organic compounds

The potent anticancer compound ecteinascidin-743 (ET-743) as its 2-propanol disolvate

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Single crystals of the title compound, $C_{39}H_{43}N_3O_{11}S\cdot2C_3H_8O$, have been obtained from 2-propanol/water solutions. ET-743 belongs to the group of ecteinascidins (ETs), which is a family of novel marine tetrahydroisoquinoline derivatives characterized by a monobridged pentacyclic skeleton. Three large principal planar groups are observed in the three-dimensional structure of the ET-743 molecule, corresponding to three aromatic units which are nearly perpendicular to each other. In the crystal, the methoxy group on the large fused ring system adopts an *anti* conformation with respect to the S atom, thus presenting the same conformation as that found in solution.

Comment

Microbe-derived compounds related to the ecteinascidins (ETs) are saframycines, safracines, naphthydinomycines and quinocarcines. The common structural features of ETs consist of three tetrahydroisoquinoline subunits and an active carbinolamine functional group (Rinehart *et al.*, 1990). ETs are currently obtained by extraction and purification from the marine tunicate *Ecteinascidia turbinate*, although recently a very efficient synthetic method has been reported (Cuevas *et al.*, 2000). Several compounds of the ET family possess potent antitumor activity. Among them, the natural compound named ET-743 has received considerable attention, as it has been shown to be a potent anticancer agent with proven high efficacy in soft tissue sarcoma and breast cancer (Garcia-Nieto *et al.*, 2000). ET-743 has been accepted for evaluation by EMEA (European Agency for the Evaluation of Medicinal Products) and the Swiss authorities. The structure of the 2-propanol disolvate of ET-743, (I), is presented here.

Selected geometrical features of (I) are given in Table 1. Although the overall molecular structure of ET-743 (Fig. 1) is

very similar to the N12-oxide derivative (Guan *et al.*, 1993), there is one remarkable difference, *viz.* the O41—C42 methoxy group, attached to C17 and in a plane perpendicular to the aromatic ring [C16—C17—O41—C42 = 99.2 (3)°], adopts a position *anti* with respect to the S atom, whereas this conformation was found to be *syn* in the N12-oxide derivative. This *anti* conformation is consistent with a previous NMR study (Seaman & Hurley, 1998) and seems to be very important since this part of the molecule is involved in the interaction with DNA (Garcia-Nieto *et al.*, 2000). Molecular simulation studies carried out on the ET-743 molecule (Garcia-Nieto *et al.*, 2000) concluded that the *syn* conformation is more stable and that the conformation of this methoxy group changes from *syn* to *anti* during the solvation process. The present study demonstrates that there is no conformational change, since the ET-743 molecule maintains the same *anti* conformation in both the solution and solid states.

(I)
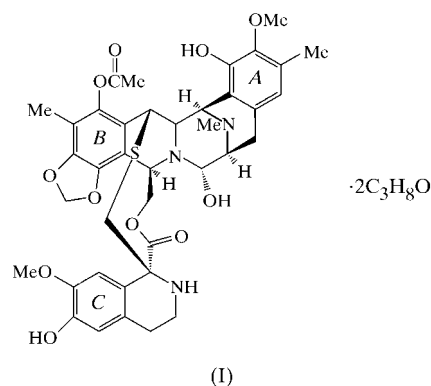
The crystal packing is mediated mainly by hydrogen bonds between the ET-743 molecule and the two interstitial 2-propanol molecules. The hydrogen-bonding parameters are presented in Table 2.
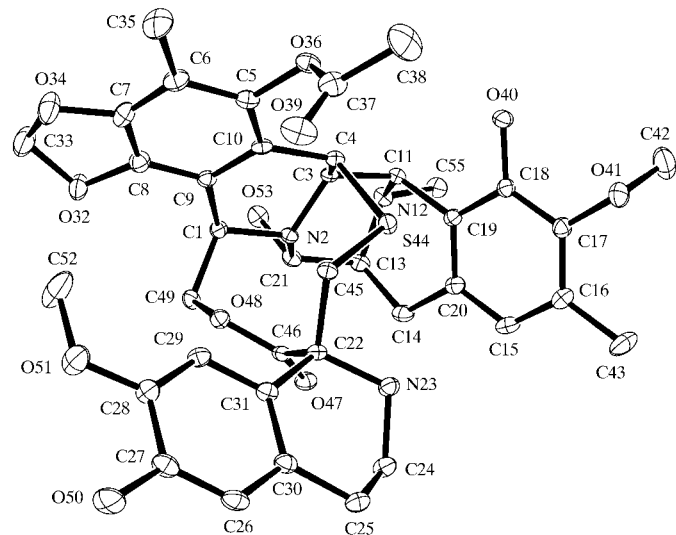
Figure 1
ORTEP-3 (Farrugia, 1999b) diagram of the asymmetric unit of the crystal lattice of (I), showing 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

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Experimental

The sample of ET-743 used for crystallization was either isolated from the Caribbean tunicate *Ecteinascidia turbinata* by an extraction and purification process (Rinehart *et al.*, 1990) or synthesized (Corey *et al.*, 1996; Cuevas *et al.*, 2000). In both cases, ET-743 was obtained as a lyophilized white-to-pale-yellow amorphous powder. The powder was stored at 253 K in an airtight container. The best and most reproducible crystals, although exhibiting rather bad scattering properties, were obtained from 2-propanol/water (19:1 *v/v*) by dissolving ET-743 (6–15 mg ml^{-1}) at 303 K and crystallizing it at 277 K. Although no water molecules were detected in the crystal structure of ET-743, the presence of water is important for obtaining single crystals. Hence, it seems that the role of water is only to control the nucleation and crystal-growth rates during the crystallization process.

Crystal data

$C_{39}H_{43}N_3O_{11}S \cdot 2C_3H_8O$
$M_r = 882.01$
Orthorhombic, $P2_12_12_1$
$a = 13.0161 (13)$ Å
$b = 13.2290 (14)$ Å
$c = 26.496 (3)$ Å
$V = 4562.3 (8)$ Å^3
$Z = 4$
$D_x = 1.284$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 115 reflections
$\theta = 10\text{--}20°$
$\mu = 0.14$ mm^{-1}
$T = 173 (2)$ K
Prism, colourless
$0.30 \times 0.25 \times 0.20$ mm

Data collection

Bruker SMART CCD 1K diffractometer
φ and ω scans
14 784 measured reflections
7901 independent reflections
3827 reflections with $I > 2\sigma(I)$

$R_{int} = 0.096$
$\theta_{max} = 26.4°$
$h = -8 \rightarrow 16$
$k = -16 \rightarrow 16$
$l = -33 \rightarrow 7$

Refinement

Refinement on F^2
$R(F) = 0.078$
$wR(F^2) = 0.132$
$S = 1.12$
13297 reflections
575 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0345P)^2 + 1.7941P]$
    where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0$
$\Delta\rho_{max} = 0.35$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}
Absolute structure: Flack (1983), 2697 Friedel pairs
Flack parameter = 0.10 (8)

Table 1
Selected geometric parameters (Å, °).

C1—N2	1.473 (3)	C13—C14	1.546 (4)
N2—C21	1.460 (3)	C17—O41	1.394 (3)
C3—C11	1.547 (3)	C21—O53	1.438 (3)
C4—S44	1.864 (2)	C28—O51	1.374 (3)
S44—C45	1.813 (3)	O34—C33	1.429 (4)
C7—O34	1.383 (4)	C33—O32	1.424 (4)
C8—O32	1.383 (3)	C37—O39	1.197 (4)
C11—N12	1.480 (3)	O41—C42	1.434 (4)
N12—C13	1.473 (3)	C46—O47	1.197 (3)
C13—C21	1.515 (4)	O51—C52	1.419 (4)
N2—C1—C49	109.4 (2)	N2—C3—C11	114.03 (19)
C21—N2—C3	113.63 (19)	N12—C11—C19	110.2 (2)
C21—N2—C1	109.66 (19)	N12—C11—C3	107.80 (19)
C3—N2—C1	113.76 (18)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O40—H40$\cdots$O90^i	0.84	1.96	2.687 (3)	145
O50—H50$\cdots$O80^{ii}	0.84	1.84	2.676 (3)	177
O80—H80$\cdots$N23	0.84	1.99	2.793 (3)	161
O90—H90$\cdots$O53^{iii}	0.84	1.96	2.783 (4)	167

Symmetry codes: (i) $1 + x, y, z$; (ii) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iii) $x - \frac{1}{2}, \frac{3}{2} - y, -z$.

The space group was deduced from the systematic absences and intensity statistics. All H atoms were found in a difference electron-density map, but they were all placed in calculated positions (C—H = 0.95–1.00 Å), with U_{iso} values taken as 1.2 times (1.5 for methyl) the U_{eq} values of the parent atoms. The absolute configuration was assigned to agree with the chirality determined for the *N*-oxide derivative (Guan *et al.*, 1993). Friedel pairs were not averaged and the refined value of the Flack (1983) parameter was in agreement with this previously established absolute configuration.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1999*b*); software used to prepare material for publication: *WinGX* (Farrugia, 1999*a*) and *PARST* (Nardelli, 1983, 1995).

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