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Two new glutarimide antibiotics from Streptomyces sp. HS-NF-780

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Abstract

Two new glutarimide antibiotics, 9-methylstreptimidone $2-\alpha$ -D-glucopyranoside (1), and hydroxyiso-9-methylstreptimidone (2), along with a known compound, 9-methylstreptimidone (3), have been isolated from the broth of *Streptomyces* sp. HS-NF-780. Their structures were determined on the basis of spectroscopic analysis, including 1D and 2D NMR techniques as well as ESI-MS and comparison with data from the literature. By modified Mosher's method and acid hydrolysis, the absolute configurations of compounds 1 and 2 were established. Compounds 1 and 2 exhibited moderate cytotoxic activity.

The antibiotics of the glutarimide group are structurally characterized by the presence of glutarimide ring bearing a side chain at the 1-position [1]. A number of distinct substances belonging to this class such as 9-methylstreptimidones [2], cycloheximide [3, 4], and migrastatin [5, 6] have been isolated from various species of Streptomyces [7]. Among 9-methylstreptimidone showed strong inhibitory them, activity against yeasts and filamentous fungi [1]. Besides, 9-methylstreptimidone inhibited NO production and iNOS expression in LPS-stimulated RAW264.7 cells, and induced apoptosis in Jurkat cells and adult T-cell leukemia cells, similar to other NF- κ B inhibitors [8]. In the course of our screening program for novel microbe-derived bioactive secondary metabolites, two new glutarimide derivatives named 9-methylstreptimidone $2-\alpha$ -D-glucopyranoside (1) and hydroxyiso-9-methylstreptimidone (2), along with a known

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compound, 9-methylstreptimidone (**3**) (Fig. 1), were isolated from the culture broth of *Streptomyces* sp. HS-NF-780. In this paper, we describe the fermentation, isolation, structure elucidation, and bioactivity of the two new compounds.

The producing strain HS-NF-780 was isolated from a soil sample collected from Linyi, Shandong province, China using the standard dilution plate method. The strain was identified as the genus *Streptomyces* because its 16S rRNA sequence (accession no: MH362834 in the GenBank) exhibited a high-sequence similarity of 100% with that of *Streptomyces* sp. NEAU-BGG209 (accession no: MG820043).

Strain HS-NF-780 was grown and maintained for 7 days at 28 °C on the YMS medium consisting of yeast extract 4.0 g, malt extract 10.0 g, glucose 4.0 g, CoCl₂·6H₂O 0.005 g and agar 20.0 g in 1.01 tap water at pH 7.0. The stock culture was transferred into 11 Erlenmeyer flasks containing 250 ml of the seed medium and incubated at 28 ° C for 48 h on a rotary shaker at 250 r.p.m. The seed medium was composed of glucose 4.0 g, malt extract 10.0 g and yeast extract 4.0 g in 1.01 tap water, pH 7.0. All of the media were sterilized at 121 °C for 20 min. The seed culture (5%) was transferred into 11 Erlenmeyer flasks containing 25% volume of production medium. The production medium was composed of glucose 1%, soluble starch 4%, yeast extract 0.4%, malt extract 1%, CaCO₃ 0.2%, FeSO₄·7H₂O 0.1%, ZnSO₄·7H₂O 0.1%, and MnCl₂·4H₂O 0.1% at pH 7.2-7.4. The flasks were incubated at 28 °C for 7 days, shaken at 250 r.p.m.

The final 201 fermentation broth was filtered to separate mycelial cake and supernatant. The mycelial cake was washed with water (31) and subsequently extracted with



Fig. 1 Structures of compounds 1, 2, and 3

MeOH (31) and the supernatant was subjected to a Diaion HP-20 resin (Mitsubushi Chemical, Tokyo, Japan) column eluting with 95% EtOH (51). The MeOH extract and the EtOH eluents were evaporated under reduced pressure at 55 °C to yield the crude extract. The crude extract was chromatographed on a silica gel (Qingdao Haiyang Chemical Group, Qingdao, China; 100-200 mesh) column and successively eluted with a stepwise gradient of CHCl₃/ MeOH (100:0-50: 50, v/v) to give three fractions (Fr.1-Fr.3) based on the TLC profiles. TLC was performed on silica-gel plates (HSGF254, Yantai Chemical Industry Research Institute, Yantai, China) with solvent system of CHCl₃/MeOH (9:1, v/v) and the developed TLC plates were observed under a UV lamp at 254 nm or by heating after spraying with sulfuric acid-ethanol, 5:95 (v/v). The Fr.2 was subjected to another silica gel column eluted with CHCl₃/MeOH (95:5-60:40, v/v) to give six fractions (Fr.2-1-Fr.2-6). The Fr.2-4 was further purified by semipreparative HPLC (Agilent 1100, Zorbax SB-C18, 5 µm, $250 \times 9.4 \text{ mm}$ inner diameter; 1.5 ml min⁻¹; 254 nm; Agilent, PaloAlto, CA, USA) eluting with CH₃CN/H₂O (20:80, v/v) to obtain compound 1 ($t_{\rm R}$ 24.68 min, 18.0 mg). The Fr.2-3 was separated by semi-preparative HPLC eluting with CH₃CN/H₂O (25:75, v/v) to afford compound 2 (t_R 20.13 min, 14.2 mg). The Fr.1 was subjected to a Sephadex LH-20 (GE Healthcare, Glies, UK) column eluted with CHCl₃/MeOH (1:1, v/v) and detected by TLC to give two subfractions (Fr.1-1-Fr.1-2). The Fr.1-2 was isolated by semi-preparative HPLC eluting with CH₃CN/ H_2O (35:65, v/v) to give compound 3 (t_R 25.06 min, 23.5 mg). ¹H and ¹³C NMR spectra were measured with a Bruker DRX-400 (400 MHz for 1 H and 100 MHz for 13 C) spectrometer (Bruker, Rheinstetten, Germany). The ESI-

MS and HR-ESI-MS spectra were taken on a Q-TOF Micro LC-MS-MS mass spectrometer (Waters Co, Milford, MA, USA).

Compound 1 was isolated as colorless oil with $\left[\alpha\right]_{D}^{25} + 125$ (c 0.03, EtOH) and UV (EtOH) λ_{max} nm (log ε): 233 (4.02). Its molecular formula was determined to be C23H35NO9 by HRESIMS at m/z 492.2207 [M + Na]⁺ (calcd as 492.2204 for C₂₃H₃₅NO₉Na) and NMR data (Table 1). In the IR spectrum of 1, absorption at 3447, 3197, and 1689 cm^{-1} indicated the presence of hydroxyl, imide, and carbonyl groups, respectively. Analysis of ¹H NMR spectrum (Table 1) of 1 revealed the presence of three olefinic protons at $\delta_{\rm H}$ 5.19 (1 H, br d, J = 9.8 Hz), 5.48 (1 H, m), 5.82 (1 H, br d, J = 11.6 Hz), one anomeric proton at $\delta_{\rm H}$ 4.87 (1 H, d, J = 3.9 Hz), one oxygenated methylene at $\delta_{\rm H}$ 3.64 (1 H, dd, J = 11.9, 5.3 Hz), 3.78 (1 H, dd, J = 11.9, 2.1 Hz), five oxygenated methine protons from $\delta_{\rm H}$ 3.27 to $\delta_{\rm H}$ 4.19, two olefinic methyls at $\delta_{\rm H}$ 1.77 (3 H, dd, J = 7.2, 2.6 Hz), 1.86 (3 H, d, J = 1.2 Hz), one doublet aliphatic methyl at $\delta_{\rm H}$ 1.14 (3 H, d, J = 6.8 Hz). The ¹³C NMR and DEPT135 spectra (Table 1) of 1 showed 23 resonances attributable to one carbonyl carbon at $\delta_{\rm C}$ 212.1, two amide carbonyl carbons at $\delta_{\rm C}$ 175.4 and 175.4, three sp^2 methines at $\delta_{\rm C}$ 125.8, 129.7, 134.1, one sp^2 quaternary carbon at $\delta_{\rm C}$ 136.7, one anomeric carbon at $\delta_{\rm C}$ 99.1, five oxygenbearing aliphatic methines between 71.6 and 75.0 ppm, one oxygenated methylene at $\delta_{\rm C}$ 62.5, two aliphatic methines at $\delta_{\rm C}$ 28.2, 48.2, four aliphatic methylenes at $\delta_{\rm C}$ 37.9, 39.2, 41.4, 44.8, and three methyl carbons at $\delta_{\rm C}$ 15.0, 16.7, 17.5. Comparison of the ¹H and ¹³C NMR data (Table 1) of **1** with those of 3 revealed significant similarities. The differences between 1 and 3 were that 1 showed six extra 13 C resonances. The six extra ¹³C resonances were postulated to glucose moiety according to one doublet anomeric proton ($\delta_{\rm H}$ 4.87), one oxygenated methylene ($\delta_{\rm H}$ 3.64, 3.78) and four oxygenated methine protons. The relatively small ${}^{3}J_{\rm HH}$ value (3.9 Hz) of the anomeric proton suggested an α linkage [9]. The linkage of the glucose to the aglycone was established by the HMBC correlation (Fig. 2) from H-1" to C-2. The NOESY correlations (Fig. 2) between H-5 and H₃-12, H-6 and H-8 demonstrated the geometry of $\Delta^{6,7}$ was *E*. In the ¹H NMR spectrum of 1, the coupling constant between H-8 and H-9 was 11.6 Hz, indicating the geometry of $\Delta^{8,9}$ was Z. Furthermore, the presence of glucose was evidenced by the acid hydrolysis. Compound 1 (2.5 mg) was dissolved in 2 ml of 2 M HCl and heated for 2 h at 80 °C, followed by neutralization with NaHCO₃. The reaction mixture was extracted with CHCl₃ to separate a sugar moiety-containing aqueous fraction from the aglycone-containing fraction. The aqueous fraction was identified by cochromatography with authentic glucose on TLC analysis using ethyl acetate/pyridine/glacial acetic acid/ H₂O (8: 5: 1: 1.5, v/v) as a developing solvent. Spots were detected by heating after spraying with sulfuric acid-ethanol (5:95, v/v). The identical $R_{\rm f}$ values of the aqueous fraction

Position	1 (in CD ₃ OD)		2 (in CD ₃ OD)		3 (in CDCl ₃)
	$\delta_{\rm H} (J \text{ in Hz})$	$\delta_{ m C}$	$\delta_{\rm H} (J \text{ in Hz})$	$\delta_{ m C}$	$\delta_{\rm H} (J \text{ in Hz})$
1	1.50 m 1.73 m	41.4	1.51 m1.56 m	42.9	1.29 m 1.54 m
2	4.19 m	72.6	4.20 m	66.8	4.08 m
3	2.72 dd (17.6, 7.5)	44.8	2.81 dd (16.2, 4.6)	46.3	2.55 m
	2.96 dd (17.6, 4.6)		2.98 dd (16.2, 7.6)		2.64 m
4		212.1		203.2	
5	3.55 m	48.2		137.2	3.62 m
6	5.19 br d (9.8)	129.7	6.99 s	144.7	5.12 d (9.6)
7		136.7		133.5	
8	5.82 br d (11.6)	134.1	5.63 d (8.2)	140.4	5.74 d (11.7)
9	5.48 m	125.8	4.66 m	65.2	5.42 m
10	1.77 dd (7.2, 1.8)	15.0	1.28 d (6.3)	23.4	1.72 dd (7.2, 1.7)
11	1.14 d (6.8)	16.7	1.95 s	13.2	1.11 d (6.8)
12	1.86 d (1.2)	17.5	1.92 s	16.7	1.80 d (1.2)
1''		175.4		175.6	
2'	2.31 m 2.60 m	39.2	2.36 m 2.75 m	38.0	2.24 m 2.70 m
3'	2.35 m	28.2	2.38 m	28.7	2.40 m
4′	2.31 m 2.77 m	37.9	2.38 m2.68 m	39.2	2.24 m 2.70 m
5'		175.4		175.5	
1″	4.87 d (3.9)	99.1			
2″	3.34 m	73.2			
3″	3.27 t (12.4)	71.6			
4″	3.57 m	74.5			
5″	3.52 m	75.0			
6″	3.78 dd (11.9, 2.1)	62.5			
	3.64 dd (11.9, 5.3)				

 Table 1 The NMR spectroscopic data of compounds 1–3

with that of authentic glucose indicated that the sugar moiety of 1 was glucose. The aglycone-containing fraction was subjected to reverse phase HPLC for analysis, with a Zorbax B-C18 column (Agilent 1100, 250 × 9.4 mm inner diameter, 5 µm), mobile phase of CH₃CN/H₂O (35:65, v/v), flow rate at 1.5 ml min^{-1} , and detection wavelength at 220 nm. Under these conditions, the aglycone-containing fraction gives peak at $t_{\rm R}$ (min) = 25.06. The peak of the known compound 9-methylstreptimidone (3) was detected at $t_{\rm R}$ (min) = 25.11. The retention time of the aglycone moiety of 1 was in good agreement with 3, which suggested that the aglycone moiety of 1 was 9-methylstreptimidone. In order to determine the absolute configuration of the glucose moiety in 1, the sugar residue was dissolved in pyridine (3 ml) containing L-cysteine methyl ester hydrochloride (1 mg) and heated at 60 °C for 1 h. A total of solution of O-torylisothiocyanate (25 µl) was added to the mixture, which was heated at 60 °C for a further 1 h. The mixture was analyzed by reversed-phase HPLC (Amethyst C18-H, 5 μ m, 250 × 4.6 mm inner diameter; 0.8 ml min ⁻¹; 250 nm) at 35 °C eluting with CH₃CN/H₂O (25:75, v/v). Under these conditions, standard sugar gave peak at $t_{\rm R}$ (min)

= 21.658 for D-glucose. The peak of the sugar residue was detected at $t_{\rm R}$ (min) = 21.789, which identified as D-glucose by comparison with the retention time of the authentic sample [10–12].

Compound 2 was isolated as pale yellowish oil with optical rotation of $[\alpha]_D^{25} + 105$ (c 0.03, EtOH) and UV (EtOH) λ_{max} nm (log ε): 276 (4.10). HR-ESI-MS showed a molecular ion peak at m/z 346.1625 $[M + Na]^+$ (calcd for C₁₇H₂₅NO₅Na, 346.1625), indicating a molecular formula of C₁₇H₂₅NO₅. In the IR spectrum of **2**, absorption at 3419 and $1684\,\mathrm{cm}^{-1}$ indicated the presence of hydroxyl and carbonyl groups, respectively. Analysis of ¹H NMR spectrum (Table 1) of 2 revealed the presence of two olefinic protons at $\delta_{\rm H}$ 5.63 (1 H, d, J = 8.2 Hz), 6.99 (1 H, s), two oxygenated methine protons at $\delta_{\rm H}$ 4.20 (1 H, m), 4.66 (1 H, m), two olefinic methyl carbons at $\delta_{\rm H}$ 1.92 (3 H, s), 1.95 (3 H, s), one doublet aliphatic methyl at $\delta_{\rm H}$ 1.28 (3 H, d, J = 6.3 Hz). The ¹³C NMR and DEPT135 spectra (Table 1) of 2 showed 17 resonances attributable to one carbonyl carbon at $\delta_{\rm C}$ 203.2, two amide carbonyl carbons at $\delta_{\rm C}$ 175.5 and 175.6, two sp^2 methines at $\delta_{\rm C}$ 140.4, 144.7,



Fig. 2 Key $^1\mathrm{H-^1H}$ COSY, HMBC, and NOESY correlations of compounds 1 and 2

two sp² quaternary carbons at $\delta_{\rm C}$ 133.5, 137.2, one aliphatic methine at $\delta_{\rm C}$ 28.7, two oxygenated methines at $\delta_{\rm C}$ 65.2, 66.8, four methylenes at $\delta_{\rm C}$ 38.0, 39.2, 42.9, 46.3, and three methyl resonances at $\delta_{\rm C}$ 13.2, 16.7, 23.4. The complete assignment of all ¹H and ¹³C NMR spectral data of 2 was subsequently accomplished by the ¹H-¹H COSY, HSQC and HMBC spectra. The correlations between H-3'/H2-1/H-2/H₂-3, H-8/H-9/H₃-10 protons in the ¹H-¹H COSY spectrum (Fig. 2) indicated the presence of two structural units of C-3'-C-3 and C-8-C-10. The observed HMBC correlations (Fig. 2) from H-2, H-6 to C-4, from H₃-11 to C-4, C-5, C-6, from H₃-12 to C-6, C-7, C-8 established the linkage of C-3'-C-10. A glutarimide ring was defined by two amide carbonyl carbons at $\delta_{\rm C}$ 175.5 and 175.6, which were coupled long range in an HMBC experiment to the protons (Table 1) of a four protons pair of methylene signals at $\delta_{\rm H}$ 2.36 (1 H, m), 2.38 (1 H, m), 2.68 (1 H, m), 2.75 (1 H, m), which were in turn coupled in a ¹H-¹H COSY spectrum to a single methine proton signal at $\delta_{\rm H}$ 2.38 (1 H, m) [13]. On the basis of the above spectroscopic data, a gross structure of 2 was established (Fig. 1). The NOESY correlation (Fig. 2) between H₃-11 and H₃-12 demonstrated the geometry of $\Delta^{5,6}$ was E. The geometry of $\Delta^{7,8}$ was also assigned as E by the NOESY correlation between H-6 and H-8. The absolute configuration of 2 was determined by the



Fig. 3 $\Delta\delta$ values for the MTPA esters (1a, 1b); $\Delta\delta$ (ppm) = $\delta_{S1a} - \delta_{R1b}$



Fig. 4 $\Delta\delta$ values for the MTPA esters (2a, 2b); $\Delta\delta$ (ppm) = $\delta_{S2a} - \delta_{R2b}$

modified Mosher's method [14, 15]. To a solution of compound 2 (2.5 mg) in dry pyridine (200 μ L) was added (-)-MTPA chloride $(15 \,\mu l)$, and the solution was stirred at room temperature for 1 h. The reaction mixture was fractionated by semi-preparative HPLC eluting with CH₃CN/ H₂O (80:20, v/v) to afford (S)-MTPA esters 1a (t_R 19.82 min, 1.2 mg) and **2a** ($t_{\rm R}$ 20.39 min, 1.0 mg). In the same way, by using (+)-MTPA chloride, the compound 2 (2.5 mg) was converted into a mixture. The mixture was isolated by semi-preparative HPLC eluting with CH₃CN/ H_2O (85:15, v/v) to obtain (R)-MTPA esters 1b (t_R 26.18 min, 1.0 mg) and **2b** (t_R 27.43 min, 1.0 mg). Based on the MTPA determination rule, calculating $\Delta \delta$ (ppm) = $\delta_{S 1a}$ - δ_{R1b} (Fig. 3), the absolute configuration at C-2 was assigned as R and the absolute configuration at C-9 was assigned as *R*. However, calculating $\Delta \delta$ (ppm) = $\delta_{S 2a} - \delta_{R 2b}$ (Fig. 4), the absolute configuration at C-2 was assigned as R and the absolute configuration at C-9 was assigned as S. It showed that 2 was a C-9 epimeric mixture. Chiral HPLC analysis of 2 with a CElluose-C column and mobile phase of CO₂/MeOH further indicated that 2 was the epimeric mixture in a ratio of ~3:2.

Compound **3** was isolated as pale yellowish oil. Its structure was elucidated as 9-methylstreptimidone by analysis of its ¹H NMR and ESI-MS spectral data (Table 1) and comparison with literature values [16].

The cytotoxicity of **1** and **2** was assayed for growthinhibition activity in vitro against three human tumor cell lines, human erythroleukemia cell line K562, human breast cancer cell line MCF-7, and human colon carcinoma cell line HCT-116 according to the CCK8 colorimetric method as reported in our previous papers [17, 18] using

Compounds	$IC_{50} \ (\mu g \ ml^{-1})$				
	K562	MCF-7	HCT-116		
1	28.37	28.79	34.83		
2	36.47	34.68	36.76		
doxorubicin	1.17	0.79	0.45		

Table 2 Cytotoxic activity of $1 \mbox{ and } 2 \mbox{ against selected human tumor cell lines}$

doxorubicin as positive control. The results (Table 2) demonstrated that the two new compounds possessed moderate cytotoxic activity towards the three tumor cell lines.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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