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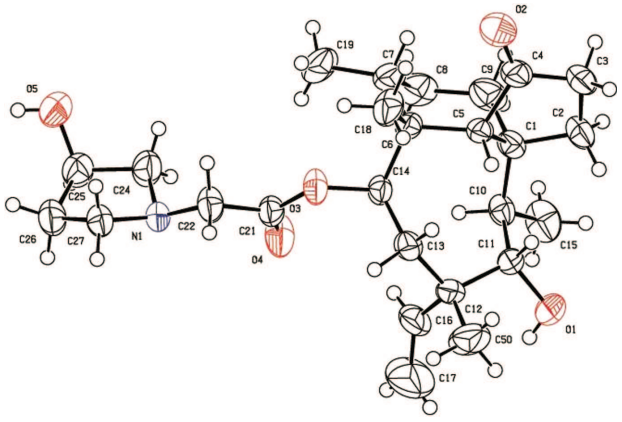
Crystal structure of (3*aR*,4*R*,5*R*,7*R*,8*S*,9*R*,9*aS*,12*R*)-7-ethyl-5-(1-hydroxy-2-((*R*)-3-hydroxypyrrolidin-1-yl)ethoxy)-4,7,9,12-tetramethyldecahydro-4,9a-propanocyclopenta[8]annulene-3,8-diol – a pleuromutilin derivative, $C_{26}H_{41}NO_5$



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Abstract

$C_{26}H_{41}NO_5$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 9.6178(8)$ Å, $b = 13.3335(11)$ Å, $c = 19.0758(16)$ Å, $V = 2446.3(4)$ Å^3, $Z = 4$, $R_{gt}(F) = 0.0389$, $wR_{ref}(F^2) = 0.0888$, $T = 296(2)$ K.

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The crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

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Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.30 × 0.20 × 0.20 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.08 mm^{-1}
Diffractometer, scan mode:	Bruker APEXII, ω
θ_{max}, completeness:	25.0°, 99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	12437, 4283, 0.024
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3728
$N(param)_{refined}$:	295
Programs:	Bruker [11], SHELX [12, 13]

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.1974(3)	0.36665(19)	0.92354(13)	0.0398(6)
C2	0.1420(3)	0.3988(2)	0.99625(14)	0.0522(8)
H2A	0.0800	0.4558	0.9918	0.063*
H2B	0.0916	0.3441	1.0181	0.063*
C3	0.2688(3)	0.4267(3)	1.03976(15)	0.0567(8)
H3A	0.2537	0.4896	1.0641	0.068*
H3B	0.2888	0.3749	1.0740	0.068*
C4	0.3861(3)	0.4363(2)	0.98822(15)	0.0508(7)
C5	0.3245(3)	0.4372(2)	0.91382(13)	0.0356(6)
H5	0.2871	0.5047	0.9062	0.043*
C6	0.4252(3)	0.4161(2)	0.85228(13)	0.0399(6)
C7	0.4755(3)	0.3064(2)	0.85957(16)	0.0572(8)
H7	0.5268	0.3032	0.9039	0.069*
C8	0.3540(4)	0.2338(2)	0.86710(19)	0.0669(10)
H8A	0.3902	0.1666	0.8740	0.080*
H8B	0.3007	0.2338	0.8239	0.080*
C9	0.2569(4)	0.2596(2)	0.92816(17)	0.0611(9)
H9A	0.3076	0.2526	0.9718	0.073*
H9B	0.1806	0.2120	0.9289	0.073*
C10	0.0823(3)	0.3743(2)	0.86717(14)	0.0402(6)
H10	0.1190	0.3436	0.8243	0.048*
C11	0.0435(3)	0.4843(2)	0.84899(14)	0.0403(6)
H11	0.0825	0.5267	0.8861	0.048*
C12	0.1012(3)	0.5245(2)	0.77815(15)	0.0465(7)
C13	0.2615(3)	0.5287(2)	0.77546(15)	0.0437(7)
H13A	0.2867	0.5608	0.7316	0.052*
H13B	0.2915	0.5731	0.8128	0.052*
C14	0.3486(3)	0.4327(2)	0.78127(13)	0.0373(6)
H14	0.2900	0.3743	0.7710	0.045*
C15	−0.0470(4)	0.3135(3)	0.88878(19)	0.0662(9)

Table 2 (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
H15A	−0.0196	0.2467	0.9014	0.099*
H15B	−0.1111	0.3107	0.8502	0.099*
H15C	−0.0910	0.3453	0.9281	0.099*
C16	0.0486(3)	0.4603(3)	0.71855(15)	0.0671(10)
H16	0.0905	0.3979	0.7136	0.081*
C17	−0.0474(5)	0.4817(5)	0.6736(2)	0.129(2)
H17A	−0.0931	0.5431	0.6759	0.155*
H17B	−0.0709	0.4356	0.6389	0.155*
C18	0.5481(3)	0.4905(3)	0.85622(17)	0.0608(9)
H18A	0.6104	0.4785	0.8178	0.091*
H18B	0.5969	0.4812	0.8997	0.091*
H18C	0.5135	0.5579	0.8537	0.091*
C19	0.5763(4)	0.2693(3)	0.8027(2)	0.0869(14)
H19A	0.6213	0.2091	0.8185	0.130*
H19B	0.6450	0.3199	0.7938	0.130*
H19C	0.5255	0.2557	0.7604	0.130*
O1	−0.1043(2)	0.4990(2)	0.84987(12)	0.0638(6)
H1	−0.1350	0.4934	0.8100	0.096*
C21	0.4415(3)	0.3962(2)	0.66600(14)	0.0422(6)
C22	0.5640(3)	0.4203(2)	0.62004(14)	0.0497(7)
H22A	0.5583	0.4901	0.6058	0.060*
H22B	0.6486	0.4121	0.6470	0.060*
C24	0.6124(4)	0.2545(2)	0.57249(17)	0.0609(9)
H24A	0.5310	0.2142	0.5830	0.073*
H24B	0.6752	0.2518	0.6122	0.073*
C25	0.6844(4)	0.2158(2)	0.50649(17)	0.0577(8)
H25	0.6293	0.1625	0.4846	0.069*
C26	0.6915(4)	0.3072(2)	0.45888(17)	0.0640(9)
H26A	0.7794	0.3096	0.4341	0.077*
H26B	0.6163	0.3065	0.4250	0.077*
C27	0.6775(3)	0.3943(2)	0.50793(15)	0.0504(7)
H27A	0.7648	0.4088	0.5313	0.061*
H27B	0.6459	0.4539	0.4835	0.061*
N1	0.5721(2)	0.35805(17)	0.55788(11)	0.0409(5)
C50	0.0541(4)	0.6337(3)	0.7714(2)	0.0854(13)
H50A	−0.0457	0.6366	0.7717	0.128*
H50B	0.0884	0.6612	0.7282	0.128*
H50C	0.0899	0.6719	0.8101	0.128*
O2	0.5069(2)	0.4398(2)	1.00501(12)	0.0818(8)
O3	0.45818(19)	0.44112(16)	0.72783(9)	0.0473(5)
O4	0.3434(2)	0.34720(19)	0.64994(11)	0.0665(7)
O5	0.8156(3)	0.1788(2)	0.52774(13)	0.0787(8)
H5A	0.8637	0.1679	0.4931	0.118*

Source of material

To a solution of 22-*O*-tosyl-pleuromutilin (0.49 g, 1 mmol) in 10 mL methanol, 3-pyrrolidinol (0.26 g, 3 mmol) was added and stirred for 7 h at room temperature, followed by evaporation under reduced pressure to dryness. The obtained crude product was extracted with a solution of ethyl acetate (30 mL) and water (10 mL) and further with saturated $NaHCO_3$. The target compound was then precipitated and purified by flash silica column chromatography (petroleum ether:ethyl acetate = 1:10–1:3 *v*/*v*). Crystals were obtained by slow evaporation from methanol solution at room temperature.

Experimental details

Hydrogen atoms were added using the standard procedures of the SHELX program system. The absolute structure was estimated from the synthesis.

Comment

Pleuromutilin was isolated from *Pleurotus mutilus* and *P. passeckerianus* in 1951 [1]. Its chemical structure includes a rather rigid 5-6-8 tricyclic carbon skeleton and a C-14 side chain [2, 3]. Pleuromutilin and its derivatives selectively inhibit bacterial protein synthesis *via* binding to the 50S subunit of ribosomes at the A-site and P-site [4, 5]. Preliminary studies showed that the modification of pleuromutilin C-14 side chain improved its biological activity [2], and there are three drugs, tiamulin, valnemulin and retapamulin, which are presently used in therapy [6]. Nabriva's lefamulin received FDA fast-track status to treat community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure (ABSSS) [7, 8].

The crystal structure of the title compound is built up of $C_{26}H_{41}NO_5$ molecules containing the well known 5-6-8 tricyclic carbon skeleton and a pyrrolidinol group, in which all bond lengths and angles are in normal ranges. The eight-membered ring (C14—C13—C12—C11—C10) exhibits a boat conformation. The six-membered ring (C6—C7—C8—C9—C1—C5) exhibits a chair conformation. The tricyclic carbon skeleton exhibits similar conformation with reported pleuromutilin derivatives [9, 10]. The side chain of pleuromutilin exhibits zigzag conformation. The torsion angles are 167.11° and 177.25° for O3—C21—C22—N1 and C22—C21—O3—C14, respectively (*cf.* the figure).

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