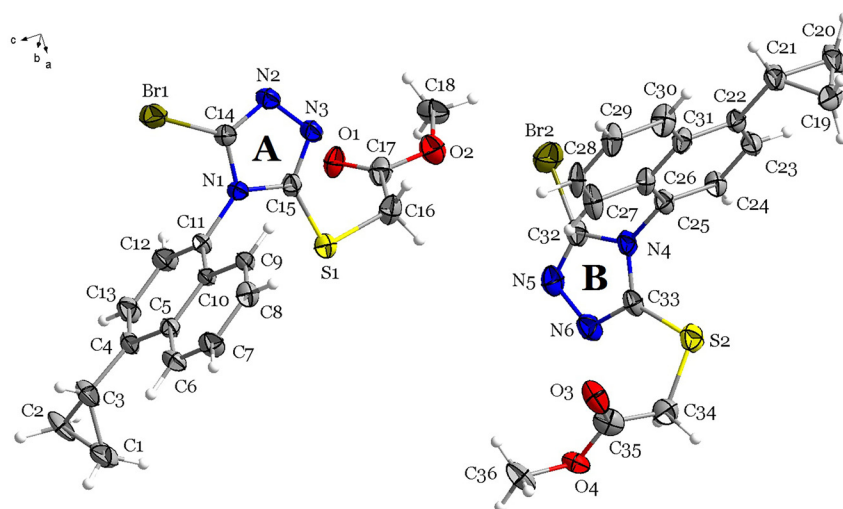


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Synthesis and crystal structure of methyl 2-((5-bromo-4-(4-cyclopropyl-naphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetate, $C_{18}H_{16}BrN_3O_2S$



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Abstract

$C_{18}H_{16}BrN_3O_2S$, triclinic, $P\bar{1}$ (no. 2), $a = 11.5820(4)$ Å, $b = 12.0492(4)$ Å, $c = 14.3048(5)$ Å, $\alpha = 73.673(3)^\circ$, $\beta = 88.190(3)^\circ$, $\gamma = 72.686(3)^\circ$, $V = 1826.02(12)$ Å³, $Z = 4$, $R_{gt}(F) = 0.0580$, $wR_{ref}(F^2) = 0.1565$, $T = 296(2)$ K.

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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 platelet
Size:	0.22 × 0.15 × 0.12 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	2.38 mm ⁻¹
Diffractionmeter, scan mode:	Multiwire proportional, φ and ω
θ_{max} , completeness:	25.0°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	19,974, 6,421, 0.038
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 4,199
$N(param)_{refined}$:	451
Programs:	Bruker, ¹ SHELX, ^{2,3} Diamond ⁴

1 Source of materials

The methyl 2-[[4-(4-cyclopropyl-1-naphthyl)-4H-1,2,4-triazole-3-yl]thio]acetate (40.0 g, 0.113 mol) was dissolved in 360 mL of dry dichloromethane at room temperature, and stirred evenly. Then, carbonyldiimidazole (0.92 g, 5.67 mmol) was added in batches, and the mixture was stirred for 30 min. Cooling to 0 °C, adding N-bromosuccinimide (22.2 g, 0.125 mol) in batches, and controlling the temperature to 0 °C for 40 min. The reaction was monitored by TLC. After the reaction, 300 mL of 10 % sodium sulfite aqueous solution was added and stirred for 1 h. Separate the organic layer, wash it once with 200 mL water and 200 mL saturated sodium chloride

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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}
Br1	0.85099 (5)	0.69458 (6)	0.47856 (5)	0.0696 (2)
Br2	1.65220 (7)	−0.05384 (7)	0.11585 (5)	0.0923 (3)
S1	1.29257 (12)	0.57124 (13)	0.31533 (10)	0.0578 (4)
S2	1.92178 (14)	0.22632 (13)	−0.09661 (10)	0.0631 (4)
O1	1.2991 (4)	0.3082 (4)	0.3375 (3)	0.0839 (13)
O2	1.3269 (4)	0.3224 (3)	0.1791 (3)	0.0717 (11)
O3	1.8655 (5)	0.4044 (5)	0.0260 (4)	0.118 (2)
O4	2.0390 (4)	0.3136 (4)	0.1130 (3)	0.0807 (12)
N1	1.0823 (3)	0.6456 (3)	0.4003 (3)	0.0403 (9)
N2	0.9482 (4)	0.6001 (4)	0.3238 (3)	0.0547 (11)
N3	1.0610 (4)	0.5662 (4)	0.2836 (3)	0.0542 (11)
N4	1.7766 (4)	0.0955 (4)	−0.0060 (3)	0.0502 (10)
N5	1.8518 (4)	0.0196 (4)	0.1464 (3)	0.0661 (13)
N6	1.9232 (4)	0.0884 (4)	0.0929 (3)	0.0624 (12)
C1	1.3831 (7)	0.8593 (9)	0.6671 (6)	0.115 (3)
H1A	1.384429	0.931709	0.683571	0.139*
H1B	1.437161	0.839139	0.617145	0.139*
C2	1.3639 (7)	0.7578 (7)	0.7465 (5)	0.097 (2)
H2A	1.405834	0.675732	0.744817	0.116*
H2B	1.353058	0.768381	0.811298	0.116*
C3	1.2685 (5)	0.8328 (5)	0.6701 (4)	0.0639 (15)
H3	1.202443	0.890637	0.692049	0.077*
C4	1.2278 (4)	0.7821 (4)	0.5969 (3)	0.0448 (12)
C5	1.1714 (4)	0.8634 (4)	0.5055 (3)	0.0385 (10)
C6	1.1608 (4)	0.9878 (4)	0.4788 (4)	0.0497 (12)
H6	1.192726	1.018675	0.521190	0.060*
C7	1.1049 (5)	1.0636 (4)	0.3926 (4)	0.0555 (14)
H7	1.098763	1.145588	0.376766	0.067*
C8	1.0564 (4)	1.0200 (4)	0.3273 (4)	0.0483 (12)
H8	1.018103	1.072903	0.268479	0.058*
C9	1.0651 (4)	0.9000 (4)	0.3497 (3)	0.0400 (11)
H9	1.032442	0.871681	0.305857	0.048*
C10	1.1231 (4)	0.8182 (4)	0.4385 (3)	0.0348 (10)
C11	1.1339 (4)	0.6930 (4)	0.4660 (3)	0.0381 (10)
C12	1.1898 (5)	0.6169 (5)	0.5512 (4)	0.0542 (13)
H12	1.196759	0.534816	0.566611	0.065*
C13	1.2376 (5)	0.6620 (5)	0.6170 (4)	0.0562 (14)
H13	1.276632	0.608680	0.675422	0.067*
C14	0.9651 (4)	0.6455 (4)	0.3928 (3)	0.0455 (12)
C15	1.1374 (4)	0.5938 (4)	0.3313 (3)	0.0434 (11)
C16	1.3093 (5)	0.4961 (5)	0.2216 (4)	0.0618 (14)
H16A	1.243420	0.540556	0.172520	0.074*
H16B	1.384268	0.499683	0.190556	0.074*
C17	1.3104 (5)	0.3654 (5)	0.2556 (4)	0.0587 (14)
C18	1.3321 (6)	0.1966 (5)	0.1963 (6)	0.093 (2)
H18A	1.344304	0.175459	0.136089	0.139*
H18B	1.398074	0.145882	0.242570	0.139*
H18C	1.257468	0.185218	0.221692	0.139*
C19	1.4901 (7)	0.2985 (9)	−0.4410 (4)	0.104 (3)
H19A	1.423724	0.361120	−0.482204	0.125*
H19B	1.566146	0.317293	−0.444200	0.125*
C20	1.4952 (6)	0.1724 (9)	−0.4276 (5)	0.104 (3)
H20A	1.574434	0.113229	−0.422357	0.124*
H20B	1.431980	0.157067	−0.460370	0.124*
C21	1.4611 (5)	0.2271 (5)	−0.3463 (4)	0.0593 (14)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
H21	1.374588	0.247099	−0.334202	0.071*
C22	1.5433 (4)	0.1932 (4)	−0.2572 (3)	0.0462 (12)
C23	1.6523 (4)	0.1064 (5)	−0.2446 (4)	0.0519 (13)
H23	1.676351	0.066866	−0.292428	0.062*
C24	1.7294 (4)	0.0748 (4)	−0.1619 (3)	0.0479 (12)
H24	1.803516	0.014971	−0.155392	0.058*
C25	1.6967 (4)	0.1307 (4)	−0.0918 (3)	0.0435 (11)
C26	1.5859 (5)	0.2244 (4)	−0.1003 (3)	0.0486 (12)
C27	1.5521 (6)	0.2886 (5)	−0.0296 (4)	0.0678 (16)
H27	1.603812	0.270458	0.024682	0.081*
C28	1.4432 (6)	0.3775 (6)	−0.0413 (5)	0.083 (2)
H28	1.420455	0.417751	0.006217	0.100*
C29	1.3670 (6)	0.4081 (6)	−0.1222 (5)	0.083 (2)
H29	1.293641	0.469059	−0.128989	0.099*
C30	1.3976 (5)	0.3503 (5)	−0.1923 (4)	0.0660 (16)
H30	1.345147	0.372983	−0.246850	0.079*
C31	1.5084 (4)	0.2559 (4)	−0.1840 (3)	0.0467 (12)
C32	1.7686 (5)	0.0260 (5)	0.0850 (4)	0.0554 (13)
C33	1.8753 (5)	0.1321 (4)	0.0026 (3)	0.0489 (12)
C34	2.0253 (5)	0.2659 (5)	−0.0326 (4)	0.0663 (15)
H34A	2.085713	0.192396	0.003863	0.080*
H34B	2.066765	0.313856	−0.079473	0.080*
C35	1.9647 (6)	0.3372 (5)	0.0373 (5)	0.0665 (16)
C36	1.9926 (7)	0.3760 (6)	0.1853 (5)	0.104 (3)
H36A	2.053495	0.352615	0.237062	0.156*
H36B	1.971436	0.462017	0.155679	0.156*
H36C	1.922060	0.354962	0.211324	0.156*

solution respectively, and dry the organic layer with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain a brownish yellow oil. Using ethyl acetate as eluent, the product was separated by rapid column chromatography, and the solvent was evaporated under reduced pressure to obtain light yellow solid product (35.9 g) with a yield of 73.5 %.

2 Experimental details

All H atoms were included in calculated positions and refined as riding atoms, with C–H = 0.90–0.97 Å with $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$ for methyl H atoms and $1.2 U_{\text{eq}}(\text{C})$ for all other H atoms.

3 Comment

Lesinurad sodium was first developed by Aread Biosciences and then continued to be developed by Astra Zeneca.⁵

Lesinurad sodium, whose chemical name is 2-[[5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4h-1,2,4-triazol-3-yl]thio]acetic acid, is the first inhibitor of uric acid selective reabsorption transporter-1 (URAT1). Lesinurad sodium is mainly used for treating hyperuricemia related to gout in combination with xanthine oxidase inhibitors (such as allopurinol and febuxostat).^{6–8} The optimization of the process of lesinurad sodium and its derivatives has attracted extensive attention of researchers.^{9–11} In order to make it more suitable for industrial production, we have been devoted to its synthesis and process optimization of lesinurad sodium. Recently, we reported the synthesis and crystal structures of two intermediates of lesinurad sodium.^{12,13} Herein we reveal the synthesis and crystal structure of the key intermediate of lesinurad sodium methyl 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetate.

In the molecules of the title structure, both bond lengths and angles are very similar to those given in the literature.^{12–14} In the asymmetric unit of the title compound, there are two molecules, molecule A and molecule B. In molecule A, the dihedral angles formed by the naphthalene ring plane, the 1,2,4-triazole plane and the cyclopropyl group plane are $51.7(4)^\circ$, $69.7(4)^\circ$, $79.3(2)^\circ$ and $63.5(1)^\circ$, respectively. The torsion angles of N1–C15–S1–C16, C15–S1–C16–C17, S1–C16–C17–O2, C16–C17–O2–C18, N4–C33–S2–C34, C33–S2–C34–C35, S2–C34–C35–O4 and C34–C35–O4–C36 are 177.4° , -75.6° , -178.1° , 179.3° , 167.2° , -64.2° , 148.8° and 179.8° , respectively. Intermolecular C–H...S hydrogen bonds connect two adjacent the title structures into a dimer. Dimers are further stabilized in the stacking structure by π – π stacking.

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

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