Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two (*E*,*E*)- and (*Z*,*E*)-thiazol-5-yl-penta-2,4-dienones

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Received 19 February 2002
Accepted 24 April 2002
Online 12 July 2002

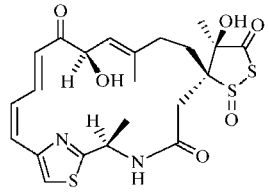
In order to characterize the structural elements that might play a role in non-covalent DNA binding by the antitumor antibiotic leinamycin, we have solved the crystal structures of the two leinamycin analogs, methyl (*R*)-5-{2-[1-(*tert*-butoxycarbonylamino)ethyl]thiazol-4-yl}penta-(*E*,*E*)-2,4-dienoate, $C_{16}H_{22}N_2O_4S$, (II), and 2-methyl-8-oxa-16-thia-3,17-diazabicyclo[12.2.1]heptadeca-(*Z*,*E*)-1(17),10,12,14-tetraene-4,9-dione, $C_{14}H_{16}N_2O_3S$, (III). The penta-2,4-dienone moiety in both of these analogs adopts a conformation close to planarity, with the thiazole ring twisted out of the plane by 12.9 (2)° in (II) and by 21.4 (4)° in (III).

Comment

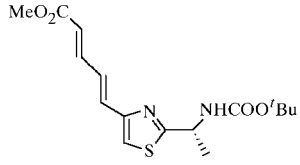
Leinamycin, (I), is a natural product with promising antitumor activity (Hara *et al.*, 1989, 1990). This activity is believed to result from the ability of the compound to damage cellular DNA (Hara *et al.*, 1990; Asai *et al.*, 1996; Mitra *et al.*, 1997; Breydo *et al.*, 2001). Leinamycin has a unique structure, containing an unusual 1,2-dithiolan-3-one 1-oxide moiety connected by a spiro linkage to an 18-membered macrocycle. This antibiotic is capable of both DNA alkylation and oxidative DNA damage (Gates, 2000).

Recent studies showing that leinamycin does not efficiently alkylate single-stranded DNA suggest that non-covalent association of leinamycin with the double helix facilitates DNA alkylation by the antibiotic (Asai *et al.*, 1996; Breydo *et al.*, 2002). It seems likely that the macrocycle of leinamycin plays a major role in non-covalent binding of the compound to DNA. Thus, in order to understand better the nature of the interaction between leinamycin and DNA, it is important to characterize the three-dimensional structure of the thiazol-5-ylpenta-2,4-dienone fragment of the antibiotic. Although the crystal structures of leinamycin and several of its derivatives have been solved previously (Hirayama & Matsuzawa, 1993; Kanda *et al.*, 1999), the coordinates for these structures have not been published.

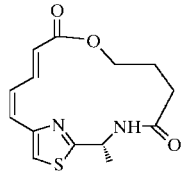
As part of an investigation of non-covalent DNA binding by leinamycin, we prepared several (*E*,*E*)- and (*Z*,*E*)-thiazol-5-ylpenta-2,4-dienones. Here, we present the crystal structures of methyl (*R*)-5-{2-[1-(*tert*-butoxycarbonylamino)ethyl]thiazol-4-yl}penta-(*E*,*E*)-2,4-dienoate, (II), and 2-methyl-8-oxa-16-thia-3,17-diazabicyclo[12.2.1]heptadeca-(*Z*,*E*)-1(17),10,12,14-tetraene-4,9-dione, (III). Our results provide the first detailed structural information regarding leinamycin analogs containing the thiazol-5-ylpenta-2,4-dienone moiety.



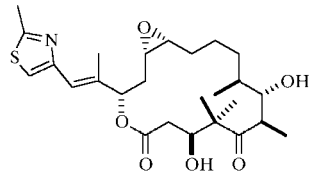
(I)



(II)



(III)



Epothilone B, (IV)

The structures of (II) and (III) reveal that the penta-2,4-dienone fragment is nearly planar [to within 0.02 Å for (II) and 0.05 Å for (III)], similar to the known structures of compounds containing an $\alpha,\beta,\gamma,\delta$-conjugated carbonyl group (Cox, 1994; Rabinovich & Schmidt, 1967). The bond lengths in the penta-2,4-dienone system indicate conjugation (Ladd & Palmer, 1993; Wiberg *et al.*, 1991) between the double bonds and with the thiazole ring. In both compounds, the thiazole ring is twisted out of plane relative to the penta-2,4-dienone moiety, by 12.9 (2)° in (II) and by 21.4 (4)° in (III) (*PLATON*; Spek, 2001). Presumably, this twist serves to minimize steric repulsion between the lone pair on the thiazole N atom and an adjacent H atom [H12 in (II) and H11 in (III)]. This assumption is supported by a comparison with the known structure of epothilone B, (IV) (Hoefle *et al.*, 1996), which contains an alkene moiety in the C4 position of the thiazole ring that is also slightly twisted out of plane.

Although the coordinates for the crystal structure of leinamycin are not available, the graphical representations that have been published (Hirayama & Matsuzawa, 1993)

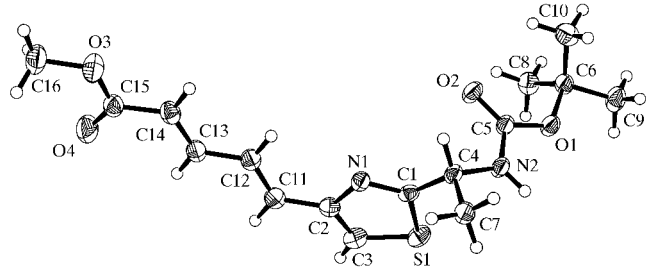


Figure 1
A view of the molecule of (II), shown with 50% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii.

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 DOI: 10.1107/S0108270102007503

indicate that the antibiotic also adopts a conformation with a nearly planar penta-2,4-dienone moiety and with the thiazole ring twisted slightly out of plane. The 18-membered macrocycle of leinamycin clearly presents a large hydrophobic surface that may drive association of the natural product with

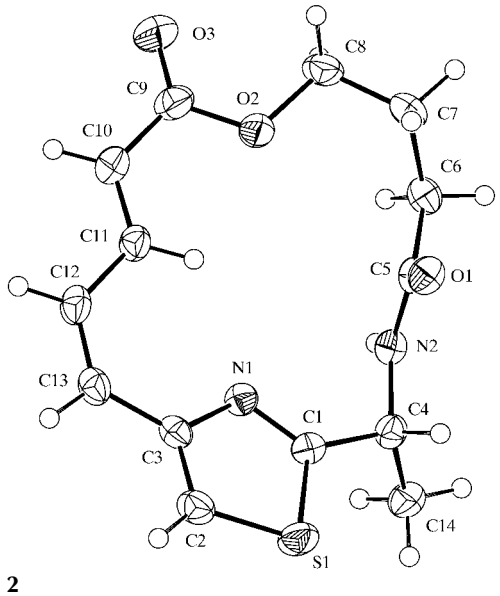

Figure 2
A view of the molecule of (III), shown with 50% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii.

the hydrophobic major groove of duplex DNA (Jadhav *et al.*, 1999). In addition, it is possible that the conjugated thiazol-5-ylpenta-2,4-dienone moiety found in leinamycin may represent a novel type of DNA intercalator, where individual double bonds are part of the intercalating system. Several examples of such small intercalators are known and include esperamycin A1 (Yu *et al.*, 1994), C-1027 (Yu *et al.*, 1995), and amiloride (Bailly *et al.*, 1993). The results reported here may provide important structural information that will ultimately help in the understanding of the detailed nature of the non-covalent interactions between leinamycin and DNA.

Experimental

Compounds (II) and (III) were prepared from (*R*)-*N*-*tert*-butoxycarbonylalanine and their syntheses will be described separately. Racemization of compound (III) occurred in the course of the synthesis. Crystals of both compounds suitable for X-ray diffraction analysis were obtained by slow evaporation of dichloromethane solutions.

Compound (II)

Crystal data

$C_{16}H_{22}N_2O_4S$
M_r = 338.42
Triclinic, *P*1
a = 5.207 (2) Å
b = 5.876 (3) Å
c = 15.339 (7) Å
α = 82.21 (1)°
β = 81.43 (1)°
γ = 72.17 (1)°
V = 439.8 (3) Å^3
Z = 1
D_x = 1.278 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 2894 reflections
θ = 2.7–27.1°
μ = 0.20 mm^{-1}
T = 173 (2) K
Prism, yellow
0.45 × 0.35 × 0.35 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
T_{min} = 0.89, T_{max} = 0.94
3484 measured reflections
2820 independent reflections
2702 reflections with $I > 2\sigma(I)$
R_{int} = 0.019
θ_{max} = 27.1°
h = −6 → 6
k = −7 → 7
l = −19 → 16

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.100
S = 1.12
2820 reflections
213 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0665P)^2 + 0.0536P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Absolute structure: Flack (1983); 908 Friedel pairs
Flack parameter = 0.07 (7)

Table 1
Selected geometric parameters (Å, °) for (II).

C2—C3	1.363 (3)	C12—C13	1.437 (4)
C2—C11	1.460 (3)	C13—C14	1.338 (4)
O4—C15	1.205 (3)	C14—C15	1.475 (4)
C11—C12	1.340 (3)		
C3—C2—N1	114.5 (2)	C14—C13—C12	124.2 (2)
C3—C2—C11	125.5 (2)	C13—C14—C15	122.1 (2)
C12—C11—C2	123.9 (2)	O4—C15—C14	125.6 (2)
C11—C12—C13	124.1 (2)		
C1—N1—C2—C11	−178.0 (2)	C2—C11—C12—C13	−179.1 (2)
C11—C2—C3—S1	177.62 (18)	C11—C12—C13—C14	177.3 (2)
C3—C2—C11—C12	−166.7 (2)	C12—C13—C14—C15	−179.6 (2)
N1—C2—C11—C12	12.4 (3)	C13—C14—C15—O4	−8.9 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O2^{i}	0.88	2.20	3.072 (3)	170

Symmetry code: (i) 1 + *x*, *y*, *z*.

Compound (III)

Crystal data

$C_{14}H_{16}N_2O_3S$
M_r = 292.35
Monoclinic, *Pc*
a = 10.078 (1) Å
b = 8.882 (1) Å
c = 8.512 (1) Å
β = 109.89 (1)°
V = 716.5 (1) Å^3
Z = 2
D_x = 1.355 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 2334 reflections
θ = 2.3–27.0°
μ = 0.23 mm^{-1}
T = 173 (2) K
Plate, colorless
0.4 × 0.3 × 0.1 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
T_{min} = 0.77, T_{max} = 0.98
4350 measured reflections
2391 independent reflections
2177 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 27.1°
h = −12 → 12
k = −10 → 11
l = −10 → 8

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0425P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.030$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.070$	$\Delta\rho_{max} = 0.24$ e Å^{-3}
$S = 1.00$	$\Delta\rho_{min} = -0.17$ e Å^{-3}
2391 reflections	Absolute structure: Flack (1983); 812 Friedel pairs
182 parameters	Flack parameter = 0.05 (7)
H-atom parameters constrained	

Table 3
Selected geometric parameters (Å, °) for (III).

O3—C9	1.205 (3)	C9—C10	1.467 (3)
N1—C1	1.292 (3)	C10—C11	1.337 (3)
C1—C4	1.522 (3)	C11—C12	1.449 (3)
C2—C3	1.359 (3)	C12—C13	1.342 (3)
C1—N1—C3	111.45 (17)	O3—C9—C10	125.2 (2)
C4—C1—S1	120.88 (14)	C11—C10—C9	123.1 (2)
C3—C2—S1	110.85 (15)	C10—C11—C12	124.28 (19)
C2—C3—C13	124.04 (18)	C13—C12—C11	126.01 (18)
N1—C3—C13	121.84 (18)	C12—C13—C3	127.78 (18)
C1—S1—C2—C3	−0.68 (17)	C10—C11—C12—C13	173.8 (2)
S1—C2—C3—C13	−177.35 (17)	C11—C12—C13—C3	−3.3 (4)
O3—C9—C10—C11	175.9 (2)	C2—C3—C13—C12	165.4 (2)
C9—C10—C11—C12	177.9 (2)	N1—C3—C13—C12	−12.7 (3)

Table 4
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O1^{i}	0.88	2.00	2.869 (2)	168

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

H atoms were placed at calculated positions and were updated with each cycle of refinement, but not refined. The C—H distances were fixed in the range 0.95–1.00 Å and N—H distances were fixed at 0.88 Å. The displacement parameters were fixed at 1.2 times the equivalent isotropic displacement parameter of the parent atom. The analysis of (II) [with a Flack (1983) parameter of 0.07 (7)] establishes the *R* absolute configuration. For racemic (III) in space group *Pc*, the Flack parameter [0.05 (7)] shows that the correct polarity has been chosen.

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *CIFTAB* in *SHELXL*97.

The authors thank the National Institutes of Health for funding (CA83925). The X-ray diffractometer used in this study was obtained with funding from the National Science Foundation (CHE 9011804).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1371). Services for accessing these data are described at the back of the journal.

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