Synthesis, Characterization and Antimicrobial Evaluation of some Thiazole-Derived Carbamates, Semicarbazones, Amides and Carboxamide

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Summary: This study comprises the synthesis and characterization of twenty thiazole-derived carbamates (**3a-e**), *N*-substituted amides (**8a-h**) and carboxamide (**10**) from 2-aminothiazoles (**1a, b**) *via* nucleophilic substitution reactions with activated carbonyl compounds including, chloroformates (**2a-d**), acid chlorides (**7a-e**) and glutaric anhydride (**9**), respectively. Sequential hydrazinolysis of carbamate (**3e**) and condensation with a variety of aldehydes and ketones (**5a-d**) afforded the corresponding semicarbazones (**6a-d**). Some selected synthesized compounds were subjected to *in vitro* antimicrobial evaluation against common pathogens including, Gram+ve bacteria *Bacillus subtilis* (NRRL B-543) and *Staphylococcus aureus*, Gram-ve bacteria *Escherichia coli* (NRRLB-21), yeasts-*Candida albicans* (NRRLY-477) and *Saccharomyces cercvisiae* (NRRL Y-567) and fungs *Asperigillus niger* (NRRL 599). Screening results revealed that most of the tested compounds possess good antimicrobial activity compared to standard drugs. The highest inhibitory effects against Gram-ve *Escherichia coli*, Gram+ve *Staphylococcus aureus*, *yeast Candida albicans* and fungus *Aspergillus niger* was displayed by amide (**8g**) bearing the thiophene moiety.

Keywords: Multidrug resistance, Drug development, 2-Aminothiazole, Acylation of 2-aminothiazole, Antimicrobial activity.

Introduction

The emergence of drug-resistant microbes [1-5] increased the awareness for the need to identify new leads which can be developed to novel therapeutics having different modes of action. Biochemical screening of large numbers of natural and synthetic compounds is one obvious way to discover promising molecules [6,7] that will undergo further rounds of chemical modifications and biological screening before entering clinical testing. This approach identified [1,3] thiazole scaffold as one of the most important and versatile building-blocks for subsequent lead generation and drug discovery [8]. Furthermore, many thiazole derivatives are proven to exhibit pronounced antimicrobial activities [9-13].

In addition to this, versatility of 2-aminothaizoles in heterocyclic synthesis has been widely documented [14]. For example, they have been converted to imidazo[2,1-*b*]thiazole by reaction with dibenzoylacetylene [15] or with α-haloketones [16,17], to hetarylazoindole dyes *via* diazotization and coupling with indole compounds [18], to Schiff bases by reactions with aldehydes [19-21], to 2-(2-chloroacetamido)-thiazole which can serve as an electrophile in a variety of nucleophilic substitution reactions: with secondary amines [22,23], thiols [24] and with phenols [25]. Furthermore, the chloroacetamide substrates may undergo heterocyclization in the presence of ammonium thiocyanate to yield 2-(1,3-thiazol-2ylimino)-1,3-thiazolidin-4-ones [26]. In addition to this, 2-aminothiazole derivatives were converted to dithiocarbamate esters [27-29]. Moreover, halogenation of 2-aminothiazoles provide facile approach to the synthetically important 2-mono- and 2,5-dihalothiazole derivatives through modified Sandmeyer conditions [30].

In view of the aforementioned findings 2-amino thiazole and 2-amino-4-phenylthiazole were allowed to react with a variety of activated carbonyl reagents to afford carbamates, amides and carboxamide derivatives. Furthermore, sequential hydrazinolysis of the carbamate substrate and treatment with a variety of aldehydes and ketones

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afforded the corresponding semicarbazone derivatives. Some of the synthetic compounds were screened for their antibacterial and antifungal activities. The screening results revealed that, the amide derived from 2-aminothiazole bearing the thiophene residue exhibited the highest inhibitory activity against Gram -ve *Escherichia coli*, Gram +ve *Staphylococcus aureu*s and yeast *Candida albicans.* Furthermore, this amide was found to be more potent against fungus *Aspergillus niger* than reference drugs.

Experimental

General Experimental Information

All reagents were purchased from commercial suppliers and were used without further purification. Melting points were determined either on an Electrothermal's IA9100 series digital capillary melting point apparatus or on a Gallenkamp melting point apparatus (°C) and are uncorrected. IR spectra were spectra were recorded in potassium bromide (KBr) discs using a Perkin Elmer FT spectrophotometer 1000 in wave number (cm^{-1}). The NMR spectra were recorded on JEOL ECP 300 NMR spectrometer operating at 300 MHz spectrometer for ^1H and at 75 MHz for ^{13}C at 25 °C, or on Bruker DPX 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C at 25 °C, or on Bruker Avance 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C at 25 °C. The chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard, coupling constants (*J*) are expressed in Hz. Deuterated chloroform ($CDCl_3$) and deuterated dimethylsulphoxide (DMSO-d_6) were used as solvents, the splitting patterns (multiplicities) in ^1HNMR were designated as: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), dd (double of doublet), m (multiplet) and app. (apparent). Mass (MS) spectra were recorded on a Varian 320 MS TQ mass spectrometer and UPLC-MS/MS from Waters Company. Starting materials and products were evaluated on TLC plates for their purity.

Chemistry

General procedures for the synthesis of carbamates **(3a-3d)**

To a cold solution of 2-amino thiazole (**1a**) (0.001 mol) in dry pyridine (15 mL) at 0-5 °C the appropriate alkyl chloroformate (**2a-d**) (0.001 mol) namely, methyl chloroformate, ethyl chloroformate, propyl chloroformate and isobutyl chloroformate was added. The resulting reaction mixture in each case was left to stir for a further one and half hour at 0 °C then allowed to warm up to room temperature then heated on a water bath for 12 h. Excess pyridine was removed under reduced pressure, the remaining residue was dissolved in ice/water to afford solid in each case was filtered, air dried and re-crystallized from ethanol to yield carbamates (**3a-d**).

Thiazole-2-yl-carbamic acid methyl ester (**3a**)

Beige solid (78%), m.p. 159-160 °C; ν_{max} (KBr)/cm^{-1} 3427, 2927, 1734, 1586, 1328, 1299, 1249, 1165, 1057, 837, 764, 701, 614; (300 MHz; DMSO-d_6) δ_H 11.81 (1H, br. s, NH), 7.39 (1H, d, *J* 3.6 Hz, C^4H-thiazole), 6.91 (1H, d, *J* 3.4 Hz, C^5H-thiazole), 3.89 (3H, s, O-CH_3); (75 MHz; DMSO-d_6) δ_C 159.2 (C^2_q-thiazole), 152.7 (C=O), 136.1 (C^4H-thiazole), 111.9 (C^5H-thiazole), 51.5 (O-CH_3).

Thiazole-2-yl-carbamic acid ethyl ester (**3b**)

Light brown solid (85%), m.p. 199-202 °C; ν_{max} (KBr)/cm^{-1} 3416, 2982, 2735, 1721, 1578, 1497, 1366, 1327, 1297, 1248, 1165, 1081, 1085, 831, 766, 615; (300 MHz; $CDCl_3$) δ_H 12.25 (1H, br. s, NH), 7.39 (1H, d, *J* 3.7 Hz, C^4H-thiazole), 6.91 (1H, d, *J* 3.7 Hz, C^5H-thiazole), 4.34 (2H, q, *J* 7.1 Hz, O-C$\underline{H}_2$-CH_3), 1.38 (3H, t, *J* 7.1 Hz, OCH_2-C$\underline{H}_3$); (75 MHz; $CDCl_3$) δ_C 160.4 (C^2_q-thiazole), 152.8 (C=O), 135.7 (C^4H-thiazole), 111.3 (C^5H-thiazole), 61.0 (O-$\underline{C}H_2$-CH_3), 13.3 (O-CH_2-$\underline{C}H_3$); *m/z* (EI) 172 (M^+, 17.69%) for $C_6H_8N_2O_2S$, 173 (4.75%), 127 (10.26%), 100 (100%), 85 (6.20%), 58 (57.27%).

Thiazole-2-yl-carbamic acid propyl ester (**3c**)

Beige solid (83%), m.p. 142-144 °C; ν_{max} (KBr)/cm^{-1} 3189, 2935, 1724, 1582, 1475, 1326, 1295, 1241, 1168, 1083, 1058, 970, 873, 778, 732, 617; (300 MHz; $CDCl_3$) δ_H 12.40 (1H, br. s, NH), 7.39 (1H, d, *J* 3.7, C^4H-thiazole), 6.92 (1H, d, *J* 3.7 Hz, C^5H-thiazole), 4.23 (2H, t, *J* 6.6 Hz, O$\underline{C}H_2$-CH_2-CH_3), 1.78 (2H, sextet, *J* 7.0 Hz, CH_2-C$\underline{H}_2$-CH_3), 1.01 (3H, t, *J* 7.3 Hz, OCH_2-CH-C$\underline{H}_3$); (75 MHz; $CDCl_3$) δ_C 160.6 (C^2_q-thiazole), 152.6 (C=O), 135.5 ($\underline{C}^4$H-thiazole), 111.1 ($\underline{C}^5$H-thiazole), 66.5 (O$\underline{C}H_2$-CH-CH_3), 20.9 (OCH_2-$\underline{C}$H-CH_3), 8.9 (OCH_2-CH-$\underline{C}H_3$).

Thiazole-2-yl-carbamic acid isobutyl ester (**3d**)

Brown solid (91%), m.p. 120-122 °C; ν_{max} (KBr)/cm^{-1} 3423, 3187, 2969, 1724, 1573, 1474, 1375,1324,1292, 1241, 1164, 1081, 1054, 978, 843, 781, 706, 616; (300 MHz; $CDCl_3$) δ_H 12.09 (1H, br. s, NH), 7.40 (1H, d, *J* 3.7 Hz, -C^4H-thiazole), 6.91 (1H, d, *J* 3.7 Hz, C^5H-thiazole), 4.03 (2H, d, *J* 6.6

Hz, OCH_2-CH-$(CH_3)_2$), 2.05 (1H, app. septet, *J* 6.6 Hz, OCH_2-CH-$(CH_3)_2$), 1.01 (6H, d, *J* 6.6 Hz, OCH_2-CH-$(CH_3)_2$); (75 MHz; $CDCl_3$) 160.4 δ_C (C^2_q-thiazole), 152.7 (C=O), 135.6 (C^4H-thiazole), 111.3 (C^5H-thiazole), 71.0 (OCH_2-CH-$(CH_3)_2$), 26.7 (OCH_2-CH-$(CH_3)_2$), 17.8 ($OCH_2CH(CH_3)_2$); *m/z* (EI) 200 (M^+, 15.60%) for $C_8H_{12}N_2O_2S$, 127 (23.17%), 99 (16.55%), 84 (18.68%), 57 (100%).

(4-Phenyl-thiazole-2-yl)-carbamic acid ethyl ester (**3e**)

To a solution of 2-amino-4-phenylthiazole (**1b**) (0.001 mol) in dry chloroform (25 mL) was added triethylamine (0.001 mol) and the resulting reaction mixture was cooled to 0-5 °C, then ethyl chloroformate (**2b**) (0.001 mol) was added drop wise. The resulting reaction mixture was stirred for further one and half hour at 0 °C, then allowed to warm up to room temperature then heated on a water bath for 12 h. The excess solvent was removed under reduced pressure and the crude residue was dissolved in ice/water. The obtained solid was filtered, air dried and purified by re-crystallization from ethanol to afford the title compound (**3**e).

Off white crystals (91%), m.p. 178-180 °C; ν_{max} (KBr)/cm^{-1} 3161, 3058, 2782, 1719, 1580, 1472, 1367, 1300, 1333. 1242, 1087, 914, 887, 837, 764, 719, 512; (300 MHz; $CDCl_3$) δ_H 10.28 (1H, br. s, NH), 7.80 (2H, app. dd, *J* 1.1 Hz, 7.4 Hz, 2x*o*-Ph-H), 7.42-7.24 (3H, m, 2x*m*-Ph-H & *p*-Ph-H), 7.09 (1H, s, CH^5-thiazole), 4.07 (2H, q, *J* 7.2 Hz, OCH_2-CH_3), 1.07 (3H, t, *J* 7.2 Hz, O-CH_2-CH_3); (75 MHz; $CDCl_3$) δ_C 159.0 (C^2_q-thiazole), 152.1 (C=O), 148.9 (C^4_q-thiazole), 132.9, 127.2, 126.5, 124.8 (C_q-Ph & 5xCH-Ph), 105.6 (C^5H-thiazole), 60.9 (OCH_2-CH_3), 12.5 (OCH_2-CH_3),); *m/z* (EI) 248 (M^+, 99.48%) for $C_{12}H_{12}N_2O_2S$, 203 (12.26%), 175 (18.64%), 148 (7.20%), 134 (100%).

4-Phenylthiazole-2-yl-semicarbazido **(4)**

To a suspension of compound (**3e**) (0.001 mol) in ethanol (10 ml) was added hydrazine hydrate (2 mL) and the resulting reaction mixture was refluxed in water bath for 20 h., then cooled and the formed solid was filtered off and air dried. Purification by flash column chromatography using silica gel eluting with ($CHCl_3$/MeOH; 9:1) afforded the *title semicarbazide* (47%) as a pale yellowish powder m.p. 160-162 °C; ν_{max} (KBr)/cm^{-1} 3432, 3341, 3268, 3111, 1689, 1603, 1553, 1464, 1331, 1273, 1146, 1069, 984, 714; (300 MHz; $CDCl_3$), δ_H 10.98 (1H, br. s, NH), 7.88-7.37 (7H, *m*, 5xPh-H, NH and thiazole-H), 5.29 (2H, br. s, NH_2); (75 MHz; $CDCl_3$) δ_C 157.6 (C^2_q-thiazole), 151.8 (C=O), 148.8 (C^4_q-thiazole), 133.36, 127.39, 126.55, 124.71 (C_q-Ph & 5xCH-Ph), 106.66 (C^5H-thiazole).

General procedures for synthesis of semicarbazones (**6a-d**)

An equimolar mixture of semicarbazide (**4**) (0.001mole) and the appropriate aldehyde or ketone namely; *p*-chlorobenzaldehyde, *p*-hydroxybenzaldehyde, cyclopentanone and cycloheptanone (**5a-d**), respectively, in 25 mL of ethanol containing 1 mL of glacial AcOH was refluxed in each case for 12 h. The excess solvent was removed under reduced pressure and the resulting crude product in each case was purified by column chromatography using silica gel and eluent ($CHCl_3$/MeOH; 9/1) to afford the corresponding semicarbazone.

2-(4-Chlorobenzylidene)-N-(4-phenyl-1,3-thiazol-2-yl)hydrazinecarboxamide **(6a)**

Light brown powder (32%), m.p. 170 °C; ν_{max} (KBr)/cm^{-1} 3450, 2927, 2370, 1695,1601,1505, 1460, 1300, 1249, 1162, 1108, 1023, 968, 830, 777, 614, 522; (300 MHz; $CDCl_3$) δ_H 9.42 (1H, br. s, NH), 8.80 (1H, br. s, NH), 8.19 (1H, s, CH=N), 8.01 (2H, d, *J* 8.8 Hz, 2x*o*-H-(*p*-Cl-C_6H_4), 7.86-7.81 (4H, m, 2x*m*-H-(*p*-Cl-C_6H_4) and 2x*o*-Ph-H), 7.45-7.36 (3H, m, 2x*m*-Ph-H & *p*-Ph-H), 7.12 (1H, s, C^5H-thiazole); (75 MHz; $CDCl_3$) δ_C 157.6, 154.8, 152.1, 136.8, 136.0, 135.2, 128.8, 128.0, 127.6, 126.5 (($3xC_q$-Ar & 9xCH-Ar), N=CH, C^2_q-thiazole, C^4_q-thiazole), 106.53 (C^5H-thiazole).

2-(4-Hydroxybenzylidene)-N-4-phenyl-1,3-thiazol-2-yl)hydrazinecarboxamide **(6b)**

Orange powder (52%), m.p. 212-214 °C; ν_{max} (KBr)/cm^{-1} 3449, 2930, 2371, 1656,1621, 1586, 1481, 1398, 1289, 1166, 957.9, 859, 817, 551, 495; (300 MHz; DMSO-d_6) δ_H 10.83 (1H, br. s, OH), 9.88 (1H, br. s, NH), 8.55 (1H, s, NH), 7.94 (1H, s, CH=N), 7.90 (2H, d, *J* 7.7 Hz, 2x*o*-Ph-H), 7.76 (2H, d, *J* 8.4Hz, 2x*o*-H-(*p*-OH-C_6H_4)), 7.44 (2H, t, *J* 7.7 Hz, 2x*m*-Ph-H), 7.32 (1H, app. t, *J* 6.9 Hz, *p*-Ph-H), 6.90-6.76 (3H, m, 2x*m*-H-(*p*-OH-C_6H_4) and C^5H-thiazole); (300 MHz; DMSO-d_6) δ_C 159.4 (C^2_q-thiazole), 157.2 (CH=N), 151.9 (C=O), 147.8 (C^4_q-thiazole), 144.4, 135.2, 130.7, 129.0, 128.8, 128.0, 126.5 ($3xC_q$-Ar and 9xCH-Ar), 106.5 (C^5H-thiazole).

2-Cyclopentylidene-N-(4-phenyl-1,3-thiazol-2-yl) hydrazine carboxamide **(6c)**

White powder (65%), m.p. 246 °C; ν_{max} (KBr)/cm^{-1} 3308, 2930, 1697, 1605, 1543, 1514,

1444, 1385, 1333, 1256, 1164, 1010, 962, 873, 825, 767, 709, 510; (300 MHz; $CDCl_3$) δ_H 9.57 (1H, br. s, NH), 8.70 (1H, br. s, NH), 7.89-7.15 (5xPh-H), 7.05 (1H, s, C^5H-thiazole), 2.41- 2.55 (4H, m, cyclopentyl group), 2.60-1.56 (4H, m, cyclopentyl group); (75 MHz; $CDCl_3$) δ_C 166.4 (C^2_q-thiazole), 163.5 (C_q-cyclopentyl group), 157.5 (C=O), 149.7 (C^4_q-thiazole), 133.3, 127.4, 126.7, 124.8 (5xC-Ph), 105.8 (C^5H-thiazole), 32.1, 26.9, 26.3, 23.5 (4xCH_2-cyclopentyl).

2-Cycloheptylidene-N-(4-phenyl-1,3-thiazol-2-yl) hydrazine carboxamide **(6d)**

Orange powder (40%), m.p. 220 °C; ν_{max}(KBr)/cm^{-1} 3374, 3191, 3101, 2924, 2852, 2369, 2340, 1682, 1544, 1471, 1439, 1405, 1328, 1274, 1245, 1104, 1006, 721, 611, 559; (300 MHz; $CDCl_3$) δ_H 9.64 (1H, br. s, NH), 8.83 (1H, br. s, NH), 7.83 (2H, app. dd, *J* 1.8, 7.3 Hz, 2xPh-H), 7.44-7.24 (3H, m, Ph-H), 7.08 (1H, s, CH^5-thiazole), 2.41- 2.55 (4H, m, cycloheptyl group), 1.54-1.85 (8H, m, cycloheptyl group); (75 MHz; $CDCl_3$) δ_C 157.6 (C^2_q-thiazole), 157.4 (C_q-cycloheptyl group), 151.8 (C=O), 148.8 (C^4_q-thiazole), 133.4, 127.4, 126.6, 124.7 (C_q-Ph and 5x<u>C</u>H-Ph), 106.7 (<u>C</u>^{5}H-thiazole), 29.4, 28.3, 26.3, 23.2 (6xCH_2-cycloheptyl).

General Procedures for Acylation of Aminothiazoles using Acid Chlorides

To a cold solution of 2-aminothiazole (**1a**) or 2-amino-4-phenyl-thiazole (**1b**) (0.01 mol) in dry $CHCl_3$ (25 ml), triethyl amine (0.01 mol) followed by addition of the appropriate acid chloride (**7a-e**) (0.011 mol, 1.1 equiv.) namely, heptaonyl chloride, 6-bromohexanoyl chloride, 5-bromovalery chloride, 2-thiophenecarbonyl chloride and 2-phenysulfanylacetyl chloride, respectively was added at 0-5 °C. The resulting reaction mixture in each case was stirred at this temperature for 1 h then allowed to warm up to room temperature then refluxed for 6 h. The excess solvent was removed under reduced pressure, water/ice mixture was added to the remaining residue in each case , the formed solid was filtered, air dried and purified either by column chromatography or by re-crystallization to afford the pure amides (**8a-i**).

Heptanoic acid thiazol-2-ylamide (**8a**)

Beige powder, yield (88%), m.p. 232-234 °C; ν_{max} (KBr)/cm^{-1} 3273, 3173, 3081, 2928, 1693, 1571, 1466, 1420, 1378, 1298, 1273, 1170, 1114, 1063, 958, 797, 776, 713, 620; (300 MHz, $CDCl_3$) δ_H 12.29 (1H, br. s, NH), 7.43 (1H, d, *J* 3.3 Hz, C^4H-thiazole), 6.99 (1H, d, *J* 3.3 Hz, C^5H-thiazole), 2.54 (2H, t, *J* 7.3 Hz, CO-C<u>H</u>$_2$-CH_2), 1.76 (2H, quintet, *J* 7.3 Hz, CH_2-heptyl), 1.29-1.39 (6H, m, 3xCH_2-heptyl), 0.87 (3H, t, *J* 7.0 Hz, CH_3); (75 MHz, $CDCl_3$) δ_C 170.0 (C^2_q-thiazole), 158.8 (CO), 134.8 (C^4H-thiazole), 112.2 (C^5H-thiazole), 34.9, 30.2, 27.6, 23.8, 21.2 (5xCH_2-heptyl), 12.7 (CH_3); *m/z* (EI) [M^+] 212 (50%) for $C_{10}H_{16}N_2OS$, 213 (14.66%), 211 (51.72%), 86 (100%).

Heptanoic acid (4-phenyl-thiazol-2-yl)-amide **(8b)**

Yellow powder, yield (81%), m.p. 180-182 °C; ν_{max} (KBr)/cm^{-1} 3465, 3152, 2861, 1686, 1563, 1443, 1374, 1329, 1279, 1174, 1071, 970, 913, 771, 714; (500 MHz, $CDCl_3$) δ_H 11.04 (1H, br. s, NH), 7.81 (2H, d, *J* 7.4 Hz, 2x*o*-Ph-H), 7.42 (2H, t, *J* 7.7 Hz, 2x*m*-Ph-H), 7.33 (1H, t, *J* 7.3 Hz, *p*-Ph-H), 7.14 (1H, s, C^5H-thiazole), 2.01 (2H, t, *J* 7.6 Hz, CO-C<u>H</u>$_2$-CH_2), 1.46 (2H, quintet, *J* 7.6 Hz, CO-CH_2-C<u>H</u>$_2$), 1.32-1.19 (6H, m, CH_3-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$), 0.83 (3H, t, *J* 7.3 Hz CH_3); (125 MHz,$CDCl_3$) δ_C 171.8 (C^2_q-thiazole), 159.74 (CO), 149.5 (C^4_q-thiazole), 134.1, 128.9, 128.3, 126.3 (C-Ph), 107.8 (C^5H-thiazole), 35.9 (CO-<u>C</u>H_2), 31.3, 28.6, 24.4, 22.4 (4xCH_2), 14.0 (CH_3).

6-Bromo-hexanoic acid thiazol-2-ylamide **(8c)**

White powder, yield (87%), m.p. 117-118 °C; ν_{max} (KBr)/cm^{-1} 3260, 3167, 3080, 2933, 2865, 1680, 1565, 1465, 1419, 1378, 1319, 1278, 1170, 1114, 960, 809, 781, 706, 628, 520; (300 MHz, $CDCl_3$) δ_H 12.07 (1H, br. s, NH), 7.43 (1H, d, *J* 3.7 Hz, C^4H-thiazole), 7.00 (1H, d, *J* 3.7 Hz, C^5H-thiazole), 3.41 (2H, t, *J* 6.6 Hz, Br-CH_2), 2.57 (2H, t, *J* 7.5 Hz, CO-C<u>H</u>$_2$), 1.95-1.75 (4H, m, 2xCH_2), 1.6-1.5 (2H, m, CH_2); (75 MHz, $CDCl_3$) δ_C 170.2 (C^2_q-thiazole), 158.5 (CO), 135.2 (C^4H-thiazole) , 112.6 (C^5H-thiazole), 34.9, 32.4, 31.3, 27.0, 23.1 (5xCH_2).

6-Bromo-hexanoic acid (4-phenyl-thiazol-2-yl)-amide **(8d)**

Beige shiny crystals, yield (82%), m.p. 129-130 °C; ν_{max} (KBr)/cm^{-1} 3433, 3147, 3051, 2929, 1683, 1563, 1534, 1481, 1442, 1331, 1281, 1194, 1072, 975, 912, 840, 773, 714; (500 MHz, DMSO-d_6) δ_H 12.24 (1H, br. s, NH), 7.90 (2H, d, *J* 7.4 Hz, 2x*o*-Ph-H), 7.43 (2H, t, *J* 7.7 Hz, 2x*m*-Ph-H), 7.33 (1H, t, *J* 7.3 Hz, *p*-Ph-H), 7.01 (1H, s, C^5H-thiazole), 3.55 (2H, t, *J* 6.7 Hz, Br-CH_2), 2.47 (2H, t, *J* 7.3 Hz, CO-CH_2), 1.83 (2H, quintet, *J* 7.2 Hz , CH_2), 1.65 (2H, quintet, *J* 7.5 Hz, CH_2), 1.42 (2H, quintet, *J* 7.5 Hz, CH_2); (125 MHz, DMSO-d_6) δ_C 171.4 (C^2_q-thiazole ring), 157.9 (CO), 148.7 (C^4_q-thiazole ring), 134.3, 128.7, 127.7, 125.6 (<u>C</u>$_q$-*ipso*-Ph, 4xCH-Ph), 107.8

(C^5H-thiazole), 34.9 (CO-$\underline{C}H_2$), 34.7, 31.9, 27.1, 23.8 (4xCH_2).

5-Bromo-pentanoic acid thiazol-2-ylamide **(8e)**

Off white powder, yield (84%), m.p. 142-143 °C; ν_{max} (KBr)/cm^{-1} 3268, 3167, 2944, 2865, 1685, 1570, 1459, 1419, 1378, 1327, 1288, 1170, 1062, 961, 873, 811, 779, 716, 623, 517; (300 MHz, $CDCl_3$) δ_H 12.3 (1H, br. s, NH), 7.4 (1H, d, *J* 3.7 Hz, C^4H-thiazole), 7.0 (1H, d, *J* 3.7 Hz, C^5H-thiazole), 3.4 (2H, t, *J* 6.2 Hz, Br-CH_2), 2.6 (2H, t, *J* 6.6 Hz, CO-CH_2), 1.99-1.92 (4H, m, CO-CH_2-$C\underline{H}_2$-$C\underline{H}_2$-CH_2-Br); (75 MHz, $CDCl_3$) δ_C 169.2 (C^2_q-thiazole), 158.7 (CO), 135.0 (C^4H-thiazole), 112.5 (C^5H-thiazole ring), 33.8, 31.8, 30.7, 22.3 (4xCH_2).

5-Bromo-pentanoic acid (4-phenyl-thiazol-2-yl)-amide **(8f)**

Shiny golden flaks, yield (93%), m.p. 172-173 °C; ν_{max} (KBr)/cm^{-1} 3150, 3053, 2928, 2955, 1688, 1563, 1481, 1430, 1329, 1280, 1171, 1072, 962, 913, 838, 775, 714; (500 MHz, $CDCl_3$) δ_H 11.37 (1H, br. s, NH), 7.85 (2H, d, *J* 7.4 Hz, 2 x *o*-Ph-H), 7.47 (2H, t, *J* 7.5 Hz, 2 x *m*-Ph-H), 7.39 (1H, t, *J* 7.3 Hz, *p*-Ph-H), 7.29 (1H, s, C^5H-thiazole), 3.37 (2H, t, *J* 6.6 Hz, Br-CH_2), 2.00 (2H, t, *J* 7.5 Hz, CO-CH_2), 1.63 (2H, quintet, *J* 7.2 Hz, CH_2), 1.52 (2H, quintet, *J* 6.6 Hz, CH_2); (125 MHz, DMSO-d_6) δ_C 170.8 (C^2_q-thiazole), 159.5 (CO), 149.6 (C^4_q-thiazole), 134.3, 129.0, 128.5, 126.3 ($\underline{C}_q$-*ipso*-Ph and 4xCH-Ph), 108.1 (C^5H-thiazole), 44.2, 34.7, 31.6, 21.9 (4xCH_2)**;** *m/z* (EI) [M^+] 399 (100.00%) for $C_{14}H_{15}BrN_2OS$.

Thiophene-2-carboxylic acid thiazol-2-ylamide **(8g)**

Pale golden crystals, yield (89%), m.p. 148-150 °C; ν_{max} (KBr)/cm^{-1} 3402, 3213, 1645, 1539, 1478, 1403, 1355, 1322, 1288, 1167, 1084, 1036, 847, 715; (400 MHz, $CDCl_3$) δ_H 12.96 (1H, br. s, NH), 7.80 (1H, app. dd, *J* 3.7, 1.4 Hz, C^5H-thiophene), 7.64 (1H, app.dd, *J* 5.1, 1.4 Hz, C^3H-thiophene), 7.38 (1H, d, *J* 3.7 Hz, C^4H-thiazole), 7.15 (1H, app. t, *J* 4.4 Hz, C^4H-thiophene), 6.97 (1H, d, *J* 3.7 Hz, C^5H-thiazole); ($CDCl_3$, 100 MHz) δ_C 160.5, 160.4, 137.4, 137.1, 132.7, 130.4, 128.0, 113.9 (CO, C_q and CH-thiophene, C_q and CH-thiazole); *m/z* (EI) [M^+] 210 (15%) for $C_{14}H_{15}BrN_2OS$, 211 (10%),209 (100%).

Thiophene-2-carboxylic acid (4-phenyl-thiazol-2-yl)-amide **(8h)**

Yellow powder, yield (85%), m.p. 135-137 °C; ν_{max} (KBr)/cm^{-1} 3258, 3112, 1633, 1552, 1481, 1446, 1289, 1065, 849, 776, 708, 729, 627; (400 MHz, $CDCl_3$) δ_H 9.77 (1H, br. s, NH), 7.71 (2H, d, *J* 7.3 Hz, 2x*o*-CH-Ph), 7.50 (1H, d, *J* 3.7 Hz, $C^5\underline{H}$-thiophene), 7.48 (1H, d, *J* 5.1 Hz, $C^3\underline{H}$-thiophene), 7.31 (2H, t, *J* 7.3 Hz, 2x*m*-CH-Ph), 7.23 (1H, t, *J* 7.3 Hz, *p*-CH-Ph), 7.18 (1H, s, C^5H-thiazole), 6.91 (1H, app. t, *J* 4.4 Hz, C^4H-thiophene); (100 MHz, $CDCl_3$) δ_C 159.9, 159.1, 150.0, 136.4, 134.1, 132.6, 130.2, 128.8, 128.3, 128.1, 126.1, 108.4 (CO, C_q and CH-thiophene, thiazole and Ph)**;** *m/z* (EI) [M^+] 286 (17%) for $C_{14}H_{10}N_2OS_2$, 111 (100%).

2-Phenylsulfanyl-N-thiazol-2-yl-acetamide **(8i)**

Dark reddish brown powder, m.p. 106-107 °C; ν_{max} (KBr)/cm^{-1} 3200, 1687, 1566, 1472, 1295, 1165, 1111, 1023, 963, 871, 785, 744, 691, 621, 541, 515, 480; (500 MHz, $CDCl_3$) δ_H 10.60 (1H, br. s, NH), 7.62 (1H, d, *J* 2.8 Hz, C^4H-thiazole), 7.58 (2H, d, *J* 7.2 Hz, 2x*o*-CH-Ph), 7.46 (2H, t, *J* 7.1 Hz, 2 x *m*-CH-Ph), 7.41 (1H, app d, *J* 6.9 Hz, *p*-CH-Ph), 7.19 (1H, d, *J* 2.8 Hz, C^5H-thiazole); (125 MHz, $CDCl_3$) δ_C 166.9 (C^2_q-thiazole ring), 159.3 (CO), 136.3 (C^4H-thiazole), 133.9, 129.9, 129.5, 127.4 ($\underline{C}_q$-*ipso*-Ph, 4xCH-Ph), 113.9 (C^5H-thiazole).

4-(Thiazole-2-yl carbamoyl)-butaric acid **(10)**

A mixture of 2-amino thiazole (**1a**) (0.01 mol) and glutaric anhydride (0.01 mol) in glacial acetic acid (25 ml) was heated under reflux for 12 h. After completion of the reaction, the excess solvent was evaporated , the crude product was purified by column chromatography using silica gel 60-120 mesh and eluent ($CHCl_3$/MeOH; 9:1) to afford the *title compound* as reddish brown powder, yield (90%), m.p. 144-146 °C; ν_{max} (KBr)/cm^{-1} 3450, 3261, 3166, 2929, 1689, 1564, 1431, 1368, 1288, 1228, 1166, 1064, 969, 818, 776, 710, 658, 624, 558, 518; (500 MHz, DMSO-d_6) δ_H 12.18 (2H, br. s, OH and NH), 7.44 (1H, d, *J* 3.4 Hz, C^4H-thiazole), 7.17 (1H, d, *J* 3.4 Hz, C^5H-thiazole), 2.47 (2H, t, *J* 7.3 Hz, HOOC-$C\underline{H}_2$-CH_2), 2.27 (2H, t, *J* 7.3 Hz, NH-CO-$C\underline{H}_2$-CH_2), 1.82 (2H, quintet, *J* 7.3 Hz, NH-CO-CH_2-$C\underline{H}_2$-CH_2); (125 MHz, DMSO-d_6) δ_C 173.9 (COOH), 170.6 (C^2_q-thiazole), 157.9 (CONH), 137.5 (C^4H-thiazole), 113.1 (C^5H-thiazole), 33.9 (HOOC-$\underline{C}H_2$), 32.8 (NH-CO-$\underline{C}H_2$), 19.9 (CO-CH_2-$\underline{C}H_2$- CH_2).

Results and Discussion

Chemistry

Due to the weak nucleophilicity of the amino group of the 2-aminothiazole and its 4-phenyl derivative by participation in resonance with the pi-system, condensation with activated acylating reagents such as chloroformates, acid chlorides and

acid anhydrides provided a good strategy to prepare a number of thiazole derivatives *via* nucleophilic substitution reactions. 2-Amino-[1,3]-thiazole is considered to be a double nucleophile as there are two operative nucleophilic centers in this species, the endocylic (imino) and exocylic (amino) nitrogen atoms. The region-selectivity of nucleophilic center is governed by the nature of the electrophiles and the pH of the reaction medium [31]. Therefore, in reactions of 2-aminothiazole and its 4-phenyl derivative with chloroformates, acyl halides, and anhydrides the exocyclic nitrogen is the main nucleophilic center which is in agreement with the reported literature [32].

Reaction of 2-aminothiazoles (**1a-b**) with various alkyl chloroformates (**2a-d**), namely methyl chloroformate, ethyl chloroformate, propyl chloroformate and isobutyl chloroformate under dry conditions and in presence of pyridine [33] or triethylamine as the basic catalyst, afforded the corresponding carbamates (**3a-e**). Hydrazinolysis of carbamate (**3e)** with hydrazine hydrate in refluxing ethanol furnished the corresponding semicarbazide **(4)**. This semicarbazide was a good candidate to prepare novel semicarbazones **(6a-d)** incorporating thiazole ring by condensation with different aldehydes and ketones (**5a-d**) namely, *p*-chlorobenzaldehyde, *p*-hydroxybenzaldehyde, cyclopentanone and cycloheptanone in ethanol containing catalytic amount of glacial acetic acid Scheme-1.

Reagents and conditions: (i) **1a**, dry pyridine, 0 ˚C, **2 a-d**, 1.5 h, r.t. 0.5 h, reflux W.B. 12 h; (ii) **1b**, dry $CHCl_3$, Et_3N, 0 ˚C, **2b**, 1.5 h., r.t. 0.5 h., reflux W.B. 12 h; (iii) EtOH, reflux 20 h.; (iv) EtOH, ACOH cat., reflux 12 h.

Analogously, acylation of amino thiazoles (**1a-b**) with a number of acid chlorides (**7a-e**) and with glutaric anhydride (**9**) afforded amides (**8a-h**) and carboxamide derivative (**10**), respectively, as shown in Scheme-2.

Reagents and conditions: (i) Dry $CHCl_3$, Et_3N, 0 ˚C 30 min., r.t. 1 h, reflux 6 h, (ii) AcOH, reflux 12 h.

Structure elucidation of the synthesized compounds is based on their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Thus carbamates (**3a-e**), generally, displayed in the IR spectra absorption bands at ν_{max} 3156-3433 cm^{-1} indicating NH groups. The carbonyl groups appeared at ν_{max} 1719-1754 cm^{-1}. The ^{1}H NMR spectra of the carbamates derived from 2-aminothiazole indicated the disappearance of NH_2 group of the starting material which appeared at δ = 5.49 (300 MHz) and emergence of new signal at δ = 11.81-13.41 corresponding to NH groups. Similarly the ^{1}H NMR spectra of the carbamates derived from 2-amino-4-phenylthiazole indicated the disappearance of the signal due to NH_2 group of the starting material which appeared at δ = 5.06 (300 MHz) and appearance of new signal at δ = 10.28-13.25 corresponding to the NH groups of these carbamates. Furthermore, the ^{13}C NMR spectra of carbamates **(3a-e)** indicated the presence of the characteristic carbonyl signals at δ_C = 152.5-154.5. Moreover, the mass spectrum of compound (**1d**) as an example exhibited a molecular ion peak at *m/z* = 200 (15.60%) for $C_8H_{12}N_2O_2S$, and the base peak (100%) was observed in the spectrum at *m/z* = 57. Plausible fragmentation pattern of compound **(1d)** may be rationalized as depicted in Fig. 1.

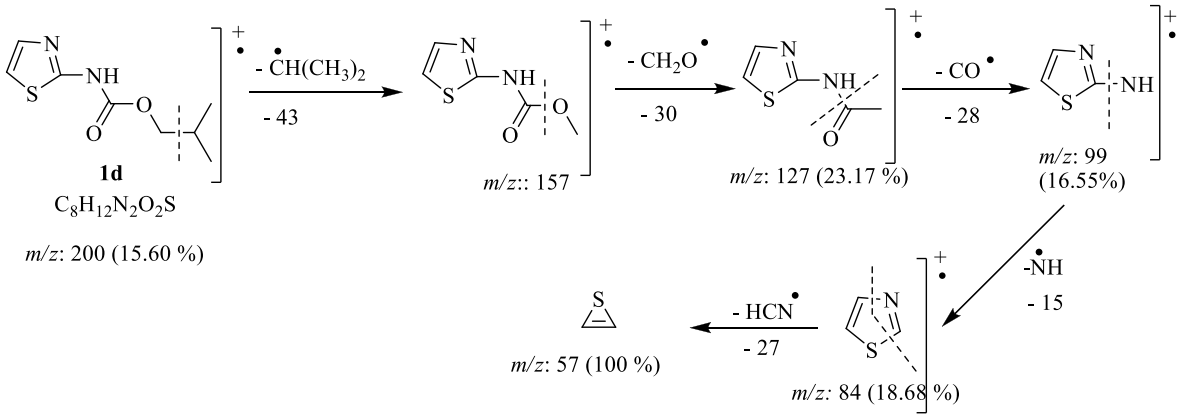
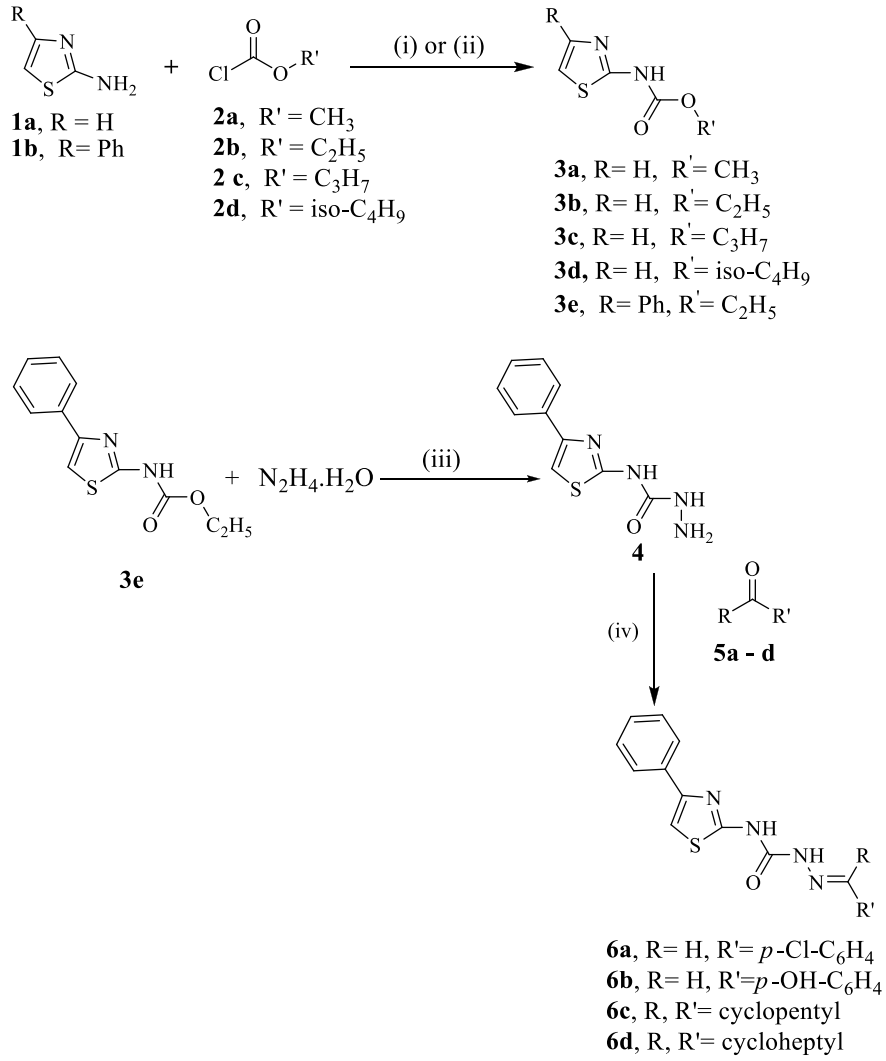
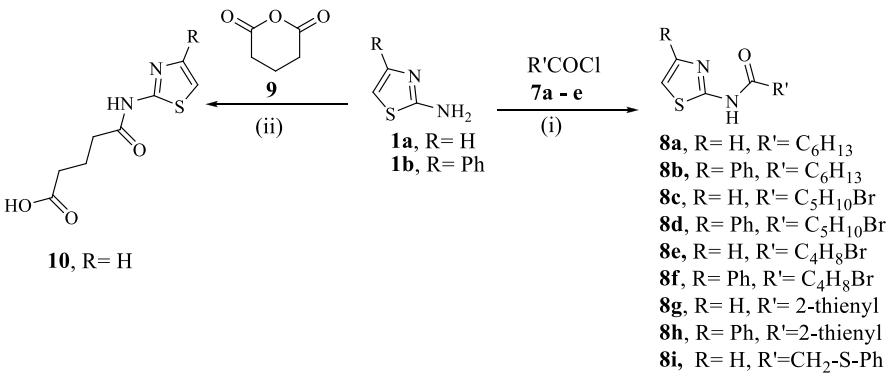


Fig. 1: Plausible fragmentation pattern of carbamate **(1d)**.



Scheme-1: Synthesis of thiazolyl carbamates, semicarbazide and semicarbazones.



Scheme-2: Synthesis of thiazolyl amides and carboxamide.

Similarly the molecular structure of semicarbazide **(4)** was confirmed based on spectral analysis. Thus the IR spectrum showed absorption bands at ν_{max} 3432, 3341, 3268 cm^{-1} for NH_2 and NH groups. The absorption bands due to aromatic CH, carbonyl group, C=N and C=C appeared at ν_{max} 3111, 1689, 1649, 1603 and 1464 cm^{-1}, respectively.

As semicarbazide (**4**) was obtained from ethyl carbamate (**3e**), the ^1H NMR spectrum (300

MHz, $CDCl_3$) of this semicarbazide indicated the disappearance of the signals due to the ethyl group of the starting material and appearance of a two protons singlet at δ = 5.29 belongs to NH_2 group and a seven protons multiplet at δ = 7.88-7.37 attributed to, the five aromatic protons, C^5H-thiazole and NH group. The remaining NH group appeared as a broad singlet at δ = 10.98.

The ^{13}C NMR (75 MHz, $CDCl_3$) data of this semicarbazide also confirmed the proposed structure as the spectral lines due to the ethyl carbons of the starting carbamate **(3e**) were disappeared indicating formation of a new product. The thiazole carbons, C^5, C^4 and C^2 appeared at δ_C = 106.6, 148.8 and 157.6, respectively. The carbonyl carbon and the six carbons of phenyl group were observed at δ_C = 151.8, 133.4, 127.4, 126.5 and 124.7.

Analogously, the spectral data of the novel semicarbazones (**6a-d**) confirmed their assigned structures. Generally, the ^{1}H NMR spectra indicated the disappearance of the signals due to protons of NH_2 group of the starting semicarbazide and appearance of the new characteristic signals corresponding to the individual identity of each structure in addition to the characteristic signal due to the azomethine (CH=N) proton at δ = 8.19, 7.94 in case of semicarbazones (**6a, 6b**) derived from aldehydes. For the semicarbazones (**6c, 6**d) derived from the ketones the spectra displayed the characteristic signals of the aliphatic cyclic groups.

Similarly the structures of amides (**8a-i**) were fully supported by their spectroscopic data with absorption bands in the IR spectrum at ν_{max} 3465-3064 cm^{-1} for the NH groups and absorption bands at ν_{max} 1693-1633 cm^{-1} for the CO groups. The ^{1}H NMR spectra indicated the disappearance of the primary amino group of starting 2-amino thiazoles (**1a** & **1b**) and the appearance of broad singlets for the NH protons at δ 12.29-9.77. The ^{13}C NMR spectra of these amides indicated the emergence of the characteristic spectral lines for carbonyl groups at δ =157.9-160.5.

Finally structure of carboxamide (**10**) was proven based on its spectral data. Its IR spectrum showed absorption bands at ν_{max} 3450, 3261, 3166, 2929, 1689 and 1564 cm^{-1} due to OH, NH, CH aliphatic, 2 x CO, C=N respectively. The ^{1}H NMR spectrum displayed a quintet signal integrating for two protons at δ = 1.82 with coupling constant *J* 7.3 Hz due to central methylene group. Also the spectrum revealed the presence of two triplets at δ = 2.27 and 2.47 with coupling constants *J* 7.3 Hz and 7.3 Hz each one of is integrating for two protons and they are attributed to the remaining two methylene groups adjacent to the carbonyl groups. The two protons at C^5 and C^4 of thiazole ring appeared as two doublets each integrating for one proton at δ = 7.17 and 7.45, respectively, with coupling constant *J* 3.5 Hz. The NH and OH protons appeared as broad singlet at δ = 12.08. Furthermore, the ^{13}C NMR spectrum revealed the presence of three signals at δ_C = 19.9, 32.8, and 33.9 attributed to aliphatic methylene groups. In addition to the emergence of three signals at δ_C = 113.1, 137.5, 157.9 attributed to C^5H-thiazole, C^4H-thiazole and amido-CO, respectively. Furthermore, signals belonging to C^2_q-thiazole and acidic-CO appeared at δ_C = 170.6 and 173.9, respectively.

Antimicrobial Examination

In the present study, antimicrobial potential of fifteen of the synthetic compounds were tested against selected microorganisms including, Gram +ve bacteria-*Bacillus subtilis* (NRRL B-543) and *Staphylococcus aureus*, Gram -ve bacteria *Escherichia coli* (NRRLB-21), yeats *Candida albicans* (NRRLY-477) and *Saccharomyces cercvisiae* (NRRL Y-567) and fungus *Asperigillus niger* (NRRL 599). The concentration of each test compound used was 50 mg/mL DMSO. Tetracycline (TE), streptomycin (S), neomycin (N) and nystatin (NS) were used as standard drugs. DMSO was used as solvent control. The antibacterial and antifungal activities of the tested compounds are expressed in inhibition zones and shown in Table-1.

Table-1: The antibacterial and antifungal activities of the selected compounds in inhibition zone in mm as a criterion of antimicrobial activities.

Compound No.	Gram -ve bacteria	Gram +ve bacteria		Yeast		Fungi
	E. coli	*B. subtilis*	*S. aureus*	*C. albicans*	*S. cervesia*	*A. niger*
3a	**15**	**16**	**16**	**16**	**18**	**12**
3b	**-ve**	**12**	**-ve**	**-ve**	**-ve**	**12**
3c	**11**	**12**	**11**	**12.5**	**-ve**	**12**
3d	**11**	**12.5**	**12**	**14**	**-ve**	**10**
3e	**-ve**	**-ve**	**-ve**	**10**	**-ve**	**11**
6d	**-ve**	**- ve**	**-ve**	**-ve**	**-ve**	**-ve**

Table-1: continued…

8a	**11.5**	**12**	**11**	**12.5**	**-ve**	**12**
8b	**12.5**	**13**	**13**	**14**	**13**	**13**
8c	**11**	**11**	**-ve**	**11**	**-ve**	**14**
8d	**13**	**13**	**13**	**13**	**13.5**	**13**
8e	**11**	**17**	**12**	**17**	**-ve**	**15**
8f	**11**	**12**	**-ve**	**12**	**-ve**	**15**
8g	**16.5**	**15**	**20**	**19**	**14**	**21**
8h	**11**	**13**	**11.5**	**13**	**-ve**	**14**
10	**12**	**13**	**14**	**14**	**-ve**	**12**
TE* = 30 mcg	**22**	**18**	**24**	**-ve**	**-**	**-ve**
S* = 10 mcg	**23**	**15**	**25**	**26**	**-**	**-ve**
N* = 30 mcg	**20**	**14**	**22**	**17**	**-**	**-ve**
NS* = 100 units	**-ve**	**-ve**	**-ve**	**20**	**-**	**15**

The standard reference drugs: TE= Tetracycline, S= Streptomycin, N= Neomycin, and NS = Nystatin.

The screening results revealed that the tested compounds displayed varied degrees of antimicrobial activities ranging from being completely inactive to being more potent when compared with the used standard drugs. Carbamate (**3a**), amides (**8b**), (**8d**), and (**8g**) exhibited high activity against all the tested microorganisms, semicarbazone (**6d**) was completely inactive. Furthermore, among the tested compounds, amide (**8g**) exhibited the highest inhibitory effects against Gram negative *Escherichia coli*, Gram positive *Staphylococcus aureu*s, yeast *Candida albicans and* fungus *Aspergillus niger*. Moreover, this amide is more potent than the reference drugs against *Aspergillus niger*. The enhanced activity of this amide may be attributed to the presence of the thiophene moiety in the side chain. In addition to this, amide (**8e**) exhibited the highest inhibitory effects against Gram positive *Bacillus subtili*s. Additionally, carbamate (**3a**) was found to be the most active and even more active than the used reference drugs against yeast *Saccharomyces cervesia*. However, the rest of the tested compounds showed moderate inhibitory effects as shown in (Table-1).

Conclusions

The synthesis and characterization of thiazolyl carbamates, amides and carboxamide have been fully described. Antimicrobial screening of some synthesized compounds revealed that they exhibited variable degrees of activities towards Gram +ve bacteria *Bacillus subtilis* (NRRL B-543) and *Staphylococcus aureus*, Gram -ve bacteria *Escherichia coli* (NRRLB-21), yeasts, *Candida albicans* (NRRLY-477) and *Saccharomyces cercvisiae* (NRRLY-567) and fungus *Asperigillus niger* (NRRL 599). Among the tested compounds, amide (**8g**) exhibited the highest inhibitory effects against *Escherichia coli*, *Staphylococcus aureu*s, *Candida albicans* and *Aspergillus niger*. In addition, on one hand, amide (**8e**) exhibited the highest inhibitory effects against *Bacillus subtili*s, on the other hand, carbamate (**3a**) was found to be the most active and even more active than the used reference drugs against yeast *Saccharomyces cervesia*. On the basis of the obtained results it may be concluded that amides derived from 2-aminothiazole are more potent than those derived from 4-phenyl analog and therefore are more interesting to be used to conduct a comprehensive study in order to obtain more significant correlations between the chemical structures of the compounds and their antimicrobial activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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