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# Verticillin chloroform solvate

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**Key indicators**

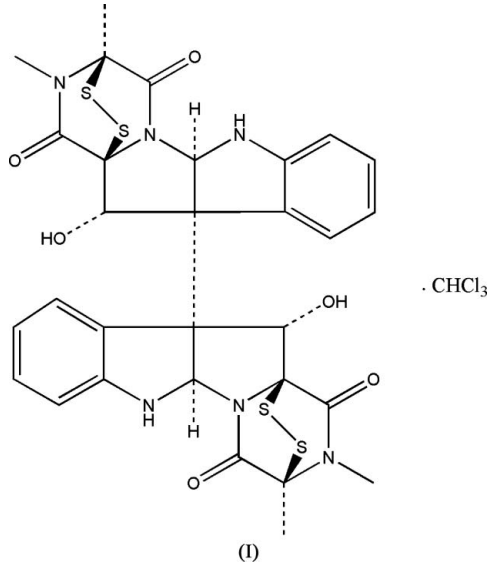
Single-crystal X-ray study
$T$ = 286 K
Mean $\sigma$(C–C) = 0.007 Å
$R$ factor = 0.054
$wR$ factor = 0.119
Data-to-parameter ratio = 14.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_{30}H_{28}N_6O_6S_4\cdot CHCl_3$, is a cytotoxic and antibacterial compound which was isolated from ethyl acetate extracts of *Amanita flavorubescens* Alk. affected by *Verticillium* sp. The molecule is a dimer with two epidithiodioxopiperazine nuclei, the two halves being related by an approximate twofold axis. The two five-membered rings are *cis*-fused. The crystal structure is stablized by a hydrogen-bond network involving both OH groups and the carbonyl group.

## Comment

In the course of our screening for compounds with antitumour activity based on cytotoxic assays, verticillin A was isolated from ethyl acetate extracts of *Amanita flavorubescens* Alk. affected by *Verticillium* sp. It shows strong cytotoxicity against HeLa cells at the 0.2 μg ml$^{-1}$ level and can inhibit *Ehrlich ascites* carcinoma in the range 0.25–1.0 μg ml$^{-1}$, but at 2.5 or 5 mg per kg per day it was toxic to the host (Katagiri *et al.*, 1970). Verticillin A is a compound of the novel epidithiodioxopiprazine structural class, which was first isolated from a species of *Verticillium*, an imperfect fungus isolated from a basidiocarp of *Coltricia cinnomea* (*Polystictus cinnamomeus*). On the basis of its spectroscopic data and chemical reactions, its structure was assigned and its absolute configuration was proposed (Minato *et al.*, 1973). However, no details were given to support these results further. We report here the crystal structure of the title compound, (I).




(I)

Fig. 1 shows the molecular structure of (I). The molecular structure and absolute configuration are very similar to those

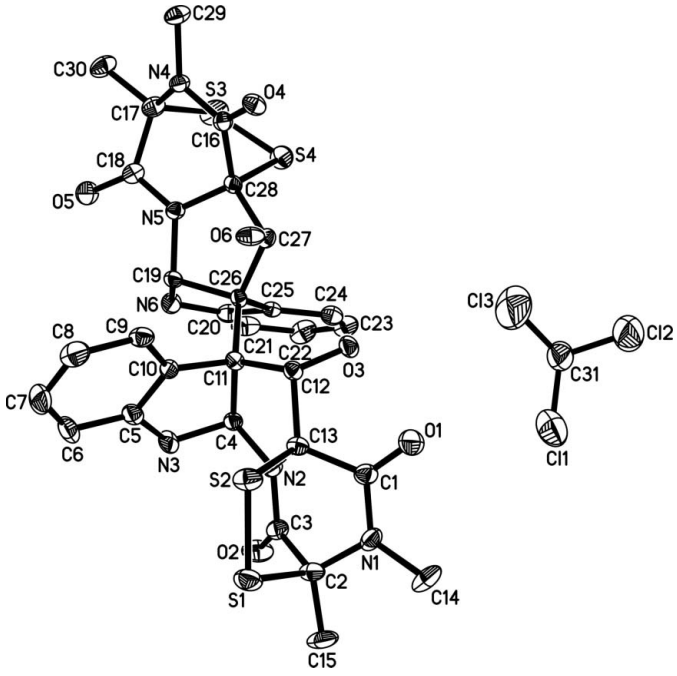



**Figure 1**
A view of (1), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms have been omitted.

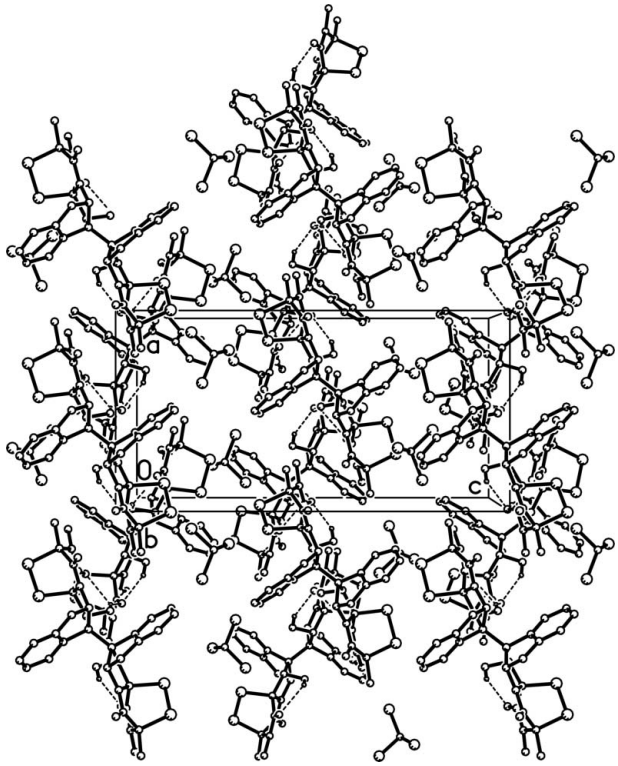



**Figure 2**
The molecular packing in the crystal of (I), viewed down the *b* axis. Dashed lines indicate hydrogen bonds. H atoms not involved in hydrogen bonding have been omitted.

of a derivative, chaetocin (Weber, 1972). Verticillin A is a molecular dimer, the two halves being related by an approximate twofold axis perpendicular to the C11—C26 bond. The two five-memembered rings are *cis*-fused. As shown in Table 1, the bond lengths and angles of the two epidithio-diketopiperazine systems in verticillin A are quite similar within the limits of error. However, some differences between chemically equivalent torsion angles are significant (Table 1).

The structure of (I) is stabilized by O—H···O interactions (Table 2). The packing of the molecules is shown in Fig. 2.

## Experimental

The title compound was isolated from ethyl acetate extracts of *Amanita flavorubescens* Alk. affected by *Verticillium* sp. which was collected from Lijiang in Yunnan Province, China, and authenticated by Professor Yongchang Zhao. The fresh bodies of the fungus (1500 g) were first lyophilized and then extracted successively by light petroleum (1 l) and ethyl acetate (2 l). The ethyl acetate extract (1.2 g) was then fractionated by countercurrent chromatography using a two-phase solvent system composed of light petroleum, chloroform and acetonitrile with a volume ratio of 6:1:3, yielding cytotoxic fraction 2. Fraction 2 was subjected to semi-preparative chromatography on a reverse-phase C8 coloumn (Hypersil ODS 20 × 250 mm), eluted by acetonitrile and water with a gradient from 10 to 100% for 120 min and a flow rate of 10 ml min$^{-1}$; this afforded 10 mg pure verticillin A. Single crystals suitable for X-ray structure analysis were obtained by slow evaporation of a chlorofom and ethanol solution (2:1 *v*/*v*) at room temperature.

*Crystal data*

$C_{30}H_{28}N_6O_6S_4{\cdot}CHCl_3$
$M_r$ = 816.19
Orthorhombic, $P2_12_12_1$
$a$ = 10.901 (2) Å
$b$ = 14.493 (3) Å
$c$ = 21.355 (3) Å
$V$ = 3373.7 (9) Å$^3$
$Z$ = 4
$D_x$ = 1.607 Mg m$^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 28 reflections
$\theta$ = 2.7–11.6°
$\mu$ = 0.57 mm$^{-1}$
$T$ = 286 (2) K
Block, colourless
0.44 × 0.40 × 0.36 mm

*Data collection*

Siemens *P*4 diffractometer
$\omega$ scans
Absorption correction: $\psi$ scan (*XSCANS*; Siemens, 1994)
$T_{min}$ = 0.766, $T_{max}$ = 0.813
8144 measured reflections
6863 independent reflections
3792 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.029
$\theta_{max}$ = 27.0°
$h = -13 \rightarrow 13$
$k = -17 \rightarrow 18$
$l = -25 \rightarrow 27$
3 standard reflections
every 97 reflections
intensity decay: 5.8%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.119
$S$ = 0.86
6863 reflections
463 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.39 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.60 e Å$^{-3}$
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0069 (5)
Absolute structure: Flack (1983), with 2981 Friedel pairs
Flack parameter: −0.05 (9)

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| S1—C2 | 1.890 (5) | S3—C17 | 1.885 (5) |
| S1—S2 | 2.068 (2) | S3—S4 | 2.073 (2) |
| S2—C13 | 1.891 (5) | S4—C28 | 1.893 (4) |
| O1—C1 | 1.213 (6) | O4—C16 | 1.241 (5) |
| O2—C3 | 1.217 (6) | O5—C18 | 1.216 (6) |
| O3—C12 | 1.411 (6) | O6—C27 | 1.416 (5) |
| N1—C14 | 1.460 (6) | N4—C29 | 1.448 (6) |
| C4—C11 | 1.566 (6) | C19—C26 | 1.558 (6) |
| | | | |
| C2—S1—S2 | 99.28 (16) | C17—S3—S4 | 99.04 (17) |
| C13—S2—S1 | 97.14 (16) | C28—S4—S3 | 97.15 (16) |
| C1—N1—C14 | 117.6 (5) | C16—N4—C29 | 119.2 (4) |
| O1—C1—N1 | 123.4 (5) | O4—C16—N4 | 123.3 (5) |
| N1—C2—C15 | 114.2 (5) | N4—C17—C30 | 114.3 (4) |
| N1—C2—S1 | 110.1 (4) | N4—C17—S3 | 110.4 (3) |
| O2—C3—N2 | 124.9 (5) | O5—C18—N5 | 122.8 (5) |
| C4—C11—C26 | 112.2 (4) | C19—C26—C11 | 111.3 (3) |
| | | | |
| C5—N3—C4—C11 | −17.2 (5) | C20—N6—C19—C26 | −20.8 (5) |
| C4—N3—C5—C10 | 6.8 (5) | C19—N6—C20—C25 | 11.2 (6) |
| N3—C5—C10—C11 | 6.7 (5) | N6—C20—C25—C26 | 3.4 (5) |

**Table 2**
Hydrogen-bond geometry (Å, °).

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O3—H3O···O1 | 0.73 (5) | 2.31 (5) | 2.785 (5) | 124 (5) |
| O3—H3O···O4$^{i}$ | 0.73 (5) | 2.20 (5) | 2.861 (5) | 152 (6) |
| O6—H6O···O4 | 0.83 (5) | 1.98 (5) | 2.709 (5) | 145 (4) |

Symmetry code: (i) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$.

The H atoms of the hydroxyl groups were located in a difference Fourier map and refined isotropically. The remaining H atoms were placed in calculated positions and refined using a riding model, with C—H = 0.93–0.98 Å and N—H = 0.86 Å, and with $U_{iso}$(H) = $1.2U_{eq}$(carrier atom).

Data collection: *XSCANS* (Siemens, 1994); cell refinement: *XSCANS*; data reduction: *SHELXTL/PC* (Siemens, 1991); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC*; software used to prepare material for publication: *SHELXTL/PC*.

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