

Full Paper

Facile Synthesis of Some Novel Pyrido[3', 2': 4, 5]thieno[2,3-*b*][1,4]thiazine-8-carboxylic Acids

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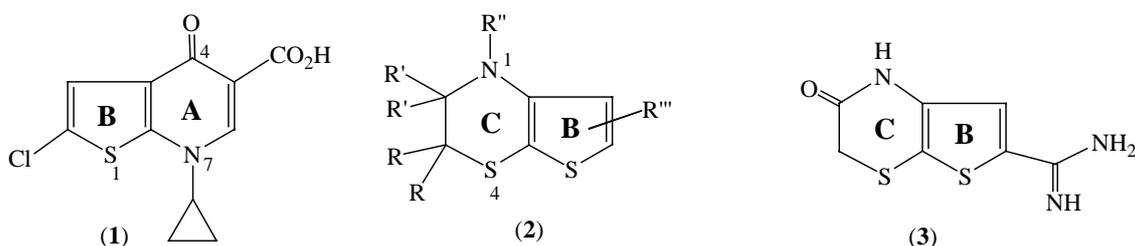
Abstract: Model tetrahydropyrido[3',2':4,5]thieno[2,3-*b*][1,4]thiazines **9a-c** were synthesized *via* reductive lactamization, using sodium dithionite, of the respective 2-[(carboxyalkyl)thio]-3-nitro-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acids **7a-c**. The latter derivatives were made *via* interaction of 2-chloro-7-cyclopropyl-3-nitro-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**6**) with each of α -mercaptoacetic, α -mercaptopropionic, and α -mercaptosuccinic acids and triethylamine in aqueous acetone at room temperature. The structures of **7a-7c** and **9a-9c** are supported by microanalytical and spectral (IR, MS, NMR) data. Compounds **9a** and **9c** showed potent inhibitory activity against the IGROV1 (Ovarian Cancer) cell line.

Keywords: 2-Chloro-7-cyclopropyl-3-nitro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid, α -mercaptoalkanoic acids, S_N-Ar reaction, reductive lactamization, tetrahydropyrido[3',2':4,5]thieno[2,3-*b*][1,4] thiazines, antitumor activity.

Introduction

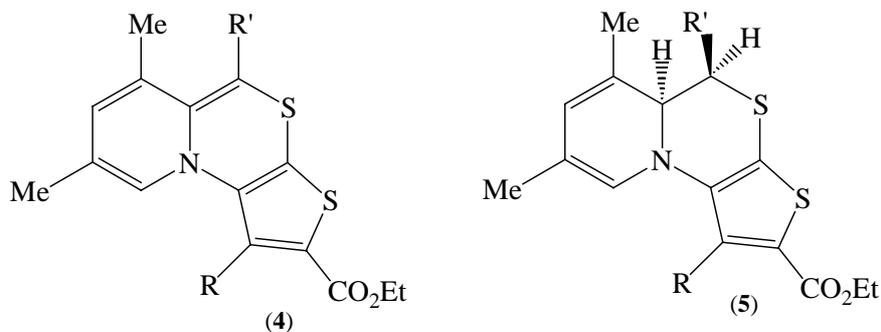
Several substituted 4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids (exemplified by **1** [1], Figure 1) bioisosteres of fluoroquinolone antibacterials (such as ciprofloxacin), were synthesized and reported to exhibit "good to excellent" levels of antibacterial potency [1-4]. On the other hand, thieno[2,3-*b*][1,4]-thiazine derivatives (e.g. **2**, Figure 1) are currently of interest due to their therapeutic properties as smooth muscle relaxants [5] and as potassium channel-opening agents [6] which make them potentially useful for the treatment of various diseases, while certain thieno[2,3-*b*][1,4]thiazine-2-ones (e.g. **3**) have been patented as urokinase inhibitors [7].

Figure 1. Structures of 4-oxothieno[2,3-*b*]pyridine (**1**) and thieno[2,3-*b*][1,4]thiazines **2**, **3**.

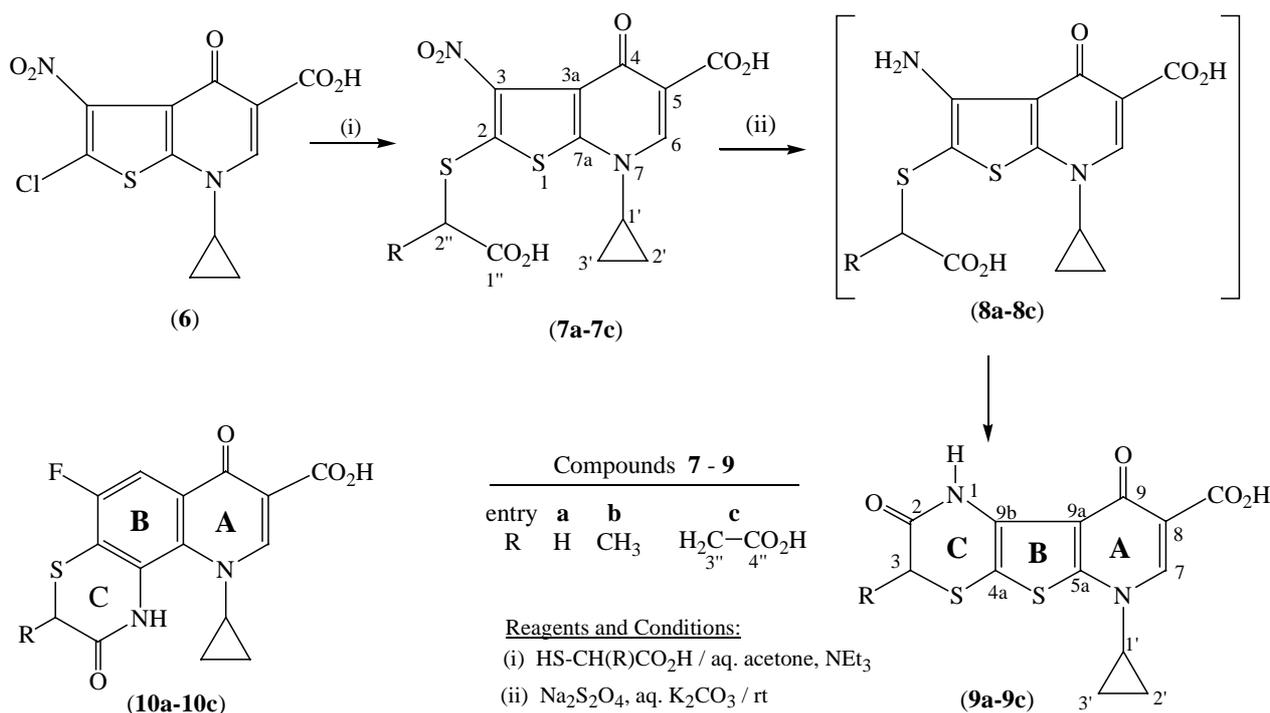


We became interested in condensed pyridothieno[1,4]thiazine tricyclic systems, for which literature data are confined to only one report [8] describing the preparation and properties of pyrido[2,1-*c*]thieno[3,2-*e*][1,4]thiazines **4** and their dihydro precursors **5** (Figure 2).

Figure 2. Structures of pyrido[2,1-*c*]thieno[3,2-*e*][1,4]thiazines **4**, **5**.



In particular, we envisaged that the hitherto undescribed tetrahydro-1*H*-pyrido[3',2':4,5]thieno[2,3-*b*][1,4]thiazine-8-carboxylic acids **9a-9c** (Scheme 1), representing a tricyclic hybrid of **1** and **3**, might exhibit interesting bioproperties such as antimicrobial and antitumor activity. Hence, the present work deals with the synthesis and properties of **9a-9c**, as outlined in Scheme 1 and detailed in the Experimental section. These novel heterocyclics **9a-9c** are potential bioisosteres of the recently described [1,4]thiazino-[2,3-*h*]quinoline-8-carboxylic acids **10a-10c** shown in Scheme 1 [9], in which the benzene nucleus (**B**) is replaced by a thiophene ring.

Scheme 1. Synthesis of pyrido[3', 2': 4, 5]thieno[2,3-*b*][1,4]thiazines **9a-9c**.

Results and Discussion

The synthesis of compounds **9a-9c** is achieved by utilizing 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**6**) [2] as a common synthon, and constructing the thiazinone nucleus thereon through two-step conversions as illustrated in Scheme 1. The first step entails the preparation of the acyclic precursors **7a-7c** via direct interaction of the appropriate α -mercapto-alkanoic acids with the synthon **6** in aqueous acetone containing triethylamine. This reaction follows an S_N-Ar (addition-elimination) path, and is facilitated by the presence of the electron-withdrawing C(4)-keto and the C(3)-nitro groups. Reduction of **7a-7c** with sodium dithionite in aqueous potassium carbonate converts the nitro group to an amino group, and is followed by spontaneous lactamization of the resultant 8-amino intermediates **8a-8c** to afford good yields of the corresponding target products **9a-9c** in fairly pure form. The required common synthon **6** is made accessible by nitration of **1**, which in turn is prepared from 3-acetyl-2,5-dichlorothiophene according to a literature procedure [1].

Antitumor Activity

Compounds **9** and **10** were tested using 10 μ M concentration against the panel of 60 human cancer cell lines used by the National Cancer Institute (NCI, USA). The most affected cell line was IGROV1 (from Ovarian Cancer). The percentage growth inhibitions at 10 μ M were 76%, 64%, 65% and 88% for compounds **9a**, **9c**, **10a** and **10c**, respectively.

Experimental

General

2,5-Dichlorothiophene, ethyl 3-(*N,N*-dimethylamino)acrylate and cyclopropylamine were purchased from Acros. (\pm)-2-Mercaptopropionic acid, (\pm)-2-mercaptosuccinic acid and mercaptoacetic acid were purchased from Aldrich. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra were measured on a Bruker DPX-300 instrument with Me_4Si as internal reference. High resolution mass spectra (HRMS) were measured in positive ion mode by Electrospray (ESI) on APEX-Qe 94 instrument. The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water 1:1 v/v + 0.1% formic acid) and infused using a syringe pump with a flow of 2 $\mu\text{L}/\text{min}$. External calibration was conducted using Arginine cluster in a mass range m/z 175-871. MS/MS spectra for **7a** and **7b** were performed in the external Qh of the APEX-Q. For all HRMS data, the mass error was 0.00-0.50 ppm. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory of the Hashemite University, Zarqa, Jordan.

2-[(Carboxymethyl)thio]-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**7a**).

Mercaptoacetic acid (0.46 g, 5 mmol) was added to a stirred solution of 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**6**, 1.32 g, 4.2 mmol) in aqueous acetone (1:2 v/v, 54 mL) and triethylamine (6 mL) at rt, and then kept in the dark for 7 h. The reaction mixture was then washed with chloroform (2 x 10 mL), the aqueous layer was acidified with 3N HCl and the precipitated product was collected and dried. The title compound was purified by stirring in boiling chloroform (10 mL) in which the soluble impurities are removed. Yield 1.37 g (88 %); mp 236-237 °C (decomp); IR (cm^{-1}) 3601, 3529, 3408, 3016, 2932, 1744, 1728, 1695, 1615, 1525, 1502, 1479, 1426, 1337, 1236, 1183; ^1H -NMR (300 MHz, DMSO-d_6) δ 1.16/1.29 (2 m, 4H, 2H-2' / 2H-3'), 3.85 (m, 1H, H-1'), 4.06 (s, 2H, 2H-2''), 8.61 (s, 1H, H-6), 13.28 [br s, 1H, C(2'')-CO₂H], 14.56 [br s, 1H, C(5)-CO₂H]; ^{13}C -NMR (75 MHz, DMSO-d_6) δ 7.8 (C-2'/C-3'), 38.2 (C-2''), 38.9 (C-1'), 113.0 (C-5), 120.3 (C-3), 133.7 (C-2), 142.3 (C-3a), 147.0 (C-6), 152.8 (C-7a), 165.4 [C(5)-CO₂H], 169.9 [C(1'')-CO₂H], 171.9 (C-4); HRMS: calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_7\text{S}_2^+ [\text{M}+\text{H}]^+$: 371.00077, found: 371.00040; calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_7\text{S}_2\text{Na}^+ [\text{M}+\text{Na}]^+$: 392.98271, found: 392.98237; MS/MS (of m/z 371): $\text{C}_8\text{H}_6\text{NS}_2^+$ (179.99367), $\text{C}_{11}\text{H}_6\text{NO}_2\text{S}_2^+$ (247.98351), $\text{C}_8\text{H}_3\text{N}_2\text{O}_4\text{S}_2^+$ (255.95301); Anal. calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_7\text{S}_2$ (370.36): C, 42.16; H, 2.72; N, 7.56; S, 17.32. Found: C, 41.78; H, 2.93; N, 7.60; S, 17.50.

2-[(Carboxyethyl)thio]-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid [(\pm)-**7b**]

Prepared from (\pm)-2-mercaptopropionic acid (0.53 g, 5 mmol) and **6** (1.32 g, 4.2 mmol) using the procedure and experimental conditions described above for the preparation of **7a**. The title compound was isolated as a yellow solid which was recrystallized from chloroform. Yield 1.26 g (78 %); mp 221-222°C (decomp); IR (cm^{-1}) 3427, 3205, 3106, 3078, 3003, 2925, 1736, 1691, 1602, 1546, 1470, 1335,

1294, 1215, 1182; $^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ 1.17 / 1.31 (m, 4H, 2H-2'/2H-3'), 1.40 (d, $J = 7.1$ Hz, 3H, CH₃), 3.87 (m, 1H, H-1'), 4.10 (q, $J = 7.1$ Hz, 1H, H-2''), 8.64 (s, 1H, H-6), 13.34 [br s, 1H, C(2'')-CO₂H], 14.40 [br s, 1H, C(5)-CO₂H]; $^{13}\text{C-NMR}$ (75 MHz, DMSO- d_6) δ 7.7 (C-2'/C3'), 18.0 (CH₃), 38.3 (C-1'), 47.9 (C-2''), 112.9 (C-5), 120.1 (C-3), 126.6 (C-2), 145.6 (C-3a), 147.6 (C-6), 154.2 (C-7a), 165.2 [C(5)-CO₂H], 172.1 (C-4), 172.5 [C(1'')-CO₂H]; HRMS: calcd. for C₁₄H₁₃N₂O₇S₂⁺ [M+H]⁺: 385.01642, found: 385.01592; calcd. for C₁₄H₁₂N₂O₇S₂Na⁺ [M+Na]⁺: 406.99836, found: 406.99781. MS/MS (of m/z 385): C₈H₆NS₂⁺ (179.99363), C₁₁H₆NO₂S₂⁺ (247.98347), C₈H₃N₂O₄S₂⁺ (255.95303), C₁₁H₉NO₃S₂⁺ (267.00185), C₁₁H₈N₂O₅S₂⁺ (311.98696); Anal. calcd. for C₁₄H₁₂N₂O₇S₂ (384.39): C, 43.74; H, 3.15; N, 7.29; S, 16.68. Found: C, 43.63; H, 3.14; N, 7.04; S, 16.66.

2-[(Carboxyl-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)thio]succinic acid [(±)-**7c**]

Prepared from (±)-2-mercaptosuccinic acid (0.75 g, 5 mmol) and **6** (1.32 g, 4.2 mmol) using the procedure and experimental conditions described above for the preparation of **7a**. The title compound was obtained as a yellow precipitate which was collected, washed successively with chloroform and methanol and dried. Yield 1.62 g (90 %); mp 211-212°C (decomp); IR (cm⁻¹) 3440 (br), 3092, 2928, 1724 (br), 1708, 1596, 1529, 1501, 1454, 1416, 1376, 1325, 1260, 1178; $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 1.17/1.31 (2 m, 4H, 2H-2' / 2H-3'), 2.74 (dd, $J = 16.8, 6.2$ Hz, 1H, H_A-3''), 2.81 (dd, $J = 16.8, 7.7$ Hz, 1H, H_B-3''), 3.87 (m, 1H, H-1'), 4.15 (dd, $J = 6.2, 7.7$ Hz, 1H, H-2''), 8.68 (s, 1H, H-6), 13.05 [br s, 2H, 2CO₂H], 14.38 [br s, 1H, C(5)-CO₂H]; $^{13}\text{C-NMR}$ (75 MHz, DMSO- d_6) δ 7.8 (C-2'/C-3'), 36.5 (C-3''), 38.4 (C-1'), 48.4 (C-2''), 112.9 (C-5), 120.0 (C-3), 126.5 (C-2), 145.6 (C-3a), 147.7 (C-6), 154.3 (C-7a), 165.2 [C(5)-CO₂H], 171.3 [C(1'')-CO₂H], 171.8 [C(4'')-CO₂H], 172.1 (C-4); HRMS: calcd. for C₁₅H₁₁N₂O₉S₂⁺ [M-H]⁺: 426.99060, found: 426.99128; Anal. calcd. for C₁₅H₁₂N₂O₉S₂ (428.40): C, 42.05; H, 2.82; N, 6.54; S, 14.97. Found: C, 42.17; H, 3.01; N, 6.60; S, 15.06.

6-Cyclopropyl-2,9-dioxo-2,3,6,9-tetrahydro-1H-pyrido[3',2':4,5]thieno[2,3-*b*][1,4]thiazine-8-carboxylic acid (**9a**)

To a vigorously stirred suspension of 2-[(carboxymethyl)thio]-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**7a**, 0.37 g, 1 mmol) in concentrated hydrochloric acid (12 mL) was added, portionwise, stannous chloride dihydrate (1.13 g, 5 mmol). The mixture was stirred for 1h, then treated with water (12 mL) and was kept under stirring at rt until a clear solution was obtained. This solution was finally neutralized with aqueous sodium carbonate whereby a deep brown precipitate was formed, which was collected, washed with cold water, cold ethanol and dried. Yield 0.27 g (84 %); mp 274-275°C (decomp); IR (cm⁻¹) 3440 (br), 3343, 3080, 3009, 2913, 1719, 1691, 1614, 1543, 1460, 1440, 1337, 1228, 1177; $^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ 1.15/1.26 (2 m, 4H, 2H-2' / 2H-3'), 3.64 (s, 2H, 2H-3), 3.82 (m, 1H, H-1'), 8.54 (s, 1H, H-7), 9.52 (s, 1H, H-1), 14.61 (br s, 1H, CO₂H); $^{13}\text{C-NMR}$ (75 MHz, DMSO- d_6) δ 7.5 (C-2'/C-3'), 30.7 (C-3), 38.2 (C-1'), 106.6 (C-4a), 111.9 (C-9b), 119.8 (C-8), 132.6 (C-9a), 145.9 (C-7), 151.9 (C-5a), 163.4 (C-2), 165.7 (CO₂H), 173.7 (C-9); HRMS: calcd. for C₁₃H₁₁N₂O₄S₂⁺ [M+H]⁺: 323.01603, found: 323.01544; calcd. for C₁₃H₁₀N₂O₄S₂Na⁺ [M+Na]⁺: 344.99797, found: 344.99737; Anal. calcd. for C₁₃H₁₀N₂O₄S₂ (322.36): C, 48.44; H, 3.13; N, 8.69; S, 19.89. Found: C, 48.39; H, 3.18; N, 8.54; S, 19.97.

6-Cyclopropyl-3-methyl-2,9-dioxo-2,3,6,9-tetrahydro-1H-pyrido[3', 2' : 4,5]thieno[2,3-b][1,4]thiazine-8-carboxylic acid [(±)-**9b**]

This compound was prepared *via* reductive cyclization of (±)- 2-[(1-carboxyethyl)thio]-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid [(±)-**7b**, 0.38 g, 1 mmol] using stannous chloride dihydrate (1.13 g, 5 mmol), and following the same procedure and experimental conditions described above for obtaining **9a**. The title product was formed as a yellow precipitate which was collected, washed with ethanol and dried. Yield 0.26 g (77 %); mp 246-247 °C (decomp); IR (cm⁻¹) 3453 (br), 3318, 3096, 3048, 1738, 1682, 1649, 1612, 1520, 1467, 1431, 1332, 1297, 1249, 1186; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.15/1.28 (2 m, 4H, 2H-2' / 2H-3'), 1.35 (d, *J* = 7 Hz, 3H, CH₃), 3.83 (m, 1H, H-1'), 3.85 (q, *J* = 7 Hz, 1H, H-3), 8.54 (s, 1H, H-7), 9.54 (s, 1H, H-1), 14.83 (br s, CO₂H); ¹³C-NMR (75 MHz, DMSO-d₆) δ 7.5 (C-2'/C-3'), 15.5 (CH₃), 37.9 (C-3), 38.2 (C-1'), 105.7 (C-4a), 112.0 (C-9b), 119.7 (C-8), 131.9 (C-9a), 145.9 (C-7), 152.0 (C-5a), 165.6 (CO₂H), 165.7 (C-2), 173.7 (C-9); HRMS: calcd. for C₁₄H₁₃N₂O₄S₂⁺ [M+H]⁺: 337.03168, found: 337.03114; calcd. for C₁₄H₁₂N₂O₄S₂Na⁺ [M+Na]⁺: 359.01362, found: 359.01313; Anal. calcd. for C₁₄H₁₂N₂O₄S₂ (336.39): C, 49.99; H, 3.60; N, 8.33; S, 19.06. Found: C, 49.97; H, 3.53; N, 8.42; S, 18.80.

3-(Carboxymethyl)-6-cyclopropyl-2,9-dioxo-2,3,6,9-tetrahydro-1H-pyrido-[3',2':4,5]thieno[2,3-b][1,4]-thiazine-8-carboxylic acid [(±)-**9c**]

This compound was prepared *via* reductive cyclization of (±)-2-[(5-carboxy-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridin-2-yl)thio]succinic acid [(±)-**7c**, 0.43 g, 1 mmol] using stannous chloride dihydrate (1.13 g, 5 mmol), and following the same procedure and experimental conditions described above for the preparation of **9a**. The title compound was isolated as a yellow solid which was washed with ethanol and dried. Yield 0.28 g (74 %); mp 239-240°C (decomp); IR (cm⁻¹) 3464 (br), 3342, 3095, 3016, 2940, 1717, 1697, 1601, 1549, 1471, 1439, 1363, 1325, 1244, 1202, 1171; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.17/1.27 (2 m, 4H, 2H-2' / 2H-3'), 2.55 (dd, *J* = 16.6, 7.8 Hz, 1H, H_A-3''), 2.87 (dd, *J* = 16.6, 6.1 Hz, 1H, H_B-3''), 3.84 (m, 1H, H-1'), 3.98 (dd, *J* = 6.1, 7.8 Hz, 1H, H-3), 8.54 (s, 1H, H-7), 9.66 (s, 1H, H-1), 12.69 [br s, 1H, C(4'')-O₂H], 14.56 [br s, 1H, C(8)-CO₂H]; ¹³C-NMR (75 MHz, DMSO-d₆) δ 7.5 (C-2'/C-3'), 33.9 (C-3''), 38.2 (C-1'), 39.5 (C-3), 106.1 (C-4a), 112.0 (C-9b), 119.8 (C-8), 132.0 (C-9a), 145.9 (C-7), 152.2 (C-5a), 164.1 (C-2), 165.7 [C(8)-CO₂H], 171.3 [C(4'')-O₂H], 173.6 (C-9); HRMS: calcd. for C₁₅H₁₃N₂O₆S₂⁺ [M+H]⁺: 381.02151, found: 381.02090; calcd. for C₁₅H₁₂N₂O₆S₂Na⁺ [M+Na]⁺: 403.00345, found: 403.00280; Anal. calcd. for C₁₅H₁₂N₂O₆S₂ (380.40): C, 47.36; H, 3.18; N, 7.36; S, 16.86. Found : C, 47.02; H, 3.17; N, 7.24; S, 16.65.

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Sample availability: Contact the authors.