Synthesis Of Some Thiazolyl And Thiadiazolyl Derivatives Of Substituted Furan And Pyrrole

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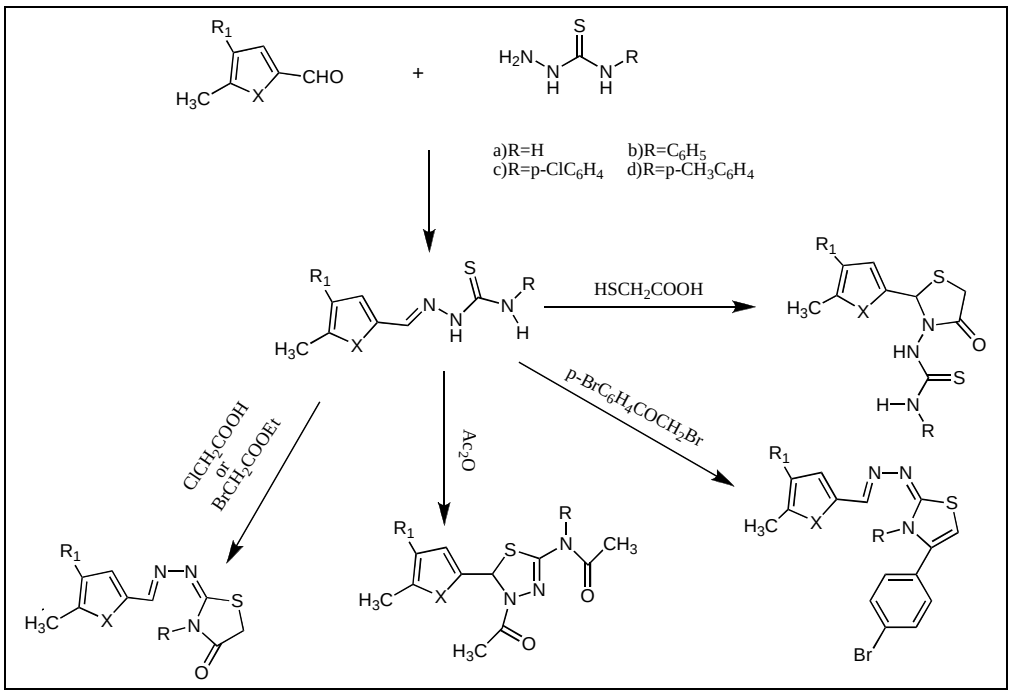

Four series of substituted furan and pyrrole have been synthesized. The first series was prepared by cyclization of the key intermediates ethyl 5-[(4-substituted thiosemicarbazido)methyl]-2-methylfuran-3-carboxylates **2a-2d** and 1-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene]-4-substituted thiosemicarbazides **8a-8d** with chloroacetic acid or (ethyl bromoacetate) to afford the corresponding 4-oxo-3-substituted thiazolidin-2-ylidene **3a-3d** or 3-substituted thiazolidin-4-one **9a-9d**. On the other hand, heating of the intermediates **2a-2d** or **8a-8d** with acetic anhydride afforded the corresponding (*N*-substituted acetylamino)-2,3-dihydro-[1,3,4]thiadiazol-2-yl derivatives **4a-4d** and [1,3,4]thiadiazol-2-yl-*N*-substituted acetamide **10a-10d** respectively, while cyclization with *p*-bromophenacyl bromide gave rise to the corresponding 3-substituted thiazol-2-yl-ylidene **5a-5d** and **11a-11d** respectively. Furthermore, 4-oxo-3-substituted thioureido-thiazolidin-2-yl **6a-6d** or 4-oxo-thiazolidin-3-yl-3-substituted thiourea **12a-12d** were obtained by reaction of the intermediates **2a-2d** or **8a-8d** with thioglycolic acid. Some of the synthesized compounds showed promising antimicrobial activities**.**

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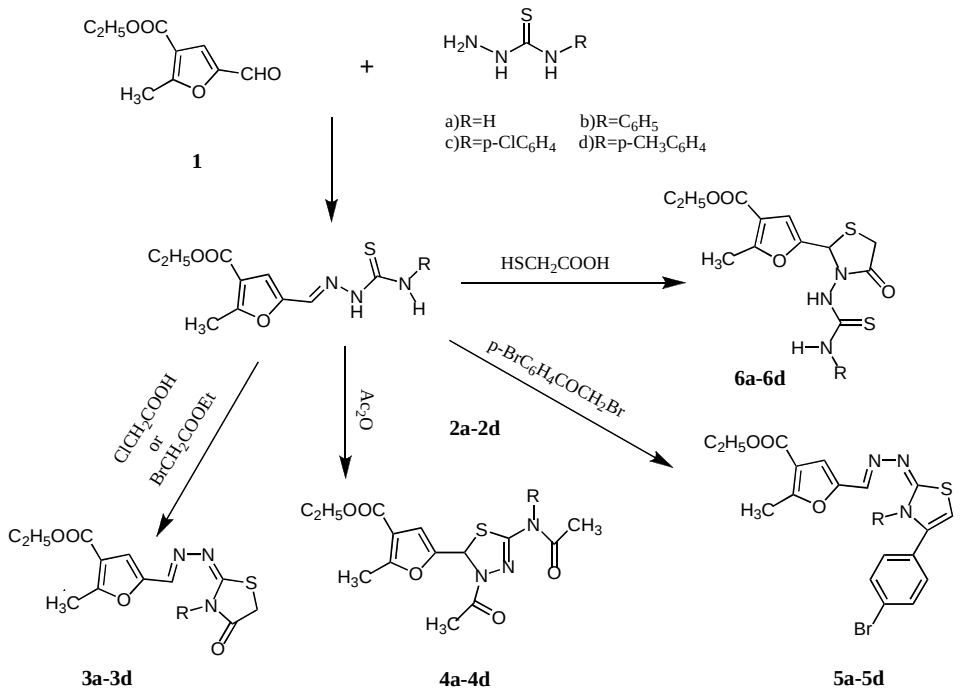
INTRODUCTION

A wide variety of pharmacological properties have been shown to be associated with thiazolidone derivatives which include anesthetic, anticonvulsant and hypnotic activities [1]. They also display a large variety of activities such as antibiotic, diuretic, organoleptic, tuberculostatic, antileukemik and antiparasitical activities [2]. Recently certain thiadizolines and thiosemicarbazones have been reported to exhibit antiviral and antibacterial properties and were evaluated for biological activity against various microorganisms [3]. Also several of these derivatives likewise, compounds possessing a thiazoline moiety often exhibit additional biological activities [19] including anti-inflammatory, antimicrobial, antitumor or antifungal activities as well as inotropic and chronotropic activities [4-14]. In addition there have been some reports concerning biological interest for furans, pyrroles and their derivatives [2, 15-18]. However; there is a little data describing compounds containing the two heterocyclic moieties, thiazoline and furan or pyrrole. Interest in this class of compounds prompted the synthesis of the several furanylthiosemicarbazones, pyrrolylthiosemicarbazones, thiazolidine, thiazolidinone and thiadiazolidine derivatives as potential antibacterial agents. We aimed at utilizing a furan or a pyrrole ring as a carrier for the bacterostatic thiosemicarbazone moiety and investigated this combination for antibacterial activity. Accordingly a

Scheme 1

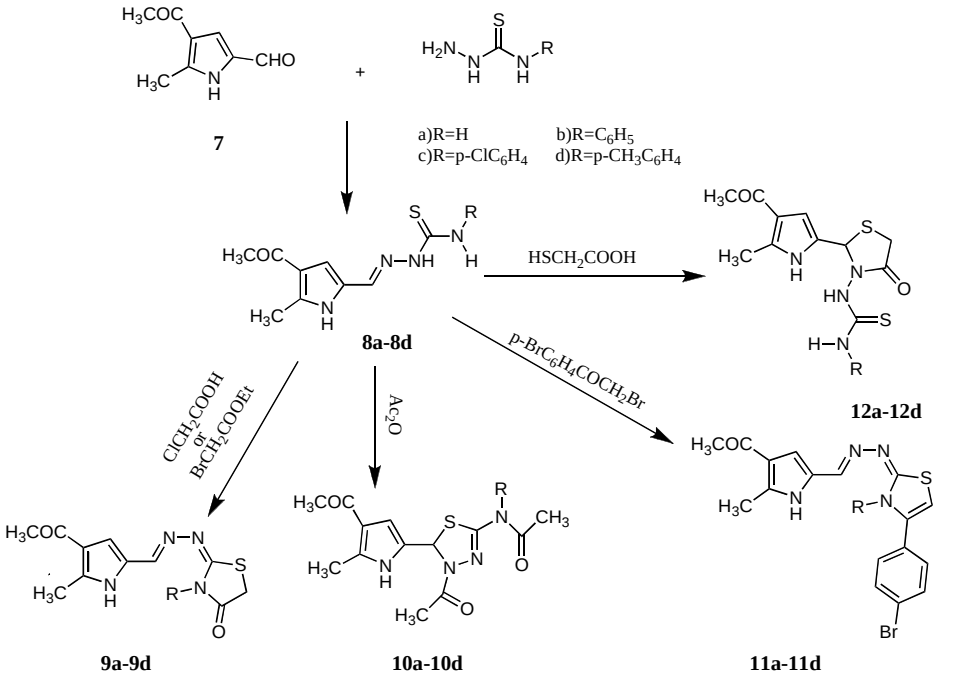


series of thiazolyl and thiadiazolyl substituted furan and pyrrole derivatives were designated and synthesized in our laboratory. Antimicrobial and antifungal activities of these compounds were measured.

RESULTS AND DISCUSSION

Chemistry. The target compounds, **2a-6d** and **8a-12d** were synthesized according to the steps outlined in Schemes 1 and 2. The key intermediates ethyl 5-[(4-substituted thiosemicarbazido)methyl]-2-methylfuran-3-carboxylates, **2a-2d**, and 1-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl) methylene]-4-substituted thiosemicarbazides, **8a-8d**, were synthesized by condensation of ethyl 5-formyl-2-methylfuran-3-carboxylate, **1**, [20] or 4-acetyl-5-methyl-1*H*-pyrrole-2-carbaldehyde, **7**, [21] with thiosemicarbazide derivatives. The ir spectra of compounds **2a-2d**

Scheme 2



and **8a-8d** showed NH bands at 3134-3440 cm^{-1}, and their proton nmr spectra showed deuterium exchangeable singlets due to NH protons at δ 9.07-11.86 ppm. Treatment of these 4-substituted thiosemicarbazides, compounds **2** and **8** with chloroacetic acid and fused sodium acetate or with ethyl bromoacetate afforded 2-methyl-5-[(4-oxo-3-substituted thiazolidin-2-ylidene)-hydrazonomethyl]-furan-3-carboxylic acid ethyl ester, **3a-3d**, or 2-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl-methylene)-hydrazono]-3-substituted thiazolidin-4-one, **9a-9d**, respectively. The ir spectra of compounds **3** and **9** showed the disappearance of NH bands of substituted thio-semicarbazone moiety and a new band at 1693-1718 cm^{-1} attributed to a carbonyl group of thiazolidin-4-one. Their proton nmr spectra lacked signals characteristic for NH protons and showed new singlet at δ 3.83-4.06 ppm attributed to CH_2-thiazolidinone. 5-(3-Acetyl-5-(*N*-substituted acetylamino)-2,3-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-furan-3-carboxylic acid ethyl ester **4a-4d**, and *N*-[4-acetyl-5-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-*N*-substituted acetamide, **10a-10d**, were prepared by heating the corresponding thio-semicarbazones **2a-2d** and **8a-8d** with acetic anhydride respectively. Their ir spectra lacked the bands due to NH and showed a new band at 1642-1698 cm^{-1} attributed to an acetyl group of [1,3,4]-thiadiazol-2-yl. Their proton nmr spectra lacked signals characteristic for NH protons and showed new singlet at δ 6.10-6.61 ppm attributed to CH of 1,3,4-thiadiazolyl in addition to signals due to methyl groups of the CH_3CO at 1.28-1.94 ppm. On the other hand, reaction of thiosemicarbazones **2a-2d** and **8a-8d** with *p*-bromo-phenacyl bromide gave 5-{[4-(4-bromo-phenyl)-3*H*-3-substituted thiazol-2-yl-ylidene]hydrazonomethyl}-2-methyl-furan-3-carboxylic acid ethyl ester, **5a-5d**, and 1-(5-{[4-(4-bromo-phenyl)-3H-3-substituted thiazol-2-yl-ylidene]hydra-zono-methyl}-2-methyl-1*H*-pyrrol-3-yl)-ethanone, **11a-11d**, respectively. Their ir spectra lacked the bands due to NH and their proton nmr spectra lacked signals characteristic for NH protons and showed new singlet at δ 6.72-7.64 ppm attributed to CH thiazol-2-yl-ylidene. Reaction of thiosemi-carbazone derivatives **2a-2d** and **8a-8d** with thioglycolic acid in dry benzene gave rise to the corresponding 2-methyl-5-(4-oxo-3-substituted thio-ureido-thiazolidin-2-yl)-furan-3-carboxylic acid ethyl ester , **6a-6d**, or [2-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4-oxo-thiazolidin-3-yl]-3-substituted thioureas **12a-12d**. Their ir spectra showed besides the bands due to NH, a carbonyl absorption band at 1645-1693 cm^{-1}. Their proton nmr spectra showed signals characteristic for NH protons and showed two new singlets at δ 3.34-3.46, 6.10-7.97 ppm attributed to CH_2 and CH of 4-oxo-thiazolidinyl respectively.

Biological Results. The designed compounds **2a-6d** and **8a-12d** have been evaluated for their antimicrobial activity. The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity [22,23]. The minimal inhibitory concentration (MIC) listed in (Table 1) showed that compounds **3a-3d**, and **9a** have antifungal activity against *C. albicans* comparable to that of Clotrimazole (Canesten®, Bayer). Other compounds are active against *S. aureus* and *E. coli*. Compound **10a** has antimicrobial activity against *S. aureus* comparable to that of ampicillin, while the activity of compounds **2a** and **6b** is about 50% of that of ampicillin. Compounds **5b** and **6a** have antimicrobial activity against *E. coli* comparable to that of

Table 1.

Minimal Iinhibitory Concentrations (MIC μg/ml) of Test Compounds

Test compound	*E. coli*	*S. aureus*	*C. albicans*	Test compound	*E. coli*	*S. aureus*	*C. albicans*
Ampicillin	25	12.5	---	**6d**	50	>200	>200
Clotrimazole	---	…..	12.5	**8a**	>200	>200	>200
2a	200	25	>200	**8b**	200	>200	>200
2b	100	>200	>200	**8c**	100	>200	200
2c	100	>200	>200	**8d**	200	>200	>200
2d	200	100	>200	**9a**	100	100	12.5
3a	100	50	12.5	**9b**	>200	>200	>200
3b	200	50	12.5	**9c**	200	100	100
3c	100	>200	12.5	**9d**	200	100	100
3d	100	100	12.5	**10a**	100	12.5	200
4a	50	>200	>200	**10b**	>200	>200	100
4b	50	100	>200	**10c**	100	50	>200
4c	>200	>200	>200	**10d**	>200	>200	100
4d	>200	>200	100	**11a**	100	>200	>200
5a	>200	>200	>200	**11b**	>200	>200	100
5b	25	>200	>200	**11c**	>200	>200	>200
5c	200	100	>200	**11d**	>200	>200	100
5d	100	100	>200	**12a**	100	>200	>200
6a	25	>200	>200	**12b**	>200	>200	100
6b	200	25	>200	**12c**	>200	>200	>200
6c	>200	>200	>200	**12d**	>200	>200	100

ampicillin, while the activity of compounds **4a, 4b** and **6d** is about 50% of that of ampicillin.

EXPERIMENTAL

Chemistry. Reagent quality solvents were used without purification. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Magnetic resonance spectra (^{1}H nmr spectra) were recorded on a Brucker 300 MHz spectrometer in DMSO-d_6. Chemical shift values reported in δ (ppm) relative to an internal standard (tetramethylsilane). Infrared data were obtained on a Perkin-Elmer 1600 series Fourier transform instrument as KBr pellets. Reactions were monitored by tlc on silica gel-protected aluminum sheets (Type 60 F 254, Merck) and the spots were detected by exposure to UV-Lamp at λ 254 nm for a few seconds. Elemental analyses were performed in the Chemistry Department, Faculty of Science, Cairo University.

The antimicrobial tests were carried out at the Pharmaceutical Department, Faculty of Pharmacy, Alexandria University.

General Procedure for the Preparation of 2a-2d and 8a-8d. To a solution of ethyl 5-formyl-2-methylfuran-3-carboxylate, **1**, or 4-acetyl-5-methyl-1*H*-pyrrole-2-carbaldehyde, **7**, (5 mmol) in ethanol:chloroform (2:1, 25 mL) was added N-substituted thiosemicarbazide (5 mmol). The reaction mixture was heated under reflux for 4-8 hours, partially concentrated and cooled. The solid product was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol.

Ethyl 2-methyl-5-(thiosemicarbazidomethyl)furan-3-carboxylate (2a). (72.1% Yield) white crystals; mp 127-128 ºC (lit. [24] 122ºC); ir: 3392, 3281, 3146 (NH), 1725 (COOEt), 1623 (C=N), 1548, 1333, 1171, 951 cm^{-1} (NCS amide I, II, III, IV respectively).

Ethyl 2-methyl 5-((4-(phenylthiosemicarbazido)methyl)-furan-3-carboxylate (2b). Yield: 77.3%; yellow crystals; mp 160-161ºC; (lit. [24] 158 ºC); ir: 3396, 3352 (NH), 1713 (COOEt), 1625 (C=N), 1533, 1321, 1196, 960 cm^{-1} (NCS amide I, II, III, IV respectively).

Ethyl 5-((4-(4-chlorophenyl)thiosemicarbazido)methyl)-2-methylfuran-3-carboxylate (2c). Yield: 85.8%; white crystals; mp 185-186ºC; ir: 3313, 3147 (NH), 1717 (COOEt), 1621 (C=N), 1550, 1369, 1129, 933 cm^{-1} (NCS amide I, II, III, IV respectively); ^{1}H nmr: δ 1.35 (t, 3H, CH_3-ester), 2.65 (s, 3H, CH_3-furan), 4.30 (q, 2H, CH_2-ester), 6.98 (s, 1H, CH-furan), 7.35 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 7.76 (s, 1H, CH=N), 9.13 (s, 1H, NH), 10.63 (s, 1H, NH). *Anal.* Calcd for $C_{16}H_{16}ClN_3O_3S$: C, 52.53; H, 4.41; N, 11.49. Found: C, 52.33; H, 4.53; N, 11.26.

Ethyl 2-methyl-5-((4-*p*-tolylthiosemicarbazido)methyl)furan-3-carboxylate (2d). Yield: 63.7%; white crystals; mp 175-176ºC; ir: 3328, 3136 (NH), 1711 (COOEt), 1619 (C=N), 1550, 1370, 1129, 945 cm^{-1} (NCS amide I, II, III, IV respectively); ^{1}H nmr: δ 1.36 (t, 3H, CH_3- ester), 2.36 (s, 3H, CH_3-furan), 2.66 (s, 3H, CH_3 tolyl), 4.30 (q, 2H, CH_2-ester), 6.98 (s, 1H, CH-furan), 7.20(d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.64 (s, 1H, CH=N), 9.07 (s, 1H, NH), 9.68 (s, 1H, NH). *Anal.* Calcd for $C_{17}H_{19}N_3O_3S$: C, 59.11; H, 5.54; N, 12.17. Found: C, 58.91; H, 5.70; N, 11.90.

1-((4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene)thiosemicarbazide (8a). Yield: 66.9%; yellow crystals; mp 230-231ºC (lit.; [24] 230 ºC); ir: 3410, 3387, 3224, 3136 (NH), 1664 ($COCH_3$), 1614 (C=N), 1548, 1333, 1171, 951 cm^{-1} (NCS amide I, II, III, IV respectively); ^{1}H nmr: δ 2.26 (s, 3H, CH_3-pyrrole), 3.34 (s, 3H, $COCH_3$), 6.68 (s, 1H, CH-pyrrole), 6.79 (s, 1H, CH=N), 10.00 (s, 1H, NH), 11.66 (s, 1H, NH), 11.75 (s, 2H, 2NH).

1-((4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene)-4-phenylthiosemicarbazide (8b). Yield: 78.6%; yellow crystals; mp 210-211ºC (lit. [24] 210ºC); ir: 3334, 3226, 3134 (NH), 1660 ($COCH_3$), 1611 (C=N), 1548, 1339, 1179, 950 cm^{-1} (NCS amide I, II, III, IV respectively); ^{1}H nmr: δ 2.29 (s, 3H, CH_3-pyrrole), 3.34 (s, 3H, $COCH_3$), 6.90 (s, 1H, CH-pyrrole), 7.20 (t, 2H, Ar-H), 7.37 (t, 1H, Ar-H), 7.53 (d, 2H, Ar-H), 7.88 (s, 1H, CH=N), 9.95(s, 1H, NH), 11.77 (s, 1H, NH), 11.86 (s, 1H, NH).

1-((4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene)-4-(4-chlorophenyl)thiosemicarbazide (8c). Yield: 74.7%; yellow crystals; mp 222-223ºC; ir: 3386, 3224, 3137 (NH), 1660 ($COCH_3$), 1611 (C=N), 1535, 1336, 1195, 922 cm^{-1} (NCS amide I, II ,III, IV respectively); ^{1}H nmr:δ 2.29 (s, 3H, CH_3-pyrrole), 3.35 (s, 3H, $COCH_3$), 7.31 (s, 1H, CH-pyrrole), 7.43 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.89 (s, 1H, CH=N), 9.97 (s, 1H, NH), 11.75 (s, 1H, NH), 11.86 (s, 1H, NH). *Anal.* Calcd for $C_{15}H_{15}ClN_4OS$: C, 53.81; H, 4.52; N, 16.73. Found: C, 54.00; H, 4.35; N, 16.96.

1-((4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene)-4-*p*-tolylthiosemicarbazide (8d). Yield 71.2%; yellow crystals; mp 230-231ºC; ir: 3440, 3204, 3134 (NH), 1661 ($COCH_3$), 1609 (C=N), 1533, 1351, 1140, 942 cm^{-1} (NCS amide I, II, III, IV respectively); ^{1}H nmr: δ 2.28 (s, 3H, CH_3-pyrrole), 2.47 (s, 3H, CH_3-tolyl), 3.33 (s,3H, $COCH_3$), 6.90 (s, 1H, CH-pyrrole),7.17 (d, 2H, Ar-H),7.38 (d, 2H, Ar-H), 7.87 (s, 1H, CH=N), 9.88 (s, 1H, NH), 11.71 (s, 1H, NH), 11.75 (s, 1H, NH). *Anal.* Calcd for $C_{16}H_{18}N_4OS$: C, 61.12; H, 5.77; N, 17.82. Found: C, 60.90; H, 5.90; N, 17.67.

General Procedure for the Preparation of 3a-3d and 9a-9d. ***Method A.*** A mixture of ethyl 5-[(4-substituted thiosemicarbazido) methyl]-2-methyl-furan-3-carboxylate, **2a-2d**, or 1-((4-acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene)-4-substituted thiosemicarbazide **8a-8d**, (1 mmol), chloroacetic acid (1 mmol) and fused sodium acetate (1.5 mmol) in 20 mL of glacial acetic acid was refluxed for 4-8 hours. The reaction mixture was poured into ice-cold water and stored overnight in the refrigerator. The crude product was collected by filtration, washed several times with water, dried, and recrystallized from ethanol.

Method B. To a solution of the ethyl 5-[(4-substituted thiosemicarbazido) methyl]-2-methylfuran-3-carboxylate, **2a-2d**, or 1-((4-acetyl-5-methyl-1*H*-pyrrol-2-yl) methylene)-4-substituted thiosemicarbazide, **8a-8d**, (1 mmol) in absolute ethanol (25 mL) was added ethyl bromoacetate (1 mmol), and the reaction mixture was heated under reflux for 4-8 hours. The mixture was concentrated, cooled, and the solid was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol.

2-Methyl-5-[(4-oxo-thiazolidin-2-ylidene)-hydrazonomethyl]-furan-3-carboxylic acid ethyl ester (3a). Yield: 67.7%; yellow crystals; mp 242-243ºC; ir: 3122 (NH), 1712 (COOEt), 1705 (CO), 1649, 1605 cm^{-1} (C=N); ^{1}H nmr: δ 1.25 (t, 3H, CH_3-ester), 2.59 (s, 3H, CH_3-furan), 3.86 (s, 2H, CH_2), 4.20 (q, 2H, CH_2-ester), 7.09 (s, 1H, CH-furan), 8.15 (s, 1H, CH=N), 11.94 (s, 1H, NH). *Anal.* Calcd for $C_{12}H_{13}N_3O_4S$: C, 48.81; H, 4.44; N, 14.23. Found: C, 49.00; H, 4.21; N, 14.48.

2-Methyl-5-[(4-oxo-3-phenylthiazolidin-2-ylidene)-hydrazonomethyl]-furan-3-carboxylic acid ethyl ester (3b). Yield: 78.1%; yellow crystals; mp 168-169ºC; ir: 1713 (COOEt), 1694 (CO), 1633, 1599 cm^{-1} (C=N); ^{1}H nmr: δ 1.24 (t, 3H, CH_3-ester),

2.59 (s, 3H, CH_3-furan), 4.06 (s, 2H, CH_2), 4.20 (q, 2H, CH_2-ester), 7.04 (s, 1H, CH-furan), 7.32 (t , 1H, Ar-H), 7.41 (t, 2H, Ar-H) , 7.47 (d, 2H, Ar-H), 8.04 (s, 1H, CH=N). *Anal*. Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31. Found: C, 57.96; H, 4.86; N, 11.12.

2-Methyl-5-[(4-oxo-3-(4-chlorophenyl)thiazolidin-2-ylidene)-hydrazonomethyl]-furan-3-carboxylic acid ethyl ester (3c). Yield: 66.5%; yellow crystals; mp 113-114ºC; ir: 1737 (COOEt), 1718 (CO), 1644, 1613 cm^{-1} (C=N); ^{1}H nmr: δ 1.35 (t, 3H, CH_3-ester), 2.66 (s, 3H, CH_3-furan), 3.98 (s, 2H, CH_2), 4.30 (q, 2H, CH_2-ester), 6.99 (s, 1H, CH-furan), 7.29 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 8.01 (s, 1H, CH=N). *Anal*. Calcd for $C_{18}H_{16}ClN_3O_4S$: C, 53.27; H, 3.97; N, 10.35. Found: C, 53.00; H, 3.82; N, 10.13.

2-Methyl-5-[(4-oxo-3-*p*-tolylthiazolidin-2-ylidene)hydrazono-methyl]furan-3-carboxylic acid ethyl ester (3d). Yield: 77.8%; yellow crystals; mp 162-163ºC; ir: 1726 (COOEt), 1708 (CO), 1643, 1609 cm^{-1} (C=N); ^{1}H nmr: δ 1.22(t, 3H, CH_3-ester), 2.31(s, 3H, CH_3-furan), 2.57 (s, 3H, CH_3-tolyl), 4.03 (s, 2H, CH_2), 4.19 (q, 2H, CH_2-ester), 7.03 (s, 1H, CH-furan), 7.18 (d, 2H, Ar-H), 7.26 (d, 2H, Ar-H), 8.01 (s, 1H, CH=N). *Anal*. Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.47; H, 4.79; N, 11.12.

2-[(4-Acetyl-5-methyl-1*H*-pyrrol-2-ylmethylene)hydrazono]thiazolidin-4-one (9a). Yield 71.9%; yellow crystals; mp 239-240ºC; ir: 344, 3133 (NH), 1698 (CO), 1660 ($COCH_3$), 1619, 1599 cm^{-1} (C=N); ^{1}H nmr: δ 2.24 (s, 3H, CH_3-pyrrole), 2.33 (s, 3H, $COCH_3$), 3.83 (s, 2H, CH_2), 6.78 (s, 1H, CH-pyrrole), 8.06 (s, 1H, CH=N), 11.55 (s, 1H, NH), 11.78 (s, 1H, NH). *Anal*. Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.99; H, 4.58; N, 21.20. Found: C, 49.76; H, 4.73; N, 20.98.

2-[(4-Acetyl-5-methyl-1*H*-pyrrol-2-ylmethylene)hydrazono]-3-phenylthiazolidin-4-one (9b). Yield 67.6%; brown crystals; mp 110-111ºC; ir: 3323 (NH), 1707 (CO), 1650 ($COCH_3$), 1630, 1598 cm^{-1} (C=N); ^{1}H nmr: δ 2.26 (s, 3H, CH_3-pyrrole), 2.30 (s, 3H, $COCH_3$), 3.83 (s, 2H, CH_2), 7.10 (s, 1H, CH-pyrrole), 7.20 (t, 1H, Ar-H), 7.35 (t, 2H, Ar-H), 7.63 (d, 2H, Ar-H), 7.90 (s, 1H, CH=N), 11.50 (s, 1H, NH). *Anal*. Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 59.72; H, 4.90; N, 16.19.

2-[(4-Acetyl-5-methyl-1*H*-pyrrol-2-ylmethylene)hydrazono]-3-(4-chlorophenyl)thiazolidin-4-one (9c). Yield: 74.7%; buff crystals; mp 239-240ºC; ir: 3399 (NH), 1693 (CO), 1661 ($COCH_3$), 1626, 1600 cm^{-1} (C=N); ^{1}H nmr: δ 2.20 (s, 3H, CH_3-pyrrole), 2.47 (s, 3H, $COCH_3$), 3.86 (s, 2H, CH_2), 6.80 (s, 1H, CH-pyrrole), 7.31 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.90 (s, 1H, CH=N), 10.04 (s, 1H, NH). *Anal*. Calcd for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; N, 14.95. Found: C, 54.49; H, 4.00; N, 14.92.

2-[(4-Acetyl-5-methyl-1*H*-pyrrol-2-ylmethylene)hydrazono]-3-p-tolylthiazolidin-4-one (9d). Yield: 70.5%; buff crystals; mp 205-206ºC; ir: 3331 (NH), 1695 (CO), 1654 ($COCH_3$), 1607, 1598 cm^{-1} (C=N); ^{1}H nmr: δ 2.21 (s, 3H, CH_3-pyrrole), 2.34 (s, 3H, CH_3-tolyl), 2.47 (s, 3H, $COCH_3$), 4.06 (s, 2H, CH_2), 6.87 (s, 1H, CH-pyrrole), 7.36 (d, 2H, Ar-H), 7.53 (d, 2H, Ar-H), 7.95 (s, 1H, CH=N), 11.02 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{18}N_4O_2S$: C, 61.00; H, 5.12; N, 15.81. Found: C, 61.22; H, 4.96; N, 15.99.

General Procedure for the Preparation of 4a-4d and 10a-10d. To a solution of ethyl 5-[(4-substituted thiosemicarbazido) methyl]-2-methyl-furan-3-carboxylate, **2a-2d,** or 1-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene]-4-substituted thiosemicarbazide, **8a-8d** (1 mmol) in acetic anhydride (10 mL) was heated under reflux for 3 hours, after the reaction mixture was attained at room temperature, excess acetic anhydride was decomposed by water and the mixture was stirred for 30 minutes. The separated product was collected by filtration, washed with water, dried, and recrystallized from ethanol.

5-(3-Acetyl-5-acetylamino-2,3-dihydro-[1,3,4]-thiadiazol-2-yl)-2-methyl-furan-3-carboxylic acid ethyl ester (4a). Yield: 76.6%; grey crystals; mp 175-176ºC (lit. [24] 175 ºC); ir: 3147 (NH), 1713 (COOEt), 1661, 1650 ($COCH_3$), 1613 cm^{-1} (C=N).

5-(3-Acetyl-5-(*N*-phenylacetylamino)-2,3-dihydro-[1,3,4]-thiadiazol-2-yl)-2-methyl-furan-3-carboxylic acid ethyl ester (4b). Yield: 86.7%; buff crystals; mp 120-121ºC(lit. [24] 120 ºC); ir: 1717 (COOEt), 1660, 1645 ($COCH_3$), 1613 cm^{-1} (C=N).

5-(3-Acetyl-5-(*N*-(4-chlorophenyl)acetylamino)-2,3-dihydro-[1,3,4]-thiadiazol-2-yl)-2-methyl-furan-3-carboxylic acid ethyl ester (4c). Yield: 68.9%; buff crystals; mp 130-131ºC; ir: 1707 (COOEt), 1675, 1655 ($COCH_3$), 1610 cm^{-1} (C=N); ^{1}H nmr δ 1.22 (t, 3H, CH_3-ester), 1.81, 1.89 (s, 6H, 2 $COCH_3$), 2.47 (s, 3H, CH_3-furan), 4.18 (q, 2H, CH_2-ester), 6.45 (s, 1H, CH), 6.90 (s,1H, CH-furan), 7.53 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H). *Anal*. Calcd for $C_{20}H_{20}ClN_3O_5S$: C, 53.39; H, 4.48; N, 9.34. Found: C, 53.60; H, 4.23; N, 9.56.

5-(3-Acetyl-5-(*N*-*p*-tolylacetylamino)-2,3-dihydro-[1,3,4]-thiadiazol-2-yl)-2-methyl-furan-3-carboxylic acid ethyl ester (4d). Yield: 69.9%; grey crystals; mp 210-211ºC; ir: 1709 (COOEt), 1661, 1654 ($COCH_3$), 1626 cm^{-1} (C=N); ^{1}H nmr: δ 1.28 (t, 3H, CH_3 ester),1.64 (s, 6H, 2 $COCH_3$), 2.47 (s, 3H, CH_3-furan), 2.57 (s, 3H, CH_3-tolyl), 4.32 (q, 2H, CH_2-ester), 6.10 (s, 1H, CH), 7.23 (s, 1H, CH-furan), 7.26 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H). *Anal*. Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.40; N, 9.78. Found: C, 58.96; H, 5.29; N, 10.00.

***N*-[4-Acetyl-5-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4,5-dihydro[1,3,4]thiadiazol-2-yl]-acetamide (10a).** Yield: 61.6%; grey crystals; mp 145-146ºC (lit. [24] 145 ºC); ir: 3413, 3240 (NH), 1691, 1677, 1642 ($COCH_3$), 1611 cm^{-1} (C=N).

***N*-[4-Acetyl-5-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-*N*-phenylacetamide (10b).** Yield: 54.6%; yellow crystals; mp 185-186ºC (lit. [24] 185 ºC); ir: 3344 (NH), 1688, 1660, 1650 ($COCH_3$), 1609 cm^{-1} (C=N).

***N*-[4-Acetyl-5-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-[1,3,4]-thiadiazol-2-yl]-*N*-(4-chlorophenyl)acetamide (10c).** Yield: 66.8%; buff crystals; mp 105-106ºC; ir: 3353 (NH), 1689, 1670, 1645 ($COCH_3$), 1599 cm^{-1} (C=N); ^{1}H nmr: δ 1.94 (s, 6H, 2 $COCH_3$), 1.97 (s, 3H, CH_3-pyrrole), 2.47 (s, 3H, $COCH_3$ - pyrrole), 6.20 (s, 1H, CH-thiadiazole), 7.23 (s, 1H,CH), 7.47 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 11.02 (s, 1H, NH). *Anal*. Calcd for $C_{19}H_{19}ClN_4O_3S$: C, 54.48; H, 4.57; N, 13.37. Found: C, 54.23; H, 4.73; N, 13.17.

***N*-[4-Acetyl-5-(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-[1,3,4]-thiadiazol-2-yl]-*N*-*p*-tolylacetamide (10d).** Yield: 67.8%; buff crystals; mp 140-141 (dec)ºC; ir: 3334 (NH), 1698, 1665, 1650 ($COCH_3$), 1599 cm^{-1} (C=N);^{1}H nmr: δ 1.28 (s, 6H, 2 $COCH_3$), 1.65 (s, 3H, CH_3-pyrrole), 2.36 (s, 3H, CH_3-tolyl), 2.39 (s, 3H, $COCH_3$-pyrrole), 6.61(s, 1H, CH-thiadiazole), 6.77 (s, 1H, CH-pyrrole), 7.10-7.95 (m, 4H, Ar-H), 11.24 (s, 1H, NH). *Anal*. Calcd for $C_{20}H_{22}N_4O_3S$: C, 60.28; H, 5.56; N, 14.06. Found: C, 60.40; H, 5.31; N, 14.26.

General Procedure for the Preparation of 5a-5d and 11a-11d. To a solution of ethyl 5-[(4-substituted thiosemicarbazide) methyl]-2-methyl-furan-3-carboxylate, **2a-2d**, or 1-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl) methylene]-4-substituted thiosemicarbazide, **8a-8d** (1 mmol) in absolute ethanol (25 mL) was added *p*-bromophenacyl bromide (1 mmol) and anhydrous

sodium acetate (1.5 mmol), the reaction mixture was heated under reflux for 4-8 hours, partially concentrated and left to cool overnight. The solid was collected by filtration, washed with ethanol, dried, and recrystallized from benzene-petroleum ether.

5-{[4-(4-Bromo-phenyl)-3*H*-thiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-furan-3-carboxylic acid ethyl ester (5a). Yield: 71.4%; grey crystals; mp 170-171ºC; ir: 3147 (NH), 1713 (COOEt), 1626, 1600 cm^{-1} (C=N); ^1H nmr: δ 1.35 (t, 3H, CH_3-ester), 2.62 (s, 3H, CH_3-furan), 4.30 (q, 2H, CH_2-ester), 6.56 (s, 1H, CH-furan), 6.82 (s, 1H, CH), 7.26-7.92 (m, 4H, Ar-H), 8.47 (s, 1H, CH=N), 11.78 (s, 1H, NH). *Anal.* Calcd for $C_{18}H_{16}BrN_3O_3S$: C, 49.78; H, 3.71; N, 9.68. Found: C, 49.54; H, 3.95; N, 9.43.

5-{[4-(4-Bromo-phenyl)-3*H*-3-phenylthiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-furan-3-carboxylic acid ethyl ester (5b). Yield: 76.4%; yellow crystals; mp 220-221ºC; ir: 1717 (COOEt), 1640, 1626 cm^{-1} (C=N); ^1H nmr: δ 1.22 (t, 3H, CH_3 ester), 2.47 (s, 3H, CH_3-furan), 4.16 (q, 2H, CH_2-ester), 6.49 (s, 1H, CH-furan), 6.72 (s, 1H, CH), 6.92-7.60 (m , 9H, Ar-H), 7.64 (s, 1H, CH=N). *Anal.* Calcd for $C_{24}H_{20}BrN_3O_3S$: C, 56.48; H, 3.95; N, 8.23. Found: C, 56.21; H, 4.21; N, 7.99

5-{[4-(4-Bromo-phenyl)-3*H*-3-(4-chlorophenyl)thiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-furan-3-carboxylic acid ethyl ester (5c). Yield: 64.2%; yellow crystals; mp 225-226ºC; ir: 1717 (COOEt), 1626, 1600 cm^{-1} (C=N); ^1H nmr: δ 1.22 (t, 3H, CH_3 ester), 2.47 (s, 3H, CH_3-furan), 4.18 (q, 2H, CH_2-ester), 6.51 (s, 1H, CH-furan), 6.85 (s, 1H, CH), 7.29-7.64 (m, 8H, Ar-H), 7.71 (s, 1H, CH=N). *Anal.* Calcd for $C_{24}H_{19}BrClN_3O_3S$: C, 52.91; H, 3.51; N, 7.71. Found: C, 53.11; H, 3.26; N, 7.96.

5-{[4-(4-Bromo-phenyl)-3*H*-3-*p*-tolylthiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-furan-3-carboxylic acid ethyl ester (5d). Yield: 68.6%; yellow crystals; mp 220-221ºC; ir:1726 (COOEt), 1626 ,1605 cm^{-1} (C=N); ^1H nmr: δ1.23 (t, 3H, CH_3-ester), 2.25 (s, 3H, CH_3-furan), 2.96 (s, 3H, CH_3-tolyl), 4.20 (q, 2H, CH_2-ester), 6.58 (s, 1H, CH-furan), 6.85(s, 1H, CH), 7.02-7.79 (m, 8H, Ar-H), 8.46 (s, 1H, CH=N). *Anal.* Calcd for $C_{25}H_{22}BrN_3O_3S$: C, 57.26; H, 4.23; N, 8.01. Found: C, 57.50; H, 4.10; N, 8.28.

1-(5-{[4-(4-Bromo-phenyl)-3*H*-thiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-1*H*-pyrrol-3-yl)-ethanone (11a). Yield: 76.9%; grey crystals; mp 200-201ºC; ir: 3358, 3235 (NH), 1669($COCH_3$), 1640, 1599 cm^{-1} (C=N); ^1H nmr: δ 2.47 (s, 3H, CH_3-pyrrole), 2.49 (s, 3H, $COCH_3$), 6.83 (s, 1H, CH-pyrrole), 7.32 (s, 1H, CH), 8.06 (d, 2H, Ar-H), 8.26 (d, 2H, Ar-H), 8.43 (s,1H, CH=N), 11.64 (s, 1H, NH), 12.44 (s, 1H, NH). *Anal.* Calcd for $C_{17}H_{15}BrN_4OS$: C, 50.63; H, 3.75; N, 13.89. Found: C, 50.41; H, 3.96; N, 13.63.

1-(5-{[4-(4-Bromo-phenyl)-3*H*-3-phenylthiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-1*H*-pyrrol-3-yl)-ethanone (11b). Yield: 70.9%; buff crystals; mp 118-119ºC; ir: 3363 (NH), 1671 ($COCH_3$), 1631,1599 cm^{-1} (C=N); ^1H nmr: δ 1.24 (s 3H, CH_3-pyrrole), 1.85 (s, 3H, $COCH_3$), 7.16 (d, 2H, Ar-H), 7.32(t, 1H, Ar-H), 7.44 (t, 2H, Ar-H), 7.54 (s, 1H, CH-pyrrole), 7.56 (d, 2H, Ar-H), 7.64 (s, 1H, CH), 7.65 (d, 2H, Ar-H), 7.76 (s, 1H, CH=N), 11.64 (s, 1H, NH). *Anal.* Calcd for $C_{23}H_{19}BrN_4OS$: C, 57.62; H, 3.99; N, 11.69. Found: C, 57.39; H, 4.16; N, 11.48.

1-(5-{[4-(4-Bromo-phenyl)-3*H*-3-(4-chlorophenyl)thiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-1*H*-pyrrol-3-yl)-ethanone (11c). Yield: 70.1%; buff crystals; mp 120-121ºC; ir: 3343 (NH), 1681 ($COCH_3$), 1634, 1609 cm^{-1} (C=N); ^1H nmr: δ 1.92 (s 3H, CH_3-pyrrole), 2.34 (s, 3H, $COCH_3$), 6.75 (s, 1H, CH-pyrrole), 6.98 (d, 2H, Ar-H), 7.15 (d, 2H, Ar-H), 7.22 (s, 1H, CH), 7.30 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 7.57 (s, 1H, CH=N), 11.83 (s, 1H, NH). *Anal.* Calcd for $C_{23}H_{18}BrClN_4OS$: C, 53.76; H, 3.53; N, 10.90. Found: C, 53.96; H, 3.45; N, 10.99.

1-(5-{[4-(4-Bromo-phenyl)-3*H*-3-*p*-tolylthiazol-2-yl-ylidene]-hydrazonomethyl}-2-methyl-1*H*-pyrrol-3-yl)-ethanone (11d). Yield: 66.9%; buff crystals; mp 180-181ºC; ir: 3343 (NH), 1689 ($COCH_3$), 1633, 1600 cm^{-1} (C=N); ^1H nmr: δ 1.70 (s, 3H, CH_3-pyrrole), 2.21 (s, 3H, CH_3-tolyl), 2.32 (s, 3H, $COCH_3$), 7.03 (s, 1H, CH-pyrrole), 7.30 (s, 1H, CH), 7.42 (d, 2H, Ar-H), 7.48 (d, 2H,Ar-H), 7.78 (d, 2H, Ar-H), 7.84 (d, 2H, Ar-H), 8.32 (s, 1H, CH=N), 12.19 (s, 1H, NH). *Anal.* Calcd for $C_{24}H_{21}BrN_4OS$: C, 58.42; H, 4.29; N, 11.35. Found: C, 58.24; H, 4.43; N, 11.19.

General Procedure for the Preparation of 6a-6d and 12a-12d. A mixture of the appropriate ethyl 5-[(4-substituted thiosemicarbazido) methyl]-2-methylfuran-3-carboxylate, **2a-2d**, or 1-[(4-acetyl-5-methyl-1*H*-pyrrol-2-yl)methylene]-4-substituted thiosemicarbazide, **8a-8d**, (1 mmol) and thioglycolic acid (1.5 mmol) in dry benzene (50 mL) was heated under reflux for 12 hours using water separator. Benzene was evaporated under reduced pressure and the residue was dissolved in ethanol (15 mL), and then poured into sodium carbonate solution (10 %). The solid was collected by filtration, washed with water, dried, and recrystallized from chloroform.

2-Methyl-5-(4-oxo-3-thioureido-thiazolidin-2-yl)-furan-3-carboxylic acid ethyl ester (6a). Yield: 72.9%; pale yellow crystals; mp 200-201ºC; ir: 325, 3300, 3153 (NH), 1717 (COOEt), 1668 (CO), 1551, 1346, 1131, 948 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ1.26 (t, 3H, CH_3-ester), 2.50 (s, 3H, CH_3-furan), 3.37 (s, 2H, CH_2-thiazolidine), 4.22 (q, 2H, CH_2-ester), 7.16 (s, 1H, CH-thiazolidine), 7.87 (s, 1H, CH-furan), 8.22 (s, 2H, NH_2), 11.47 (s, 1H, NH). *Anal.* Calcd for $C_{12}H_{15}N_3O_4S_2$: C, 43.76; H, 4.59; N, 12.76. Found: C, 43.53; H, 4.75; N, 12.51.

2-Methyl-5-(4-oxo-3-phenylthioureido-thiazolidin-2-yl)-furan-3-carboxylic acid ethyl ester (6b). Yield: 64.1%; yellow crystals; mp175-176ºC; ir: 3300, 3158 (NH), 1719 (COOEt), 1669 (CO), 1550, 1346, 1138, 940 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ.1.27 (t, 3H, CH_3-ester), 2.50 (s, 3H, CH_3-furan), 3.35 (s, 2H, CH_2-thiazolidine), 4.23 (q, 2H, CH_2-ester), 7.16 (s, 1H, CH-thiazolidine), 7.20 (s, 1H, 2-furan), 7.34 (d, 2H, Ar-H), 7.54 (t, 1H, Ar-H), 8.01 (t , 2H, Ar-H), 9.97 (s, 1H, NH), 11.86 (s, 1H, NH). *Anal.* Calcd for $C_{18}H_{19}N_3O_4S_2$: C, 53.32; H, 4.72; N, 10.36. Found: C, 53.10; H, 4.98; N, 10.13.

2-Methyl-5-(4-oxo-3-(4-chlorophenyl)thioureido-thiazolidin-2-yl)-furan-3-carboxylic acid ethyl ester (6c). Yield: 63.6%; brown crystals; mp 150-151ºC; ir: 3310, 3163 (NH), 1715 (COOEt), 1666 (CO), 1551, 1336, 1139, 944 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 1.27 (t, 3H, CH_3-ester), 2.26 (s, 3H, CH_3-furan), 3.36 (s, 2H, CH_2-thiazolidine), 4.23 (q, 2H, CH_2-ester), 7.30 (s, 1H, CH-thiazolidine), 7.40 (d, 2H, Ar-H), 7.50 (d, 2H, Ar-H), 7.90 (s, 1H, CH-furan), 9.90 (s, 1H, NH), 11.86 (s, 1H, NH). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_4S_2$: C, 49.14; H, 4.12; N, 9.55. Found: C, 49.36; H, 3.89; N, 9.76.

2-Methyl-5-(4-oxo-3-*p*-tolylthioureidothiazolidin-2-yl)-furan-3-carboxylic acid ethyl ester (6d). Yield: 64.4%; pale yellow crystals; mp 165-166ºC; ir: 3325, 3135 (NH), 1708 (COOEt), 1661(CO), 1550, 1369, 1127, 942 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 1.26 (t, 3H, CH_3-ester), 2.27 (s, 3H, CH_3-furan), 2.58 (s, 3H, CH_3-tolyl), 3.34 (s, 2H, CH_2-thiazolidine), 4.22 (q, 2H, CH_2-ester), 7.97 (s, 1H, CH-thiazolidine), 8.23 (s, 1H, CH-furan), 7.01-7.51 (m, 4H, Ar-H), 9.88 (s, 1H, NH), 11.80 (s, 1H, NH). *Anal.* Calcd for $C_{19}H_{21}N_3O_4S_2$: C, 54.40; H, 5.05; N, 10.02. Found: C, 54.19; H, 5.25; N, 9.88.

[2-(4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)-4-oxo-thiazolidin-3-yl]-thiourea (12a). Yield: 60.3%; white crystals; mp 229-300ºC; ir: 3475, 3344, 3331, 3133 (NH), 1691, 1645 (CO), 1551, 1335, 1186, 948 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 2.25 (s, 3H, CH_3-pyrrole), 2.35 (s, 3H, $COCH_3$), 3.37 (s, 2H, CH_2-thiazolidine), 6.75 (s, 1H, CH), 7.99 (s, 1H, CH-pyrrole), 9.22 (s, 2H, NH_2), 11.44 (m, 2H, 2NH). *Anal*. Calcd for $C_{11}H_{14}N_4O_2S_2$: C, 44.28; H, 4.73; N, 18.78. Found: C, 44.47; H, 4.49; N, 18.99.

[2-(4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)-4-oxo-thiazolidin-3-yl]-3-phenylthiourea (12b). Yield: 66.8%; white crystals; mp 238-239ºC; ir: 3458, 3438, 3298 (NH), 1693, 1660 (CO), 1551, 1335, 1186, 948 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 2.26 (s, 3H, CH_3-pyrrole), 2.45 (s, 3H, $COCH_3$), 3.46 (s, 2H, CH_2-thiazolidine), 6.62 (s, 1H, CH), 6.99 (s, 1H, CH-pyrrole), 7.10 (d, 2H, Ar-H), 7.27 (t, 1H, Ar-H), 7.51 (t, 2H, Ar-H), 9.85 (s, 1H, 1NH), 11.44 (m, 2H, 2 NH). *Anal*. Calcd for $C_{17}H_{18}N_4O_2S_2$: C, 54.52; H, 4.84; N, 14.96. Found: C, 54.59; H, 4.80; N, 14.99.

[2-(4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)-4-oxo-thiazolidin-3-yl]-3-(4-chlorophenyl)thiourea (12c). Yield: 61.1%; white crystals; mp 229-300ºC; ir: 3440, 3225, 3173 (NH), 1693, 1661 (CO), 1543, 1356, 1169, 956 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 2.16 (s, 3H, CH_3-pyrrole), 2.55 (s, 3H, $COCH_3$) 3.38 (s, 2H, CH_2-thiazolidine), 6.10 (s, 1H, CH), 6.19 (s, 1H, CH-pyrrole), 6.40 (d, 2H, Ar-H), 7.02 (d, 2H, Ar-H), 9.22 (s, 1H, NH), 11.44 (m, 2H, 2NH). *Anal*. Calcd for $C_{17}H_{17}ClN_4O_2S_2$: C, 49.93; H, 4.19; N, 13.70. Found: C, 49.90; H, 4.29; N, 13.59.

[2-(4-Acetyl-5-methyl-1*H*-pyrrol-2-yl)-4-oxo-thiazolidin-3-yl]-3-*p*-tolylthiourea (12d). Yield: 61.8%; white crystals; mp 241-242ºC; ir: 3457, 3389, 3238 (NH), 1693, 1645 (CO), 1562, 1317, 1187, 952 cm^{-1} (NCS amide I, II, III, IV respectively); ^1H nmr: δ 2.19 (s, 3H, CH_3-pyrrole), 2.21 (s, 3H, CH_3-tolyl), 2.47 (s, 3H, $COCH_3$), 3.36 (s, 2H, CH_2-thiazolidine), 6.10 (s, 1H, CH), 6.30 (s, 1H, CH-pyrrole), 7.06 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 9.89 (s, 1H, NH), 11.14 (m, 2H, 2NH). *Anal*. Calcd for $C_{18}H_{20}N_4O_2S_2$: C, 55.65; H, 5.19; N, 14.42. Found: C, 55.60; H, 5.23; N, 14.38.

***In Vitro* Antimicrobial Activity.** The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity [22,23]. The utilized test organisms were: *Escherichia coli* (*E. coli*) ATCC 25922 as an example of Gram-negative bacteria, *Staphylococcus aureus* (*S. aureus*) ATCC 19433 as an example of Gram-Positive bacteria and *Candida albicans* (*C. albicans*) as yeast-like fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at concentration of 1600 μg/ml. The twofold dilution of the compounds were prepared (800, 400,...6.25 μg/ml).

The microorganism suspensions at 10^6 CFU/ml (Colony Forming Unit/ml) concentrations were inoculated to the corresponding wells. Plates were incubated at 36 °C for 24 h to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the minimal inhibitory concentrations (MIC) were determined.

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REFERENCES AND NOTES

[1] A. K. Dimri and S. S. Parmar, *J. Heterocyclic Chem*., **15**, 335 (1978).

[2] F. Aydogan, N. Öcal, Z. Turgut and C. Yolacan, *Bull. Korean Chem. Soc*., **22**, 476 (2001).

[3] B. N. Brousse, R. Massa, A. G. Moglioni, M. M. Alho, N. D' Accorso, G. Gutkind and G. Y. Moltrasio, *J. Chil. .Chem. Soc*., **49**, 45 (2004).

[4] A. M. Farghaly, N. S. Habib, M. A. Khalil, O. A. El-Sayed, *Arch. Pharm (Weinheim),* **324**, 19 (1991).

[5] A. A. Farghaly, A. A. Bekhit, Ji Young Park, *Archiv der Pharmazie*, **333**, 53 (2000).

[6] B. Kalluraya, A. Rahiman, D. Banji; *Archiv der Pharmazie*, **334**, 263 (2001).

[7] A. Kocabalkanli, O. Ates, G. Otuk, *Archiv der Pharmazie*, **334**, 35 (2001).

[8] H. T. Y. Fahmy, S. A. F. Rostom, A. A. Bekhit, *Archiv der Pharmazie*, **335**, 213 (2002).

[9] N. Ulusoy, M. Kiraz, Ö. Küçükbasmacl, *Monatshefte für Chemie*, **133**, 1305 (2002).

[10] A. A. Bekhit, H. T. Fahmy, S. A. Rostom, A. M. Baraka, *Eur J. Med. Chem*., **38**, 27 (2003).

[11] S. I. El-Desoky, S. B. Bondock, H. A. Etman, A A. Fadda, M. A. Metwally, *Sulfur Letters,* **26**, 127 (2003).

[12] A. A. Bekhit, H. T. Y. Fahmy, *Arch. Pharm. Pharm. Med. Chem*., **2**, 111 (2003).

[13] A. A. Bekhit, N. S. Habib, Ji Young Park, *Boll. Chim. Farmac. –Anno*., **143**, 34 (2004).

[14] T. I. El-Emary, A. Khalil, G. A. M. El-Hag Ali, A. A. A. M. El-Adasy, Phosphorus, *Sulfur and Silicon and the Related Elements*, **180**, 19 (2005).

[15] D. Deidda, G. Lampis, R. Fioravanti, M. Biava, G. C. Porretta, S. Zanettiand R. Pompei, *Antimicrobial Agents and Chemotherapy*, **42**, 3035 (1998).

[16] A. Leonardi, D. Nardi, M. Veronese, *Boll Chim. Farm.,* **114**, 70 (1975).

[17] Y. Katsura, T. Tomishi, Y. Inoue, K. Sakana, Y. Matsumoto, H. Ishikawa, H. Takasugi, *J. Med. Chem*., **40**, 2462 (1997).

[18] L. Racanè, V. Tralic-Kulenovic, D. W. Boykin and G. Karminski-Zamola, *Molecules,* **8**, 342 (2003).

[19] E. Corte's and R. Martínez, *J. Heterocyclic Chem.* **28**,1413 (1991).

[20] G. Gonzalez and A. Gomez Sanchez, *Adv. Carbohyd. Chem*., **20**, 303 (1965).

[21] G. Gonzalez, A. G. Sanchez and M. Gonide Rey, *Carbohyd. Res*., **1**, 261 (1965).

[22] B. Henderson. In *Textbook of Iimmunopharmacology, 3rd ed*., M. M. Dale; J. C. Foreman; T-P. D. Fan (eds): Blackwell Scientific Publications, London, 1994, pp 16, 193.

[23] P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover; R. H. Yolken, Manual of clinical microbiology. In: *Antimicroboal Agents and Susceptibility Testing*; G. L. Woods, J. A. Washington (Eds.), American Society for Microbiology: Washington, DC 1995.

[24] S. Y. Hassan, H. M. Faidallah, A. M. El-Massry, M. A. Al Haiza and M. M. El-Sadek, *J. Saudi Chem. Soc*., **3**, 171 (1999).