

SYNTHESIS, CHARACTERIZATION AND CRYSTAL STRUCTURES OF HYDRAZONE COMPOUNDS DERIVED FROM ISONICOTINOHYDRAZIDE

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ABSTRACT. New isonicotinohydrazone compounds, *N'*-(3-bromobenzylidene)isonicotinohydrazone (**1**) and *N'*-(2,3-difluorobenzylidene)isonicotinohydrazone (**2**), were prepared and structurally characterized by elemental analysis, IR, UV and ¹H NMR spectra, and single crystal X-ray determination. Compound **1** crystallizes in the monoclinic space group *P*2₁/*n* with unit cell dimensions *a* = 7.600(2) Å, *b* = 11.365(2) Å, *c* = 14.412(2) Å, β = 101.748(2)°, *V* = 1218.7(4) Å³, *Z* = 4, *R*₁ = 0.0335, and *wR*₂ = 0.0745. Compound **2** crystallizes in the triclinic space group *P*-1 with unit cell dimensions *a* = 7.6241(6) Å, *b* = 11.3937(9) Å, *c* = 14.335(1) Å, α = 79.664(1)°, β = 75.990(1)°, γ = 71.159(1)°, *V* = 1136.5(2) Å³, *Z* = 4, *R*₁ = 0.0345, and *wR*₂ = 0.0940. Structures of both compounds are stabilized by hydrogen bonds and $\pi \cdots \pi$ interactions.

KEY WORDS: Isonicotinohydrazone, Crystal structure, Hydrogen bonds, X-ray diffraction

INTRODUCTION

Isonicotinohydrazone is a well known anti-tuberculosis drug. It can react with aldehydes to form isonicotinohydrazones, which show interesting biological activities [1-4]. Moreover, isonicotinohydrazone compounds usually possess three or more donor atoms, which can readily form complexes with various metal atoms [5-12]. Recently, we found that halido-substituted hydrazones have potential antimicrobial activities [13]. Study on the synthesis and structures of such compounds are important for medicinal chemistry. In the present work, two new isonicotinohydrazone compounds, *N'*-(3-bromobenzylidene)isonicotinohydrazone (**1**) and *N'*-(2,3-difluorobenzylidene)isonicotinohydrazone (**2**), were prepared and structurally characterized.

EXPERIMENTAL

Materials and measurements

Starting materials, reagents and solvents were purchased from commercial suppliers and used as received. Elemental analyses were performed on a Perkin-Elmer 240 Elemental analyzer. IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets in the 4000-400 cm⁻¹ region. UV spectra were recorded on a Lambda 900 spectrometer. ¹H NMR and ¹³C NMR data were recorded on a Bruker 300MHz and 75 MHz instrument. HRMS data was obtained with ESI (electrospray ionization) mode.

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Synthesis of N'-(3-bromobenzylidene)isonicotinohydrazide

(1). 3-Bromobenzaldehyde (1.0 mmol, 0.185 g) and isonicotinohydrazide (1.0 mmol, 0.137 g) were mixed in methanol, and stirred at room temperature for 1 h. The solvent was evaporated by distillation to give colorless solid, which was washed with methanol. Yield: 87%. Single crystals of the compound suitable for X-ray diffraction were obtained by recrystallization of the product in methanol. Anal. calcd. for $C_{13}H_{10}BrN_3O$: C, 51.3; H, 3.3; N, 13.8; found: C, 51.5; H, 3.3; N, 13.7%. HRMS (ESI): m/z calcd for $C_{13}H_{10}BrN_3O$ $[M + H]^+$ 305.0762; found: 305.0765. IR data (KBr, cm^{-1}): 3197 (w), 1682 (s), 1620 (m), 1546 (s), 1411 (w), 1349 (w), 1268 (s), 1216 (w), 1136 (w), 1062 (w), 946 (w), 847 (w), 787 (w), 745 (w), 682 (m), 635 (w). UV (λ , ϵ): 300 nm, 1.07×10^4 L mol $^{-1}$ cm $^{-1}$. 1H NMR (300 MHz, d^6 -DMSO): δ 12.31 (s, 1H, NH), 8.85 (d, 2H, py-H), 8.46 (s, 1H, CH=N), 8.0-7.4 (m, 6H, ArH). ^{13}C NMR (75 MHz, d^6 -DMSO): δ 161.5, 151.5, 151.3, 146.3, 140.0, 134.5, 132.3, 131.9, 130.2, 128.7, 122.5, 121.6, 121.5.

Synthesis of N'-(2,3-difluorobenzylidene)isonicotinohydrazide

(2). 2,3-Difluorobenzaldehyde (1.0 mmol, 0.142 g) and isonicotinohydrazide (1.0 mmol, 0.137 g) were mixed in methanol, and stirred at room temperature for 1 h. The solvent was evaporated by distillation to give colorless solid, which was washed with methanol. Yield: 95%. Single crystals of the compound suitable for X-ray diffraction were obtained by recrystallization of the product in methanol. Anal. calcd. For $C_{13}H_9F_2N_3O$: C, 59.8; H, 3.5; N, 16.1; found: C, 60.0; H, 3.4; N, 15.9%. HRMS (ESI): m/z calcd for $C_{13}H_9F_2N_3O$ $[M + H]^+$ 262.0786; found: 262.0780. IR data (KBr, cm^{-1}): 3190 (w), 1687 (s), 1618 (w), 1555 (s), 1480 (s), 1406 (m), 1288 (s), 1208 (w), 1141 (w), 1089 (w), 1062 (w), 995 (m), 853 (w), 786 (w), 685 (w). UV (λ , ϵ): 300 nm, 2.20×10^4 L mol $^{-1}$ cm $^{-1}$. 1H NMR (300 MHz, d^6 -DMSO): δ 12.27 (s, 1H, NH), 8.81 (d, 2H, py-H), 8.70 (s, 1H, CH=N), 7.9-7.3 (m, 5H, ArH). ^{13}C NMR (75 MHz, d^6 -DMSO): δ 161.7, 151.6, 151.5, 150.4, 148.4, 148.2, 140.7, 125.3, 125.2, 121.6, 121.5, 118.9, 118.7.

Data collection, structural determination and refinement

Diffraction intensities for the compounds were collected at 298(2) K using a Bruker D8 VENTURE PHOTON diffractometer with MoK α radiation ($\lambda = 0.71073$ Å). The collected data were reduced using the SAINT program [14], and multi-scan absorption corrections were performed using the SADABS program [15]. The structures were solved by direct methods and refined against F^2 by full-matrix least-squares methods using the SHELXTL [16]. All of the non-hydrogen atoms were refined anisotropically. The amino H atoms were located in difference Fourier maps and refined isotropically with N–H distances restrained to 0.90(1) Å. All other H atoms were placed in idealized positions and constrained to ride on their parent atoms. The crystallographic data for the compounds are summarized in Table 1. Hydrogen bonding information is given in Table 2.

Table 1. Crystallographic and experimental data for the compounds.

Compound	1	2
Formula	$C_{13}H_{10}BrN_3O$	$C_{13}H_9F_2N_3O$
<i>Mr</i>	304.1	261.2
<i>T</i> (K)	298(2)	298(2)
Crystal shape/color	block/colorless	block/colorless
Crystal size (mm 3)	0.27×0.27×0.26	0.18×0.18×0.15
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	$P-1$
<i>a</i> (Å)	7.600(2)	7.6241(6)

<i>b</i> (Å)	11.365(2)	11.3937(9)
<i>c</i> (Å)	14.412(2)	14.335(1)
α (°)	90	79.664(1)
β (°)	101.748(2)	75.990(1)
γ (°)	90	71.159(1)
<i>V</i> (Å ³)	1218.7(4)	1136.4(2)
<i>Z</i>	4	4
<i>D_c</i> (g cm ⁻³)	1.658	1.527
μ (Mo-K α) (mm ⁻¹)	3.363	0.123
<i>F</i> (000)	608	536
Reflections collected	11803	5956
Unique reflections	2311	4176
Observed reflections ($I \geq 2\sigma(I)$)	1695	3618
Parameters	166	350
Restraints	1	2
Min. and max. transmission	0.4637, 0.4751	0.9782, 0.9818
Goodness-of-fit on F^2	1.032	1.046
R_1, wR_2 [$I \geq 2\sigma(I)$] ^a	0.0335, 0.0745	0.0345, 0.0940
R_1, wR_2 (all data) ^a	0.0566, 0.0847	0.0404, 0.1002

^a $R_1 = F_o - F_c / F_o$, $wR_2 = [\sum w(F_o^2 - F_c^2) / \sum w(F_o^2)]^{1/2}$.

Table 2. Hydrogen bond distances (Å) and bond angles (°) for the compounds.

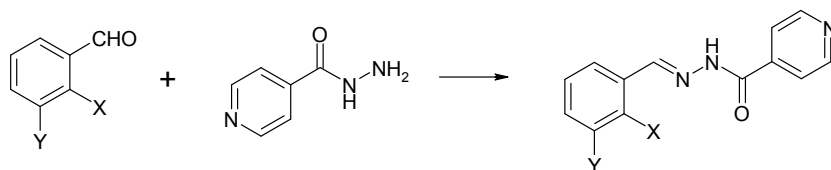
<i>D</i> -H \cdots <i>A</i>	<i>d</i> (<i>D</i> -H)	<i>d</i> (H \cdots <i>A</i>)	<i>d</i> (<i>D</i> \cdots <i>A</i>)	Angle (<i>D</i> -H \cdots <i>A</i>)
1				
O1-H1 \cdots N3 ⁱ	0.90(1)	2.30(1)	3.158(3)	162(3)
2				
N2-H2 \cdots N6	0.90(1)	2.23(1)	3.101(2)	165(2)
N5-H5 \cdots N3 ⁱⁱ	0.90(1)	2.29(1)	3.162(2)	165(2)

Symmetry codes: i) 1 - *x*, -1 - *y*, -*z*; ii) *x*, 1 + *y*, *z*.

RESULTS AND DISCUSSION

Chemistry

Compounds **1** and **2** were readily synthesized by reaction of 1:1 molar ratio of isonicotinohydrazide with 3-bromobenzaldehyde and 2,3-dichlorobenzaldehyde, respectively, in methanol at room temperature, with high yields (over 90%) and purity (Scheme 1). Single crystals suitable for X-ray diffraction were obtained by slow evaporation of the methanol solutions containing the compounds in air. The compounds have been characterized by various physico-chemical methods. Structures of the compounds were further confirmed by single crystal X-ray crystallography.



Scheme 1. The synthetic procedure of the compounds. **1**: X = H, Y = Br; **2**: X = Y = F.

Structure description of the compounds

Figures 1 and 2 give perspective views of compounds **1** and **2**, respectively, with atomic labeling systems. X-ray crystallography reveals that the molecules of the compounds adopt *E* configuration with respect to the methyldene units. The distances of the C7-N1 bonds in both compounds, and the C20-N4 bond in **2**, ranging from 1.26 to 1.27 Å, confirm them as typical double bonds. The shorter distances of the C-N bonds and the longer distances of the C=O bonds for the -C(O)-NH- units than usual, suggests the presence of conjugation effects in the molecules. The remaining bond lengths in the compounds are comparable to each other, and within normal values [17, 18]. The dihedral angles between the benzene and pyridine rings are 5.3(3)° for **1**, and 4.9(3)° and 1.1(3)° for **2**. The crystal structures of the compounds are stabilized by hydrogen bonds and $\pi \cdots \pi$ interactions (Table 3, Figures 3 and 4).

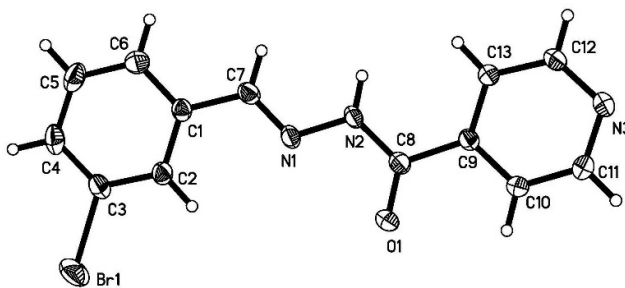


Figure 1. A perspective view of the molecular structure of **1** with the atom labeling scheme. Thermal ellipsoids are drawn at the 30% probability level.

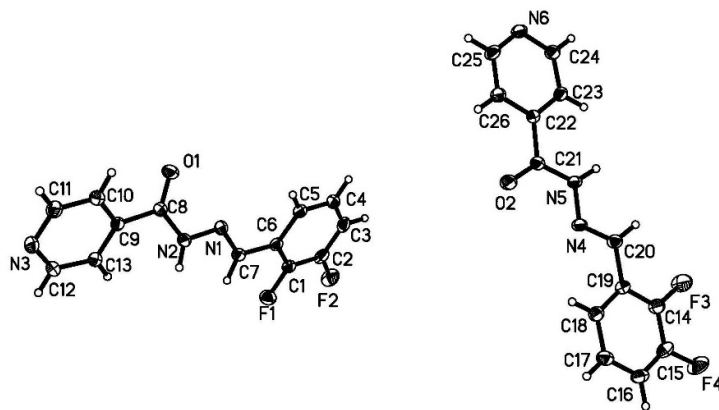


Figure 2. A perspective view of the molecular structure of **2** with the atom labeling scheme. Thermal ellipsoids are drawn at the 30% probability level.

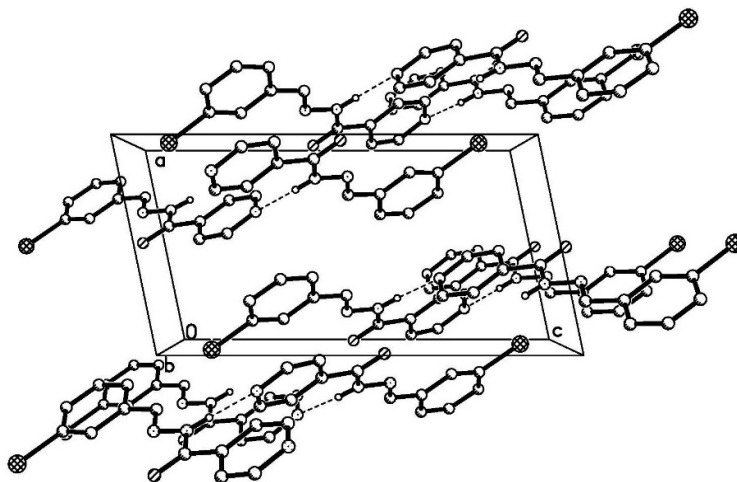


Figure 3. Molecular packing diagram of **1**. Hydrogen bonds are shown as dashed lines.

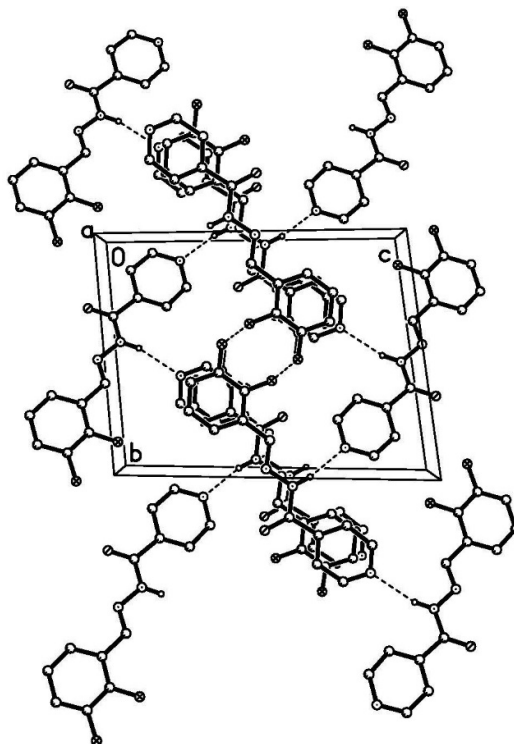


Figure 4. Molecular packing diagram of **2**. Hydrogen bonds are shown as dashed lines.

Table 3. Parameters among planes for the compounds.

Cg	Distance between ring centroids (Å)	Dihedral angle (°)	Perpendicular distance of Cg(I) on Cg(J) (Å)	Perpendicular distance of Cg(J) on Cg(I) (Å)	Beta angle (°)	Gamma angle (°)
1						
Cg(1)-Cg(2) ⁱⁱⁱ	3.854	5	-3.598	-3.461	26.1	21.0
Cg(2)-Cg(1) ^{iv}	4.783	55	-1.970	4.666	12.7	65.7
2						
Cg(3)-Cg(4) ^v	3.746	5	-3.358	-3.451	22.9	26.3
Cg(3)-Cg(4) ^{vi}	3.979	5	3.528	3.541	27.2	27.5
Cg(5)-Cg(6) ^{vii}	3.715	1	-3.490	-3.503	19.4	20.1
Cg(5)-Cg(6) ^{viii}	3.939	1	3.442	3.468	28.3	29.1

Symmetry codes: iii) $-x, 1-y, 1-z$; iv) $1/2+x, 1/2-y, -1/2+z$; v) $-x, -y, 1-z$; vi) $1-x, -y, 1-z$; vii) $1-x, 1-y, -z$; viii) $2-x, 1-y, -z$. Cg(1) and Cg(2) are the centroids of N3-C11-C10-C9-C13-C12 and C1-C6 of **1**; Cg(3), Cg(4), Cg(5) and Cg(6) are the centroids of N3-C11-C10-C9-C13-C12, C1-C6, N6-C24-C23-C22-C26-C25, and C14-C19 of **2**.

Spectra description

In the FT-IR spectra of the compounds, the vibrations of the hydrogen-bonded NH protons are shown as sharp and weak bands at 3197 and 3190 cm^{-1} . The intense bands at 1682 cm^{-1} for **1** and 1687 cm^{-1} for **2** are generated by $\nu(\text{C}=\text{O})$ vibrations, whereas the bands at 1620 cm^{-1} for **1** and 1618 cm^{-1} for **2** are generated by the $\nu(\text{C}=\text{N})$ vibrations.

UV spectra of the compounds are shown in Figure 5. Both compounds have single bands centered at 300 nm, which can be assigned to the $\pi \rightarrow \pi^*$ transitions.

The ^1H and ^{13}C NMR of the compounds were run in d^6 -DMSO. In the ^1H NMR spectra of the compounds, the singlet at about 12.3 ppm can be attributed to the proton of the $-\text{NH}$ groups. The protons of the azomething groups are shown at 8.46 and 8.70 ppm as a singlet for **1** and **2**, respectively. The multiplets in the 8.0–7.3 ppm range can be assignable to the protons of the benzene rings. The doublet peaks in the 8.9–8.8 ppm range can be assignable to the protons of the pyridine rings. In the spectra of the ^{13}C NMR, the resonances at 162 ppm may be assigned to the carbon atoms of the $\text{CH}=\text{N}$ groups. The aromatic carbon atoms are shown in the 118–152 ppm range.

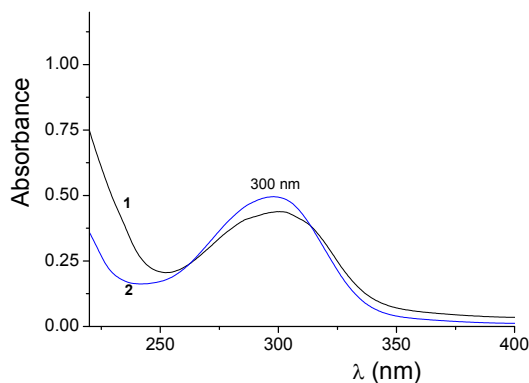


Figure 5. UV spectra of the compounds in methanol solutions.

CONCLUSION

Two isonicotinohydrazone compounds *N'*-(3-bromobenzylidene)isonicotinohydrazide and *N'*-(2,3-difluorobenzylidene)isonicotinohydrazide were prepared and structurally characterized. The crystal structures of the compounds are detailed described. Structures of both compounds are stabilized by hydrogen bonds and $\pi \cdots \pi$ interactions.

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Supporting information

CCDC–1012074 for **1**, and 1012075 for **2** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/const/retrieving.html> or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

REFERENCES

1. Raval, J.P.; Patel, N.H.; Patel, H.V.; Patel, P.S. *In vitro* antimycobacterial activity of novel *N'*-(4-(substituted phenyl amino)-6-(pyridin-2-ylamino)-1,3,5-triazin-2-yl)isonicotino-hydrazide. *Med. Chem. Res.* **2011**, *20*, 274-279.
2. Lourenco, M.C.D.; Ferreira, M.D.; de Souza, M.V.N.; Peralta, M.A.; Vasconcelos, T.R.A.; Henriques, M.D.M.O. Synthesis and anti-mycobacterial activity of (*E*)-*N'*-(monosubstituted-benzylidene)isonicotinohydrazide derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 1344-1347.
3. Ferreira, M.D.; Cardoso, L.N.D.; Goncalves, R.S.B.; da Silva, E.T.; Lourenco, M.C.S.; Vicente, F.R.; de Souza, M.V.N. Synthesis and antitubercular evaluation of *N'*-(*E*)-(hydroxy, methoxy and ethoxy-substituted-phenyl)methylidene]isonicotinohydrazide derivatives. *Lett. Drug Des. Discov.* **2008**, *5*, 137-140.
4. Sriram, D.; Yogeewari, P.; Madhu, K. Synthesis and *in vitro* and *in vivo* antimycobacterial activity of isonicotinoyl hydrazones. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4502-4505.
5. Tsay, O.G.; Manjare, S.T.; Kim, H.; Lee, K.M.; Lee, Y.S.; Churchill, D.G. Novel reversible Zn²⁺-assisted biological phosphate “turn-on” probing through stable aryl-hydrazone salicylaldehyde conjugation that attenuates ligand hydrolysis. *Inorg. Chem.* **2013**, *52*, 10052-10061.
6. Alagesan, M.; Bhuvanesh, N.S.P.; Dharmaraj, N. Potentially cytotoxic new copper(II) hydrazone complexes: Synthesis, crystal structure and biological properties. *Dalton Trans.* **2013**, *42*, 7210-7223.
7. Datta, A.; Liu, P.-H.; Huang, J.-H.; Garribba, E.; Turnbull, M.; Machura, B.; Hsu, C.-L.; Chang, W.-T.; Pevec, A. End-to-end thiocyanato-bridged zig-zag polymers of Cu^{II}, Co^{II} and Ni^{II} with a hydrazone ligand: EPR, magnetic susceptibility and biological study. *Polyhedron* **2012**, *44*, 77-87.
8. Hegazy, W.H.; Al-Motawaa, I.H. Synthesis, characterization, and biological activities of lanthanide(III) complexes of β -diketone hydrazone derivatives. *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.* **2011**, *41*, 1172-1181.
9. Shakhdofa, M.M.E.; Al-Hakimi, A.N.; Elsaied, F.A.; Alasbahi, S.O.M.; Alkwlani, A.M.A. Synthesis, characterization and bioactivity Zn²⁺, Cu²⁺, Ni²⁺, Co²⁺, Mn²⁺, Fe³⁺, Ru³⁺, VO²⁺ and

- UO₂²⁺ complexes of 2-hydroxy-5-((4-nitrophenyl)diazanyl)benzylidene)-2-(*p*-tolylamino)-acetohydrazide. *Bull. Chem. Soc. Ethiop.* **2017**, 31, 75-91.
10. Moksharagni, B.; Reddy, K.H. Spectral characterization and DNA binding properties of Lanthanide(III) complexes with 2-acetylpyridine isonicotinoylhydrazone (APINH). *Bull. Chem. Soc. Ethiop.* **2016**, 30, 221-230.
 11. Kane, C.H.; Tinguiano, D.; Tamboura, F.B.; Thiam, I.E.; Barry, A.H.; Gaye, M.; Retailleau, P. Synthesis and characterization of novel M(II) (M = Mn(II), Ni(II), Cu(II) or Zn(II)) complexes with tridentate N₂O-donor ligand (*E*)-2-amino-*N'*-[1-(pyridin-2-yl)-ethylidene]benzohydrazide. *Bull. Chem. Soc. Ethiop.* **2016**, 30, 101-110.
 12. Zhang, X.-Z.; Li, L.-X.; Li, H.-H.; You, Z.-L.; Zhu, H.-L. Synthesis, characterization and crystal structures of oxovanadium(V) complexes derived from similar aroylhydrazone ligands. *Bull. Chem. Soc. Ethiop.* **2015**, 29, 423-430.
 13. Zhang, M.; Xian, D.-M.; Li, H.-H.; Zhang, J.-C.; You, Z.-L. Synthesis and structures of halo-substituted aroylhydrazones with antimicrobial activity. *Aust. J. Chem.* **2012**, 65, 343-350.
 14. Bruker, *SMART and SAINT*, Bruker AXS Inc.: Madison, Wisconsin, USA; **2002**.
 15. Sheldrick, G.M. *SADABS Program for Empirical Absorption Correction of Area Detector*, University of Göttingen: Germany; **1996**.
 16. Sheldrick, G.M. *SHELXTL V5.1 Software Reference Manual*, Bruker AXS, Inc.: Madison, Wisconsin, USA; **1997**.
 17. Zhang, M.; Xian, D.-M.; Li, H.-H.; Zhang, J.-C.; You, Z.-L. Synthesis and structures of halo-substituted aroylhydrazones with antimicrobial activity. *Aust. J. Chem.* **2012**, 65, 343-350.
 18. Gupta, S.; Rodrigues, L.M.; Esteves, A.P.; Oliveira-Campos, A.M.F.; Nascimento, M.S.J.; Nazareth, N.; Cidade, H.; Neves, M.P.; Fernandes, E.; Pinto, M. Synthesis of *N*-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors. *Eur. J. Med. Chem.* **2008**, 43, 771-780.