

Cytotoxic Terphenyl Neolignans from Fungus *Terana coerulea*: New Natural Corticins D and E, and Revised Structure for Corticin AMaitane Maisterra^{a,b,c}, M^a Ángeles Castro^a, Luz M^a Muñoz-Centeno^b, Ricardo C. Calhelha^c, Isabel C.F.R. Ferreira^c and Pablo A. García^{a,*}^aDepartamento de Ciencias Farmacéuticas, Sección de Química Farmacéutica, Facultad de Farmacia, CIETUS-IBSAL, University of Salamanca, Campus Miguel de Unamuno, 37007 Salamanca, Spain^bDepartamento de Botánica y Fisiología Vegetal, Sección de Botánica, Facultad de Farmacia, University of Salamanca, Campus Miguel de Unamuno, 37007 Salamanca, Spain^cCentro de Investigação de Montanha (CIMO), Escola Superior Agrária, Instituto Politécnico de Bragança, Campus de Santa Apolónia, 1172, 5300-253 Bragança, Portugal

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Received: December 22nd, 2016; Accepted: February 3rd, 2017

The cobalt crust fungus *Terana coerulea* (*Phanerochaetaceae* family) was selected for a bio-guided study after an ethnobotanical survey at the Irati's Forest (Navarra, Spain) for its local use as antibiotic. Six extracts of increasing polarity, from hexane to hot water, were obtained from powdered dry fungi and tested for cytotoxicity against four human tumour cell lines and one non-tumour primary cell culture. From the most cytotoxic, EtOAc extract, we isolated and identified three terphenyl neolignans: two of them new natural products, named corticins D and E, and one previously described as corticin A, whose earlier structure has been revised. Their structural elucidation and biological evaluation as cytotoxic agents are described.

Keywords: *Terana coerulea*, *Terana caerulea*, *Corticium caeruleum*, Neolignans, Terphenyls, Corticin, Thelephoric acid, Cytotoxic activity.

The cobalt crust fungus, *Terana coerulea* (Lam.) Kuntze (*T. caerulea* and formerly named *Corticium caeruleum* (Lam.) Fr.), belongs to the *Phanerochaetaceae* family and it is a saprotrophic fungus rare in Central and Western Europe but more commonly distributed in Southern Europe and subtropical and tropical regions. This species, easy to recognize by the indigo-blue colour of its hymeneal surface, is associated with all sorts of deciduous wood and on dead stems of big herbs [1]. No medicinal uses have been reported for this fungus, however an ethnobotanical study carried out by us with people from Irati's Forest (Navarra, Spain), highlighted that it is locally used for its antibiotic properties, and this prompted us to perform the present work. Our investigation on this fungus led to the identification of three terphenyl neolignans, one of them previously described as corticin A, whose earlier proposed structure has been revised by us, and two new corticins. Here we describe their structural elucidation and biological evaluation as cytotoxic agents.

Previous mycochemical investigations of *T. coerulea* cultures reported the isolation of secondary metabolites as the antibiotic cortalcerone, **1** [2], or the corticiolic acid, **2** [3] (Figure 1). Additionally, some blue or violet pigments were also obtained from the cultures of this fungus. They are structurally related with the violet lignanic metabolite thelephoric acid, **3**, (Figure 1) or with polymerization products after their oxidation [4]. They are neolignans with a terphenyl structure that includes two oxygen bridges forming a benzo[1,2-*b*:4,5-*b'*]bisbenzofuranoid skeleton. These terphenyl metabolites are only biosynthesized by fungi and lichens [5]. Several derivatives of leuco-thelephoric acid (the *p*-quinol form of thelephoric acid), methylated in any of its hydroxyl groups, have also been identified such as corticins A, **4**, and B, **5** [6], and the permethyl ether of leuco-thelephoric acid, **6** [7]. Corticins A and B, with three and four methyl groups respectively, were isolated as a mixture by washing the surface of the fungus

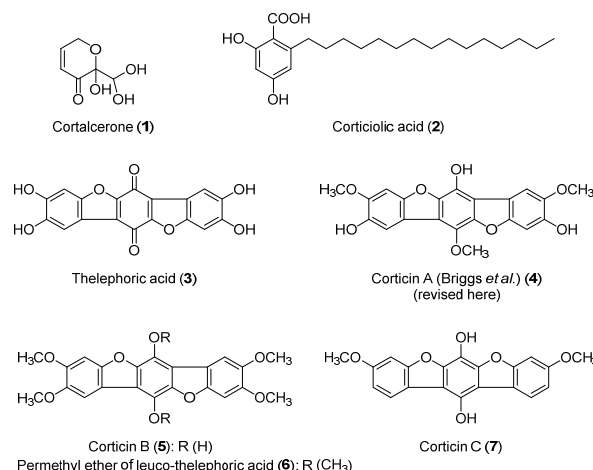


Figure 1: Thelephoric acid and compounds isolated from *Terana coerulea* cultures (formerly named as *Corticium caeruleum*).

culture with cold chloroform [6]. Corticin C, **7**, was another neolignan identified from the same culture and assigned to have a different benzo[1,2-*b*:5,4-*b'*]bisbenzofuranoid skeleton [6] (Figure 1). These natural pigments were mainly characterized through some semisynthetic derivatives obtained from the mixtures of these neolignans, as the peracetylcorticins [8], or the peracetyl, permethyl or pertrimethylsilyl derivatives of thelephoric acid [9]. Thelephoric acid is active *in vitro* against mouse leukemic cells P388 and its use as antitumor agent was patented [10].

In this work, six extracts of increasing polarity, from hexane to hot water, were obtained from powdered dry fungi and tested for cytotoxicity against four human tumour cell lines and one non-tumour primary cell culture. The results are shown in Table 1. The

best cytotoxicity was observed for the EtOAc extract, followed by the CH_2Cl_2 extract; both of them were the most coloured ones (dark violet-blue-red). In fact, the EtOAc extract was the most potent against all human tumour cell lines, with GI_{50} values of 3 $\mu\text{g/mL}$ against breast adenocarcinoma MCF-7 or 6 $\mu\text{g/mL}$ against cervical carcinoma HeLa, and showing a lower cytotoxicity against non-tumour porcine liver cells primary culture (PLP2) of 31 $\mu\text{g/mL}$. These results prompted us to identify the components responsible for the activity. Thus, the column chromatography (CC) of the EtOAc extract on silica gel led to the isolation of the compound **8** and some fractions where it was accompanied with its analogues **9** and **10**.

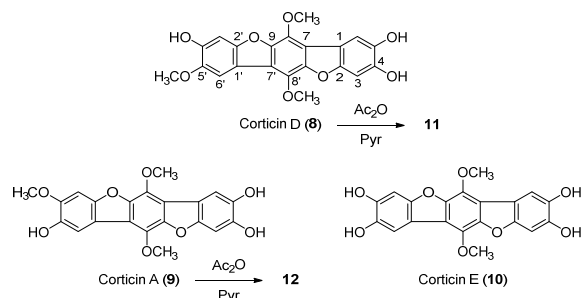


Figure 2: Structures of terphenyl neolignans **8–10** from the fungus *Terana coerulea* and preparation of the triacetyl derivatives **11** and **12**.

Table 1: Cytotoxic activity of extracts and compounds obtained from the fungus *Terana coerulea* ($\text{GI}_{50} \pm \text{SD}$, in $\mu\text{g/mL}$).

Sample	HeLa	NCI-H460	HepG2	MCF-7	PLP2
Hexane ext	73 $\pm$ 3	71 $\pm$ 3	77 $\pm$ 6	75 $\pm$ 3	157 $\pm$ 5
CH_2Cl_2 ext	13 $\pm$ 2	20 $\pm$ 1	50 $\pm$ 4	15 $\pm$ 1	8.7 $\pm$ 0.8
EtOAc ext	5.7 $\pm$ 0.5	12 $\pm$ 1	175 $\pm$ 8	3.2 $\pm$ 0.2	31 $\pm$ 3
BuOH ext ^a	55 $\pm$ 6	100 $\pm$ 8	341 $\pm$ 13	77 $\pm$ 5	> 400
H_2O ext ^a	62 $\pm$ 2	215 $\pm$ 16	339 $\pm$ 25	93 $\pm$ 4	> 400
Decoction	224 $\pm$ 14	> 400	> 400	279 $\pm$ 17	> 400
8	20 $\pm$ 1	68.7 $\pm$ 0.6	43.4 $\pm$ 0.9	57 $\pm$ 4	128 $\pm$ 9
8+9 (9:1)	14 $\pm$ 1	15 $\pm$ 1	20 $\pm$ 2	12.5 $\pm$ 0.9	59 $\pm$ 5
8+9+10 (2:1:1)	19 $\pm$ 1	23.8 $\pm$ 0.1	35 $\pm$ 2	18.3 $\pm$ 0.6	84 $\pm$ 8
Ellipticine	0.91 $\pm$ 0.04	1.03 $\pm$ 0.09	1.91 $\pm$ 0.06	1.1 $\pm$ 0.2	3.2 $\pm$ 0.7

^aBuOH and H_2O soluble fractions from the MeOH extract.

Compound **8** was obtained as a yellowish gum that turned black violet in presence of oxygen and light. Its molecular formula was determined to be $\text{C}_{21}\text{H}_{16}\text{O}_8$ from the HRMS-ESI ion peak at m/z 419.0726 $[\text{M}+\text{Na}]^+$ (calcd 419.0737) and ^1H and ^{13}C NMR spectroscopic data. The ^1H NMR spectrum (Table 2) indicated the presence of four singlet aromatic protons at δ 7.60, 7.52, 7.04 and 7.01 ppm, and three methoxy groups at δ 4.34, 4.31 and 3.98 ppm. The ^{13}C NMR spectrum confirmed the four aromatic methines at δ 108.4, 105.5, 99.3 and 99.0 ppm, and the three oxygenated methyl groups at δ 61.2 (x 2C) and 57.2 ppm. Ten oxygenated aromatic quaternary carbons (between δ 134.5 and 152.7 ppm) and other four non-oxygenated ones (between δ 116.1 and 117.9 ppm) suggested a skeleton analogue to thelephoric acid [11] but in its *p*-quinol or leuco- form as occurs with corticin A described by Briggs *et al.* [6]. This structure was confirmed by two-dimensional NMR experiments performed in the present work and also by comparison with other natural products described in the literature as candidusins [12]. The chemical shifts found for the methoxy groups and their comparison with 4''-deoxycandidusin A and 4,5-dimethoxycandidusin A [12] confirmed that two of the three methoxy groups were the substituents at C-8 and C-8'. The HMBC correlations between these methoxy groups at δ 4.34 and 4.31 ppm with the two quaternary aromatic carbon signals at δ 134.5 ppm agree with the same *p*-dimethoxybenzenic ring present in candidusin derivatives. The HMBC correlations among the

additional methoxy group (δ 3.98 ppm), the H-3' (δ 7.04 ppm) and the H-6' (δ 7.60 ppm) signals with six aromatic carbons (δ 152.7, 148.4, 146.2, 117.4, 105.5 and 99.3 ppm) allowed us to place all these signals at the same aromatic ring and thus, the assignment of the rest of the signals in the spectra. Moreover, a definitive ROESY correlation between protons of the methoxy group at C-5' and H-6' (δ 3.98 and 7.60 ppm) confirmed unequivocally a new terphenyl neolignan structure for the compound **8**, with the IUPAC systematic name according to Moss [13]: 5',8,8'-trimethoxy-2,9':2',9'-diepoxy-9,7'-ciclo-7,9'-neoligna-7(9'),8,7'-triene-4,4',5-triol, and named as corticin D (Figure 2). Several of those representative correlations are shown in Figure 3.

Table 2: ^1H NMR (400 MHz, CD_3OD) data of compounds **8–10** (δ in ppm).

Position	8	9	10
H-3	7.01 (1H, s)	6.99 (1H, s)	7.00 (2H, s)
H-6	7.52 (1H, s)	7.51 (1H, s)	7.51 (2H, s)
H-3'	7.04 (1H, s)	7.19 (1H, s)	7.00 (2H, s)
H-6'	7.60 (1H, s)	7.51 (1H, s)	7.51 (2H, s)
$\text{CH}_3\text{O-4'}$		3.96 (3H, s)	
$\text{CH}_3\text{O-5'}$	3.98 (3H, s)		
$\text{CH}_3\text{O-8}$	4.31 (3H, s)	4.30 (3H, s)	4.30 (6H, s)
$\text{CH}_3\text{O-8'}$	4.34 (3H, s)	4.30 (3H, s)	4.30 (6H, s)

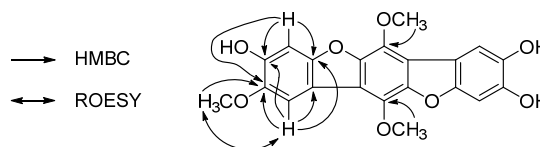


Figure 3: Key HMBC and ROESY correlations for the structure elucidation of compound **8**.

The next fractions from the CC of the EtOAc extract contained compound **8** with a minor analogue **9** in a 9:1 ratio. This mixture **8** + **9** showed only a pair of ions MS-ESI in both positive (m/z 397, $[\text{M}+\text{H}]^+$) and negative (m/z 395, $[\text{M}-\text{H}]^-$) ion modes that suggested isomeric structures for these compounds. The negative MS/MS investigation of ion m/z 395 detected for compound **9** led to the fragments at m/z 380 and 365 due to the loss of a methyl group and formaldehyde respectively from the parent ion. The ^1H NMR chemical shifts for compound **9** (Table 2), the residual signals in ^{13}C NMR spectrum, the 2D-NMR experiments together with the comparison with substituted dibenzofurans described in literature [12] and with **8**, led us to propose its isomeric structure 4',8,8'-trimethoxy-2,9':2',9'-diepoxy-9,7'-ciclo-7,9'-neoligna-7(9'),8,7'-triene-4,5,5'-triol for compound **9** (Figure 2).

Our compounds **8** and **9**, identified through the spectroscopic studies shown above, have three methoxy groups in their structures, the same number that corticin A has [6], so we wondered if any of our isolated terphenyl derivatives were or not different from corticin A. At the moment corticins were described first by Briggs *et al.* [6], they proposed the structure represented as **4** (Figure 1) for corticin A on the basis of its UV, IR and MS fragments of a mixture of corticins A and B and through the ^1H NMR signals of the isolated triacetyl derivative. Thus, a mixture of **8** + **9**, in a 3:1 ratio, was acetylated in order to compare with the triacetate described by them. The NMR data obtained for the triacetate **11**, derived from the major component **8**, did not coincide with any of those described in the literature, but the signals obtained for the triacetate **12**, derived from the minor component **9**, were identical to those described by Briggs [6] for the corticin A triacetate (Table 3). Considering that the structure of **9** has been properly established in this work, it would be concluded that the earlier structure for corticin A (compound **4** in Figure 1) would be corrected to structure **9** (Figure 2).

Table 3: ^1H NMR (400 MHz, CDCl_3) spectroscopic data of triacetylneolignans **11-12** and corticin A triacetate from Briggs *et al.* [6] (δ in ppm).

Position	11	12	Corticin A triacetate [6]
H-3	7.29 (1H, s)	7.17 (1H, s)	7.16 (1H, s)
H-6	7.73 (1H, s)	7.83 (1H, s)	7.83 (1H, s)
H-3'	7.42 (1H, s)	7.41 (1H, s)	7.42 (1H, s)
H-6'	7.96 (1H, s)	7.95 (1H, s)	7.96 (1H, s)
$\text{CH}_3\text{O}-4'$		3.92 (3H, s)	3.92 (3H, s)
$\text{CH}_3\text{O}-5'$	3.96 (3H, s)		
$\text{CH}_3\text{O}-8/8'$	4.37 (3H, s)	4.35 (3H, s)	4.36 (3H, s)
	4.35 (3H, s)	4.33 (3H, s)	4.34 (3H, s)
$\text{CH}_3-\text{COO}-$	2.34 (3H, s)	2.34 (3H, s)	2.35 (3H, s)
	2.37 (6H, s)	2.35 (6H, s)	2.36 (6H, s)
	2.37 (6H, s)	2.35 (6H, s)	2.36 (6H, s)

A different terphenyl derivative **10** was detected in the more polar fractions. It showed only three singlets in the ^1H NMR spectrum (Table 2) that indicated a symmetric structure with only two methoxy groups at C-8 and C-8' and with the chemical shifts of the aromatic protons corresponding with two symmetric catechol moieties in both other aromatic rings. The $[\text{M}-\text{H}]^-$ ion for **10** was easily obtained (MS-ESI m/z 381), but the $[\text{M}+\text{H}]^+$ ion could not be observed. Therefore, the MS/MS investigations for this compound was also in negative mode, observing the ions m/z 379 $[\text{M}-\text{H}-\text{H}_2]^-$, 366 $[\text{M}-\text{H}-\text{CH}_3]^-$ and 351 $[\text{M}-\text{H}-\text{CH}_2\text{O}]^-$, which concludes in the assignment of a new neolignan structure, 8,8'-dimethoxy-2,9':2',9'-diepoxy-9,7'-ciclo-7,9'-neoligna-7(9'),8,7'-triene-4,4',5,5'-tetraol, named as corticin E (Figure 2) for the compound **10** (Figure 2).

The three compounds (**8-10**) present catechol moieties on their structures, which suggest that its aerial oxidation to 1,2-quinone could be the reason for its instability and the formation of blue-violet pigments in the presence of oxygen and light. Particularly, corticin E (**10**), which has two catechol moieties, was a compound impossible to isolate alone. The yellow compound that went down through the CC in more polar fractions than those described in the experimental section, turned in a black dust as coal just in the drop that eluted from the column. This black dust could be the insoluble polymer described by Neveu *et al.* in the first studies with this fungus, in which they showed that fungal mycelia cultivated in the dark were white and only produced leuco-derivatives, which turned blue and decomposed when they were isolated in contact with the air [4].

The terphenyl derivatives were subjected to the same cytotoxicity assay as the extracts. As can be seen in Table 1, they were cytotoxic but the GI_{50} values observed for the compound **8** and the other mixtures of neolignans indicated somewhat less potency than the EtOAc extract itself. This could be due to the degradation that these compounds suffer under different conditions or even because they are not the only active ones in this extract, so, further chemical studies will be necessary to clarify it.

Carefully analysis of the ^1H NMR spectra (CDCl_3 and CD_3OD) of the second most potent extract, CH_2Cl_2 extract, showed, at least, the presence of the same neolignans **8** and **9** and a new set of signals that coincide with those described in the literature for corticiolic acid (**2**) [3]. These compounds could explain the bioactivity observed for this extract too (Table 1).

In summary, the cobalt crust fungus *Terana coerulea* (*Phanerochaetaceae* family) was selected for a bio-guided study after an ethnobotanical survey at the Irati's Forest (Navarra, Spain), where it is locally used for its antibiotic properties. Six extracts of increasing polarity, from hexane to hot water, were obtained from powdered dry fungi and tested for cytotoxicity against four human tumour cell lines and one non-tumour primary culture. CC of the most cytotoxic EtOAc extract led to the identification and structure

elucidation of three terphenyl neolignans, which differ in the position and number of methoxy groups. One of them was previously described as corticin A, whose earlier structure has been revised in this work. The other two neolignans are new natural products, named corticins D and E. They were cytotoxic although less potent than the EtOAc extract itself, maybe due to possible degradations under different conditions or to the presence of other bioactive compounds, which merit further chemical investigations of this fungus.

Experimental

General: ^1H and ^{13}C NMR experiments were recorded on a Bruker Avance 400DRX (400 or 100 MHz, respectively) spectrometer in CD_3OD or CDCl_3 using the residual solvent signal as reference. Chemical shift (δ) values are expressed in ppm followed by multiplicity. HRMS were run in a QSTAR XL Q-TOF (Applied Biosystems) using electrospray ionization (ESI) with an Agilent 1100 HPLC. MS were obtained in a ZQ4000 (Waters) using ESI with a Waters Alliance 2795 HPLC. MS/MS analyses were recorded on an Agilent 1100 LC/MS Trap XCT using ESI. All reagents and solvents (analytical grade) were purchased from commercial sources and were used without further purification. Deionised water was purified using a Millipore Direct-Q (TGI Water Systems). Column chromatography purifications were performed using silica gel 60 (40-63 μm , 230-400 mesh, Merck).

Fungal Material: Dead branches of apple tree (*Malus silvestris* (L.) Mill.) with the fungus *T. coerulea* were collected in Irati's Forest (Navarra, Spain) in 2016, 22nd February, at 750 m (42°58'35.78'' N 1°13'45.91'' W). A voucher specimen was deposited at the Herbarium of the University of Salamanca (SALA-FUNGI 4195). The fungus was identified as *Terana coerulea* (Lam.) Kuntze [1].

Extraction: *T. coerulea*'s fruiting bodies were separated from its natural support (dead branches of apple tree) with a knife, air-dried and powdered with a mortar. 2.00 g were extracted successively at room temperature for 20 h with hexane (2 x 100 mL), CH_2Cl_2 (2 x 100 mL), EtOAc (2 x 100 mL), MeOH (2 x 100 mL) and finally a decoction with hot water (100 mL). The evaporated MeOH extract was partitioned between water (100 mL) and *n*-BuOH (3 x 50 mL). Each organic extract was filtered and evaporated under reduced pressure, and aqueous extracts were lyophilized, to yield 24 mg of hexane extract (1.2% from dry weight of *T. coerulea*), 93 mg of CH_2Cl_2 extract (4.7%), 53 mg of EtOAc extract (2.7%), 107 mg of *n*-BuOH soluble fraction from the MeOH extract (5.4%), 18 mg of H_2O soluble fraction from the MeOH extract (0.9%) and 75 mg of final aqueous decoction (3.8%).

Isolation: The EtOAc extract (45 mg) was loaded on a silica gel column, eluted with a gradient of $\text{CH}_2\text{Cl}_2/\text{Me}_2\text{CO}$ (100:0–0:100, v/v) to afford 57 fractions. The sum of the fractions 9-10 (eluted with 97:3) led to the isolation of the 2.2 mg of compound **8** (0.11% from dry weight of *T. coerulea*). Fractions 11-14 (eluted with 97:3) gave 3.8 mg of a mixture of compounds **8** and **9** (9:1), fractions 15-36 (eluted with 80:20 to 50:50) gave 7 mg of a mixture of neolignans **8** and **9** (3:1) and fractions 37-45 (eluted with 0:100) gave 3.8 mg of a mixture of compounds **8**, **9** and **10** (2:1:1).

Corticin D (**8**)

Yellowish gum that turned black violet in presence of oxygen and light.

^1H NMR (400 MHz, CD_3OD): Table 2.

^{13}C NMR (100 MHz, CD_3OD): 57.2 ($\text{CH}_3\text{O}-5'$), 61.2 ($\text{CH}_3\text{O}-8'$), 61.2 ($\text{CH}_3\text{O}-8$), 99.0 (CH-3), 99.3 (CH-3'), 105.5 (CH-6'), 108.4 (CH-6), 116.1 (C-7'), 116.1 (C-7), 117.4 (C-1'), 117.9 (C-1), 134.5

(C-8'), 134.5 (C-8), 143.3 (C-4), 143.7 (C-9'), 143.8 (C-9), 146.2 (C-5'), 147.2 (C-5), 148.4 (C-4'), 152.2 (C-2), 152.7 (C-2').
HRMS-ESI: m/z [M + Na]⁺ calcd for C₂₁H₁₆O₈Na: 419.0737; found: 419.0726.

Mixture of Corticins D (8), A (9) and E (10)

Yellowish gum mixtures of compounds that turned black violet in presence of oxygen and light.

Corticin A (9)

¹H NMR (400 MHz, CD₃OD): Table 2.

MS-ESI (positive): m/z 397 [M + H]⁺.

MS-ESI (negative): m/z 395 [M – H][–].

MS/MS m/z 395 [M – H][–]: m/z 380 [M-H-CH₃][–], 365 [M-H-CH₂O][–].

Corticin E (10)

¹H NMR (400 MHz, CD₃OD): Table 2.

MS-ESI (negative): m/z 381 [M – H][–].

MS/MS m/z 381 [M – H][–]: m/z 379 [M-H-H₂][–], 366 [M-H-CH₃][–], 351 [M-H-CH₂O][–].

Acetylation of neolignans: A mixture of neolignans **8** and **9** (6 mg in proportion 3:1 from fraction 15-36) was acetylated with Ac₂O (100 μL) in pyridine (100 μL) at room temperature for 12 h. The reaction was quenched with ice and extracted with EtOAc, washing the organic phase successively with aqueous solutions of HCl (2 N), NaHCO₃ (satd.) and brine. After drying (anhydrous Na₂SO₄) and evaporating the solvent under vacuum, 7 mg of a mixture of compounds **11** and **12** (3:1) were obtained.

Corticin D triacetate (11)

¹H NMR (400 MHz, CDCl₃): Table 3.

Corticin A triacetate (12)

¹H NMR (400 MHz, CDCl₃): Table 3.

Cytotoxicity assay: Compound **8** and mixtures of **8+9** and **8+9+10** were evaluated against four human tumour cell lines: NCI-H460 (non-small cell lung cancer), HeLa (cervical carcinoma), HepG2 (hepatocellular carcinoma) and MCF-7 (breast adenocarcinoma) and against a non-tumour cell culture, designed as PLP2, prepared from a freshly harvested porcine liver according to an established procedure [14]. The corresponding cell line was plated at an appropriate density (1.0×10^4 cells/well) in 96-well plates and allowed to attach for 24 h. Cells were then treated for 48 h with the different diluted compound solutions. Afterwards, sulforhodamine B assay [15] was applied. The results were expressed as GI₅₀ values: sample concentration that inhibited 50% of the net cell growth. Ellipticine was used as positive control. For each compound, two independent experiments were performed, each one carried out in duplicate. Detailed procedure is described in the Supplementary material.

Supplementary data: NMR and MS spectra relating to this article and detailed cytotoxicity assay are available.

Acknowledgments - This work was financially supported by Spanish MINECO co-funded by FSE (CTQ2015-68175-R) and Portuguese Foundation for Science and Technology (FCT) through CIMO (Pest-OE/AGR/UI0690/2014) and R. C. Calhelha (SFRH/BPD/68344/2010) grant. We thank to Dr Anna M. Lithgow (NMR) and Dr César A. Raposo (MS) at Plataforma Nucleus (University of Salamanca) for running some spectra, and to Koldo Villalba for collecting the sample.

References

- [1]. (a) Moreno G, Manjón JL. (2010) *Guía de hongos de la Península Ibérica*. Omega, Barcelona, Spain, 1-1417; (b) Floudas D, Hibbett DS. (2015) Revisiting the taxonomy of *Phanerochaete* (Polyporales, Basidiomycota) using a four gene dataset and extensive ITS sampling. *Fungal Biology*, **119**, 679-719; (c) *Index Fungorum* [Internet]. Royal Botanic Garden Kew, Landcare Research-NZ, Institute of Microbiology - Chinese Academy of Science [custodians]. Available from: <http://www.indexfungorum.org> [Accessed 28th November, 2016].
- [2]. Baute R, Baute MA, Deffieux G, Filleau MJ. (1976) Cortalcerone, a new antibiotic induced by external agents in *Corticium caeruleum*. *Phytochemistry*, **15**, 1753-1755.
- [3]. Deffieux G, Baute R, Baute MA, Neveu A. (1979) A new metabolite produced by the fungus *Corticium caeruleum* (Schr. ex Fr.) Fr. (Aphylllophorales): corticiolic acid, isolation and chemical structure. *Comptes Rendus des Seances de l'Academie des Sciences, Serie D: Sciences Naturelles*, **288**, 647-649.
- [4]. Neveu A, Baute R, Bourgeois G, Deffieux G. (1974) Recherches sur le pigment bleu du champignon *Corticium caeruleum* (Schr. ex Fr.) Fr. (Aphylllophorales). *Bulletin de la Société de Pharmacie de Bordeaux*, **113**, 77-85.
- [5]. (a) Liu JK. (2006) Natural terphenyls: Developments since 1877. *Chemical Reviews*, **106**, 2209-2223; (b) Spatafora C, Calì V, Tringali C. (2003) Polyhydroxy-*p*-terphenyls and related *p*-terphenylquinones from fungi: overview and biological properties. *Studies in Natural Products Chemistry*, **29**, Part J, 263-307.
- [6]. Briggs LH, Cambie RC, Dean IC, Hodges R, Ingram WB, Rutledge PS. (1976) Chemistry of fungi. XI. Corticins A, B, and C, benzobisbenzofurans from *Corticium caeruleum*. *Australian Journal of Chemistry*, **29**, 179-190.
- [7]. Weisgraber K, Weiss U, Milne GWA, Silvertown JV. (1972) Hexamethyl ether of leuco-thelephoric acid from *Corticium caeruleum*. *Phytochemistry*, **11**, 2585-2587.
- [8]. Newsome AG, Culver CA, van Breemen RB. (2014) Nature's palette: the search for natural blue colorants. *Journal of Agricultural and Food Chemistry*, **62**, 6498-6511.
- [9]. (a) Gripenberg J. (1960) Fungus pigments. XII. Structure and synthesis of thelephoric acid. *Tetrahedron*, **10**, 135-143; (b) Lounasmaa M, Karjalainen A. (1973) Mass spectral fragmentation of 2,5-diphenyl-*p*-benzoquinones. *Acta Chemica Scandinavica*, **27**, 3427-3434.
- [10]. Tateishi K, Hoshi H, Matsunaga K. (2005) Thelephoric acid as antitumor agent. *PCT International Applications*, WO 2005095413 A1 20051013.
- [11]. Jokela R, Lounasmaa M. (1997) *p*-Terphenyl- and phenanthraquinone derivatives: an NMR study. *Planta Medica*, **63**, 381-383.
- [12]. Guo ZK, Yan T, Guo Y, Song YC, Jiao RH, Tan RX, Ge HM. (2012) *p*-Terphenyl and diterpenoid metabolites from endophytic *Aspergillus* sp. YXf3. *Journal of Natural Products*, **75**, 15-21.
- [13]. Moss GP. (2000) Nomenclature of lignans and neolignans (IUPAC recommendations 2000). *Pure and Applied Chemistry*, **72**, 1493-1523.
- [14]. Barros L, Pereira E, Calhelha RC, Dueñas M, Carvalho AM, Santos-Buelga C, Ferreira ICFR. (2013) Bioactivity and chemical characterization in hydrophilic and lipophilic compounds of *Chenopodium ambrosioides* L. *Journal of Functional Foods*, **5**, 1732-1740.
- [15]. Vichai V, Kirtikara K. (2006) Sulforhodamine B colorimetric assay for cytotoxicity screening. *Nature Protocols*, **1**, 1112-1116.