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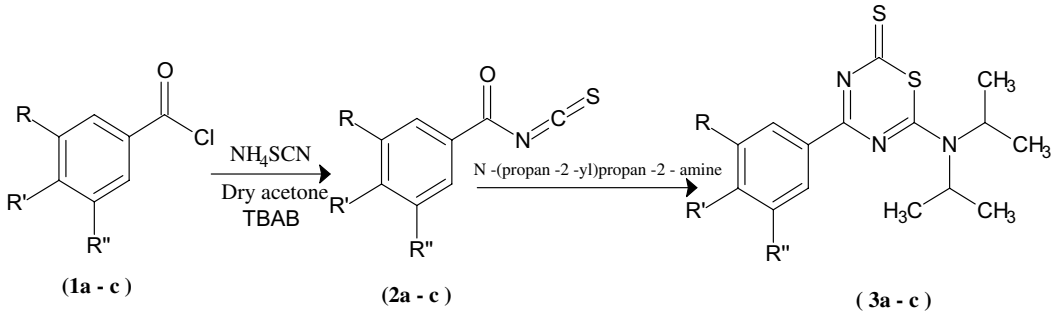
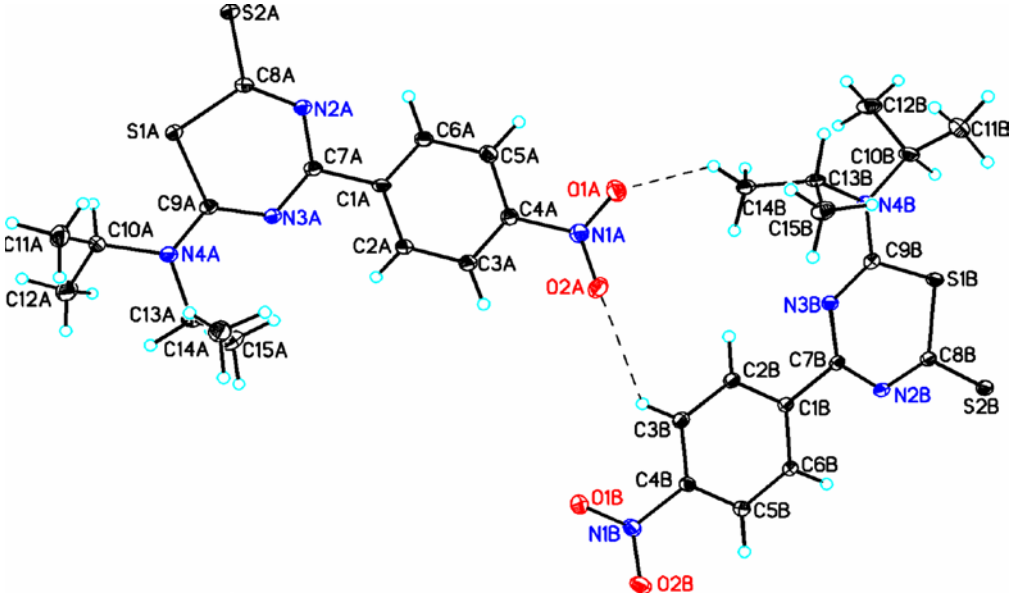


(1a - c) (2a - c) (3a - c)

Where **3a** R, R" = H, R' = NO_2
3b R, R" = NO_2, R' = H
3c R, R" = H, R' = Br



ORGANIC CHEMISTRY | RESEARCH ARTICLE

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Sohail Saeed

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A simple, convenient, and one pot synthetic route for the preparation of 1,3,5-thiadiazines-2-thione heterocyclic compounds and their antifungal activity

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Abstract: A series of new heterocyclic 1,3,5-thiadiazines-2-thione with aroyl/aryl substituents (**3a-c**) were synthesized by reacting isothiocyanates with N- (propan-2-yl) propan-2- amine in the presence of tetrabutylammonium bromide as phase transfer catalyst. The structures of these novel compounds were characterized by IR, mass spectrometry, and elemental analysis. The crystal structures were determined from single-crystal X-ray diffraction data. The synthesized compounds were tested *in vitro* against *Fusarium solani, A. fumigatus,* and *Aspergillus flavus* using standard drugs.

Subjects: Chemical Spectroscopy; Crystallography; Organic Chemistry

Keywords: thiadiazines; heterocyclic compounds; single-crystal X-ray diffraction; phase transfer catalyst (PTC); antimicrobial activity

1. Introduction

Heterocyclic compounds are attractive to medicinal chemists because of their unique chemical properties and wide-ranging biological activities. Despite significant research progress on heterocyclic ring systems, efforts are ongoing to identify novel heterocyclic compounds with potent bioactivities.

Sohail Saeed

ABOUT THE AUTHOR

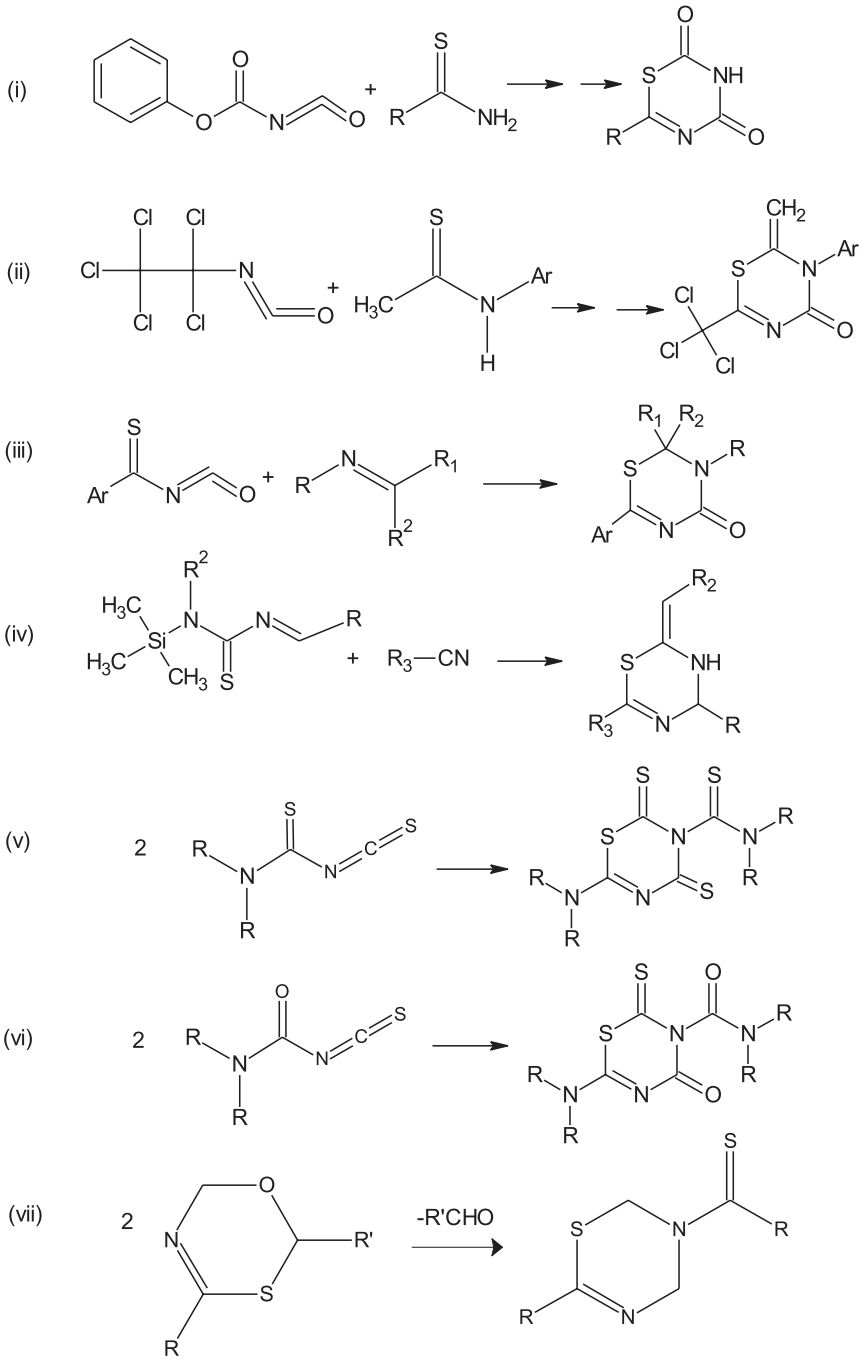
Sohail Saeed has completed his MSc in Organic Chemistry from the University of the Punjab, Lahore, and PhD in Organic Chemistry in 2013 under the supervision of Naghmana Rashid from the Allama Iqbal Open University, Islamabad, Pakistan. He has commissioned a state-of-the-art "Phenolic and Epoxy based Prepregging Laboratory" in the Centers of Excellence in Science and Applied Technologies, Islamabad. He has 15 years' experience in the field of prepregs development, high-pressure curing, bagging techniques for autoclave curing, and various other processes for the production of hi-tech composite structures. His current research interest focuses on hi-tech composite materials, CVD, semiconducting thin films from single-source precursors, medicinal chemistry, and heterocyclic chemistry. He has published more than 60 research papers in well-reputed international journals. He has won three consecutive Research Productivity Awards (2010–2012) from the Ministry of Science and Technology, Pakistan. He is presently working as a deputy project director in CESAT, Islamabad, Pakistan.

PUBLIC INTEREST STATEMENT

Compounds derived from thiadiazines-2-thione have received particular attention due to their pharmacological properties. Numerous studies have been published on the antiparasitic properties of these derivatives. These compounds also present antibacterial, antifungal, antiviral, and anticancer activity. In addition, the high lipid solubility and ease of enzymatic hydrolysis generally associated with this heterocycle have promoted its use as a biolabile prodrug in the design of drug delivery systems. Generally, lipophilic groups at both the N-3 and N-5 positions lead to compounds with high antimicrobial activity, but also high toxicity. The presence of a hydrophobic group at N-5 favored the antimicrobial activity of the thiadiazine derivatives. The aforementioned properties and the possibility to attach several structurally distinct substituents to the heterocycle ring to modify either the biological or physicochemical properties of these compounds prompted to use this heterocycle as a template in many research programs aimed at the development of new bioactive compounds.

Five-membered heterocycles, such as thiazine, imidazole, oxazole, thiazole, oxadiazole, and thiadiazole, are common and typically possess biological activities. In recent decades, research has indicated that the thiazine ring is an important framework with broad-spectrum biological activity. 1,3,5-Thiadiazines are useful as herbicides (Rodríguez, Suárez, & Albericio, 2012), antimicrobial drugs (El-Shorbagi, 2000), insecticides (Coro, Piñeiro, Monzote, Rodríguez, & Suárez 2011), and miticides (Aboul-Fadl, Hussein, El-Shorbagi, & Khallil, 2002). Most reported 3,4-dihydro-2*H*-1,3,5-thiadiazines contain ring carbonyl or thiocarbonyl groups: such compounds were previously synthesized (Scheme 1) by (i) treatment of heterocyclic primary thioamides with phenoxycarbonyl isocyanate (Coburn, Ho, & Bronstein, 1982; (ii) cyclization of perchloroethyl isocyanate with thioamides (Eltsov et al., 2008); (iii) reaction of

Scheme 1. General procedures for the synthesis of thiadiazines.



thiobenzoyl isocyanates with C=N bonds in arylhydrazones, benzaldazines (Tsuge & Kanemasa, 1972), carbodiimides, or anils (Tsuge & Sakai, 1972); (iv) [4 + 2] cycloaddition of 1-thia-3-azadienes with electron-deficient nitriles; (v) dimerization of thiocarbamoylisothiocyanates; or (vi) dimerization of carbamoyl isothiocyanates (Goerdeler & Lüdke, 1968). Previously reported compounds of type 5 were made by thermolysis of 4-substituted and 2,4-disubstituted 6*H*-1,3,5-oxathiazines followed by dimerization (Giordano, Belli, & Abis, 1979) (Scheme 1), (vii). In view of the utility of these compounds in various fields and as a part of the wider program to provide alternative routes for the synthesis of various five and six-membered organic heterocyclic compounds, now the method for the synthesis 1,3,5-thiathiazines-2-thione heterocyclic is reported.

2. Experimental protocols

2.1. Materials and physical measurements

Analytical grade 3,5-dinitrobenzoyl chloride (≥98.0%), 4-bromobenzoyl chloride (99%), 4-nitroobenzoyl chloride (99%), sodium thiocyanate (99%), tetrabutylammonium bromide (TBAB) (≥98%), and *N*-(propan-2-yl) propan-2-amine were purchased from Sigma-Aldrich. Analytical grade solvents, such as tetrahydrofuran, acetonitrile, dichloromethane, ethanol, and others, were purchased from Riedel-de Haën (Germany). The ethanol and acetone were dried using standard procedures (Perrin, Armarego, & Perrin, 1988). Infrared spectra were recorded on a Specac single reflectance Attenuated Total Reflectance instrument (4,000–400 cm^{-1}, resolution 4 cm^{-1}). Melting point was recorded on Electrothermal IA9000 series digital melting point apparatus. Elemental analysis was carried out using Perkin Elmer CHNS/O 2400. Obtained results were within 0.4% of the theoretical values. The mass spectrum was run on a Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV). Thin layer chromatography analysis were carried out on 5 × 20 cm plate coated with silica gel GF_{254} type 60 (25–250 mesh) using an ethyl acetate–petroleum ether mixture (1:2) as solvent.

2.2. X-ray structure determination

A red-orange plate 0.42 × 0.18 × 0.06 mm^3 was mounted on a glass fiber in inert oil. Measurements were performed at 123 K on an Oxford Diffraction Xcalibur Ruby Gemini diffractometer with mirror-focused Cu-Kα radiation to $2\theta_{max}$ 67.50° (99.1% complete to 67.50°). The data were corrected for absorption using the multi-scan method. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2 using the program SHELXL-97 (Sheldrick, 2008). The non-hydrogen atoms were refined anisotropically. NH hydrogens were refined freely, other H atoms using a riding model.

2.3. Synthesis

2.3.1. Synthesis of 6-(dipropan-2-ylamino)-4-(4-nitrophenyl)-2H-1,3,5-thiadiazine-2-thione **(3a)**

A solution of 4-nitrobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of the corresponding *N*-(propan-2-yl) propan-2-amine (0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its volume of cold water, whereupon the red-orange target compound precipitated. The solid product was washed with water and purified by recrystallization from an ethanol–dichloromethane mixture (1:2). M.p.: 127–128°C. Yield: 3.5 g (89%). IR (ν_{max}/cm): 2,932, 2,839 (C–H), 1,584 (C=N), 1,280 (C–N), 1,258 (C=S). Elemental analysis for $C_{15}H_{18}N_4O_2S_2$ (MW = 350.45) in wt % calc. C = 51.41, H = 5.18, N = 15.99, S = 18.30 and found to be C = 51.37, H = 5.21, N = 16.10, S = 18.28. EI MS, m/z (%): 350.42.

2.3.2. Synthesis of 4-(3,5-dinitrophenyl)-6-(dipropan-2-ylamino)-2H-1,3,5-thiadiazine-2-thione **(3b)**

A solution of 3,5-dinitrobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a

solution of the corresponding *N*-(propan-2-yl)propan-2-amine (0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its volume of cold water, whereupon the target compound precipitated. The solid product was washed with water and purified by recrystallization from ethanol. M.p.: 155–156°C. Yield: 3.4 g (86%). IR (ν_{max}/cm): 2,931, 2,840 (C–H), 1,586 (C=N), 1,282 (C–N), 1,259 (C=S). Elemental analysis for $C_{15}H_{17}N_5O_4S_2$ (MW = 395.45) in wt % calc. C = 45.56, H = 4.33, N = 17.71, S = 16.22 and found to be C = 45.59, H = 4.31, N = 17.68, S = 16.25. EI MS, m/z (%): 395.44.

2.3.3. Synthesis of 6-(dipropan-2-ylamino)-4-(4-bromophenyl)-2H-1,3,5-thiadiazine-2-thione **(3c)**

A solution of 4-bromobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of the corresponding *N*-(propan-2-yl) propan-2-amine (0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its volume of cold water, whereupon the target compound precipitated. The solid product was washed with water and purified by re-crystallization from ethanol. M.p.: 129–130°C. Yield: 3.3 g (91%). IR (ν_{max}/cm): 2,933, 2,838 (C–H), 1,587 (C=N), 1,281 (C–N), 1,255 (C=S). Elemental analysis for $C_{15}H_{18}BrN_3S_2$ (MW = 384.35) in wt % calc. C = 46.87, H = 4.72, N = 10.93, S = 16.68 and found to be C = 46.85, H = 4.73, N = 10.91, S = 16.67. EI MS, m/z (%): 384.33.

3. Antifungal screening

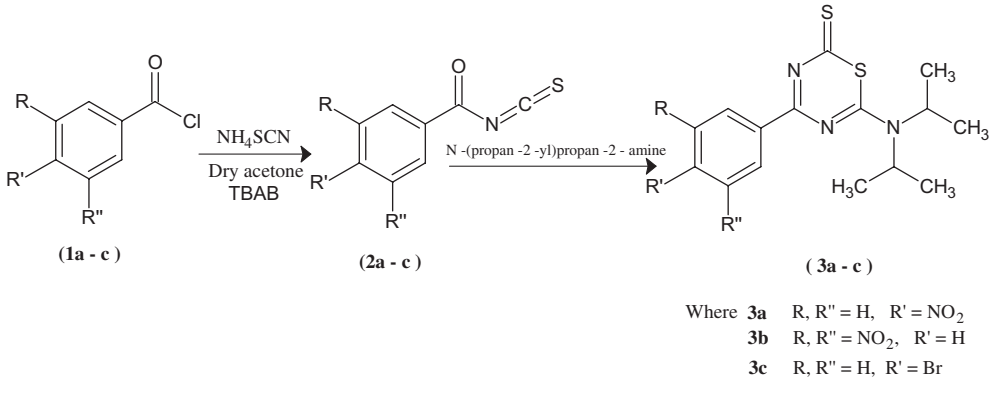
The antifungal activity was carried out in DMSO using the agar tube dilution method. Sabouraud dextrose agar (Merck) was prepared by dissolving 6.5 g/mL in distilled water and the pH was adjusted to 5.6. The contents were dissolved and dispensed in 4 mL aliquots into screw-capped tubes and were autoclaved at 121°C for 21 min. The tubes were allowed to cool to 50°C and non-solidified SDA was loaded with 66.6 µL of compound by pipette from stock solution, giving a final concentration of 200 µg/mL. The tubes were then allowed to solidify in a leaning position at room temperature. Tubes were prepared in triplicate for each fungus species. The tubes containing solidified media and test compound were inoculated with 4 mm diameter pieces of inocula, taken from a 7-day-old culture of fungus. Other media supplemented with DMSO and nystatin were used as negative and positive control, respectively. The tubes were incubated at 27°C for 7 days. Cultures were examined twice weekly during the incubation. Growth in media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control (Saeed, Rashid, Jones, Hussain, & Bhatti, 2010).

4. Results and discussion

4.1. Synthesis and characterization

A series of new heterocyclic 1,3,5-thiadiazines **3a-c** with aroyl substituents (Scheme 2) were prepared by slight modification of published procedures (Saeed, Rashid, Hussain, Jasinski et al., 2013; Saeed,

Scheme 2. Synthesis of heterocyclic 1,3,5-thiadiazines.



Rashid, Hussain, & Jones, 2009; Saeed, Rashid, Hussain, Malik, & O'Brien, 2013; Saeed, Rashid, Jones, & Tahir, 2011). The use of phase transfer catalysts (PTCs) as a method of promoting a heterogeneous reaction system is gaining recognition (Saeed, Rashid, Jones, Ali, & Hussain, 2010; Saeed & Wong, 2012). In search of improved methods to prepare the target heterocyclic 1,3,5-thiadiazines-2-thione by reacting isothiocyanates with nucleophiles, we have found the use of TBAB as PTC can afford substituted aroyl isothiocyanates in good yield, as reported here. All the structures of newly synthesized compounds were assigned on the basis of their IR, elemental analysis, and mass spectrometric data. All the synthesized heterocyclic compounds were soluble in DMF, DMSO, ethanol, and ethyl acetate.

4.2. Single-crystal X-ray crystallography

Single crystals of **3a** suitable for X-ray diffraction studies were obtained by evaporation from dichloromethane: ethanol mixture (2:1). The bond lengths and angles are similar to those in structurally related compounds (Bélai, Sohár, Maekawa, Párkányi, & Matolcsy, 1981). The thiadiazine ring exists in a half-chair conformation with S1A, C8A, C9A, N2A, and N3A all coplanar. The phenyl ring is slightly inclined to the above plane. There are no unusually short intermolecular interactions. The structures of the other compounds were assigned by analogy and by spectral comparison. Figure 1 shows a perspective view of the molecular structure and Figure 2 represents the packing diagram. The crystal data and structure refinement and selected bond lengths and angles are listed in Tables 1 and 2, respectively. Table 3 illustrates the data of hydrogen bonding.

4.3. Pharmacological evaluation

Primary bioassay screening provides the first indication of bioactivities and helps in the selection of lead compounds for secondary screening for detailed pharmacological evaluation. The synthesized heterocyclic 1,3,5-thiadiazines **3a-c** were checked for their antifungal activity against three fungal strains: *Fusarium solani, A. fumigatus,* and *Aspergillus flavus*. The antifungal activity was carried out in DMSO using the agar tube dilution method (Reiner, 1980). Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control. No significant activity against yeast was detected. All the compounds in the series showed weak antimicrobial activity against *F. solani, A. fumigatus* and *A. flavus* with 25–30% inhibition, which shows low activity.

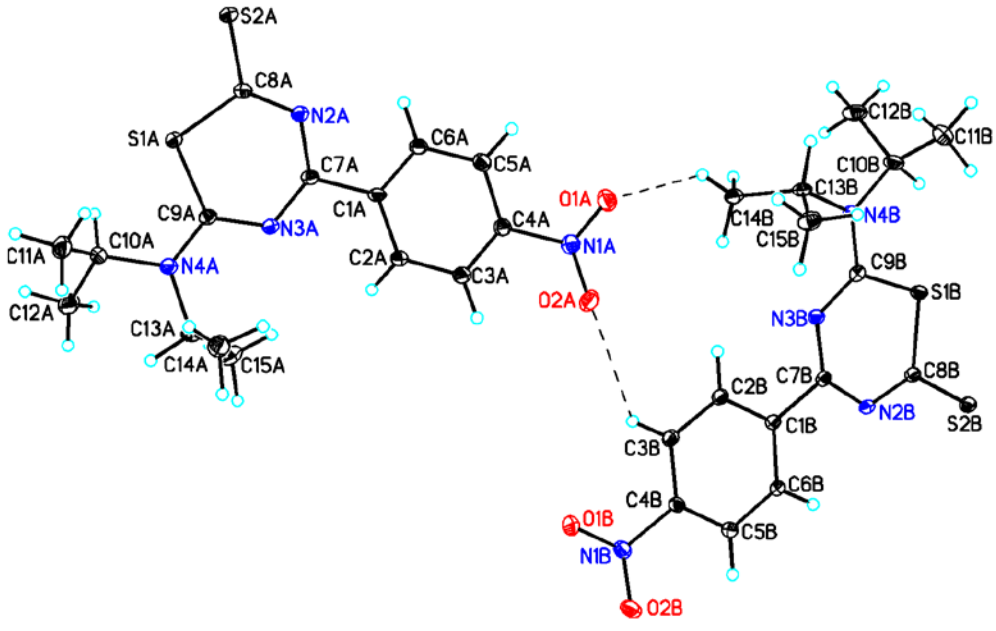


Figure 1. Perspective view of the X-ray structure of 3a.

Figure 2. Unit cell diagram of 3a.

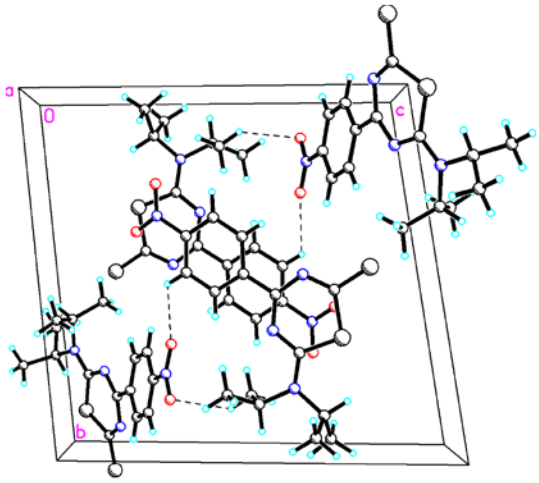


Table 1. Crystal data and structure refinement for 3a

Empirical formula	**$C_{15}H_{18}N_4O_2S_2$**
Formula weight	350.45
Temperature	123(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P −1
Unit cell dimensions	a = 7.5609(4) Å α = 81.481(4)°
	b = 15.0360(8) Å β = 84.569(4)°
	c = 15.4171(8) Å γ = 75.774(5)°
Volume	1,677.12(16) Å^3
Z	4
Density (calculated)	1.388 Mg/m^3
Absorption coefficient	3.005 mm^{-1}
F(000)	736
Crystal size	0.42 × 0.18 × 0.06 mm^3
Theta range for data collection	2.90–78.53°
Index ranges	−9<=h<=9, −18<=k<=17, −19<=l<=13
Reflections collected	11,213
Independent reflections	6,648 [*R*(int) = 0.0558]
Completeness to θ = 67.50°	99.1%
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	1.00000 and 0.55357
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6,648/0/423
Goodness of fit on F^2	1.182
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0628, w*R*2 = 0.2002
R indices (all data)	*R*1 = 0.0835, w*R*2 = 0.2661
Largest diff. peak and hole	0.945 and −0.736 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for 3a

Bond lengths (Å)	
S(1A)–C(9A)	1.765(4)
S(1A)–C(8A)	1.774(4)
S(2A)–C(8A)	1.659(4)
O(1A)–N(1A)	1.230(5)
O(2A)–N(1A)	1.225(5)
N(1A)–C(4A)	1.467(5)
N(2A)–C(8A)	1.328(5)
N(2A)–C(7A)	1.344(5)
N(3A)–C(7A)	1.333(5)
N(3A)–C(9A)	1.335(5)
N(4A)–C(9A)	1.325(5)
Bond angles (°)	
C(9A)–S(1A)–C(8A)	101.61(18)
O(2A)–N(1A)–O(1A)	123.5(3)
O(2A)–N(1A)–C(4A)	118.7(3)
O(1A)–N(1A)–C(4A)	117.8(3)
C(8A)–N(2A)–C(7A)	121.4(3)
C(7A)–N(3A)–C(9A)	120.9(3)
C(9A)–N(4A)–C(10A)	119.4(3)
C(9A)–N(4A)–C(13A)	122.0(3)
C(10A)–N(4A)–C(13A)	117.8(3)
C(2A)–C(1A)–C(6A)	119.4(3)
C(2A)–C(1A)–C(7A)	121.3(3)
C(6A)–C(1A)–C(7A)	119.3(3)
C(3A)–C(2A)–C(1A)	120.8(4)
Torsion angles [°]	
C(7A)–C(1A)–C(2A)–C(3A)	−177.6(3)
C(1A)–C(2A)–C(3A)–C(4A)	1.2(6)
C(2A)–C(3A)–C(4A)–C(5A)	−1.2(6)
C(2A)–C(3A)–C(4A)–N(1A)	178.6(3)
O(2A)–N(1A)–C(4A)–C(3A)	1.9(5)
O(1A)–N(1A)–C(4A)–C(3A)	−177.5(3)
O(2A)–N(1A)–C(4A)–C(5A)	−178.3(3)
O(1A)–N(1A)–C(4A)–C(5A)	2.3(5)
C(3A)–C(4A)–C(5A)–C(6A)	0.4(6)
N(1A)–C(4A)–C(5A)–C(6A)	−179.4(3)
C(4A)–C(5A)–C(6A)–C(1A)	0.4(6)
C(2A)–C(1A)–C(6A)–C(5A)	−0.4(6)
C(7A)–C(1A)–C(6A)–C(5A)	176.8(3)
C(9A)–N(3A)–C(7A)–N(2A)	−9.9(6)

5. Conclusion

In this work, a series of 1,3,5-thiadiazines-2-thione with aroyl/aryl substituents (**3a-c**) were synthesized and tested for antimicrobial activity. In spite of the variations of the antimicrobial activity with the three different nitro and bromophenyl groups, all the three compounds exhibited a weak antimicrobial

Table 3. Hydrogen bonds [Å and °] for 3a

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
C(14B)–H(14E)...O(1A)	0.98	2.47	3.284(5)	140.3
C(3B)–H(3BA)...O(2A)	0.95	2.60	3.257(5)	126.3

activity and can be considered for further future studies to improve the biological activities by substitution with other functional groups. Preparation of other derivatives with various types of side chain and testing of their antimicrobial activity and structure–activity relationship will be carried out in future.

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Supplementary material
Crystallographic data for the structure reported in this article have been deposited with Cambridge Crystallographic Data Centre, CCDC 894864 (**3a**). Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ IEZ, UK. Facsimile (44) 01223 336 033, E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.com.ac.uk/deposit.

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References
Aboul-Fadl, T., Hussein, M. A., El-Shorbagi, A.-N., & Khallil, A.-R. (2002). New 2H-tetrahydro-1, 3, 5-thiadiazine-2-thiones incorporating glycine and glycinamide as potential antifungal agents. *Archiv der Pharmazie, 335*, 438–442. http://dx.doi.org/10.1002/1521-4184(200212)335:9<438::AID-ARDP438>3.0.CO;2-E

Bélai, I., Sohár, P., Maekawa, K., Párkányi, L., & Matolcsy, G. (1981). Tetrahydro-2-thioxo-2 *H*-1,3,5-thiadiazin-4-ones and their derivatives representing a novel heterocyclic ring system. *Journal of Heterocyclic Chemistry, 18*, 283–286. http://dx.doi.org/10.1002/jhet.v18:2

Coburn, R. A., Ho, C. H., & Bronstein, M. L. (1982). Synthesis and in vitro antimicrobial activity of 6-substituted 2H-1,3,5-thiadiazine-2,4(3H)-diones. *Journal of Medicinal Chemistry, 25*, 481–483. http://dx.doi.org/10.1021/jm00346a028

Coro, J., Piñeiro, R., Monzote, L., Rodríguez, H., & Suárez, M. (2011). Thiadiazine derivatives as antiprotozoal new drugs. *The Open Medicinal Chemistry Journal, 5*, 51–60.

El-Shorbagi, A.-N. (2000). New tetrahydro-2h-1,3,5-thiadiazine-2-thione derivatives as potential antimicrobial agents. *Archiv der Pharmazie, 333*, 281–286. http://dx.doi.org/10.1002/(ISSN)1521-4184

Eltsov, O. S., Smirnova, M. V., Yu, Y., Morzherin, Y. Y., Belskaiya, N. P., & Mokrushin, V. S. (2008). Two ways of cyclization of 5-imidazolylthioureaswith dimethylacetylenedicarboxylate. *Archive for Organic Chemistry (ARKIVOC), xvii*, 306–317.

Giordano, C., Belli, A., & Abis, L. (1979). Thermolysis of 6h-1,3,5-oxathiazines synthesis of 3,4-dihydro-2h-1,3,5-thiadiazines. *Tetrahedron Letters, 20*, 1537–1538. http://dx.doi.org/10.1016/S0040-4039(01)86200-6

Goerdeler, J., & Lüdke, H. (1968). Monomere und dimere thiocarbamoyl-isothiocyanate. *Tetrahedron Letters, 9*, 2455–2456. http://dx.doi.org/10.1016/S0040-4039(00)76154-5

Perrin, D. D., Armarego, W. L. F., & Perrin, D. R. (1988). *Purification of laboratory chemicals* (3rd ed.). Oxford: Pergamon Press.

Rodríguez, H., Suárez, M., & Albericio, F. (2012). Thiadiazines, N,N-heterocycles of biological relevance. *Molecules, 17*, 7612–7628. http://dx.doi.org/10.3390/molecules17077612

Reiner, R. (1980). *Antibiotics: An introduction*. Stuttgart: Thieme Verlag.

Saeed, S., Rashid, N., Hussain, R., Jasinski, J. P., Keeley, A. C., & Khan, S. (2013). Nanoparticles and nanocrystals of a new bidentate nickel(II) complex of N -[ethyl(propan-2-yl)carbamothioyl]-4-nitrobenzamide: Synthesis, characterization, and crystal structures. *Journal of Coordination Chemistry, 66*, 126–138. http://dx.doi.org/10.1080/00958972.2012.744834

Saeed, S., Rashid, N., Hussain, R., & Jones, P. G. (2009). Crystal structure of 1-(4-bromophenyl)-3-(2-thienylcarbonyl) thiourea. *Acta Crystallographica, 65*, 2568–2569.

Saeed, S., Rashid, N., Hussain, R., Malik, M. A., & O'Brien, P. (2013). Semiconducting nanostructured copper sulfide thin films from bidentate copper(ii) complexes of N-(dialkylcarbamothioyl)-nitrosubstituted benzamides by chemical vapour deposition. *New Journal of Chemistry, 37*, 3214–3221. http://dx.doi.org/10.1039/c3nj00668a

Saeed, S., Rashid, N., Jones, P. G., Ali, M., & Hussain, R. (2010). Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. *European Journal of Medicinal Chemistry, 45*, 1323–1331. http://dx.doi.org/10.1016/j.ejmech.2009.12.016

Saeed, S., Rashid, N., Jones, P. G., Hussain, R., & Bhatti, M. H. (2010). Synthesis, spectroscopic characterization, crystal

structure and antifungal activity of thiourea derivatives containing a thiazole moiety. *Central European Journal of Chemistry, 8*, 550–558. http://dx.doi.org/10.2478/s11532-010-0014-2

Saeed, S., Rashid, N., Jones, P. G., & Tahir, A. (2011). Synthesis and pharmacological properties of N-substituted-N'-(4,6-dimethylpyrimidin-2-yl)-thiourea derivatives and related fused heterocyclic compounds. *Journal of Heterocyclic Chemistry, 48*, 74–82. http://dx.doi.org/10.1002/jhet.510

Saeed, S., & Wong, W.-T. (2012). A simple, convenient, and efficient synthetic route for the preparation of (*Z*)-3,5-dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylide) benzamide heterocyclic compounds from aroyl thiourea derivatives via S- cyclization mechanism. *Journal of Heterocyclic Chemistry, 49*, 580–584. http://dx.doi.org/10.1002/jhet.820

Sheldrick, G. M. (2008). A short history of SHELX. *Acta Crystallographica Section A Foundations of Crystallography, 64*, 112–122. http://dx.doi.org/10.1107/S0108767307043930

Tsuge, O., & Kanemasa, S. (1972). Studies of acyl and thioacyl isocyanates. X. The cycloaddition reaction of benzoyl and thiobenzoyl isocyanates with benzaldazines. *Bulletin of the Chemical Society of Japan, 45*, 3591–3595. http://dx.doi.org/10.1246/bcsj.45.3591

Tsuge, O., & Sakai, K. (1972). Studies of acyl and thioacyl isocyanates. VIII. Cycloaddition reactions of benzoyl and thiobenzoyl isocyanates with carbodiimides. *Bulletin of the Chemical Society of Japan, 45*, 1534–1539. http://dx.doi.org/10.1246/bcsj.45.1534