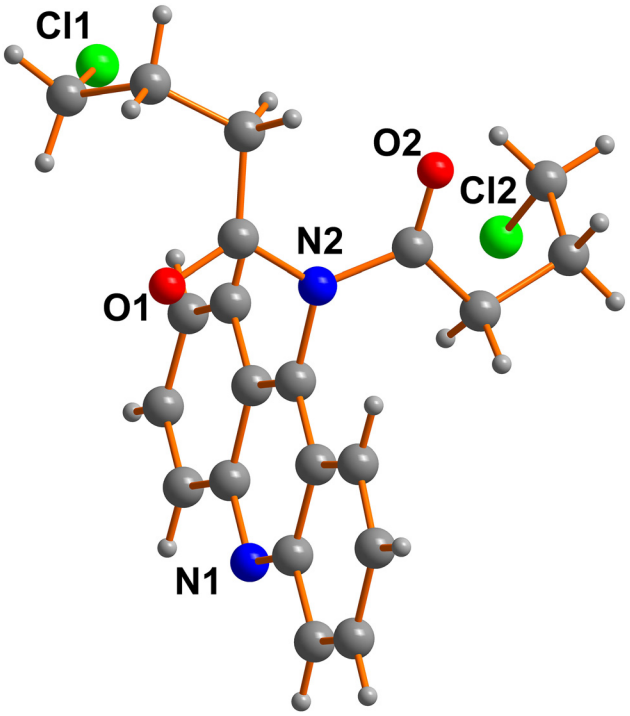
Dan Zhou, Chen Yang Jing, Hong-ji Li, Xinyi Zhang, Pei Rong Zhao and Wen Li*

The crystal structure of *N*-(acridin-9-yl)-4-chloro-*N*-(4-chloro-butanoyl) butanamide, $C_{21}H_{20}Cl_2N_2O_2$



https://doi.org/10.1515/ncrs-2024-0090
Received February 26, 2024; accepted March 27, 2024;
published online April 22, 2024

Abstract

$C_{21}H_{20}Cl_2N_2O_2$, orthorhombic, $P2_1$ (no. 4), a = 8.3667(14) Å, b = 15.444(3) Å, c = 15.105(2) Å, V = 1951.9(6) Å^3, Z = 4, $R_{gt}(F)$ = 0.0481, $wR_{ref}(F^2)$ = 0.1574, T = 292 K.

CCDC no.: 2325358

The molecular structure is shown in the figure. 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:	0.12 × 0.10 × 0.08 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.35 mm^{-1}
Diffractometer, scan mode:	Bruker D8 quest, Φ and ω
θ_{max}, completeness:	25.1°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	23412, 3413, 0.066
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2328
$N(param)_{refined}$:	244
Programs:	SHELX [1, 2]

1 Source of materials

The 9-aminoacridine (0.97 g, 5 mmol) and triethylamine (2.75 ml, 25 mmol) was initially added to 15 mL tetrahydrofuran. Subsequently, the 4-chloro-butyryl chloride (3.5 ml, 25 mmol) was slowly added to the reaction mixture and continued stirring for 120 min at 0 °C. The solvent was removed under reduced pressure and the solid product was dissolved in ethyl acetate. The solids were removed by vacuum filtration, and the filtrate was washed with 100 ml sodium carbonate solution (10 %). The ethyl acetate was removed under reduced pressure to give a solid-liquid mixture. The pure product was obtained by washing the above mixture with ethanol. The solid product was recrystallized from 10 mL of anhydrous diethyl ether. Colorless block crystals were obtained after one day.

***Corresponding author: Wen Li**, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, People's Republic of China; and Henan Province Collaborative Innovation Center of New Drug Research and Safety Evaluation, Ministry of Education, Key Laboratory of Advanced Drug Preparation Technologies and Key Laboratory of Henan Province for Drug Quality and Evaluation, Zhengzhou, People's Republic of China, E-mail: liwen@zzu.edu.cn

Dan Zhou, Chen Yang Jing, Hong-ji Li and Xinyi Zhang, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, People's Republic of China, E-mail: xiaozhou9468326@163.com (D. Zhou), j18272681059@163.com (C.Y. Jing), lhj1551615@163.com (H.-j. Li), 2036324275@qq.com (X. Zhang). https://orcid.org/0009-0002-4425-0311 (D. Zhou). https://orcid.org/0009-0007-1420-4468 (C.Y. Jing)

Pei Rong Zhao, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, People's Republic of China; and Henan Province Collaborative Innovation Center of New Drug Research and Safety Evaluation, Ministry of Education, Key Laboratory of Advanced Drug Preparation Technologies and Key Laboratory of Henan Province for Drug Quality and Evaluation, Zhengzhou, People's Republic of China, E-mail: 2431766265@qq.com

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.6711 (6)	0.4913 (4)	0.3678 (4)	0.0442 (14)
C2	0.7409 (6)	0.4072 (5)	0.3575 (4)	0.0526 (16)
H2	0.7835	0.3911	0.3030	0.063*
C3	0.7453 (9)	0.3515 (5)	0.4257 (5)	0.068 (2)
H3	0.7923	0.2974	0.4181	0.082*
C4	0.6797 (9)	0.3736 (4)	0.5090 (5)	0.0616 (17)
H4	0.6813	0.3335	0.5549	0.074*
C5	0.6148 (7)	0.4528 (4)	0.5226 (4)	0.0491 (14)
H5	0.5735	0.4670	0.5779	0.059*
C6	0.6095 (6)	0.5142 (4)	0.4530 (3)	0.0386 (13)
C7	0.5448 (6)	0.5973 (4)	0.4615 (3)	0.0376 (12)
C8	0.5409 (6)	0.6541 (4)	0.3907 (3)	0.0377 (13)
C9	0.6023 (6)	0.6239 (4)	0.3081 (4)	0.0423 (14)
C10	0.5968 (8)	0.6809 (5)	0.2346 (4)	0.0618 (18)
H10	0.6344	0.6620	0.1800	0.074*
C11	0.5390 (9)	0.7606 (5)	0.2422 (5)	0.0691 (18)
H11	0.5367	0.7967	0.1929	0.083*
C12	0.4809 (7)	0.7913 (5)	0.3247 (4)	0.0592 (17)
H12	0.4431	0.8478	0.3293	0.071*
C13	0.4798 (7)	0.7399 (4)	0.3962 (4)	0.0495 (15)
H13	0.4390	0.7603	0.4495	0.059*
C14	0.6006 (8)	0.6511 (4)	0.6079 (4)	0.0449 (14)
C15	0.5592 (8)	0.6531 (4)	0.7040 (4)	0.0545 (16)
H15A	0.5076	0.5989	0.7194	0.065*
H15B	0.4826	0.6992	0.7140	0.065*
C16	0.6994 (8)	0.6665 (5)	0.7648 (4)	0.069 (2)
H16A	0.7433	0.7235	0.7532	0.083*
H16B	0.6600	0.6665	0.8252	0.083*
C17	0.8327 (9)	0.6021 (6)	0.7589 (5)	0.089 (3)
H17A	0.9078	0.6127	0.8066	0.106*
H17B	0.8889	0.6104	0.7033	0.106*
C18	0.3174 (6)	0.6122 (4)	0.5648 (4)	0.0409 (13)
C19	0.2226 (7)	0.5734 (4)	0.4906 (4)	0.0495 (16)
H19A	0.2826	0.5259	0.4649	0.059*
H19B	0.2070	0.6167	0.4449	0.059*
C20	0.0600 (7)	0.5401 (4)	0.5213 (5)	0.0566 (16)
H20A	0.0049	0.5864	0.5520	0.068*
H20B	−0.0031	0.5252	0.4696	0.068*
C21	0.0679 (8)	0.4628 (4)	0.5811 (5)	0.0649 (18)
H21A	−0.0387	0.4491	0.6022	0.078*
H21B	0.1337	0.4764	0.6321	0.078*
Cl1	0.7649 (3)	0.49210 (16)	0.76526 (16)	0.1020 (8)
Cl2	0.1495 (3)	0.37042 (12)	0.52476 (13)	0.0849 (7)
N1	0.6671 (5)	0.5444 (3)	0.2977 (3)	0.0474 (12)
N2	0.4833 (5)	0.6220 (3)	0.5474 (3)	0.0393 (10)
O1	0.7312 (5)	0.6686 (3)	0.5794 (3)	0.0584 (12)
O2	0.2596 (5)	0.6349 (3)	0.6340 (3)	0.0555 (11)

2 Experimental details

The structure was solved by Direct Methods and refined with the SHELX [1, 2] crystallographic software package. Hydrogen atoms were placed in their geometrically idealized positions and constrained to ride on their parent atoms. The crystal structure was visualized by OLEX2 software package.

3 Comment

The monosubstituted derivatives of 9-aminacridine have good activity as LSD1 inhibitors [3]. In order to investigate the inhibitory activity of 9-aminoacridine bissubstituted derivatives on LSD1, we synthesized a series of compounds, one of which is the title compound. Due to the imide isomeric form of 9-aminoacridine, the location of acylation of the title compound cannot be determined by Nuclear Magnetic Resonance [4, 5]. Single crystal diffraction is an effective and intuitive method for determining the structure of compounds [6–8].

In the structure of acridine dibutyrylation products, all geometric parameters of the title compound are in the normal range. The asymmetric unit contains 4 molecules of title compound. The dihedral angle between the plane of acridine skeleton and the plane of C14–N2–C18 was determined as 83.5°, which is nearly perpendicular. The dihedral angle formed by the plane of N2–C14–C15 and the plane of N2–C18–C19 is 18.2°. Crystal structures of many aminoacridine compounds have been reported [9–11]. N-(acridin-9-yl)-2-(4-methylpiperidin-1-yl) acetamide (CCDC no. 2325357) has the similar chemical structure to the title compound [10]. The structural difference between the two compounds is that the title compound is a diacylation product, while the other is a monoacetylation product. In addition, the difference in crystal structure between the two compounds lies in the bond length and bond angle of the C–N bond formed by the amino group on the acridine moieties. The C–N bond lengths of the title compound are 1.448 Å(C7–N2) and 1.415 Å (N2–C14), and that of N-(acridin-9-yl)-2-(4-methylpiperidin-1-yl) acetamide are 1.420 Å (C7–N2) and 1.346 Å (N2–C14). The bond angles of the title compound and N-(acridin-9-yl)-2-(4-methylpiperidin-1-yl) acetamide are 114.6° (C7–N2–C14) and 124.4° (C7–N2–C14), respectively.

Acknowledgments: The Analysis and Testing Center of Zhengzhou University is acknowledged for the single crystal X-ray diffraction facility.

Author contributions: The synthesis of compounds and crystal preparation were completed by Dan Zhou, while the data analysis, writing and revision of the paper were

completed by Chen–Yang Jing, Dan Zhou and Yu–Qian Kan; supervision, Wen Li. All authors have read and agreed to the published version of the manuscript.

Competing interests: The authors declare no conflicts of interest regarding this article.

Research funding: This work was supported by the Key Technologies R & D Program of Henan Province of China (No. 222102310279 for WL) and Sinopharm Scholarship of Zhengzhou University (For XYZ).

References

1. Sheldrick G. M. *SHELXTL*-integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, *A71*, 3–8.
2. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
3. Dai X.-J., Liu Y., Wang N., Chen H.-X., Wu J.-W., Xiong X.-P., Ji S.-K., Zhou Y., Shen L., Wang S.-P., Liu H.-M., Liu H.-M., Zheng Y.-C. Novel acridine-based LSD1 inhibitors enhance immune response in gastric cancer. *Eur. J. Med. Chem.* 2023, *259*, 115684.
4. Krzyminski K., Zadykowicz B., Storoniak P., Wera M., Zamojc K. Tautomerism of *N*-substituted acridin-9-amines in the context of dynamic NMR and matrix isolation–FT–IR spectroscopy supported by DFT calculations and structural analysis. *J. Mol. Struct.* 2020, *1218*, 128424.
5. Stanovnik B., Tisler M., Katritzky A. R., Denisko O. V. The tautomerism of heterocycles: substituent tautomerism of six-membered ring heterocycles. *Adv. Heterocycl. Chem.* 2006, *91*, 1–134.
6. Chang Y.-J., Ding Y.-M., Zhu L.-Y., Liu H.-M., Li W. Crystal structure of {tetraaqua-bis(1-(4-hydroxy-2-oxotetrahydrofuran-3-yl)-2-((4a*S*,6*R*,8a*S*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethane-1-sulfonato-κ^2O,O') calcium(II)}–{triaqua-bis(1-(4-hydroxy-2-oxotetrahydrofuran-3-yl)-2-((4a*S*,6*R*,8a*S*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethane-1-sulfonato-κ^2O,O') calcium(II)} – water – acetone (1/1/8/2), $C_{43}H_{78}CaO_{22}S_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 87–91.
7. Ding Y.-M., Li R.-P., Chang Y.-J., Zhao J., Liu H.-M., Li W. Crystal structure of triaqua-bis(2-(6-hydroxy-5-(hydroxymethyl)-5,8*a*-dimethyl-2-methylenedecahydronaphthalen-1-yl)-1-(2-oxo-2,5-dihydrofuran-3-yl)ethane-1-sulfonato-κ^2O,O')calcium(II)– ethanol (1/2), $C_{44}H_{76}CaO_{19}S_2$. *Z. Kristallogr. N. Cryst. Struct.* 2020, *235*, 515–517.
8. Fang Z.-Y., Zhang B.-X., Xing W.-H., Jia H.-L., Wang X., Gong N.-B., Lu Y., Du G.-H. A series of stable, metastable and unstable salts of Imatinib with improved solubility. *Chin. Chem. Lett.* 2022, *33*, 2159–2164.
9. Seeman N. C., Day R. O., Rich A. Nucleic acid-mutagen interactions: crystal structure of adenylyl-3′,5′-uridine plus 9-aminoacridine. *Nature* 1975, *253*, 324–327.
10. Jing C.-Y., Zhou D., Kan Y.-Q., Zhao P.-R., Li W. Crystal structure of *N*-(acridin-9-yl)-2-(4-methylpiperidin-1-yl) acetamide monohydrate, $C_{21}H_{25}N_3O_2$. *Z. Kristallogr. N. Cryst. Struct.* 2024, *239*, 469–471.
11. Leardini R., McNab H., Nanni D., Parsons S., Reed D., Tenan A. G. Gas-phase cyclisation reactions of 1-(2-arylaminophenyl)alkaniminyl radicals. *J. Chem. Soc., Perkin Trans.* 1998, *1*, 1833–1838.