Bo Fang, Jiang Ping Meng* and Lin Ling Gan*

Crystal structure of methyl 2-(4-(3-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate, C₁₉H₁₇N₅O₂

<https://doi.org/10.1515/ncrs-2018-0580>

Received December 12, 2018; accepted February 1, 2019; available online February 21, 2019

Abstract

C₁₉H₁₇N₅O₂, monoclinic, *C*2/*c* (no. 15), *a* = 14.734(6) Å, *b* = 13.565(5) Å, *c* = 33.385(12) Å, β = 91.311(9)°, *V* = 6671(4) Å³, *Z* = 16, *R*_{gt}(*F*) = 0.0638, *wR*_{ref}(*F*²) = 0.1783, *T* = 293(2) K.

CCDC no.: 1895023

Title crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

A suspension of methyl 2-(4-(3-bromopyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate (692 mg, 2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (416 mg, 2 mmol), potassium phosphate (636 mg,

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.33 × 0.29 × 0.25 mm
Wavelength:	Mo <i>K</i> α radiation (0.71073 Å)
μ:	0.09 mm ^{−1}
Diffractometer, scan mode:	APEX2, φ and ω
θ _{max} , completeness:	25.0°, >99%
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} , <i>R</i> _{int} :	16687, 5862, 0.090
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ(<i>I</i> _{obs}), 2559
<i>N</i> (<i>param</i>) _{refined} :	470
Programs:	Bruker [1], SHELX [2, 3], Olex2 [4]

3 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (146 mg, 0.2 mmol) in dioxane (5 mL) and water (1 mL) was sealed, degassed by nitrogen and heated under microwave irradiation at 120 °C for 30 min. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water and brine. The organic phase was dried over MgSO₄ and concentrated. The raw product was purified by column chromatography over silica gel eluting with a gradient of methanol/dichloromethane (*v/v*, 0–3%) to afford the light yellow solid. Yield, 437 mg, 63%. The title compound was dissolved in dichloromethane, and the solvent was evaporated slowly at room temperature. After three days, light yellow crystals suitable for X-ray diffraction analysis were obtained.

Experimental details

Data reduction was carried out using the Bruker software APEX2 including SADABS [1]. The structure was determined by the intrinsic phasing routines in the SHELXT program [2] and refined by full-matrix least-squares methods in SHELXL [3] using Olex2 [4]. All of hydrogen atoms were placed in the calculated positions and all the non-hydrogen atoms were refined anisotropically. The *R*¹ factor for all reflections and the *R*_{int} factor are both enlarged, as the ratio of observed/unique reflections is low (44%).

Comment

Pyrazolo[1,5-*a*]pyrimidine scaffold, as a multifunctional structure, is widely used in organic chemistry, drug synthesis

*Corresponding authors: **Jiang Ping Meng**, Chongqing Engineering Laboratory of Targeted and Innovative Therapeutics, Chongqing Key Laboratory of Kinase Modulators as Innovative Medicine, IATTI, Chongqing University of Arts and Sciences, Chongqing 402160, P.R. China, e-mail: mengjp2006@163.com; and **Lin Ling Gan**, Chongqing Engineering Research Center of Pharmaceutical Sciences, School of Pharmacy, Chongqing Medical and Pharmaceutical College, Chongqing 401331, P.R. China, e-mail: ganlinling2012@163.com

Bo Fang: Chongqing Engineering Laboratory of Targeted and Innovative Therapeutics, Chongqing Key Laboratory of Kinase Modulators as Innovative Medicine, IATTI, Chongqing University of Arts and Sciences, Chongqing 402160, P.R. China

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}
N1	0.4448(2)	0.33592(19)	0.07507(8)	0.0540(8)
N2	0.4320(2)	0.49946(19)	0.05008(8)	0.0477(7)
N3	0.4535(2)	0.59353(19)	0.05963(9)	0.0577(8)
N4	0.5978(3)	0.3698(2)	0.19686(10)	0.0705(10)
N5	0.6424(3)	0.4561(3)	0.19987(10)	0.0793(11)
N6	0.2956(2)	0.9128(2)	−0.05457(8)	0.0508(8)
N7	0.3419(2)	0.75185(19)	−0.03390(8)	0.0464(7)
N8	0.3411(2)	0.65683(19)	−0.04654(9)	0.0564(8)
N9	0.1694(2)	0.8709(2)	−0.18054(9)	0.0615(9)
N10	0.1606(3)	0.7764(3)	−0.19187(10)	0.0801(11)
O1	0.3551(2)	0.25476(19)	−0.17647(9)	0.0911(10)
O2	0.2999(2)	0.1092(2)	−0.18532(10)	0.1183(13)
O3	0.4355(2)	0.9967(2)	0.20028(9)	0.0909(10)
O4	0.4341(3)	1.1540(2)	0.18884(10)	0.1155(13)
C1	0.4196(4)	0.2380(3)	−0.20765(12)	0.0937(15)
H1A	0.458514	0.294421	−0.209852	0.141*
H1B	0.455583	0.180909	−0.201161	0.141*
H1C	0.387713	0.227458	−0.232677	0.141*
C2	0.2965(3)	0.1854(3)	−0.16921(11)	0.0627(11)
C3	0.2288(3)	0.2127(3)	−0.13873(11)	0.0722(12)
H3A	0.194272	0.154369	−0.131971	0.087*
H3B	0.186841	0.260213	−0.150454	0.087*
C4	0.2538(3)	0.3514(3)	−0.08944(11)	0.0620(11)
H4	0.219008	0.391893	−0.106213	0.074*
C5	0.2880(3)	0.3885(3)	−0.05413(10)	0.0544(10)
H5	0.275311	0.453487	−0.047345	0.065*
C6	0.3408(2)	0.3323(2)	−0.02836(10)	0.0467(9)
C7	0.3581(3)	0.2361(2)	−0.03995(11)	0.0590(11)
H7	0.394225	0.195901	−0.023605	0.071*
C8	0.3225(3)	0.1995(3)	−0.07522(12)	0.0624(11)
H8	0.334659	0.134469	−0.082114	0.075*
C9	0.2696(3)	0.2557(3)	−0.10066(11)	0.0588(10)
C10	0.3797(2)	0.3717(2)	0.00931(10)	0.0458(9)
C11	0.4057(3)	0.3091(2)	0.04137(11)	0.0545(10)
H11	0.393665	0.242265	0.038129	0.065*
C12	0.4610(2)	0.4338(2)	0.07932(10)	0.0472(9)
C13	0.3939(2)	0.4699(2)	0.01528(10)	0.0492(9)
H13	0.377412	0.515487	−0.004379	0.059*
C14	0.5023(3)	0.4887(2)	0.10931(10)	0.0496(9)
C15	0.4954(3)	0.5849(3)	0.09525(11)	0.0580(10)
H15	0.518187	0.638748	0.109504	0.070*
C16	0.5484(3)	0.4546(2)	0.14540(10)	0.0511(10)
C17	0.6112(3)	0.5069(3)	0.16860(12)	0.0690(12)
H17	0.629381	0.570881	0.162814	0.083*
C18	0.5420(3)	0.3664(3)	0.16494(11)	0.0634(11)
H18	0.505344	0.313518	0.157298	0.076*
C19	0.6156(3)	0.2942(3)	0.22660(13)	0.1009(16)
H19A	0.675378	0.267850	0.223102	0.151*
H19B	0.571614	0.242411	0.223511	0.151*
H19C	0.611687	0.322238	0.252904	0.151*
C20	0.3631(4)	1.0087(4)	0.22840(13)	0.1073(17)
H20A	0.348270	0.945836	0.239719	0.161*
H20B	0.382466	1.052841	0.249391	0.161*
H20C	0.310598	1.035414	0.214763	0.161*
C21	0.4636(3)	1.0756(3)	0.18227(11)	0.0623(11)
C22	0.5347(3)	1.0535(3)	0.15253(11)	0.0659(11)

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
H22A	0.578933	1.008646	0.164450	0.079*
H22B	0.565968	1.113958	0.145779	0.079*
C23	0.4953(2)	1.0082(3)	0.11504(10)	0.0520(9)
C24	0.4702(3)	0.9106(3)	0.11350(11)	0.0638(11)
H24	0.479215	0.871053	0.136011	0.077*
C25	0.4320(3)	0.8704(3)	0.07934(11)	0.0584(10)
H25	0.415718	0.804199	0.079273	0.070*
C26	0.4172(2)	0.9257(2)	0.04505(9)	0.0436(9)
C27	0.4431(3)	1.0232(2)	0.04711(10)	0.0544(10)
H27	0.435091	1.062604	0.024514	0.065*
C28	0.4806(3)	1.0644(3)	0.08146(11)	0.0557(10)
H28	0.495864	1.130956	0.081807	0.067*
C29	0.3760(2)	0.8832(2)	0.00844(10)	0.0461(9)
C30	0.3796(2)	0.7852(3)	0.00067(10)	0.0484(9)
H30	0.407425	0.742056	0.018768	0.058*
C31	0.3016(2)	0.8146(2)	−0.06197(10)	0.0466(9)
C32	0.3310(3)	0.9432(2)	−0.02032(11)	0.0539(10)
H32	0.326150	1.010060	−0.014511	0.065*
C33	0.2757(3)	0.7570(2)	−0.09425(10)	0.0496(9)
C34	0.3015(3)	0.6628(3)	−0.08238(11)	0.0565(10)
H34	0.291636	0.607787	−0.098511	0.068*
C35	0.2310(3)	0.7866(2)	−0.13113(10)	0.0513(10)
C36	0.1983(3)	0.7259(3)	−0.16186(12)	0.0765(13)
H36	0.202460	0.657515	−0.161379	0.092*
C37	0.2105(3)	0.8789(3)	−0.14483(11)	0.0578(10)
H37	0.223193	0.937629	−0.131429	0.069*
C38	0.1357(3)	0.9486(3)	−0.20657(11)	0.0803(13)
H38A	0.109252	0.920100	−0.230447	0.120*
H38B	0.090474	0.985990	−0.192959	0.120*
H38C	0.184868	0.991132	−0.213594	0.120*

and food chemistry and so on [5–8]. In addition, aryl bromides are very important pharmaceutical intermediates, which can be easily used in many coupling reactions. For example the brominated pyrazolo[1,5-*a*]pyrimidine derivatives are key intermediates to synthesize AMPK inhibitors in anticancer field [9, 10]. In this work, we describe the synthesis of methyl 2-(4-(3-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate in good yield by coupling reaction of methyl 3-(4-(3-bromopyrazolo[1,5-*a*]pyrazin-6-yl)phenyl)propanoate with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, this compound will be used for the development of novel AMPK inhibitors. The NMR results are consistent with the crystal structure of methyl 2-(4-(3-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl) acetate. The bond lengths and angles in both crystallographically independent molecules are in the normal ranges [11]. In a word, methyl 2-(4-(3-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate was synthesized under a mild condition, which can be readily used to synthesize a diverse range of AMPK inhibitors for the development of anticancer drugs.

Acknowledgements: This work was supported by the Science and Technology Research Program of Chongqing Municipal Education Commission (Grant NO. KJQN201801305 and KJQN201801321), Program of Chongqing Medical and Pharmaceutical College (YGZ2018102), Natural Science Foundation Project of Yongchuan CSTC (YCSTC, 2016NC5001) and Chongqing University of Arts and Sciences (2017RBX08, P2017BX12).

References

1. Bruker. SAINT+, version 7.60A (Includes XPREP and SADABS). Bruker AXS Inc., Madison, WI, USA (2009).
2. Sheldrick, G. M.: SHELXT – integrated space-group and crystal structure determination. *Acta Crystallogr.* **A71** (2015) 3–8.
3. Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Crystallogr.* **C71** (2015) 3–8.
4. 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.* **42** (2009) 339–341.
5. Reddy Kotla, S. K.; Vandavasi, J. K.; Wang, J.; Parang, K.; Tiwari, R. K.: Palladium-catalyzed intramolecular cross-dehydrogenative coupling: synthesis of fused imidazo[1,2-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidines. *ACS Omega* **2** (2017) 11–19.
6. Shin, Y.; Lee, J.; Lee, J.; Kim, E.; Liu, K.; Lee, H. S.; Kim, J.: Validation of a multiresidue analysis method for 379 pesticides in human serum using liquid chromatography-tandem mass spectrometry. *J. Agric. Food Chem.* **66** (2018) 3550–3560.
7. Golubev, P.; Karpova, E. A.; Pankova, A. S.; Sorokina, M.; Kuznetsov, M. A.: Regioselective synthesis of 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*] pyrimidines *via* reaction of pyrazolamines with enynones. *J. Org. Chem.* **81** (2016) 11268–11275.
8. Devi, A. S.; Kaping, S.; Vishwakarma, J. N.: A facile environment-friendly one-pot two-step regioselective synthetic strategy for 3,7-diarylpyrazolo[1,5-*a*]pyrimidines related to zaleplon and 3,6-diarylpyrazolo[1,5-*a*]pyrimidine-7-amines assisted by KHSO₄ in aqueous media. *Mol. Divers.* **19** (2015) 759–771.
9. Carling, D.: AMPK signalling in health and disease. *Curr. Opin. Cell Biol.* **45** (2017) 31–37.
10. Nguyen, P.; Choi, H. S.; Ha, T. K. Q.; Seo, J. Y.; Yang, J.; Jung, D.; Williams, D. R.; Oh, W.: Anthraquinones from morinda longissima and their insulin mimetic activities *via* AMP-activated protein kinase (AMPK) activation. *Bioorg. Med. Chem. Lett.* **27** (2017) 40–44.
11. Zimmerman, J. R.; Myers, B. J.; Bouhall, S.; McCarthy, A.; JohnTony, O.; Manpadi, M.: A two-step, single pot procedure for the synthesis of substituted dihydropyrazolo-pyrimidines. *Tetrahedron Lett.* **55** (2014) 936–940.