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Four new minor brominated indole related alkaloids with antibacterial activities from *Laurencia similis*



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ABSTRACT

Four new minor brominated indole related alkaloids (one indoles, **1**, one 1,3-dihydro-indole-2-one, **2**, one carbazole, **3**, and one 2-carboxylamino-benzoate, **4**) were isolated and identified from *Laurencia similis* by extensive chromatographic and spectrometric methods. Among them, **1** and **2** were the first example of naturally occurring indole with 3-benzyl group and 1,3-dihydro-indole-2-one with 2-isopropylidene group, respectively, whereas **3** and **4** were the first carbazole alkaloids and 2-carboxylamino-benzoate, respectively, isolated from the genus *Laurencia*. Moreover, **1** showed the most potent antibacterial activity against seven bacterial strains with MIC values ranging from 2 to 8 µg/mL.

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The genus *Laurencia* (division Rodophyta, order Ceramiales, family Rhodomelaceae), mainly distributed on the inter-tidal rocks of the warm sea throughout the world, is a rich source of structurally unique secondary metabolites characteristic of relatively high degree of halogenation. Up to date, more than 1100¹ metabolites have been characterized from this genus and the vast majority of these metabolites are mainly consist of terpenes,^{2–6} indole alkaloids^{7,8} and C₁₅ acetogenins⁹ with diverse biological activities such as antifeedant,¹⁰ anthelmintic,¹¹ antifouling,¹² antimicrobial,¹² and cytotoxic properties.¹³ Indole alkaloids, a very important class of bioactive structures with unique promise in the development of new drug leads, have been isolated from three *Laurencia* species, including *L. brongniartii*,^{14–16} *L. decumbens*,⁴ and *L. similis*^{7,8,17} by now. Our previous phytochemical investigations on *L. similis*, collected in the South China Sea, led to the isolation of three sesquiterpens⁵ and nine indole alkaloids including a pair of unprecedented spiro-trisindole enantiomers and seven known indole monomers and dimmers,¹⁷ among which three brominated indoles, 2,3,5,6-tetrabromoindole, 1-methyl-2,3,5-tribromoindole and 1-methyl-2,3,5,6-tetrabromoindole, were proved to be the main constituents. The present continuous research on the minor constituents of *L. similis* resulted in the discovery of four new minor brominated indole related alkaloids, including one indole, **1**, one 1,3-dihydro-indole-2-one, **2**, one carbazole, **3**, and one

2-carboxylamino-benzoate, **4**. Among them, compounds **1** and **2** were the first example of naturally occurring indole with 3-benzyl group and 1,3-dihydro-indole-2-one with 2-isopropylidene group, respectively, compound **3** was the first carbazole alkaloids isolated from the genus *Laurencia*, while compound **4** was the first 2-carboxylamino-benzoate from the genus *Laurencia*, which might be a degradation product of indole skeleton. The antibacterial activities of the isolates against seven bacterial strains were also evaluated and compound **1** exhibited the most potent antibacterial activity with the MIC values ranging from 2 to 8 µg/mL. Herein, we report the isolation,¹⁸ structural elucidation, and antibacterial activities of compounds **1–4** (Fig. 1).

Compound **1**¹⁹ was obtained as yellow oil. Its molecular formula was deduced as C₁₅H₉NOBr₄ (10 degrees of unsaturation) by negative HR-ESI-MS at *m/z* 533.7336 [M–H][–] (calcd for C₁₅H₈NOBr₄). The ¹H and ¹³C NMR data (Table 1) exhibited signals characteristic of a 2,3,5,6-tetrasubstituted indole moiety and a 1,2,4-trisubstituted benzene moiety evidenced by proton signals for one NH at δ_H 8.09 (1H, br s), two para aromatic protons at δ_H 7.53 (1H, s) and 7.51 (1H, s), an aromatic ABX spin system protons at δ_H 7.19 (1H, d, *J* = 3.0 Hz), 6.98 (1H, dd, *J* = 8.4, 3.0 Hz), 6.85 (1H, d, *J* = 8.4 Hz), and the corresponding 14 aromatic or olefinic carbons, five of which were protonated. Extensive analysis of two-dimensional NMR data of compound **1**, including ¹H–¹H COSY, HSQC and HMBC, further confirmed the presence of 2,3,5,6-tetrasubstituted indole and 1,2,4-trisubstituted benzene moieties. Additionally, a hydroxy and a methylene were identified by the

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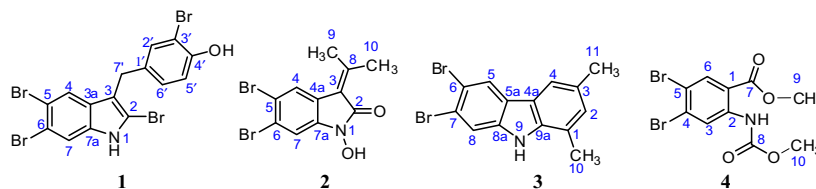


Figure 1. Structures of compounds 1–4.

Table 1
 ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectral data of compounds 1–4

Position	1 ^a		Position	2 ^b		3 ^b		4 ^a	
	δ_{H} (mult, J in Hz)	δ_{C}		δ_{H} (mult, J in Hz)	δ_{C}	δ_{H} (mult, J in Hz)	δ_{C}	δ_{H} (mult, J in Hz)	δ_{C}
1	8.09 (1H, br s)		1	9.62 (1H, br s)					141.3
2		110.9	2		168.7	7.10 (1H, br s)			114.9
3		114.0	3		122.4			8.84 (1H, s)	123.9
3a		128.3	3a		126.4				
4	7.53 (1H, s)	122.7	4	7.82 (1H, s)	128.8	7.75 (1H, br s)			132.0
5		117.9	4a						
6		115.9	5		123.1	8.37 (1H, s)			116.6
7	7.51 (1H, s)	115.2	5a						
7a		135.7	6		115.8			8.21 (1H, s)	135.1
1'		133.0	7	7.25 (1H, s)	114.6				167.1
2'	7.19 (1H, d, 3.0)	131.3	7a		141.8				
3'		110.2	8		158.6	7.82 (1H, s)			153.8
4'		150.1	8a						
5'	6.85 (1H, d, 8.4)	116.0	9	2.39 (3H, s)	25.4	10.38 (1H, br s)		3.93 (3H, s)	52.8
6'	6.98 (1H, dd, 8.4, 3.0)	128.9	9a						
7'	3.85 (2H, s)	29.5	10	2.57 (3H, s)	23.0	2.50 (3H, s)		3.80 (3H, s)	52.9
OH	5.33 (1H, br s)		11			2.44 (3H, s)			
			NH					10.42 (1H, br s)	

^a recorded in CDCl_3 .

^b recorded in $\text{Acetone-}d_6$.

remaining signals at δ_{H} 5.33 (1H, br s), and δ_{H} 3.85 (2H, s) and the corresponding δ_{C} 29.5. The 1,2,4-trisubstituted benzene moiety was assumed to be linked to C-3 through the methylene moiety based on the HMBC interactions of H-7' with C-2, C-3, C-3a, C-1', C-2' and the NOESY correlations between H-4 and H-7', H-2', H-6'. The HMBC interactions of δ_{H} 5.33 (OH) with C-3', C-5' indicated the attachment of 4'-OH. The remaining four bromine atoms were accordingly placed at C-2, C-5, C-6, and C-3' respectively based on the biogenetic consideration, multiplicities of the aromatic protons and HMBC correlations. Thus, the structure of compound **1** was characterized definitely as 2,5,6-tribromo-3-[(3'-bromo-4'-hydroxyl-phenyl)-methyl]-1H-indole, which was the first example of naturally occurring indole with 3-benzyl group.

Compound **2**²⁰ was isolated as yellow solid, and its molecular formula was determined to be $\text{C}_{11}\text{H}_9\text{NO}_2\text{Br}_2$ (7 degrees of unsaturation) by negative HR-ESI-MS at m/z 343.8922 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{11}\text{H}_8\text{NO}_2\text{Br}_2$). The ^1H NMR spectrum displayed nine proton signals characteristic for one hydroxy at δ_{H} 9.62 (1H, br s), two para aromatic protons at δ_{H} 7.82 (1H, s), 7.25 (1H, s), and two methyl groups at δ_{H} 2.57 (3H, s), 2.39 (3H, s). The ^{13}C NMR and HSQC spectra showed eleven signals for one carbonyl carbon at δ_{C} 168.7, eight aromatic or olefinic carbons (two of which were protonated), and two methyl carbons at δ_{C} 25.4, 23.0. The above features suggested the presence of 5,6-disubstituted-1,3-dihydro-indole-2-one, which was confirmed unambiguously by the HSQC and HMBC. The key HMBC correlations of H-9 with C-2, C-3, C-8, C-10 and H-10 with C-2, C-3, C-8, C-9 proved the presence of an isopropenyl group and its linkage at C-3. Consequently, the remaining OH was placed at N-1. Thus, compound **2** was identified unambiguously as 5,6-dibromo-1-hydroxy-3-isopropylidene-1,3-dihydro-indole-2-one, which was the first example of naturally occurring 1,3-dihydro-indole-2-one with 2-isopropylidene group.

Compound **3**²¹ isolated as white powder, had molecular formula of $\text{C}_{14}\text{H}_{11}\text{NBr}_2$ (9 degrees of unsaturation) by negative HR-ESI-MS at m/z 349.9174 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{14}\text{H}_{10}\text{NBr}_2$). The ^1H and ^{13}C NMR data (Table 1) exhibited signals characteristic of 1,3,6,7-tetrasubstituted carbazole with two CH_3 evidenced by signals for one NH at δ_{H} 10.38 (1H, br s), four aromatic protons at δ_{H} 8.37 (1H, s), 7.82 (1H, s), 7.75 (1H, br s), 7.10 (1H, br s), two methyl groups at δ_{H} 2.50 (3H, s), 2.44 (3H, s), and the corresponding twelve aromatic carbon signals (four of which were protonated) and two methyl carbons at δ_{C} 17.1, 21.5. The 1D and 2D NMR spectra allowed the assignment of all signals and further confirmation of the above deduction. The two methyl groups were attached to C-1 and C-3 respectively based on the NOE correlations of H₃-10 with H-2, H-9 and H₃-11 with H-2, H-4. The remaining two bromine atoms were placed at C-6 and C-7 based on the multiplicities of the aromatic protons and biogenetic consideration. Thus, compound **3** was characterized unambiguously as 6,7-dibromo-1,3-dimethyl-9H-carbazole, which was the first carbazole alkaloids isolated from the genus *Laurencia*.

Compound **4**²² was isolated as white solid and assigned with the molecular formula of $\text{C}_{10}\text{H}_9\text{NO}_4\text{Br}_2$ (6 degrees of unsaturation) by HR-EI-MS at m/z 364.8903 $[\text{M}]^+$ (calcd for $\text{C}_{10}\text{H}_9\text{NO}_4\text{Br}_2$). The ^1H and ^{13}C NMR data were not in good agreement with those of 5,6-dibromoindole derivatives, which were the most common structures of the secondary metabolites from *L. similis*. The substructure of 2-carboxylamino-4,5-dibromo-benzoate was deduced by the characteristic signals for NH at δ_{H} 10.42 (1H, br s), two para aromatic protons at δ_{H} 8.84 (1H, s), 8.21 (1H, s) and the corresponding six aromatic carbons (two of which were protonated), and two carbonyl groups at δ_{C} 167.1, 153.8, and further confirmed by the HSQC and HMBC correlations. The remaining two methoxy groups [δ_{H} 3.93 (3H, s), 3.80 (3H, s); δ_{C} 52.8, 52.9] were attached to the two

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