A New Indole Derivative from the Red Alga *Chondria atropurpurea*. Isolation, Structure Determination, and Anthelmintic Activity[1]

Danilo Davyt,[†] Walter Entz,[†] Rafael Fernandez,[†] Raúl Mariezcurrena,[‡,§] Alvaro W. Mombrú,[‡] Jenny Saldaña,[∥] Laura Domínguez,[∥,⊥] Javier Coll,[#] and Eduardo Manta*[,†]

Facultad de Química, Universidad de la República, Av. Gral. Flores, 2124 Montevideo, Uruguay

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Chondriamide C (**3**), a new bis(indole) amide, was isolated from the red alga *Chondria atropurpurea*, and its structure was established from spectroscopic data and chemical transformations. A new natural product, 3-indoleacrylamide (**4**), and the previously described chondriamides A and B (**1**, **2**) and 3-indoleacrylic acid (**5**) were also isolated**.** The anthelmintic activities of compounds **1**, **3**, **4**, and **6** (the O,N_1,$N_{1'}$-trimethyl derivative of compound **2**) against *Nippostrongylus brasiliensis* in vitro were evaluated.

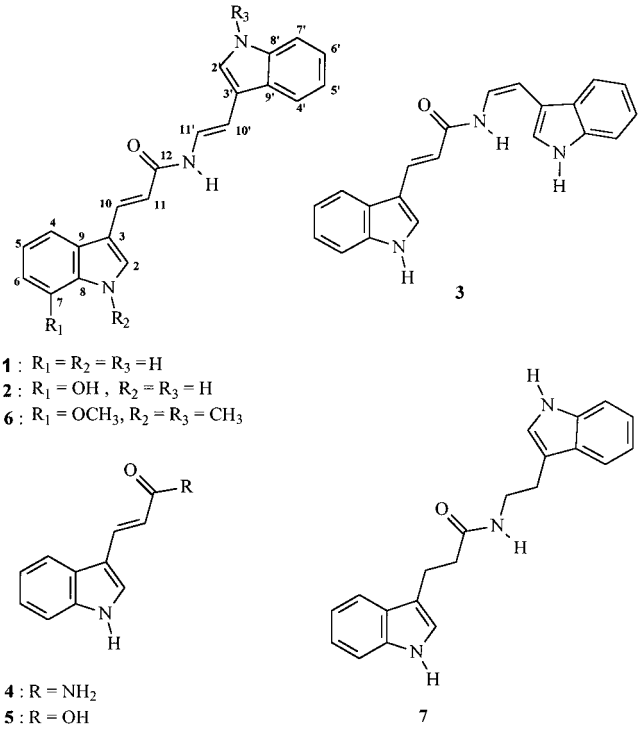
Chemotherapy is important in the treatment of parasitic infections due to helminths in both human and veterinary practice. The search for new anthelmintic agents is necessary for both medical and economic considerations,[2] and metabolites of marine origin have exhibited anthelmintic activities.[3]

A systematic biological screening of algae and other marine organisms of the Uruguayan coast for anthelmintic activity[4] led to the chemical study of the acetone extract from the red alga *Chondria atropurpurea* Harvey (Rhodomelaceae). Red algae of the genus *Chondria* are a source of terpenoids,[5,6] novel amino acids,[7−9] and cyclic polysulfides.[10] Recently two bis(indoles), chondriamides A and B, together with other indole derivatives, were isolated from an Argentinian *Chondria sp*.[11]

In this paper we report the isolation and structural elucidation of the new bis(indole)amide derivative chondriamide C (**3**) and 3-indoleacrylamide (**4**) from *C. atropurpurea*. No references about the isolation of **4** from nature, neither about its spectroscopy were found in the literature reviewed.[12] The known compounds chondriamides A and B (**1**, **2**) and 3-indoleacrylic acid (**5**) were also isolated.

The acetone extract of the alga was fractionated by column chromatography on silica gel using a gradient of *n*-hexane, EtOAc, and MeOH. The fraction eluted with EtOAc was further chromatographed on a column of Sephadex LH-20 to yield crude chondriamides A−C (**1**−**3**), which were purified by MPLC on silica gel using *n*-hexane/acetone. The fraction eluted with EtOAc/MeOH (95:5) was also further chromatographed on a column of Sephadex LH-20 to yield crude **4** and **5**.

Chondriamides A (**1**; 333 mg) and B (**2**; 66 mg) and 3-indoleacrylic acid (**5**; 385 mg) were identified by comparison of their spectral data with reference data.[11,13] Chondriamide B (**2**) was unstable under the experimental biological assay conditions. To obtain a suitable derivative to assay anthelmintic activity, compound **2** was methylated under the usual conditions (CH_3I/K_2CO_3/acetone) to afford the stable trimethyl derivative **6**.[14]



Compound **3** (22 mg) had the molecular formula $C_{21}H_{17}O_2N_3$, as established by HRMS. IR absorption of **3** at 1610 cm^{-1} implied the presence of a conjugated carbonyl amide. Its ^1H NMR spectrum (Table 1) was very similar to that of chondriamide A (**1**), except for the signals of H-10′, H-11′, H-2′, and H-4′, suggesting **3** to be the 10′-*Z* isomer of **1**. The *Z* configuration of the C-10′−C-11′ double bond was determined by the coupling constant between the olefinic protons H-10′ and H-11′ (J = 9.5 Hz). The EIMS of **3** also supported this structure. The fragments at *m*/*z* 170 and 157, due to the cleavage of the C−N bond of the amide system, are in agreement with the proposed structure of an unsaturated indoleamide derivative of indoleacrylic acid. Finally, 2D NMR data (COSY, HMBC, HMQC, and ROESY) were in agreement with the proposed structure and H and C assignments for **3**. The structure of **3** was confirmed unambiguously by chemical methods, since both compound **3** and chondriamide A (**1**) gave the same bis(indole) derivative **7** upon catalytic hydrogenation.

* To whom correspondence should be addressed. Phone: (598 2) 924 18 05. Fax: (598 2) 924 19 06. E-mail: emanta@bilbo.edu.uy.
[†] Cátedra de Química Farmacéutica.
[‡] Cátedra de Cristalografía.
[§] To whom correspondence regarding the X-ray structure should be addressed.
[∥] Cátedra de Farmacología.
[⊥] To whom correspondence regarding biological assays should be addressed.
[#] Cátedra de Botánica.

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Table 1. NMR Data for Chondriamides A (1) and C (3) in Acetone-d_6

position no.	chondriamide A (**1**)[a]			chondriamide C (**3**)			
	$\delta(^{13}C)$	$\delta(^{1}H)$	HMBC	$\delta(^{13}C)$	$\delta(^{1}H)$	COSY	HMBC
1					10.74 br s		
2	131.1	7.75 br s	H-10	130.9	7.75 s		H-10
3	114.0		H-2, H-11	113.9			H-2, H-4, H-11
4	120.9	8.01 dd (6.8, 1.7)		121.0*	7.95 dd (7.8, 1.1)	H-5	
5	123.6	7.26 ddd (7.0, 7.0, 1.5)		121.2*	7.13 ddd (8.1, 7.8, 1.1)	H-4, H-6	
6	121.7	7.28 ddd (7.1, 7.0, 1.5)		123.1	7.19 ddd (8.1, 8.0, 1.1)	H-5, H-7	H-4
7	113.0	7.52 dd (7.0, 1.8)		112.7	7.48 dd (8.0, 1.1)	H-6	H-5
8	139.0		H-2	139.7			H-2, H-4, H-6
9	126.4		H-2, H-4	126.0			H-2, H-7, H-10
10	136.7	7.97 d (15.6)		136.0	7.91 d (15.6)	H-11	
11	115.1	6.77 d (15.6)		116.0	6.93 d (15.6)	H-10	H-10
12	166.3		H-10, H-11	164.9			H-11, H-10
1′					10.40 br s		
2′	124.0	7.38 br s	H-10′	123.8	7.61 br s		H-10′
3′	113.6		H-2′, H-11′	111.5			H-2′
4′	120.5	7.88 br d (7)		119.3	7.62 dd (6.7, 1.2)	H-5′	H-6′
5′	120.4	7.15 ddd(7.7, 7.1, 1.2)		119.9	7.07 ddd (7.0, 6.7, 1.2)	H-4′, H-6′	H-7′
6′	122.4	7.20 ddd (7.6, 7.1, 1.2)		122.5	7.15 ddd (8.1, 7.0, 1.2)	H-5′, H-7′	H-4′
7′	112.5	7.44 br d (8)		111.9	7.43 dd (8.1, 1.2)	H-6′	H-5′
8′	138.4		H-2′, H-10′	138.4			H-4′, H-6′
9′	126.4		H-2′, H-4′	127.8			H-2′, H-5′, H-7′, H-10′
10′	108.1	6.58 dd (14.8, 0.5)		101.6	5.92 d (9.5)	H-11′	
11′	121.0	7.69 d (14.8)	H-10′	121.1*	7.09 dd (9.5, 9.0)	H-10′	
NH					8.71 d (9.0)		

[a] ^{1}H NMR δ values of H-10 and H-11 and ^{13}C NMR δ values of C-8, C-9, C-10, C-11, C-8′, and C-9′ are reassigned on the basis of HMBC spectral data, with respect to previously reported values.[11] These assignments are in accord with recent reports for similar compounds.[15] [b] Values marked with asterisks can be interchanged.

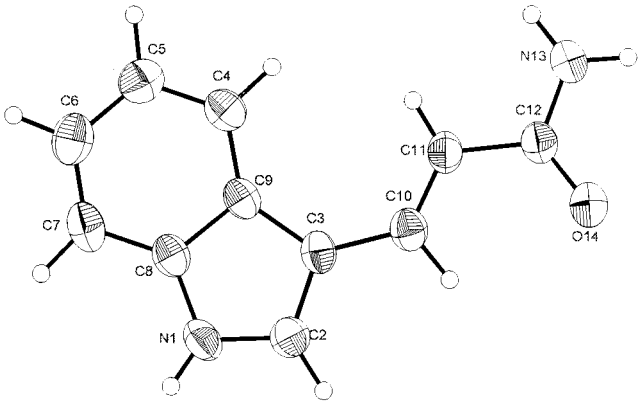

Figure 1. ORTEP drawing with labeling scheme for compound **4**. Displacement ellipsoids are represented at 50% probability. Hydrogen atoms are represented as spheres of arbitrary radii.

The mixture of compounds **4** and **5** was purified by MPLC over silica gel with elution with EtOAc. Compound **4** (733 mg) was crystallized from acetone. Elemental analysis corresponded with the molecular formula $C_{11}H_{10}N_2O$. Its structure was deduced by NMR and EIMS data and was confirmed by X-ray crystallographic analysis (Figure 1).[16,17]

We could find no previous reports of anthelmintic activity for these compounds. Compounds **1**, **3**, **4** and **6**, showed moderate anthelmintic activity, with compound **3** showing the highest activity (Table 2, EC_{80} = 0.09 mM). These preliminary results indicated that further studies of the anthelmintic activity of this type of indole derivative, such as compound **3**, may prove useful.

Table 2. In Vitro Anthelmintic Activity, against *N. Brasiliensis*, of Compounds **1**, **3**, **4**, and **6**[a]

compd	EC_{80} (mM)
1	0.26
3	0.09
4	2.37
6	0.30

[a] EC_{80}: effective concentration to kill 80% of parasites. Confidence limits: 1%.

Experimental Section

General Experimental Procedures. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Chemical shifts are related to TMS as internal standard. Multiplicities of ^{13}C NMR were assigned using a standard DEPT experiment. Low-resolution mass spectra (MS) were obtained on a GCMS Shimadzu QP 1100-EX spectrometer and high-resolution mass spectra (HRMS) on a ZAB-SEQ4F spectrometer. Elemental analyses were obtained from vacuum-dried samples and performed on a Fisons EA 1108 CHNS-O analyzer. MPLC chromatography was carried out with silica gel 60 for flash cromathography (J. T. Baker, 40 μm average particle diameter). All reactions and chromatographic separations were monitored by TLC analyses, conducted on 0.25 mm silica gel plastic sheets (Macherey-Nagel, Polygram SIL G/UV 254). Spots were visualized under UV light (254 nm), iodine vapor, or 50% phosphomolybdic acid in EtOH.

Plant Material. The parts of *Chondria atropurpurea* were collected at Punta del Diablo, Rocha State, Uruguay, in December of 1994. The algae was identified by Dr. Javier Coll, and voucher specimens were deposited at the Herbarium of the Department of Botany of the Facultad de Química, Universidad de la República Oriental del Uruguay.

Extraction and Isolation. The air-dried alga (22 kg) was extracted three times with acetone for 2 days each time. Solvents were removed by evaporation at reduced pressure. The dark green oil (88 g) was chromatographed on a silica gel 60 flash chromatography column, with increasingly polar *n*-hexane/EtOAc/MeOH mixtures as eluent. Fractions were further purified by a Sephadex LH-20 column with *n*-hexane/$CHCl_3$/MeOH (1:1:1). Crude compounds were purified by medium-pressure liquid chromatography on silica gel 100 with *n*-hexane/acetone mixtures to obtained pure compounds before spectroscopy and biological experiments.

Chondriamide C (3): yellow powder; mp 230.5−232.0 °C; λ_{max} (log ϵ) 208 (4.43), 275 (3.70), 358 (4.33) nm; IR (KBr) ν_{max}

3387, 1610, 1533, 1497, 1457, 1186 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 327 $[M]^+$ (25), 170 (61), 159 (12), 158 (100), 130 (18), 115(38); HREIMS *m/z* 327.1371 (calcd for $C_{21}H_{17}ON_3$ 327.1371).

3-Indoleacrylamide (3-(1*H*-Indol-3-yl)acrylamide; (4): amber crystals (acetone); mp 212.8−214.2 °C; UV (MeOH) λ_{max} (log ϵ) 226 (1.49), 275 (1.25), 322 (1.55) nm; IR (KBr) ν_{max} 3414, 3147, 1650, 1565 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 4.77 (2H, s, NH_2), 6.55 (1H, d, J = 15.8 Hz, H-11), 7.09 (1H, ddd, J = 7.8, 7.8, 1.4, H-5), 7.12 (1H, ddd, J = 7.9, 7.8, 1.3, H-6), 7.35 (1H, dd, J = 7.9, 1.4, H-7), 7.5 (1H, s, H-2), 7.75 (2H, d, J = 15.8 Hz, H-10), 7.83 (1H, dd, J = 7.8, 1.3, H-4); ^{13}C NMR (acetone-d_6, 100 MHz) 113.01 (d, C-7), 113.84 (s, C-3), 115.07 (d, C-11), 120.99 (d, C-4), 121.74 (d, C-5), 123.62 (d, C-6), 126.66 (s, C-9), 130.91 (d, C-2), 137.31 (d, C-10), 139.15 (s, C-8), 172.86 (s, C-12); EIMS *m/z* 187 $[M]^+$ (14), 186 (100), 185 (35), 170 (55), 169 (12), 141 (26), 115 (50), 71 (11). Anal. C 70.41%, H 5.35%, N 14.95%, calcd for $C_{11}H_{10}N_2O$, C 70.95%, H 5.41%, N 15.04%.

Compound 6. A mixture of chondriamide B (**2**; 55 mg, 0.16 mmol), K_2CO_3 (100 mg), and CH_3I (0.2 mL) in dry acetone (5 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 × 25 mL), the extract dried (Na_2SO_4), and the solvent removed in vacuo. The residue was submitted to flash chromatography (silica gel 60, acetone/*n*-hexane (1:1)) to afford compound **6** (45 mg, 73%). Compound **6** was obtained as a yellow powder (acetone): mp 194.0−195.6 °C; UV (MeOH) λ_{max} (log ϵ) 231 (4.47), 272 (4.13), 373 (4.55), 526 (3.70) nm; ^1H NMR (acetone-d_6, 400 MHz) δ 3.81 (3H, s, $N_{1'}$-Me), 3.96 (3H, s, O-Me), 4.09 (3H, s, N_1-Me), 6.45 (1H, d, J = 14.8 Hz, H-10′), 6.69 (1H, d, J = 15.6 Hz, H-11), 6.79 (1H, d, J = 7.8 Hz, H-6), 7.08−7.14 (2H, m, H-5 and H-5′), 7.19 (1H, ddd, J = 8.0, 7.5, 1.1 Hz, H-6′), 7.29 (1H, s, H-2′), 7.39 (1H, d, J = 8.2 Hz, H-7′), 7.51 (1H, s, H-2), 7.51 (1H, d, J = 7.9 Hz, H-4), 7.68 (1H, m, H-11′), 7.79 (1H, d, J = 7.9, H-4′), 7.84 (1H, d, J = 15.5 Hz, H-10); ^{13}C NMR (acetone-d_6, 100 MHz) (values marked *, †, and # can be interchanged) δ 32.28 (q, $N_{1'}$-Me), 36.70 (q, N_1-Me), 55.49 (q, O-Me), 104.19 (d, C-6), 105.03 (d, C-10′), 109.97 (d, C-7′), 112.47 (s, C-3*), 112.53 (s, C-3′*), 113.36 (d, C-4), 115.54 (d, C-11), 119.67 (d, C-5′), 119.91 (d, C-4′), 121.30 (d, C-11′), 121.97 (d, C-5†), 122.04 (d, C-6′†), 126.43 (s, C-9′), 127.14 (d, C-2′), 128.10 (s, C-8), 128.84 (s, C-9), 134.59 (d, C-10#), 134.72 (d, C-2#), 138.10 (s, C-8′), 148.58 (s, C-7), 163.95 (s, C-12); EIMS *m/z* 385 $[M]^+$ (34), 214 (100), 198 (15), 172 (16).

Compound 7. A solution of chondriamide A (**1**: 10 mg, 0.03 mmol) in MeOH (5 mL) containing 1.5 mg of 10% Pd/C was hydrogenated (1.1 atm) at room temperature over 4 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was submitted to flash chromatography (silica gel, EtOAc/*n*-hexane (6:4) to afford compound **7** (7 mg, 70%). Compound **7** was obtained as a white powder (MeOH): mp 152.7−153.9 °C; HPLC t_R 13.0 min (μPorasil 125 Å, 10 μm, 150 × 3.9 mm i.d., Waters, gradient elution mode from $t_{0\ min}$ acetone 40% in *n*-hexane to $t_{20\ min}$ acetone 60% in *n*-hexane), flow 1 mL/min, detector λ = 350 nm; ^1H NMR (acetone-d_6, 400 MHz) δ 2.54 (2 H, t, J = 7.5 Hz, H-11), 2.90 (2 H, t, J = 7.2 Hz, H-10′), 3.07 (2 H, t, J = 7.7 Hz, H-10), 3.50 (2 H, dd, J = 13.1, 7.2 Hz, H-11′), 7.00−7.03 (2 H, m, H-5, H-5′), 7.07−7.12 (4 H, m, H-2, H-2′, H-6, H-6′), 7.36 (1 H, s, H-7′), 7.38 (1 H, s, H-7), 7.58 (1 H, s, H-4′), 7.60 (1 H, s, H-4), 9.93 (1H, br s, CON*H*); ^{13}C NMR (acetone-d_6, 100 MHz) (values marked *, †, and # can be interchanged) δ 21.60 (t, C-10), 25.60 (t, C-10′), 37.39 (t, C-11), 40.17 (t, C-11′), 111.56 (d, C-7#), 111.60 (d, C-7′#), 113.06 (s, C-3′), 115.18 (s, C-3), 118.8 (d, C-4, C-4′, C-5, and C-5′), 121.50 (d, C-6†), 121.54 (d, C-6′†), 122.36 (d, C-2), 122.79 (d, C-2′), 128, 00 (s, C-9*), 128, 13 (s, C-9′*) 137.23 (s, C-8 and C-8′), 172.24 (s, C-12); EIMS *m/z* 331 $[M]^+$ (15), 188 (36), 143 (100), 130 (99). Compound **3** (3 mg, 0.01 mmol) was hydrogenated under the same conditions as those used for compound **1**. An identical result was achieved to give compound **7** in 50% yield (1.5 mg, 0.005 mmol).

Assays for Anthelmintic Activities. The procedure for the anthelmintic activity assay using *Nippostrongylus brasiliensis* L4 parasitant in vitro model has been described by us in a previous paper.[18] Briefly, tests were carried out in tissue-culture 24-well plates. Compounds were dissolved in DMSO and the solutions added to the wells to make 0.5% final concentration of the solvent. Appropriate dilutions in DMSO were prepared for each compound in order to obtain the desired concentration after the addition of 10 μL into each well. The same number of control wells without product and others containing 10 μL of DMSO were included in all experiments. The corresponding calibration curves were determined using a double serial dilution model with six wells for each concentration assayed. The anthelmintic activity of the compounds was assessed by comparing the percentage of dead worms following the addition of the test substance with that of the vehicle-treated worms on day 5. All the wells were checked on days 1 and 5 under an inverted microscope (Olympus CK) at ×100 magnification.

Each sample assayed was examined in parallel with one control and one of the standards used to calibrate the model (albendazol). The corresponding linear regressions were carried out (verified by F test for equality of variances), and the EC_{80} (effective concentration to kill 80% of parasites) for each product was interpolated and experimentally confirmed.

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(16) Crystal data: $C_{11}H_{10}N_2O$, orthorhombic, *Pbca*, $a = 14.284(2)$ Å, $b = 17.085(2)$ Å, $c = 7.7244(12)$ Å, $V = 1885.1(5)$ Å^3, $Z = 8$, $\rho = 1.312$ Mg/m^3, 2542 collected reflections ($4.76° < 2\theta < 50.0°$). Suitable prismatic single crystals were obtained by slow evaporation from *n*-hexane/acetone in the orthorrombic system. Intensities were collected on a Rigaku AFC7S diffractometer (MSC, 1993) at room temperature with Mo Kα radiation. The structure was solved by direct methods, and all atoms were freely refined. The final residuals were $R(F) = 0.0474$ and weighted $R(F^2) = 0.1182$ for the observed reflections.

(17) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax, +44-(0)1223-336033; e-mail, deposit@ccdc.cam.uk).

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