Itumeleng B. Setshedi and Mark G. Smith*

The crystal structure of 4-phenyl-4-[2-(pyridine-4-carbonyl)hydrazinylidene]butanoic acid, $C_{16}H_{15}N_3O_3$

<https://doi.org/10.1515/ncrs-2021-0429>

Received November 3, 2021; accepted December 9, 2021;
published online January 4, 2022

Abstract

$C_{16}H_{15}N_3O_3$, monoclinic, $P2_1/c$ (no. 14), $a = 9.4957(3)$ Å, $b = 18.2275(5)$ Å, $c = 9.0896(3)$ Å, $\beta = 114.372(1)^\circ$, $V = 1433.05(15)$ Å³, $Z = 4$, $R_{gt}(F) = 0.0380$, $wR_{ref}(F^2) = 0.1011$, $T = 173$ K.

CCDC no.: 2120068

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.

*Corresponding author: Mark G. Smith, Chemistry Department, University of South Africa, Unisa Science Campus, 28 Pioneer Avenue, Florida, Roodepoort, Gauteng, South Africa, E-mail: Smithm2@unisa.ac.za. <https://orcid.org/0000-0003-2553-2540>

Itumeleng B. Setshedi, Department of Life Science, University of South Africa, Unisa Science Campus, 28 Pioneer Avenue, Florida, Roodepoort, Gauteng, South Africa, E-mail: Setshib@unisa.ac.za. <https://orcid.org/0000-0001-8865-4735>

Table 1: Data collection and handling.

Crystal:	Colourless cuboid
Size:	$0.62 \times 0.25 \times 0.23$ mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.10 mm^{-1}
Diffractometer, scan mode:	BRUKER D8 VENTURE, ω
θ_{max} , completeness:	28.0° , >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	20,811, 3446, 0.072
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2\sigma(I_{\text{obs}})$, 3009
$N(\text{param})_{\text{refined}}$:	199
Programs:	BRUKER [1], SHELX [2], WINGX [3], PLATON [4], ORTEP-III [5, 6]

Source of material

All reagents were commercially sourced and used without further purification. 1.035 g of isonicotinic acid hydrazide (7.55 mmol) and 1.359 g of 3-benzoylpropionic acid (7.63 mmol) were added into a screw-cap dram vial (with rubber septum). 5 mL of methanol was added and stirred at 70°C for 24 h. The solution was then left slightly open to allow slow evaporation at room temperature. Colourless block crystals were observed after three days.

Experimental details

The collection method involved ω -scans of width 0.5° . Data reduction was carried out using SAINT-Plus version 6.02.6 software, and SADABS was used to process empirical absorption corrections [1]. The crystal structure was solved through direct methods using SHELXS [2]. Hydrogen atoms were positioned geometrically and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. Diagrams and publication material were generated using WinGX [3], PLATON [4] and Ortep [5, 6].

Comment

Isonicotinic acid hydrazide (isoniazid) is primarily used as a treatment for Tuberculosis (TB). It is effective against both latent and active *Mycobacteria tuberculosis* [7]. However, improper and long term use of the drug has resulted in the

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}
C1	0.61662 (13)	0.15765 (6)	−0.15151 (13)	0.0196 (2)
C2	0.53059 (14)	0.11646 (7)	−0.08990 (15)	0.0252 (3)
H2	0.539844	0.124459	0.016986	0.03 [*]
C3	0.43079 (14)	0.06337 (7)	−0.18705 (15)	0.0260 (3)
H3	0.370744	0.035936	−0.144879	0.031 [*]
C4	0.50060 (14)	0.08846 (7)	−0.39467 (14)	0.0237 (2)
H4	0.491771	0.07815	−0.500585	0.028 [*]
C5	0.60104 (14)	0.14341 (7)	−0.30792 (14)	0.0229 (2)
H5	0.657964	0.170748	−0.353972	0.028 [*]
C6	0.71859 (13)	0.21952 (6)	−0.05705 (13)	0.0199 (2)
C7	1.02496 (13)	0.23387 (6)	0.32495 (14)	0.0193 (2)
C8	1.07640 (13)	0.15568 (6)	0.37160 (14)	0.0220 (2)
H8A	1.190778	0.154373	0.424005	0.026 [*]
H8B	1.042697	0.125597	0.272244	0.026 [*]
C9	1.01330 (13)	0.12102 (6)	0.48624 (14)	0.0212 (2)
H9A	1.093684	0.088636	0.563263	0.025 [*]
H9B	0.992392	0.160471	0.549382	0.025 [*]
C10	0.86795 (14)	0.07715 (6)	0.40142 (14)	0.0217 (2)
C11	1.11203 (13)	0.29500 (6)	0.43327 (13)	0.0206 (2)
C12	1.06091 (14)	0.36753 (7)	0.39634 (14)	0.0245 (3)
H12	0.967967	0.377376	0.304194	0.029 [*]
C13	1.14419 (17)	0.42516 (7)	0.49252 (16)	0.0301 (3)
H13	1.108799	0.474128	0.465188	0.036 [*]
C14	1.27918 (16)	0.41148 (8)	0.62870 (16)	0.0330 (3)
H14	1.336257	0.451024	0.694349	0.04 [*]
C15	1.33022 (16)	0.34035 (8)	0.66842 (16)	0.0341 (3)
H15	1.422212	0.330898	0.761944	0.041 [*]
C16	1.24725 (15)	0.28234 (7)	0.57182 (15)	0.0283 (3)
H16	1.283044	0.233508	0.600454	0.034 [*]
N1	0.82074 (11)	0.19997 (5)	0.09310 (11)	0.0210 (2)
H1	0.829793	0.15393	0.124855	0.025 [*]
N2	0.41509 (11)	0.04898 (5)	−0.33750 (12)	0.0225 (2)
N3	0.91012 (11)	0.25417 (5)	0.19479 (11)	0.0203 (2)
O1	0.70748 (10)	0.28075 (5)	−0.11510 (10)	0.0275 (2)
O2	0.80366 (11)	0.06912 (5)	0.25575 (10)	0.0284 (2)
O3	0.81920 (10)	0.04563 (5)	0.50306 (10)	0.0271 (2)
H3A	0.738051	0.021825	0.450823	0.041 [*]

resistance of the microorganism [8]. This in turn has led to research focused on the modification of isoniazid to develop derivatives that may be effective against drug resistant mycobacteria strains [9, 10]. The crystal structure being reported in this article represents one such covalently modified isoniazid derivative.

The asymmetric unit shown in the figure contains one molecule of 4-phenyl-4-[2-(pyridine-4-carbonyl)hydrazinylidene]butanoic acid. There is an intramolecular hydrogen bond between the O2 oxygen and the H1 donor atom, forming an S₁¹(8) ring in graph set notation [11]. Every molecule is bonded to an adjacent molecule which is flipped over, thus forming a symmetrical dimer with an inversion center

between the two molecules. This results in each molecule being hydrogen bonded to its neighbour twice *via* COOH...N heterosynthons, namely O3–H3A...N2. The COOH...N heterosynthons are as expected in literature [12]. The bonding between the two adjacent molecules is further stabilized by a weak C–H...O interaction between H3 and O2.

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

Research funding: This work was supported by the National Research Foundation (NRF) Thuthuka Grant Number 118127 as well as Thuthuka Grant Number 117850.

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

References

1. Bruker. *SAINT-Plus and SADABS*; Bruker AXS Inc.: Wisconsin, Madison, USA, 2004.
2. Sheldrick G. M. A short history of *SHELX*. *Acta Crystallogr.* 2008, *A64*, 112–122.
3. Farrugia L. J. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* 1999, *32*, 837–838.
4. Spek A. L. Structure validation in chemical crystallography. *Acta Crystallogr.* 2009, *D65*, 148–155.
5. Burnett M. N., Johnson C. K. *ORTEP-III. Report ORNL-6895*; Oak Ridge National Laboratory: Tennessee, USA, 1996.
6. Farrugia L. J. ORTEP-3 for Windows – a version of ORTEP-III with a graphical user interface (GUI). *J. Appl. Crystallogr.* 1997, *30*, 565.
7. Torres E., Moreno E., Ancizu S., Barea C., Galiano S., Aldana I., Monge A., Silanes S. P. New 1,4-di-*N*-oxide-quinoxaline-2-ylmethylene isonicotinic acid hydrazide derivatives as anti-mycobacterium tuberculosis agents. *Bioorg. Med. Chem. Lett.* 2011, *21*, 3699–3703.
8. Setshedi I. B., Smith M. G. The crystal structure of the co-crystal: 2-hydroxybenzoic acid *N*-(butan-2-ylidene)pyridine-4-carbohydrazide, C₁₀H₁₃N₃O·C₇H₆O₃. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 1093–1095.
9. Hu Y.-Q., Zhang S., Zhao F., Gao C., Feng L.-S., Lv Z.-S. Isoniazid derivatives and their anti-tubercular activity. *Eur. J. Med. Chem.* 2017, *133*, 255–267.
10. Lemmerer A., Bernstein J., Kahlenberg V. Covalent assistance in supramolecular synthesis: in situ modification and masking of the hydrogen bonding functionality of the supramolecular reagent isoniazid in co-crystals. *CrystEngComm* 2011, *13*, 5692–5708.
11. Bernstein J., Davis R. E., Shimon L., Chang N.-L. Patterns in hydrogen bonding: functionality and graph set analysis in crystals. *Angew. Chem. Int. Ed. Engl.* 1995, *34*, 1555–1573.
12. Aakeröy C. B., Hussain I., Forbes S., Desper J. Exploring the hydrogen-bond preference of N–H moieties in co-crystals assembled via O–H(acid)...N(py) intermolecular interactions. *CrystEngComm* 2007, *9*, 46–54.