Jia-Zhen Wang, Wei-Zhao Weng, Ying Ma, Xiu-Ting He and Qing-Guo Meng*

Crystal structure of (1*S*,3*aR*,3*bR*,10*aR*,10*bR*,12*aR*)-8-amino-3*a*,3*b*,6,6,10*a*-pentamethyl-1-((*S*)-2,6,6-trimethyltetrahydro-2*H*-pyran-2-yl)-2,3,3*a*,3*b*,4,5,5*a*,6,10,10*a*,10*b*,11,12,12*a*-tetradecahydro-1*H*-cyclopenta[7,8]phenanthro[2,3-*d*]thiazol-12-ol – a panaxadiol derivative, C₃₁H₅₀N₂O₂S

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.42 × 0.32 × 0.30 mm
Wavelength:	Cu K α radiation (1.54178 Å)
μ :	1.20 mm ⁻¹
Diffractometer, scan mode:	Bruker SMART, φ and ω
$\theta_{\max}$, completeness:	66.0°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	13666, 9090, 0.052
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 4692
$N(\text{param})_{\text{refined}}$:	666
Programs:	Bruker [1], SHELX [2–4]

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Abstract

C₃₁H₅₀N₂O₂S, orthorhombic, $P2_12_12_1$ (no. 19), $a = 11.9922(9)$ Å, $b = 16.7099(8)$ Å, $c = 29.1262(16)$ Å, $V = 5836.6(6)$ Å³, $Z = 8$, $R_{\text{gt}}(F) = 0.0654$, $wR_{\text{ref}}(F^2) = 0.1230$, $T = 293(2)$ K.

CCDC no.: 1858965

The asymmetric unit, consisting of two independent title molecules, of 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.

Source of material

Panaxadiol (PD; systematic name: (3*S*,5*R*,8*R*,9*R*,10*R*,12*R*,13*R*,14*R*,17*S*)-4,4,8,10,14-pentamethyl-17-((*R*)-2,6,6-trimethyltetra-

hydro-2*H*-pyran-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,12-diol) was isolated from the degradation residues of Panax ginseng treated with 10% H₂SO₄, and purified by silica gel column chromatography. After recrystallization in ethyl acetate and CH₂Cl₂, the pure white needle-like crystal line product was obtained. PD was oxidized by pyridinium chlorochromate in dry dichloromethane to get the 3-Oxo-PD; then the products occur bromine reaction with pyridinium tribromide in acetic acid and stirred at room temperature to get the 2-bromo-3-oxo-PD. 2-Bromo-3-oxo-PD, thiourea was added in ethanol, stirred at 80 °C for 8 h. The solution was then washed successively with water and saturated with sodium chloride solution, and dried over anhydrous sodium sulfate. After filtration, the ethyl acetate was evaporated in vacuo to yield a white solid, which was purified using silica-gel column chromatography (petroleum ether:ethyl acetate = 3:1, v/v). Crystals were obtained by slow concentration of an ethyl acetate solution. HRMS calcd. for C₃₁H₅₀N₂O₂S [M+H]⁺ 515.36; found 515.33. ¹H NMR (400 MHz, CDCl₃) δ 6.31 (s, 1H), 3.55 (tt, $J = 10.3$, 4.9 Hz, 1H), 2.58 (d, $J = 15.4$ Hz, 1H), 2.17 (d, $J = 15.2$ Hz, 1H), 1.98 (s, 2H), 1.77 (dd, $J = 22.3$, 11.4 Hz, 2H), 1.66 (dd, $J = 19.9$, 9.2 Hz, 1H), 1.59 (d, $J = 12.7$ Hz, 6H), 1.51 – 1.45 (m, 2H), 1.41 – 1.30 (m, 3H), 1.26 (s, 3H), 1.24 (d, $J = 2.3$ Hz, 3H), 1.20 (s, 6H), 1.19 (s, 3H), 1.11 (d, $J = 3.5$ Hz, 3H), 1.02 (d, $J = 2.5$ Hz, 3H), 0.93 (d, $J = 2.5$ Hz, 3H), 0.89 (d, $J = 2.5$ Hz, 6H).

Experimental details

All H atoms were included in calculated positions and refined as riding atoms, with O–H = 0.82 Å (–OH), U_{iso}

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
N1A	0.5240(5)	0.0172(4)	0.54813(19)	0.0494(17)
N2A	0.5564(5)	−0.0442(3)	0.6197(2)	0.067(2)
H2A1	0.564385	−0.090852	0.607676	0.081*
H2A2	0.562238	−0.038141	0.648910	0.081*
O1A	0.5350(5)	0.5452(3)	0.53723(16)	0.0780(19)
H1A	0.527543	0.591195	0.527868	0.094*
O2A	0.4914(4)	0.6838(3)	0.49602(15)	0.0476(13)
S1A	0.51516(19)	0.11615(12)	0.61583(6)	0.0601(6)
C1A	0.4800(6)	0.2399(4)	0.5495(2)	0.049(2)
H1A1	0.520914	0.271623	0.571765	0.058*
H1A2	0.401860	0.254408	0.551443	0.058*
C2A	0.4938(6)	0.1533(4)	0.5600(2)	0.0444(19)
C3A	0.5022(6)	0.0923(4)	0.5305(2)	0.0426(18)
C4A	0.4923(7)	0.1036(5)	0.4789(2)	0.049(2)
C5A	0.4721(6)	0.1942(4)	0.4679(2)	0.0430(19)
H5A	0.391524	0.201595	0.471578	0.052*
C6A	0.4948(8)	0.2142(4)	0.4173(2)	0.064(2)
H6A1	0.574229	0.210444	0.411457	0.077*
H6A2	0.457488	0.175231	0.398003	0.077*
C7A	0.4547(7)	0.2975(4)	0.4046(2)	0.063(3)
H7A1	0.374004	0.298709	0.407053	0.075*
H7A2	0.473766	0.307619	0.372798	0.075*
C8A	0.5025(6)	0.3649(4)	0.4340(2)	0.0449(19)
C9A	0.4868(6)	0.3419(4)	0.4855(2)	0.0395(18)
H9A	0.405706	0.340904	0.489636	0.047*
C10A	0.5249(5)	0.2571(4)	0.5002(2)	0.0389(17)
C11A	0.5261(6)	0.4092(4)	0.5171(2)	0.048(2)
H11A	0.507064	0.394986	0.548414	0.057*
H11B	0.606732	0.412310	0.515268	0.057*
C12A	0.4788(6)	0.4916(4)	0.5072(2)	0.050(2)
H12A	0.399135	0.491731	0.514676	0.060*
C13A	0.4928(6)	0.5124(4)	0.4565(2)	0.0407(18)
H13A	0.573201	0.513146	0.450504	0.049*
C14A	0.4428(6)	0.4464(4)	0.4254(2)	0.0437(19)
C15A	0.4576(7)	0.4847(4)	0.3776(2)	0.064(2)
H15A	0.532676	0.476261	0.366123	0.077*
H15B	0.404854	0.462515	0.355789	0.077*
C16A	0.4352(7)	0.5737(4)	0.3857(3)	0.064(2)
H16A	0.360857	0.587340	0.375118	0.077*
H16B	0.488516	0.605706	0.368612	0.077*
C17A	0.4460(6)	0.5915(4)	0.4380(2)	0.048(2)
H17A	0.370449	0.597739	0.450358	0.058*
C18A	0.6287(6)	0.3727(4)	0.4215(2)	0.065(2)
H18A	0.660189	0.320343	0.417455	0.097*
H18B	0.667210	0.399861	0.445869	0.097*
H18C	0.636320	0.402675	0.393595	0.097*
C19A	0.6537(5)	0.2484(4)	0.5036(2)	0.057(2)
H19A	0.671790	0.201012	0.520664	0.086*
H19B	0.684227	0.294351	0.518881	0.086*
H19C	0.684756	0.244520	0.473278	0.086*
C20A	0.5094(7)	0.6696(5)	0.4474(2)	0.049(2)
C21A	0.6352(6)	0.6601(4)	0.4378(3)	0.067(3)
H21A	0.669303	0.712012	0.436127	0.101*
H21B	0.645550	0.632574	0.409213	0.101*
H21C	0.668965	0.629885	0.462144	0.101*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
C22A	0.4594(7)	0.7389(4)	0.4201(2)	0.067(3)
H22A	0.378833	0.734233	0.420584	0.080*
H22B	0.483481	0.734580	0.388412	0.080*
C23A	0.4919(8)	0.8215(4)	0.4383(3)	0.079(3)
H23A	0.571673	0.829324	0.435098	0.095*
H23B	0.454100	0.862722	0.420808	0.095*
C24A	0.4589(7)	0.8272(5)	0.4888(3)	0.069(3)
H24A	0.483376	0.878406	0.500925	0.083*
H24B	0.378251	0.825230	0.491278	0.083*
C25A	0.5086(7)	0.7607(5)	0.5176(3)	0.052(2)
C26A	0.4507(6)	0.7534(5)	0.5636(2)	0.072(3)
H26A	0.374308	0.738335	0.558887	0.108*
H26B	0.453697	0.803836	0.579293	0.108*
H26C	0.487398	0.713291	0.581744	0.108*
C27A	0.6342(6)	0.7761(5)	0.5267(3)	0.077(3)
H27A	0.666444	0.729996	0.541212	0.116*
H27B	0.642407	0.821771	0.546385	0.116*
H27C	0.671445	0.786009	0.498083	0.116*
C28A	0.3910(6)	0.0551(4)	0.4623(2)	0.072(3)
H28A	0.402963	−0.000607	0.468561	0.108*
H28B	0.381514	0.062764	0.429868	0.108*
H28C	0.325372	0.073038	0.478116	0.108*
C29A	0.5967(6)	0.0683(4)	0.4553(2)	0.067(3)
H29A	0.661444	0.097831	0.464668	0.100*
H29B	0.588370	0.071813	0.422610	0.100*
H29C	0.605067	0.013193	0.464067	0.100*
C30A	0.3143(5)	0.4401(4)	0.4334(3)	0.065(2)
H30A	0.281374	0.492282	0.431131	0.098*
H30B	0.300365	0.418495	0.463439	0.098*
H30C	0.282205	0.405517	0.410660	0.098*
C31A	0.5342(7)	0.0204(5)	0.5923(3)	0.052(2)
N1B	0.7183(5)	0.4890(3)	0.68917(19)	0.0481(17)
N2B	0.6965(5)	0.5467(3)	0.6161(2)	0.068(2)
H2B1	0.712595	0.593948	0.625804	0.081*
H2B2	0.680854	0.539180	0.587628	0.081*
O1B	0.6989(5)	−0.0377(3)	0.70210(17)	0.084(2)
H1B	0.701687	−0.082627	0.713356	0.101*
O2B	0.7016(4)	−0.1729(3)	0.74797(16)	0.0499(14)
S2B	0.66584(19)	0.38746(13)	0.62595(6)	0.0603(6)
C1B	0.6787(7)	0.2658(4)	0.6939(2)	0.052(2)
H1B1	0.707128	0.233908	0.668653	0.062*
H1B2	0.601480	0.250966	0.699036	0.062*
C2B	0.6858(6)	0.3521(4)	0.6821(2)	0.050(2)
C3B	0.7121(6)	0.4140(4)	0.7092(2)	0.044(2)
C4B	0.7354(7)	0.4027(4)	0.7600(2)	0.051(2)
C5B	0.7173(6)	0.3130(4)	0.7735(2)	0.0403(18)
H5B	0.636320	0.307983	0.777092	0.048*
C6B	0.7640(7)	0.2927(4)	0.8212(2)	0.057(2)
H6B1	0.844795	0.292946	0.819946	0.068*
H6B2	0.740699	0.333371	0.842897	0.068*
C7B	0.7241(7)	0.2112(4)	0.8377(2)	0.056(2)
H7B1	0.643797	0.213036	0.841666	0.068*
H7B2	0.756924	0.200479	0.867533	0.068*
C8B	0.7529(6)	0.1422(4)	0.8053(2)	0.0441(19)
C9B	0.7133(6)	0.1654(4)	0.7561(2)	0.0400(18)
H9B	0.632037	0.169050	0.759071	0.048*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
C10B	0.7474(6)	0.2489(4)	0.7375(2)	0.0411(18)
C11B	0.7305(6)	0.0967(4)	0.7222(2)	0.052(2)
H11C	0.700563	0.112251	0.692618	0.062*
H11D	0.809934	0.087760	0.718426	0.062*
C12B	0.6763(7)	0.0188(4)	0.7369(2)	0.053(2)
H12B	0.595455	0.027254	0.738072	0.064*
C13B	0.7152(6)	−0.0040(4)	0.7843(2)	0.0419(19)
H13B	0.796505	−0.008529	0.782229	0.050*
C14B	0.6920(6)	0.0635(4)	0.8198(2)	0.0418(19)
C15B	0.7285(6)	0.0227(4)	0.8649(2)	0.056(2)
H15C	0.809094	0.022466	0.867735	0.067*
H15D	0.696732	0.049739	0.891280	0.067*
C16B	0.6832(6)	−0.0623(4)	0.8606(2)	0.058(2)
H16C	0.610306	−0.065966	0.874884	0.070*
H16D	0.732851	−0.099751	0.875717	0.070*
C17B	0.6747(6)	−0.0820(4)	0.8086(2)	0.047(2)
H17B	0.595334	−0.088130	0.801393	0.057*
C18B	0.8817(5)	0.1297(4)	0.8079(2)	0.058(2)
H18D	0.918658	0.179937	0.803035	0.087*
H18E	0.904370	0.092317	0.784718	0.087*
H18F	0.901169	0.109196	0.837647	0.087*
C19B	0.8732(5)	0.2537(4)	0.7233(2)	0.055(2)
H19D	0.917699	0.265811	0.749863	0.083*
H19E	0.882828	0.295040	0.700775	0.083*
H19F	0.896299	0.203336	0.710688	0.083*
C20B	0.7320(6)	−0.1609(5)	0.7957(2)	0.045(2)
C21B	0.8590(6)	−0.1551(4)	0.8011(3)	0.063(2)
H21D	0.890640	−0.207870	0.800951	0.094*
H21E	0.876483	−0.129102	0.829602	0.094*
H21F	0.889394	−0.124654	0.776103	0.094*
C22B	0.6861(7)	−0.2307(4)	0.8242(2)	0.058(2)
H22C	0.718010	−0.228400	0.854738	0.070*
H22D	0.606011	−0.224680	0.827107	0.070*
C23B	0.7113(7)	−0.3123(4)	0.8032(3)	0.063(2)
H23C	0.677169	−0.354039	0.821638	0.076*
H23D	0.791239	−0.321276	0.802843	0.076*
C24B	0.6655(7)	−0.3156(4)	0.7542(3)	0.062(2)
H24C	0.684116	−0.366826	0.740612	0.075*
H24D	0.584855	−0.311183	0.755144	0.075*
C25B	0.7122(7)	−0.2491(5)	0.7245(3)	0.054(2)
C26B	0.6445(7)	−0.2380(5)	0.6806(2)	0.075(3)
H26D	0.568626	−0.225696	0.688362	0.112*
H26E	0.646734	−0.286462	0.662919	0.112*
H26F	0.675646	−0.194969	0.662973	0.112*
C27B	0.8342(6)	−0.2663(4)	0.7108(3)	0.069(3)
H27D	0.865407	−0.219848	0.696317	0.104*
H27E	0.836356	−0.310633	0.689906	0.104*
H27F	0.876695	−0.279083	0.737796	0.104*
C28B	0.6484(7)	0.4543(4)	0.7863(2)	0.077(3)
H28D	0.658170	0.509625	0.778281	0.116*
H28E	0.658803	0.447693	0.818709	0.116*
H28F	0.574508	0.437539	0.777985	0.116*
C29B	0.8510(7)	0.4365(4)	0.7715(2)	0.079(3)
H29D	0.907371	0.403590	0.757612	0.119*
H29E	0.861110	0.437049	0.804149	0.119*
H29F	0.856963	0.490070	0.759778	0.119*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
C30B	0.5629(5)	0.0762(4)	0.8246(2)	0.059(2)
H30D	0.525746	0.025438	0.822721	0.089*
H30E	0.537093	0.110339	0.800302	0.089*
H30F	0.546889	0.100658	0.853686	0.089*
C31B	0.6960(6)	0.4839(5)	0.6459(3)	0.052(2)

(H) = $1.5U_{eq}(O)$, and with O–H = 0.82 or 0.85 Å (–OH), U_{iso} (H) = $1.2U_{eq}(O)$ (SHELX [1–4]). The methylene and methyl H atoms were placed in geometrically idealized positions and constrained to ride on their parent C atoms, with C–H = 0.96 Å (–CH), 0.97 Å (–CH₂), U_{iso} (H) = $1.2U_{eq}(C)$ and C–H = 0.96 Å (–CH₃), U_{iso} (H) = $1.5U_{eq}(C)$.

The absolute configuration was verified by a Flack-Parsons parameter of 0.01(2) based on 1015 quotients [4].

Comment

20(*R*)-panaxadiol (PD) is a significant apogenin of ginsenosides, which can be achieved by acid hydrolysis from leaves and stems of ginseng. It has been reported to have strong anticancer activities, and the mechanism involved in inducing apoptosis [5]. It has been reported that 20(*R*)-panaxadiol emerged significant inhibiting effect toward the Du-145, Hela, HepG2, and MCF-7 cells [6]. It is also a potent approach to diversifying the structures of natural products and preparing a variety of derivatives for the search of new leading compounds [7]. PD and panaxatriol type saponins and ophioponins, might exert tremendous cardio-protective effects and anti-inflammatory activities by blocking nuclear factor-kappa B (NF-κB) pathway [8]. Compared with PD, panaxadiol halogen-derivatives showed higher inhibitory activity toward HCT-116, BGC-823, 21SW-480 [9]. Consequently, the structural modification of 20(*R*)-panaxadiol may be valuable in obtaining new chemical derivatives for pharmacological screening and structure-activity relationship studies.

As shown in figure, there are two molecules in the asymmetric unit of the title structure. Each of them contains one classical intramolecular O–H···O hydrogen bond. Furthermore, the two crystallographically independent molecules are connected by classical intermolecular N–H···O hydrogen bonds. The distances of H(1B)···O(2B) and O(2A)···H(1A) are 1.809(34) and 1.852(33), respectively. While the distances of H(2A2)···O(1B) and H(2B2)···O(1A) are 2.261(43) and 2.288(36), respectively. The molecules extends into an infinite two-dimensional network through weak non-classical intermolecular C–H···N hydrogen bond. Bond lengths and angles are in the expected ranges [10, 11].

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