Synthesis, X-ray Crystallographic Studies and Antibacterial Screening of 1-(5-(4-Chlorophenyl) thiazol-2-yl)hydrazine hydrobromide

Imtiaz Khan[1*], Aliya Ibrar[1], Muhammad Waqas[1] and Jonathan M. White[2]

[1]Department of Chemistry, Quaid-i-Azam University, Islamabad-45320, Pakistan
[2]Bio-21 Institute, School of Chemistry, University of Melbourne, Parkville-3052, Australia

ABSTRACT

The synthesis of 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide was achieved in a single step by condensation of 2-bromo-1-(4-chlorophenyl)ethanone with thiosemicarbazide in absolute ethanol. The structure of the target compound was deduced by modern spectroscopic techniques including FTIR, ^{1}H and ^{13}C NMR spectroscopy and unequivocally confirmed by crystallographic data. The title compound crystallized in the orthorhombic space group P 2_1 2 2_1 with unit cell parameters a = 6.6861(6) Å, b = 8.9683(12) Å, c = 20.4035(5) Å, $\alpha = \beta = \gamma = 90°$, V = 1223.5(2) Å^3, Z = 4, Dc = 1.751 mg/m^3, F(000) = 640 and μ = 8.058 mm^{-1}. The synthesized compound was also evaluated for antibacterial activity.

Keywords: Condensation; thiazole; crystal structure; antibacterial activity.

1. INTRODUCTION

Thiazole is a diverse scaffold in heterocyclic chemistry and is found in various natural products (e.g., epothilone) and pharmacologically essential compounds including anticancer, antiviral and antidiabetic drugs [1-4]. These are ubiquitous building blocks in medicinal chemistry and found to exhibit broad spectrum of biological activities including antibacterial and antifungal activities. Thiazoles and their derivatives are reported as herbicidal, fungicidal, antiallergic, anti-inflammatory, antitubercular, antiarthritic, anti-HIV, analgesic and psychotropic agents [5-7]. In the recent literature [8-12], their considerable antimicrobial activity against a variety of clinically vital fungal strain has been investigated. In particular, these studies confirmed that thiazole derivatives are excellent pharmacophores for the design of bioactive molecules [13,14].

Infectious diseases remain serious and growing threatens to human health worldwide during the past few decades [15,16]. The decrease of susceptibility to antimicrobial agents in current use has also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more rampant for several microorganisms. Therefore, the urgent need for innovation or optimization of antimicrobial agents active against these defiant strains is of vital significance [17,18].

In corollary of the fascinating biological and pharmaceutical properties and synthetic efficacy, we report herein the synthesis of a novel thiazole derivative combined with crystallographic studies.

* Tel.: +92 51 90642232; fax: +92 51 90642241.
Corresponding author E-mail: ikhanqau@gmail.com.

2. MATERIAL AND METHODS

2.1. GENERAL

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AV-300 spectrometer at 300 and 75 MHz respectively. Spectra were recorded in DMSO-d_6 solution using residual solvent peak as the reference and coupling constants were measured in Hertz. Infrared spectrum was recorded on Bruker Optics Alpha FTIR Spectrophotometer. Melting point was recorded on a Sanyo Gallenkamp melting point apparatus in open capillary tube and remains uncorrected. Analytical thin-layer chromatography was carried out with Merck silica gel 60 F_{254} aluminum backed sheets.

2.2. Synthesis

2.2.1. Synthesis of 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide (3)

4-Chlorophenacyl bromide **(1)** (1 mmol) and thiosemicarbazide **(2)** (1 mmol) in ethanol (5 mL) were refluxed for 30 min. The excess solvent was removed under reduced pressure on a rotary evaporator. The crude solid obtained was recrystallized from ethanol to afford the title compound [19].

Yield: 88 %; m.p 181-182 °C; IR (neat, cm^{-1}): 3447-3289 (N-H), 3054 (C_{sp2}-H), 1653 (C=N), 1585, 1499 (C=C_{Ar}), 1187 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (s, 1H, N-H), 7.95 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.62 (s, 1H, C-$H_{thiazole}$), 7.50 (d, 2H, *J* = 8.4 Hz, Ar-H), 5.62 (s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.8, 148.4, 133.0, 132.9, 129.2, 128.0, 107.9.

2.3. X-ray Structure Determination

A suitable single crystal of the target compound having dimensions 0.4048 × 0.2270 × 0.2195 mm was selected. All the reflection data for the title compound were collected on an Oxford SuperNova CCD diffractometer using Cu-Kα (λ = 1.54184 Å) X-radiation at 130 K. A total of 2813 reflections were collected, of which 1883 (-7<=h<=7, -6<=k<=10, -24<=l<=23) were treated as observed. The structure was solved by direct methods and refined by full-matrix least squares using *SHELX*-97 [20]. With the exception of those hydrogen atoms bonded to nitrogen, all other hydrogen atoms were refined in idealized positions.

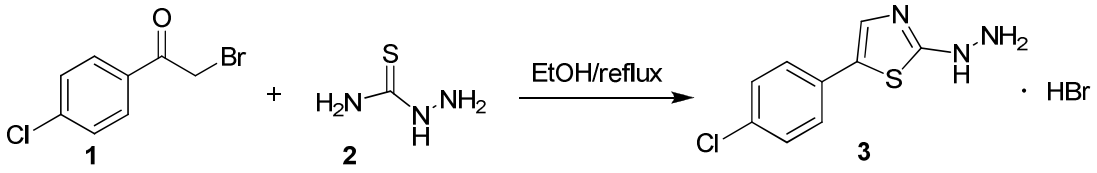
2.4. Biological Screening

2.4.1. Antibacterial activity

In vitro evaluation of antibacterial activity of the newly synthesized compounds was carried out by agar well diffusion assay against ten different Gram positive and Gram negative bacteria [21]. Antibacterial activity was determined by using the Mueller Hinton Agar (MHA). The fresh inoculums of these bacteria were prepared and diluted by sterilized normal saline. The turbidity of these cultures was adjusted by using 0.5Mc-Farland. A homogeneous bacterial lawn was developed by sterile cotton swabs. The inoculated plates were bored by 6 mm sized borer to make the wells. The sample dilutions were prepared by dissolving sample (1.0 mg) in 1.0 mL of DMSO used as negative control in this bioassay. The equimolar concentration of Levofloxacin (1.0 mg/mL), a broad spectrum antibiotic (positive control) was prepared. These plates were incubated at 37 °C for 24 hours. Antibacterial activity of the prepared compound was determined by measuring the diameter of zone of inhibition (mm, ± standard deviation) and presented by subtracting the activity of the negative control.

3. RESULTS AND DISCUSSION

The synthetic pathway that leads to the formation of the title compound **3** is sketched in Scheme-1. By adopting the literature procedure [19], condensation of 2-bromo-1-(4-chlorophenyl)ethanone with thiosemicarbazide in absolute ethanol afforded the title compound in good yield. In IR spectrum, strong bands at 3447-3289 cm^{-1} and 1653 cm^{-1} were assigned to the N-H and C=N group, respectively. The disappearance of methylene stretching frequency in reactant **1** around 3000 cm^{-1} also indicated the formation of required product. The ^{1}H NMR spectrum displayed a distinctive singlet at 7.62 ppm for thiazole proton and two other singlets at 10.05 and 5.62 ppm attributed to N-H and NH_2 groups respectively, confirmed the formation of target molecule. In ^{13}C NMR spectrum, two characteristic signals at 166.8 and 148.4 ppm also confirmed the formation of thiazole ring. Other aromatic carbons were found at appropriate chemical shift values.



Scheme 1. Synthesis of title compound 3

The molecular structure was further confirmed by single crystal X-ray diffraction studies. Experimental details, atomic coordinates with equivalent isotropic temperature factors, selected bond distances, angles and dihedral angles were measured (see supporting information). H-bond geometries of compound **3** are tabulated in Table 1. A thermal ellipsoid plot at 20% probability level for compound **3** is presented in Fig. 1.

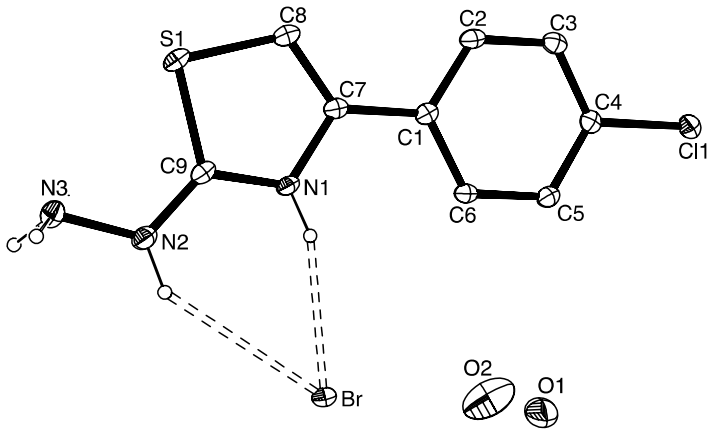


Fig. 1. Thermal ellipsoid plot for compound 3. Ellipsoids are at the 20% probability level. Hydrogen atoms attached to the disordered water molecules were not located

Crystals of compound **3** are racemically twinned as indicated by the absolute structure parameter, which refined to 0.45(3). Disordered water molecules form a column running along the x-axis (Fig. 2) and make weak contacts with the bromide counterion (O1…Br; 3.329(7) Å, O2…Br; 3.50(1) Å), however there are no significant contacts with the hydrazine nitrogen's (N2 and N3) or with the thiazole nitrogen (N1). The phenylthiazole rings are

essentially coplanar and are π-stacked along the x-axis with an interplanar distance of ca. 3.42 Å (Fig. 2).

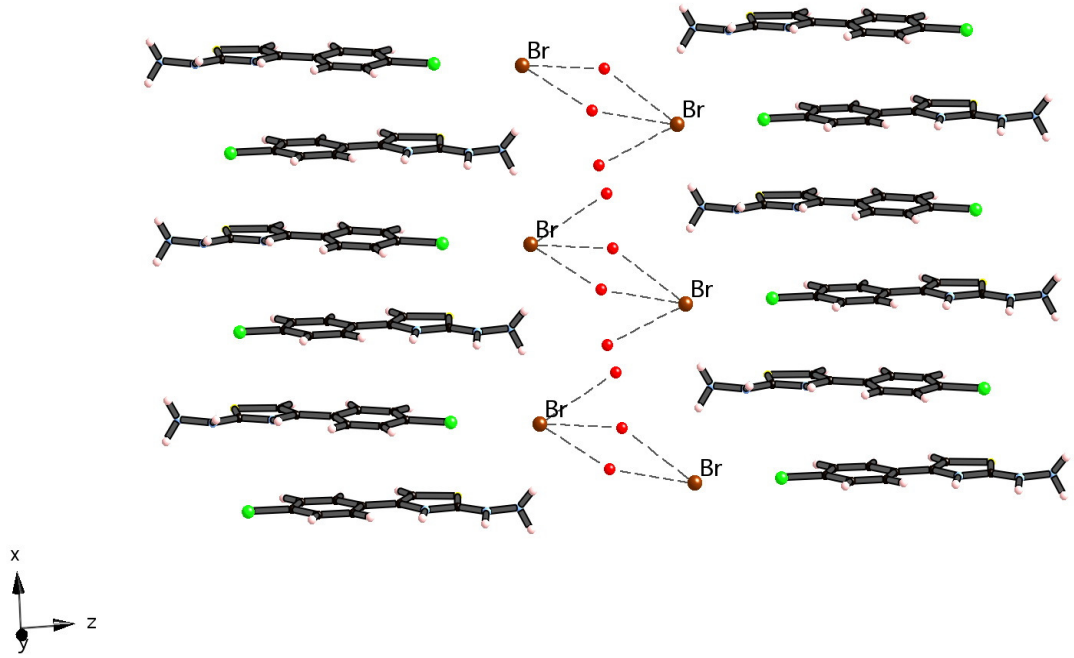


Fig. 2. Partial crystal packing diagram of compound 3 showing disordered water molecules, and the off-set π-stacking arrangement of the planar phenylthiazole groups extending along the x-axis

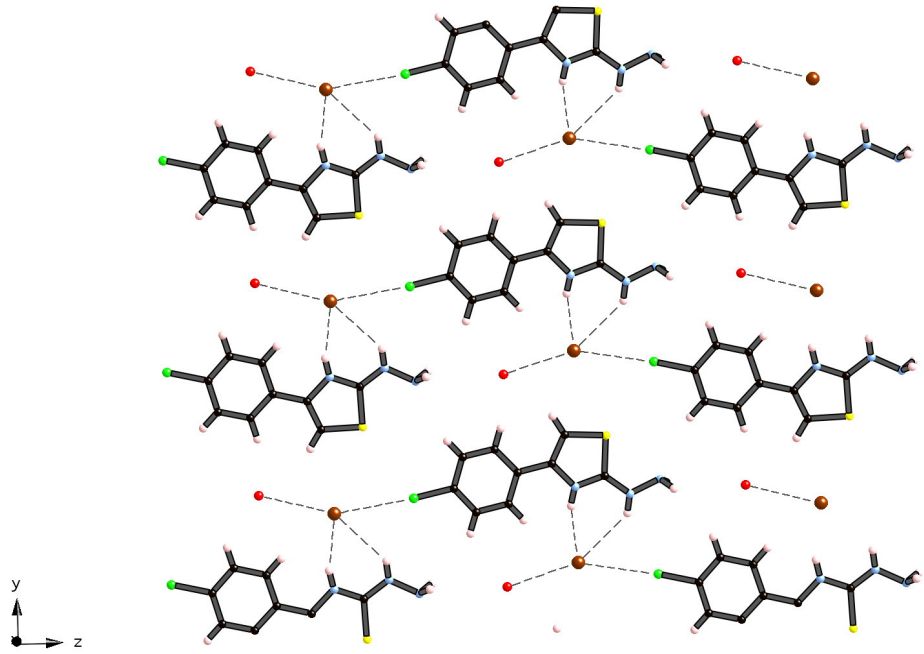


Fig. 3. Partial crystal packing diagram of compound 3 showing the hydrogen bond contacts involving the bromide counterion in the y-z plane

The bromide counterion forms hydrogen bonds with imidazole nitrogen N1 and the hydrazine nitrogen N2 within the y-x plane (Table 1), while there are hydrogen bonds between the bromide ion and the hydrogens attached to N3 which project above and below this plane (Fig. 3).

Table 1 Hydrogen bonds for compound 3 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H...Br	0.83(4)	2.43(4)	3.222(3)	160(3)
N(2)-H(2A)...Br	0.87(4)	2.96(4)	3.635(3)	136(3)
N(3)-H(3A)...Br#1	0.96(5)	2.75(5)	3.612(4)	150(3)
N(3)-H(3B)...Br#1	0.92(5)	2.76(5)	3.652(4)	165(4)

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1,-z+3/2 ; #2 x+1/2,-y+1,-z+3/2

3.1. Antibacterial evaluation of target compound

In vitro antibacterial screening of the newly synthesized compound **3** was carried out by agar well diffusion method against ten different Gram positive and Gram negative bacteria and the results are summarized in Table 2. The results revealed that the synthesized compound showed moderate to good antibacterial efficacy against different bacterial strains. The title compound exhibited strong activity against *B. subtilis* and *S. aureus* respectively, as compared to standard drug.

Table 5 Antibacterial activity of the title compound 3

Compound	***P.m.***	***B.s.***	***E.c.***	***S.a.***	***P.p.***	***P.a.***	***S.t.***	***M.l.***	***S.f.***	***K.p.***
3	17	19	08	24	17	23	11	18	21	07
Standard Levofloxacin	30	20	30	25	30	28	30	25	30	25

Activity is presented in millimeter (mm)

Pasteurella multocida ***(P.m.)***, *Bacillus subtilis* ***(B.s.)***, *Escherichia coli* ***(E.c.)***, *Staphylococcus aureus* ***(S.a.)***, *Pseudomonas putida* ***(P.p.)***, *Pseudomonas aeruginosa* ***(P.a.)***, *Salmonella typhi* ***(S.t.)***, *Micrococcus luteus* ***(M.l.)***, *Shigella flexineri* ***(S.f.)*** and *Klebsiella pneumonae* ***(K.p.)***.

4. CONCLUSION

In summary, 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide has been made conveniently and successfully characterized by spectroscopic techniques and single crystal X-ray diffraction data. The title compound has also been screened for antibacterial activity which exhibited strong efficacy against *B. subtilis* and *S. aureus*, respectively. The synthesized thiazole scaffold may be used as an important building block in heterocyclic chemistry.

SUPPLEMENTARY DATA

CCDC 867531 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Department of Chemistry, Quaid-i-Azam University, Islamabad-45320, Pakistan, for providing spectroscopic facilities.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

[1] Wu YJ, Yang BV, In Progress in Heterocyclic Chemistry; Gribble GW, Joule JA. New York. 2010;22:259-348.
[2] Doggrell SA. A novel drug with potential for the treatment of imatinib-resistant chronic myeloid leukaemia. Expert Opin Invest Drugs. 2005;14:89-91.
[3] Lin TI, Lenz O, Fanning G, Verbinnen T, Delouvroy F, Scholliers A, et al. *In vitro* activity and preclinical profile of TMC435350, a potent hepatitis C virus protease inhibitor. Antimicrob. Agents Chemother. 2009;53:1377-1385.
[4] Dang Q, Kasibhatla SR, Jiang T, Fen K, Liu Y, Taplin F, et al. Discovery of Phosphonic Diamide Prodrugs and Their Use for the Oral Delivery of a Series of Fructose 1,6-Bisphosphatase Inhibitors. J Med Chem. 2008;51:4331-4339.
[5] Katsura Y, Nishino S, Ohno M, Sakane K, Matsumoto Y, Morinaga C, et al. Anti-Helicobacter pylori Agents. 3. 2-[(Arylalkyl)guanidino]-4-furylthiazoles. J Med Chem. 1999;42:2920-2926.
[6] Yu XY, Hill JM, Yu G, Wang W, Kluge AF, Wendler P, et al. Synthesis and structure-activity relationships of a series of novel thiazoles as inhibitors of aminoacyl-tRNA synthetases. Bioorg Med Chem Lett. 1999;9:375-380.
[7] Karegoudar P, Karthikeyan MS, Prasad DJ, Mahalinga M, Holla BS, Kumari NS. Synthesis of some novel 2,4-disubstituted thiazoles as possible antimicrobial agents. Eur J Med Chem. 2008;43:261-267.
[8] Cukurovali A, Yilmaz I, Gur S, Kazaz C. Synthesis, antibacterial and antifungal activity of some new thiazolylhydrazone derivatives containing 3-substituted cyclobutane ring. Eur J Med Chem. 2006;41:201-207.
[9] Maccioni E, Cardia MC, Bonsignore L, Plumitallo A, Pellerano ML, De Logu E. Synthesis and anti-microbial activity of isothiosemicarbazones and cyclic analogues. Farmaco. 2002;57:809-817.
[10] Özdemir A, Turan-Zitouni G, Kaplancikli ZA, Demirci F, Iscan G. Studies on Hydrazone Derivatives as Antifungal Agents. J Enzym Inhib Med Chem. 2008;23:470-475.
[11] Turan-Zitouni, G, Fehrentz JA, Chevallet P, Martinez J, Kaplancikli ZA, Özdemir A, et al. Synthesis and Antibacterial Activity of tert-Butyl [1-benzyl-2[(4-aryl-2-thiazolyl)hydrazono]ethyl]carbamate Derivatives. Arch Pharm Chem Life Sci. 2007;340:310-314.
[12] Bharti SK, Nath G, Tilak R, Singh SK. Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring. Eur J Med Chem. 2010;45:651-660.
[13] De Souza MVN. Synthesis and Biological Activity of Natural Thiazoles: An Important Class of. Heterocyclic Compounds. J Sulfur Chem. 2005;26:429-449.
[14] Vicini P, Geronikaki A, Incerti M, Zani F, Dearden J, Hewitt M. 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones with antimicrobial activity: Synthesis and structure–activity relationship. Bioorg Med Chem. 2008;16:3714-3724.
[15] Talbot GH, Bradley J, Edwards GE, Gilbert D, Scheld M, Bartlett JG. Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task

Force of the Infectious Diseases Society of America. Clin Infect Dis. 2006;42:657-668.
[16] Shao PL, Huang LM, Hsueh PR. Recent advances and challenges in the treatment of invasive fungal infections. Int J Antimicrob Agents. 2007;30:487-495.
[17] Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov. 2007;6:29-40.
[18] Bayrak H, Demirbas A, Karaoglu SA, Demirbas N. Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. Eur J Med Chem. 2009;44:1057-1066.
[19] Bhat KS, Holla BS. Novel three component synthesis of 1,2,4-triazolo[3,4-b]thiazoles and their antimicrobial activity. Phosphorus Sulfur Silicon Relat Elem. 2004;179:1019-1026.
[20] Sheldrick GM. A short history of SHELX. Acta Cryst. 2008;A64:112-122.
[21] Okeke MI, Iroegbu CU, Eze EN, Okoli AS, Esimone CO. Evaluation of extracts of the root of Landolphia owerrience for antibacterial activity. Ethnopharmacol. 2001;78:119-127.