7	131.8	131.7
9’	25.8	25.7	25.8	25.7
10’	17.7	17.6	17.7	17.6

The yields of *N*-butylmahanimbine (**2**) and *N*-(3-methylbutyl) mahanimbine (**3**) were rather low (18% and 32%, respectively). When the solvent is changed to another aprotic solvent, such as DMF or THF, or the base is changed, there is no significant variation in yield. TLC analysis of these reactions revealed that several spots developed after several hours of reaction, despite the presence of the starting material. Due to the higher nucleophilicity of the desired tertiary amine, direct *N*-alkylation of secondary amines such as mahanimbine typically results in the formation of quaternary ammonium salt. The presence of the starting amine and the production of this mixture make the purification procedure extremely challenging. This is most likely the reason for the low yield. Furthermore, the flexibility of the long carbon chain and the prenyl-pyran ring are likely to hinder the substitution reaction. In contrast, the absence of a prenyl group in the girinimbine structure resulted in inverse alkylation results, with yields of 72% and 70% obtained for identical alkyl groups, respectively (Mohd Nor et al., 2017).

4. CONCLUSION

This study describes the semi-synthesis of three novel mahanimbine derivatives. The alkylation of mahanimbine's *N*-terminal with readily accessible alkyl bromides yielded *N*-butylmahanimbine, *N*-(3-methylbutyl) mahanimbine, and *N*-benzylmahanimbine. These

derivatives may have potential for medicinal applications, and further biological testing may be performed in the future.

Declaration of Interest
The authors state that there is no conflict of interest.

Acknowledgements
The authors are grateful to Universiti Putra Malaysia for financial support and the Department of Chemistry for providing the facilities. Thank you also to the collaborator from Universiti Pendidikan Sultan Idris for the isolated mahanimbine.

REFERENCES

Ahmad K, Tan S, Sukari M, Ali A, Nafiah M. (2014). Cytotoxic and anti-tumour promoting activities of carbazole alkaloids from Malayan *Murraya koenigii* (L.) Spreng. *American Journal of Plant Sciences*, 5, 2869-2877.

Bashir M, Bano A, Ijaz AS, Chaudhary BA. (2015). Recent developments and biological activities of *N*-substituted carbazole derivatives: a review. *Molecules*, 20(8), 13496-13517.

Bhattacharyya P, Roy S, Biswas A, Bhattacharyya L, Chakraborty DP. (1978). Mahanimbine and murrayazoline from *Murraya exotica* Linn. (Syn. *Murraya paniculata*). *Journal of the Indian Chemical Society*, 308-308.

Birari R, Javia V, Bhutani KK. (2010). Antiobesity and lipid lowering effects of *Murraya koenigii* (L.) spreng leaves extracts and mahanimbine on high fat diet induced obese rats. *Fitoterapia*, 81(8), 1129-1133.

Chakraborty M. (2020). Reactions of the carbazole alkaloid mahanimbine with mineral acid, Lewis acid and m-chloroperbenzoic acid. *Indian Journal of Chemistry*, 59, 837-841.

Chakraborty M. (2018). Nitration of C13, C18 and C23 carbazole alkaloids using ceric ammonium nitrate (CAN). *Asian Journal of Research in Chemistry*, 11(2), 337-343.

Chowdhury BK, Jha S, Bhattacharya P, Mukherjee J. (2001). Two new carbazole alkaloids form *Murraya koenigii*. *Indian Journal of Chemistry*, 40(6), 490-494.

Cuong NM, Hung TQ, Sung TV, Taylor WC. (2004). A new dimeric carbazole alkaloid from *Glycosmis stenocarpa* roots. *Chemical and Pharmaceutical Bulletin*, 52(10), 1175-1178.

Dahiya J, Singh J, Kumar A, Sharma A. (2016). Isolation, characterization and quantification of an anxiolytic constituent-mahanimbine, from *Murraya koenigii* Linn. Spreng leaves. *Journal of Ethnopharmacology*, 193, 706-711.

Dineshkumar B, Mitra A, Mahadevappa M. (2010). Antidiabetic and hypolipidemic effects of mahanimbine carbazole alkaloid from *Murraya koenigii* Rutaceae leaves. *International Journal of Phytomedicine*, 2, 22-30.

Hobani YH. (2022). Cytotoxicity of mahanimbine from curry leaves in human breast cancer cells (MCF-7) via mitochondrial apoptosis and anti-angiogenesis. *Molecules*, 27(3), 971.

Ito C, Katsuno S, Ohta H, Omura M, Kajiura I, Furukawa H. (1997). Constituents of *Clausena excavate*-isolation and structural elucidation of new carbazole alkaloids. *Chemical and Pharmaceutical Bulletin*, 45(1), 48-52.

Ito C, Itoigawa M, Nakao K, Murata T, Tsuboi M, Kaneda N, Furukawa H. (2006). Induction of apoptosis by carbazole alkaloids isolated from *Murraya koenigii*. *Phytomedicine*, 13(5), 359-365.

Joshi BS, Kamat VN, Gawad DH. (1970). On the structures of girinimbine, mahanimbine, isomahanimbine, koenimbidine and murrayacine. *Tetrahedron*, 26(5), 1475-1482.

Liu K, Zang Y, Shen C, Li C, Ma J, Yang J, Sun X, Chen X, Wang N, Zhang, D. (2021). Synthesis and biological evaluation of pyranocarbazole derivatives as anti-tumor agents. *Bioorganic and Medicinal Chemistry Letters*, 33, 127739.

Ma X, Chen H, Zhu S, Tu P, Jiang Y. (2021). Trimeric and dimeric carbazole alkaloids from *Murraya microphylla*. *Molecules*, 26, 5689.

Ma XL, Zhu SS, Liu Y, Chen HW, Shi YT, Zeng KW, Tu PF. (2021). Carbazole alkaloids with potential cytotoxic activities targeted on PCK2 protein from *Murraya microphylla*. *Bioorganic Chemistry*, 114, 105-113.

Mani V, Mohd Azahan NS, Ramasamy K, Lim SM, Abdul Majeed AB. (2021). Mahanimbine improved aging-related memory deficits in mice through enhanced cholinergic transmission and suppressed oxidative stress, amyloid levels, and neuroinflammation. *Brain Science*, 12(1), 12.

Meragelman KM, McKee TC, Boyd MR. (2000). Siamenol, a new carbazole alkaloid from *Murraya siamensis*. *Journal of Natural Products*, 63(3), 427-428.

Mohd Nor SM, Osman FNA, Ahmad K, Nafiah MA. (2017). Synthesis of *N*-alkylated and *N*-acylated derivatives of girinimbine. *Asian Journal of Chemistry*, 29(4), 801-804.

Mondal P, Natesh J, Abdul Salam AA, Meeran SM. (2022). Mahanimbine isolated from *Murraya koenigii* inhibits P-glycoprotein involved in lung cancer chemoresistance. *Bioorganic Chemistry*, 129, 106170.

Nakahara K, Trakoontivakorn G, Alzoreky NS, Ono H, Onishi-Kameyama M, Yoshida M. (2002). Antimutagenicity of some edible Thai plants, and a bioactive carbazole alkaloid, mahanine, isolated from *Micromelum minutum*. *Journal of Agricultural and Food Chemistry*, 50, 4796-4802.

Ng RC, Kassim NK, Yeap YSY, Ee GCL, Yazan SL, Musa KH. (2018). Isolation of carbazole alkaloids and coumarins from *Aegle marmelos* and *Murraya koenigii* and their antioxidant properties. *Sains Malaysiana*, 47(8), 1749-1756.

Osman FNA, Mohd Nor SM, Nafiah MA. (2021). Cytotoxicity effect of natural and synthetic girinimbines and their derivatives against human lung cancer cell lines A549. *Malaysian Journal of Analytical Sciences*, 25(6), 1020-1031.

Pei C, He Q, Liang S, Gong X. (2018). Mahanimbine exerts anticancer effects on human pancreatic cancer cells by triggering cell cycle arrest, apoptosis, and modulation of AKT/mammalian target of rapamycin (mTOR) and signal transducer and activator of transcription 3 (STAT3) signalling pathways. *Medical Science Monitor*, 24, 6975-6983.

Ramsewak RS, Nair MG, Strasburg GM, DeWitt DL, Nitiss JL. (1999). Biologically active carbazole alkaloids from *Murraya koenigii*. *Journal of Agricultural and Food Chemistry*, 47(2), 444-447.

Rao LJM, Ramalakshmi K, Borse BB, Raghavan B. (2006). Chemical composition of volatiles from coconut sap neera and effect of processing. *Food Chemistry*, 100, 742-747.

Sakunpak A, Saingam W, Jaisamut, S, Issuriya A, Ruangrungsi N. (2021). Pyranocarbazole alkaloids, isolated from *Clausena cambodiana* leaves, as a pancreatic cholesterol esterase inhibitor, and their HPLC–DAD quantitative determination method. *Chemistry Papers*, 75, 2451-2458.

Sim KM, Teh HM. (2011). A new carbazole alkaloid from the leaves of Malayan *Murraya koenigii. Journal of Asian Natural Products Research*, 13(10), 972-975.

Sukari MA, Mohd Noor HS, Abu Bakar NH, Ee GCL, Ismail IS, Rahmani M, Abdul AB. (2013). Larvicidal carbazole alkaloids from *Murraya koenigii* against dengue fever mosquito *Aedes aegypti* Linnaeus. *Asian Journal of Chemistry*, 25(14), 7719-7721.

Tan SP, Nafiah MA, Ahmad K. (2014). C23-carbazole alkaloids from Malayan *Murraya koenigii* (L.) Spreng. *Journal of Chemical and Pharmaceutical Research*, 6(4), 1093-1098.

Tan SP, Nafiah MA. (2021). A simple BF_3•Et_2O-mediated cycloaddition reaction to the formation of cyclic monoterpenoid pyrano[3,2-a]carbazole alkaloids. *Letters in Organic Chemistry*, 18(5), 395-399.

Wu TS, Wang ML, Wu PL, Ito C, Furukawa H. (1996). Carbazole alkaloids from the leaves of *Murraya euchrestifolia*. *Phytochemistry*, 41, 1433-1435.

Xie H, Zhang T, Yang N, Li Z, Liu Y. (2020). Anticancer effects of mahanimbine alkaloid on the human bladder cancer cells are due to the induction of G0/G1 cell cycle arrest, apoptosis and autophagy. *Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology*, 25(2), 1166-1171.

Yedukondalu N, Thakur V, Mohmmed A, Gupta VK, Ali A. (2017). $POCl_3$-mediated cyclization of (+)-S-mahanimbine led to the divergent synthesis of natural product derivatives with antiplasmodial activity. *New Journal of Chemistry*, 41(12), 4923-4930.

Yedukondalu N, Gupta G, Nadkarni JR, Gupta VK, Syed SH, Ali A. (2016). Divergent synthesis of prenylated carbazole alkaloid (+)-*S*-mahanimbine led to the discovery of a notch activator. *RSC Advance*, 6, 83069-83077.