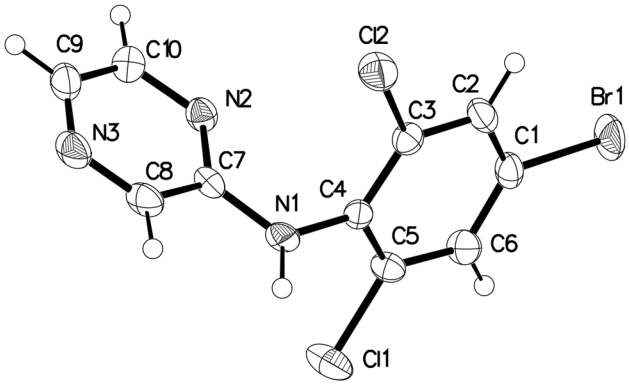
Zhoujing Zhu, Bin Liu* and Xiaona Xu

Crystal structure of *N*-(4-bromo-2,6-dichlorophenyl)pyrazin-2-amine, $C_{10}H_6BrCl_2N_3$



https://doi.org/10.1515/ncrs-2022-0017
Received January 15, 2022; accepted February 21, 2021;
published online March 7, 2022

Abstract

$C_{10}H_6BrCl_2N_3$, monoclinic, $P2_1/c$ (no. 14), a = 9.2229(13) Å, b = 14.709(2) Å, c = 8.6472(13) Å, β = 104.851(3)°, V = 1133.9(3) Å^3, Z = 4, $R_{gt}(F)$ = 0.0312, $wR_{ref}(F^2)$ = 0.0839, T = 173 K.

CCDC no.: 1974803

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:	0.19 × 0.12 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	4.07 mm^{-1}
Diffractometer, scan mode:	φ and ω
θ_{max}, completeness:	27.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	10,023, 2604, 0.038
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 2049
$N(param)_{refined}$:	145
Programs:	Bruker [1], Olex2 [2], SHELX [3, 4]

Source of material

A mixture of 3-((4-bromo-2,6-dichlorophenyl) amino) pyrazine-2-carbonitrile (344 mg) and concentrated sulfuric acid (5 mL) was stirred in ethanol (50 mL) at 80 °C for 24 h (monitored by TLC). After the reaction was completed, the crude reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried and then concentrated to dryness under reduced pressure. The title compound was separated by silica-gel column chromatography with ethyl acetate-petroleum ether (10%) gradient solvent system. Suitable crystals of the title molecule were attained by crystallization in the petroleum ether and ethyl acetate (10:1, *v*/*v*) system and dried at room temperature.

Experimental details

All the H atoms of carbon were included using a riding-model, with C–H = 0.95 Å and C-N = 0.88 Å, respectively, and their U_{iso} = 1.2 U_{eq} (parent atom).

Comment

2-Benzylpyrazine derivatives were designed as a novel structure and core architecture for human carbonic anhydrase-II (hCA-II) inhibitors, which were important in developing antiglaucoma drugs [5]. Factually, many potent and effective hCA-II inhibitors were designed by introducing different substituents in sulphonamides [5–10]. However, sulphonamide compounds non-selectively target on carbonic anhydrase, and in this way increase many undesired adverse effects, like gastrointestinal irritations, numbness, depression, fatigue, renal calculi, depression [5, 11–14]. Therefore, it is still a hot research topic on developing potent

***Corresponding author: Bin Liu**, Xianyang Key Laboratory of Molecular Imaging and Drug Synthesis, School of Pharmacy, Shaanxi Institute of International Trade & Commerce, Xianyang, Shaanxi, China, E-mail: lb125lb@163.com. https://orcid.org/0000-0003-2852-7739
Zhoujing Zhu, Xianyang Key Laboratory of Molecular Imaging and Drug Synthesis, School of Pharmacy, Shaanxi Institute of International Trade & Commerce, Xianyang, Shaanxi, China
Xiaona Xu, School of Pharmaceutical & Chemical Engineering, Xianyang Vocational Technical College, Xianyang, Shaanxi, China

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.99403 (3)	0.63793 (2)	0.44560 (4)	0.04282 (13)
C1	0.8329 (3)	0.6744 (2)	0.5307 (3)	0.0279 (6)
C2	0.8049 (2)	0.76616 (18)	0.5405 (3)	0.0275 (6)
H2	0.866507	0.810214	0.508149	0.033*
C3	0.6848 (2)	0.79229 (17)	0.5988 (3)	0.0240 (5)
C4	0.5904 (2)	0.72944 (17)	0.6448 (3)	0.0209 (5)
C5	0.6239 (3)	0.63829 (17)	0.6328 (3)	0.0250 (5)
C6	0.7456 (3)	0.60910 (18)	0.5784 (3)	0.0281 (6)
H6	0.768056	0.546255	0.574163	0.034*
C7	0.3534 (2)	0.81010 (16)	0.6170 (3)	0.0220 (5)
C8	0.2536 (3)	0.85180 (18)	0.6940 (3)	0.0322 (6)
H8	0.267999	0.842969	0.805796	0.039*
C9	0.1253 (3)	0.91259 (19)	0.4594 (4)	0.0366 (7)
H9	0.044873	0.948235	0.398584	0.044*
C10	0.2225 (3)	0.87269 (18)	0.3837 (3)	0.0312 (6)
H10	0.207684	0.882206	0.272064	0.037*
Cl1	0.51121 (8)	0.55647 (5)	0.68725 (9)	0.04195 (19)
Cl2	0.65617 (7)	0.90748 (5)	0.61843 (9)	0.03730 (18)
N1	0.4693 (2)	0.75760 (14)	0.7049 (2)	0.0258 (5)
H1	0.467541	0.741014	0.802171	0.031*
N2	0.3383 (2)	0.82052 (15)	0.4615 (2)	0.0255 (4)
N3	0.1404 (2)	0.90283 (16)	0.6159 (3)	0.0381 (6)

and specific hCA-II inhibitors based on novel scaffolds like 2-benzylpyrazine.

The asymmetric unit of the title structure consists of one molecule. As displayed in the Figure, the 4-bromo-2,6-dichlorophenyl moiety is strictly planar. A chain motif was created by a weak hydrogen bond (N–H···N, 2.232 Å) formed by the N1 atom and N2 atom of the adjacent molecule, which is the same as in similar crystal structures like *N*-(pyrazin-2-yl) aniline [15], 4-chloro-*N*-(pyrazin-2-yl) aniline [16]. Compared to these similar crystal structures, the dihedral angle between the aromatic rings is increased to 75.5(4)°, and the bridging C4–N1–C7 angle is decreased to 122.5(2)°, due to the introduction of chlorine and bromine substituents.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: This study was supported by the Natural Science Foundation of Shaanxi Province (2021JM-540, 2021JQ-885), Key Breeding Program by Collaborative Innovation Center of Green Manufacturing Technology for Traditional Chinese Medicine in Shaanxi Province (2019XT-1-05, 2019XT-2-05) and Key Laboratory of Molecular Imaging and Drug Synthesis of Xianyang City (2021QXNL-PT-0008).

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

References

1. Bruker. Smart Apex-II; CCD Bruker AXS Inc.: Madison, WI, USA, 2006.
2. Dolomanov O. V., Bourhis L. J., Gildea R. J., Howard J. A. K., Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* 2009, *42*, 339–341.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Sheldrick G. M. *SHELXTL* – integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, *A71*, 3–8.
5. Ghorai S., Pulya S., Ghosh K., Panda P., Ghosh B., Gayen S. Structure-activity relationship of human carbonic anhydrase-II inhibitors: detailed insight for future development as anti-glaucoma agents. *Bioorg. Chem.* 2020, *95*, 103557.
6. Bilginer S., Gonder B., Gul H. I., Kaya R., Gulcin I., Anil B., Supuran C. T. Novel sulphonamides incorporating triazene moieties show powerful carbonic anhydrase I and II inhibitory properties. *J. Enzym. Inhib. Med. Chem.* 2020, *35*, 325–329.
7. Wani T. V., Bua S., Khude P. S., Chowdhary A. H., Supuran C. T., Toraskar M. P. Evaluation of sulphonamide derivatives acting as inhibitors of human carbonic anhydrase isoforms I, II and Mycobacterium tuberculosis β-class enzyme Rv3273. *J. Enzym. Inhib. Med. Chem.* 2018, *33*, 962–971.
8. Kurt B. Z., Sönmez F., Bilen Ç., Ergun A., Gençer N., Arslan O., Kucukislamoglu M. Synthesis, antioxidant and carbonic anhydrase I and II inhibitory activities of novel sulphonamide-substituted coumarylthiazole derivatives. *J. Enzym. Inhib. Med. Chem.* 2016, *31*, 991–998.
9. Kumar R., Sharma V., Bua S., Supuran C. T., Sharma P. K. Synthesis and biological evaluation of benzenesulphonamide-bearing 1,4,5-trisubstituted-1,2,3-triazoles possessing human carbonic anhydrase I, II, IV, and IX inhibitory activity. *J. Enzym. Inhib. Med. Chem.* 2017, *32*, 1187–1194.
10. Ekinci D., Kurbanoglu N. I., Salamci E., Şentürk M., Supuran C. T. Carbonic anhydrase inhibitors: inhibition of human and bovine isoenzymes by benzenesulphonamides, cyclitols and phenolic compounds. *J. Enzym. Inhib. Med. Chem.* 2012, *27*, 845–848.
11. Mincione F., Scozzafava A., Supuran C. T. The development of topically acting carbonic anhydrase inhibitors as antiglaucoma agents. *Curr. Pharmaceut. Des.* 2008, *14*, 649–654.

12. Sağlık B. N., Çevik U. A., Osmaniye D., Levent S., Çavuşoğlu B. K., Demir Y., Ilgın S., Özkay Y., Koparal A. S., Beydemir Ş., Kaplancıklı Z. A. Synthesis, molecular docking analysis and carbonic anhydrase I-II inhibitory evaluation of new sulfonamide derivatives. *Bioorg. Chem.* 2019, *91*, 103153.
13. Lomelino C. L., Supuran C. T., McKenna R. Non-classical inhibition of carbonic anhydrase. *Int. J. Mol. Sci.* 2016, *17*, 1150.
14. Sugrue M. F. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Prog. Retin. Eye Res.* 2000, *19*, 87–112.
15. Wan Saffiee W. A., Idris A., Abdullah Z., Aiyub Z., Ng S. W. *N*-(Pyrazin-2-yl)aniline. *Acta Crystallogr.* 2008, *E64*, o2105.
16. Wan Saffiee W. A., Idris A., Aiyub Z., Abdullah Z., Ng S. W. 4-Chloro-*N*-(pyrazin-2-yl)aniline. *Acta Crystallogr.* 2008, *E65*, o113.