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Tiamulin–hydrogen fumarate–methanol (1/1/1)

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Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.003 Å
R factor = 0.038
wR factor = 0.085
Data-to-parameter ratio = 17.3

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

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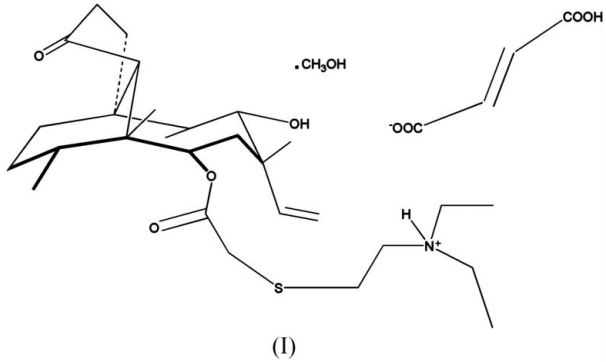
The structure of the title complex, 6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [2-(diethylammonio)ethylsulfanyl]acetate (*E*)-3-carboxyprop-2-enoate methanol solvate, $C_{28}H_{48}NO_4S^+\cdot C_4H_3O_4^-\cdot CH_4O$, is presented. The cation of the complex consists of an eight-membered ring with boat–chair conformation, a six-membered ring with a chair conformation and a five-membered ring with a twisted conformation. The fumarate anion adopts an *E* configuration. The methanol molecule is linked to the cation and the anion by O—H···O hydrogen bonds. A network of O—H···O, N—H···O and C—H···O intermolecular hydrogen bonds links the molecules, forming a layered structure.

Comment

The complex tiamulin–hydrogen fumarate–methanol (1/1/1), (I), a semi-synthetic derivative of pleuromutilin, was discovered by Sandoz in 1975, and has attracted considerable pharmaceutical and academic attention due to its potent activity against drug-resistant Gram-positive bacteria and the fascinating chemistry exhibited by the tricyclic cores (Drews *et al.*, 1975). This complex is currently employed in veterinary medicine for promoting the growth of turkey poults, suckling pigs and other newborn animals.



(I)

The title salt-like adduct (Fig. 1) contains a 1:1 ratio of tiamulin cations and fumarate anions. The tiamulin cation consists of a tricyclic core and substituent groups. The eight-membered ring (C1–C6/C11/C10) of the tricyclic core adopts a boat–chair conformation attributed to the bridged bicyclic ring fusion (C6/C11/C10), with the puckering parameter (Cremer & Pople, 1975) Q = 1.287 (2) Å. The five-membered ring (C10–C14) adopts a conformation twisted on C10—C11, the C12—C11—C10—C14 torsion angle being 38.1 (2)°. This conformation is established by an intramolecular C19—

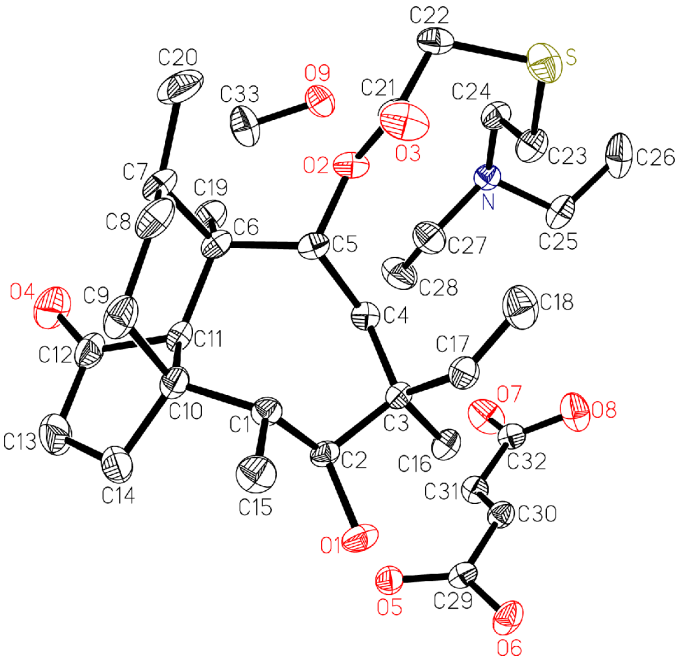


Figure 1
A view of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are omitted for clarity.

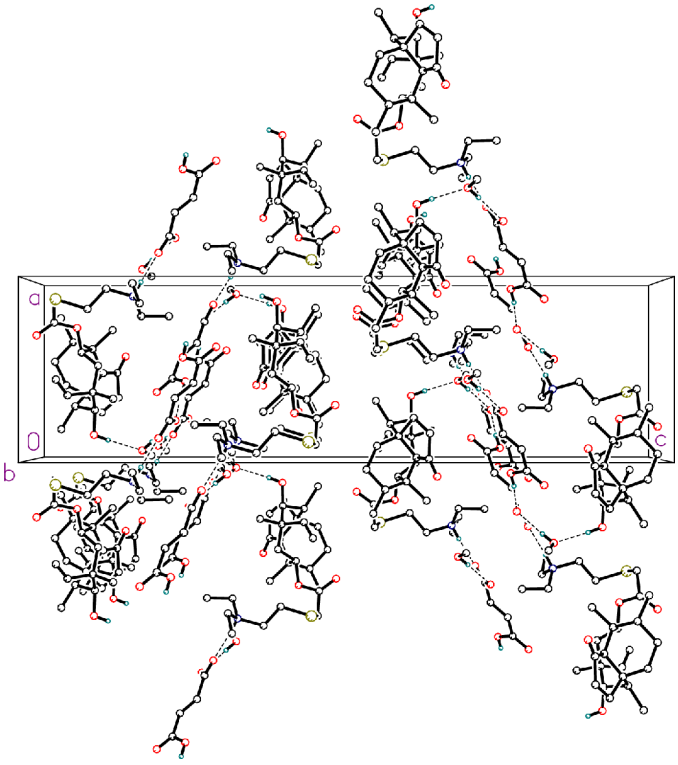


Figure 2
The molecular packing in the crystal of (I), viewed down the *b* axis. Hydrogen bonds are indicated by dashed lines.

H19*C*···O4 interaction, with a C···O distance of 2.961 (3) Å, which is less than the sum of the van der Waals radii of C and O (3.22 Å). The six-membered ring (C6–C11) adopts a chair conformation, with Q = 0.559 (2) Å, θ = 175.6 (3)° and φ = 191 (3)°. It is interesting that the environment of the cyclohexyl ring of the system is crucial to the biological activity of tiamulin hydrogen fumarate (Springer *et al.*, 2003). All the substituents (except the vinyl group) on the tricyclic core reside in equatorial environments. There are eight stereogenic centers (C1, C2, C3, C5, C6, C7, C10 and C11) in the tricyclic skeleton; all but one reside in the cyclooctane ring. The absolute configurations are given assignments 1*R*, 2*S*, 3*S*, 5*R*, 6*R*, 7*R*, 10*S* and 11*R*, respectively. The conformation of the alkyl ester side chain is constrained by intramolecular C19—H19*B*···O2 and C5—H5···O3 interactions. The C29—C30—C31—C32 torsion angle of −178.68 (19)° describes the *E* configuration of the fumaric anion about the C30—C31 bond. Selected bond distances and angles are listed in Table 1.

The molecular structure of (I) is stabilized by C—H···O interactions (Table 2). A network of intermolecular O—H···O, N—H···O and C—H···O interactions (Fig. 2) stabilize the molecular packing in the crystal structure. These interactions link the cations, anions and methanol solvate to form layers parallel to the *ab* plane.

Experimental

The title compound was purchased from Zhejiang Shenghua Biok Biology Limited and was dissolved in a chloroform–methanol solution (3:2). Single crystals suitable for X-ray structure analysis were obtained by slow evaporation of the chloroform–methanol solution at room temperature.

Crystal data

$C_{28}H_{48}NO_4S^+\cdot C_4H_3O_4^-\cdot CH_4O$
M_r = 641.84
Orthorhombic, $P2_12_12_1$
a = 9.935 (1) Å
b = 10.072 (1) Å
c = 34.987 (7) Å
V = 3501.0 (8) Å^3
Z = 4
D_x = 1.218 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 39 reflections
θ = 3.4–14.8°
μ = 0.14 mm^{-1}
T = 296 (2) K
Block, pale yellow
0.56 × 0.50 × 0.44 mm

Data collection

Siemens *P*4 diffractometer
ω scans
Absorption correction: ψ scan (*XSCANS*; Siemens, 1994)
T_{min} = 0.922, T_{max} = 0.941
8625 measured reflections
7293 independent reflections
4560 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 27.0°
$h = -12 \rightarrow 12$
$k = -12 \rightarrow 12$
$l = -43 \rightarrow 44$
3 standard reflections
every 97 reflections
intensity decay: 5.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.085
S = 0.84
7293 reflections
421 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0444P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0069 (5)
Absolute structure: Flack (1983), 2981 Friedel pairs
Flack parameter = 0.03 (8)

Table 1
Selected geometric parameters (Å, °).

O5—C29	1.259 (2)	C11—C12	1.532 (3)
O6—C29	1.236 (2)	C12—C13	1.502 (4)
C10—C14	1.544 (3)	C13—C14	1.517 (3)
C10—C11	1.551 (3)		
C14—C10—C11	102.64 (18)	C13—C14—C10	106.1 (2)
C12—C11—C10	102.18 (19)	O3—C21—O2	125.4 (2)
C13—C12—C11	107.7 (2)	O3—C21—C22	124.6 (2)
C12—C13—C14	106.5 (2)	O2—C21—C22	110.04 (19)
C14—C10—C11—C12	38.1 (2)	C29—C30—C31—C32	−178.68 (19)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1O···O9^{i}	0.82	1.95	2.772 (2)	176
O8—H8O···O5^{ii}	0.82	1.77	2.586 (2)	171
O9—H9O···O5^{iii}	0.82	1.92	2.738 (2)	176
N—H34N···O6^{iii}	0.87 (1)	1.851 (12)	2.702 (2)	165 (3)
C5—H5···O3	0.98	2.33	2.757 (3)	106
C11—H11···O7^{iv}	0.98	2.52	3.399 (3)	149
C19—H19*B*···O2	0.96	2.31	2.743 (3)	106
C19—H19*C*···O4	0.96	2.35	2.961 (3)	121
C22—H22*B*···O1^{iii}	0.97	2.50	3.439 (3)	163
C25—H25*B*···O4^{v}	0.97	2.40	3.357 (3)	168
C26—H26*A*···O6^{iii}	0.96	2.46	3.185 (3)	132
C30—H30···O8	0.93	2.40	2.744 (3)	101

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

The H atom on the N atom was located in a difference Fourier map and refined isotropically with the N—H distance restrained to 0.86 (1) Å. The positions of the remaining H atoms were calculated geometrically (O—H = 0.82 Å and C—H = 0.93–0.98 Å) and refined using a riding model. The U_{iso} values of the methyl H atoms attached to C15, C19 and C33 were refined, and for other H atoms the values were set at $1.2U_{eq}$(C,O).

Data collection: *XSCANS* (Siemens, 1994); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Siemens, 1991); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXL*97.

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