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Original Research Article

Synthesis, characterization, x-ray structure and antimicrobial activity of N-(4-chlorophenyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide

Mashooq Ahmad Bhat[1]*, Abdul Arif Khan[2], Hazem A Ghabbour[1,3], Ching Kheng Quah[4] and Hoong-Kun Fun[4]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, [2]Department of Pharmaceutics, College of Pharmacy, King Saud University, PO Box 2457, Riyadh 11451, Kingdom of Saudi Arabia, [3]Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt, [4]X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, 11800, USM, Penang, Malaysia

For correspondence: **Email: mashooqbhat@rediffmail.com; **Tel:** +966-1-4677343; **Fax:** +966-1-4676220*

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Abstract

Purpose: *To synthesize thiosemicarbazide and determine its antimicrobial properties.*
Methods: *Pyridine-based thiosemicarbazide was synthesized, characterized and evaluated for antimicrobial activity. The structure of the synthesized compound was established by spectral analysis, namely, Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance spectroscopy (1H NMR), carbon 13 magnetic resonance spectroscopy (13C NMR), liquid chromatography-mass spectroscopy (LC-MS), single crystal x-ray analysis as well as by elemental analysis.*
Results: *The title compound crystallized in monoclinic form with space group $P2_{1/c}$ of a = 11.6050 (3) Å, b = 13.3130 (4) Å, c = 9.9884 (3) Å, β = 94.911 (2)°, V = 1537.52 (8) Å3, Z = 4 and R_{int} = 0.033. The pyridine ring formed dihedral angles of 74.1(3) and 88.2(5)° with major and minor components of disordered benzene ring, respectively. In the crystal packing, molecules were linked via intermolecular N—H•••N, N—H•••S and N—H•••O hydrogen bonds into zigzag layers. Compound 2 was most effective against Bacillus subtilis ATCC 10400, MRSA 85N, MRSA 66N and MRSA 15G, compared to the reference drugs, ampicillin and ceftriaxone.*
Conclusion: *The title compound represents a good lead for the development of potent antibacterial agent against Gram positive bacteria and MRSA strains.*

Keywords: *Isoniazid, Thiosemicarbazide, Single crystal x-ray, Antimicrobial activity*

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INTRODUCTION

Thiosemicarbazide (NH_2-NH-$CSNH_2$) is the simplest hydrazine derivative of thiocarbamic acid. The chemical behavior of thiosemicarbazide is similar to its analogue semicarbazide, because of the versatility of thione group as compared to keto group, and is responsible for diversified behavior of thiosemicarbazide. The chemistry of thiosemicarbazide and its derivatives is interesting because of their synthetic, analytical applications and biological activities [1].

Thiosemicarbazides and their derivatives display interesting biological activities, including antibacterial [2-6], antifungal [7,8], antimalarial [9,10], anti-trypanosomal [11,12], anti-

mycobacterial [13], anticancer [14], anti-HIV [15], anticonvulsant [16,17] and topoisomerase inhibition activity [18,19]. The titled compound, N-(4-chlorophenyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide, has been reported as the most potent anti-*Candida* agent against *Candida albicans* ATCC 66027, *Candida* spp. 12810 (blood) and *Candida* spp.178 (HVS) with MIC value of 0.09 - 0.78 µg/mL, compared with standard Iitraconazole, which exhibits the inhibitory activity with MIC value of 0.04-1.56 µg/mL [20]. Solubility studies of the titled compound have also been previously reported by our group [21-24].

In the light of previous research and in continuation of our interest in the synthesis of compounds containing thiosemicarbazide [25-27], herein, we report the synthesis, characterization, single crystal X-ray analysis and antimicrobial activity of the title compound, a pyridine based thiosemicarbazide.

EXPERIMENTAL

Chemistry

All the solvents were obtained from Merck. The homogeneity of the compounds was checked by TLC performed on Silica gel G coated plates (Merck). Iodine chamber was used for visualization of TLC spots. The FT-IR spectra were recorded in KBr pellets on a (Spectrum BX) Perkin Elmer FT-IR spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus, and thermometer was uncorrected. NMR Spectra were scanned in DMSO-d6 on a Bruker NMR spectrophotometer operating at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts δ are expressed in parts per million (ppm) relative to TMS as an internal standard and D_2O was added to confirm the exchangeable protons. Coupling constants (J) are in hertz. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), m (multiplet).

The mass spectrum was measured on an Agilent Triple Quadrupole 6410 TQ LC/MS equipped with ESI (electrospray ionization) source. X-ray data were collected on a Bruker APEX-II CCD diffractometer equipped with graphite monochromatic CuKα radiation (λ = 1.54178) at 296 K. Cell refinement and data reduction were done by Bruker SAINT whereas program used to solve structure and refine structure is SHELXS-97. The elemental analysis for C, H, N and S were within the limit of ± 0.4 and ± 0.3 % of the theoretical values respectively.

The title compound, N-(4-chlorophenyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide (**2**), was prepared by the reaction of pyridine-4-carbohydrazide (isoniazid) with p-chlorophenyl isothiocyanate in absolute ethanol (99.8 %).

Synthesis of N-(4-chlorophenyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide

To a solution of pyridine-4-carbohydrazide (isoniazid) **1** (0.01 mmol) in absolute ethanol (99.8 %, 25 mL), p-chlorophenyl isothiocyanate (0.01 mmol) was added. The mixture was refluxed for 2 h and left to cool. The mixture was poured into cold water and solid product was filtered off, washed with water and petroleum ether. The product was dried and finally recrystallized from EtOH to afford compound **2** [28,29].

X-ray crystallography

Single crystals were obtained by slow evaporation from absolute ethanol. A good crystal with dimensions of 0.44 mm x 0.32 mm x 0.14 mm was selected for X-ray diffraction analysis. The final refinement was performed by full-matrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on $F2$. The N-bound and C-bound hydrogen atoms were located in difference Fourier maps (N–H = 0.77(3) - 0.99(5) Å) and positioned geometrically (C–H = 0.93 Å), respectively. Multi-scan absorption correction was applied by the use of SADABS software. The chlorobenzene ring is statistically disordered over two conformations with a site-occupancy ratio of 0.654(6): 0.346(6). Similarity (SAME), similar-ADP (SIMU) and FLAT restraints were used for the major and minor components of the disordered chlorobenzene ring (Cl1/C1–C6). The highest peak is located at 0.88 Å from atom C2, whereas the deepest hole is located at 0.52 Å from atom C1X.

Antimicrobial activity

Microorganisms: Standard bacterial cultures were obtained from American Type Culture Collection (ATCC)/National Collection of type Culture (NCTC) while the methicillin resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta lactamase *E. coli* (ESBL) culture were obtained from Microbiology Unit, Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The drug resistant strains were

characterized by phenotypic testing. All strains were maintained on Mueller Hinton Agar during the experiment.

The tested compounds were dissolved in Muller Hinton Broth with 10 µl/mL DMSO as co-solvent. The concentrations ranging from 500 - 0.976 µg/mL were prepared in 96-well plates with serial dilutions. The control without tested compound was also used to compare antimicrobial efficacy. The organisms were grown in 5 mL Muller Hinton broth overnight at 37 ^{o}C. The overnight growth culture of microorganisms were checked with 0.5 McFarland standards and diluted to match this turbidity standard. Fifty (50) µL of diluted bacterial culture was added to each well of tested compound. The turbidity was recorded and compared with control. IC_{50} was determined with standard method of plotting straight line equation on obtained values. Two drugs, i.e., ceftriaxone and ampicillin were used as standard drug in the experiment.

The MIC of the above drugs was determined through commercial MIC E-test strips for antimicrobial susceptibility testing (AB Biodisc, Dalvagen, SOLNA, Sweden). The 0.5 McFerland standard matched bacterial culture was spread on Mueller Hinton Agar plate and e test strips were placed on it. The lowest concentration of drug inhibiting growth of bacteria on culture plate was determined as MIC [30]. All experiments were performed in triplicate.

RESULTS

The synthesis of isoniazid (INH) derivatives was carried out as shown in (Scheme 1).

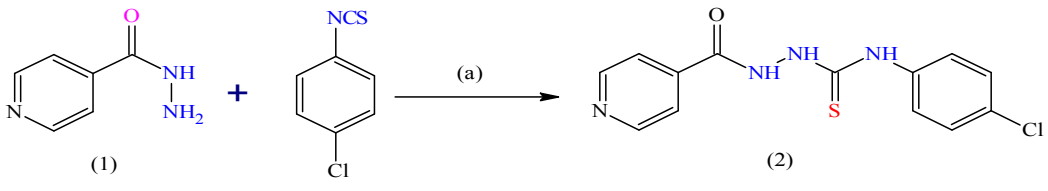
Isoniazid was reacted with p-chlorophenyl isothiocyanate in the presence of absolute ethanol to yield (**2**). The purity of the compound was checked by elemental analysis and thin layer chromatography (TLC). The compound was identified by spectral data. Analytical and spectral data of the synthesized compounds were in good agreement with composition of the synthesized compounds. X-ray analysis reveals that compound **2** crystallizes in monoclinic system with space group $P2_{1/c}$ with a = 11.6050 (3) Å, b = 13.3130 (4) Å, c = 9.9884 (3) Å, β = 94.911 (2)° and V = 1537.52 (8) Å3 (Table 1). Yield: 70 %; M.p. 210-212 °C; IR (KBr) cm^{-1}: 3414 (NH str.), 1663 (C=O str.), 1395 (C=S str.); ^{1}H NMR (DMSO-d6, 500 MHz) δ 7.3-7.4 (4H, m, Ar-H), 7.8 (2H, d, J = 5.0 Hz), 8.7 (2H, d, J = 4.5 Hz), 9.9 (bs, 2H, NH, D_2O exchange), 10.8 (s, 1H, CONH, D_2O exchange.). ^{13}C NMR (DMSO-d6, 125 MHz) δ 206.0, 150.1, 128.5, 127.9, 121.6; MS (ESI) m/z 306.99 $[M]^+$, 308.03 [M+1]+. Analysis: for $C_{13}H_{11}N_4OSCl$ (306.77), calcd. C 50.90, H 3.61, N 18.26, S 10.45 %; found C 50.75, H 3.60, N 18.30, S 10.43 %.

The selected geometric parameters and hydrogen-bond geometry are shown in Table 2 and Table 3, respectively.

In the screening for antimicrobial activity for compound **2**, the compound was evaluated against twelve strains of Gram positive, bacteria Gram negative bacteria and methicillin resistant *Staphylococcus aureus* (MRSA) (Table 4). Compound **2** was effective against Gram-positive bacteria and most promising against *Bacillus subtilis* ATCC 10400. Compound **2** was also effective against methicillin-resistant *Staphylococcus aureus* (MRSA); MRSA 85N, MRSA 66N and MRSA 15G, compared to the reference drugs, ampicillin and ceftriaxone. MRSA 85N was the most susceptible to compound **2**. Compound **2** was ineffective against Gram-negative bacteria.

DISCUSSION

The ^{1}H NMR (DMSO-d6, 500 MHz) of compound **2** revealed the singlet signal for NHC=O at δ 10.8 in addition to broad singlet of NH protons which appeared at δ 9.9.The four aromatic protons of pyridine ring appeared as two doublets at δ 8.7 (J = 4.5 Hz) and δ 7.8 (J = 5.0 Hz). The other four protons of chlorophenyl ring appeared at δ 7.3-7.4 as multiplet. The ^{13}C NMR (DMSO-d6, 125 MHz) of compound 2 exhibited the signal of C=S at δ 206.40, while the signal of C=O appeared at δ 150.19. The aromatic carbons appear at δ 128.55-121-63. The MS (ESI) of compound **2** reveals a peak at m/z 306.99 equal to $[M]^+$ and m/z 308.03 equal to $[M+1]^+$.



Scheme 1: Synthetic pathway of compound **2**. Reagents and conditions: (a) Absolute EtOH, reflux 2 h

Table 1: Crystal data and structure refinement for compound **2**

Crystal data	
Chemical formula	$C_{13}H_{11}ClN_4OS$
M_r	306.77
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	296
a, *b*, *c* (Å)	11.6050 (3), 13.3130 (4), 9.9884 (3)
β (°)	94.911 (2)
V (Å^3)	1537.52 (8)
Z	4
Radiation type	Cu *K*α
μ (mm^{-1})	3.48
Crystal size (mm)	0.44 × 0.32 × 0.14
Data collection	
Diffractometer	Bruker *APEX*-II CCD diffractometer
Absorption correction	Multi-scan *SADABS* Bruker 2014
T_{min}, T_{max}	0.81, 0.87
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10937, 2938, 2537
R_{int}	0.033
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.068, 0.211, 1.09
No. of reflections	2938
No. of parameters	249
No. of restraints	175
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.65, −0.42

Table 2: Selected geometric parameters (Å, °)

Cl1—C3	1.722 (10)	N2—N3	1.388 (3)
Cl1X—C3X	1.727 (17)	N2—C7	1.342 (4)
S1—C7	1.680 (3)	N3—C8	1.337 (3)
O1—C8	1.209 (3)	N4—C12	1.315 (4)
N1—C7	1.341 (4)	N4—C11	1.316 (5)
N1—C6	1.421 (4)		
C6—N1—C7	126.8 (2)	N1—C6—C5	121.2 (4)
N3—N2—C7	122.3 (2)	N1—C6—C1	116.5 (4)
N2—N3—C8	119.6 (2)	S1—C7—N1	125.6 (3)
C11—N4—C12	117.1 (3)	N1—C7—N2	116.9 (2)
Cl1—C3—C2	119.7 (9)	S1—C7—N2	117.6 (2)
Cl1—C3—C4	120.1 (7)	O1—C8—C9	122.1 (2)
Cl1X—C3X—C4X	122.1 (14)	O1—C8—N3	122.2 (2)
Cl1X—C3X—C2X	118.8 (13)	N3—C8—C9	115.69 (19)
N1—C6—C1X	119.0 (7)	N4—C11—C10	123.7 (3)
N1—C6—C5X	134.2 (6)	N4—C12—C13	124.0 (3)

Table 3: Hydrogen-bond geometry (Å, °)

D—H···A	**D—H**	**H···A**	**D···A**	**D—H···A**
N3—H1N1···O1^{i}	0.77 (3)	2.08 (3)	2.786 (3)	152 (3)
N1—H1N3···N4^{ii}	0.99 (5)	2.05 (5)	3.013 (3)	163 (4)
N2—H1N2···S1^{iii}	0.81 (4)	2.51 (4)	3.299 (2)	166 (3)

Symmetry codes: (i) x, −y+3/2, z+1/2; (ii) −x+2, −y+1, −z+1; (iii) −x+2, −y+2, −z+1

Table 4: Antimicrobial activity of compound **2** against tested microorganisms

S/no.	Microorganisms	#MIC_{50} (µg/mL)	MIC (µg/mL) determined through E test strips (AB Biodisc)*	
			TX	AM
1	*MRSA 216P*	577.19	>32	>256
2	*MRSA 66N*	256.5	>32	>256
3	*MRSA 85N*	286.59	>32	>256
4	*MRSA 15G*	210.14	>32	>256
5	*Salmonella typhi ATCC 13311*	1089.96	>32	>256
6	*Escherichia coli ATCC 35218*	--	>32	>256
7	*Escherichia coli ESBL*	6969.73	>32	>256
8	*Bacillus subtilis ATCC 10400*	290.43	>32	>256
9	*Shigella sonii ATCC 11060*	1469.36	>32	6
10	*Proteus vulgaris ATCC 6380*	5653.4	>32	>256
11	*Staphylococcus aureus ATCC 6538*	514.57	>32	1.5
12	*Staphylococcus aureus ATCC 6571*	2372.64	>32	4

**TX = ceftriaxone; AM = ampicillin; #Actual MIC of the compound was difficult to determine due to solubility issue, so 50 % reduction with minimal concentration of compound against tested microorganism was determined All experiments were performed in triplicate*

In the compound **2** (Figure. 1), the chlorobenzene ring is disordered over two positions with a dihedral angle of 64.2(6)° and refined site-occupancies of 0.654(6) : 0.346(6). The pyridine ring (N4/C9-C13) forms dihedral angles of 74.1(3)° and 88.2(5)° with the major and minor components of the disordered benzene ring (C1-C6) respectively, indicating the pyridine ring and benzene ring of the major component are almost perpendicular to each other.

In the crystal packing, molecules are connected to each other, in a zigzag fashion to form sheets (Fig. 2a) and these sheets are stacked along the a axis (Fig. 2b). Molecules are linked *via* intermolecular N1—H1N3•••N4 and N2—H1N2•••S1 hydrogen bonds (Table 2) (into chains propagating in [010]) together with intermolecular N3—H1N1•••O1 hydrogen bonds (Table 2), resulting in the formation of zigzag layers lying parallel to (100) (Fig. 2b). The existence of π•••π interactions involving the centroid of the N4/C9-C13 pyridine ring (π•••π distance = 3.5108(18) Å) further stabilize the molecular packing. The structure of compound **2** was confirmed using spectral data and x-ray single crystal analysis (crystallographic data for the structure **2** has been deposited with the Cambridge Crystallographic Data Center (CCDC) under the number CCDC 1404136.

CONCLUSION

The title compound **2** has been prepared efficiently by the reaction of pyridine-4-carbohydrazide (isoniazid) with p-chlorophenyl isothiocyanate in absolute ethanol under reflux for 2 h and fully characterized by spectral analysis. The 3D structure of the synthesized compound **2** was confirmed by the single crystal X-ray analysis. Compound **2** is more effective against Gram-positive *Bacillus subtilis* ATCC 10400 and methicillin-resistant Staphylococcus aureus strains, viz, MRSA 85N, MRSA 66N and MRSA 15G, than the reference drugs, ampicillin and ceftriaxone. Finally, the titled compound represents a good lead for the development of newer and potent antibacterial agent against Gram-positive and MRSA strains.

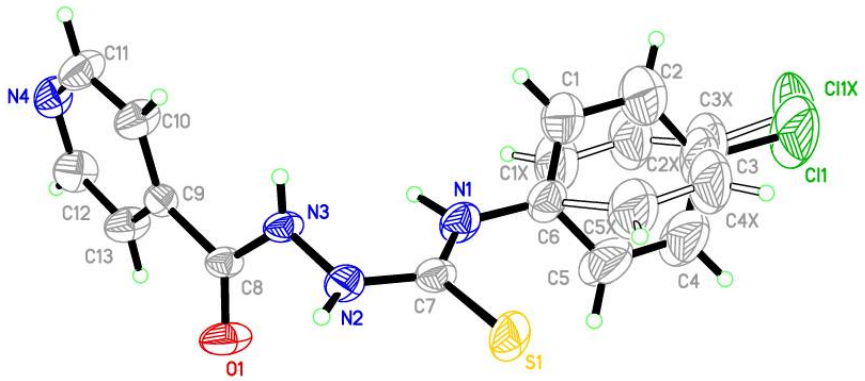


Figure 1: ORTEP diagram of compound **2** with thermal ellipsoids at 40 % probability showing phenyl ring disorder

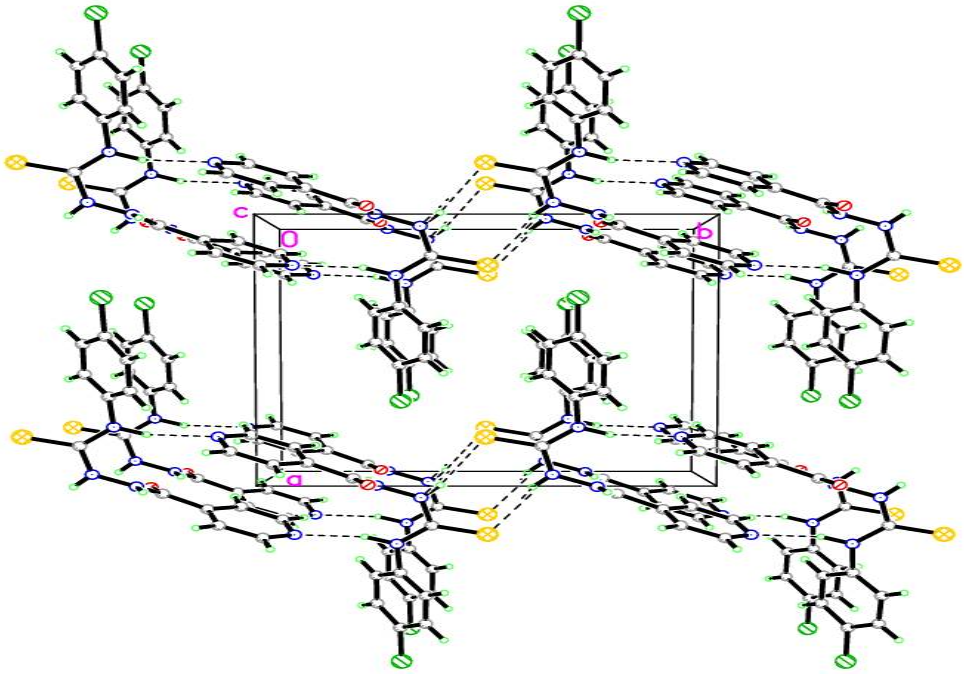


Figure 2: Crystal packing of compound **2**, viewed along (a) *a* and *b* axes and (b) *c* axis. H atoms not involved in intermolecular interactions (dashed lines) and minor disordered component have been omitted for clarity

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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