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A new potent fusidic acid analogue

Inger Søtofte[a] and Tore Duvold[b]*

[a]Department of Chemistry, DTU 207, Technical University of Denmark, Kemitorvet, 2800 Kgs. Lyngby, Denmark, and [b]Leo Pharmaceutical Products, Industriparken 55, 2750 Ballerup, Denmark

Correspondence e-mail: tore.duvold@leo-pharma.com

Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.005 Å
R factor = 0.069
wR factor = 0.175
Data-to-parameter ratio = 12.5

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

The crystal structure of the compound, 17*S*,20*S*-dihydrofusidic acid diethylene glycol hydrate, $C_{31}H_{50}O_6{\cdot}C_4H_{10}O_3{\cdot}H_2O$, consists of 17*S*,20*S*-dihydrofusidic acid, diethylene glycol and water. The fusidic acid moiety contains three six-membered rings and one five-membered ring. The fused-ring system adopts a chair, a twist boat, a chair and an envelope conformation. The crystal packing is influenced by hydrogen bonds.

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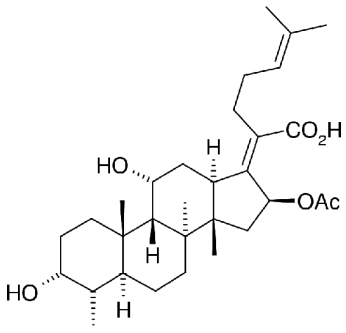
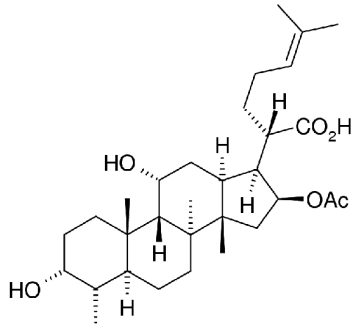
Comment

Fusidic acid belongs to a family of naturally occurring antibiotics known as fusidanes having in common a tetracyclic ring system with the unique chair–boat–chair conformation, a carboxylic acid-bearing side chain linked to the ring system at C17 *via* a double bond and an acetate group at C16. The fusidanes show a high degree of antibacterial activity and have a similar spectrum. Fusidic acid, the most potent of the fusidanes, was first isolated from Fusidium coccineum in 1960 (Godtfredsen *et al.*, 1962) and has, since 1962, been used clinically in treatment of both topical and systemic infections caused by staphylococci. The clinical importance of fusidic acid is furthermore due to its excellent distribution in various



Fusidic acid



17S,20S-Dihydrofusidic acid

tissues, low degree of toxicity and allergic reactions and the absence of cross-resistance with other clinically used antibiotics (Christiansen, 1999; Turnidge & Collignon, 1999; Collign & Turnidge, 1999; Spelman, 1999). The structure–activity relationship (SAR) of fusidic acid has earlier undergone extensive studies (von Daehne *et al.*, 1979) and a large number of related analogues have been prepared. However, only a very few of these analogues showed activities comparable with that of fusidic acid and most of them had a similar antibacterial spectrum and were cross-resistant. In spite of extensive functional and structural modifications of the fusidic acid molecule, side-chain modifications are limited (Godtfredsen *et al.*, 1965; von Daehne *et al.*, 1979). As part of

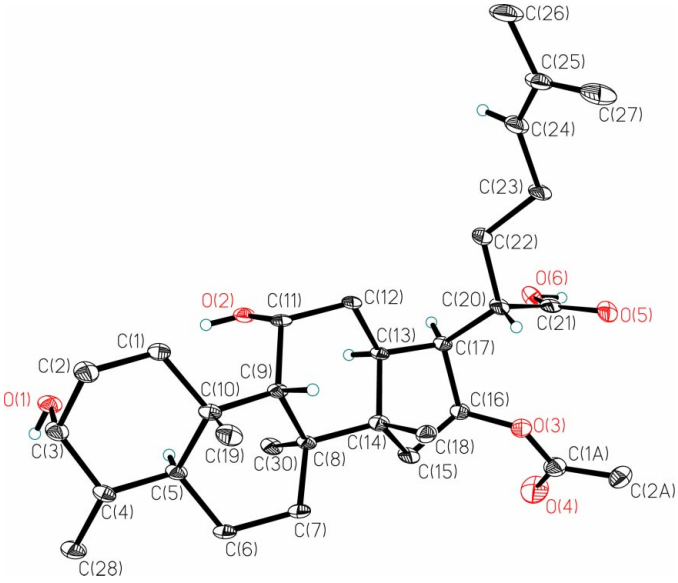


Figure 1
A view of 17*S*,20*S*-dihydrofisidic acid showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level. Selected H atoms have been omitted for clarity.

our renewed interest in improving the antibiotic properties of fusidic acid, we decided to focus on the relatively unexplored side chain. Two saturated fusidic acid analogues were synthesized several years ago (Godtfredsen *et al.*, 1966). They have in common the 17*R* configuration but are epimers at C20 and were both found to be virtually inactive. The corresponding analogues with the opposite 17*S* configuration have not been available until now due to the lack of appropriate synthetic methodology. We recently developed such a methodology for the preparation of 17*S*,20*R*- and 17*S*,20*S*-dihydrofusidic acid (Duvold *et al.*, 2001). Antibacterial testing has revealed potent antibacterial activities of one of these epimers, the 17*S*,20*S*-dihydrofusidic acid.

The molecule of 17*S*,20*S*-dihydrofusidic acid is composed of four fused rings of which three are six-membered rings, *A* (C1–C5/C10), *B* (C5–C10) and *C* (C8–C9/C11–C14) and one is five-membered, *D* (C13–C17). The rings *A*, *B* and *C* adopt chair, twist boat, chair conformations respectively and *D* is in an envelope form with apex at C14. The same conformations of the tetracyclic ring system were found in fusidic acid methyl ester 3-*p*-bromobenzene (Cooper & Hodgkin, 1968). Bond lengths and angles of the present structure are in the expected ranges. The molecular geometry and the numbering are displayed in Fig. 1. The acetate group at C16 is twisted from the plane *E* (C13/C15–C17) with torsion angles of 92.3 (4) (C15—C16—O3—C1*A*) and −150.3 (3)° (C17—C16—O3—C1*A*). Also, the carboxylic acid group is twisted from plane *E*, the torsion angles being −179.2 (3) (C13—C17—C20—C21) and 57.5 (4)° (C16—C17—C20—C21). The major side chain attached at C17 is elongated as is the case with saturated side chains. It does not curl back on itself as found in fusidic acid methyl ester 3-*p*-bromobenzene (Cooper & Hodgkin, 1968), where the C17—C20 bond is a double bond. The crystal packing is influenced by hydrogen bonds (Table 2). The O1 and O2 hydroxyl groups form hydrogen bonds with the carboxylic acid group.

There are also hydrogen bonds between the water molecule and the O1 and O2 hydroxyl groups. The carboxylic acid group is involved in hydrogen bonds with the diethylene glycol. Finally, the symmetry-related diethylene glycol molecules are linked by hydrogen-bond interactions through O8 and O9.

Experimental

See above for synthesis details.

Crystal data

$C_{31}H_{50}O_6{\cdot}C_4H_{10}O_3{\cdot}H_2O$
M_r = 642.85
Orthorhombic, $P2_12_12_1$
a = 12.6246 (3) Å
b = 13.0962 (3) Å
c = 21.2134 (5) Å
V = 3507.30 (14) Å^3
Z = 4
D_x = 1.217 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from no reflections
θ = 1.8–29.7°
μ = 0.09 mm^{-1}
T = 120 (2) K
Block, colourless
0.33 × 0.33 × 0.26 mm

Data collection

Siemens SMART CCD Platform diffractometer
ω scans
24 333 measured reflections
5146 independent reflections
4433 reflections with $I > 2\sigma(I)$
R_{int} = 0.182
θ_{max} = 29.7°
$h = -17 \rightarrow 17$
$k = -17 \rightarrow 10$
$l = -28 \rightarrow 28$
Intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.069
$wR(F^2)$ = 0.175
S = 1.13
5146 reflections
412 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0767P)^2 + 2.9938P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.53 e Å^{-3}
$\Delta\rho_{min}$ = −0.52 e Å^{-3}

Table 1
Selected torsion angles (°).

C15—C16—O3—C1*A*	92.3 (4)	C22—C20—C21—O5	98.7 (4)
C17—C16—O3—C1*A*	−150.3 (3)	C17—C20—C21—O5	−140.3 (3)
C16—O3—C1*A*—O4	−4.6 (6)	C22—C20—C21—O6	−78.1 (4)
C16—O3—C1*A*—C2*A*	175.8 (3)	C17—C20—C21—O6	42.9 (4)
C13—C17—C20—C21	−179.2 (3)	C17—C20—C22—C23	−171.9 (3)
C16—C17—C20—C21	57.5 (4)	C20—C22—C23—C24	−173.7 (3)
C13—C17—C20—C22	−61.4 (4)	C22—C23—C24—C25	137.0 (4)
C16—C17—C20—C22	175.3 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···O6^{i}	0.84	1.95	2.732 (4)	154
O2—H2···O5^{ii}	0.84	1.91	2.690 (3)	153
O6—H6···O7^{iii}	0.84	1.96	2.701 (4)	147
O8—H8···O5^{iv}	0.81	1.88	2.670 (4)	165
O9—H90···O8^{iv}	0.82	1.94	2.736 (4)	165
O10—H101···O1^{v}	0.91 (4)	1.89 (4)	2.795 (4)	172
O10—H102···O2^{v}	0.86 (6)	1.88 (5)	2.717 (4)	166

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

The absolute configuration of the structure could not be determined due to the lack of heavy atoms. Therefore, the Friedel pairs were merged. The high values of R_{int} and R are related to the rather poor quality of the crystals. The H atoms were placed in calculated positions (C—H = 0.99 and 1.00 Å and O—H = 0.84 Å).

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

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