European Journal of Chemistry 1 (3) (2010) 221-227

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis, spectroscopic characterization, crystal structure and pharmacological properties of some novel thiophene-thiourea core derivatives

Sohail Saeed[a,*], Naghmana Rashid[a], Muhammad Ali[b], Rizwan Hussain[c] and Peter Jones[d]

[a] *Department of Chemistry, Research Complex, Allama Iqbal Open University, Islamabad, 44000, Pakistan*
[b] *Department of Pharmacy, University of the Punjab, Lahore, 54590, Pakistan*
[c] *National Engineering & Scientific Commission, P.O. Box 2801, Islamabad, Pakistan*
[d] *Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Braunschweig, D-38023, Germany*

**Corresponding author at: Department of Chemistry, Research Complex, Allama Iqbal Open University, Islamabad, 44000, Pakistan. Tel.: +92.51.9250081; fax: +92.51.9250081. E-mail address: sohail262001@yahoo.com (S. Saeed).*

ARTICLE INFORMATION

Received: 23 May 2010
Received in revised form: 19 July 2010
Accepted: 19 July 2010
Online: 30 September 2010

KEYWORDS

Thiourea derivatives
Thiophene
Single crystal structure determination
Mass fragmentation
Antifungal activity

ABSTRACT

This article presents our research concerning the synthesis of new thiophene-thiourea derivatives (1-12) and their pharmacological properties. These novel thiophene-thiourea derivatives were synthesized and characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The crystal structure of *N*,*N*-diphenyl-*N*'-(thiophene-2-carbonyl)-thiourea was determined from single crystal X-ray diffraction data. It crystallizes in the monoclinic space group $P2_1$ with unit cell dimensions of a=11.7469(5) Å, b=6.0849(2) Å, c=12.5792(6) Å, β= 117.736(7) ° and V = 795.8(6) Å^3. The mass fragmentation pattern has also been discussed. The synthesized compounds were screened for their in vitro antifungal activities against the standard strains: *C. Albicans*, *C. Glabrata*, and *C. Tropicalis*. The compounds *N*-thiophene-*N*',*N*'-*bis*(dimethyl-phosphinoylmethyl)thiourea, *N*-[(4-nitro-1*H*-imidazol-2-yl)carbamothioyl]thiophene-2-carboxamide and *N*,*N*-diethyl-*N*'-(thiophene-2-carbonyl)-thiourea showed significant antifungal activities against microbial species.

1. Introduction

Sulphur has been an interesting element particularly for the varieties of its compounds and varieties of bondings it is involved in [1]. It has a prominent bioorganic chemistry and a large number of enzymes and other proteins such as the iron sulphur proteins exhibit fantastic properties involving the sulphur atoms in them [2,3]. It is an important element forming chains [4] and more interestingly, bridges in polymers and in varieties of composite materials, giving rise to strength and resistance to aging.

Thioureas are potentially very versatile ligands, able to coordinate to a range of metal centres as neutral ligands, monoanions or dianions [5-13]. In addition, the oxygen, nitrogen and sulphur donor atoms provide a multitude of bonding possibilities. The coordination chemistry of substituted thioureas has led to some interesting practical applications, including liquid-liquid extraction, pre-concentration and highly efficient chromatographic separation, fluorimetric detection of the platinum group metals, and the selective on-line pre-concentration of ultra-traces of palladium, followed by its determination using graphite furnace atom absorption spectrometry [14,15].

Thiourea and its derivatives have found extensive applications in the fields of medicine, agriculture and analytical chemistry. They are known to exhibit a wide variety of biological activities such as antiviral, antibacterial, antifungal [16], antitubercular, herbicidal, insecticidal [17], and to act as chelating agents [18], in catalysis [19], in anion recognition [20] and to play a role in some epoxy resin curing agents containing amino functional groups [16].

Substituted thioureas are an important class of compounds, precursors or intermediates for the synthesis of a variety of heterocyclic systems such as imidazole-2-thiones [21], 2-imino-1,3-thiazolines [22], pyrimidine-2-thiones and benzothiazolyl-4-quinazolinones [23], *N*-(Substituted phenyl)-*N*-phenylthio ureas have been developed as anion-binding sites in a hydrogen-bonding receptor [24], calixarenes containing thioureas as neutral receptors towards α,α-dicarboxylate anions [25], and *N*-4-substituted-benzyl-*N*-*tert*-butylbenzyl thioureas as vanilloid receptor ligands and antagonists in rate DRG neurons [26].

As part of our research on coordination chemistry of thioureas, we are interested in the study of the influence of non-covalent interactions, especially hydrogen bonds and π-π stacking interactions, on the coordination modes of thiocarbonyl donor groups with transition metal ions. Such coordination compounds of thiourea have been studied for various biological systems with respect to antibacterial, antifungal and anticancer activities [27]. The remarkable pharmacological efficiency of the compounds with thiophene nucleus in their structure such as: duloxetine, phethenylate sodium, pyrantel, tiemonium iodide, chlorothen, carticaine, thennaldine, tipepidine, tenosal known for their antidepresant, anticonvulsant, anthelmintic (nematodes), antispasmoidic, antihistaminic, anesthetic, antipruritic, antitussive, analgesic action [28] and low side effects, and the positive results of the previous synthesized thioureides, led us to obtain new thiophene-thiourea derivatives.

The importance of such work lies in the possibility that the next generation of thiophene-thiourea derivatives might be more efficacious as antifungal and anticancer agents. However, a thorough investigation relating structure and activity of

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.1.3.221-227.124

thiourea derivatives and their stability under biological conditions is required. In this communication, we describe the synthesis, characterization, crystal structure and antifungal activity of thiophene-thiourea derivatives.

2. Experimental

2.1. Chemicals and Instrumentation

Thiophene-2-carbonyl chloride, ammonium thiocyanate, diphenylamine, *p*-chloroaniline, *p*-nitroaniline, 4-methylaniline, 1-naphthylamine, diethylamine, 5-methoxy-1,3-benzothiazol-2-amine, 2-amino-5-nitrothiazole, dipropylamine of analytical grade from Merck and were used as received. *Bis*(dimethyl-phosphinoylmethyl)-amine was prepared according to reference [29]. Solvents; acetone, ethyl acetate, ethanol, methanol, dichloromethane were obtained from RIEDEL and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solvent on a Bruker 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). Melting points were recorded on Electrothermal IA9000 series digital melting point apparatus. 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. Obtained results were within 0.4 % of the theoretical values. The mass spectra were run on a Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV. Single crystal X-ray data were collected on an Oxford Diffraction Xcalibur diffractometer using monochromated Mo-K$_\alpha$ radiation. Thin layer chromatography (TLC) analysis were carried out on 5 × 20 cm plates coated with silica gel GF$_{254}$ type 60 (25-250 mesh) using an ethyl acetate-petroleum ether mixture (1:2) as solvent.

2.2. Synthesis

2.2.1 Preparation of compounds 1-12

All the chemicals used for the preparation were of reagent grade quality. The ammonium thiocyanate was dried by heating at 100 °C and the acetone using potassium carbonate. A solution of thiophene-2-carbonyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 3% tetrabutylammonium bromide (TBAB) in anhydrous acetone was added dropwise to a suspension of dry ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min (Scheme 1). After cooling to room temperature, a solution of primary/secondary amine (0.01 mol) in anhydrous acetone (25 mL) was added and the resulting mixture refluxed for 2 h. Hydrochloric acid (0.1N, 400 mL) was added, and the solution was filtered. The solid product was washed with water and purified by re-crystallization from an ethanol-dichloromethane mixture (1:2).

***N*-Thiophene-*N'*,*N'*-*bis*(dimethyl-phosphinoylmethyl)thio-urea (1):** White. Yield: 95%. M.p.:131-132 °C. FT-IR (KBr pellet) in cm^{-1}: 3365, 3208 (N-H), 3065-3046 (C-H), 1678 (C=O), 1593 (aromatic C=C), 1308 (CH$_3$P), 1292 (C=S), 1162 (P=O). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 11.92 (1H, s, CONH), 8.21 (2H, d, *J* = 9.1 Hz, Ar H), 7.62 (2H, d, *J* = 6.5 Hz, Ar H), 8.28 (1H, dd, J_1 = 7.8 Hz, J_2 = 8.4 Hz, Thiophene CH), 8.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH),7.21 (1H, dd, J_1 = 6.7 Hz, J_2 = 9.0 Hz, Thiophene CH), 2.43 (4H,s, -NCH$_2$), 0.98 (12H, s, -CH$_3$). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 178.0 (C=S), 162.2 (C=O), 141.4 (C), 136.2 (C), 135.7 (C), 132.0 (C), 61.1 (2C), 21.2 (4C). EI MS, m/z (%): 366. Anal. Calcd. for $C_{12}H_{20}N_3O_3P_2S_2$: C, 39.34; H, 5.50; N, 7.65; S,17.50. Found: C, 39.38; H, 5.55; N, 7.63; S, 17.48.

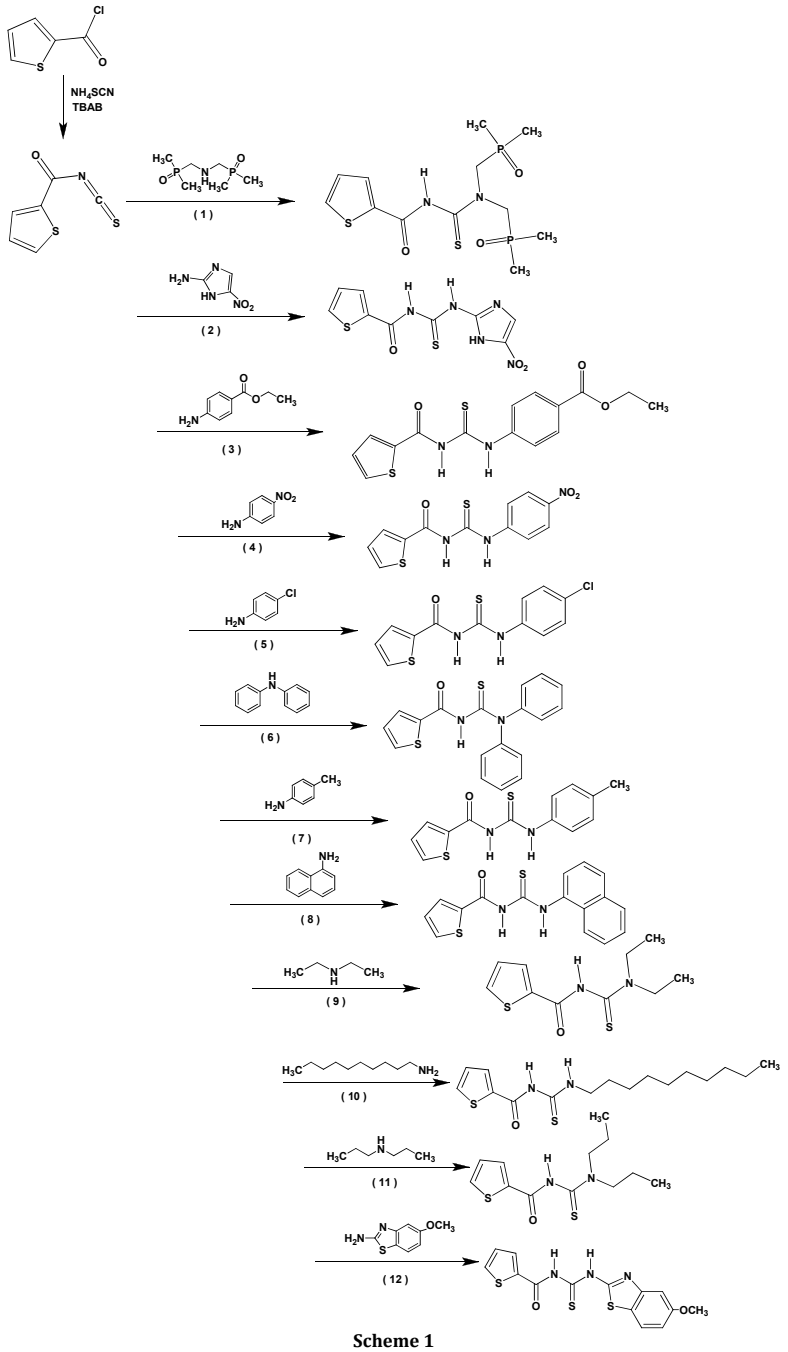
***N*-[(4-nitro-1*H*-imidazol-2-yl)carbamothioyl] thiophene-2-carboxamide (2):** Light yellow solid. Yield: 88%. M.p.: 174-175 °C. FT-IR (KBr pellet) in cm^{-1}: 3263, 3209 (N-H), 3063-3031 (C-H), 1675 (C=O), 1593 (aromatic C=C), 1234 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.65 (1H, s, CSNH), 11.33 (1H, s, CONH), 8.2 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.05 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 8.01 (2H, d, *J* = 8.2 Hz), 7.65 (2H, d, *J* = 6.9 Hz), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.8 (C=S), 170.1 (C=O), 165.0 (C=N), 149.1 (C), 145.5 (C), 141.3 (C), 133.7(C), 132.5 (C), 121.0 (C). EI MS, m/z (%):297. Anal. Calcd. for $C_9H_7N_5O_3S_2$.: C, 36.36; H, 2.37; N, 23.56; S, 21.57. Found: C, 36.39; H, 2.40; N, 23.54; S, 21.55.

Ethyl 4-{[(thiophen-2-ylcarbonyl) carbamothioyl] amino} benzoate (3): Light yellow crystals. Yield: 91%. M.p.: 160-161 °C. FT-IR (KBr pellet) in cm^{-1}: 3363 (free NH), 3210 (assoc NH), 1725 (C=O ester), 1676 (C=O amide), 1593 (aromatic C=C), 1276 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.78 (1H, br s, CSNH), 11.63 (1H, br s, CONH), 8.30 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.01 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.75 (2H, d, *J* = 8.2 Hz), 7.65 (2H, d, *J* = 6.9 Hz), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH), 4.32 (2H, q, -OCH$_2$), 1.31 (3H, t, -CH$_3$). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.8 (C=S thioamide), 168.2 (C=O ester), 165.0 (C=O amide), 145.4 (C), 142.5 (C), 134.4 (C), 132.2 (C), 128.8 (C), 128.1 (C), 127.5 (C), 123.4 (C), 60.7 (C), 14.1 (C). EI MS, m/z (%): 334 (M$^+$, 15), 169 (30.5), 161 (52), 141 (4.7), 135 (6.5), 111 (100), 95 (25.2), 73 (20), 31 (10), 15 (3.4). Anal. Calcd. for $C_{15}H_{14}N_2O_3S_2$: C, 53.87; H, 4.22; N, 8.38; S,19.18. Found: C, 53.89; H, 4.28; N, 8.38; S, 19.20.

***N*-(4-nitrophenyl)-*N'*-(thiophene-2-carbonyl)-thiourea (4):** Dark yellow solid. Yield: 94%. M.p.: 163-164 °C. FT-IR (KBr pellet) in cm^{-1}: 3265, 3189 (N-H), 3065-3046 (C-H), 1678 (C=O), 1593 (aromatic C=C), 1512 (NO$_2$), 1236 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.41 (1H, s, CSNH), 11.92 (1H, s, CONH), 8.21 (2H, d, *J* = 9.1 Hz, Ar H), 7.62 (2H, d, *J* = 6.5 Hz, Ar H), 8.30 (1H, dd, J_1 = 7.9 Hz, J_2 = 8.4 Hz, Thiophene CH), 8.01 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.21 (1H, dd, J_1 = 6.7 Hz, J_2 = 9.0 Hz, Thiophene CH). ^{13}C NMR (300 MHz,DMSO-d_6) in δ (ppm): 178.1 (C=S), 168.0 (C=O), 145.4 (C), 136.2 (C), 135.7 (C), 135.0 (C), 132.2 (C), 129.8 (C), 128.7 (2C), 127.4 (2C). EI MS, m/z (%): 307 (M$^+$, 18), 273 (5.1), 180 (10), 137 (7.5), 127 (8.7), 111 (100), 92 (17.1), 84 (55). Anal. Calcd. for $C_{12}H_9N_3O_3S_2$: C, 46.89; H, 2.95; N, 13.67; S, 20.87. Found: C, 46.90; H, 2.98; N, 13.65; S, 20.86.

***N*-(4-chlorophenyl)-*N'*-(thiophene-2-carbonyl)-thiourea (5):** White crystals. Yield: 92%. M.p.: 151-152 °C. FT-IR (KBr pellet) in cm^{-1}: 3263, 3209 (N-H), 3063-3031 (C-H), 1675 (C=O), 1593 (aromatic C=C), 1234 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.20 (1H, s, CSNH), 11.55 (1H, s, CONH), 8.31 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.6 Hz, Thiophene CH), 8.01 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.5 Hz, Thiophene CH), 7.76 (2H, d, *J* = 8.2 Hz, Ar H), 7.61 (2H, d, *J* = 6.5 Hz, Ar H). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.1 (C=S), 162.3 (C=O), 141.0 (C), 135.5 (C), 133.0 (C), 132.2 (C), 132.0 (C), 130.5 (C), 128.0 (2C), 127.2 (2C). EI MS, m/z(%): 298 (M$^+$, 5.5), 296 (M$^+$, 20), 262 (6.4), 169 (52), 170 (3), 126 (5.5), 111 (100), 84 (57). Anal. Calcd. for $C_{12}H_9ClN_2OS_2$: C, 48.56; H, 3.06; N, 9.44; S, 21.61. Found: C, 48.57; H, 3.09; N, 9.46; S, 21.61.

***N*,*N*-diphenyl-*N'*-(thiophene-2-carbonyl)-thiourea (6):** Dark yellow crystals. Yield: 91%. M.p.: 153-154 °C. FT-IR (KBr pellet) in cm^{-1}: 3245 (NH), 3063-3031 (C-H), 1680 (C=O), 1593



Scheme 1

(aromatic C=C), 1230 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 11.41 (1H, s, broad, CONH), 8.32 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.10 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.23 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.3 Hz, Thiophene CH), 7.63-7.27 (m, 10H, arom-H). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 178.4 (C=S), 162.5 (C=O), 136.3 (C), 133.1 (C), 131.4 (C), 129.1 (C), 128-125.1 (phenyl carbons). EI MS, m/z (%): 338 (M^+, 23), 228 (4.3), 169 (52), 141 (3), 127 (7.5), 111 (100), 93 (29.1), 84 (62). Anal. Calcd. for $C_{18}H_{14}N_2OS_2$: C, 63.88 ;H, 4.17; N, 8.28; S, 18.95. Found: C, 63.89; H, 4.18; N, 8.28; S, 18.94.

***N*-(4-methylphenyl)-*N'*-(thiophene-2-carbonyl)-thiourea (7):** White solid. Yield: 94%. M.p.: 158-159 °C. FT-IR (KBr pellet) in cm^{-1}: 3265, 3189 (N-H), 3065-3046 (C-H), 1678 (C=O), 1591 (aromatic C=C), 1236 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 12.36 (1H, s, CSNH), 11.53 (1H, s, CONH), 8.36 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.0 Hz, Thiophene CH), 8.01 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.20 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.8 Hz, Thiophene CH), 7.74 (2H, d, J = 8.1 Hz, Ar H), 7.62 (2H, d, J = 6.5 Hz, Ar H), 2.31 (3H, s,CH_3,Ph CH_3). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 178.9 (C=S), 162.3 (C=O), 136.0 (C), 135.7 (C), 135.3 (C), 132.2 (C), 128.5 (C), 129.2 (2C), 128.6 (C), 124.1 (C), 20.5 (CH_3). EI MS, m/z (%): 276 (M^+, 16), 242 (6.3), 149 (20), 127 (7.5), 111 (100), 106 (3.8), 84 (58), 15 (6.1). Anal. Calcd. for $C_{13}H_{12}N_2OS_2$: C, 56.49; H, 4.38; N, 10.14; S, 23.20. Found: C, 56.51; H, 4.40; N, 10.14; S, 23.25.

***N*-(naphthalene-2-yl)-*N'*-(thiophene-2-carbonyl)-thiourea (8):** White solid. Yield: 93%. M.p.: 175-176 °C. FT-IR (KBr pellet) in cm^{-1}: 3256, 3175 (NH), 3063-3031 (C-H), 1680 (C=O), 1593 (aromatic C=C), 1234 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 12.26 (1H, s, CSNH), 11.75 (1H, s,CONH),

8.32 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.5 Hz, Thiophene CH), 8.04 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.24 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.7 Hz, Thiophene CH), 7.95-7.84 (m, 7H, arom-H). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.7 (C=S), 164.3 (C=O), 136.5 (C), 134.3 (C), 133.4 (C), 132.5 (C), 129.2-123.4 (naphthalene carbons). EI MS, m/z (%): 312 (M^+, 18), 228 (4.3), 169 (52), 141 (3), 127 (7.5), 111 (100), 93 (29.1), 84 (38). Anal. Calcd. for $C_{16}H_{12}N_2OS_2$: C, 61.51; H, 3.87; N, 8.97; S, 20.53. Found: C, 61.53; H, 3.89; N, 8.99; S, 20.52.

***N*,*N*-diethyl-*N'*-(thiophene-2-carbonyl)-thiourea (9):** White solid. Yield: 90%. M.p.: 136-137 °C. FT-IR (KBr pellet) in cm^{-1}: 3263, 3209 (N-H), 3063-3031 (C-H), 1675 (C=O), 1593 (aromatic C=C), 1238 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 11.43 (1H, s, CONH), 8.2 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH), 2.16 (4H,q, -CH_2), 0.96 (6H, t, -CH_3 , J = 7.1 Hz). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.8 (C=S), 170.1 (C=O), 135.3 (C), 133.7 (C), 132.5 (C), 132.0 (C), 34.2 (2C), 21.8 (2C). EI MS, m/z (%): 242 (M^+, 15), 217 (3.4), 169 (52), 141 (4.7), 127(7.5), 111 (100), 93 (21.1), 84 (45), 28 (15), 15 (3.4). Anal. Calcd. for $C_{10}H_{14}N_2OS_2$: C, 49.56; H, 5.82; N, 11.56; S, 26.46. Found: C, 49.54; H, 5.86; N, 11.53; S, 26.47.

***N*-decyl-*N'*-(thiophene-2-carbonyl)-thiourea (10):** Light yellow solid. Yield: 88%. M.p.: 145-146 °C. FT-IR (KBr pellet) in cm^{-1}: 3263, 3209 (N-H), 3063-3031 (C-H), 1670 (C=O), 1593 (aromatic C=C), 1237 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 12.43 (1H, s, CSNH), 11.53 (1H, s, CONH), 8.2 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH), 2.17 (2H, t, -NCH_2), 1.45-1.14 (2H,m, CH_2), 0.93 (3H, t, -CH_3, J = 7.1 Hz). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.6 (C=S), 169.8 (C=O), 135.3 (C), 133.7 (C), 132.5 (C), 132.0 (C), 34.2 (2C), 21.8 (2C). EI MS, m/z (%): 326 (M^+, 15), 217 (3.4), 169 (52), 141 (4.7), 127 (7.5), 111 (100), 93 (21.1), 84 (45), 28 (15), 15 (3.4). Anal. Calcd. for $C_{16}H_{26}N_2OS_2$: C, 58.85; H, 8.03; N, 8.58; S, 19.64. Found: C, 58.83; H, 8.15; N, 8.59; S, 19.65.

***N*-(dipropylcarbamothioyl)thiophene-2-carboxamide (11):** White solid. Yield: 86%. M.p.: 135-136 °C. FT-IR (KBr pellet) in cm^{-1}: 3261 (N-H), 3064-3031 (C-H), 1673 (C=O), 1590 (aromatic C=C), 1236 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 11.48 (1H, s, CONH), 8.2 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.03 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH), 2.45 (4H, q, -NCH_2), 1.15 (4H, m, -CH_2), 0.95 (6H, t, -CH_3, J = 7.1 Hz). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.8 (C=S), 170.1 (C=O), 135.3 (C), 133.7 (C), 132.5 (C), 132.0 (C), 46 (2C), 34.2 (2C), 21.8 (2C). MS (70 eV) m/z (%): 270. Anal. Calcd. for $C_{12}H_{18}N_2OS_2$:C, 53.30; H, 6.71; N, 10.36; S, 23.72. Found: C, 53.33; H, 6.75; N, 10.35; S, 23.72.

***N*-[(5-methoxy-1,3-benzothiazol-2-yl)carbamothioyl]thiophene-2-carboxamide (12):** Dark yellow solid. Yield: 89%. M.p.: 167-168 °C. FT-IR (KBr pellet) in cm^{-1}: 3263, 3209 (N-H), 3063-3031(C-H), 1671 (C=O), 1591 (aromatic C=C), 1233 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6) in δ (ppm) and J (Hz): 12.25 (1H, s, CSNH), 11.37 (1H, s, CONH), 8.10 (1H, dd, J_1 = 7.2 Hz, J_2 = 8.1 Hz, Thiophene CH), 8.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 8.2 Hz, Thiophene CH), 7.35 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.50 (1H, dd, J_1 = 6.7 Hz, J_2 = 8.6 Hz, Thiophene CH), 7.01 (1H, s, Ph), 4.35 (3H, s, OCH_3). ^{13}C NMR (300 MHz, DMSO-d_6) in δ (ppm): 180.0 (C=S), 174.2 (C=N), 168.2 (C=O), 149.7, 145.5, 137.0, 135.7, 130.3, 128.4, 122.3, 120.7, 62.5. EI MS (70 eV) m/z (%): 349. Anal. Calcd. for $C_{14}H_{11}N_3O_2S_3$: C, 48.12; H, 3.17; N, 12.02; S, 27.53. Found: C, 48.15; H, 3.17; N, 12.04; S, 27.51.

2.2.2 Crystal structure determination of *N*,*N*-diphenyl-*N'*-(thiophene-2-carbonyl)-thiourea (6)

Crystal data: $C_{18}H_{14}N_2OS_2$, monoclinic, space group $P2_1$, a=11.7469(5), b=6.0849(2), c=12.5792(6) Å, β=117.736(7) °, V=795.8(6) Å^3, T=100(2) K, Z=2, F (000)=352, D_x=1.412 g cm^{-3}, μ=3.0 mm^{-1}. Single crystals suitable for X-ray diffraction studies were obtained from an ethanol-dichloromethane mixture. A yellow lath 0.15 × 0.05 × 0.02 mm^3 was mounted on a glass fibre in inert oil. Measurements were performed at 100 K on an Oxford Diffraction Xcalibur Nova diffractometer with mirror-focused Cu-K$_\alpha$ radiation to $2\theta_{max}$ 152° (99.3% complete to 72.50°). The data were corrected for absorption using the multi-scan method. Of 17408 intensities, 3097 were independent (R_{int} 0.0404). The structure was refined anisotropically using SHELXL-97 [30]. The NH hydrogen was refined freely, other H atoms using a riding model. The final $wR2$ was 0.074, with a conventional $R1$ of 0.029, for 212 parameters; S = 1.06; max. Δρ = 0.23 e Å^{-3}. The Flack parameter refined to 0.019(14); the compound is achiral but crystallizes by chance in a chiral space group.

2.2.3 Antifungal Screening

The compounds were screened for their in vitro antifungal activity. Antifungal activity was determined by the broth micro-dilution procedures and principles of the Clinical and Laboratory Standards Institute (CLSI) [31,32]. 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. All of the dilutions were done with distillated water. The concentrations of tested compounds were 100, 50, 25, 12.5, 6.25, 3.125 μg/mL. 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 fungi. The lowest concentration of the compounds that prevented visible growth was considered minimal inhibitor concentrations (MICs).

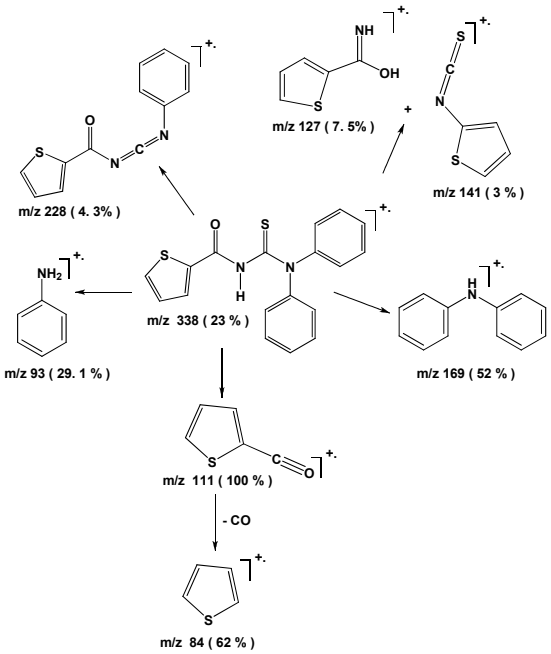
3. Results and Discussion

3.1. Synthesis and spectral studies

All thioureas (**1-12**) were synthesized according to the method of our published papers [33,34] and were obtained in yields ranging from 86 to 95%. The synthesis involves the reaction of thiophene-2-carbonyl chloride with ammonium thiocyanate in dry acetone followed by condensation of the resulting thiophene-2-carbonyl isothiocyanate with an appropriate primary and secondary amine. The reaction proceeds via a nucleophilic addition of the amine to the isothiocyanate. The synthesized compounds were purified by recrystallization from an ethanol: dichloromethane mixture (1:2) and characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy. The ^{1}H NMR data of the compound obtained in DMSO-d_6 solution is given in the experimental section and is consistent with the structural results. The elemental analyses closely corresponded to calculated values. The analytical and spectroscopic data are consistent with the proposed structures [35]. The synthesized compounds are easily dissolved in DMF, DMSO, ethanol and

ethyl acetate. They are sparingly soluble in diethyl ether, dioxane, tetrahydrofurane while insoluble in aliphatic and aromatic hydrocarbons. The main vibrational bands of the compounds **1-12** are given in the experimental section. IR (KBr) spectra of the target compounds had strong N-H absorptions at about 3345-3200 cm^{-1}, and displayed absorptions at about 1680-1670 cm^{-1} and ~1240 cm^{-1} that were assigned to C=O and C=S functions respectively. The medium-strong $\upsilon_{C=O}$ band in the IR spectra of the compound appeared at 1680 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 the data in the literature [36].

In ^{1}H NMR, the compounds exhibited broad signals in the range of 12.78-12.20 ppm and 11.92-11.37 ppm, which were assigned to the N-H protons. Generally the NMR signals of NH protons for amides are observed in the range of 9-10 ppm. The low-field shift of the signal for the imine proton for synthesized compounds can be attributed to the deshielding effect of the electron-withdrawing carbonyl and thiocarbonyl group. ^{13}C NMR spectrum showed the peaks at about δ 180.0-178 and 170.1-162.2 for C=S (thioamide) and C=O (amide), respectively. The mass spectrum of compound **6** showed the molecular ion peak at m/z 338 (Scheme 2). The major fragment at m/z 127 (7.5%) was derived from the N-McLafferty rearrangement and the base peak at m/z 111 (100%) originated from the thiophenoyl cation (Scheme 2). Similarly, the mass spectrum of compounds **1** and **2** showed the molecular ion peak at m/z 366 and m/z 297, respectively. The base peak for all the compounds (**1-12**) was m/z 111 (100%), originated from the thiophenoyl cation and the fragmentation pattern was also same.



Scheme 2

3.2. Single crystal X-Ray crystallography

The molecular structure of *N*,*N*-diphenyl-*N*'-(thiophene-2-carbonyl)-thiourea (**6**) is shown in Figure 1. The C1-S1 and C2-O bonds show a typical double bond character with bond lengths of 1.666(2) Å and 1.215(3) Å, respectively. All of the C-N bonds, C1-N1 1.353(3) Å, C21-N1 1.442(2) Å, C11-N1 1.442(2) Å, C2-N2 1.397(3) Å and C1-N2 1.400(2) Å also indicate a partial double bond character (Table 1). The C1-N2 bond, adjacent to the carbonyl group, is slightly shorter than C1-N1. 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 [37]. Defining a molecular backbone as S2-C3-C2-N2-C1-N1-C11, the geometry is antiperiplanar about all bonds except C1-N2 (torsion angles in the same order: -174 °, -177 °, 45 ° and -162 °). The phenyl rings subtend an interplanar angle of 81.6 °. The molecular packing (Figure 2) involves layers parallel to the plane (10$\bar{1}$). The classical H bond N2-H02···S, with H···S 2.71(3) Å, angle 154(2) °, is surprisingly long. Also observed are the weak H bonds H4···S1 (2.90 Å), H24···S2 (3.03 Å) and H24···O (2.52 Å), the latter two forming a three-centre system but with a narrow C24-H24···S2 angle of 114 °, and the contact S1···O 3.22 Å (Table 2). The intramolecular hydrogen bonding will influence the coordination behaviour of the compounds. Thiourea derivatives such as *N*,*N*'-dialkyl-*N*'-benzoylthiourea easily coordinate to a metal atom to participate in the coordination with transition metal atoms because it is involved in intramolecular hydrogen bonding.

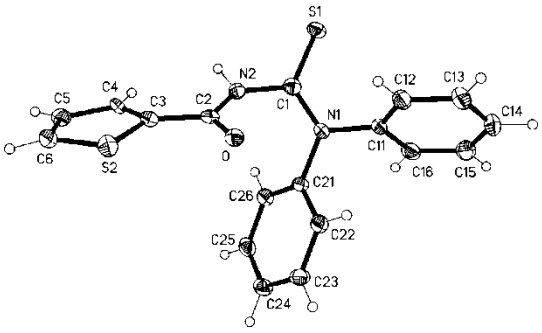


Figure 1. The molecule of the compound **6** in the crystal; ellipsoids represent 50% probability levels.

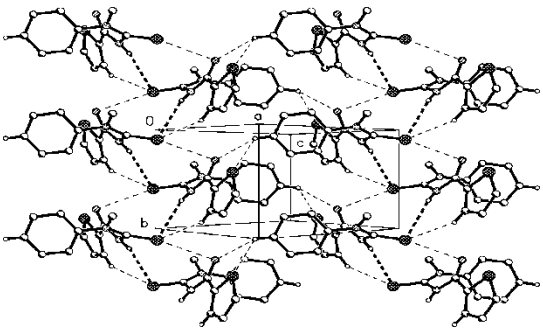


Figure 2. Packing diagram of the compound **6** viewed perpendicular to the plane (10$\bar{1}$). The ring C11-16 is represented only be the *ipso* C atom. Thick dashed lines represent H···S hydrogen bonds, thin dashed lines represent "weak" hydrogen bonds or S···O contacts (see text).

3.3. Biological activity studies

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 thiourea derivatives (**1-12**) were checked for their antifungal activity against 3 fungal strains: *C. glabrata*, *C. albicans* and *C. tropicalis*. The antifungal activity was carried out in DMSO using the broth micro-dilution procedure [31]. All the compounds inhibited the growth of fungi with MIC values ranging between 20 and >100μg/mL. When all the anti-yeast MIC values are compared, three out of twelve compounds show good activity against *C. glabrata* and three against *C. tropicalis* (Table 3). Lipophilicity is a factor, which correlates well with the bioactivity of chemicals, is a very important molecular descriptor and different lipophilic behaviour of compounds plays an important role in their biological activity mechanisms.

The *n*-octanol/water partition coefficient (log P_{ow}) is widely used as a general measure of lipophilicity [18,38]. The compounds **3, 5, 8, 10** and **12** have relatively higher log P_{ow} values of 3.36 ± 0.61, 3.41 ± 0.6, 3.65 ± 0.60, 5.45 ± 0.60, and 3.15 ± 0.93, respectively, and hence show more lipophilic character. Antifungal activity (MIC values) for these compounds is comparatively lower than those which are less lipophilic. The compounds **1**, **2** and **9** which have the log P_{ow} values of -2.51 ± 0.81, 0.49 ± 0.91 and 1.69 ± 0.61, respectively show higher antifungal activity than other investigated compounds due probability to their lower lipophilic character.

Table 1. Bond lengths [Å], angles [°] and torsion angles [°] of *N*,*N*-diphenyl-*N*'-(thiophene-2-carbonyl)-thiourea (6).

Bond lengths	
S1-C1	1.666(2)
S2-C6	1.696(2)
S2-C3	1.722(2)
O1-C2	1.215(3)
N1-C1	1.353(3)
N1-C21	1.442(2)
N1-C11	1.442(2)
N2-C1	1.400(2)
C2-C3	1.473(3)
Bond angles	
C6-S2-C3	91.76(11)
C1-N1-C21	124.57(16)
C1-N1-C11	119.70(16)
C21-N1-C11	115.68(15)
N1-C1-N2	116.15(16)
N1-C1-S1	124.73(15)
N2-C1-S1	119.07(14)
O1-C2-N2	122.93(18)
O1-C2-C3	122.28(19)
N2-C2-C3	114.78(18)
C4-C3-C2	131.51(19)
C4-C3-S2	112.17(14)
C3-C4-C5	109.8(2)
C5-C6-S2	112.80(15)
Torsion angles	
C21-N1-C1-N2	21.2(3)
C11-N1-C1-N2	-161.53(18)
C21-N1-C1-S1	-156.10(16)
C11-N1-C1-S1	21.1(3)
C2-N2-C1-N1	45.2(3)
C2-N2-C1-S1	-137.27(16)
C1-N2-C2-C3	-177.42(17)
O1-C2-C3-C4	-169.6(2)
N2-C2-C3-C4	9.7(3)
O1-C2-C3-S2	7.0(2)
N2-C2-C3-S2	-173.70(13)
C6-S2-C3-C4	-0.59(16)
C6-S2-C3-C2	-177.85(15)
S2-C3-C4-C5	0.5(2)
C3-S2-C6-C5	0.48(17)

Table 2. Hydrogen bonds [Å and °] of *N*,*N*-diphenyl-*N*'-(thiophene-2-carbonyl)-thiourea (6).

D-H...A	d (D-H)	d (H...A)	d (D...A)	< (DHA)
N2-H02...S1^{i}	0.86(3)	2.71(3)	3.5022(19)	154(2)
C4-H4...S1^{i}	0.95	2.90	3.770(2)	153.3
C24-H24...S2^{ii}	0.95	3.03	3.516(2)	113.7
C24-H24...O^{ii}	0.95	2.52	3.390(3)	151.7

Symmetry transformations used to generate equivalent atoms: (*i*) -*x*, *y*+1/2, -z; (*ii*) -*x*+1, *y*+1/2, -*z*+1.

4. Conclusion

To summarize, we have described a simple and efficient method for the synthesis of thiourea derivatives in high purity and high yield using tetrabutylammonium bromide (TBAB) as phase-transfer catalyst (PTA). Products yield was improved from 4-5% as compared to reactions when carried out without TBAB. Finally, the structure of compound **6** was determined by X-ray crystallographic studies. The antifungal activity of this series suggests the thiophene-thiourea core offers a novel template for the development of a new class of antifungal agents. The structure of compounds **1**, **2** and **9** waits for further modification, in expectation of getting better biological activities.

Table 3. MIC values (μg/mL) of the synthesized thiourea derivatives against the tested fungi.

Compound	*C. Glabrata* (ATCC32554)	*C. Albicans* (ATCC 90028)	*C. Tropicalis* (ATCC 20336)
1	20	20	25
2	25	25	25
3	100	100	50
4	50	50	50
5	100	100	100
6	50	100	100
7	50	50	50
8	100	100	100
9	25	25	20
10	>100	>100	>100
11	100	50	50
12	100	50	100
Nystatin	2	1	4

Acknowledgement

The authors are grateful to National Engineering & Scientific Commission, Islamabad for providing the facility of spectroscopic techniques, elemental analyzer and chemicals free of cost.

Supplementary material

CCDC-755273 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

References

[1]. Verma, R. K.; Verma, L.; Ranjan, M.; Verma, B. P.; Mojumdar, S. C. *J. Therm. Anal. Cal.* **2008**, *94*, 27-31.
[2]. Stiffel, E. I.; George, G. N.; Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S. *Bioinorganic Chemistry*, University Science Books, 1998.
[3]. Cotton, F. A.; Wilkinson, G.; Murillo, A.; Bochman, M. *Advanced Inorganic Chemistry*, 6th edition, John Wiley & Sons, 1999.
[4]. D'hooghe, M.; Waterinckx, A.; De Kimpe, N. *J. Org. Chem*. **2005**, *70*, 227-232.
[5]. Handerson, W.; Nicholson, B. K.; Dinger, M. B.; Bennett, R. L. *Inorg. Chim. Acta* **2002**, *338*, 210-218.
[6]. Sacht, C.; Datt, M. S.; Otto, S.; Roodt, A. *J. Chem. Soc. Dalton Trans.* **2000**, *24*, 4579-4586.
[7]. Lipowska, M.; Hayes, B. L.; Hansen, L.; Taylor, A.; Marzilli, L. G. *Inorg. Chem*. **1996**, *35*, 4227-4231.
[8]. Zuckerman, R. L.; Bergman, R. G. *Organometallics* **2000**, *19*, 4795-4809.
[9]. Henderson, W.; Kemmitt, R. D. W.; Mason, S.; Moore, M. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc. Dalton Trans*. **1992**, *1*, 59-66.
[10]. Arslan, H.; Külcü, N.; Flörke, U. *Trans. Metal Chem*. **2003**, *32(7)*, 816-819.
[11]. Binzet, G.; Arslan, H.; Flörke, U.; Külcü, N.; Duran, N. *J. Cood. Chem*. **2006**, *59(12)*, 1395-1406.
[12]. Ugur, D.; Arslan, H.; Külcü, N. *Russ. J. Coord. Chem*. **2006**, *32(9)*, 669-675.
[13]. Emen, M. F.; Arslan, H.; Külcü, N.; Flörke, U.; Duran, N. *Polish. J. Chem*. **2005**, *79(10)*, 1615-1626.
[14]. Yesilkaynak, T.; Binzet, G.; Emen, F. M.; Flörke, U.; Külcü, N.; Arslan, H. *Eur. J. Chem.* **2010**, *1(1)*, 1-5.
[15]. Koch, K. R.; Sacht, C.; Grimmbacher, T.; Bourne, S. *S. Afr. J. Chem*. **1995**, *48 (1-2)*, 71-77.
[16]. Saeed, S.; Rashid, N.; Hussain, R.; Ali, M.; Jones, P. G. *Eur. J. Med. Chem*. **2010**, *45*, 1323-1331.
[17]. Zhang, Y. M.; Wei, T. B.; Xian, L.; Gao, L. M. *Phosphorus Sulfur Silicon Relat. Elem*. **2004**, *179*, 2007-2013.
[18]. Arslan, H.; Duran, N.; Borekci, G.; Ozer, C. K.; Akbay, C. *Molecules* **2009**, *14*, 519-527.
[19]. Gu, C. L .; Liu, L.; Zhao, J. L.; Wang, D.; Chen, Y. J. *Tetrahedron* **2007**, *18*, 455-463.
[20]. Saeed, S.; Bhatti, M. H.; Yunus, U.; Jones, P. G. *Acta Crystallogr. E* **2008**, *64*, o1369-o1369.

[21]. D'hooghe, M.; Waterinckx, A.; De Kimpe, N. *J. Org. Chem*. **2005**, *70*, 227-232.
[22]. Jain, V. K.; Rao, J. T. *J. Institute Chem. (India),* **2003**, *75*, 24-28.
[23]. Lakhan, R.; Ral, B. J. *J. Chem. Eng. Data* **1986**, *31*, 501-508.
[24]. Saeed, A.; Parvez, M. *Cent. Eur. J. Chem*. **2005**, *3(4)*, 780-791.
[25]. Nie, L.; Li, Z.; Han, J.; Zhang, X.; Yang, R.; Liu, W. X.; Wu, F. Y.; Xie, J. W.; Zhao , Y. F.; Jiang, Y. B. *J. Org. Chem*. **2004**, *69*, 6449-6454.
[26]. Park, H.; Choi, J.; Choi, S.; Park, M.; Lee, J.; Suh, J. Y.; Cho, H.; Oh, H. U.; Lee, J.; Kang, S. U.; Lee, J.; Kim, H. D.; Park, Y. H.; Jeong, Y. S.; J. K. Choi, J. K.; Jew, J. S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 787-791.
[27]. Maquoi, E.; Sounni, N. E.; Devy, L.; Olivier, F.; Frankenne, F.; Krell, H. W.; Grams, F.; Foidart, J. M. *Agnes. Noel. Clin. Cancer Res*. **2004**, *10*, 4038-4042.
[28]. Merck Index, 13th Edition, Merck &Co, Inc., Whitehouse Station, New Jersery, 2001.
[29]. Varbanov, S.; Tosheva, T.; Russeva, E. *Phosphorus Sulfur Silicon Relat. Elem*. **1997**, *127*, 27-35.
[30]. Sheldrick, G. M. *Acta Crystallogr*. *A* **2008**, *64*, 112-122.
[31]. National Committee for Clinical Laboratory Standards, M7-A4 (NCCLS, Viallanova, PA, USA, **1997**).
[32]. National Committee for Clinical Laboratory Standards, M27-A2 (NCCLS, Wayne, PA, USA, **2002**).
[33]. Saeed, S.; Rashid, N; Jones, P. G.; Hussain, R.; Bhatti, M. H. *Cent. Eur. J. Chem*. **2010**, *8(3)*, 550-558.
[34]. Saeed, S.; Rashid, N.; Wong, W. T. *Acta Crystallogr*. *E* **2010**, *66*, o980-o980.
[35]. Sacht, C.; Datt, M. S. *Polyhedron* **2000**, *19*, 1347-1355.
[36]. Zhang, Y. M.; Wei, T. B.; Xian, L.; Gao, L. M. *Phosphorus Sulfur Silicon Relat. Elem*. **2007**, *179*, 2007-2013.
[37]. Allen, F. H. *Acta Crystallogr*. *B* **2002**, *58*, 380-388.
[38]. Hoey, A. J.; Jackson, C. M.; Pegg, G. G.; Sillence, M. N. *Br. J. Pharmacol*. **1996**, *119*, 564-571.