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Crystal structures of mollugin and lucidin

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Mollugin was isolated from the extract of *Rubia tinctorum* roots. Lucidin was obtained by semisynthesis from xanthopurpurin. Mollugin crystallises in space group *P*-1 (No. 2), $a = 8.5857(7)$, $b = 11.473(4)$, $c = 15.024(1)$ Å, $\alpha = 77.64(2)^\circ$, $\beta = 89.36(1)^\circ$, $\gamma = 89.71(2)^\circ$, and $V = 1445.5(5)$ Å^3, lucidin crystallises in space group $P2_1/c$ (No.14), $a = 16.800(6)$, $b = 9.637(2)$, $c = 7.073(7)$ Å, $\beta = 98.01(5)^\circ$, and $V = 1134(1)$ Å^3.

KEY WORDS: Madder root; mollugin; lucidin; *Rubia tinctorum*.

Introduction

Pigments extracted from the roots of *Rubia tinctorum* belong to the oldest natural colorants (madder colour). In modern medicine they have found use for the treatment of kidney stones and as antimicrobial agents.[1] Lucidin (1,3-dihydroxy-2-hydroxymethyl-anthraquinone) and lucidin primeveroside sometimes occurring in *Rubia tinctorum*, are apparently responsible for the potential mutagenic and genotoxic activity of the madder root extracts.[2–4] Recently, drosophila wing spot test revealed that naphthoquinone mollugin can also contribute to the mutagenity of *Rubia tinctorum* extracts.[5] However, the general problem of madder colour analysis is the lack of standards. The majority of pigments present in *Rubia tinctorum* are not commercially available. Present work aims to provide primary analytical standards of two mutagenic components of the madder root.

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Experimental

Plant material

Rubia tinctorum roots from Iran were used for preparative isolation of xanthopurpurin. Dried plant roots (500 kg) were extracted with methanol (12,000 L). The extract was concentrated on a vacuum drier to 500 kg, conc. hydrochloric acid was added (36%, 150 L) and hydrolysis of isolated glycosides was carried out in 12 h, at 80°C. Crude pigments were isolated by filtration, rinsed with water and dried (yield 33 kg).

A mixture of pigments (1 kg) was mixed with diethyl ether (2:l) and stirred for 24 h. The soluble part was separated by filtration and the insoluble precipitate was rinsed with diethyl ether (1:l). Pooled filtrates were mixed with *n*-hexane (1:1, v/v), insoluble precipitate was removed (38 g), and the solution was applied on silica gel (Silica gel 60, Grace, 1.5 kg). Purified pigments were obtained by subsequent elution with mixtures of

diethyl ether/hexane = 3:7 v/v (175 g, xanthopurpurin, mollugin, 3,4-dihydromollugin), 2:3 v/v (35 g, xanthopurpurin, alizarin), and 1:1 v/v (19 g, 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone).

Isolation of xanthopurpurin and mollugin

Naphthoquinones mollugin and dihydromollugin were isolated from the fraction diethyl ether/hexane: 3:7 containing a mixture of xanthopurpurin, mollugin, and 3,4-dihydromollugin. Crude pigments (30 g) were heated under reflux with *n*-heptane (250 mL) for 1 h. The insoluble fraction containing xanthopurpurin was separated by filtration, rinsed with *n*-heptane (100 mL) and dried (yield 15 g). Pure xanthopurpurin was obtained by repeated crystallisation from diethyl ether. Pooled filtrates containing mollugin and 3,4-dihydromollugin were evaporated and mollugin was separated from 3,4-dihydromollugin by repeated crystallisation from hot acetone. Alternatively, mollugin and 3,4-dihydromollugin were separated by preparative HPLC on a reversed phase column (Column 250 × 25 mm I.D., C-18, 7 μm, isocratic elution with an aqueous acetonitrile (72:28, v/v), flow 5 mL min^{-1}, detection at 320 nm.

Synthesis and characterization of lucidin

Lucidin was synthesised according to a modified procedure.[6] Xanthopurpurin (180 mg) was dissolved in methanol (80 mL) and aqueous sodium hydroxide (650 mg in 3 mL) and formaldehyde (30%, 5 mL) were subsequently added with stirring. After 5 h of stirring at ambient temperature, distilled water was added (160 mL) and the pH was adjusted with aqueous H_3PO_4 (10%) using lucidin itself as an indicator (sharp transition from deep violet to orange). Fine micro crystals of lucidin were separated by filtration, washed with a methanol/water mixture (1:2, v/v) in order to remove trace impurities of other anthraquinones present already in the original xanthopurpurin (particularly alizarin), and dried *in vacuo*.

Spectral data

NMR spectra were measured with a Varian INOVA-400 spectrometer (399.90 MHz for ^{1}H, 100.57 MHz for ^{13}C) at 30°C in the solvents stated. Chemical shifts are given on the δ-scale (ppm) and coupling constants in Hz. Signal assignment is based on COSY, HMQC, and HMBC experiments. Numbering of atoms according to chemical nomenclature is used for the NMR data (Fig. 1). Since this chemical numbering is not applicable for substituents and symmetry independent molecules, consecutive numbering of atoms is used for the X-ray data (Figs. 2 and 3). Electrospray ionisation (ESI) mass spectra were recorded on a Finnigan LCQ-DECA quadrupole ion trap mass spectrometer (ThermoQuest, San Jose, U.S.A.). The high-resolution mass spectrum of lucidin was measured on a Finnigan MAT 95 (double-focusing, BE geometry) instrument.

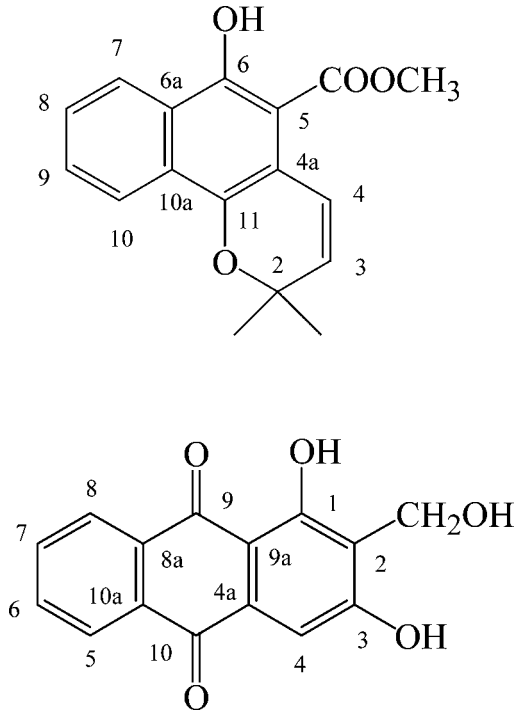

Fig. 1. Structure of mollugin (top) and lucidin (bottom).

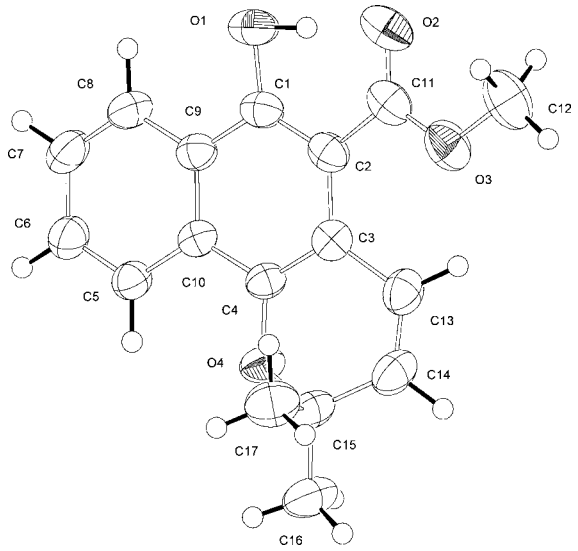

Fig. 2. ORTEP drawing of mollugin with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

Mollugin

^{1}H NMR ($CDCl_3$, 30°C): 1.505 (6 H, s, CMe_2), 4.002 (3 H, s, OMe), 5.675 (1 H, d, $J = 10.1$ Hz, H-3), 7.116 (1 H, d, $J = 10.1$ Hz, H-4), 7.512 (1 H, ddd, $J = 8.3, 6.9, 1.3$ Hz, H-8), 7.615 (1 H, ddd, $J = 8.3, 6.9, 1.4$ Hz, H-9), 8.183 (1 H, ddd, $J = 8.3, 1.3, 0.7$ Hz, H-10), 8.378 (1 H, ddd, $J = 8.3, 1.4, 0.7$ Hz, H-7), 12.159 (1 H, s, OH). ^{13}C NMR ($CDCl_3$, 30°C): 26.86 q (2 C, Me_2), 52.21 q (OMe), 74.63 s (C-2), 102.23 s (C-5), 112.54 s (C-4a), 121.90 d (C-10), 122.28 d (C-4), 124.01 d (C-7), 125.09 s (C-6a), 126.25 d (C-8), 128.81 d (C-3), 129.01 s (C-10a), 129.28 d (C-9), 141.57 s (C-11), 156.46 s (C-6), 172.44 s (C=O). ESI MS: $[M-H]^-$ at *m/z* 283, the CID of the deprotonated molecule revealed ions at *m/z* 269 (10%), 251 (100%), 224 (16%) and peak at *m/z* 209 (35%). Proton NMR spectrum roughly corresponds to that found in literature.[7]

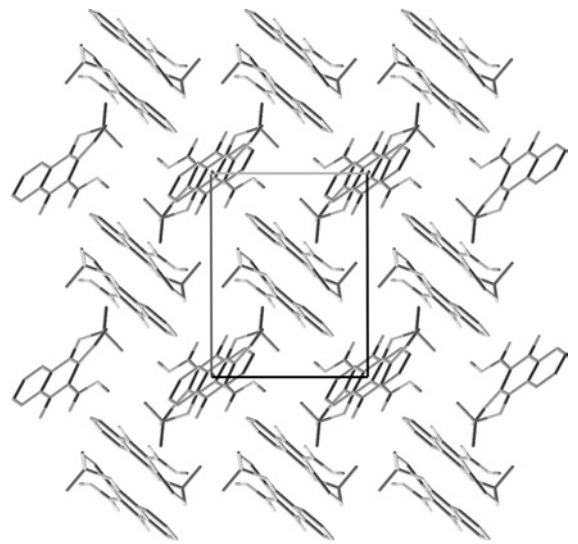

Fig. 3. Packing scheme for mollugin. Projection along *c*-axis.

Lucidin

^{1}H NMR (d_6-DMSO): 4.531 (2 H, s, CH_2O), 7.228 (1 H, s, H-4), 7.875 (1 H, ddd, $J = 7.4$, 7.4, 1.7 Hz, H-6), 7.907 (1 H, ddd, $J = 7.4$, 7.4, 1.8 Hz, H-7), 8.124 (1 H, dd, $J = 7.4$, 1.8 Hz, H-5), 8.189 (1 H, dd, $J = 7.4$, 1.7 Hz, H-8), 13.166 (1 H, s, 1-OH). ^{13}C NMR (d_6-DMSO): 51.41 t (CH_2O), 107.96 d (C-4), 109.19 s (C-9a), 120.40 s (C-2), 126.49 d (C-8), 126.86 d (C-5), 132.95 s (C-10a), 133.13 s (C-8a), 133.43 s (C-4a), 134.58 d (C-6), 137.74 d (C-7), 163.21 s (C-1), 164.74 s (C-3), 181.89 s (C-10), 186.31 s (C-9). APCI MS: 269 (100, $[M-H]^-$), 252 (96), 239 (48), 224 (15). ESI MS: $[M-H]^-$ at *m/z* 269.0445, for $C_{15}H_90_5$ calculated 269.0450.

Crystallography

A summary of crystallographic data is given in Table 1, bond lengths and angles are summarised in Tables 2 and 3. The structures were solved by direct methods and anisotropically refined by full-matrix least squares. The following programs were used for calculations and visualisations: CRYSTALS,[8] PARST,[9] SHELXS86,[10] ORTEP-3,[11] and Mercury.[12]

Mollugin

Needle crystals were obtained by cooling of the mollugin solution in hot acetone. Hydrogen

Table 1. Crystal Data and Structure Refinement

	Mollugin	Lucidin
CCDC no.	184039	184038
Color/shape	Yellow/needles	Yellow/needles
Chemical formula	$C_{17}H_{16}O_4$	$C_{15}H_{10}O_5$
Formula weight	283.31	270.24
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	$P2_1/c$
a (Å)	8.5857(7)	16.800(6)
b (Å)	11.473(4)	9.637(2)
c (Å)	15.024(1)	7.073(7)
α (°)	77.64(2)	90
β (°)	89.36(1)	98.01(5)
γ (°)	89.71(2)	90
V (Å^3)	1445.5(5)	1134(1)
Z	4	4
D_{calc} (g cm^{-3})	1.302	1.583
Crystal dimensions (mm)	0.07 × 0.25 × 0.28	0.14 × 0.25 × 0.46
Diffractometer and radiation used	Enraf-Nonius CAD4, CuKα, $\lambda = 1.54184$ Å	
Scan technique	$\omega/2\theta$	
Temperature	293 K	
No. and θ range of reflections for lattice parameter refinement	20; 38–40°	
Range of *h*, *k*, and *l*	$-10 \rightarrow 10$, $-13 \rightarrow 13$, $-18 \rightarrow 18$	$-20 \rightarrow 20$, $-11 \rightarrow 11$, $0 \rightarrow 8$
Standard reflections monitored in the interval; intensity fluctuation	60 min; 2.4%	60 min; −0.43%
Total number of reflections measured; 2θ range	10,377; 5–136°	4,366; 5–136°
No. of observed reflections	4,052	1,076
Criterion for observed reflections		$I \geq 1.96\sigma(I)$
Function minimised		$w(\|F_o\| - \|F_c\|)^2$
Weighting scheme		Chebychev polynomial[13]
Parameters refined	379	181
Value of *R*, *wR*, and *S*	0.0644, 0.0643 and 1.086	0.1212, 0.1205 and 1.1853
Ratio of the maximum least-squares shift to e.s.d. in the last cycle	0.0006	0.000061
Maximum and mininimum heights in final $\Delta\rho$ map	0.35, −0.48 eÅ^{-3}	0.75, −0.64 eÅ^{-3}

atoms were localised from $\Delta\rho$-maps and expected geometry. The position of H801 was set to follow the O1—H801···O2 intra-molecular hydrogen bond, according to the O51—H851···O52, found from the $\Delta\rho$-map.

Lucidin

Needle crystals were obtained by slow evaporation of the solution containing lucidin (50 mg), methanol (16 mL) and conc. aqueous ammonium (4 mL). Hydrogen atoms were located from the expected geometry. Those hydrogen atoms of alcohol groups were found in the $\Delta\rho$ map.

Results and discussion

Mollugin and 3,4-dihydromollugin were isolated taking advantage of their solubility in aliphatic hydrocarbons, which makes it possible to separate them from *Rubia tinctorum* anthraquinones. Thus short boiling of the crude xanthopurpurin, mollugin, and 3,4-dihydromollugin

Table 2. Bond Lengths (Å) and Angles (°) for Mollugin

Bond lengths (Å)			
O1−C1	1.352(2)	O51−C51	1.356(2)
O2−C11	1.222(2)	O52−C61	1.226(2)
O3−C11	1.322(2)	O53−C61	1.318(2)
O3−C12	1.446(2)	O53−C62	1.447(2)
O4−C4	1.3657(19)	O54−C54	1.3730(19)
O4−C15	1.4564(19)	O54−C65	1.461(2)
C1−C2	1.389(3)	C51−C52	1.384(3)
C1−C9	1.425(2)	C51−C59	1.426(3)
C2−C3	1.444(2)	C52−C53	1.454(2)
C2−C11	1.473(2)	C52−C61	1.472(2)
C3−C4	1.374(2)	C53−C54	1.372(2)
C3−C13	1.472(2)	C53−C63	1.467(2)
C4−C10	1.427(2)	C54−C60	1.420(2)
C5−C6	1.365(3)	C55−C56	1.369(3)
C5−C10	1.411(2)	C55−C60	1.410(2)
C6−C7	1.398(3)	C56−C57	1.401(3)
C7−C8	1.361(3)	C57−C58	1.361(3)
C8−C9	1.411(2)	C58−C59	1.410(3)
C9−C10	1.411(2)	C59−C60	1.416(2)
C13−C14	1.326(3)	C63−C64	1.330(3)
C14−C15	1.503(3)	C64−C65	1.497(3)
C15−C16	1.513(3)	C65−C66	1.515(3)
C15−C17	1.523(3)	C65−C67	1.519(3)
Bond angles (°)			
C11−O3−C12	116.87(18)	C61−O53−C62	116.72(18)
C4−O4−C15	116.19(12)	C54−O54−C65	116.35(13)
O1−C1−C2	123.50(16)	O51−C51−C52	123.41(16)
O1−C1−C9	115.31(15)	O51−C51−C59	115.04(15)
C2−C1−C9	121.19(15)	C52−C51−C59	121.53(15)
C1−C2−C3	119.61(15)	C51−C52−C53	119.28(16)
C1−C2−C11	116.40(16)	C51−C52−C61	116.93(16)
C3−C2−C11	123.84(16)	C53−C52−C61	123.69(16)
C2−C3−C4	118.56(15)	C52−C53−C54	118.32(15)
C2−C3−C13	125.85(16)	C52−C53−C63	125.53(16)
C4−C3−C13	115.40(15)	C54−C53−C63	115.99(16)
O4−C4−C3	122.41(14)	O54−C54−C53	122.04(14)
O4−C4−C10	115.08(14)	O54−C54−C60	114.74(14)
C3−C4−C10	122.39(14)	C53−C54−C60	123.04(15)
C6−C5−C10	120.38(16)	C56−C55−C60	120.40(16)
C5−C6−C7	120.61(17)	C55−C56−C57	120.61(18)
C6−C7−C8	120.18(17)	C56−C57−C58	120.10(17)
C7−C8−C9	120.86(16)	C57−C58−C59	120.97(17)
C1−C9−C8	121.95(15)	C51−C59−C58	121.89(16)
C1−C9−C10	119.18(15)	C51−C59−C60	119.14(15)
C8−C9−C10	118.84(16)	C58−C59−C60	118.93(16)
C4−C10−C5	122.25(14)	C54−C60−C55	122.71(15)
C4−C10−C9	118.64(15)	C54−C60−C59	118.32(15)
C5−C10−C9	119.10(15)	C55−C60−C59	118.97(15)
O2−C11−O3	121.17(17)	O52−C61−O53	121.28(17)
O2−C11−C2	123.82(18)	O52−C61−C52	123.18(18)
O3−C11−C2	115.00(16)	O53−C61−C52	115.53(16)
C3−C13−C14	119.30(17)	C53−C63−C64	119.39(17)
C13−C14−C15	120.32(16)	C63−C64−C65	120.73(16)
O4−C15−C14	107.37(15)	O54−C65−C64	107.79(15)
O4−C15−C16	104.15(14)	O54−C65−C66	104.13(15)
C14−C15−C16	113.14(17)	C64−C65−C66	113.08(17)
O4−C15−C17	108.95(15)	O54−C65−C67	108.55(15)
C14−C15−C17	111.53(16)	C64−C65−C67	111.31(18)
C16−C15−C17	111.28(17)	C66−C65−C67	111.57(18)

Table 3. Bond Lengths (Å) and Angles (°) for Lucidin

Bond lengths (Å)			
O1−C1	1.347(8)	C5−C6	1.386(9)
O2−C15	1.430(9)	C5−C13	1.373(10)
O3−C3	1.364(7)	C6−C7	1.388(12)
O4−C10	1.217(8)	C7−C8	1.359(11)
O5−C9	1.232(7)	C8−C14	1.407(8)
C1−C2	1.423(8)	C9−C11	1.464(7)
C1−C11	1.393(9)	C9−C14	1.48(1)
C2−C3	1.384(10)	C10−C12	1.469(9)
C2−C15	1.512(9)	C10−C13	1.510(8)
C3−C4	1.384(10)	C11−C12	1.409(8)
C4−C12	1.396(8)	C13−C14	1.393(9)
Bond angles (°)			
O1−C1−C2	117.3(6)	O4−C10−C12	123.5(5)
O1−C1−C11	121.1(5)	O4−C10−C13	119.7(6)
C2−C1−C11	121.6(6)	C12−C10−C13	116.8(5)
C1−C2−C3	116.6(6)	C1−C11−C9	119.8(5)
C1−C2−C15	121.4(5)	C1−C11−C12	119.4(5)
C3−C2−C15	122.0(5)	C9−C11−C12	120.8(5)
O3−C3−C2	116.5(6)	C4−C12−C10	118.5(5)
O3−C3−C4	120.3(6)	C4−C12−C11	119.5(6)
C2−C3−C4	123.1(5)	C10−C12−C11	122.0(5)
C3−C4−C12	119.6(6)	C5−C13−C10	119.2(6)
C6−C5−C13	120.3(6)	C5−C13−C14	121.0(6)
C5−C6−C7	119.4(7)	C10−C13−C14	119.7(6)
C6−C7−C8	120.4(6)	C8−C14−C9	119.8(6)
C7−C8−C14	121.2(6)	C8−C14−C13	117.7(6)
O5−C9−C11	121.8(6)	C9−C14−C13	122.5(5)
O5−C9−C14	120.6(5)	O2−C15−C2	112.7(6)
C11−C9−C14	117.5(5)		

mixture with *n*-heptane provided pure insoluble xanthopurpurin and a mixture of mollugin and 3,4-dihydromollugin in solution. The presence of 3,4-dihydromollugin was inferred from its mass spectrum and several NMR signals observed in spectrum of crude mollugin (singlets at 1.413 and 4.015 ppm, triplets at 1.839 and 3.065 ppm, $J = 6.8$ Hz) giving a good match to the literature values.[14]

Mollugin (Figs. 1–3) crystallises as an anhydrate. There is an apparent *pseudo*-symmetry manifested by two cell angles fairly close to 90°. The merging of reflections for monoclinic setting (a unique) provided *R*-merge values of 0.77 compared with 0.023 for triclinic setting providing thus proof that the triclinic cell is correct. There are two independent molecules in the asymmetric unit, which differ in puckering parameters of the 2,2-dimethyl-2*H*-pyrane

ring. The existence of two possible conformations of 2,2-dimethyl-2*H*-pyrane results from the presence of two sp^3-hybridised atoms and both conformers have been found in 2,2-dimethyl-2*H*-pyrane-containing structures without any apparent preference. However, the puckering parameters of the 2,2-dimethyl-2*H*-pyrane ring in mollugin are unusually high ($\varphi_1 = -41.91^\circ$, $\theta_1 = 69.14^\circ$, $Q_1 = 0.419$ Å; $\varphi_2 = -135.55^\circ$, $\theta_2 = 110.21^\circ$, $Q_2 = 0.435$ Å). Two independent molecules in the asymmetric unit with such high puckering parameters have been found apparently with 3,12-dihydro-3,3,6,12-tetramethyl-7*H*-pyrano(2,3-c)acridin-7-one only. In the crystal, molecules are packed into pillars along the *a*-axis, and each molecule is bound to its centrosymmetric neighbour giving a broad double-pillar (Fig. 3). An intramolecular hydrogen bond involving O1—H···O2 was found.

Lucidin tends to crystallise in a form of fibrous needles, which are far from to be suitable for X-ray crystal structure determination. The use of a trick consisting in the crystallisation of lucidin from its ammonium phenolate solution was only manner providing few measurable lucidin crystals. The poor quality of crystals influenced also the resulting *R*-factor. Since the attempts of truncating the high angle data resulted in insignificant lowering of the *R*-factor only, all measured data were used for the refinement. The structural study of lucidin (Figs. 1, 4 and 5) was carried out also in order to elucidate its striking insolubility in practically all solvents. There are different types of packing found in structures of natural anthraquinones reported so far.[15–20] The molecules are mostly bound to each other by π–π interactions forming various cross-linked motifs, frequently in columns involving various parts of the anthraquinone molecule in the π–π stacking. Lucidin molecules are close packed in L-shape pillars in the *c*-axis, all ring oxygen atoms are involved in the stacking (Fig. 5). There are two intramolecular hydrogen bonds O1—H···O5 and O3—H···O2. The packing is stabilised by two bifurcated hydrogen bonds O2—H···O4 (x, $y + 1$, z), d(O2—O4) = 3.392(6) Å, angle O2—H···O4=130(7)° and O2—H···O3 ($-x + 1$, $+y + 1/2$, $-z + 1/2$), d(O2—O3) = 2.654(6) Å, angle O2—H···O3 = 119(6)°. The complex hydrogen bonding system seems likely to explain the insolubility of lucidin. It is also worth to mention that the close packing is

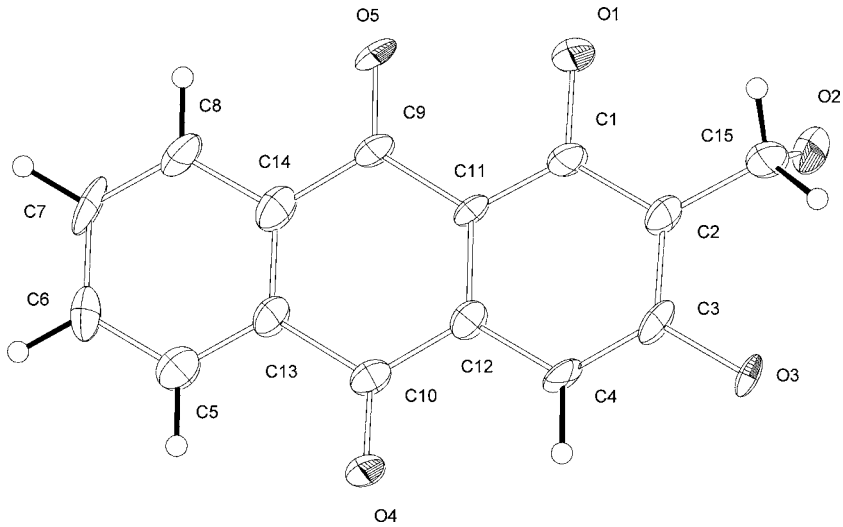

Fig. 4. ORTEP drawing of lucidin with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

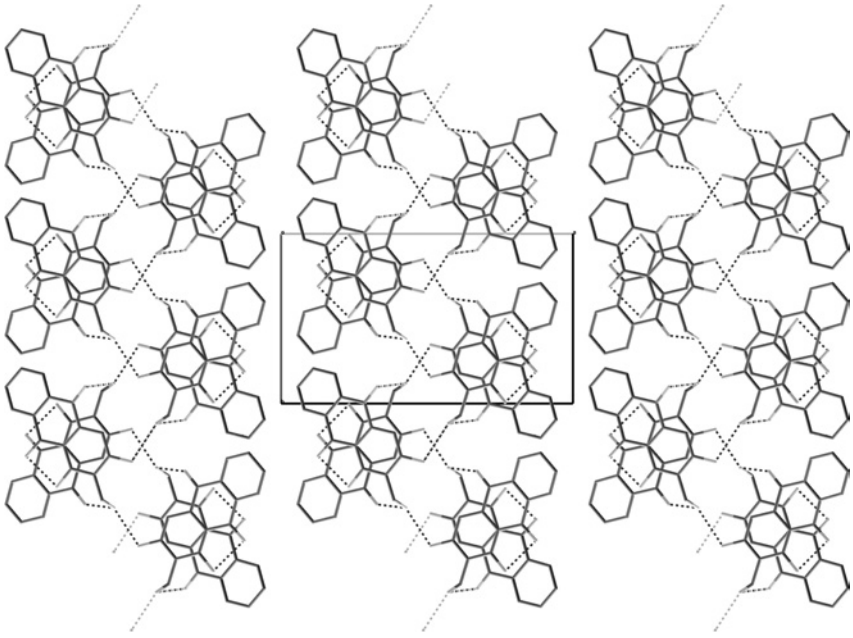

Fig. 5. Packing scheme for lucidin. Projection along *c*-axis.

most probably responsible also for a remarkably high density of lucidin.

Supplementary material CCDC 184038 (lucidin) and 184039 (mollugin) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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