Raed A. Al-Qawasmeh*, Sadeekah O. W. Saber, Yaseen A. Al-Soud and Monther A. Khanfar

The crystal structure of 1-(*N*1-benzyl-2-methyl-4-nitro-imidazol-5-yl)-4-(prop-2-yn-1-yl)piperazine, C₁₈H₂₁N₅O₂

Table 1: Data collection and handling.

Crystal:	Yellow needle
Size:	0.12 × 0.08 × 0.02 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.08 mm ⁻¹
Diffractometer, scan mode:	Xcalibur, ω
$\theta_{\max}$, completeness:	29.5°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	27,507, 4593, 0.029
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2681
$N(\text{param})_{\text{refined}}$:	238
Programs:	CrysAlis ^{PRO} [1], Olex2 [2], SHELX [3, 4]

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.

<https://doi.org/10.1515/ncrs-2021-0447>

Received November 22, 2021; accepted January 3, 2022;

published online January 20, 2022

Abstract

C₁₈H₂₁N₅O₂, monoclinic, $P2_1/c$ (no. 4), $a = 10.0914(6)$ Å, $b = 11.8919(7)$ Å, $c = 15.545(1)$ Å, $\beta = 102.321(6)^\circ$, $V = 1822.5(2)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0503$, $wR_{\text{ref}}(F^2) = 0.1419$, $T = 293(2)$ K.

CCDC no.: 2132118

*Corresponding author: Raed A. Al-Qawasmeh, Department of Chemistry, Pure and Applied Chemistry Group, College of Sciences, University of Sharjah, Sharjah 27272, UAE; and Department of Chemistry, The University of Jordan, Amman 11942, Jordan, E-mail: ralqawasmeh@sharjah.ac.ae

Sadeekah O. W. Saber, Faculty of Pharmacy, Jerash University, Jerash 26150, Jordan, E-mail: s.saber@jpu.edu.jo. <https://orcid.org/0000-0003-4547-005X>

Yaseen A. Al-Soud, Department of Chemistry, College of Science, University of Al al-Bayt, Al-Mafraq, Jordan, E-mail: alsoud@aabu.edu.jo

Monther A. Khanfar, Department of Chemistry, Pure and Applied Chemistry Group, College of Sciences, University of Sharjah, Sharjah 27272, UAE; and Department of Chemistry, The University of Jordan, Amman 11942, Jordan, E-mail: mkhanfar@sharjah.ac.ae. <https://orcid.org/0000-0003-4718-4006>

Source of materials

The commercially available 2-methyl-4-nitro-1*H*-imidazole was reacted with benzyl chloride to produce 1-benzyl-2-methyl-4-nitro-1*H*-imidazole **1** [5]. Bromination of **1** with liquid bromine in DMF, in the presence potassium carbonate as a base afforded 1-benzyl-5-bromo-2-methyl-4-nitro-1*H*-imidazole **2** [5]. Reaction of **2** with piperazine using isopropanol as solvent gave 1-(1-benzyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)piperazine **3** [5]. The title compound **4** has been prepared *via* reaction of the piperazine derivative **3** with propargyl bromide using NaH as base to produce the new compound 1-(*N*1-benzyl-2-methyl-4-nitro-imidazol-5-yl)-4-(prop-2-yn-1-yl) piperazine **4** as yellow flakes in 82% yield. M.p. = 122–124°. HRMS-ESI m/z : 362.15719 ($M + Na$)⁺. ¹H NMR (500 MHz, DMSO-*d*₆, 298 K): δ 2.25 (s, 3H, H–C4); 2.46 (br.s, 4H, H–C13, H–C14); 2.99 (br.s, 4H, H–C12, H–C15); 3.17 (t, 1H, $J = 2.2$, H–C18); 3.28 (d, 2H, $J = 2.2$, H–C16); 5.17 (s, 2H, H–C5); 7.12 (d, 2H, $J = 7.4$ Hz, H–C7, H–C11); 7.32 (t, 1H, $J = 7.3$ Hz, H–C9); 7.39 (pseudo t, 2H, H–C8, H–C10). ¹³C NMR (125 MHz, DMSO-*d*₆, 298 K): δ 14.1 (C4); 46.2 (C5); 46.4 (C16); 48.5 (C12, C15); 51.4 (C13, C14); 76.3 (C17); 79.6 (C18); 126.9 (C7, C11); 128.1 (C9); 129.4 (C8, C10); 136.6 (C6); 138.8 (C2); 140.2 (C1); 140.9 (C3).

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}
C1	0.39788 (18)	0.85662 (14)	0.39620 (13)	0.0678 (5)
C2	0.50765 (16)	0.85408 (13)	0.52762 (11)	0.0571 (4)
C3	0.59947 (16)	0.81652 (12)	0.48078 (10)	0.0546 (4)
C4	0.2893 (3)	0.8728 (2)	0.31574 (19)	0.0961 (8)
H4A	0.275 (2)	0.801 (2)	0.2832 (15)	0.104 (7)*
H4B	0.206 (4)	0.889 (3)	0.334 (2)	0.177 (15)*
H4C	0.313 (2)	0.931 (2)	0.2772 (17)	0.124 (9)*
C5	0.5772 (2)	0.78057 (17)	0.31923 (12)	0.0787 (5)
H5A	0.6695	0.8077	0.3255	0.094*
H5B	0.5231	0.8146	0.2666	0.094*
C6	0.57666 (16)	0.65507 (15)	0.30680 (10)	0.0610 (4)
C7	0.6547 (2)	0.6106 (2)	0.25229 (14)	0.0929 (7)
H7	0.7078	0.6580	0.2260	0.111*
C8	0.6548 (3)	0.4979 (3)	0.23653 (18)	0.1177 (9)
H8	0.7054	0.4698	0.1978	0.141*
C9	0.5823 (3)	0.4256 (2)	0.27636 (17)	0.1012 (7)
H9	0.5849	0.3487	0.2663	0.121*
C10	0.5061 (2)	0.46734 (19)	0.33090 (16)	0.0926 (7)
H10	0.4561	0.4187	0.3585	0.111*
C11	0.50232 (19)	0.58224 (17)	0.34585 (14)	0.0791 (6)
H11	0.4487	0.6101	0.3828	0.095*
C12	0.83549 (17)	0.87279 (14)	0.52832 (13)	0.0686 (5)
H12A	0.8435	0.8849	0.5909	0.082*
H12B	0.8079	0.9429	0.4979	0.082*
C13	0.97004 (17)	0.83487 (14)	0.51051 (13)	0.0692 (5)
H13A	0.9623	0.8260	0.4476	0.083*
H13B	1.0385	0.8915	0.5314	0.083*
C14	0.90817 (17)	0.64230 (14)	0.52541 (13)	0.0652 (4)
H14A	0.9360	0.5726	0.5565	0.078*
H14B	0.8999	0.6287	0.4630	0.078*
C15	0.77311 (17)	0.67826 (14)	0.54216 (13)	0.0662 (5)
H15A	0.7051	0.6215	0.5204	0.079*
H15B	0.7791	0.6872	0.6049	0.079*
C16	1.14421 (18)	0.69196 (17)	0.54303 (13)	0.0743 (5)
H16A	1.1727	0.6279	0.5811	0.089*
H16B	1.2087	0.7521	0.5621	0.089*
C17	1.14980 (19)	0.66082 (16)	0.45276 (15)	0.0742 (5)
C18	1.1442 (3)	0.63501 (19)	0.37957 (18)	0.0970 (7)
H18	1.1398	0.6145	0.3213	0.116*
N1	0.38429 (14)	0.87939 (12)	0.47618 (11)	0.0666 (4)
N2	0.52531 (14)	0.81809 (11)	0.39517 (9)	0.0626 (4)
N3	0.53046 (17)	0.87016 (12)	0.62039 (10)	0.0692 (4)
N4	0.73480 (13)	0.78517 (10)	0.49693 (9)	0.0572 (3)
N5	1.01089 (13)	0.72848 (11)	0.55473 (9)	0.0609 (4)
O1	0.64251 (15)	0.84369 (13)	0.66527 (8)	0.0857 (4)
O2	0.44060 (16)	0.91050 (15)	0.65223 (10)	0.1051 (5)

The chemicals were purchased from Aldrich (Germany), Fluka (Switzerland), and Scharlau; they were used without further purification. The NMR spectra were recorded on a Bruker Avance III-(500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. ¹H NMR (500 MHz), ¹³C-NMR (125 MHz), and 2D were recorded

in Dimethylsulfoxide (DMSO-*d*₆). The following abbreviations are used to describe peak patterns: s = singlet, t = triplet, br.s = broad singlet. High-resolution mass spectra (HRMS) were measured (in positive/or negative ion mode) using the electrospray ion trap (ESI pos low mass) technique by collision-induced dissociation on a Bruker APEX-IV (7 Tesla) instrument. Melting points were determined on a Stuart (SMP-10) melting point apparatus.

Single crystal of C₁₈H₂₁N₅O₂ was obtained through crystallization of the pure compound from CHCl₃/Et₂O.

Experimental details

A suitable crystal was selected and mounted on a Xcalibur, Eos diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2 [2], the structure was solved with the ShelXT [3] structure solution program using Intrinsic Phasing and refined with the ShelXL [4] refinement package. All H atoms bonded to C atoms were refined as riding, with C–H distances of 0.93 Å (for aromatic ring).

Comment

Imidazole is an important nucleus with diverse biological properties. The high therapeutic properties of the imidazole-related drugs have encouraged medicinal chemists to design and synthesize a large number of novel chemotherapeutic agents like Pantoprazole [6] (a proton pump inhibitor used for treatment of gastroesophageal reflux disease), Trifenagrel [7] (a potent arachidonate cyclooxygenase inhibitor), Eprosartan [8] (an angiotensin II receptor antagonist), and Cimetidine [9] (a histamine H₂ receptor antagonist that inhibits stomach acid production). In view of the interest in the activity spectrum and profile of the nitroimidazoles and in continuation of our research on the synthesis and biological evaluation of imidazole analogs [10–17], we here present the imidazolyl containing title structure. Herein, the propargyl bromide was couples with imidazole ring to produce the target compound.

This title crystal structure consists of the C₁₈H₂₁N₅O₂ molecules, in which all bond lengths are in normal ranges. The crystal is stabilized *via* CH⋯O (H18⋯O1 = 2.482(1) Å) and CH⋯O (H4A⋯O1 = 2.66(3) Å). The average plane of imidazole ring is perpendicular (90.17(7)°) to the average plane of the methylene groups of piperazine (C12–C13–C14–C15). A further intramolecular CH⋯O interactions can be also seen (H12A⋯O1 = 2.586(1) Å) and (H15B⋯O1 = 2.607(1) Å).

Acknowledgments: Part of this work has been carried out during sabbatical leave granted to RAA from the University of Jordan during the academic year 2020–2021.

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

Research funding: This study was financially supported by Scientific Research Support Fund/Ministry of Higher Education, Jordan (grant no. Bas 1/1/2017).

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

References

1. Rigaku Oxford Diffraction. CrysAlis^{PRO}; Yarnton: England, 2015.
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. SHELXTL – integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, A71, 3–8.
4. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, C71, 3–8.
5. Al-Soud Y. A., Al-Ahmad A. H., Abu-Qatouseh L., Shtaiwi A., Alhelal K. A. S., Al-Suod H. H., Alsawakhneh S. O., Al-Qawasmeh R. A. Nitroimidazoles Part 9. Synthesis, molecular docking, and anticancer evaluations of piperazine-tagged imidazole derivatives. *Z. Naturforsch, B: Chem. Sci.* 2021, B72, 293–302.
6. Senn-Bilfinger J., Sturn E. The development of a new proton-pump inhibitor: the case history of pantoprazole. In *Analogue-Based Drug Discovery*; Fischer J., Ganellin C. R., Eds. Wiley-VCH: Weinheim, 2006, pp. 115–136.
7. Abrahams S. L., Hazen R. J., Batson A. G., Phillips A. P. Trifenagrel: a chemically novel platelet aggregation inhibitor. *J. Pharmacol. Exp. Therapeut.* 1989, 249, 359–365.
8. Grange R. L., Ziogas J., North A. J., Angus J. A., Schiesser C. H. Selenosartans: novel selenophene analogues of milfasartan and eprosartan. *Bioorg. Med. Chem. Lett* 2008, 18, 1241–1244.
9. Beggs W. H., Andrews F. A., Sarosi G. A. Action of imidazole-containing antifungal drugs. *Life Sci.* 1981, 28, 111–118.
10. Al-Masoudi N. A., Al-Soud Y. A., Kalogerakisa A., Pannecouque C., De Clercq E. Nitroimidazoles part 2. Synthesis, antiviral and antitumor activity of new 4-nitroimidazoles. *Chem. Biodivers.* 2006, 3, 515–526.
11. Al-Soud Y. A., Al-Sa'doni H., Amajaour H. A. S., Al-Masoudi N. A. Nitroimidazole part 3. Synthesis and anti-HIV activity of new *N*-alkyl 4-nitroimidazoles, bearing benzothiazole and benzoxazole backbones. *Z. Naturforsch, B: Chem. Sci.* 2007, B62, 523–528.
12. Al-Soud Y. A., Al-Masoudi N. A., De Clercq E., Pannecouque C. Nitroimidazoles part 4. Synthesis and anti-HIV activity of new 5-alkylsulfanyl and 5-(4'-arylsulphonyl) piperazine 4-nitroimidazole derivatives. *Heteroat. Chem.* 2007, 18, 333–340.
13. Al-Soud Y. A., Al-Masoudi N. A., Hassan H., De Clercq E., Pannecouque C. Nitroimidazoles v. Synthesis and anti-HIV evaluation of new 5-substituted piperazinyl-4-nitroimidazole derivatives. *Acta Pharm.* 2007, 57, 379–393.
14. Al-Masoudi N. A., Al-Soud Y. A., De Clercq E., Pannecouque C. Nitroimidazoles part 6. Synthesis, structure and in vitro anti-HIV activity of new 5-substituted piperazinyl-4-nitroimidazole derivatives. *Antiviral Chem. Chemother.* 2007, 18, 191–200.
15. Al-Soud Y. A., Al-Masoudi N. A., Al-Suod H. H., Pannecouque C. Nitroimidazoles part 8. Synthesis and anti-HIV activity of new 4-nitroimidazole derivatives using the suzuki cross-coupling reaction. *Z. Naturforsch, B: Chem. Sci.* 2012, B67, 925–934.
16. Al-Soud Y. A., Alhelal K. A. S., Bahjat A. S., Abu-Qatouseh L., Al-Suod H. H., Al-Ahmad A. H., Al-Masoudi N. A., Al-Qawasmeh R. A. Synthesis, anticancer activity and molecular docking studies of new 4-nitroimidazole derivatives. *Arkivoc* 2021, viii, 296–309.
17. Huesca M., Al-Qawasmeh R. A., Young A. H., Lee Y. Aryl Imidazoles and Their Use as Anti-cancer Agents. U.S. Patent, 2015; p. 8969372.