Li-Mei Jia, Peng Luo and Wei-Gao Pan*

Crystal structure of 2-chloro-3-((thiophen-2-ylmethyl)amino)naphthalene-1,4-dione, $C_{30}H_{20}O_4N_2Cl_2S_2$

Table 1: Data collection and handling.

Crystal:	Red block
Size:	0.35 × 0.29 × 0.21 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.44 mm ⁻¹
Diffraction, scan mode:	Bruker APEX3, φ and ω -scans
$\theta_{\max}$, completeness:	27.5°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	39,478, 6092, 0.060
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 4101
$N(\text{param})_{\text{refined}}$:	341
Programs:	Bruker programs [1], OLEX2 [2, 3], SUPERFLIP [4], EDMA [5, 6], SHELX [7]

of the atoms including atomic coordinates and displacement parameters.

Source of materials

2,3-Dichloro-1,4-naphthoquinone (0.22 mmol) and NaHCO_3 (0.44 mmol) were mixed uniformly and moved to a 100 mL double mouth flask. Thiophen-2-ylmethan-amine (0.22 mmol, dissolved with 40 mL of anhydrous methanol) was added to the above mixed solid to start reaction with magnetic stirring at 0 °C in anhydrous environment. The reaction process was monitored by TLC using petroleum ether (60–90 °C boiling range)/acetic ether (6:1 v/v) as developing phase. After 24 h, the reacting mixture was concentrated by a rotary evaporator (60 °C) to achieve a crude solid. This solid was subsequently dissolved in a mixed solvent of methanol-tetrahydrofuran to give a clear red solution after filtration, from which red flat crystals were obtained during the course of volatilization at room temperature. The melting point was determined as 411–412 K using a XT-4 melting point instrument (Beijing Taike Instrument Co., Ltd, China). NMR spectra were performed on a DRX-400 Bruker NMR spectrometer (Bruker, Germany). **HRAPCI-MS:** $[\text{M}+\text{H}]^+$ found 304.01892; $\text{C}_{15}\text{H}_{11}\text{O}_2\text{NClS}$ $[\text{M}+\text{H}]^+$ requires 304.01935. **^1H NMR** (400 MHz, CDCl_3) δ : [ppm] 8.15 (dd, $J = 7.6, 1.3$ Hz, 1H, H-4), 8.04 (dd, $J = 7.6, 1.4$ Hz, 1H, H-1), 7.73 (td, $J = 7.6, 1.4$ Hz, 1H, H-5), 7.64 (td, $J = 7.6, 1.3$ Hz, 1H, H-6), 7.29 (dd, $J = 5.1, 1.2$ Hz, 1H, H-15), 7.07 (dd, $J = 3.5, 1.2$ Hz, 1H, H-13), 7.00 (dd,

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Abstract

$\text{C}_{30}\text{H}_{20}\text{O}_4\text{N}_2\text{Cl}_2\text{S}_2$, Orthorhombic, $Pca2_1$, $a = 16.9808(14)$ Å, $b = 7.5227(6)$ Å, $c = 20.8027(16)$ Å, $V = 2657.4(4)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0642$, $wR_{\text{ref}}(F^2) = 0.1809$, $T = 293$ K.

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One of the two crystallographically independent molecules of the title crystal structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list

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

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
Cl1	−0.19535 (13)	0.0023 (2)	−0.08712 (12)	0.0551 (6)
S1A ^a	−0.4205 (4)	0.4825 (8)	−0.1413 (3)	0.0572 (9)
S1B ^b	−0.3088 (4)	0.3830 (7)	−0.0421 (2)	0.0572 (9)
O1	−0.2790 (3)	0.2241 (7)	−0.3049 (2)	0.0509 (12)
O2	−0.0461 (3)	0.0888 (9)	−0.1424 (3)	0.0714 (17)
N1	−0.3209 (3)	0.1229 (7)	−0.1912 (3)	0.0392 (12)
H1	−0.348883	0.099891	−0.224556	0.047*
C1	−0.1265 (3)	0.3137 (6)	−0.3464 (2)	0.0484 (17)
H1A	−0.167155	0.337263	−0.375116	0.058*
C2	−0.14331 (19)	0.2425 (6)	−0.2863 (2)	0.0398 (17)
C3	−0.0826 (2)	0.2073 (6)	−0.2433 (2)	0.0443 (17)
C4	−0.0051 (2)	0.2432 (6)	−0.2604 (3)	0.064 (2)
H4	0.035524	0.219673	−0.231691	0.076*
C5	0.0117 (2)	0.3145 (7)	−0.3206 (3)	0.075 (3)
H5	0.063524	0.338538	−0.332028	0.090*
C6	−0.0490 (3)	0.3497 (7)	−0.3635 (2)	0.068 (2)
H6	−0.037815	0.397334	−0.403741	0.081*
C7	−0.2253 (3)	0.2047 (7)	−0.2686 (3)	0.0354 (14)
C8	−0.2425 (3)	0.1411 (7)	−0.2011 (3)	0.0307 (12)
C9	−0.1820 (4)	0.1018 (8)	−0.1612 (3)	0.0381 (14)
C10	−0.0999 (4)	0.1308 (8)	−0.1789 (4)	0.0454 (16)
C11	−0.3637 (4)	0.1380 (9)	−0.1299 (3)	0.0391 (14)
H11A	−0.339189	0.060979	−0.098350	0.047*
H11B	−0.417472	0.097800	−0.136060	0.047*
C12	−0.3646 (3)	0.3238 (9)	−0.1049 (3)	0.0389 (16)
C13A ^a	−0.3055 (17)	0.421 (3)	−0.0564 (12)	0.0572 (9)
H13A ^a	−0.260820	0.371588	−0.037770	0.069*
C13B ^b	−0.4039 (16)	0.465 (3)	−0.1255 (11)	0.0572 (9)
H13B ^b	−0.440066	0.458116	−0.158958	0.069*
C14	−0.3325 (5)	0.5899 (12)	−0.0472 (5)	0.069 (2)
H14 ^a	−0.315837	0.664645	−0.014319	0.082*
H14A ^b	−0.309934	0.674803	−0.020466	0.082*
C15	−0.3865 (5)	0.6346 (13)	−0.0919 (5)	0.072 (3)
H15 ^a	−0.404455	0.751174	−0.094774	0.086*
H15A ^b	−0.407988	0.746210	−0.099887	0.086*
Cl2	−0.05384 (12)	0.9930 (2)	−0.47863 (11)	0.0534 (6)
S2A ^c	0.0555 (5)	0.5925 (11)	−0.5214 (5)	0.0483 (7)
S2B ^d	0.17186 (17)	0.5038 (3)	−0.42562 (17)	0.0483 (7)
O3	0.0315 (3)	0.7682 (7)	−0.2609 (2)	0.0526 (13)
O4	−0.2030 (3)	0.9040 (8)	−0.4229 (3)	0.0653 (15)
N2	0.0727 (3)	0.8673 (7)	−0.3768 (3)	0.0413 (12)
H2	0.101284	0.890664	−0.343725	0.050*
C16	−0.1210 (2)	0.6810 (6)	−0.21950 (19)	0.0477 (17)
H16	−0.080097	0.655324	−0.191214	0.057*
C17	−0.10454 (18)	0.7534 (5)	−0.2795 (2)	0.0365 (15)
C18	−0.1656 (2)	0.7918 (5)	−0.32177 (18)	0.0411 (16)
C19	−0.2431 (2)	0.7578 (6)	−0.3041 (2)	0.053 (2)
H19	−0.283933	0.783530	−0.332339	0.064*
C20	−0.2595 (2)	0.6854 (6)	−0.2441 (3)	0.062 (2)
H20	−0.311327	0.662666	−0.232203	0.074*
C21	−0.1984 (3)	0.6470 (6)	−0.2018 (2)	0.059 (2)
H21	−0.209410	0.598562	−0.161640	0.071*
C22	−0.0223 (4)	0.7878 (8)	−0.2975 (3)	0.0352 (14)
C23	−0.0053 (3)	0.8517 (7)	−0.3653 (3)	0.0334 (13)
C24	−0.0672 (4)	0.8932 (8)	−0.4045 (3)	0.0382 (14)

Table 2: (continued)

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
C25	−0.1492 (3)	0.8664 (8)	−0.3866 (3)	0.0407 (15)
C26	0.1156 (4)	0.8500 (9)	−0.4376 (3)	0.0418 (15)
H26A	0.169278	0.890456	−0.431589	0.050*
H26B	0.091109	0.925967	−0.469581	0.050*
C27	0.1167 (3)	0.6627 (10)	−0.4622 (2)	0.0401 (16)
C28A ^c	0.142 (2)	0.510 (2)	−0.4309 (10)	0.0483 (7)
H28A ^c	0.157516	0.508141	−0.388066	0.058*
C29	0.1409 (5)	0.3505 (10)	−0.4730 (4)	0.059 (2)
H29 ^d	0.157910	0.233581	−0.468600	0.071*
H29A ^c	0.168864	0.244904	−0.468470	0.071*
C28B ^d	0.0812 (7)	0.5920 (13)	−0.5164 (6)	0.0483 (7)
H28B ^d	0.054888	0.658046	−0.547458	0.058*
C30	0.0911 (5)	0.3955 (9)	−0.5179 (4)	0.064 (2)
H30 ^d	0.065959	0.317940	−0.546068	0.077*
H30A ^c	0.075901	0.311728	−0.548380	0.077*

^aOccupancy: 0.501(6), ^bOccupancy: 0.499(6), ^cOccupancy: 0.209(6), ^dOccupancy: 0.791(6).

J = 5.1, 3.5 Hz, 1H, H-14), 6.19 (s, 1H, N-H), 5.23 (d, *J* = 6.1 Hz, 2H, H-11). ¹³C NMR (101 MHz, CDCl₃) δ: [ppm] 180.3 (C-10), 176.9 (C-7), 143.6 (C-8), 140.2 (C-12), 134.9 (C-6), 132.6 (C-5), 132.5 (C-3), 129.8 (C-2), 127.2 (C-15), 126.9 (C-1), 126.5 (C-4, 13), 125.9 (C-14), C-9 (signal absence), 43.7 (C-11).

Experimental details

Using Olex2 [2], the structure was solved with the olex2.solve [3] structure solution program using Charge Flipping and refined with the SHELXL [7] refinement package using Least Squares minimization. The H atoms were placed in idealized positions and treated as riding on their parent atoms, with d(C-H) = (0.97) Å (methylene), *U*_{iso}(H) = 1.2*U*_{eq}(C), d(C-H) = (0.93) Å (aromatic), *U*_{iso}(H) = 1.2*U*_{eq}(C), and d(N-H) = (0.86) Å, *U*_{iso}(H) = 1.2*U*_{eq}(N).

Comment

Derivatives with similar structure to that of the title compound have been reported to possess various bioactivities: 2-chloro-3-((furan-2-ylmethyl)amino)-1,4-naphthoquinone showed high antifungal activity against *Candida albicans* and *Aspergillus niger*, while 2-chloro-3-((pyridin-2-ylmethyl) or (pyridin-3-ylmethyl) amino)-1,4-naphthoquinone manifested excellent activity against gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) [8]. The compound 2-chloro-3-(benzylamino)-naphthalene-1,4-dione is one of the best performing multitarget-directed molecules in the

anti-Alzheimer's Disease agents screening, which experienced a high potency profile in inhibiting β -amyloid ($A\beta_{40}$) aggregation, PHF6 tau fragment, AChE enzyme jointly with a remarkable inhibitory activity against MAO B [9]. It also had some effect on neutrophil degranulation in anti-inflammatory investigation and significant inhibitory effect on mast cell degranulation in antiallergic assay [10]. In our group, the title compound was synthesized for anti-cancer assay and further to investigate its interactions with Caspase-3 and Topoisomerase-II α/β , so it is necessary to study the single crystal structure.

The asymmetric unit of the title structure contains two molecules 2-chloro-3-((thiophen-2-ylmethyl)amino)naphthalene-1,4-dione, in which the thiophene moieties are disordered, but all other values of the geometric parameters are normal. The crystal packing is stabilized by intermolecular hydrogen bonds: $N1-H1\cdots O3$ ($d(N1-H1\cdots O3) = 3.010 \text{ \AA}$; $\angle N1-H1\cdots O3 = 130^\circ$), $N2-H2A\cdots O1$ ($d(N2-H2A\cdots O1) = 3.008 \text{ \AA}$; $\angle N2-H2A\cdots O1 = 133^\circ$).

By a search for a similar molecular scaffold three similar compounds, 2-chloro-3-((2-thienylethyl) amino)-1,4-naphthoquinone [11], 2-bromo-3-((2-thienylmethyl)amino)-1,4-na-phthoquinone [12] and 2-chloro-3-((2-furylmethyl) amino)-1,4-naphthoquinone [8] were found, in which, the first one owned one more methylene than the title compound at the fatty-thienyl moiety [11], the second one was not 2-chloro but 2-bromo substituent [12], while the third one had a furan ring instead of the thienyl group in the title compound [8]. Furthermore, amazing difference among them was the number of molecules in the asymmetric unit of crystal structure, the three reported crystals had only one molecule in their asymmetric units [8, 11, 12].

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