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A benzoisofuranone derivative and carbazole alkaloids from *Murraya koenigii* and their antimicrobial activity

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Abstract

A benzoisofuranone derivative, 3ξ-(1ξ-hydroxyethyl)-7-hydroxy-1-isobenzofuranone, and a dimeric carbazole alkaloid, 3,3′-[oxybis(methylene)]bis(9-methoxy-9*H*-carbazole), along with six known carbazole alkaloids and three known steroids were isolated from the stem bark of *Murraya koenigii*. The structures of these compounds were established unambiguously by UV, IR, MS and a series of 1D and 2D NMR analyses. The minimum inhibitory concentrations (MIC) of these compounds were found to be in the range 3.13–100 μg/ml.
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Keywords: *Murraya koenigii*; Rutaceae; Benzoisofuranone; Carbazole alkaloids; 3ξ-(1ξ-hydroxyethyl)-7-hydroxy-1-isobenzofuranone; 3,3′-[oxybis-(methylene)]bis(9-methoxy-9*H*-carbazole); Antimicrobial

1. Introduction

Murraya koenigii (L) Spreng. (Fam. Rutaceae), a small tree with dark grey bark, is distributed throughout Bangladesh, India, Nepal, Malaysia, Sri Lanka and Burma (Hooker, 1879; Kirtikar et al., 1993; Yusuf et al., 1994). Traditionally, the plant is used as a stimulant, stomachic, febrifuge, analgesic and for the treatment of diarrhoea, dysentery and insect bites (Kirtikar et al., 1993; Yusuf et al., 1994). Previous phytochemical investigations on this plant revealed the occurrence of carbazole alkaloids (Narasimhan et al., 1968; Chowdhury and Chakraborty, 1971; Chakraborty et al., 1978; Rao et al., 1980; Bhattacharyya et al., 1982; Roy et al., 1982; Fiebig et al., 1985; Bhattacharyya and Chowdhury, 1985; Ito et al., 1993; Reisch et al., 1994; Saha and Chowdhury, 1998; Nutan et al., 1999; Ramsewak et al., 1999; Tachibana et al., 2001; Knolker and Reddy, 2002) and coumarins (Adebajo and Reisch, 2000; Murray et al., 1982). As a part of our research project focussing on Bangladeshi rutaceous species, we here report the isolation of a new benzoisofuranone derivative (**10**) and a new dimeric carbazole alkaloid (**11**) together with six known carbazoles and three known steroids from the stem bark of *M. koenigii* as well as the antimicrobial activities of compounds **1**–**3** and **6**–**11**.

2. Results and discussion

The stem bark of *M. koenigii* was extracted sequentially with petroleum ether (60–80°) and chloroform. VLC fractionation of the petroleum ether extract followed by preparative TLC yielded compounds **1**–**5** which were identified as mahanimbine (**1**) (Tachibana et al., 2001), girinimbine (**2**) (Furukawa et al., 1985), sitoster-4-en-3-one (**3**) (Onocha et al., 1995), β-sitosterol

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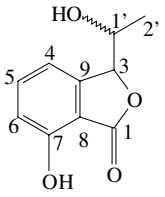
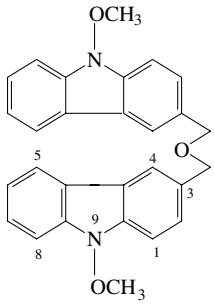
(**4**) and stigmasterol (**5**) (Kojima et al., 1990) by direct comparison of the spectral data to those published in the literature.



10



11

VLC fractionation of the chloroform extract followed by gel filtration over Sephadex LH-20 and preparative TLC led to the isolation of four known carbazole alkaloids (**6**–**9**) and two new compounds (**10** and **11**). Comparison of the spectral data to those previously reported, the known compounds **6**–**9** were identified as 3-formylcarbazole (**6**) (Chowdhury et al., 1990), 3-formyl-1-methoxycarbazole (**7**) (Knolker and Bauermeister, 1993), 3-formyl-9-methoxycarbazole (**8**) (Ito et al., 1988) and carbazole-3-carboxylic acid (**9**) (Li et al., 1991). Among these known carbazoles, this is the first report of compound **8** from this plant and one of only two examples of *N*-methoxycarbazole alkaloids in nature (DNP, 2004).

The high resolution EIMS of **10** showed a molecular ion peak at *m*/*z* 194.0584, corresponding to the molecular formula $C_{10}H_{10}O_4$. The ^{1}H NMR spectrum (Table 1) of this compound exhibited an H-bonded hydroxyl group at δ_H 11.00, three aromatic protons as an ABC system for H-4, 5 and 6 and protons for a short aliphatic chain. The *J*-modulated ^{13}C NMR spectrum (100 MHz, $CDCl_3$) revealed a carbonyl (δ_C 168.6, C-1), an oxygenated quaternary (δ_C 162.3), five methines (three aromatic and two oxygenated aliphatic), two other quaternary carbons and one methyl (δ_C 18.1). The ^{1}H–^{1}H COSY spectrum showed a correlation between the methyl protons and one of the protons at δ_H 4.62 while one of the latter protons (H-3) had a weak correlation to the aromatic proton H-4 (δ_H 7.03). In the HMBC experiment (Table 1), H-4 had strong correlations with an oxygen-bearing methine at δ_C 69.4 (C-3), an aromatic methine at δ_C 118.1 (C-6) and a quaternary δ_C 106.9 (C-8). These latter two carbons, along with the quaternary carbon δ_C 162.3 (C-7), had correlations with the H-bonded proton at δ_H 11.00 thus placing the hydroxyl group in C-7. H-4 showed a very weak (^4J) long-range correlation with the carbonyl carbon (δ_C 168.6, C-1) but the carbonyl must be attached at C-8 *ortho* to, and H-bonded with, the hydroxyl in C-7. H-5 (δ_H 7.55) exhibited strong ^3J correlation to C-7 and another quaternary carbon C-9 (δ_C 141.4), the latter carbon also showing correlation with the proton(s) at δ_H 4.62, completing the assignments of all protons and carbons for this molecule (Table 1). The compound gave a negative specific rotation but the absolute configurations at C-3 and C-1′ remain undetermined. On this basis, the compound was identified as 3ξ-(1ξ-hydroxyethyl)-7-hydroxy-1-isobenzofuranone (**10**) which appears to be new.

The FAB-MS of **11** showed a $[M + 1]^+$ peak at *m*/*z* 437 corresponding to $C_{28}H_{25}N_2O_3$ and its molecular formula was established as $C_{28}H_{24}N_2O_3$. The *J*-modulated ^{13}C NMR spectrum (Table 2) of **11** in $CDCl_3$ revealed only 14 carbons that included one oxymethylene, one methoxyl, five quaternary and seven methine carbons. The mass spectrum gave a total of 28 carbons, thus the compound must be a symmetrical dimer. The molecular formula of **11** was the same as those of the dimeric carbazole alkaloids bismurrayafolinol and oxydimurrayafoline isolated from the stem bark

Table 1
^{1}H (400 MHz), ^{13}C (100 MHz), ^{1}H–^{1}H COSY90 (400 MHz) and HMBC NMR data of **10** in $CDCl_3$

Position	$^\delta$H	$^\delta$C	^{1}H–^{1}H COSY90	HMBC(C → H)	
				^2J	^3J
1	–	168.6	–	–	–
3	4.62 (*m*)	69.4	H-4	C-1′, C-9	–
4	7.03 (*brd*, *J* = 8.0 Hz)	116.4	H-3, H-5	–	C-3, C-6
5	7.55 (*t*, *J* = 8.0 Hz)	137.1	H-4, H-6	–	C-7, C-9
6	7.01 (*d*, *J* = 8.0 Hz)	118.1	H-5	C-7	C-4, C-8
7	–	162.3	–	–	–
8	–	106.9	–	–	–
9	–	141.4	–	–	–
HO-7	11.00 (*s*)	–	–	C-7	C-6, C-8
1′	4.62 (*m*)	80.1	H-2′	C-3, C-2′	C-9
2′	1.53 (*d*, *J* = 6.2 Hz)	18.1	H-1′	C-1′	C-3

Table 2
^{1}H (400 MHz), ^{13}C (100 MHz) and HMBC (400 MHz) NMR data of **11** in $CDCl_3$ and acetone-d_6; *J* in Hz, in parentheses

Position	$^{\delta}H$		$^{\delta}C$		HMBC	
	$CDCl_3$	Acetone-d_6	$CDCl_3$	Acetone-d_6	^{2}J	^{3}J
1, 1′	7.53 *br. s*	7.56 *br. s*	108.5	109.2	–	C-3/3′
2, 2′	7.53 *br. s*	7.56 *br. s*	126.9	127.6	–	CH_2, C-9a/9′a
3, 3′	–	–	130.4	132.0	–	–
4, 4′	8.08 *br. s*	8.15 *br. s*	120.7	121.2	–	CH_2, C-9a/9′a
5, 5′	8.05 *d* (7.9)	8.13 *dd* (7.9, 1.0)	120.8	121.5	–	C-8a/8′a, C-7/7′, C-4a/4′a
6, 6′	7.26 *t* (7.9)	7.25 *dt* (1.0, 7.9)	120.4	121.2	–	C-8/8′, C-4b/4′b
7, 7′	7.48 *t* (7.9)	7.49 *dt* (1.0, 7.9)	126.4	127.2	–	C-5/5′, C-8a/8′a
8, 8′	7.53 *br. s*	7.57 *dd* (7.9, 1.0)	108.6	109.4	–	C-6/6′
9, 9′	4.14 *s*	4.14 *s*	63.7	64.3	–	–
CH_2	4.78 *s*	4.77 *s*	72.7	73.1	C-3/3′	CH_2, C-2/2′, C-4/4′
4a, 4′a	–	–	120.2	120.8	–	–
4b, 4′b	–	–	120.3	120.9	–	–
8a, 8′a	–	–	138.2	139.2	–	–
9a, 9′a	–	–	137.6	138.4	–	–

of *Murraya euchrestifolia* (Ito et al., 1987; DNP, 2004), however, the UV and ^{1}H NMR data are quite different. For example, in the case of oxydimurrayafoline, the methoxy signal δ_H 4.01 and aromatic signals for H-2 (δ_H 6.98) and H-4 (δ_H 7.68) were more shielded than the corresponding signals in compound **11** (Table 2). Unfortunately, Ito et al. (1987) did not give ^{13}C data for bismurrayafolinol or oxydimurrayafoline but one would expect the methoxys attached in position-1 and 1′ in either compound to resonate at δ_C 55–56 while the methoxys of **11**, attached to the nitrogens, are more deshielded (δ_C 63.7 in $CDCl_3$ and 64.3 in acetone-d_6). One would also expect the methoxy protons in bismurrayafolinol or oxydimurrayafoline to correlate with aromatic carbons (C-1/C-1′) but the methoxy protons of **11** did not have long-range correlation in the HMBC with any carbons. The UV spectrum and proton and carbon shifts of **11** (Table 2) compared very favourably with those of the monomeric carbazole alkaloid 3-hydroxymethyl-9-methoxy-9*H*-carbazole, isolated from the root bark of *M. euchrestifolia* by Ito et al. (1992). The methylene protons (δ_H 4.78 in $CDCl_3$) of **11** showed the expected HMBC correlations to C-2, C-3 and C-4 as well as direct (^{1}J) and long-range (^{3}J) correlations to the methylene carbons at δ_C 72.7. This latter correlation confirmed the dimeric linkage as a bismethylene ether similar to that of oxydimurrayafoline. On the basis of these observations and spectral data, the compound was identified as 3,3′-[oxybis(methylene)]bis(9-methoxy-9*H*-carbazole) (**11**). Many types of biscarbazole alkaloid have been discovered, particularly those with C–C or C–N linkages between the monomeric parts (Knolker and Reddy, 2002) but, to our knowledge, this is only the second example of an ether-linked carbazole dimer and the first example of such a dimer with *N*-methoxy groups.

The compounds **1**–**3** and **6**–**11** were tested for their antimicrobial activities by a microdilution technique (Drummond and Waigh, 2000). The results of the test are presented in Table 3 in terms of minimum inhibitory concentration (MIC). It is evident from Table 3 that girinimbine (**2**) had the strongest activity against *Staphylococcus aureus* (MIC = 3.17 μg/ml; 0.012 μmol). In terms of molar concentration, the order of activity against *S. aureus* was **2 > 7 > 11 > 3 > 1 > 8 > 9 > 6**. However, the dimeric carbazole (**11**) was found to be the most potent compound against the Gram negative bacteria (*E. coli* and *Proteus vulgaris*) and fungi (*Aspergillus niger* and *Candida albicans*). The sequence of relative potencies against *E. coli* was **11 > 1 > 2 > 7 = 8 > 9 > 3 > 10 > 6** and against *P. vulgaris* was **11 > 2 > 3 > 1 > 8 > 7 > 9 > 6 > 10**. The order of activity against *A. niger* was **11 > 2 > 7 > 6 > 1 > 8 > 9 > 10** and the sequence was almost the same for *C. albicans*.

Mahanimbine (**1**) has been reported to possess insecticidal (vs. mosquito; 20% mortality of *Aedes aegypti* at a concentration of 100 μg/ml) and antimicrobial properties (Ramsewak et al., 1999). Murrayaquinone and murrayafoline-A from the root of *M. euchrestifolia* (Furukawa et al., 1985) have been found to have weak but fairly selective cytotoxic activity against a panel of about 60 tumour cell lines (Itoigawa et al., 2000). Itoigawa et al. (2000) also found that several other natural and synthetic carbazoles had more selective cytotoxicities. The activities of the carbazole alkaloids from *M. koenigii* described here would seem to justify some of the folk medicinal uses of the plant, for example in the treatment of diarrhoea, dysentery and against biting insects (Kirtikar et al., 1993; Yusuf et al., 1994).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Perkin Elmer Polarimeter 341. IR spectra were recorded in dry film on a Mattson Galaxy 5000 FT-IR spectrometer. UV

Table 3
MIC values of compounds **1–3**, **6–11** in μg/ml and μmol against a range of microorganisms

Compounds	*Staphylococcus aureus*		*Bacillus subtilis*		*Escherichia coli*		*Proteus vulgaris*		*Aspergillus niger*		*Candida albicans*	
	μg/ml	μmol	μg/ml	μmol	μg/ml	μmol	μg/ml	μmol	μg/ml	μmol	μg/ml	μmol
1	50	0.151	25	0.076	50	0.151	25	0.076	50	0.151	100	0.392
2	3.13	0.012	25	0.095	50	0.190	12.5	0.047	25	0.095	100	0.302
3	50	0.122	–	–	100	0.243	25	0.061	–	–	50	0.122
6	200	1.026	100	0.513	200	1.026	100	0.513	25	0.128	25	0.128
7	25	0.111	50	0.222	50	0.222	50	0.222	25	0.111	100	0.444
8	100	0.444	–	–	50	0.222	25	0.111	50	0.222	25	0.111
9	–	–	–	–	50	0.258	100	0.516	100	0.516	50	0.258
10	100	0.474	50	0.237	50	0.237	50	0.237	100	0.474	100	0.474
11	50	0.115	–	–	25	0.057	6.25	0.014	25	0.057	25	0.057
K	3.13		6.25		12.5		12.5					
F									–	–	25	0.082

K = Kanamycin; F = Fluconazole.

spectra were obtained on a Unicam UV 4-100 UV/Vis spectrophotometer in MeOH. HREIMS were recorded on a JEOL JMS-AX505HA double-focusing instrument at 70 eV while FAB-MS were taken using a VG ZAB-E spectrometer with glycerol as matrix. NMR spectra (both 1D and 2D) were obtained on a Bruker AMX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer, using the residual solvent peaks as internal standard. *J*-modulated ^{13}C spectra were acquired with a relaxation delay (d_1) of 6 s. HMBC spectra were optimized for a long range J_{H-C} of 7Hz ($d_6 = 0.07$s). Vacuum-liquid chromatography (VLC) was carried out using Merck Si gel 60 H. Gel filtration was performed using Sephadex LH-20 (Sigma). PTLC was carried out with Merck Si gel 60 PF_{254} on glass plates (20 cm × 20 cm) at a thickness of 0.5 mm. Flash chromatography was achieved using Biotage Flash 40S columns (7.0 × 4.0 cm; KP-Sil silica 32–63 m) with a flow rate of 15 ml/min. TLC was conducted on normal-phase Merck Si gel 60 PF_{254} on plates. Spots on TLC and PTLC plates were visualised under UV light (254 and 366 nm) and spraying with 1% vanillin-H_2SO_4 followed by heating at 110 °C for 5–10 min. Carbazole alkaloids were also detected by spraying with Dragendorff's reagent.

3.2. Plant material

The stem bark of *M. koenigii* was collected from Rajshahi University Campus, Bangladesh in August, 1999. A voucher specimen (DACB28076) has been deposited at the Bangladesh National Herbarium, Mirpur, Dhaka.

3.3. Extraction and isolation

The dried and ground plant material (600 g) was sequentially extracted with petroleum ether (b.p. 60–80 °C) followed by $CHCl_3$ in a Soxhlet apparatus. VLC fractionation of the petroleum ether extract (3.4 g) on Si gel was performed using mobile phases petroleum ether, EtOAc and MeOH in order of increasing polarity. Recrystallisation of the solid from the VLC fraction eluting with 100% petroleum ether to 8% EtOAc in petroleum ether yielded **1** (65.6 mg). The VLC fraction eluting with 12% EtOAc in petroleum ether was further subjected to sephadex column and preparative TLC (5% EtOAc in toluene) to yield **2** (12.5 mg) and **3** (5.4 mg). Sephadex column and subsequent preparative TLC (5% EtOAc in toluene) of the VLC fraction eluted with 20–25% EtOAc in petroleum ether afforded 10.2 mg of needle crystals as a mixture (1:1) of **4** and **5**.

The $CHCl_3$ extract (4.5 g) was fractionated by VLC over Si gel 60H using petroleum ether–EtOAc and EtOAc–MeOH mixtures of increasing polarity. The eluates were combined on the basis of TLC analysis. The VLC fraction that eluted with 10% EtOAc in petroleum ether was further subjected to preparative TLC (7% EtOAc in toluene) to yield **8** (5.6 mg). The VLC fraction eluting with 20% EtOAc in petroleum ether was then subjected to gel filtration over Sephadex LH20. Concentration of the eluate from the Sephdex column (100% $CHCl_3$ to 5% MeOH in $CHCl_3$) gave **6** (12.2 mg), whereas **7** (15.4 mg) was obtained from the eluate (20–100% MeOH in $CHCl_3$). The VLC fraction eluting with 22% EtOAc in petroleum ether was further subjected to PTLC (15% EtOAc in petroleum ether) affording **10** (16.5 mg) and **11** (4.5 mg). Compound **9** was obtained from the VLC fraction eluted with 50% EtOAc in petroleum ether followed by Biotage flash chromatography (40–50% EtOAc in petroleum ether).

3.4. 3ξ-(1ξ-Hydroxyethyl)-7-hydroxy-1-isobenzofuranone (*10*)

Brown solid; m.p. 102–103°; $[\alpha]_D^{20}$ − 50.0° ($CHCl_3$, *c* 0.08); UV λ_{max}^{MeOH} nm (log ϵ) 208 (4.01), 242 (3.47), 311 (3.24); $IR_{max}^{CHCl_3}$ cm^{-1}: 3404, 2923, 2850, 1671, 1615, 1465, 1235, 1165, 1113, 1069, 1056, 955, 823, 747, 696;

^{1}H and ^{13}C NMR (Table 1); HREIMS *m/z* 194.0584 (calcd for $C_{10}H_{10}O_4$, 194.0579), EIMS (rel. int.) 194 [M^+] (36), 150 (67), 122 (61), 121 (100).

3.5. 3,3′-[Oxybis(methylene)]bis(9-methoxy-9H-carbazole) (*11*)

Brown gum; UV λ_{max}^{MeOH} nm (log ϵ) 237 (4.87), 264 (4.55), 293 (4.42), 329 (sh) (3.79); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3415, 2920, 1682, 1605, 1491, 1432, 1319, 1055, 953, 891, 803, 745; ^{1}H and ^{13}C NMR (Table 2); FAB-MS: $[M + H]^+$ 437 (29), M^+ analysed for $C_{28}H_{24}N_2O_3$.

3.6. Antimicrobial screening

The antimicrobial assay was performed by a micro-dilution titre technique (Drummond and Waigh, 2000) using 96-well plates that offers the advantage of determining the minimum inhibitory concentration (MIC) at the same time. In this test, 100 μg/ml indicator solution (resazurin, 750 μg/ml) was first placed into the sterility control wells (11th column) on the 96 well plates. About 7.5 ml of indicator solution was then mixed with 5 ml test organism (10^8 cfu/ml) followed by transferring (100 μl each) into growth control wells (12th column) and all test wells (1st–10th columns) on the plates. Sample solutions (100 μl each) were then applied to the 1st column of the plates. In a plate, up to six samples could be applied leaving two for negative and positive controls. Once all samples and controls were applied to the 1st column of wells on the plate, half of the content (100 μl) from these wells was then transferred to the 2nd column of wells and each subsequent well was treated similarly (doubling dilution) up to the 10th column, followed by discarding last 100 μl aliquot. Finally, the plates were incubated at 37 °C for around 5–6 h, until growth control wells developed the growth (pink colour). In the case of the fungi, the incubation period was around 12–16 h. The activity was marked by observing the change of colour from pink to blue. As the process operates on a doubling dilution of test materials, the lowest concentration at which change of colour occurred was considered as the minimum inhibitory concentration (MIC) of a test compound.

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