

Synthesis, spectroscopic characterization, crystal structure and antifungal activity of thiourea derivatives containing a thiazole moiety

Research Article

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Abstract: Four novel thiourea derivatives containing a thiazole moiety were synthesized and characterized by IR, ¹H and ¹³C NMR, mass spectrometry and elemental analysis. The crystal structure of 1a was determined from single crystal X-ray diffraction data. It crystallizes in monoclinic space group P2₁/n with unit cell dimensions a = 11.7752(6) Å, b = 3.8677(2) Å, c = 27.4126(13) Å and β = 92.734(5) Å. There is a strong intramolecular hydrogen bond of the type N–H···O, with H···O distance of 2.5869(19) Å. The mass fragmentation pattern has also been discussed. The antifungal activity of the synthesized compounds was studied by broth micro-dilution method and poisoned food technique. The compounds 1b and 1c possessed a broad spectrum of antifungal activity.

Keywords: Thiourea derivatives • Thiazole • X-ray structure determination • Mass fragmentation • Antifungal activity

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1. Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Heterocycles form the basis of a variety of pharmaceutical compounds [1]. The thiazole moiety belongs to an important class of N & S-containing heterocycles and when attached to a thiourea functional group forms the building block for pharmaceutical agents. They exhibit a wide spectrum of pharmaceutical activity, such as bactericidal, fungicidal [2], analgesic [3], anti-hypertensive [4], and anti-tumor [5]. Thiouracils are similarly used as anti-inflammatory and virucidal agents [6].

The biological and synthetic significance, places this group (thiazole and thiourea) in an important position in medicinal chemistry research. Substituted thioureas are an important class of compounds, precursors or intermediates towards the synthesis of a variety of heterocyclic systems such as imidazole-2-thiones [7], 2-imino-1, 3-thiazolines [8], pyrimidine-2-thiones, (benzothiazolyl)-4-quinazolinones [9], N-(substituted phenyl)-N-phenylthioureas which serve as anion-binding sites in a hydrogen-bonding receptor [10], calix [11], arenes containing thioureas as neutral receptors towards α, α-dicarboxylate anions [12], and N-4-substituted-benzyl-N-tert-butylbenzyl thioureas as vanilloid receptors ligands and antagonists in rate DRG neurons [13]. Thioureas are also known to exhibit

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a wide range of biological activities including antiviral, antibacterial, antifungal, anti-tubercular, anti-thyroidal, herbicidal and insecticidal activities [14] organocatalyst [15] and as agrochemicals [16,17].

As a part of our continuing interest in biologically active thiourea derivatives, we are reporting a route for synthesis of these compounds by using tetrabutyl ammonium bromide as phase transfer catalyst to augment the yield of products.

In this contribution, results of synthesis, spectroscopic studies, and antifungal activity of thiourea derivatives bearing the thiazole moiety are presented.

2. Experimental Procedure

2.1 Materials and Chemicals

4-nitrobenzoyl chloride, thiophene-2-carbonyl chloride, butanoyl chloride, 4-morpholine carbonyl chloride, ammonium thiocyanate, tetrabutyl ammonium bromide (TBAB), 2-aminothiazole of analytical grade from Merck were used as received. Solvents; chloroform, acetone, ethyl acetate, ethanol, methanol, dichloromethane were obtained from RIEDEL and used without further purification.

2.2 Instrumentation

Synthetic starting material, reagents and solvents were of analytical grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co., Merck Chemical Co. and were dried when necessary. Melting points were recorded on Electrothermal IA9000 series digital melting point apparatus. The proton NMR and ^{13}C spectra were recorded in DMSO- d_6 solvent on Jeol ECS- 400 and 300 MHz spectrophotometer using tetramethylsilane as an internal reference. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). Infrared measurements were recorded in the range 400-4000 cm^{-1} on spectrum 2000 by Perkin Elmer. Elemental analysis was carried out using Perkin Elmer CHNS/O 2400. The mass spectra were run on a Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV. X-ray diffraction data was collected on Oxford Diffraction Xcalibur Nova diffractometer. Thin layer chromatography (TLC) analyses were carried out on 5×20 cm plates coated

with silica gel GF254 type 60 (25-250 mesh) using an ethyl acetate-petroleum ether mixture (1:2) as solvent.

2.3 General Procedure for Synthesis

A solution of substituted carbonyl chloride (26 mmol) in anhydrous acetone (80 mL) and 3% tetrabutyl ammonium bromide (TBAB) in acetone was added dropwise to a suspension of ammonium thiocyanate in acetone (50 mL) and the reaction mixture was refluxed for 45 minutes. After cooling to room temperature, a solution of the corresponding 2-aminothiazole (26 mmol) 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 thiourea precipitated. The solid product was washed with water and purified by re-crystallization from an ethanol-dichloromethane mixture (1:2).

2.3.1 1-(4-nitrobenzoyl)-3-(thiazol-2-yl)thiourea (1a)

Elemental analysis for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_3\text{S}_2$ (MW=308) in wt % calc. C= 42.85, H= 2.62, N=18.17, S= 20.80, found C= 42.86, H=2.63, N=18.17, S= 20.79. m.pt. 194 - 195 °C, yield 93 %. IR (KBr pellet) in cm^{-1} : 3352 (free NH), 3208 (assoc. NH), 1686 (C=O), 1615 (C=N stretching), 1592 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6) in δ (ppm) and J (Hz): 12.80 (1H, s, broad, NH), 11.63 (1H, s, broad, NH), 7.74 (2H, d, J = 8.1 Hz, Ar CH), 7.66 (2H, d, J = 6.7 Hz, Ar CH), 6.75 (1H, d, J = 9.5 Hz, thiazole CH), 6.55 (1H, d, J = 9.5 Hz, thiazole CH); ^{13}C NMR (300 MHz, DMSO- d_6) in δ (ppm): 180.3 (C=S), 168.2 (C=O), 164.5 (C=N), 162.4 (C), 153.5 (C), 140.2 (C), 128.0 (C), 123.4 (C); EI MS, m/z (%): 308 (M+, 12) 262 (6), 166 (7), 150 (100), 142 (25), 123 (55), 100 (20), 85 (9).

2.3.2 N-[(1, 3-thiazol-2-ylamino) carbonothioyl] thiophene-2-carboxamide (1b)

Elemental analysis for $\text{C}_9\text{H}_7\text{N}_3\text{OS}_3$ (MW=269) in wt % calc. C= 40.13, H= 2.60, N=15.60, S=35.71, found C= 40.15, H=2.62, N=15.58, S= 35.70. m.pt 179-180 °C, yield 89 %. IR (KBr pellet) in cm^{-1} : 3350 (free NH), 3201 (assoc. NH), 1691 (C=O), 1613 (C=N stretching), 1590 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6) in δ (ppm) and J (Hz): 12.56 (1H, s, broad, NH), 11.61 (1H, s, broad, NH), 7.62 (1H, d, J = 7.2 Hz, Thiophene CH), 7.15 (1H, dd, J1 = 7.5 Hz, J2 = 8.2 Hz, Thiophene CH), 7.03 (1H, d, J = 6.7 Hz, Thiophene CH), 6.75 (1H, d,

$J = 9.5$ Hz, thiazole CH), 6.55(1H, d, $J = 9.5$ Hz, thiazole CH); ^{13}C NMR (300 MHz, DMSO- d_6) in δ (ppm): 179.5 (C=S), 169.1 (C=O), 165.0 (C=N), 160.8 (C), 141.2 (C), 130.0 (C), 121.4 (C); EI MS, m/z (%): 269 (M $^+$, 7), 235 (10), 187 (8), 142 (13), 111 (100), 83 (4).

2.3.3 *N*-[(1,3-thiazol-2-ylamino) carbonothioyl] morpholine-4-carboxamide (1c)

Elemental analysis for $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_2\text{S}_2$ (MW=272) in wt % calc. C=39.70, H= 4.41, N=20.57, S=23.52, found C= 39.72, H= 4.45, N=20.56, S= 23.54. m.pt 167-168 °C, yield 90 %. IR (KBr pellet) in cm^{-1} : 3350 (free NH), 3203 (assoc. NH), 1690 (C=O), 1614 (C=N stretching), 1589 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6) in δ (ppm) and J (Hz): 12.87 (1H, s, broad, NH), 11.59 (1H, s, broad, NH), 6.75(1H, d, $J = 9.5$ Hz, thiazole CH), 6.55(1H, d, $J = 9.5$ Hz, thiazole CH), 3.7(4H, t, $J = 7.6$ Hz, morpholine $-\text{OCH}_2$), 2.9(4H, t, $J = 7.2$ Hz, morpholine $-\text{NCH}_2$); ^{13}C NMR (300 MHz, DMSO- d_6) in δ (ppm): 180.3 (C=S), 168.2 (C=O), 164.8 (C=N), 162.4 (C), 153.5 (C), 143.3 (C), 131.2 (C), 123.0 (C); EI MS, m/z (%): 272 (M $^+$, 5), 238 (9), 142 (13), 130 (100), 114 (7), 101 (20), 85 (23).

2.3.4 *N*-[(1,3 - thiazol -2 - ylamino) carbonothioyl] butanamide (1d)

Elemental analysis for $\text{C}_8\text{H}_{11}\text{N}_3\text{OS}_2$ (MW=229) in wt % calc. C=41.92, H= 4.80, N=18.34, S=27.97, found C= 41.90, H= 4.83, N=18.31, S= 27.96. m.pt 155- 156 °C, yield 85 %. IR (KBr pellet) in cm^{-1} : 3351 (free NH), 3202 (assoc. NH), 1685 (C=O), 1615 (C=N stretching), 1590 (aromatic C=C); ^1H NMR (400 MHz, DMSO- d_6) in δ (ppm) and J (Hz): 12.85 (1H, s, broad, NH), 11.61 (1H, s, broad, NH), 6.75(1H, d, $J = 9.5$ Hz, thiazole CH), 6.55(1H, d, $J = 9.5$ Hz, thiazole CH), 2.48 (2H, t, $-\text{CH}_2$, $J = 7.3$ Hz), 1.95 (2H, m, $-\text{CH}_2$), 0.93 (3H, t, $-\text{CH}_3$, $J = 7.1$ Hz); ^{13}C NMR (300 MHz, DMSO- d_6) in δ (ppm): 179.1 (C=S), 168.5 (C=O), 164.0 (C=N), 162.4 (C), 153.1 (C), 140.2 (C), 130.6 (C), 121.4 (C), 25.1, 22.5, 20.0; EI MS, m/z (%): 229 (M $^+$, 6), 195 (11), 142 (12), 100 (20), 87 (9), 71 (100), 44 (15).

2.4 X-ray Structure Determination of 1a

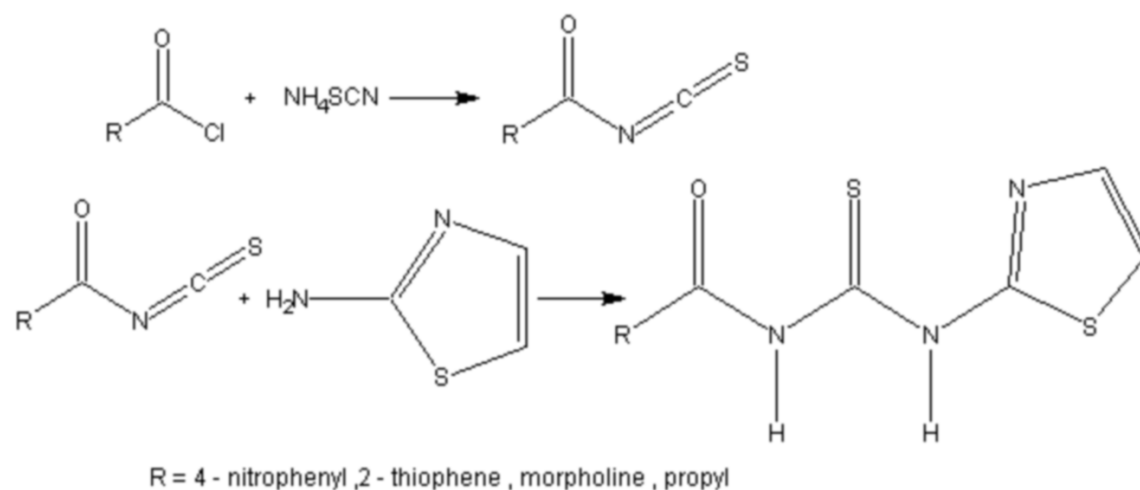
Crystal data: $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_3\text{S}_2$, monoclinic, space group $\text{P2}_1/\text{n}$, $a = 11.7752(6)$, $b = 3.8677(2)$, $c = 27.4126(13)$ Å, $\beta = 92.734(5)^\circ$, $V = 1247.03$ Å 3 , $T = 100\text{K}$, $Z = 4$, $F(000) = 632$, $D_x = 1.642$ g cm^{-3} , $\mu = 4.0$ mm $^{-1}$. Single crystals suitable for X-ray diffraction studies were obtained from

an ethanol-dichloromethane mixture (1:2). A colorless plate $0.15 \times 0.08 \times 0.005$ mm 3 was mounted on a glass fiber in inert oil. Measurements were performed at 100 K on an Oxford Diffraction Xcalibur Nova diffractometer with mirror-focussed Cu-K α radiation to $2\theta_{\text{max}} 152^\circ$ (99.3% complete to 145°). The data were corrected for absorption using the multi-scan method. Of 19592 intensities, 2554 were independent ($R_{\text{int}} 0.051$). The structure was refined anisotropically using SHELXL-97 [32]. NH hydrogens were refined freely, other H atoms using a riding model. The final $wR2$ was 0.081, with a conventional $R1$ of 0.032, for 189 parameters; $S = 1.04$; max. $\Delta\rho 0.27$ e Å $^{-3}$.

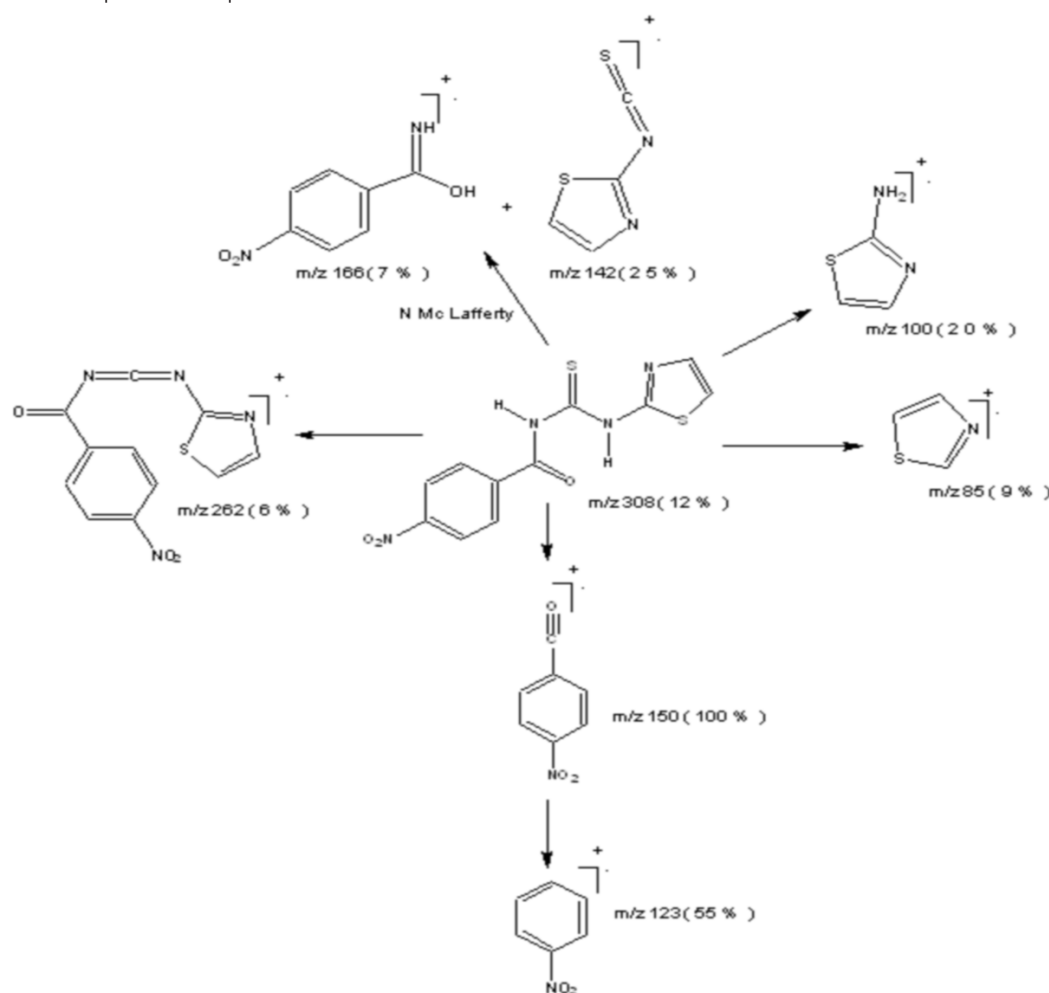
2.5 Evaluation of Fungicidal Activity

2.5.1 Broth micro-dilution procedure

Antifungal activity was determined by the *broth micro-dilution* procedures and principles of the Clinical and Laboratory Standards Institute (CLSI) [33,34]. Minimal inhibitory concentrations for each compound were investigated against standard yeast-like fungi, *C. albicans* (ATCC90028), *C. glabrata* (ATCC 32554), *C. tropicalis* (ATCC 20336). Fungal colonies of the test organisms were suspended directly into a small volume of 0.9% saline and further diluted until turbidity matched the Mc Farland Standard no: 0.5 Petri dishes Sabouraud and Dextrose agar for fungi were impregnated with these microbial suspensions. The stock solutions of the synthesized compounds were prepared in dimethyl sulfoxide (DMSO), which had no effect on the organisms in the concentrations studied. The initial concentration was 200 mg mL $^{-1}$. All of the dilutions were done with distilled water. The concentrations of tested compounds were 100, 50, 25, 12.5, 6.25, 3.125 $\mu\text{g mL}^{-1}$. DMSO was used as negative control. Nystatin was used as reference drug for anti-fungal activity. All the inoculated plates were incubated at 37°C and results were evaluated after 48 h for formation of colonies. The lowest concentration of the compounds that prevented visible growth was considered minimal inhibitor concentration (MIC).



Scheme 1. Preparation of compounds 1a-1d



Scheme 2. Mass fragmentation of 1-(4-nitrobenzoyl)-3-(thiazol-2-yl) thiourea (1a)

2.5.2 Poisoned food technique

In the blotter paper method, surface-sterilized seeds (with 2.5% bleach-NaOCl for one minute) and untreated seeds were placed on moistened blotter paper. In this method, five seeds, sterilized and un-sterilized, were used and replicated four times. The Petri plates were incubated at $25 \pm 2^\circ\text{C}$ under 12 h alternating cycle of fluorescent light and darkness for a week. Fungi were identified on the basis of their typical structure and basic characters as suggested by Barnett [35] and Melone [36].

2.6. Statistical Analysis

Data were analyzed statistically by applying ANOVA and comparing means by using Least Significant Difference test [38].

The pure cultures of the fungi isolated were maintained on PDA in tubes, which were stored in the refrigerator at 4°C and used frequently. These were multiplied on 2% PDA for two-three weeks. The Inoculum was prepared by taking 1mg culture in 20 mL distilled water. Twenty seeds of sunflower cultivar, both sterilized and untreated lots were planted in each pot, replicated five times. All the target compounds 1a, 1b and 1c were tested for the fungicidal activity Three seed dressing fungicides (1a-c) were tested as growth inhibitors of fungi isolated through Poisoned Food Technique [37]. 1 mg of each thiourea derivative was dissolved in 20 mL of Potato Dextrose Agar (PDA) in Petri plates, and one set of agar plates without addition of fungicide was kept as control. The plates were incubated at 25°C for seven days, colony of each fungus was measured in cm and percentage inhibition was calculated as:

$$\% \text{ inhibition} = \frac{\text{Diameter of colony of control} - \text{diameter of colony of fungi}}{\text{Diameter of colony of control}} \times 100$$

3. Results and Discussion

3.1 Chemistry

The synthetic route for the target compounds is outlined in Scheme 1. Target compounds were synthesized by a slight modification of our earlier published procedures [18-20]. The use of phase transfer catalysts to agitate

a heterogeneous reaction system is gaining recognition [21,22]. In an attempt to improve syntheses of the target substituted thiourea derivatives by reacting isothiocyanates with nucleophiles, we have found the use of tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst (PTC), it can improve the yield of aroyl, thiophenoyl, morpholinoyl and butanoyl based isothiocyanates. In this paper, we have carried out reactions using tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst to synthesize intermediate aroyl, thiophenoyl, morpholinoyl and butanoyl thiourea derivatives containing a thiazole moiety (1a-1d).

The chemical structure and purity of compounds were assessed by using elemental analysis, ^1H NMR, ^{13}C NMR, and FTIR spectroscopy. The ^1H NMR data of the compounds obtained in DMSO are given in the experimental section and are consistent with the structural results. The elemental analyses closely corresponded to calculated values. The analytical and spectroscopic data are consistent with the proposed structures [23]. All the compounds were soluble in DMF, DMSO, ethanol and ethyl acetate. IR (KBr) spectra of 1a-1d had strong N-H absorptions at about $3353\text{--}3208\text{ cm}^{-1}$ and displayed absorptions at about $1691\text{--}1685\text{ cm}^{-1}$ and 1440 cm^{-1} which were assigned to C=O and C=S functionalities respectively. The medium-strong $\nu\text{ C=O}$ band in the IR spectra of all the compounds of series 1a-1d appeared at $1691\text{--}1686\text{ cm}^{-1}$, which is lower than that of the ordinary carbonyl absorption (1730 cm^{-1}); this may be attributed to the formation of hydrogen bonds. These results agree with previously reported data [24].

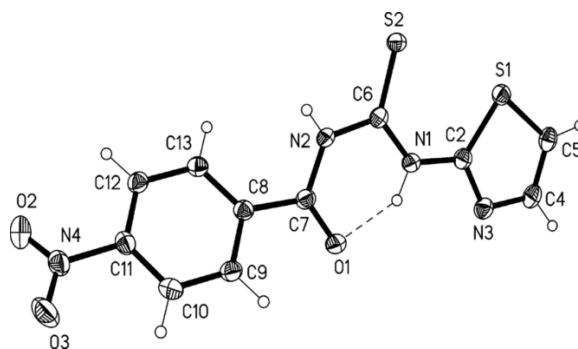


Figure 1. A thermal ellipsoid drawing of 1-(4-nitrobenzoyl)-3-(thiazol-2-yl)thiourea (1a) at 50% probability level. The dashed line shows intramolecular hydrogen bond.

Table 1. Hydrogen bonds [Å and °] for compound 1a

D-H...A	d (D-H)	d (H...A)	d (D...A)	<(DHA)
N (1)-H (01)...O (1)	0.89(3)	1.82(3)	2.5869(19)	143(2)
N (2)-H (02)...S (2) #1	0.79(3)	2.65(3)	3.4208(16)	167(2)
C (10)-H (10)...N (3) #2	0.95	2.53	3.471(2)	168.7
C (9)-H (9)...O (1) #2	0.95	2.47	3.401(2)	167.4
C (13)-H (13)...S (2) #3	0.95	2.87	3.7747(18)	160.5
C (12)-H (12)...O (2) #4	0.95	2.53	3.383(2)	150.3
C (5)-H (5)...O (3) #5	0.95	2.43	3.228(2)	141.7

Symmetry transformations used to generate equivalent atoms:

- #1 -x+1,-y+2,-z+1
- #2 -x,-y+2,-z+1
- #3 -x+1,-y+1,-z+1
- #4 -x+1/2,y-1/2,-z+1/2
- #5 x+1/2,-y+3/2,z+1/2

Table 2. MIC values ($\mu\text{g mL}^{-1}$) of the promising thiourea derivatives against the tested fungi

Compound	<i>C. glabrata</i>	<i>C. albicans</i>	<i>C. tropicalis</i>
Code	(ATCC32554)	(ATCC 90028)	(ATCC 20336)
1a	100	100	200
1b	50	50	50
1c	25	50	50
1d	100	50	50
Nystatin	2	1	4

The ^1H NMR of the compounds 1a-1d exhibited broad signals at 12.80-11.59 ppm, which were assigned to the N-H protons. ^{13}C NMR of compound 1a-1d showed peaks at about δ 170.2-165.1, 180-179.5 for C=O (amide) and C=S (thioamide), respectively. Mass spectrum of compound 1a showed molecular ion peak at m/z 308. The major fragment at m/z 142 (25%) was derived from N-McLafferty rearrangement and a base peak at m/z 150 (100 %) originated from the aroyl cation (Scheme 2). Mass spectrum of compounds 1b and 1c showed molecular ion peaks at m/z 269 and m/z 272, respectively. The base peak for both compounds appeared at m/z 111 and 130 (100%), respectively.

3.2 Crystal Structure study

Molecular structure of compound 1a is shown in Fig 1. The C6-S2 and C7-O1 bonds show a typical double bond character with bond lengths of 1.6562(18) and 1.229(2) Å, respectively. All of the C-N bonds, C6-N1 = 1.343(2) Å, C6-N2 = 1.396(2) Å, C2-N3 = 1.307(2) Å, C2-N1 = 1.389(2) Å, C4-N3 = 1.373(2) Å, C7-N2 = 1.379(2) Å also indicate a partial double bond character. The C6-N2 bond due to its vicinity to the carbonyl group is slightly shorter than to the C2-N1 bond [25,26]. These bond distances are in good agreement with those

observed in structures containing the N-benzoyl-N'-phenylthiourea moiety, as reported in the Cambridge Structural Database [27]. Disregarding the oxygens on nitro groups, the molecule consists of two planar moieties: the C6 ring plus immediate substituents in one plane and all other atoms in the second plane. Mean deviations from planarity for both are 0.03 Å, with an interplanar angle of 34.7° (cf. torsion angle N2-C7-C8-C13 33.4°). The molecule displays an intramolecular hydrogen bond N1-H01...O1. The packing is three-dimensional, but a representative two-dimensional view along the short axis is given in Fig. 2. One classical H bond N2-H02...S2 and five "weak" H bonds of the form C-H...X (X = O, N, S) are observed. Numerical details are given in Table 1.

3.3 Antifungal Activity

To determine the antifungal activity of synthesized compounds, two methods, broth micro-dilution procedure and poisoned food technique were adopted. In the light of interesting antimicrobial activity, the thiourea derivatives were screened for antifungal activity against 3 fungal strains: *C. glabrata*, *C. albicans* and *C. tropicalis* by broth micro-dilution procedure (see Table 2).

All the compounds inhibited the growth yeast with MIC (minimum inhibitory concentration) ranging from 25 to 200 $\mu\text{g mL}^{-1}$. When all the anti-yeast MIC values are compared, two of four compounds showed good activity against *C. glabrata* and other two of four compounds showed low activity against *C. tropicalis*. The investigated compounds antifungal activity values for our compounds were similar to those reported [28-30]. The main difference in the thiourea derivatives reported in this paper is the presence of the thiazole moiety.

Lipophilicity is a factor, which correlates well with the bioactivity of chemicals. It is a very important molecular descriptor and the lipophilic behavior of compounds plays an important role in their biological activity. The n-octanol/water partition coefficient ($\log P_{ow}$) is widely used as a general measure of lipophilicity. Compound with 4-nitrophenyl (1a) has relatively higher $\log P_{ow}$ value of 1.94 ± 0.65 and hence show more lipophilic character [31]. Its antifungal activity is lower than all the other promising compounds (1a-d). The calculated value of partition coefficient ($\log P_{ow}$) for n-butyl derivative (1d) is 1.29 ± 0.64 . Its antifungal activity is comparatively lower than the compounds (1c) and (1b) due to its higher partition coefficient ($\log P_{ow}$) value. The compounds with a morpholine ring (1c) and

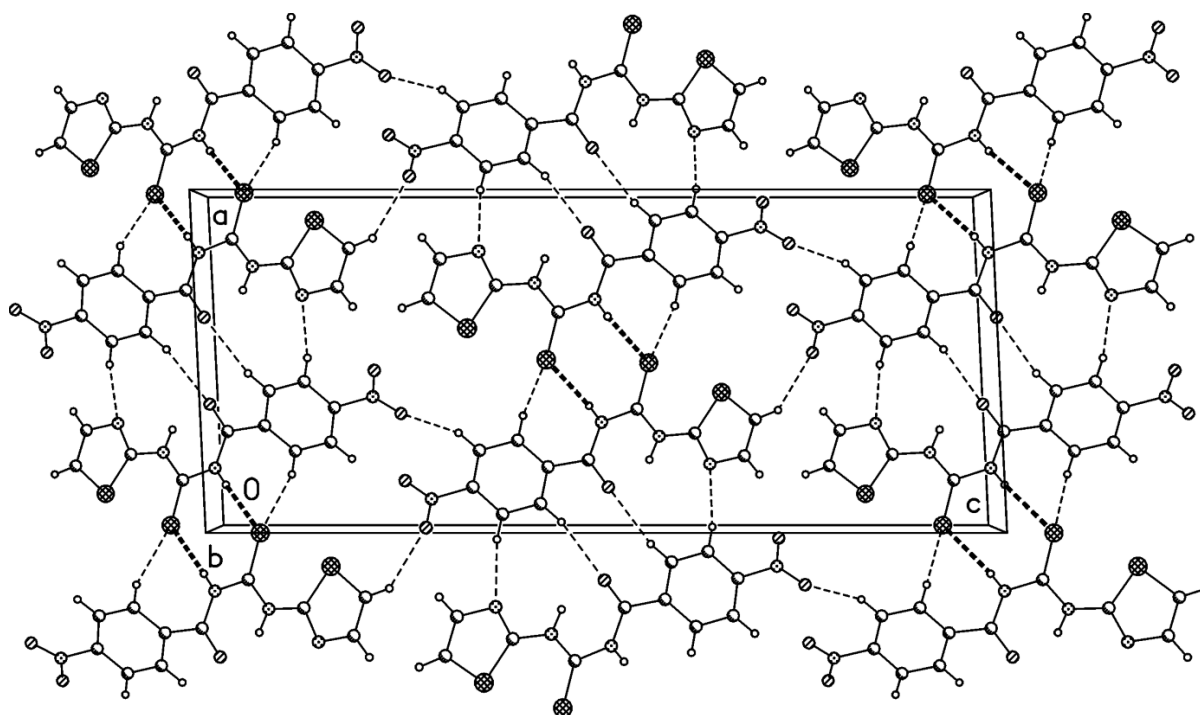


Figure 2. Packing diagram of 1a viewed parallel to the y axis. The dashed lines denote hydrogen bonds, thick lines denote N-H...S; thin lines represent C-H...X with X = N, O, S). Non-hydrogen bonded H atoms and intramolecular H bonds have been omitted for clarity.

thiophene ring (1b), which have the $\log P_{ow}$ value of 0.76 ± 0.68 and 1.59 ± 0.65 , respectively show higher antifungal activity than other investigated compounds probably due to their lower lipophilic character. In poisoned food technique the prepared thiourea derivatives were tested against seven isolated fungi namely, *A. alternata*, *A. flavus*, *A. niger*, *Rhizopus spp*, *Curvularia lunata*, *D. tetramera* and *Penicillium spp*. as presented in Table 3. The results showed that 1b and 1c produced significant decrease in mycelial growth as compared to 1a. All the treated fungi showed significant decrease in fungal colony diameter with respect to control. The compound 1b gave 79.93% inhibition of *Rhizopus spp*. 61.73% of *A.niger* and 58.01% of *A.alternata* (Fig.3b). In conclusion, treatment with compounds 1b and

1c showed significant reduction in fungal colonies. It can be hypothesized that these active molecules might have entered the fungal mycelium, interacted with in a short time and paralyzed it. Chemical ingredients present in these two fungicides may be inhibitory to germination of fungal propagules.

Fungicidal seed treatments are known to reduced the seed-borne mycoflora and thereby improve seed germination. However, chemical seed treatment can produce serious problems leading to toxicity, phytotoxicity, environmental and soil pollution, bioaccumulation etc. Nevertheless, it is quite economical and easily applicable.

Table 3. Effect of thiourea derivatives (1a-c) on the % inhibition of fungal colonies (cm) on agar medium at 25°C

Treatment	a	b	c	d	e	f	g
Control	3.550 A	4.400 A	4.375 A	3.175 A	2.925 B	2.675 A	3.125 A
1b	1.475C	1.975 B	1.675 B	1.950 B	1.475 B	0.55 D	1.500 B
1c	1.275 C	2.025 B	1.975 B	1.125 C	0.875 D	1.250 C	0.825 C
1a	3.100 A	2.800 A	2.375 B	2.825 A	2.800 A	1.625 BC	2.050 B
LSD value	0.57	0.72	0.56	0.69	0.52	0.43	0.45

Alternaria alternates (a), *A. flavus* (b), *A. Niger*(c), *Curvularia lunata* (d), *D.tetramera* (e), *Rhizopus spp* (f), *Penicillium spp* (g) P<0.05 values within the same column show the same letters are not significantly different from each other.

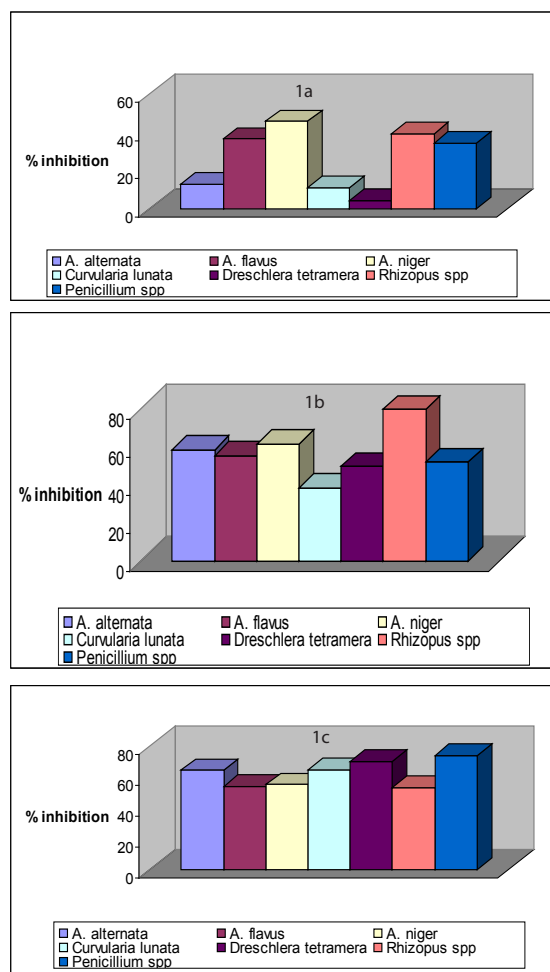


Figure 3. Effect of thiourea derivatives (1a-c) on the % inhibition growth of seven different fungi.

4. Conclusions

In conclusion, we have described a simple and efficient method for synthesis of aroyl, thiophenoyl, morpholinoyl and butanoyl thiourea derivatives containing thiazole moiety. These compounds were successfully prepared in high purity and high yield using tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst (PTC). The crystal structure of one thiourea derivative (1a) was determined by single crystal X-ray diffraction data. The in vitro antifungal study of synthesized compounds, N-[(1, 3-thiazol-2-ylamino) carbonothioyl] thiophene-2-carboxamide (1b) and N-[(1,3-thiazol-2-ylamino) carbonothioyl] morpholine-4-carboxamide (1c) shows good activity measured by broth micro-dilution method (BMD) and corroborated by poisoned food technique (PFT).

5. Supplementary crystallographic data

Crystallographic data for the structure reported in this article have been deposited with Cambridge Crystallographic Data Center, CCDC 752674. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, 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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