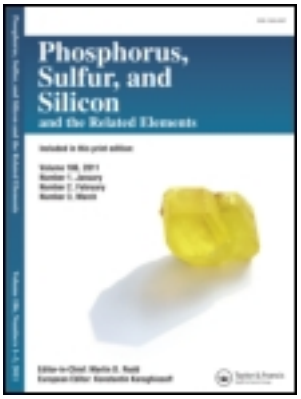

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Antimicrobial Activities of Novel Series of 1-((4-Methyl-2-Substituted Thiazol-5-yl)Methyleneam INO)-2-Substituted Isothiourea Derivatives

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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF NOVEL SERIES OF 1-((4-METHYL-2-SUBSTITUTED THIAZOL-5-YL)METHYLENEAM INO)-2-SUBSTITUTED ISOTHIOUREA DERIVATIVES

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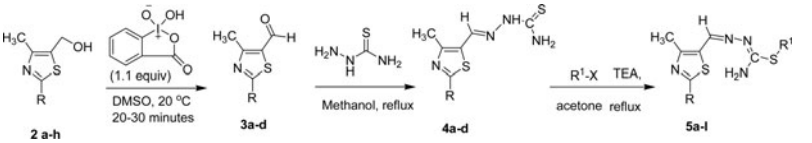
GRAPHICAL ABSTRACT



A novel series of 1-((4-methyl-2-substituted thiazol-5-yl)methyleneamino)-2-substituted isothiourea derivatives was synthesized by alkylation of (Z/E)-1-((4-methyl-2-substituted thiazol-5-yl)methylene)thiosemicarbazide with alkylhalide in acetone. All the newly synthesized compounds were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry) methods. The newly synthesized compounds were screened for in vitro antimicrobial activity. Most of the compounds show moderate to excellent antimicrobial activity.

[Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files:* Additional figures and tables.*]*

Keywords Thiazole; thiosemicarbazone; isothiourea; antimicrobial activity

INTRODUCTION

Sulfur-containing heterocyclic compounds hold a specific place among pharmaceutically active products. The thiazole ring system is one of the most important heterocyclic nuclei existing in many naturally occurring biologically active compounds.[1–4] Many

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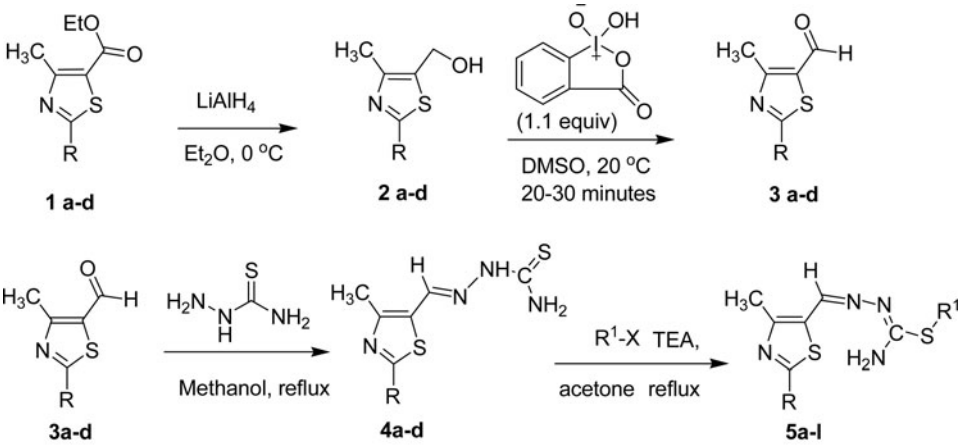
thiazole-containing compounds exhibit important biological and pharmaceutical activities.[5–14] Thiosemicarbazone derivatives of aldehydes and ketones have been reported to possess antibacterial,[15] antiprotozoal,[16] cytotoxic,[17–19] and antimalerial[20] activities, whereas S-substituted thiosemicarbazone derivatives show antibacterial and antitubercular[21] and antiviral[22] activities. On the basis of these observations and in continuation with our earlier work,[23,24] we herein report the synthesis and antimicrobial screening of 1-((4-methyl-2-substituted thiazol-5-yl)methyleneamino)-2-substituted isothiourea derivatives.

RESULTS AND DISCUSSION

Ester **1a–d** was synthesized by treatment of substituted thioamide with ethyl-2-chloro-3-oxobutanoate in ethanol.[24] Alcohol **2a–d** was conveniently prepared in high yield from ester **1a–d** with lithium aluminium hydride in diethyl ether. In the literature, such a type of alcohol was oxidized by using transition metal-containing oxidizing reagents.[25–28] We have achieved the selective and efficient synthesis of aldehyde **3a–d** from alcohol **2a–d** by using 2-iodoxybenzoic acid[29–31] in DMSO (Scheme 1).



Compound	R	R¹	Compound	R	R¹
4a	C_6H_5-	-	5e	C_6H_5-	-nC_3H_7
4b	3-Cl-C_6H_4-	-	5f	3-Cl-C_6H_4-	-nC_3H_7
4c	4-Cl-C_6H_4-	-	5g	4-Cl-C_6H_4-	-nC_3H_7
4d	4-Cl-$C_6H_4CH_2$-	-	5h	4-Cl-$C_6H_4CH_2$-	-nC_3H_7
5a	C_6H_5-	-C_2H_5	5i	C_6H_5-	-iC_3H_7
5b	3-Cl-C_6H_4-	-C_2H_5	5j	3-Cl-C_6H_4-	-iC_3H_7
5c	4-Cl-C_6H_4-	-C_2H_5	5k	4-Cl-C_6H_4-	-iC_3H_7
5d	4-Cl-$C_6H_4CH_2$-	-C_2H_5	5l	4-Cl-$C_6H_4CH_2$-	-iC_3H_7

Scheme 1

Compound **3a** shows, in its IR spectrum, strong absorption bands at 2730 and 1690 cm^{-1} due to C–H and C=O stretching frequency of aldehyde functional group. ^{1}H NMR spectrum of **3a** showed the singlet at δ 2.78 integrating for three protons of methyl group; five aromatic protons appeared between δ 7.17–7.85. The aldehyde proton resonated at δ 10.08. The ^{13}C NMR of aldehyde **3a** shows peak at δ 16.2 corresponds to methyl group of thiazole ring. The phenyl ring and thiazole carbons appeared at δ 127.1,

128.9, 129.1, 131.6, 132.5, 162.4, and 173.7, whereas a peak at δ 182.0 was due to the C=O of aldehyde group.

Aldehyde **3a–d**, when subjected to a condensation reaction with semicarbazide, furnished thiosemicarbazone **4a–d**. The structure of thiosemicarbazone was confirmed by IR spectroscopy. The IR spectrum of **4a** show absent of peaks at 2730 and 1690 cm^{-1} and new peaks observed at 3421, 3309, 3157 cm^{-1} due to presence of NH and NH_2 group of thiosemicarbazone, the peak observed at 1599 (C=N) confirms the formation of thiosemicarbazone. The thiosemicarbazone **4a–d** on nucleophilic substitution reaction with alkyl halide gave 1-((4-methyl-2-substituted thiazol-5-yl)methyleneamino)-2-substituted isothiourea **5a–l**. The IR spectrum of compound **5e** showed presence of two peaks at 3393 and 3236 cm^{-1} (asymmetric and symmetric stretching of $–NH_2$ group) indicated the formation of S-alkylation, which was further confirmed by its ^{1}H NMR data. The ^{1}H NMR spectrum of **5e** displayed peaks at δ 1.04 (t, J = 7.2 Hz, 3H); 1.75 (m, 2H); 3.08 (t, J = 7.6 Hz, 2H) that confirmed the presence of S-propyl group. The singlet at δ 2.57 integrated for three protons corresponding to the methyl group of thiazole ring. Two $–NH_2$ protons showed bs at δ 5.59, confirming the S-alkylation, and the aromatic protons resonated between δ 7.42 and 8.01. The singlet at δ 8.55 corresponds to the imine proton. The ^{13}C NMR spectrum of **5e** showed peaks at 13.4, 15.8, 22.9, 32.2, 121.5, 126.6, 129.0, 130.4, 133.3, 141.1, 145.8, 155.3, 161.9, and 167.8. The structure was further confirmed by LCMS spectrum, which showed $(M + H)^+$ at 319.00. From the NMR and LCMS data, it was observed that there is formation of E and Z isomers in different proportions.

Antimicrobial Activity

Analysis of the antimicrobial activity (Tables S1 and S2, Supplemental Materials) provides some lead molecules with good antibacterial and antifungal activity. Thiosemicarbazone derivatives (**4a–d**) are less active against all bacterial strains, but most of the S-alkyl thiosemicarbazone showed moderate to excellent antibacterial activity. The compounds **5b** (R = 3-ClC_6H_4, $R^1 = –C_2H_5$) and **5g** (R = 4-ClC_6H_4, R^1 = -nC_3H_7) expressed excellent activity against all the tested pathogens. They inhibited Gram-positive pathogen more than the Gram-negative pathogens. The compounds **5c** (R = 4-ClC_6H_4, R^1 = $–C_2H_5$), **5j** (R = 3-ClC_6H_4, $R^1 = –iC_3H_7$), and **5k** (R = 4-ClC_6H_4, $R^1 = –iC_3H_7$) showed good antibacterial activity.

The result of antifungal activity revealed that thiosemicarbazone derivative **4a** and **4c** (R = C_6H_5 and 4-ClC_6H_5) showed excellent antifungal activity when compared with standard drug ketoconazole. It is also interesting to note that few S-alkyl derivatives **5a** (R = $–C_6H_5$, $R^1 = –C_2H_5$), **5g** (R = 4-ClC_6H_4, $R^1 = nC_3H_7$), **5j** (R = C_6H_5, $R^1 = –iC_3H_7$), and **5k** (R = 4-ClC_6H_4 and $R^1 = iC_3H_7$) also showed comparable activity with ketoconazole. It is, however, worth noting that thiosemicarbazone **4c**, which showed excellent antifungal activity, loses its activity considerably upon S-alkylation **5c** (R = 4-ClC_6H_4, $R^1 = –C_2H_5$). The thiosemicarbazone **4d** also showed moderate to good antifungal activity, but its alkyl derivatives **5d**, **5h,** and **5l** were found to be less active.

It is thus concluded that the S-alkyl group is responsible for enhanced antibacterial activity. It is also concluded that derivatives derived from 4-chloro phenyl on thiazole ring show better antifungal activity than their corresponding 4-chloro benzyl derivatives. Out of all the tested compounds, **5g** shows excellent antibacterial, as well as antifungal activity.

CONCLUSION

In conclusion, a series of new thiosemicarbazone **4a–d** and S-alkyl thiosemicarbazone **5a–l** was synthesized. S-alkylated thiosemicarbazone derivatives showed better antibacterial activity than their corresponding thiosemicarbazones. Some of the synthesized compounds exhibited good to excellent activity toward Gram-positive, Gram-negative bacteria as well as the fungal species. Thus, compound **5g** can serve as a lead molecule for further studies on structure activity relationship.

EXPERIMENTAL

Melting points were determined with Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu model FTIR-435 spectrometer. ^{1}H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR at 75 or 100 MHz on a Varian Mercury spectrometer. Low-resolution mass spectra were measured on a Shimadzu LCMS-QP8000. High resolution mass spectra were obtained using a Jeol SX 102 mass spectrometer and/or Q-TOF micro mass spectrometer. The isotopic peak at M + 2 was observed in the mass spectrum of all the compounds due to S and/or Cl. The reaction monitoring was accomplished by thin-layer chromatography (TLC) on silica-gel plates. Selected ^{1}H, ^{13}C NMR, and HRMS spectra of **2a**, **3a**, **4a**, and **5e** are shown in the Supplemental Materials (Figures S1–S10).

(4-Methyl-2-phenylthiazole-5-yl)methanol (2a)

To a cold solution of lithium aluminium hydride (20 mmol) in dry diethyl ether (25 mL), ethyl 4-methyl-2-phenylthiazole-5-carboxylate, **1a** (10 mmol) in diethyl ether (25 mL) was added dropwise over a period of 30 min, and the reaction mixture was further stirred for 1 h at 0 °C. After completion of the reaction (TLC), the reaction mixture was quenched by saturated solution of sodium sulfate. The reaction mixture was filtered on a sintered funnel. The aqueous layer was extracted with diethyl ether (2 × 30 mL), the combined organic layer was washed with water, brine, and dried over sodium sulfate. Ether was removed by distillation to obtain (4-methyl-2-phenylthiazole-5-yl)methanol (**2a**) on good yield.

(4-Methyl-2-phenylthiazol-5-yl)methanol (**2a**): White solid, mp 94–95 °C; **IR** (KBr): 3295, 1597 1494, 1437, 1091 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.45 (s, 3H), 4.82 (s, 2H), 7.38–7.41 (m, 3H), 7.87–7.90 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): 15.1, 55.2, 127.2, 129.3, 129.8, 130.6, 133.4, 154.2, 168.1.

(2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methanol (**2b**): White solid, mp 122–123 °C; **IR** (KBr): 3282, 1597 1494, 1437, 1090, 1015, 830 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.49 (s, 3H), 4.80 (s, 2H), 7.29–7.38 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.66 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 14.9, 55.1, 125.8, 126.5, 129.2, 130.0, 130.5, 133.1, 134.5, 154.8, 169.2.

(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)methanol (**2c**): White solid; mp. 134–136 °C; IR (KBr): 3279, 1593, 1496, 1437, 1091, 1014, 831 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 2.45 (s, 3H), 4.82 (s, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 15.5, 55.1, 127.2, 128.7, 129.7, 131.9, 134.4, 158.0, 169.5.

(2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)methanol (**2d**): Brown colored thick oil; **IR** (KBr): 3280, 1597, 1495, 1435, 1088, 1010, 830 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.46 (s, 3H), 4.18 (s, 2H), 4.78 (s, 2H), 7.10 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): 15.3, 39.5, 55.5, 128.8, 129.3, 130.5, 132.0, 134.4, 158.5, 170.2.

General Procedure for Synthesis of Aldehyde

To a solution of (4-methyl-2-phenylthiazole-5-yl)methanol, **2a** (10 mmol) in DMSO (30 mL), 2-iodoxybenzoic acid (11 mmol) was added, and the reaction mixture was stirred at 20 °C. The progress of the reaction was monitored on TLC. After completion of the reaction (20 min), the reaction mixture was filtered and washed with DMSO (5 mL). Water (90 mL) was added to the filtrate and extracted with diethyl ether (3 × 30 mL). The organic layer was washed with water, brine, and dried over sodium sulfate. The solvent was distilled to afford white solid **3a** (1.93 g) in 95% yield.

4-Methyl-2-phenylthiazole-5-carbaldehyde (3a): White solid, mp 110–112 °C; **IR** (KBr): 2730, 1690, 1605 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.78 (s, 3H), 7.49 (m, 3H), 7.99 (m, 2H), 10.10 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 16.2, 127.1, 128.9, 129.6, 131.6, 132.5, 162.4, 173.7, 182.0. LCMS: 204 $(M+H)^+$; **HRMS**: 236.0756 $(M + MeOH + H)^+$.

2-(3-Chlorophenyl)-4-methylthiazole-5-carbaldehyde (3b): White solid, mp 124–126 °C; **IR** (KBr): 2728, 1692, 1610 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.79 (s, 3H), 7.38–7.49 (m, 2H), 7.85 (d, $J = 7.8$ Hz, 1H), 8.02 (s, 1H), 10.11 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 16.2, 125.2, 126.9, 130.3, 131.5, 133.0, 134.1, 135.2, 162.4, 171.8, 182.0. **LCMS**: 239 $(M+H)^+$; **HRMS**: 270.0369 $(M + MeOH + H)^+$.

2-(4-Chlorophenyl)-4-methylthiazole-5-carbaldehyde (3c): White solid, mp 144–146 °C; **IR** (KBr): 2732, 1695, 1608 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.77 (s, 3H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.93 (d, $J = 7.8$ Hz, 2H), 10.08 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 16.1, 127.6, 128.8, 129.9, 131.8, 134.6, 162.0, 171.8, 184.0. **LCMS**: 239 $(M+H)^+$; **HRMS**: 270.0366 $(M + MeOH + H)^+$.

2-(4-Chlorobenzyl)-4-methylthiazole-5-carbaldehyde (3d): Brown solid, mp 88–90 °C; **IR** (KBr): 2740, 1686, 1591 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.76 (s, 3H), 4.21 (s, 2H), 7.25 (d, 7.8 Hz, 2H), 7.50 (d, $J = 7.8$ Hz, 2H), 10.02 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 15.9, 39.4, 128.9, 130.3, 133.1, 133.3, 134.9, 161.5, 176.6, 181.8. **LCMS**: 253 $(M+H)^+$; **HRMS**: 284.0522 $(M + MeOH + H)^+$.

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methylene) Thiosemicarbazide

To a solution of (2-(3-chlorophenyl)-4-methylthiazol-5-yl) carbaldehyde **3b** (1.19 g, 5.0 mmol) in methanol (30 mL), thiosemicarbazide (0.55 g, 6.0 mmol) was added. The reaction mixture was allowed to warm on a water bath for 2 h and then allowed to cool in ice water. The reaction was monitored by TLC. After completion of reaction, the product was filtered, washed with cold water, and re-crystallized from methanol (1.20g, 78%).

1-((2-Phenyl)-4-methylthiazol-5-yl)methylene) thiosemicarbazide (4a): Yellow solid, mp 222–224 °C; **IR**: 3474, 3432, 3261, 3158, 3018, 2978, 1688, 1647, 1597, 1546, 1491, 1369, 1318, 1284, 1111, 841 cm^{-1}; **^{1}H NMR** (DMSO-d_6, 400 MHz): 2.47 (s, 3H), 7.51–7.52 (m, 3H), 7.62 (s, 1H), 7.91–7.93 (m, 2H), 8.29 (s, 1H), 8.36 (s, 1H), 11.46 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 15.5, 126.2, 127.9, 129.4, 130.8, 132.7, 132.8, 135.5, 154.8, 166.5, 177.5; **MF**: $C_{12}H_{12}N_4S_2$; **MS**: 276.97 $(M+H)^+$.

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methylene) thiosemicarbazide (4b): Yellow solid, mp 226–228 °C; **IR**: 3464, 3429, 3260, 3154, 3020, 2969, 1679, 1645,

1599, 1539, 1497, 1370, 1320, 1280, 1126, 842, 801 cm^{-1}; **^{1}H NMR** (DMSO-d_6, 400 MHz): 2.46 (s, 3H), 7.46–7.54 (m, 2H), 7.62 (s, 1H), 7.91–7.93 (m, 1H), 7.96 (s, 1H), 8.30 (s, 1H), 8.36 (s, 1H), 11.45 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): 15.8, 126.1, 127.8, 128.5, 129.0, 129.7, 130.6, 135.0, 135.5, 155.4, 165.9, 177.8; **MF**: $C_{12}H_{11}ClN_4S_2$; **MS**: 311.15 $(M+H)^+$.

1-((2-(4-Chlorophenyl)-4-methylthiazol-5-yl)methylene) thiosemicarbazide (4c): Yellow solid, mp 245–247 °C; **IR**: 3465, 3428, 3260, 3166, 3010, 2976, 1687, 1646, 1598, 1546, 1502, 1368, 1320, 1284, 1124, 1001, 840, 801 cm^{-1}; **^{1}H NMR** (DMSO-d_6, 400 MHz): 2.46 (s, 3H), 7.57 (d, $J = 8$ Hz, 2H), 7.62 (s, 1H), 7.91 (d, $J = 8$ Hz, 2H), 8.30 (s, 1H), 8.35 (s, 1H), 11.48 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.0, 128.3, 128.8, 129.9, 131.9, 135.7, 135.8, 155.3, 165.5, 178.0; **MF**: $C_{12}H_{11}ClN_4S_2$; **MS**: 311.08 $(M+H)^+$.

1-((2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)methylene) thiosemicarbazide (4d): Yellow solid, mp 178–180 °C; **IR**: 3440, 3377, 3261, 3177, 3011, 2978, 1687, 1646, 1600, 1542, 1529, 1364, 1320, 1282, 1168, 1001, 841, 804 cm^{-1}; **^{1}H NMR** (DMSO-d_6, 400 MHz): 2.36 (s, 3H), 4.28 (s, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.55 (s, 1H), 8.16 (s, 1H), 8.27 (s, 1H), 11.32 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 15.7, 38.5, 127.9, 129.1, 131.5, 132.2, 136.2, 137.2, 154.1, 170.6, 177.8; **MF**: $C_{13}H_{13}ClN_4S_2$; **MS**: 325.15 $(M+H)^+$.

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-propylisothiourea

To a solution of 1-((2-(chlorophenyl)-4-methylthiazol-5-yl)methylene)thiosemicarbazide, Schiff's base (0.170 g, 0.55 mmol) in dry acetone (20 mL), propyl bromide (0.080 g, 0.65 mmol) was added, and the reaction mixture was refluxed for 2–3 h (TLC). After completion of reaction, the mixture was cooled in ice water. The product crystallized out as a white solid 0.150 g (77%).

1-((4-methyl-2-phenylthiazol-5-yl)methyleneamino)-2-ethylisothiourea (5a): Yellow solid, mp 174–178 °C; **IR**: 3393, 3236, 3140, 3094, 2968, 1593, 1516, 1431, 1313, 1282, 1226, 991, 920, 820, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.30 (t, $J = 6.6$ Hz, 3H), 2.57 (s, 3H), 3.05 (q, $J = 6.6$ Hz, 2H), 5.58 (bs, 2H), 7.40–7.44 (m, 3H), 7.90–8.00 (m, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.4, 16.5, 32.2, 121.5, 126.7, 129.1, 130.5, 133.2, 145.7, 155.2, 162.1, 168.0; **MF**: $C_{14}H_{16}N_4S_2$; **HRMS**: 305.0894 $(M+H)^+$.

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-ethylisothiourea (5b): Yellow solid, mp 163–165 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.31 (t, $J = 6.6$ Hz, 3H), 2.58 (s, 3H), 3.09 (q, $J = 6.6$ Hz, 2H), 5.54 (bs, 1H), 7.30–7.39 (m, 2H), 7.72–7.80 (m, 1H), 7.90 (s, 1H), 8.50 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.5, 16.5, 32.1, 121.5, 126.3, 128.0, 129.5, 130.7, 135.1, 136.1, 145.4, 155.5, 162.2, 168.7. **MF**: $C_{14}H_{15}ClN_4S_2$; **HRMS**: 339.0505 $(M+H)^+$.

1-((2-(4-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-ethylisothiourea (5c): Yellow solid, mp 162–164 °C; **IR**: 3389, 3238, 3138, 3093, 2966, 1591, 1519, 1437, 1313, 1091, 987, 827, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.31 (t, $J = 6.9$ Hz, 3H), 2.56 (s, 3H), 3.10 (q, $J = 6.9$ Hz, 2H), 5.54 (bs, 2H), 7.33 (d, $J = 7.2$ Hz, 2H), 7.88 (d, $J = 7.2$ Hz, 2H), 8.54 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.3, 16.3, 32.1, 121.5, 128.3, 129.5, 131.8, 135.0, 145.4, 155.0, 162.0, 167.9; **MF**: $C_{14}H_{15}ClN_4S_2$; **HRMS**: 339.0505 $(M+H)^+$.

1-((2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)methyleneamino)-2-ethylisothiou rea (5d): Yellow solid, mp 137–139 °C; **IR**: 3388, 3239, 3137, 3092, 2965, 1592, 1517, 1437, 1311, 1089, 985, 820, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.32 (t, $J = 6.6$ Hz, 3H), 2.57 (s, 3H), 3.10 (q, $J = 6.6$ Hz, 2H), 4.20 (s, 2H), 5.55 (bs, 2H), 7.12 (d, $J = 7.5$ Hz, 2H), 7.43 (d, $J = 7.5$ Hz, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.4, 16.6, 32.1, 41.0, 121.8, 128.5, 130.2, 131.5, 134.5, 145.3, 155.0, 162.2, 167.8; **MF**: $C_{15}H_{17}ClN_4S_2$; **HRMS**: 353.0661 $(M+H)^+$.

1-((4-Methyl-2-phenylthiazol-5-yl)methyleneamino)-2-propylisothiourea (5e): Yellow solid, mp 136–138 °C; **IR**: 3393, 3236, 3140, 3094, 2968, 1593, 1516, 1431, 1313, 1282, 1226, 991, 920, 820, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.04 (t, $J = 7.2$ Hz, 3H), 1.75 (m, 2H), 2.57 (s, 3H), 3.08 (t, $J = 7.6$ Hz,2H), 5.59 (bs, 2H), 7.42–7.44 (m, 3H), 7.92–8.01 (m, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.4, 15.8, 22.9, 32.2, 121.5, 126.6, 129.0, 130.4, 133.3, 145.8, 155.3, 161.9, 167.8. MF: $C_{15}H_{18}N_4S_2$; **HRMS**: 319.1065 $(M+H)^+$.

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-propylisothio urea (5f): Yellow solid, mp 126–128 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 935, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.04 (t, $J =$ 7.2 Hz, 3H), 1.75 (m, 2H), 2.57 (s, 3H), 3.07 (t, $J = 7.5$ Hz, 2H), 5.51 (bs,1H), 7.32–7.40 (m, 2H), 7.75–7.83 (m, 1H), 7.95 (s, 1H), 8.51 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.4, 15.8, 22.9, 32.0, 124.6, 126.5, 129.7, 129.9, 130.2, 135.0, 141.1, 145.4, 155.5, 162.1, 167.8; **MF**: $C_{15}H_{17}ClN_4S_2$; **HRMS**: 353.0662 $(M+H)^+$.

1-((2-(4-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-propylisothio urea (5g): Yellow solid, mp. 149–150 °C; **IR**: 3389, 3238, 3138, 3093, 2966, 1591, 1519, 1437, 1313, 1091, 987, 827, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.04 (t, $J = 6.9$ Hz, 3H), 1.80 (m, 2H), 2.57 (s, 3H), 3.08 (t, $J = 7.6$ Hz, 2H), 5.53 (bs, 2H), 7.35 (d, $J = 7.2$ Hz, 2H), 7.90 (d, $J = 7.2$ Hz, 2H), 8.54 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.3, 15.7, 22.8, 32.0, 121.7, 128.7, 129.4, 131.8, 135.2, 145.5, 155.1, 161.9, 168.0; **MF**: $C_{15}H_{17}ClN_4S_2$; **HRMS**: 353.0661 $(M+H)^+$.

1-((2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)methyleneamino)-2-propylisothiou rea (5h): Yellow solid, mp 118–120 °C; **IR**: 3388, 3239, 3137, 3092, 2965, 1592, 1517, 1437, 1311, 1089, 985, 820, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.04 (t, $J = 7.2$ Hz, 3H), 1.82 (m, 2H), 2.56 (s, 3H), 3.08 (t, $J = 7.5$ Hz, 2H), 4.21 (s, 2H), 5.54 (bs, 2H), 7.13 (d, $J = 7.5$ Hz, 2H), 7.44 (d, $J = 7.5$ Hz, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.3, 15.7, 22.8, 32.0, 41.1, 122.1, 128.3, 129.6, 131.5, 134.5, 145.5, 155.0, 162.1, 167.8; **MF**: $C_{16}H_{19}ClN_4S_2$; **HRMS**: 367.0823 $(M+H)^+$.

1-((4-Methyl-2-phenylthiazol-5-yl)methyleneamino)-2-isopropylisothiourea (5i): Yellow solid, mp 208–201 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.40 (d, $J = 6$ Hz, 6H), 2.58 (s, 3H), 3.07 (t, $J = 6.1$ Hz, 1H), 5.51(bs,1H), 7.40–7.45 (m, 3H), 7.90–8.00 (m, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz):13.8, 24.6, 24.7, 32.5, 121.5, 127.6, 129.0, 129.6, 133.3, 145.8, 155.3, 162.3, 169.0; **MF**: $C_{15}H_{18}N_4S_2$; **HRMS**: 319.1067 (M+H).

1-((2-(3-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-isopropylisoth iourea (5j): Yellow solid, mp 120–122 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.41 (d, $J = 6$ Hz, 6H), 2.58 (s, 3H), 3.08 (t, $J = 6$ Hz, 1H), 5.56 (bs,1H), 7.33–7.44 (m, 2H), 7.76–7.85 (m, 1H), 7.94 (s, 1H), 8.50 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.7, 24.6, 24.7, 32.4, 121.7, 126.0, 127.5, 129.7, 129.4, 130.9, 135.3, 140.7, 145.3, 155.4, 162.0, 168.8; **MF**: $C_{15}H_{17}ClN_4S_2$; **HRMS**: 353.0679 $(M+H)^+$.

1-((2-(4-Chlorophenyl)-4-methylthiazol-5-yl)methyleneamino)-2-isopropylisothiourea (5k): Yellow solid, mp 210–212 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 935, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.40 (d, $J = 6$ Hz, 6H), 2.57 (s, 3H), 3.08 (t, $J = 6$ Hz, 1H), 5.55 (bs,1H), 7.35 (d, $J = 7.2$ Hz, 2H), 7.88 (d, $J = 7.2$ Hz, 2H), 8.55 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.7, 24.5, 24.6, 32.2, 121.6, 128.8, 129.9, 131.8, 135.3, 145.5, 155.1, 162.1, 168.2; **MF**: $C_{15}H_{17}ClN_4S_2$; **HRMS**: 353.0661 $(M+H)^+$.

1-((2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)methyleneamino)-2-isopropylisothiourea (5l): Yellow solid, mp 144–146 °C; **IR**: 3398, 3232, 3132, 3093, 1593, 1518, 1448, 1315, 1255, 1103, 999, 935, 781, 680 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): 1.40 (d, $J = 6$ Hz, 6H), 2.57 (s, 3H), 3.08 (t, $J = 6.1$ Hz, 1H), 4.20 (s, 2H), 5.55 (bs, 2H), 7.15 (d, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 8.56 (s, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.5, 24.4, 24.5, 32.2, 41.2, 121.8, 128.2, 129.5, 131.4, 134.4, 145.6, 154.8, 162.0, 168.0; **MF**: $C_{16}H_{19}ClN_4S_2$; **HRMS**: 367.0828 $(M+H)^+$.

REFERENCES

1. Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002,** 45, 744-447.
2. Nicolaou, K. C.; Roschanger, F.; Vourloumis, D. *Angew. Chem. Int. Ed.* **1998,** 37, 2014-2045.
3. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998,** 51, 275-281.
4. Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. *Tetrahedron.* **1998,** 54, 11399-11404.
5. Dondoni A.; Marra, A. *Chem. Rev.* **2004,** 104, 2557-2599.
6. Zhang, C.; Zink, D. L.; Ushio, M.; Burgess, B.; Onishi, R.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *Bioorg. Med. Chem.* **2008,** 16, 8818-8823.
7. Kalkhambkar, R. G.; Kulkarni, G. M.; Shivkumar, H.; Rao, N. R. *Eur. J. Med. Chem.* **2007**, 42, 1272-1276.
8. Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S.; Nivsarkar, M.; Padh, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2008,** 43, 129-134.
9. Zitouni, G. T.; Ozdemir, A.; Kaplancikli, Z. A.; Benkli, K.; Chevallet, P.; Akalin, G. *Eur. J. Med. Chem.* **2008,** 43, 981-985.
10. Bekhit, A. A.; Ashour, H. M. A.; Abdel Ghany, Y. S.; Bekhit, A. E. A.; Baraka, A. *Eur. J. Med. Chem.* **2008,** 43, 456-463.
11. Karegoudar, P.; Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem.* **2008**, 43, 261-267.
12. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008,** 43, 897-905.
13. EI-Subbagh, H. I.; Al-Obaid, A. M. *Eur. J. Med. Chem.* **1996**, 31, 1017-1021.
14. Kumar, A.; Rajput, C. S. *Eur. J. Med. Chem.* **2009,** 44, 83-90.
15. Kasuga, N. C.; Sekino, K.; Ishikawa, M.; Honda, A.; Yokoyama, M.; Nakano, S.; Shimada, N.; Koumo, C.; Nomiya, K. *J. Inorg. Biochem.* **2003,** 96, 298-310.
16. Feun, L.; Modiano, M.; Lee, K.; Mao, J.; Marini, A.; Savaraj, N.; Plezia, P.; Almassian, B.; Colacino, E.; Fischer, J.; MacDonal, S. *Cancer Chemother. Pharmacol.* **2002,** 50, 223-229.
17. Bharti, N.; Husain, K.; Gonzalez Garza, M. T. D.; Cruz-Vega, E. C.; Castro-Garza, J.; Mata-Cardenas, B. D.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2002,** 12, 3475-3478.
18. Karali, N. *Eur. J. Med. Chem.* **2002,** 37, 909-918.
19. Bernhardt, P. V.; Sharpe, P. C.; Islam, M.; Lovejoy, D. B.; Kalinowski, D. S.; Richardson, D. R. *J. Med. Chem.* **2009,** 52, 407-415.
20. Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Mason, C. J. *J. Med. Chem.* 1979, 22, 1367-1373.

21. Cocco, M. T.; Congiu, C.; Onnis, V.; Pellerano, M. L.; Logu, A. D. *Bioorg. Med. Chem.* **2002,** 10, 501-506.
22. Easmon, J.; Heinisch, G.; Holzer, W.; Rosenwirth, B. *J. Med. Chem.* **1992**, 35, 3288-3296.
23. Mhaske, P. C.; Shelke, S. H.; Jadhav, R. P.; Raundal, H. N.; Patil, S. V.; Patil, A. A.; Bobade, V. D. *J. Heterocycl. Chem.* **2010,** 47, 1415-1420.
24. Mhaske, P. C.; Vadgaonkar, K. S.; Jadhav, R. P.; Bobade, V. D. *J. Korean Chem. Soc.* **2011,** 55, 882-886.
25. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999,** 64, 4537-4538.
26. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995,** 60, 7272-7276.
27. Wirth, T. *Angew. Chem. Int. Ed.* **2001,** 40, 2812-2814.
28. Van Arman, S. A. *Tetrahedron Lett.* **2009,** 50, 4693-4695.
29. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999,** 64, 4537-4538.
30. Munari, S. De; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996,** 61, 9272-9279.
31. Wirth, T. *Angew. Chem. Int. Ed.* **2001,** 40, 2812-2814.