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# Streptocarbazoles A and B, Two Novel Indolocarbazoles from the Marine-Derived Actinomycete Strain *Streptomyces* sp. FMA

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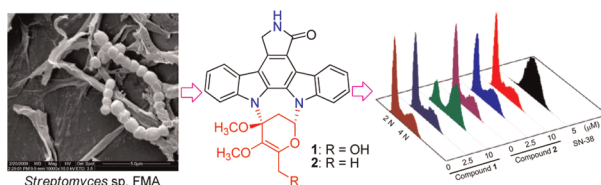
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## ABSTRACT



Streptocarbazoles A (1) and B (2), two novel indolocarbazoles featuring unprecedented cyclic *N*-glycosidic linkages between 1,3-carbon atoms of the glycosyl moiety and two indole nitrogen atoms of the indolocarbazole core, were isolated from the marine-derived actinomycetes strain *Streptomyces* sp. FMA. Their structures were established by spectroscopic methods, CD spectra, and ECD quantum mechanical calculations. Compound 1 was cytotoxic on HL-60 and A-549 cell lines and could arrest the cell cycle of Hela cells at the G<sub>2</sub>/M phase.

During the last 35 years, more than 130 indolocarbazoles (ICZs) have been isolated from different organisms including bacteria, fungi, and invertebrates.<sup>1</sup> ICZs, kinds of alkaloids featuring a K252c<sup>2</sup> skeleton and represented by staurosporine,<sup>3</sup> have succeeded in attracting great attention from chemists, biologists, physicians, and pharmaceutical companies for their unusual structures and

important biological activities.<sup>4</sup> Cytotoxicity,<sup>5</sup> protein kinase C (PKC),<sup>6</sup> and topoisomerase (Topo)<sup>7</sup> inhibitions are by far the most widely searched and reported biological activities for ICZs. Several ICZs, such as UCN-01,<sup>8</sup> lestaurtinib,<sup>9</sup> and NSC655649,<sup>10</sup> are currently being tested in the cancer clinical trials. As part of our ongoing research on new antitumor compounds from marine-derived actinomycetes,<sup>11</sup> strain FMA, identified as *Streptomyces*

<sup>¶</sup> These authors contributed equally to this paper.

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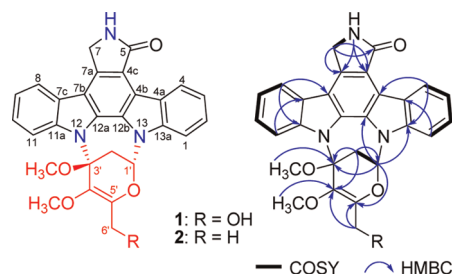
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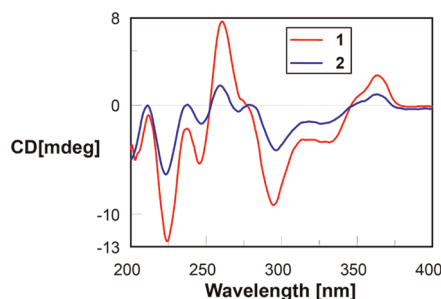
sp., was isolated from a mangrove soil collected in Sanya, Hainan Province of China. The EtOAc extracts of the fermentation broth of strain FMA exhibited significant cytotoxic effect on the P388 cell line. A series of metabolites contained in the extracts showed UV absorptions similar to those of ICZs at 227, 282, 325, and 355 nm<sup>3,12</sup> in an HPLC–UV profile (Figure S14, Supporting Information). Chemical investigation resulted in the isolation of two novel ICZs, which have been named the streptocarbazoles A (**1**) and B (**2**),<sup>13</sup> as well as five known analogues, K252c (indolocarbazole core),<sup>2</sup> K252a,<sup>14</sup> 3'-*epi*-K252a,<sup>14</sup> RK 286c,<sup>15</sup> and 4-bis(3-indolyl)-1*H*-pyrrole-2,5-dione.<sup>16</sup> Streptocarbazoles A (**1**) and B (**2**) possess exceptional cyclic *N*-glycosidic linkages between the 1,3-carbons of the glycosyl moiety and two indole nitrogen atoms of K252c. This connection was first discovered in the family of ICZs, and all 66 reported cyclic indolocarbazole glycosides were *N*-glycosidic linkages between the 1,5-carbons of the glycosyl moiety and the indolocarbazole core. In addition, there were only seven examples of cyclic *O*-glycosides in the literature, and the two glycosidic bonds were formed between the 1,2-carbons of the glycosyl moiety and the aglycone.<sup>11b,17</sup>

Streptocarbazole A (**1**) was assigned a molecular formula of C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub> on the basis of HRESIMS,<sup>18</sup> requiring 19 degrees of unsaturation. Its UV spectrum showed a characteristic peak of indolocarbazole chromophore at λ<sub>max</sub> 227, 282, 325, and 355 nm.<sup>3,12</sup> The IR absorption bands at 3329, 1681, 1590, and 1454 cm<sup>-1</sup> suggested the presence of hydroxy, aromatic nucleus, and carbonyl groups. The <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) displayed signals similar to those of staurosporine,<sup>19</sup> further indicating an indolocarbazole unit that was confirmed by <sup>1</sup>H–<sup>1</sup>H COSY of H-1/H-2/H-3/H-4 and H-8/H-9/H-10/H-11 and by the key HMBC correlations of H-4 to C-13a and C-4b, H-6 to C-4c and C-7a, H-8 to C-7b and C-11a, and H-11 to C-7c (Figure 1). Moreover, careful comparison of its <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) with those of staurosporine<sup>19</sup> revealed that the glycosyl moiety is different, and two olefinic quaternary carbons (δ<sub>C</sub> 134.2 and 145.2) are present in the sugar moiety of **1**. This could be explained by the oxidation followed by enolization of the sugar moiety. <sup>1</sup>H–<sup>1</sup>H COSY from H-1' to H-2' and the key HMBC



**Figure 1.** Structures and key <sup>1</sup>H–<sup>1</sup>H COSY and HMBC correlations of **1** and **2**.

correlations of H-2' to C-1', C-3' and C-4', 3'-OCH<sub>3</sub> to C-3', 4'-OCH<sub>3</sub> to C-4', H-6' to C-4' and C-5', and H-1' to C-3', C-5' and C-12b suggested that the glycosyl moiety is 1,3-disubstituted 3,4-di-*O*-methyl-2-deoxy-4,5-dehydropyranoglucose and the glycosides are formed via the linkages of C<sub>1'</sub>–N<sub>13</sub> and C<sub>3'</sub>–N<sub>12</sub>. *Cis*- and *trans*- could be two possible candidate relative configurations of **1**.



**Figure 2.** CD spectra of streptocarbazoles A (**1**) and B (**2**).

Model building of each via HyperChem 7.5 soft MM+ energy minimization calculations suggested that *trans*-**1** possessed significant intraring strain and higher molecular energy (Figure S1, Supporting Information). Furthermore, chemical shifts of <sup>13</sup>C NMR were computed at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level.<sup>20</sup> The magnetic shielding values were converted into chemical shifts after the corrections using slope and intercept of the linear-square functions,<sup>20</sup> and the relative errors of chemical shifts were computed by subtracting the calculated <sup>13</sup>C NMR from the experimental shifts. The relative errors between the measured <sup>13</sup>C shifts and the calculated <sup>13</sup>C shifts are less than 7.2 ppm in *cis*-**1**, while the maximum error at C-5' reached 14.9 ppm in *trans*-**1** (Table S2, Supporting Information). Thus, the relative configuration of **1** was deduced as *cis*.

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(18) Streptocarbazole A (**1**): yellow, amorphous powder, [α]<sub>D</sub><sup>21</sup> –54 (c 0.1, MeOH); UV (MeOH) λ<sub>max</sub> (log ε) 227 (3.32), 282 (3.65), 325 (3.15), 355 (3.09) nm; CD (MeOH) λ<sub>max</sub> (Δε) 364 (+1.5), 292 (–4.3), 259 (+4.1), 246 (–2.7), 237 (+0.6), 224 (–6.1), 212 (+1.5), 202 (–3.5) nm; IR (KBr) ν<sub>max</sub> 3329, 2936, 1590, 1454, 1398, 1354, 1330, 1139, 1099, 1057, 1021, 746 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR, see Table 1; HRESIMS *m/z* 482.1715 [M + H]<sup>+</sup> (calcd for C<sub>28</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub>, 482.1716).

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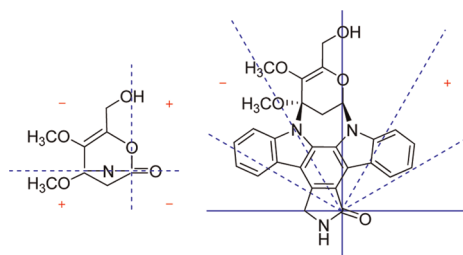
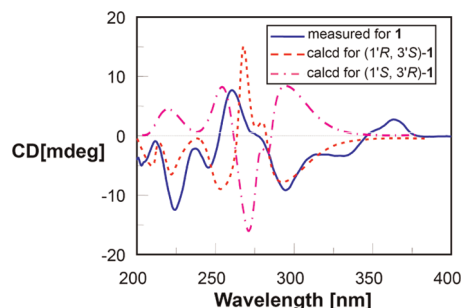
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**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for Streptocarbazoles A (**1**) and B (**2**) (600, 150 MHz, DMSO- $d_6$ , TMS,  $\delta$  ppm)

position	<b>1</b>		<b>2</b>	
	$\delta_{\text{C}}$	$\delta_{\text{H}}$ (J in Hz)	$\delta_{\text{C}}$	$\delta_{\text{H}}$ (J in Hz)
1	110.5, CH	7.82, d (8.3)	110.3, CH	7.82, d (8.2)
2	126.5, CH	7.55, t (8.3)	126.5, CH	7.55, t (8.2)
3	121.1, CH	7.35, t (7.8)	121.1, CH	7.36, t (7.8)
4	126.2, CH	9.37, d (7.8)	126.3, CH	9.37, d (8.2)
4a	123.4, C		123.4, C	
4b	116.3, C		116.3, C	
4c	120.1, C		120.1, C	
5	172.3, C		172.3, C	
6-NH		8.65, s		8.67, s
7	45.8, CH <sub>2</sub>	4.98, s	45.8, CH <sub>2</sub>	4.99, s
7a	134.2, C		133.3, C	
7b	116.9, C		116.8, C	
7c	123.5, C		123.5, C	
8	121.6, CH	8.03, d (7.8)	121.6, CH	8.03, d (7.8)
9	121.2, CH	7.35, t (7.8)	121.1, CH	7.36, t (7.8)
10	126.5, CH	7.53, t (8.2)	126.5, CH	7.52, t (8.2)
11	115.4, CH	8.23, d (8.7)	115.4, CH	8.24, d (8.2)
11a	141.1, C		141.1, C	
12a	133.9, C		133.9, C	
12b	125.5, C		125.5, C	
13a	139.7, C		139.6, C	
1'	77.5, CH	7.04, d (5.1)	77.6, CH	7.04, d (6.0)
2'	37.9, CH <sub>2</sub>	3.41, dd (14.5, 6.0); 3.57, d (14.5)	37.8, CH <sub>2</sub>	3.42, dd (15.6, 5.9); 3.55, d (15.6)
3'	87.8, C		87.8, C	
4'	134.2, C		134.0, C	
5'	145.3, C		142.9, C	
6'	56.3, CH <sub>2</sub>	3.68, d (12.8); 3.82, d (12.8)	14.8, CH <sub>3</sub>	1.59, s
3'-OCH <sub>3</sub>	51.6, CH <sub>3</sub>	3.56, s	51.6, CH <sub>3</sub>	3.57, s
4'-OCH <sub>3</sub>	64.0, CH <sub>3</sub>	3.28, s	62.1, CH <sub>3</sub>	3.14, s

An extension of the lactone sector rule<sup>21</sup> could be used to determine the absolute configuration of **1**. The molecule was viewed from the line on the plane of the amide group along the bisectrix of the N–C=O angle, i.e., the line from C-5 to C-1' as shown in Figure 3 for (1'R, 3'S)-**1**. The functional group at C-3' lying in the back upper left sector was responsible for the negative Cotton effect ( $\pi$ – $\pi^*$  transition of conjugated lactam), which was good in accordance with the measured negative CD Cotton effect at  $\lambda_{\text{max}}$  292 nm of **1** (Figure 2). Moreover, the quantum chemical ECD calculation method<sup>22</sup> was used to confirm the absolute configuration of **1**. The preliminary conformational distribution search was performed by HyperChem 7.5 software. The corresponding minimum geometries were further fully optimized by using DFT at the B3LYP/6-31G(d) level as implemented in the Gaussian 03 program package. The stable conformers obtained were submitted to ECD calculation by the TDDFT [B3LYP/6-31G(d)] method. The overall predicted ECD spectrum of **1** was subsequently compared with the measured one. The measured

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**Figure 3.** Application of an amide sector rule to **1**.**Figure 4.** Measured and calculated ECD spectra for **1**.

CD curve of **1** showed Cotton effect at  $\lambda_{\text{max}}(\Delta\epsilon)$  292 (–4.3), 259 (+4.1) and 224 (–6.1) nm, matching with the calculated ECD curve of (1'R, 3'S)-**1** and opposite to that of (1'S, 3'R)-**1** (Figure 4), and the B3LYP/6-31G(d)-optimized conformations were also used in optical rotation ( $[\alpha]_{\text{D}}$ ) computations at the B3LYP/6-311G(d,p) level.<sup>23</sup> The calculated  $[\alpha]_{\text{D}}$  value for (1'R, 3'S)-**1** was –56.6, close to the measured value of –54. Thus, the absolute configuration of **1** was unambiguously established to be (1'R, 3'S).

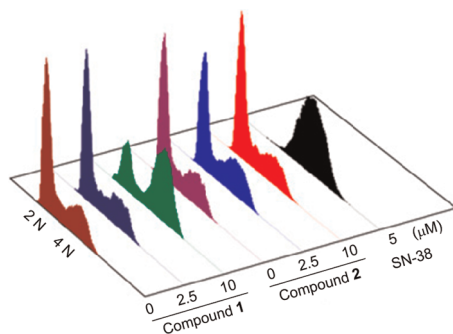
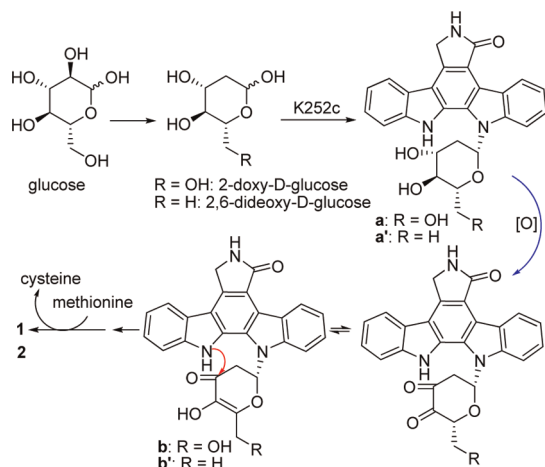
The molecular formula of streptocarbazole B (**2**) was assigned to be C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub> based on the HRESIMS,<sup>24</sup> which was only one oxygen less than that of **1**. Careful comparison of its  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (Table 1) with those of **1** showed that a methyl signals at  $\delta_{\text{C/H}}$  14.8/1.59 in **2** replaced the corresponding hydroxymethyl signals at  $\delta_{\text{C/H}}$  56.2/3.68 and 3.82 in **1**, suggesting that the glycosyl moiety in **2** is 6-deoxygenated. The HMBC correlations from H<sub>3</sub>-6' to C-5' and C-4' also supported this change in **2** (Figure 1). The CD Cotton effects at  $\lambda_{\text{max}}(\Delta\epsilon)$  292 nm ( $\Delta\epsilon$  –1.4), 259 nm ( $\Delta\epsilon$  +1.2) and 224 nm ( $\Delta\epsilon$  –2.4) (Figure 2) and the specific rotation ( $[\alpha]_{\text{D}}$  –23) were almost

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(24) Streptocarbazole B (**2**): yellow, amorphous powder,  $[\alpha]_{\text{D}}^{21}$  –23 ( $c$  0.1, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 227 (3.30), 282 (3.58), 325 (3.13), 355 (3.05) nm; CD (MeOH)  $\lambda_{\text{max}}$  ( $\Delta\epsilon$ ) 364 (+0.4), 292 (–1.4), 259 (+1.2), 246 (–0.8), 236 (+0.3), 224 (–2.4), 211 (+0.7), 200 (–2.2) nm; IR (KBr)  $\nu_{\text{max}}$  2924, 1632, 1454, 1387, 1354, 1330, 1295, 1144, 1062, 1020, 747 cm<sup>–1</sup>;  $^1\text{H}$  and  $^{13}\text{C}$  NMR, see Table 1; HRESIMS  $m/z$  466.1758 [ $\text{M} + \text{H}$ ]<sup>+</sup> (calcd for C<sub>28</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>, 466.1767).



**Scheme 1.** Plausible Biosynthetic Pathway of **1** and **2**



**Figure 5.** DNA histograms of HeLa cells treated with different concentrations of streptocarbazoles A (**1**) and B (**2**).

the same to those of **1**, indicating the same absolute configuration. Thus, the structure of streptocarbazole B (**2**) was clearly elucidated as 6'-deoxystreptocarbazole A.

A plausible biogenetic pathway for streptocarbazoles A (**1**) and B (**2**) was postulated (Scheme 1). The indolocarbazole unit (K252c) was derived from tryptophan,<sup>25</sup> while the glycosyl moiety was probably developed from 2-deoxy-D-pyranoglucose. The glycosidation of 12-NH of K252c with 2-deoxypyranoglucose produced glycoside **a** that serves the key biosynthetic precursor. Glycoside **a** underwent an

oxidation and an enolization to yield another glycoside **b** which further underwent aldol condensation followed by methylation to yield **1**. Streptocarbazole B (**2**) was probably formed from K252c and 2,6-dideoxy-D-pyranoglucose by the same biogenetic procedures.

Compounds **1** and **2** were tested for cytotoxic effects on the HL-60, A-549, and P388 cell lines using the SRB method<sup>26</sup> and on the HeLa cell line using the MTT method.<sup>27</sup> The results showed that compound **1** is effective on HL-60, A-549, P388 and HeLa cells, with IC<sub>50</sub> values of 1.4,<sup>13</sup> 5.0,<sup>13</sup> 18.9, and 34.5 μM, respectively. And compound **2** was active against P388 and HeLa cells with IC<sub>50</sub> values of 12.8 and 22.5 μM, respectively, but no effects on HL-60 and A-549 cells were observed (IC<sub>50</sub> > 50 μM). The inhibitory effects of **1** and **2** on the cell cycle<sup>28</sup> and the kinase<sup>29</sup> were also evaluated. The results showed that compound **1** arrested the cell cycle of HeLa cells in the G<sub>2</sub>/M phase at a concentration of 10 μM (Figure 5) and both new compounds did not show obvious inhibitory effects on the kinase GSK3-beta, Aurora-A, PKC-beta and PKC-epsilon (Table S1, Supporting Information).

Compounds **1** and **2** had been applied for the invention patents in China for the novel structures and the cytotoxicity against HL-60 and A-549 cell lines.<sup>13</sup> In this paper, the absolute configurations were revised and the bioactivities such as inhibition of cell cycle and the kinases and the cytotoxicity against HeLa and P388 cell lines were complemented.

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**Supporting Information Available.** Experimental details, the NMR spectra of **1** and **2**, and bioassay protocols used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.