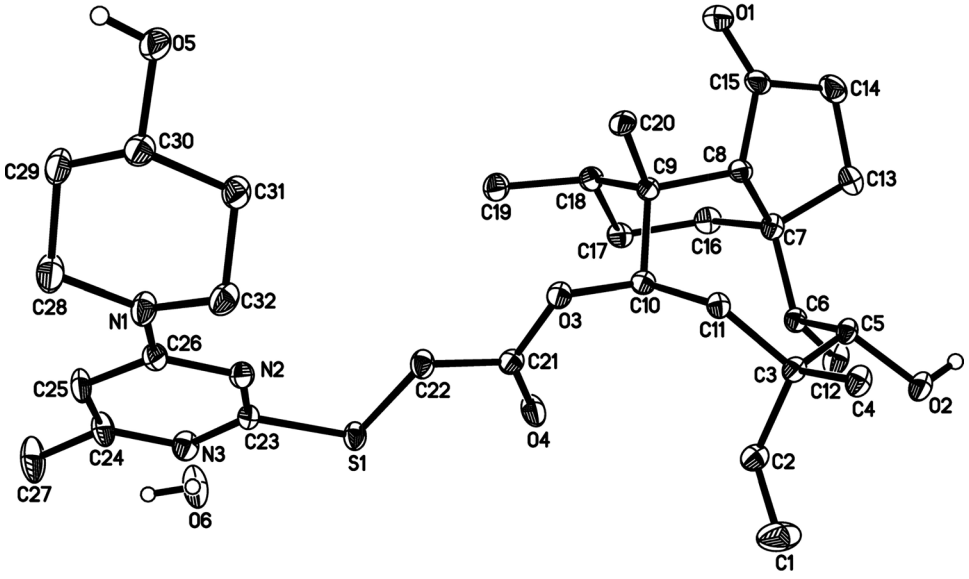
Si-Jie Liu*, Yuan Fan and Ruofeng Shang

Crystal structure of 14-*O*-[(4-(4-hydroxypiperidine-1-yl)-6-methylpyrimidine-2-yl)thioacetyl]-mutilin monohydrate, $C_{32}H_{49}N_3O_6S$



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Abstract

$C_{32}H_{49}N_3O_6S$, orthorhombic, $P2_12_12_1$ (no. 19), a = 9.2618(2) Å, b = 12.4066(2) Å, c = 27.2256(5) Å, V = 3128.42(12) Å^3, Z = 4, $R_{gt}(F)$ = 0.0517, $wR_{ref}(F^2)$ = 0.1355, T = 173.20(2) K.

CCDC no.: 2111927

The molecular structure is shown in the figure (the carbon bound hydrogen atoms are omitted for clarity). Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	0.18 × 0.15 × 0.12 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	1.31 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
θ_{max}, completeness:	66.6°, 98%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	9661, 5241, 0.041
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 4775
$N(param)_{refined}$:	397
Programs:	Olex2 [1], SHELX [2], CrysAlis^{PRO} [3]

Source of material

Triethylamine (0.73 g, 7.2 mmol), 4-dimethylaminopyridine (0.01 g, 0.1 mmol) and mesitylene-2-sulfonyl chloride (0.50 g, 2.3 mmol) were added to a solution of 14-*O*-[(4-ol-6-methylpyrimidine-2-yl)thioacetyl] mutilin (0.75 g, 1.5 mmol) in 20 ml dry dichloromethane. After the mixture was stirred at room temperature for 3 h, piperidin-4-ol (0.76 g, 7.5 mmol) and 1-methylpyrrolidine (1.27 g, 15 mmol) were then added in one portion for stirring for 1.5 h at 273.15 K. The mixture was washed with 5% citric acid, followed by drying with Na_2SO_4 overnight and rotary evaporation to dryness. The crude

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
S1	−0.12855 (13)	−0.43111 (8)	−0.13950 (3)	0.0269 (2)
O1	−0.9226 (5)	−0.0675 (3)	−0.19578 (13)	0.0473 (10)
O2	−0.6185 (4)	−0.2359 (3)	−0.40201 (10)	0.0302 (7)
H2	−0.700767	−0.230071	−0.412812	0.045*
O3	−0.3779 (4)	−0.2201 (2)	−0.20234 (9)	0.0258 (6)
O4	−0.3271 (4)	−0.3949 (3)	−0.21774 (12)	0.0403 (9)
O5	0.0149 (5)	0.1497 (3)	0.00810 (11)	0.0388 (8)
H5	0.043678	0.169810	0.035059	0.058*
N1	0.1182 (5)	−0.1675 (3)	−0.03142 (13)	0.0329 (9)
N2	0.0100 (4)	−0.2957 (3)	−0.08025 (12)	0.0255 (8)
N3	0.0126 (5)	−0.4842 (3)	−0.06024 (13)	0.0300 (8)
C1	−0.2764 (9)	−0.3181 (5)	−0.3737 (3)	0.065 (2)
H1A	−0.256 (9)	−0.285 (7)	−0.401 (3)	0.08 (3)*
H1B	−0.225 (7)	−0.385 (6)	−0.373 (2)	0.052 (18)*
C2	−0.3687 (5)	−0.2942 (3)	−0.34063 (15)	0.0286 (9)
H2A	−0.382369	−0.345965	−0.316370	0.034*
C3	−0.4593 (5)	−0.1926 (3)	−0.33547 (14)	0.0231 (8)
C4	−0.3986 (5)	−0.1031 (3)	−0.36821 (14)	0.0281 (9)
H4A	−0.396006	−0.127420	−0.401665	0.042*
H4B	−0.302605	−0.085233	−0.357660	0.042*
H4C	−0.459054	−0.040452	−0.365819	0.042*
C5	−0.6189 (5)	−0.2146 (3)	−0.35041 (13)	0.0224 (8)
H5A	−0.673578	−0.148010	−0.345063	0.027*
C6	−0.6979 (5)	−0.3077 (3)	−0.32141 (14)	0.0242 (9)
H6	−0.622497	−0.345356	−0.302918	0.029*
C7	−0.8043 (5)	−0.2602 (3)	−0.28204 (15)	0.0245 (9)
C8	−0.7534 (5)	−0.1614 (3)	−0.25153 (14)	0.0242 (9)
H8	−0.713034	−0.109552	−0.274977	0.029*
C9	−0.6355 (5)	−0.1810 (3)	−0.21214 (13)	0.0226 (8)
C10	−0.4917 (5)	−0.2186 (3)	−0.23766 (13)	0.0223 (8)
H10	−0.506039	−0.292530	−0.249300	0.027*
C11	−0.4465 (5)	−0.1492 (3)	−0.28211 (14)	0.0213 (8)
H11A	−0.346340	−0.129169	−0.277127	0.026*
H11B	−0.502398	−0.083137	−0.280575	0.026*
C12	−0.7659 (6)	−0.3903 (4)	−0.35360 (16)	0.0364 (11)
H12A	−0.812351	−0.443843	−0.333651	0.055*
H12B	−0.693088	−0.423825	−0.373479	0.055*
H12C	−0.836217	−0.356405	−0.374419	0.055*
C13	−0.9411 (5)	−0.2168 (4)	−0.30832 (17)	0.0326 (10)
H13A	−0.915097	−0.180107	−0.338515	0.039*
H13B	−1.006605	−0.275318	−0.316103	0.039*
C14	−1.0110 (5)	−0.1385 (4)	−0.27232 (18)	0.0389 (11)
H14A	−1.040277	−0.073063	−0.289058	0.047*
H14B	−1.095403	−0.170935	−0.257265	0.047*
C15	−0.8973 (6)	−0.1139 (4)	−0.23374 (16)	0.0325 (10)
C16	−0.8516 (5)	−0.3471 (4)	−0.24431 (15)	0.0288 (9)
H16A	−0.941663	−0.324349	−0.229337	0.035*
H16B	−0.870175	−0.413855	−0.261740	0.035*
C17	−0.7419 (5)	−0.3692 (3)	−0.20363 (16)	0.0272 (9)
H17A	−0.656507	−0.401842	−0.217878	0.033*
H17B	−0.782938	−0.420177	−0.180497	0.033*
C18	−0.6982 (5)	−0.2665 (3)	−0.17607 (15)	0.0271 (9)
H18	−0.787980	−0.235676	−0.163184	0.033*
C19	−0.6053 (6)	−0.2946 (4)	−0.13087 (15)	0.0332 (10)
H19A	−0.524769	−0.338013	−0.140908	0.050*
H19B	−0.662635	−0.333798	−0.107558	0.050*
H19C	−0.570645	−0.229360	−0.115998	0.050*
C20	−0.6014 (5)	−0.0749 (3)	−0.18531 (15)	0.0288 (9)
H20A	−0.515813	−0.083831	−0.165835	0.043*
H20B	−0.680883	−0.056064	−0.164375	0.043*
H20C	−0.586233	−0.018702	−0.208972	0.043*
C21	−0.3053 (5)	−0.3114 (3)	−0.19607 (14)	0.0252 (9)
C22	−0.1931 (5)	−0.2979 (3)	−0.15656 (15)	0.0279 (9)
H22A	−0.234786	−0.262103	−0.128238	0.034*
H22B	−0.113654	−0.254318	−0.168622	0.034*
C23	−0.0217 (5)	−0.3981 (3)	−0.08732 (14)	0.0232 (8)
C24	0.0880 (6)	−0.4604 (4)	−0.01980 (17)	0.0333 (11)
C25	0.1277 (6)	−0.3573 (4)	−0.00738 (15)	0.0324 (10)
H25	0.179876	−0.343606	0.021132	0.039*
C26	0.0866 (5)	−0.2722 (4)	−0.03939 (15)	0.0271 (9)
C27	0.1285 (8)	−0.5551 (4)	0.0121 (2)	0.0506 (15)
H27A	0.042728	−0.593002	0.021774	0.076*
H27B	0.178093	−0.529761	0.040867	0.076*
H27C	0.190520	−0.602776	−0.005938	0.076*
C28	0.1883 (7)	−0.1263 (4)	0.01269 (18)	0.0419 (13)
H28A	0.287636	−0.107604	0.005257	0.050*
H28B	0.188982	−0.181752	0.037810	0.050*
C29	0.1094 (6)	−0.0276 (4)	0.03170 (16)	0.0364 (11)
H29A	0.160352	0.001030	0.059957	0.044*
H29B	0.013152	−0.048068	0.042186	0.044*
C30	0.0987 (6)	0.0592 (4)	−0.00782 (15)	0.0304 (10)
H30	0.195971	0.083615	−0.016566	0.036*
C31	0.0264 (6)	0.0123 (4)	−0.05274 (15)	0.0303 (10)
H31A	0.024181	0.066028	−0.078617	0.036*
H31B	−0.072394	−0.006902	−0.044833	0.036*
C32	0.1065 (6)	−0.0869 (4)	−0.07072 (14)	0.0315 (10)
H32A	0.055511	−0.117761	−0.098472	0.038*
H32B	0.202348	−0.066417	−0.081627	0.038*
O6	−0.1157 (5)	−0.7014 (3)	−0.05776 (15)	0.0516 (10)
H6A	−0.064702	−0.645259	−0.061959	0.077*
H6B	−0.082198	−0.737619	−0.033828	0.077*

residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate 1:1–1:10 *v*/*v*) to afford the pure product with a yield of 63%. The clear light colorless crystals were obtained by slow evaporation from a solution of dichloromethane and *n*-hexane (1:1) at room temperature.

Experimental details

All hydrogen atoms were placed in geometrically idealized positions. The U_{iso} values were set to 1.5U_{eq} of the carrier atom for methyl and oxygen H atoms and 1.2 for the remaining H atoms.

Comment

The title compound may possess antibacterial activities against some Gram-positive bacteria, including *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis* (MRSE), methicillin-resistant *S. aureus* (MRSA), *Streptococcus dysgalactiae* and *Streptococcus agalactiae* and merited further drug development as a potential agent [4]. The starting material was pleuromutilin, which was first isolated in a crystalline form from cultures of two species of basidiomycetes, *Pleurotus mutilus* and *Pleurotus passeckerianus* in 1951 [5]. The pleuromutilin class showed high antibacterial activities with no target-specific cross-resistance to other antibiotics with an unique mode of action, which involve inhibtion of protein synthesis by primarily inhibiting ribosomal peptidyl transferase center (PTC) [6, 7]. The molecular modifications of pleuromutilin led to four drugs: tiamulin, valnemulin, retapamulin and lefamulin [8–10].

The asymmetric unit is composed of a molecule of 14-*O*-[(4-(4-Hydroxypiperidine-1-yl)-6-methylpyrimidine-2-yl) thioacetyl] mutilin and a molecule of water. The title molecule is comprised of a 5-6-8 tricyclic carbon skeleton and a methyl pyrimidine group, in which all bond lengths are in normal ranges [11, 12]. The six-membered ring (C9, C8, C7, C16–C18) exhibits a chair conformation and the eight-membered ring (C3, C5–C11) exhibits an irregular boat conformation, which were similar as the previous reported pleuromutilin derivative [11]. The structure is stabilized by some intramolecular hydrogen bonds (for example: C10—H10···O4, C18–H18···O1, C20–H20A···O3, C32–H32A···N2). Notably, the hydrogen bond of O2–H2···O6, O6–H6A···N3 and O6–H6B···O5 between the target and water molecules are present.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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