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PHANEROSPORIC ACID, A β-RESORCYLATE OBTAINED FROM *PHANEROCHAETE CHRYSOSPORIUM**

ALBERTO ARNONE, *GEMMA ASSANTE, GIANLUCA NASINI and ORSO VAJNA DE PAVA

Dipartimento di Chimica del Politecnico, Centro del C.N.R. per le Sostanze Organiche Naturali, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy, *Istituto di Patologia Vegetale, Facoltà di Agraria, Università di Milano, Via Celoria 2, 20133 Milano, Italy

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Abstract—The structure of phanerosporic acid, a β-resorcylate isolated from cultures of *Phanerochaete chrysosporium*, has been assigned on the basis of its ^1H and ^{13}C NMR data and chemical transformations. Its use as a synthon for macrolide synthesis is also described.

INTRODUCTION

Previous investigations on the products obtained from wood partly decayed by white-rot fungi such as *Phanerochaete* sp., *Sporotrichum* sp. and *Panus* sp., led to the isolation of various polymeric lignins, vanillic, isovanillic and veratric acids [1, 2]; recently *Phanerochaete chrysosporium* inoculated on *Betula lutea* (yellow birch) wood tissues gave a derivative of *p*-benzoquinone: the betulachrysoquinone hemiketal [3], which is probably a fungal metabolite rather than a product of lignin degradation. There have been no reports of metabolites produced by *P. chrysosporium* grown on synthetic substrates.

Here we report the characterization of the most abundant product contained in the ethyl acetate extracts of cultures of *P. chrysosporium*. The metabolite for which we propose the name phanerosporic acid (**1**), is the (*R*)-2,4-dihydroxy-6-(14′-hydroxypentadecyl)-benzoic acid. The absolute configuration at C-14′ was deduced as (*R*) by means of the Horeau method carried out on the trimethyl derivative **3**.

Several naturally occurring mould metabolites have been reported [4] to have structures characterized by the presence of an aromatic ring fused to a macrolide moiety, some showing interesting biological effects. With the aim of obtaining new compounds of this class, we transformed the 14′-hydroxy ester **3** into the aromatic macrolide **8**, by base-catalysed intramolecular ester exchange. This resorcylate is similar in molecular structure, but not in biological activity, to zearalenone, a fungal hormone produced from *Fusarium graminearum* [5], lasiodiplodin [6], some resorcylic acid lactones (active as plant-growth regulators) [7], and asperentin [8].

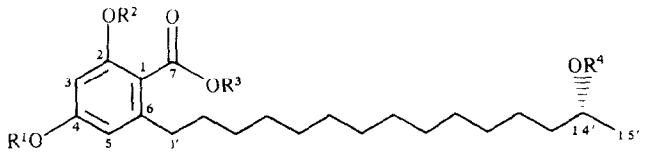
RESULTS AND DISCUSSION

When *Phanerochaete chrysosporium* was grown on MPGA (malt extract–peptone–glucose–agar) for three weeks, one main metabolite (**1**) was produced, together with small amounts of other metabolites (see Experimental). The ethyl acetate extracts of the fungus were evaporated, dissolved in dichloromethane, and hexane was added. crude compound **1** precipitated. After chromatography of the precipitate on buffered silica gel, pure phanerosporic acid (**1**) was obtained, which crystallized from dichloromethane–hexane as white crystals, mp 168°.

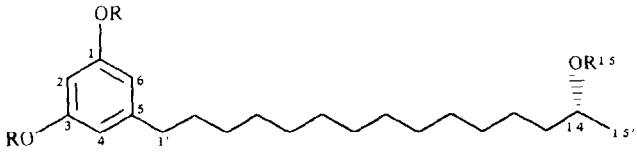
The molecular formula $C_{22}H_{36}O_5$ was assigned on the basis of fast atom bombardment (FAB) mass spectrometry. Absorptions in the IR region at 3350 and 1640 cm^{-1} were attributed to the presence of hydroxy and carbonyl groups. The ^1H NMR spectrum of **1** (see Experimental) in acetone-d_6 showed two *meta*-coupled aromatic protons ($J=2.5$ Hz), a $C(13')H_2CH(14')OHMe$ grouping and methylene protons resonating at δ_H 2.94 (H_2-1′) and between 1.1–1.7. In addition, it presented a broad signal centred at δ_H 7.15, which disappeared on adding D_2O, attributable to the presence in the molecule of carboxylic and hydroxy protons in rapid exchange with the water contained in the solvent. Accordingly, the ^{13}C NMR spectrum of **1** (see Experimental) exhibited signals attributable to a tetrasubstituted aromatic ring (δ_C 101.72–167.17), to a carboxylic acid ($\delta_C=174.07$), to an sp^3 oxygen-bearing methine and to a methyl carbon, the remaining resonances (δ_C 40.20–26.59) being due to methylene carbons. Treatment of **1** with pyridine–acetic anhydride afforded the triacetyl derivative **5** together with the decarboxylated compound **7**. In the ^1H NMR spectrum of **5**, H-14′ exhibited a characteristic downfield shift ($\Delta\delta=1.11$), this fact indicating the presence in compound **1** of one aliphatic and, hence, of two phenolic hydroxy groups. The above NMR data coupled with mass spectral evidence suggest that the structure of **1** consists of a dihydroxy benzoic acid nucleus substituted with a 14′-hydroxy-*n*-pentadecyl side chain. More conclusive evidence on the structure of **1** derived from the analysis of the ^1H and ^{13}C NMR data (Table 1) of its dimethyl derivative **2** ($C_{24}H_{40}O_5$) obtained by reacting **1** with diazomethane.

The ^1H NMR spectrum of **2** revealed the presence of two OMe groups resonating at δ_H 3.91 and 3.77 (H_3-8 and H_3-10), of two *meta*-coupled aromatic protons at δ_H 6.33

*Part 27, in the series 'Secondary Mould Metabolites'. For part 26 see Albinati, A., Arnone, A., Assante, G., Meille, S. V., and Nasini, G., (1989) *Phytochemistry* **28**, 923



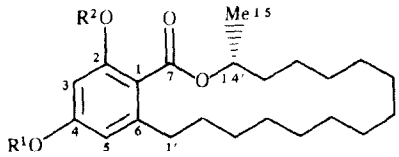
1 $R^1 = R^2 = R^3 = R^4 = H$
2 $R^1 = {}^{10}Me$, $R^3 = {}^{8}Me$, $R^2 = R^4 = H$
3 $R^1 = R^2 = R^3 = Me$, $R^4 = H$
4 $R^1 = R^2 = R^3 = Me$, $R^4 = Ac$
5 $R^1 = R^2 = R^4 = Ac$ $R^3 = H$



5 ⟵ II — **1** — I ⟶ **6**
7

6 R = H
7 R = Ac

3 —III⟶



8 $R^1 = R^2 = Me$
9 $R^1 = Me$, $R^2 = H$

Reagents I, KOH–MeOH, II, pyridine–Ac_2O, III, Na -*t*- amylate–toluene

Table 1 ^{13}C and ^1H NMR data for compound **2** in $CDCl_3$

Atom	δ_C/ppm*	^1J(CH) (Hz)		$^{>1}J$(CH) (Hz)	δ_H (ppm)†	J(HH) (Hz)
1	104 58	*Sdddt*		4 0 (H-3), 8 0 (H-5), 4 0 (OH-2), 4 0 (H_2-1′)		
2	165 54	*Sdd*		4 0 (H-3), 4.5 (OH)		
3	98 74	*Ddd*	161 4	4 5 (H-5), 7 8 (OH)	6 33 *d*	2 6
4	163 94	*Sdddq*		*ca*3 (H-3), *ca*3 (H-5), 1.5 (OH), 4 3 (H_3-10)		
5	110 63	*Ddt*	160 7	5 0 (H-3), 6 3 (H_2-1′)	6 27 *d*	2 6
6	148 03	*Stt*		5 5 (H_2-1′), 3 0 (H_2-2′)		
7	171 98	*Sq*		4 0 (H_3-8)		
8	51 82	*Qs*	147.5		3 91 *s*	
10	55 22	*Qs*	144 4		3 77 *s*	
1′	36 94	*Tm*	129 0		2 83 *m*	
14′	68 04	*Dm*	141 0		3 75 *m*	
15′	23 45	*Qm*	125 0		1 18 *d*	6 2

*Capital letters refer to the pattern resulting from direct bonded (C, H) couplings and small letters to that from (C, H) couplings over more than one bond The remaining 12 methylene carbons appears at δ_C39 37, 31 89, 29 88, 29 69 (7 carbons), 29 54 and 25 82

†The protons of the phenolic and the aliphatic hydroxy groups appear at δ_H11 75 and 2 00, respectively, and the remaining 24 methylene protons at δ1 1–1 7

and 6.27 (H-3 and H-5), and of one phenolic hydroxy proton at δ_H11 75 (OH-2) which must be hydrogen-bonded with the adjacent CO_2Me group. Their assignment, as well as that of the ^{13}C resonances of the aromatic portion, followed from a series of ^{13}C-{^1H} low-power specific decoupling experiments, the results of which are reported in Table 1, from the multiplicities observed in the ^1H-coupled ^{13}C NMR spectrum and from chemical shift considerations. In particular the chelated 2-hydroxy proton presented two-, three- and four-bond couplings with the carbons resonating at δ_C165 54 (^2J = 4 5 Hz), 104 58 (^3J = 4.0 Hz), 98 74 (^3J = 7 8 Hz), and 163 94 (^4J = 1.5 Hz) which were therefore assigned to C-2, C-1, C-3, and C-4 [9] respectively, the methoxy substituents were placed at C-4 and at the carbonyl C-7 (δ_C = 171.98) as these carbons presented three-bond couplings of 4.3 and 4 0 Hz with H_3-10 and H_3-8, respectively; the side chain was located at C-6, as irradiation of either H_2-1′ or H_2-2′ caused the quaternary carbon at δ_C = 148 03 to decouple to a triplet (^2J = 5 5 and ^3J = 3 0 Hz) while the remaining methine aromatic carbon which presented, as well as C-1, three-bond couplings with H_2-1′ (^3J = 6 3 and 4 0 Hz respectively) was assigned to C-5. Phanerosporic acid decarboxylates by heating with bases to give the resorcyl-

ate **6**, similar to other analogous natural *meta*-diphenolic acids such as corticiolic acid, isolated from *Corticium caeruleum* grown on yeast extract medium [10].

In order to transform the open chain compound **1** into a macrolide, attempts were made to protect the two phenolic hydroxy functions. By reaction of **1** with diazomethane, compound **2** was obtained with the phenolic OH in position 2 unprotected; by reaction of **1** with two equivalents of methyl iodide in the presence of potassium carbonate–acetone, trimethylated compound **3** was obtained, besides small amounts of the desired 2,4-dimethoxy acid; therefore lactonization methods by simultaneous activation of both hydroxyl and carboxylic functions (Corey–Nicolau system) were unsuitable [11]. Attempts to obtain cyclization using pellets of *Phanerochaete chrysosporium* or *Fusarium graminearum* grown on liquid medium were unsuccesful, as only decarboxylated product **6** was obtained.

The cyclization was finally obtained by intramolecular transesterification of the corresponding dimethyl ether, methyl ester **3**. The reaction was performed in dilute solution in toluene, in the presence of sodium *t*-amylalcoholate, at reflux for 15 hr [12]. Compound **8** was so obtained in moderate yield (32%). Its structure was derived from the following evidence: the mass spectrum displayed a molecular ion at *m/z* 390 ($C_{24}H_{38}O_4$), indicating loss of methanol from the parent compound **3**; and in the ^{1}H NMR spectrum (see Experimental) H-14′ exhibited a characteristic downfield shift of 1.38 ppm compared with **3**, this fact confirming the lactone ring formation. Because active β-resorcylate macrolides have free phenolic OH groups, attempts were made to demethylate macrolide **8**. Demethylation of **8** with boron trichloride gave only the monomethyl-derivative **9**, while open products were obtained by reaction with boron tribromide.

From a biological point of view phanerosporic acid, but not macrocyclic derivatives **8** and **9** has antibacterial activity. All three compounds **1**, **8** and **9** showed a stimulatory effect on root elongation of *Lepidium sativum* (see Experimental).

EXPERIMENTAL

Mps: uncorr. UV absorptions were measured for solns in 95% EtOH. Mass spectra were taken at 70 eV on an instrument equipped with a FAB source. NMR spectra were recorded at 300.13 MHz for ^{1}H and 75.47 for ^{13}C nuclei with TMS as int. standard. Flash CC was performed on Merck silica gel (0 040–0.063 mm). TLC with Merck HF_{254} silica gel. The purity of products was checked by TLC, NMR and MS, and deemed sufficient for the purpose of structural elucidation.

Isolation and purification of metabolite **1** The strain *Phanerochaete chrysosporium* CBS 481.83 was inoculated in 20 Roux flasks containing MPGA (100 ml) (malt extract–peptone–glucose–agar 40 · 4 · 40 · 15 g/l). After 21 days at 24°, the flasks were extracted twice with EtOAc containing 1% MeOH. The crude extracts were chromatographed on a column of flash silica gel (containing 3% NaH_2PO_4) using CH_2Cl_2–MeOH (15:1) as eluent The main fraction (2 g) was crystallized from CH_2Cl_2–hexane to give pure phanerosporic acid **1** (1.2 g).

Phanerosporic acid (**1**). White crystals, mp 168°, $[\alpha]_D$ −6.10° (MeOH, *c* 0.5); (Found: C, 69 5; H, 9.6, $C_{22}H_{36}O_5$ requires· C, 69.44, H, 9 54%); EIMS *m/z* 336 (28) [M − 44], 318 (20), 138 (56), 124 (100), 110 (9), FABMS *m/z*· 380, UV λ_{max}nm: 210, 255, 295 (ε26 100, 10 000, 4500); IR ν_{max}cm^{-1}· 3350 (OH), 1640 (CO); NMR (Me_2CO-d_6) δ7 15 (*br* signal, COOH + 3OH), 6 30 and 6.23 (2H, *d*, *J* = 2.5 Hz, H-3 and H-5), 3 72 (1H, *m*, H-14′), 2.94 (2H, *m*, H_2-1′), 1.7–1.1 (24 H, *m*, 12 CH_2), and 1.12 (3H, *d*, *J* = 6 1 Hz, H_3-15′) ^{13}C NMR (Me_2CO-d_6): δ174.07 (*s*, C-7), 167.17 and 163.34 (*s*, C-2 and C-4), 149.89 (*s*, C-6), 111.61 (*d*, C-5), 104.35 (*s*, C-1), 101.72 (*d*, C-3), 67.71 (*d*, C-14′), 37 26 (*t*, C-1′), 23 97 (*q*, C-15′). The remaining 12 methylene carbons resonate at δ40.20, 32.81, 30.54, 30.48, 30 40, 30 35 (5 carbons), 30 20, and 26.59.

Phanerosporic acid 4-methyl ether methyl ester (**2**). Compound **1** (200 mg) was dissolved in CH_2Cl_2–MeOH and treated with CH_2N_2–Et_2O at 0° overnight Evapn of the solvent and PLC in CH_2Cl_2–MeOH (15:1) gave **2** (180 mg) as crystals mp 53° (from $CHCl_3$), EIMS *m/z*: 408 $[M]^+$ (1), 376 (5), 332 (8), 182 (26), 151 (17), 138 (100); (M^+ found. *m/z* 408.2887, $C_{24}H_{40}O_5$ requires 408 2875); UV λ_{max}nm: 212, 256, 295 (ε13 850, 6900, 2700), IR ν_{max}cm^{-1}: 3350 (OH), 1650 (ester CO) ^{1}H and ^{13}C NMR· see Table.

Phanerosporic acid 2,4-dimethyl ether methyl ester (**3**) Compound **2** (200 mg) was dissolved in dry Me_2CO (10 ml) and refluxed (5 hr) with K_2CO_3 (800 mg) and MeI (1 ml). Filtration of the solid and evapn of the solvent afforded **3** as an oil; $[\alpha]_D$ −3.49° ($CHCl_3$; *c* 0.1); EIMS *m/z*: 422 $[M]^+$ (16), 390 (21), 210 (100), 191 (66), 151 (32); UV λ_{max}nm: 202, 245, 275 (ε26 900, 47 600, 29 000); IR ν_{max}cm^{-1}: 3440 (OH), 1730 (CO); ^{1}H NMR ($CDCl_3$): δ6.33 and 6.31 (2H, *d*, *J* = 2.1 Hz, H-3 and H-5), 3 87, 3.80 and 3.78 (9H, *s*, 3OMe), 3.78 (1H, *m*, H-14′), 2.53 (2H, *m*, H_2-1′), 1 70 (1H, *br s*, OH), 1 6–1.1 (24H, *m*, 12 CH_2), and 1.17 (3H, *d*, *J* = 6 2 Hz, H_3-15′).

Reaction of **3** *with* (+)-*2-phenylbutyric anhydride* (+)-2-Phenylbutyric anhydride (170 mg) was added to a soln of **3** (120 mg) in dry pyridine (0 5 ml) The soln was kept for 20 hr at room temp., (+)-2-phenylbutyric acid with $[\alpha]_D$ + 1 7° (pyridine; *c* 4.5) was obtained upon work-up of the reaction mixture according the method of ref. [13].

Phanerosporic acid-2,4-dimethyl-ether, methyl ester, 14′-acetate (**4**). Compound **3** (100 mg) was dissolved in dry pyridine (3 ml) and treated with Ac_2O (6 ml) The soln was left to stand at 0° overnight, then the mixture was poured into ice-H_2O, neutralized and extracted with EtOAc prep TLC (hexane–EtOAc, 2.1) gave **4** (80 mg) as an oil; IR ν_{max}cm^{-1}· 1740, 1730 (CO), ^{1}H NMR ($CDCl_3$)· δ6 31 (2H, *s*, H-3 and H-5), 4 86 (1H, *m*, H-14′), 3.85 and 3 80 (9H, *s*, OMe), 2 53 (2H, *m*, H_2-1′), 2 00 (3H, *s*, OAc), 1.7–1.0 (24H, *m*, 12 CH_2), and 1 20 (3H, *d*, *J* = 6 1 Hz, H_3-15′).

Phanerosporic acid triacetate (**5**) Phanerosporic acid **1** (200 mg) was dissolved in dry pyridine (2 ml) and treated with Ac_2O (4 ml). The soln was left to stand at 0° for 24 hr, the mixt was then poured into ice-H_2O, neutralized and extracted with EtOAc. Prep. TLC (hexane–EtOAc, 2·1) gave **5** (80 mg) and **7** (70 mg). Compound **5**, ^{1}H NMR (Me_2CO-d_6). δ6.99 (1H, *d*, *J* = 2 2 Hz, H-5), 6.88 (1H, *d*, *J* = 2.2 Hz, H-3), 4 83 (1H, *ddq*, *J* = 7.2, 5.4 and 6.2 Hz, H-14′), 2.77 (2H, *m*, H_2-1′), 2.27, 2.21 and 1 96 (9H, *s*, 3 OAc), 1 7–1 1 (24H, *m*, 12 CH_2), and 1.17 (3H, *d*, *J* = 6.2 Hz, H_3-15′) Compound **7**, ^{1}H NMR (Me_2CO-d_6): δ6 85 and 6.76 (3H, *m*, ArH), 4 83 (1H, *ddq*, *J* = 7.2, 5 4 ad 6.2 Hz, H-14′), 2.63 (2H, *m*, H_2-1′), 2.24 and 1.96 (9H, *s*, 3 OAc), 1 7–1 1 (24H, *m*, 12 CH_2), and 1 17 (3H, *d*, *J* = 6.2 Hz, H_3-15′).

5-(14′-hydroxy-n-pentadecyl)-Resorcinol **6**. Phanerosporic acid (160 mg) was treated with a soln of KOH (200 mg) in MeOH (6 ml) at 80° for 6 hr. The reaction mixture was neutralized with HOAc, extracted with EtOAc; evapn of solvent and prep. TLC (hexane–EtOAc, 1 2) gave **6** (120 mg) mp 135 $[\alpha]_D$ −23.72° ($CHCl_3$; *c* 0.1); EIMS *m/z*. 336 $[M]^+$ (25), 166 (14), 137 (36), 124 (100); UV λ_{max}nm 207, 220 sh, 280 (ε23 300, 4000, 3000); IR ν_{max} 3400 and 3000 (OH), ^{1}H NMR (Me_2CO-d_6) δ6 21 (H, *s*, ArH), 3.75 (1H, *m*, H-14′), 2.46 (2H, *m*, H_2-1′), 1.8–1.0 (24H, *m*, 12 CH_2), 1.12 3H, *d*, *J* = 6.2 Hz, H_3-15′).

2,4-Dimethoxy-6 (14'-hydroxy-pentadecyl)-benzoic acid lactone (**8**) Metallic sodium (300 mg) was added to *t*-amyl alcohol (300 ml), and heated to complete dissolution The resulting soln was added to compound **3** (100 mg) dissolved in dry toluene (1 l), distilled during a period of 6 hr and 200 ml of distillate were collected Excess of HOAc was added, and the solvent removed *in vacuo* Extraction of the residue with CH_2Cl_2, evapn of the solvent and flash CC using hexane–EtOAc (4 1) gave macrolide **8** (30 mg 32%) as an oil, $[\alpha]_D -21^\circ$ ($CHCl_3$; *c* 0 43), EIMS *m/z* 390 $[M]^+$ (73), 346 (6), 196 (100), 178 (11), 165 (18), 152 (61), UV λ_{max}nm 208, 254 sh, 280 (ε26 600, 4600, 2750); IR ν_{max} cm^{-1} 1720 (lactone CO), ^{1}H NMR ($CDCl_3$) δ6 34 and 6 31 (2H, *d*, *J* = 2 2 Hz, H-3 and H-5), 5 16 (1H, *tq*, *J* = 6.5 and 6 2 Hz, H-14', 3 81 and 3 79 (6H, *s*, 2 OMe), 2 57 (2H, *m*, H_2-1'), 1 9–1 1 (24H, *m*, 12 CH_2), and 1 33 (3H, *d*, *J* = 6 2 Hz, H_3-15', ^{13}C NMR ($CDCl_3$) δ168 13 (*s*, C-7), 161 17 and 157 76 (*s*, C-2 and C-4), 142 54 (*s*, C-6), 117 33 (*s*, C-1), 105 41 and 96 25 (*d*, C-3 and C-5), 72 04 (*d*, C-14', 55 82 and 55 34 (*q*, 2 OMe), 36 24 (*t*, 13 CH_2), and 19 73 (*q*, C-15')

2-Hydroxy, 4-methoxy-6-(14'-hydroxy-pentadecyl)-benzoic acid lactone (**9**) Compound **8** (12 mg) was dissolved in dry CH_2Cl_2 (5 ml) and treated with BCl_3 (0 11 ml) at -30°, after 1 hr H_2O was added and the product extracted with Et_2O Evapn of the solvent and prep TLC in hexane–EtOAc (7 3) gave **9** (5 mg), mp 50°, EIMS *m/z* 376 $[M]^+$, 337, 182, 139 (100), ^{1}H NMR ($CDCl_3$) δ12 0 (1H, *br s*, OH-2), 6 35 and 6 31 (2H, *d*, *J* = 2 5 Hz, H-3 and H-5), 5 20 (1H, *tq*, *J* = 6 5 and 6 2 Hz, H-14'), 3 80 (3H, *s*, OMe), 3 18 and 2 60 (2H, *m*, H_2-1'), 1 9–1 1 (24H, *m*, 12 CH_2), and 1 33 (3H, *d*, *J* = 6 2 Hz, H_3-15')

Antifungal and antibacterial tests were performed using paper discs (6 mm ϕ) soaked with 200 μg of the test compound dissolved in EtOH, dried and placed in suitable culture medium. After 24 hr phanerosporic acid only produced a clean growth inhibition halo (6 mm ray of circular crown) against. *Bacillus cereus*, *B subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, *Aspergillus niger*, *Ophiostoma ulmi*, *Ustilago maydis*, *Cladosporium cucumerinum*, *C cladosporioides*, and *Botrytis cinerea*

Bioassay on *Lepidium sativum* for growth activity 600 μg of the tested compounds (**1**, **8** and **9** respectively) were dissolved in 3 ml Me_2CO Solutions have been used to soak a filter paper disc (Whatman no 4 placed in a Petri dish mm) previously sterilized After evaporating the solvent, 7 ml of demineralized H_2O were added *Lepidium sativum* seeds were surface sterilized in NaOCl 1% for 5 min, rinsed twice in sterile H_2O, and placed in the moist Petri chamber (50 seeds/dish) After 72 hr the roots elongation was measured discarding 10 values min and 10 values max The value obtained is the average of three separate experiments (150 seeds) carried out with every metabolite tested For compounds **1**, **8** and **9** the average lengths were 33, 29 5 and 39 mm respectively versus control (17 5 mm)

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