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Polyether antibiotic CP44,161

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The crystal structure of antibiotic CP44,161, 6-(7-{2-ethyl-2-[5-(1-hydroxymethyl)-5-methyl-2,3,4,5-tetrahydro-2-furyl]-4,10,-12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl}-4-hydroxy-3,5-dimethyl-6-oxononyl)-2-hydroxy-3-methylbenzoic acid monohydrate, $C_{43}H_{66}O_{10}\cdot H_2O$, has been determined by X-ray crystallography. The molecule adopts a cyclic conformation, with a centrally located water molecule contributing to the stability of the conformation through hydrogen-bonding interactions.

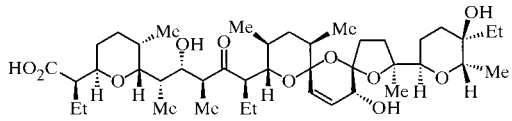
Comment

The polyether family of antibiotics have adopted an important role in that they can act as ionophores transporting ions through biological membranes (Dobler, 1981). A fundamental property of many of the polyether antibiotics is their ability to adopt a cyclic conformation whereby several of the O atoms present in the backbone of the molecule are available to complex to a metal ion and transport the ion across a lipophilic membrane.

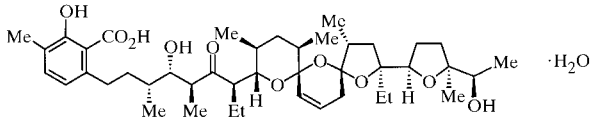
Salinomycin is a member of the polyether family of antibiotics that was isolated from *Streptomyces albus*. The structure of salinomycin was elucidated by X-ray analysis of its *p*-iodophenacyl ester (Kinashi *et al.*, 1975). Salinomycin has a unique tricyclic bis-spiroacetal moiety which has been proposed to act as a hinge to aid metal binding. The *cis* stereochemistry of the bis-spiroacetal ring system is a key feature of the structure and is implicated in the mechanism of ionophoric action (Mronga *et al.*, 1993).

Closely related to salinomycin is the polyether antibiotic CP44,161, which is produced by three strains of a *Dactylosporangium* species. CP44,161 exhibits anticoccidial activity and improves feed utilization efficiency in ruminants (Celmer *et al.*, 1978). It also contains the same *cis* bis-spiroacetal ring system found in salinomycin.

As part of our synthetic programme directed towards the synthesis of the bis-spiroacetal moiety of antibiotic CP44,161, we needed to establish the stereochemistry of the bis-spiroacetal ring system of our synthetic intermediates by comparison of the NMR data of our compounds with the natural product. In order to do this, we needed to establish unequivocally the stereochemistry of the bis-spiroacetal ring system of the naturally occurring antibiotic CP44,161, hence a crystallographic analysis of this natural product was carried out.



Salinomycin



CP44,161

The crystal structure of CP44,161 (Fig. 1) establishes the *cis* stereochemistry of the bis-spiroacetal ring system, and demonstrates that the molecule can adopt a cyclic conformation. Presumably contributing to the stabilization of the cyclic conformation, a centrally located water molecule participates in hydrogen-bond interactions with O10 and O8 on one side, and with O4 on the other side of the molecule (Table 1). There is also a weak interaction between the water molecule and O9. The conformation may also be influenced by weak interactions between C8 and O1, and between C11 and O5. An oligomeric hydrogen-bond network is formed with O1 hydrogen bonded to O4 on a neighbouring molecule at $(-x+\frac{1}{2}, -y, z-\frac{1}{2})$.

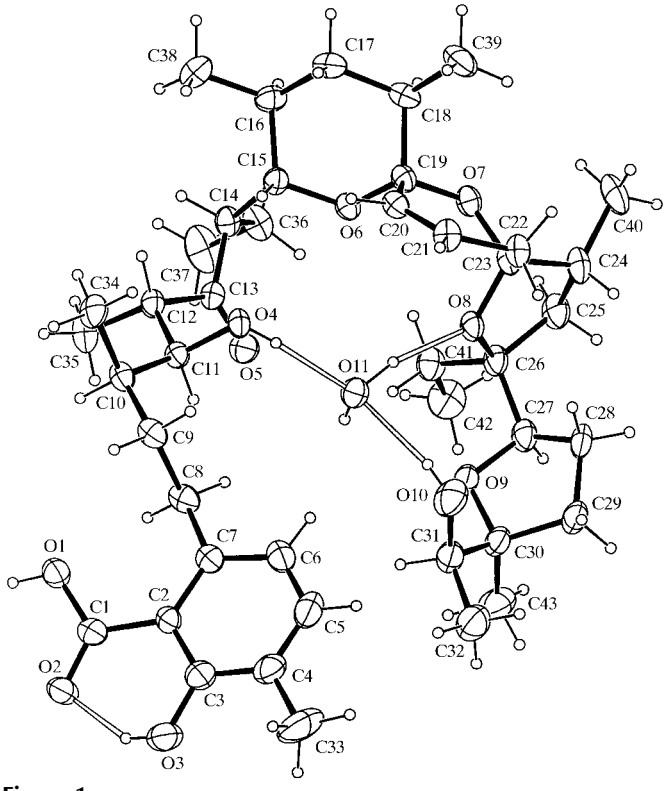


Figure 1
An *ORTEP* (Johnson, 1976; Hall *et al.*, 1999) depiction of CP44,161, with displacement ellipsoids shown at the 20% probability level. Unfilled bonds have been used to emphasize hydrogen bonds.

The crystal structure of antibiotic CP44,161 suggests that the molecule is likely to be ionophoric, and it should be possible to replace the water molecule with a metal ion.

Experimental

CP44,161 was obtained from the pharmaceutical company Pfizer and was isolated from *Dactylosporangium salmoneum* Routien, *sp. nov*. The sample of CP44,161 obtained from Pfizer was recrystallized from ethyl acetate.

Crystal data

$C_{43}H_{66}O_{10}\cdot H_2O$
$M_r = 760.97$
Orthorhombic, $P2_12_12_1$
$a = 12.373\ (2)$ Å
$b = 31.939\ (2)$ Å
$c = 11.064\ (2)$ Å
$V = 4372.3\ (11)$ Å^3
$Z = 4$
$D_x = 1.156$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 8.47$–$11.88°$
$\mu = 0.082$ mm^{-1}
$T = 294\ (2)$ K
Plate, colourless
$0.34 \times 0.32 \times 0.17$ mm

Data collection

Rigaku AFC-7*R* diffractometer
ω:θ scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
$T_{min} = 0.97$, $T_{max} = 0.99$
5472 measured reflections
4325 independent reflections
2144 reflections with $I > 2\sigma(I)$
$R_{int} = 0.049$
$\theta_{max} = 24.99°$
$h = -1 \rightarrow 14$
$k = -1 \rightarrow 37$
$l = -1 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity decay: none

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O4^{i}	0.82	1.78	2.584 (4)	165
O3—H3O···O2	0.82	1.80	2.529 (6)	147
O4—H4O···O11	0.82	1.84	2.659 (4)	175
O10—H10O···O11	0.82	2.13	2.942 (6)	170
O11—H11O···O9	0.87 (6)	2.60 (6)	3.009 (4)	110 (5)
O11—H12O···O8	0.96 (6)	1.80 (7)	2.742 (5)	167 (6)
C8—H8*A*···O1	0.97	2.23	2.757 (5)	113
C11—H11···O5	0.98	2.48	2.822 (5)	100

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.039$
$wR(F^2) = 0.126$
$S = 0.942$
4325 reflections
508 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0590P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.14$ e Å^{-3}
$\Delta\rho_{min} = -0.15$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0043 (5)

The data did not permit the determination of the absolute structure; the stereochemistry is the relative configuration based on the absolute stereochemistry of related compounds. The water H atoms were refined isotropically. Other H atoms were refined as riding (O—H = 0.82 Å and C—H = 0.93–0.98 Å).

Data collection and cell refinement: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1997); data reduction: *TEXSAN* (Molecular Structure Corporation, 1995); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *TEXSAN* (Molecular Structure Corporation, 1997–1998).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1483). Services for accessing these data are described at the back of the journal.

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