Pyrodysinoic Acid Derivatives from the Marine Sponge *Dysidea robusta*

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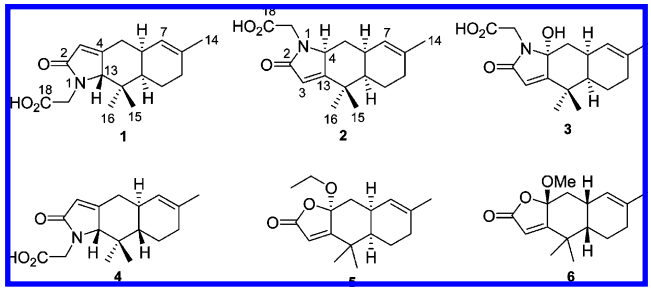
Three new nitrogen-containing terpenes related to pyrodysinoic acid (**1**) have been isolated from the sponge *Dysidea robusta* collected in Brazil. Isopyrodysinoic acid (**2**), 13-hydroxyisopyrodysinoic acid (**3**), and pyrodysinoic acid B (**4**) were obtained from the crude extract of *D. robusta* and identified by analysis of spectroscopic data. Pyrodysinoic acid B (**4**) is the first furodysin or furodysinin sesquiterpene derivative with a *trans* junction between the two six-membered rings of the 1,2,3,4,4a,7,8,8a-octahydro-1,1,6-trimethylnaphthalene moiety.

Marine sponges belonging to the genus *Dysidea* have been investigated for over 40 years as a source of diverse natural products.[1] Typical metabolites isolated from *Dysidea* spp. include polybrominated diphenyl ethers,[2] terpenes,[3] modified peptides,[4] and fatty acid derivatives.[5] Moreover, unusual metabolites have also been isolated, such as neurotoxic amino acids,[6] a meroterpene-nucleoside conjugate,[7] and a guanidine-bearing peptidic alkaloid.[8] Several of the metabolites first reported from *Dysidea* spp. have subsequently been ascribed to microbial symbionts, such as cyanobacteria.[9] A large number of *Dysidea* spp. natural products are likely derived from marine microorganisms, which are known for producing notable bioactive secondary metabolites.[1] The fact that *Dysidea* sponges have evolved this close association with symbionts helps to make them a unique source of bioactive and structurally diverse secondary metabolites.

The sponge *Dysidea robusta* (Vilanova & Muricy, 2001) has recently been ascribed as endemic to Brazil.[10] Considering the species novelty, a chemical investigation was conducted that has led to the isolation of three new derivatives of pyrodysinoic acid (**1**),[11] namely, isopyrodysinoic acid (**2**), 13-hydroxyisopyrodysinoic acid (**3**), and pyrodysinoic acid B (**4**). The isolation and structure elucidation of these compounds are the subject of the present report.



The MeOH/EtOH extract of *D. robusta* was defatted with petroleum ether. The alcoholic extract was chromatographed on a C_{18} reversed-phase column to yield two fractions that each showed three singlet methyl resonances in the ^{1}H NMR spectrum. Further purification of these two fractions by C_{18} reversed-phase HPLC resulted in the isolation of the three novel compounds, isopyrodisinoic acid (**2**), 13-hydroxyisopyrodisinoic acid (**3**), and pyrodysinoic acid B (**4**), along with the known pyrodysinoic acid (**1**).

Pyrodysinoic acid (**1**) gave a $[M - H]^-$ ion at *m*/*z* 288.1598 in the negative ion HRESIMS spectrum, appropriate for a molecular formula of $C_{17}H_{22}NO_3$. Comparison of the NMR data showed that the structure of **1** was identical to that previously reported for pyrodysinoic acid isolated from a *Dysidea* sp. collected in the Philippines. The original report, however, did not establish the relative configuration of **1**.[11] Analysis of the tROESY spectrum of pyrodysinoic acid (**1**) supported a *cis* junction between the two six-membered rings since a dipolar coupling was observed between H-6 (δ 2.36) and H-11 (δ 1.38). In addition, in the tROESY spectrum H-13 (δ 3.97) correlated to both H-5_{ax} (δ 2.14) and H-10_{ax} (δ 1.58) as well as to Me16_{eq} (δ 1.18).These observations established that the two six-membered rings in **1** have a *cis* ring junction and that N-1 is in an equatorial orientation (Figure 1). Since the $[\alpha]^{25}_D$ +18.9 (*c* 0.13, MeOH) measured for **1** by us compares favorably with the literature value of $[\alpha]_D$ +9.1 (*c* 0.066, MeOH),[11] the two samples of pyrodysinoic acid likely possess the same undefined absolute configuration.

The negative ion HRESIMS spectrum of isopyrodysinoic acid (**2**) indicated that the molecular formula for **2** was the same as that of pyrodysinoic acid (**1**), and the ^{1}H and ^{13}C NMR spectra of **1** and **2** were markedly similar. Analysis of the 1D and 2D NMR data (Tables 1 and 2) clearly showed that compounds **1** and **2** presented practically identical ^{13}C chemical shifts from C-5 to C-12. However, there were some significant ^{1}H and ^{13}C NMR chemical shift differences observed for both the lactam and the central six-membered ring. For example, the H-5 methylene protons resonate at δ 0.87 and 2.25 in **2** but in **1** are observed at δ 2.14 and 2.71. In addition, C-4 and C-13 appear to be switched in compound **2**, since these are seen at δ 59.2 and 169.7, while in **1** these are observed at δ 161.9 and 67.2, respectively. Therefore, we suspected that isopyrodysinoic acid (**2**) might well be a positional isomer of **1** at the ring junction between the lactam and the central six-membered ring.

Confirmation of this hypothesis was obtained by analysis of the 2D NMR data for **2**. In the COSY spectrum the methylene H-5 protons correlated not only to the H-6 methine resonance (δ 2.59) but, unlike **1**, also to H-4 (δ 4.17). Key long-range correlations in the ^{1}H−^{13}C HMBC spectrum observed between H-3 (δ 5.67) and C-2 (δ 170.2), C-4 (δ 59.2), C-12 (δ 37.1), and C-13 (δ 169.7), between the methine H-4 and C-3 (δ 116.9), C-5 (δ 35.6), and C-13, and between both Me-15 (δ 1.21) and Me-16 (δ 1.16) and C-11 (δ 46.6), C-12, and C-13 confirmed the position of the lactam functionality as reversed to its position in compound **1**. Further

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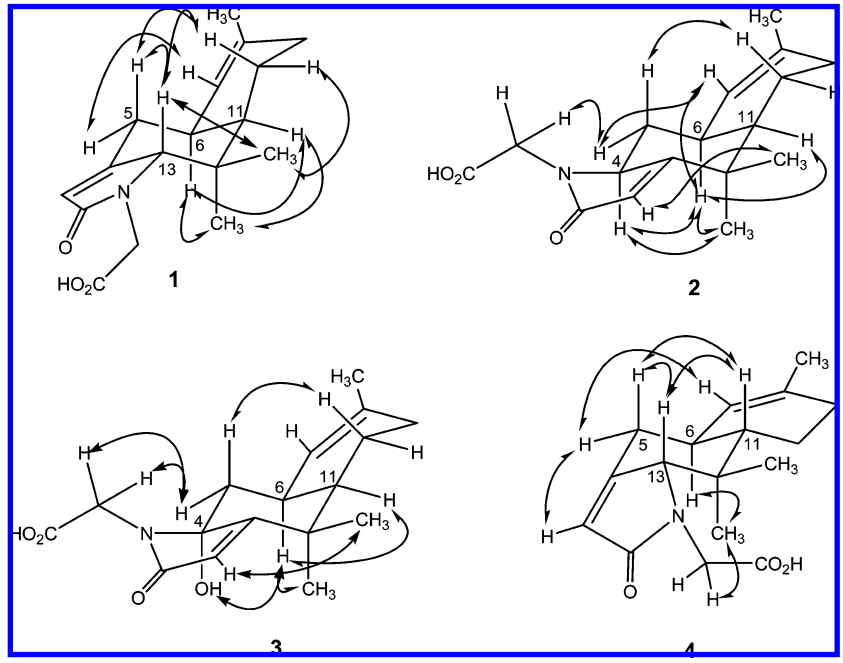


Figure 1. Relevant ROESY correlations observed for pyrodysinoic acid (**1**), isopyrodysinoic acid (**2**), 13-hydroxyisopyrodysinoic acid (**3**), and pyrodysinoic acid B (**4**).

Table 1. ^{1}H NMR Data for Compounds **1**, **2**, **3**, and **4** in DMSO-d_6 [δ, multiplicity (J in Hz)]

atom #	1	2	3	4
3	5.78, s	5.67, s	5.66, s	5.82, s
4		4.17, dd (6.1, 12.1)		
5_{eq}	2.71, dd (4.9, 13.8)	2.25, m	1.93, dd (3.6, 13.5)	2.72, dd (1.7, 11.9)
5_{ax}	2.14, dd (13.8, 13.8)	0.87, ddd (12.1,12.1,12.1)	1.29, dd (13.5, 13.5)	1.94, dd (11.9, 11.9)
6	2.36, m	2.59, m	2.67, m	1.97, m
7	5.41, bd (4.3)	5.36, bd (4.8)	5.34, bd (5.1)	5.17, bs
9_{eq}	1.98, m	1.91, m	1.90, m	1.97, m
9_{ax}	1.98, m	1.86, m	1.90, m	1.97, m
10_{eq}	1.76, bd (11.5)	1.59, m	1.58, m	1.86, bd (10.1)
10_{ax}	1.58, m	1.03, ddd (13.5, 13.5, 6.2)	1.02, m	1.15, m
11	1.38, bd (11.0)	1.59, m	1.55, m	1.18, bt (11.3)
13	3.97, bs			3.88, bs
14	1.61, bs	1.57, bs	1.56, bs	1.62, bs
$Me15_{ax}$	0.70, s	1.21, s	1.32, s	1.14, s
$Me16_{eq}$	1.18, s	1.16, s	1.13, s	0.51, s
17a	4.27, d (18.0)	4.07, d (17.8)	3.89, d (17.8)	4.39, d (18.0)
17b	3.81, d (18.0)	3.85, d (17.8)	3.72, d (17.8)	3.87, d (18.0)
CO_2H	12.72, bs	12.67, bs	12.54, bs	12.78, bs
4-OH			5.93, bs	

Table 2. ^{13}C (150 MHz) and ^{15}N (60.797) Data[a] for Compounds **1**, **2**, **3**, and **4** in DMSO-d_6

atom #	1	2	3	4
1	−263.0	−256.9	−244.3	n.o.[b]
2	172.6	170.2	168.2	172.6
3	117.8	116.9	118.2	118.0
4	161.9	59.2	88.2	161.6
5	31.3	35.6	39.9	34.6
6	32.9	30.5	29.5	36.2
7	125.1	124.4	124.7	125.0
8	133.4	133.0	133.0	133.8
9	31.5	30.6	30.6	31.0
10	18.0	18.5	18.3	21.7
11	46.1	46.6	46.7	46.0
12	40.0	37.1	37.3	40.7
13	67.2	169.7	167.9	71.2
14	23.0	23.0	23.0	22.8
15	20.6	29.3	27.3	26.0
16	27.0	24.3	25.5	13.5
17	44.2	41.3	38.9	44.2
18	170.8	170.9	170.9	170.9

[a] Assignments based on HMQC long-range correlations. [b] n.o., not observed.

analysis of the HMBC spectrum showed correlations between the methylene H-17 protons (δ 3.85 and 4.07) and C-2, C-4, and C-18 (δ 170.9), which, along with a tROESY correlation between H-5_{eq} (δ 2.25) and H-17b (δ 3.85), established that the $-CH_2CO_2H$ moiety was attached to the lactam nitrogen. Finally, correlations observed in the ^{15}N−^{1}H lrHMQC spectrum between N-1 (δ −256.9) and H-3, H-4, and H-17b confirmed the planar structure of isopyrodysinoic acid (**2**).

As with pyrodysinoic acid (**1**), analysis of the tROESY spectrum of isopyrodysinoic acid (**2**) supported a *cis* junction between the two six-membered rings, since a dipolar coupling was observed between H-6 and H-11. H-4 appeared as a dd with one large coupling to H-5_{ax} (δ 0.87) of ~12 Hz. Additionally, in the tROESY spectrum H-4 correlated to both H-6 and Me-15_{ax}, while H-5_{ax} correlated to H-10_{ax} (δ 1.03). These observations established that the two six-membered rings in **2** have a *cis* ring junction and that N-1 is in an equatorial orientation (Figure 1).

The NMR spectroscopic data obtained for 13-hydroxyisopyrodysinoic acid (**3**) were remarkably similar to the data obtained for **2**. An $[M - H]^-$ ion at m/z 304.1637 in the HRESIMS of **3** established a molecular formula of $C_{17}H_{22}NO_4$, which corresponds to the addition of an oxygen to the formula of **2**. The presence of a hydroxy group at C-4 in **3** was evident. The signals corresponding to CH-4 (δ_H 4.17; δ_C 59.2) in **2** had been replaced by resonances at δ_C 88.2 and a broad singlet at δ_H 5.93 (4−OH). Long-range correlations observed in the HMBC spectrum between C-4 (δ 88.2) and H-3 (δ 5.66), and the H-5/H-5′ (δ 1.93 and 1.29) and H-17/H-17′ (δ 3.89 and 3.72) protons confirmed the position of the hydroxy group at C-4. Correlations observed in the tROESY spectrum between H-5_{eq} (1.93) and both of the H-17 methylene protons, as well as between the equatorial methyl substituent Me-

16 (δ 1.13) and H-3, established that the OH substituent at C-4 was in an axial orientation. This was confirmed by a weak correlation seen between H-6 and the 4-OH proton resonance. Detailed analysis of the 2D tROESY data demonstrated that the relative configuration at the junction between the two six-membered rings in **3** was *cis*, the same as that observed in **2**. All other structural features of **2** and **3** were the same, and the structure of 13-hydroxyisopyrodysinoic acid was assigned as that of **3**.

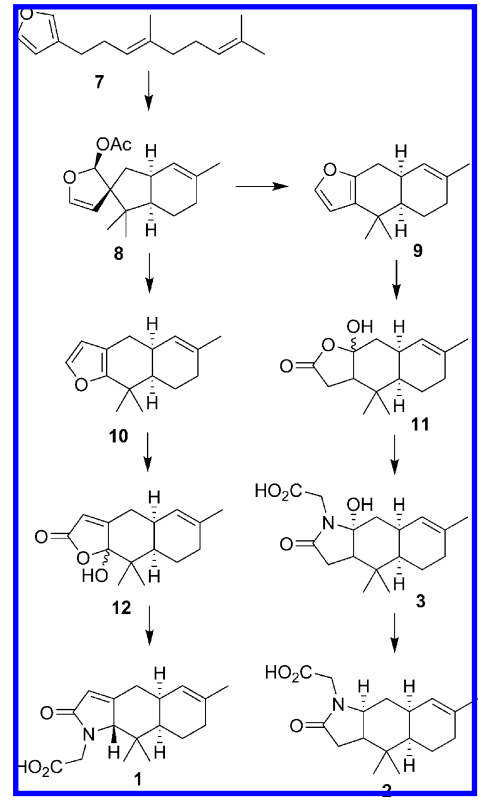
HRESIMS analysis of pyrodysinoic acid B (**4**) indicated that the molecular formula, $C_{17}H_{22}NO_3$, was the same as that of **1** and **2**. The 1D and 2D NMR data readily established that the planar structure of **4** was the same as that of **1**. Detailed analysis of the 2D tROESY and *J* coupling values indicated that the only difference between **4** and **1** was the relative configuration at the ring junction of the two six-membered rings. Considering that H-5_{ax} (δ 1.94) is a dd with J = 11.9 and 11.9 Hz, it must present a *trans*-pseudodiaxial relationship with H-6 (δ 1.97). Since a dipolar coupling was observed between H-5_{ax} and both H-11 (δ 1.18) and H-13 (δ 3.88), the relative configuration of **4** required that the two six-membered rings have a *trans* ring junction instead of the *cis* junction seen in pyrodysinoic acid (**1**) and that N-1 is in an equatorial orientation. Additional tROESY correlations confirmed the assignment of the relative configuration of pyrodysinoic acid B (**4**) (Figure 1).

Comparison of the sign of the specific rotations and relative configurations of **2** and **3** with related compounds with known absolute configuration makes it possible to propose absolute configurations for isopyrodysinoic acid (**2**) and 13-hydroxyisopyrodysinoic acid (**3**). The absolute configuration of (+)-tuphabutenolide (**5**) ($[\alpha]_D$ +222) isolated from *Dysidea tupha* was established as 4(*S*), 6(*R*), 11(*R*).[12] Furthermore, the absolute configuration of a series of related metabolites was investigated and indicated that (−)-**6** with $[\alpha]_D$ −85 (*c* 0.5, $CHCl_3$) has the 4(*R*), 6(*S*), 11(*S*) configuration.[13] Considering the relative configuration and the specific rotation values herein recorded for isopyrodysinoic acid (**2**) ($[\alpha]^{25}_D$ +91.4 *c* 0.33, MeOH) and 13-hydroxyisopyrodysinoic acid (**3**) ($[\alpha]^{25}_D$ +98.9 *c* 0.86, MeOH), we propose that the absolute configurations of **2** and **3** are 4(*S*), 6(*S*), 11(*R*) and 4(*R*), 6(*S*), 11(*R*), respectively.

Scheme 1 shows a proposed biogenesis for compounds **1** to **3**. Dendrolasin (**7**)[14,15] can be converted to (+)-spirodysin (**8**)[16] via a proton-initiated intramolecular cyclization and subsequent functional group transformations. Ring expansion of spirodysin (**8**) leads to either furodysinin (**9**) or furodysin (**10**).[17−19] Both **9** and **10** have been isolated from *Dysidea* spp. sponges, and they are the putative biogenetic intermediates in the formation of furodysinin lactone (**11**) and furodysin lactone (**12**).[11,18−24] Hydroxybutenolide **12** can be converted to pyrodysinoic acid (**1**) via glycine incorporation, dehydration, and reduction, while **11** should be the corresponding precursor of both **3** and **2**. Assuming a common biogenetic origin for both the pyrodysinoic and isopyrodysinoic acid skeletons as shown in Scheme 1 suggests that the absolute configuration of pyrodysinoic acid (**1**) is 6(*S*), 11(*R*), 13(*S*).

None of the furodysin or furodysinin sesquiterpenes reported to date have a *trans* junction between the two six-membered rings of the 1,2,3,4,4a,7,8,8a-octahydro-1,1,6-trimethylnaphthalene moiety.[11−20] The isolation of pyrodysinoic acid B (**4**) represents the first report of a furodysin skeleton with this structural feature.

Scheme 1. Biogenetic Pathway Proposed for the Formation of Pyrodysinoic Acid (**1**), Isopyrodysinoic Acid (**2**), and 13-Hydroxyisopyrodysinoic Acid (**3**)



Experimental Section

General Experimental Procedures. Optical rotations were measured using a Jasco P-1010 polarimeter with sodium light (589 nm). The ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-600 spectrometer with a 5 mm CPTCI cryoprobe. ^1H chemical shifts are referenced to the residual DMSO-d_6 signal (δ 2.49 ppm), and ^{13}C chemical shifts are referenced to the DMSO-d_6 solvent peak (δ 39.5 ppm). Low- and high-resolution ESI-QIT-MS were recorded on a Bruker-Hewlett-Packard 1100 Esquire-LC system mass spectrometer. Solvents used for extraction and flash chromatography were glass distilled prior to use. HPLC-grade solvents were utilized without further purification in HPLC separations. Analytical TLC analyses were performed with Polygram precoated TLC sheets of Si gel on polyester, Merck type 5554 silica gel plates, or Whatman MKC18F plates. Plates were observed under a UV lamp (λ_{max} 254 and 365 nm). HPLC separations were performed either with a Waters quaternary pump 600, double beam UV detector 2487, and data module 746 or with a Waters 600E system controller liquid chromatography attached to a Waters 996 photodiode array detector, on which the UV spectra have been recorded as well. All solvents used for HPLC were either Fisher or J. T. Baker HPLC grade.

Animal Material. *Dysidea robusta* (BA99ES-111) was collected during a 1999 expedition to Baía de Todos os Santos, Salvador, Bahia State. The sponge was collected by hand using scuba, at depths between 10 and 15 m. Animals were frozen shortly after collection and transported frozen to the Instituto de Química de São Carlos. The animals were freeze-dried and stored in 1:1 EtOH/MeOH at − 20 °C. A voucher specimen has been deposited at the Porifera collection of Museu Nacional (MNRJ 2480).

Extraction and Isolation. The sample of *D. robusta* (100 g) was removed from the EtOH/MeOH and re-extracted exhaustively with MeOH. The EtOH/MeOH and MeOH extracts were pooled and evaporated to a final volume of 300 mL. The alcoholic extract was partitioned with petroleum ether (30−60 °C, 3 × 300 mL). After evaporation to dryness, 146 mg of the petroleum ether extract and 907 mg of the alcoholic extract were obtained. TLC and ^1H NMR analysis of the petroleum ether extract indicated the presence of only sterols and fatty acids. The more polar alcoholic extract (Dr-AQ) was subjected to chromatography on a C_{18} reversed-phase cartridge (10 g) with a gradient of MeOH in H_2O, to give 10 fractions. ^1H NMR analysis of the fractions eluting with 1:1 and 4:5 H_2O/MeOH (Dr-AQ-6 and Dr-AQ-7, respectively) indicated the presence of several singlet methyl groups. The 1:1 H_2O/MeOH eluting fraction (Dr-AQ-6) was further fractionated by HPLC using a phenyl-bonded silica gel column (Inertsil, 250 × 4.6 mm, 5 m), with a gradient of 0.1% HCO_2H in MeOH, from 95:5 to 100% MeOH over 30 min, to generate six fractions (Dr-AQ-6A to Dr-QA-6F). From fraction Dr-AQ-6B (5.5 mg) a pure sample of 13-hydroxyisopyrodysinoic acid (**3**) (1.3 mg) was obtained via C_{18}

reversed-phase HPLC using a CSC-Inertsil 150A/ODS2, 5 μm 25 × 0.94 cm column, with 3:2 (0.05% TFA/H_2O)/MeCN as eluent, while fraction DR-Aq-6D (3.7 mg), using the same HPLC conditions, yielded a pure sample of pyrodysinoic acid B (**4**) (0.2 mg) and a mixture of pyrodysinoic acid (**1**) and isopyrodisinoic acid (**2**). From the mixture of **1** and **2**, after fractionation with a second C_{18} reversed-phase HPLC, using the same column but with 3:2 MeOH/(0.05% TFA/H_2O) as eluent, pyrodysinoic acid (**1**) (0.2 mg) and isopyrodysinoic acid (**2**) (0.5 mg) were obtained.

Pyrodysinoic Acid (1): clear glass; $[\alpha]^{25}_D$ +18.9 (*c* 0.13, MeOH); ^{1}H NMR (DMSO-d_6, 600 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 150 MHz), see Table 2; negative ion HRESIMS $[M - H]^-$ *m*/*z* 288.1598 (calcd for $C_{17}H_{22}NO_3$, 288.1600).

Isopyrodysinoic Acid (2): clear glass; $[\alpha]^{25}_D$ +91.4 (*c* 0.33, MeOH); UV (3:2 (0.05% TFA/H_2O)/MeCN) λ_{max} 212 nm; ^{1}H NMR (DMSO-d_6, 600 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 150 MHz), see Table 2; negative ion HRESIMS $[M - H]^-$ *m*/*z* 288.1608 (calcd for $C_{17}H_{22}NO_3$, 288.1600).

13-Hydroxyisopyrodysinoic Acid (3): clear glass; $[\alpha]^{25}_D$ +98.9 (*c* 0.86, MeOH); UV (3:2 (0.05% TFA/H_2O)/MeCN) λ_{max} 208, 256 nm; ^{1}H NMR (DMSO-d_6, 600 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 150 MHz), see Table 2; negative ion HRESIMS $[M - H]^-$ *m*/*z* 304.1637 (calcd for $C_{17}H_{22}NO_4$, 304.1549).

Pyrodysinoic Acid B (4): clear glass; $[\alpha]^{25}_D$ +21.9 (*c* 0.13, MeOH); UV (3:2 (0.05% TFA/H_2O)/MeCN) λ_{max} 212 nm; ^{1}H NMR (DMSO-d_6, 600 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 150 MHz), see Table 2; negative ion HRESIMS $[M - H]^-$ *m*/*z* 288.1576 (calcd for $C_{17}H_{22}NO_3$, 288.1600).

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Supporting Information Available: Tables of HMBC and ^{1}H−^{1}H COSY correlations for compounds **1**−**4**, as well as ^{1}H and ^{13}C NMR spectra of compounds **1**−**4** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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