NEW THIAZOLONE DERIVATIVES: DESIGN, SYNTHESIS, ANTICANCER AND ANTIMICROBIAL ACTIVITY

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In order to explore the anticancer and antimicrobial activity associated with the thiazolone framework, several new (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)carboxylic acid derivatives have been synthesized in water as a solvent. All synthesized compounds were evaluated for anticancer and antimicrobial activity in vitro. Amongst these, the 3-methylbutanoic and the 3- or 4-methylpentanoic acid derivatives, the 3-hydroxy-, the 3-(1H-imidazol-4-yl) and the 3-(4-hydroxyphenyl)propanoic acid derivatives and the succinic acid derivative showed high antibacterial and antifungal activity. The unsubstituted propanoic acid derivative exhibited significant antibacterial activity against *B. subtilis* and significant antifungal activity against fungal strains, i.e., *A. flavus*. The in vitro anticancer studies revealed that the 3-(hydroxy)-, the 3-(1H-imidazol-4yl)- and the 3-(4-hydroxyphenyl)propanoic acid, or the succinic acid derivatives are the most active compounds against MCF-7 and BT-474 human breast cancer cell lines.

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INTRODUCTION

Since the last five decade very rapid progress has been made in the area of cancer cell biology, though most cancer treatments are still multimodal, involving the chemotherapy.[1] Cancer is the second leading cause of death in the world after cardiovascular diseases and it is projected to begin the primary cause of death there within the coming year.[2,3] The breast cancer may be one of the oldest known forms of cancerous tumors in humans. Worldwide, breast cancer is the most common cancer in women, after skin cancer, representing 16 % of all female cancers.[4]

The heterocyclic chemistry has great importance for the medicinal chemists due to the high therapeutic activity of heterocyclic compounds. The compounds containing the 2-thioxothiazolidin-4-one (rhodanine) ring scaffold has been gaining prominence in recent years, because its derivatives are known to possess a broad spectrum of pharmacological activities, such as antimicrobial,[5-9] antidiabetic,[10] anticancer,[11-14] antiviral,[15,16] antifungal,[17] anticonvulsant,[18] anti-tuberculosis[19,20] and anti-HIV.[21,22] The identification of new structures that can be potentially useful in designing new, potent selective and less toxic anticancer agent is still a significant challenge to medicinal chemistry researchers.[23,24] The recent reports suggested that a chain containing free carboxyl group at the rhodanine nucleus had importance in the observed anticancer and antimicrobial activity.[25,26]

We initiated a program to synthesize thiazolone derivatives having amino acids chain as antimicrobial agents. In continuation of our work,[27] we have developed the new protocol for the synthesis of (Z)-5-(3-fluorobenzylidene)-2-thioxothiazolidin-4-one (**3**) (Scheme 1) by the condensation of 2-thioxothiazolidin-4-one and 3-fluorobenzaldehyde. The compound (**3**) was then subjected to a Knoevenagel condensation with the appropriate rhodamines synthesized using the reported procedure.[28,29]

EXPERIMENTAL SECTION

The compounds 2-thioxothiazolidin-4-one, 3-fluorobenzaldehyde, anhydrous sodium acetate, triethylamine, amino acids, dichloromethane, iodomethane and various solvents were commercially available (Sigma-Aldrich and Avra labs). Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded on an FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer and were recorded in DMSO-d_6 solvent ^{13}C NMR spectra were recorded in DMSO-d_6 solvent on a 100 MHz Bruker spectrometer. Chemical shifts are reported as δ ppm units (TMS). The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

The general procedure of (Z)-5-(3-fluorobenzylidene)-2-thioxothia-zolidin-4-one (3)

In a 100 ml round bottom flask, the equimolar amount of the 2-thioxothiazolidin-4-one (1 mmol) and anhydrous sodium acetate (1 mmol) were mixed in glacial acetic acid (1 ml) with 3-fluorobenzaldehyde. The reaction mixture was stirred under reflux condition for 4 h. The progress of the reaction was monitored by TLC (20 % ethyl acetate: n-

hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered, washed with water (3×10 mL), dried, and purified by recrystallization from ethanol as a solvent to give a 90 % yield.

Yellow solid. Yield: 90 %. m.p. 198–200 ºC; ES-MS m/z (%): 239.29, IR ν_{max}/cm^{-1}: 3010 (NH), 1702 (C=O), 1594 (C=C), 1483 (C=N), 1436 (C=S), 1279 (C–N). ^{1}H NMR (DMSO-d_6): δ = 7.30–7.32 (m, 4H, Ar–CH), 7.60 (s, 1H, =CH), 13.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 113.5, 114.5, 116.3, 124.7, 130.9, 136.4, 143.2, 163.5, 168.4, 193.7.

General procedure of (Z)-5-(3-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (4)

In a 100 ml round bottom flask, the compound (**3**) (1 mmol) and triethylamine (1.5 mmol) were added in dichloromethane (10 ml) at room temperature. Iodomethane (1.5 mmol) was added to the stirred reaction mixture and the mixture was stirred for 2 h at room temperature. The progress of the reaction was monitored by TLC (10 % chloroform: methanol). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed out with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent.

Yellow solid. Yield: 92 %. m.p. 160–162 ºC; ES-MS m/z (%): 253.05, IR ν_{max}/cm^{-1}: 1703 (C=O), 1599 (C=C), 1577 (C=N), 1287 (C=S), 1086 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.90 (s, 3H, S-CH3), 7.10–7.21 (m, 4H, Ar–CH), 7.82 (s, 1H, =CH), ^{13}C NMR (DMSO-d_6): δ = 14.5, 113.9, 114.5, 124.1, 130.9, 136.4, 143.2, 152.0, 162.8, 163.5, 167.4.

General procedure of (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted carboxylic acids (6a-l).

In a 100 ml round bottom flask, the compound (**4**) (1 mmol), amino acids (**5a-l**) (1.5 mmol) and potassium carbonate (1.5 mmol) were mixed in water (1 mL) at room temperature and the reaction mixture was stirred for 30-55 min at room temperature. The progress of reaction was monitored by TLC (10 % chloroform: methanol). After completion of reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The compounds (**6a-l**) were recrystallized from ethanol and isolated as yellowish solids.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (6a)

Yellow solid. Yield: 92 %, m.p. 189–191 ºC; ES-MS m/z (%): 294.28, IR ν_{max}/cm^{-1}: 3744 (COOH), 3397 (OH), 1742 (HO–C=O), 1642 (C=O), 1564 (C=C), 1549 (C=N), 1206 (C-S), 1086 (C–N). ^{1}H NMR (DMSO-d_6): δ = 1.40–1.42 (d, 3H, C–CH3), 4.55–4.57 (q, 1H, CH), 7.30–7.32 (m, 4H, Ar–CH), 7.70 (s, 1H, =CH), 10.20 (s, 1H, NH), 12.65 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ=16.8, 53.5, 113.9, 114.5, 124.2, 129.7, 132.7, 136.5, 152.1, 158.3, 162.3, 167.7, 174.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methylbutanoic acid (6b)

Yellow solid. Yield: 94 %, m.p. 204–206 ºC; ES-MS m/z (%): 322.35, IR ν_{max}/cm^{-1}: 3414 (OH), 3215 (NH), 3013 (CH–Ar), 1732 (HO–C=O), 1684 (C=O), 1551 (C=C), 1593 (C=N), 1012 (C-S), 1091 (C–N). ^{1}H NMR (DMSO-d_6): δ = 0.91–0.93 (d, 6H, CH(CH3)2), 1.50–1.52 (m, 1H, CH), 4.41–4.43 (d, 1H, CH), 7.25–7.27 (m, 4H, Ar–CH), 7.88 (s, 1H, =CH), 11.62 (s, 1H, NH), 13.12 (s, 1H, COOH). 13C NMR (DMSO-d_6): δ = 18.8, 30.5, 61.3, 113.8, 114.4, 124.2, 130.2, 132.3, 135.9, 152.3, 158.1, 162.7, 167.2, 174.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methylpentanoic acid (6c)

Yellow solid. Yield: 92 %, m.p. 165–167 ºC; ES-MS m/z (%): 336.38, IR ν_{max}/cm^{-1}: 3398 (OH), 3212 (NH), 3017 (CH–Ar), 1735 (HO–C=O), 1692 (C=O), 1557 (C=C), 1583 (C=N), 1013 (C-S), 1097 (C–N). ^{1}H NMR (DMSO-d_6): δ = 0.91–0.93 (t, 3H, CH_2–CH_3), 1.15–1.17 (d, 3H, CH3) 1.52–1.54 (m, 2H, CH_2), 1.81–1.83 (m, 1H, CH), 4.43–4.45 (d, 1H, CH), 7.21–7.23 (m, 4H, Ar–CH), 7.80 (s, 1H, =CH), 11.64 (s, 1H, NH), 13.29 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 11.2, 15.4, 25.7, 36.4, 58.4, 113.4, 114.5, 124.9, 130.6, 132.3, 135.9, 152.9, 158.1, 162.4, 167.3, 175.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-3-phenylpropanoic acid (6d)

Yellow solid. Yield: 90 %, mp 138–140 ºC; ES-MS m/z (%): 370.40, IR ν_{max}/cm^{-1}: 3396 (OH), 3211 (NH), 2992 (CH–Ar), 1737 (HO–C=O), 1692 (C=O), 1551 (C=C), 1581 (C=N), 1017 (C-S), 1098 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.51–2.53 (d, 2H, CH2), 4.45–4.47 (q, 1H, CH), 7.25–7.27 (m, 9H, Ar–CH), 7.89 (s, 1H, =CH), 11.75 (s, 1H, NH), 13.31 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 36.4, 58.4, 113.5, 114.6, 124.9, 125.9, 125.7, 128.6, 128.9, 130.7, 132.3, 135.3, 136.9, 152.2, 158.5, 167.1, 175.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-4-(methylthio)butanoic acid (6e)

Yellow solid. Yield: 92 %, mp 142–144 ºC; ES-MS m/z (%): 354.42, IR ν_{max}/cm^{-1}: 3396 (OH), 3210 (NH), 2980 (CH–Ar), 1732 (HO–C=O), 1698 (C=O), 1541 (C=C), 1586 (C=N), 1014 (C-S), 1091 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.01–2.03 (q, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.61–2.63 (t, 2H, CH2), 4.43–4.45 (q, 1H, CH), 7.30–7.32 (m, 4H, Ar–CH), 7.78 (s, 1H, =CH), 11.61 (s, 1H, NH), 13.15 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 15.3, 29.8, 30.5, 56.8, 113.5, 114.6, 124.9, 127.7, 128.6, 136.9, 152.2, 158.5, 162.4, 167.3, 174.7.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-4-methylpentanoic acid (6f)

Yellow solid. Yield: 94 %, mp 187–189 ºC; ES-MS m/z (%): 336.38, IR ν_{max}/cm^{-1}: 3397 (OH), 3217 (NH), 3011 (CH–Ar), 1736 (HO–C=O), 1695 (C=O), 1555 (C=C), 1583 (C=N), 1013 (C-S), 1091 (C–N). ^{1}H NMR (DMSO-d6): δ = 0.92–0.94 (d, 6H, CH–(CH_3)$_2$), 1.41–1.43 (m, 1H, CH),

1.71–1.73 (t, 2H, CH2), 4.44–4.46 (q, 1H, CH), 7.29–7.31 (m, 4H, Ar–CH), 7.76 (s, 1H, =CH), 11.72 (s, 1H, NH), 13.35 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 22.7, 24.4, 40.3, 55.4, 113.4, 114.4, 124.9, 129.2, 132.1, 135.4, 152.2, 159.1, 162.3, 167.1, 174.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-3-hydroxypropanoic acid (6g)

Yellow solid. Yield: 96 %, m.p. 185–187 ºC; ES-MS m/z (%): 310.30, IR ν_{max}/cm^{-1}: 3450 (OH), 3211 (NH), 3008 (CH–Ar), 1738 (HO–C=O), 1688 (C=O), 1551 (C=C), 1511 (C=N), 1019 (C-S), 1097 (C–N). ^{1}H NMR (DMSO-d_6): δ = 3.62 (s, 1H, CH), 4.02–4.04 (t, 1H, CH), 4.23–4.25 (d, 2H, CH_2), 7.31–7.33 (m, 4H, Ar–CH), 7.93 (s, 1H, =CH), 11.60 (s, 1H, NH), 13.13 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 59.2, 62.2, 113.4, 114.4, 124.9, 129.2, 130.3, 132.1, 136.4, 151.9, 158.1, 167.9, 172.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-3-mercaptopropanoic acid (6h)

Yellow solid. Yield: 94 %, mp 179–181 ºC; ES-MS m/z (%): 326.70, IR ν_{max}/cm^{-1}: 3455 (OH), 3201 (NH), 3017 (CH–Ar), 2500 (SH), 1738 (HO–C=O), 1695 (C=O), 1559 (C=C), 1503 (C=N), 1014 (C-S), 1095 (C–N). ^{1}H NMR (DMSO-d_6): δ = 1.50 (s, 1H, SH), 3.11–3.13 (d, 2H, CH_2), 4.13–4.15 (t, 1H, CH), 7.22–7.24 (m, 4H, Ar–CH), 7.68 (s, 1H, =CH), 11.61 (s, 1H, NH), 13.11 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 26.3, 60.4, 113.4, 114.4, 124.9, 127.5, 132.5, 135.6, 152.9, 158.3, 162.3, 167.2, 178.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)succinic acid (6i)

Yellow solid. Yield: 92 %, mp 214–216 ºC; ES-MS m/z (%): 338.40, IR ν_{max}/cm^{-1}: 3464 (OH), 3213 (NH), 3020 (CH–Ar), 1732 (HO–C=O), 1689 (C=O), 1549 (C=C), 1503 (C=N), 1030 (C-S), 1089 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.60–2.62 (d, 2H, CH_2), 3.71–3.73 (t, 1H, CH), 7.35–7.37 (m, 4H, Ar–CH), 7.88 (s, 1H, =CH), 11.70 (s, 1H, NH), 13.12 (s, 2H, COOH). ^{13}C NMR (DMSO-d_6): δ = 35.9, 53.3, 113.4, 114.4, 124.9, 130.1, 132.5, 135.6, 136.4, 152.9, 158.3, 162.3, 167.2, 178.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)-3-(1H-imidazol-4-yl)propanoic acid (6j)

Yellow solid. Yield: 94 %, m.p. 152–154 ºC; ES-MS m/z (%): 360.38, IR ν_{max}/cm^{-1}: 3435 (OH), 3215 (NH), 3011 (CH–Ar), 1739 (HO–C=O), 1681 (C=O), 1552 (C=C), 1508 (C=N), 1033 (C-S), 1092 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.92–3.94 (d, 2H, CH_2), 3.73–3.86 (t, 1H, CH), 7.31–7.33 (m, 4H, Ar–CH), 7.77 (s, 1H, =CH), 7.86 (s, 1H, =CH), 8.98 (s, 1H, =CH), 11.62 (s, 1H, NH), 13.12 (s, 1H, NH), 13.34 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 28.9, 58.3, 113.4, 114.4, 117.9, 124.9, 124.7, 124.7, 127.9, 128.6, 132.1, 136.2, 152.3, 158.2, 167.5, 176.2.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(4-hydroxyphenyl)propanoic acid (6k)

Yellow solid. Yield: 92 %, m.p. 212–214 ºC; ES-MS m/z (%): 386.44, IR ν_{max}/cm^{-1}: 3462 (O=C-OH), 3392 (OH), 3211 (NH), 2992 (CH–Ar), 1732 (HO–C=O), 1697 (C=O), 1553 (C=C), 1591 (C=N), 1011 (C-S), 1089 (C–N). ^{1}H NMR (DMSO-d_6): δ = 2.80–2.98 (d, 2H, CH2), 4.43–4.45 (t, 1H, CH), 5.30 (s, 1H, OH), 7.30–7.32 (m, 8H, Ar–CH), 7.87 (s, 1H, =CH), 11.72 (s, 1H, NH), 13.32 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 36.3, 58.6, 113.9, 114.7, 115.8, 127.7, 128.9, 129.2, 130.2, 135.3, 136.9, 152.2, 155.7, 158.5, 162.7, 167.8, 174.3.

(Z)-2-((5-(3-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-hydroxybutanoic acid (6l)

Yellow solid. Yield: 90 %, m.p. 173–175 ºC; ES-MS m/z (%): 324.56, IR ν_{max}/cm^{-1}: 3462 (OH), 3201 (NH), 3010 (CH–Ar), 1733 (HO–C=O), 1682 (C=O), 1534 (C=C), 1516 (C=N), 1042 (C-S), 1115 (C–N). ^{1}H NMR (DMSO-d6): δ = 1.10–1.12 (d, 3H, CH_3), 3.51–3.55 (d, 1H, CH), 3.63 (s, 1H, OH), 3.93–3.95 (m, 1H, CH), 7.25–7.27 (m, 4H, Ar–CH), 7.75 (s, 1H, =CH), 11.60 (s, 1H, NH), 13.10 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 19.6, 64.3, 66.5, 113.9, 114.7, 124.8, 130.3, 132.4, 136.1, 152.2, 158.3, 162.4, 167.8, 174.2.

Antimicrobial tests

The antimicrobial activity of compounds were tested against six bacteria; *Bacillus subtilis* (NCIM-2063), *Staphylococcus aureus* (NCIM-2901), *Escherichia coli* (NCIM-2256), *Enterococcus faecalis* (NCIM-5443), *Pseudomonas aeruginosa* (NCIM-2037), *Salmonella typhimurium* (NCIM-2501) and six fungal strains; *Aspergillus oryzae* (NCIM-570), *Penicillium chrysogenum* (NCIM-707), *Fusarium oxysporum* (NCIM-1282), *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196). The antibacterial activity of compounds was monitored by observing their Minimum inhibitory concentration (MIC, μg mL^{-1}) as previously mentioned[30] by broth dilution methods with Ciprofloxacin and Ampicillin as control drugs.

The antifungal study was carried by the standard agar dilution method and Fluconazole and Miconazole were used as control drugs. Ethanol was used as solvent control for both antibacterial and antifungal testing.

All the synthesized compounds were also tested for their general cytotoxicity on MCF-7 and BT-474 human breast cancer cell line. This test is performed as previously mentioned MTT colorimetric assay.[31] Cytotoxicity of the compounds was determined by calculating their IC_{50} values (μM mL^{-1}), the concentration of compound required to inhibit 50 % of cell growth compared to untreated control cells. The results are given as percentage cytotoxicity after 24 h. Adriamycin was used as positive control for the comparison of cytotoxicity of synthesized compounds. Assays were performed in triplicate on three independent experiments.

RESULT AND DISCUSSION

Several new (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted organic acid derivatives (**6a-l**) were synthesized and characterized by ^{1}H and ^{13}C NMR, IR spectroscopy.

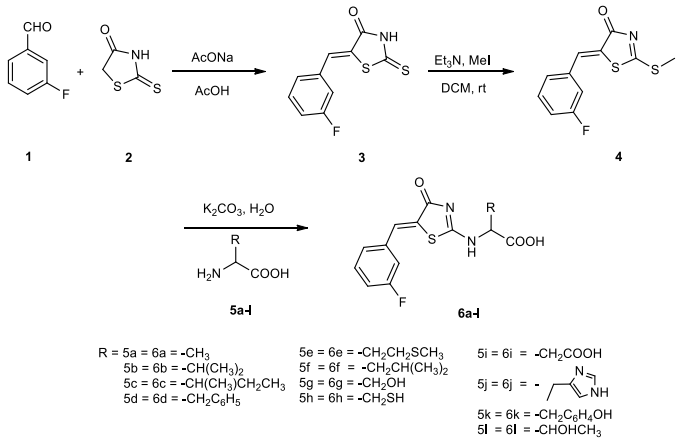
A new protocol for the synthesis of (Z)-5-(3-fluorobenzylidene)-2-thioxothiazolidin-4-one (**3**) by the condensation of 2-thioxothiazolidin-4-one and 3-fluorobenzaldehyde as the initial step of the reaction route has been developed.

Table 1. Physical data of the synthesized compounds **3**, **4** and **6a-l**[a]

Comp.	Substituent (R)	Time, min	Yield, %[b]	M.P., °C
3	-	240	90	198-200
4	-	120	92	160-162
6a	$-CH_3$	35	92	189-191
6b	$-CH(CH_3)_2$	30	94	204-206
6c	$-CH(CH_3)CH_2CH_3$	35	92	165-167
6d	$-CH_2C_6H_5$	35	90	138-140
6e	$-CH_2CH_2SCH_3$	40	92	142-144
6f	$-CH_2CH(CH_3)_2$	55	94	187-189
6g	$-CH_2OH$	50	96	185-187
6h	$-CH_2SH$	40	94	179-181
6i	$-CH_2COOH$	50	92	214-216
6j	3-(1H-imidazol-4yl)	35	94	152-154
6k	$-CH_2C_6H_4OH$	45	92	212-214
6l	$-CHOHCH_3$	35	90	173-175

[a]Reaction condition (**6a-l**): Compound (**4**) (1 mmol), amino acids (**5a-l**) (1.5 mmol), K_2CO_3 (1.5 mmol), 1 ml water at room temperature.[b]Isolated yields

The compound (**3**) was then subjected to a Knoevenagel condensation with the appropriate 2-thioxothiazolidin-4-one, to synthesize a new series of target compounds (**6a-l**).



Scheme 1 Synthesis of (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid (**6a-l**).

The structures of the desired compounds were confirmed by IR, ^{1}H NMR and ^{13}C NMR. The compound **3** was prepared in prominent good yields via a Knoevenagel condensation between the corresponding heterocyclic cores of Rhodanine and 3-fluorobenzaldehyde (Scheme 1).

The 2-thioxothiazolidin-4-one based compounds were synthesized by conventional heating with sodium acetate, which acts as a base and glacial acetic acid as catalysts. In theory, of E and Z geometrical isomers may exist according to the configuration around the exocyclic double bond (CH=C) for (Z)-5-(3-fluorobenzylidene)-2-thioxothiazolidin-4-one (**3**).

The ^{1}H NMR spectrum of the compound **3** shows only one signal for the methine proton in the range δ 7.66, which show the presence of one isomer only, and at lower field values than those expected for the E-isomers, which was strongly indicated that the compounds have the Z-configuration. The IR spectrum of compound **3**, showed a strong absorption band at 1702 cm^{-1} that is due to a carbonyl group. The mass spectrum revealed a molecular ion peak at m/z=239.29 corresponding to a molecular formula $C_{10}H_6FNOS_2$. The latter has been reported as thermodynamically more stable than the E-configuration.[32,33]

Compound **4** was synthesized from compound **3** and the structures of the desired product were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The IR spectrum of (Z)-5-(3-fluorobenzylidene)-2-(methylthio)-thiazol-4(5H)-one (**4**), showed a strong absorption band at 1704 cm^{-1} belongs to a carbonyl group. The mass spectrum revealed a molecular ion peak at m/z = 253.05 corresponding to a molecular formula $C_{11}H_8FNOS_2$. The ^{1}H NMR spectra of the compound **4** show only one signal for the methine proton in the range δ 7.82, sulfur attached methyl group proton shows a singlet at δ 2.85.

We synthesized a series of new (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted carboxylic acids (**6a-l**) from the compound **4** and different types of amino acids (**5a-l**), (Scheme 1, Table 1). The displacement of a methylthio group by various amino acids from the C2 position of the thiazolone ring and the structures of the desired compounds (**6a-l**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR analysis.

The IR spectrum of (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-amino)propanoic acid (**6a**), showed a strong absorption band at 1742 cm^{-1} belongs to the carbonyl of a carboxylic group and 3397 cm^{-1} due to the presence hydroxyl group. The mass spectrum revealed a molecular ion peak at m/z=294.28 corresponding to a molecular formula $C_{13}H_{11}FN_2O_3S$. The ^{1}H NMR spectrum revealed that the signals of **6a** (as a representative example), show the methyl group protons doublet in the range of δ 1.40–1.50, the methine proton (adjacent to carboxylic acid group) shows a quartet in the range of δ 4.50–4.70, phenyl ring protons show a multiplet in the range of δ 7.40–7.70, one signal appears for the alkene proton in the range δ 7.72, amine group proton shows singlet at δ 10.10, and the carboxylic acid proton shows singlet at δ 12.65.

Table 2. Antibacterial activity of synthesized compounds **3**, **4** and **6a-6l**

Compound		*B.s.*	*S.a.*	*E.c.*	*E.f.*	*P.a.*	*S.t.*
3	MIC	35.70	35.57	10.37	34.70	30.90	30.95
	MBC	55.13	56.15	36.40	46.14	33.76	34.75
4	MIC	31.70	31.50	31.39	35.13	35.30	33.90
	MBC	45.13	45.17	45.40	45.12	55.73	31.75
6a	MIC	36.14	36.12	33.17	34.16	28.35	28.35
	MBC	44.55	44.56	44.53	47.54	37.16	32.18
6b	MIC	7.10	13.10	48.40	48.10	52.13	52.15
	MBC	18.20	23.30	69..40	63.10	52.20	51.90
6c	MIC	55.70	56.57	56.37	33.70	33.90	6.85
	MBC	58.14	58.16	48.40	58.10	38.76	19.85
6d	MIC	33.70	33.50	32.39	35.10	25.30	37.90
	MBC	48.15	47.10	47.40	47.10	58.60	32.70
6e	MIC	9.50	8.75	30.10	34.10	28.50	27.30
	MBC	32.10	32.10	48.50	48.50	32.70	33.10
6f	MIC	7.45	8.78	48.40	48.10	52.13	52.15
	MBC	16.20	20.30	59..40	60.10	55.20	56.90
6g	MIC	38.70	38.57	19.37	38.70	32.90	6.95
	MBC	54.13	55.15	35.40	58.10	37.76	18.75
6h	MIC	33.70	33.50	33.39	35.10	26.30	36.90
	MBC	47.10	47.15	47.47	48.10	58.60	32.70
6i	MIC	9.50	8.10	30.10	34.10	28.50	27.30
	MBC	34.10	34.10	48.50	45.50	35.70	33.10
6j	MIC	7.10	8.50	38.40	38.10	42.13	51.15
	MBC	16.20	20.30	59..40	60.10	55.20	56.90
6k	MIC	38.70	38.57	18.37	39.70	33.90	8.95
	MBC	59.13	54.15	36.40	36.10	36.76	16.75
6l	MIC	37.10	38.10	39.40	36.10	32.13	32.15
	MBC	44.20	42.30	58..40	63.10	55.20	56.90
Ciprofloxacin	MIC	14.70	13.69	12.69	15.69	11.69	15.69
	MBC	33.19	33.10	22.10	32.10	14.10	34.10
Ampicillin	MIC	3.71	3.20	3.20	3.20	3.86	3.46
	MBC	5.29	5.43	1.43	1.43	2.71	1.86

[a]Values are the average of three readings. MIC= minimal inhibitory concentration, in mg L^{-1}, MBC = 1.43-5.43 in mg L^{-1}. B.s.- *Bacillus subtilis* (NCIM-2063), S.a.-*Staphylococcus aureus* (NCIM-2901), E.c.- *Escherichia coli* (NCIM-2256), E.f. - *Enterococcus faecalis* (NCIM-5443), P.a.- *Pseudomonas aeruginosa* (NCIM-2037), S.t.- *Salmonella typhimurium* (NCIM-2501)

The antimicrobial activities of the synthesized compounds against selected Gram-positive and Gram-negative bacteria and multidrug-resistant bacteria are illustrated in Table 2 and Table 3. The majority of the synthesized compounds show a variety of antibacterial, antifungal and cytotoxic activity. The compounds **3** was found to be the most active against *E. coli* and the compounds **6c**, **6g** and **6k** were found to be active against *S. typhimurium*.

Some of the studied compounds are more potent against selected microorganisms than a standard antibacterial drug Ciprofloxacin. For example, against *E. Coli* the compound **3** while against *B. subtilis* the compounds **6b**, **6e**, **6f**, and **6j** have better MIC values than the values found for Ciprofloxacin. Against *S. aureus*, the compounds **6b**, **6e**, **6f,6i** and **6j** proved to be more active than Ciprofloxacin.

The compounds **6g** and **6k** showed antifungal activity against four fungus strains, namely *A. oryzae*, *P. chrysogenum*, *C. albicans* and *A. flavus*. The compound **6a** showed activity against *A. flavus*, the compound **6c** against *P. Chrysogenum* and *F. oxysporum* while the compound **6e** was found to be active against *P. chrysogenum*. Remaining compounds of the series (**3**, **4**, **6d**, **6f**, **6h**, **6i**, **6j** and **6l** were found to be inactive against fungi.

All the synthesized compounds were tested for their cytotoxic activity against MCF-7 and BT-474 cell lines (Table 4). (Table 4). Three compounds, **6g**, **6i** and **6l** showed good activity against the studied cancer cell lines, the IC_{50} values against MFC-7 and BT-474 cell lines were found to be 1.4 and 1.3, 1.5 and 0.6, or 1.1 and 1.4 μM mL^{-1}, respectively. The IC_{50} values for reference drug Adriamycin against MFC-7 and BT-474 cells were found to be 0.9 and 0.5 μM mL^{-1}, respectively. The cytotoxicity of the newly synthesized thiazolones depends on the type of substituents on thiazolone moiety. The compounds containing hydroxyl groups attached to the amino acid parts linked to the thiazolone ring have the highest cytotoxic activity. The presence of electron releasing alkyl chain, methyl-1H-imidazole ring or thiol group on the amino acid attached to the thiazolone rings resulted in the loss of activity.

Table 3. Antifungal activity of synthesizing compounds **3**, **4** and **6a-l**

Compound		*A.o.*	*P.c.*	*F.o.*	*C.a.*	*A.f.*	*A.n.*
3	MIC	32.50	52.39	34.50	34.50	18.30	18.30
	MFC	53.10	53.10	74.12	54.10	35.20	75.33
4	MIC	37.00	37.20	33.20	33.20	33.20	30.00
	MFC	36.20	46.60	81.10	42.30	34.88	35.00
6a	MIC	31.50	31.39	31.50	34.50	12.30	19.30
	MFC	46.10	46.10	62.12	32.10	33.20	41.33
6b	MIC	33.00	31.20	31.20	32.20	32.20	34.00
	MFC	43.20	44.50	45.10	66.30	33.88	48.00
6c	MIC	35.50	17.39	17.50	57.50	36.30	39.30
	MFC	49.40	34.40	34.32	36.30	34.30	35.33
6d	MIC	32.30	35.40	32.30	57.50	67.50	34.50
	MFC	42.30	52.20	84.10	52.00	72.30	51.50
6e	MIC	36.30	13.80	51.20	31.25	44.25	30.55
	MFC	36.80	34.70	65.18	60.18	30.64	45.69
6f	MIC	34.00	34.20	34.20	55.20	34.70	31.00
	MFC	43.20	44.60	49.10	65.35	35.88	48.00
6g	MIC	5.55	16.36	39.50	18.50	16.30	36.30
	MFC	10.10	44.10	32.11	35.10	32.22	32.23
6h	MIC	32.00	32.50	34.40	68.40	58.10	34.40
	MFC	51.34	52.25	84.15	72.05	33.30	54.50
6i	MIC	42.35	55.80	41.26	31.26	74.26	35.58
	MFC	55.80	35.78	62.38	62.38	32.84	43.29
6j	MIC	43.40	34.24	54.26	34.66	34.26	33.07
	MFC	53.25	42.65	43.15	64.48	33.89	58.08
6k	MIC	34.55	17.30	16.50	16.50	16.30	33.30
	MFC	45.10	33.75	53.52	32.10	34.20	35.33
6l	MIC	42.00	32.60	62.50	59.50	58.70	34.00
	MFC	58.30	55.20	64.10	62.50	62.30	51.50
Fluconazole	MIC	5.60	1.68	28.65	5.70	9.42	2.28
	MFC	9.35	5.75	46.00	9.62	17.80	5.75
Miconazole	MIC	40.25	5.30	7.18	1.34	43.20	156.30
	MFC	85.18	151.28	20.20	6.18	142.20	140.12

[a]Values are the average of three readings. A.o.- Aspergillus oryzae (NCIM-570), P.c.- Penicillium chrysogenum (NCIM-707), F.o.- Fusarium oxysporum (NCIM-1282), C.a.- Candida albicans (NCIM-3471), A.f.- Aspergillus flavus (NCIM-539) and A.n.- Aspergillus Niger (NCIM-1196).

Structure-activity relationship (SAR)

The results of the antimicrobial screening demonstrated some facts about the structural-activity relationship (SAR) of the synthesized thiazolone derivatives. The notable highlights of structure-activity relationship are the followings:

The biological activity profile of molecules is strongly affected by the branching pattern and chain length of alkyl moieties. Attachment of a methyl group at C2 position on the thiazolone moiety (**6a**) makes molecule active against bacterial and fungal strains, probably due to its small size and electron donating effects. When this methyl group is replaced by isopropyl (**6b**) and 2-methylbutyl (**6c**) groups, the molecules become active on a broader spectrum (against the majority of the studied strains). This shows that the presence of branching at the carbon located on the C2 position of the thiazolone ring has a positive effect on appearing or strengthening of antimicrobial activity. Attachment of 2-methylpropyl group (**6f**) at the same position makes the molecule to be specific towards the *B. subtilis* and ***S. aureus***. Substitution of the alkane chain with a carboxylic group (**6i**), also resulted in specificity towards *B. subtilis* and *S. aureus.*

Table 4. In vitro cytotoxicity of compounds towards the MCF-7 and BT-474 cells, after 24 h.

Sr. No.	Compounds	IC_{50},[a] µM[b]	
		MCF-7[c]	BT-474[d]
1	**3**	38.6	53.4
2	**4**	54.8	25.0
3	**6a**	44.9	43.4
4	**6b**	46.2	62.2
5	**6c**	56.3	56.6
6	**6d**	82.4	48.6
7	**6e**	76.5	48.6
8	**6f**	82.4	56.8
9	**6g**	1.4	0.6
10	**6h**	72.2	77.1
11	**6i**	1.3	1.1
12	**6j**	78.7	74.5
13	**6k**	10.1	10.0
14	**6l**	1.5	1.4
	Adriamycin	0.9	0.5

[a]GI_{50}(Growth inhibition of 50 %): Concentration of drug that decreases the growth of the cells by 50 % compared to a non-treated control cell. [b]Values are the average of three readings; [c]MCF-7: Human Breast cancer cell line, [d]BT-474: Human Breast cancer cell line; e-Adriamycin: positive control compound

Substitution by phenylmethyl group (**6d**) at the C2 position of the thiazolone moiety gave completely inactive molecule towards all tested strains, while the 4-hydroxyphenyl (**6k**) substitution made the molecule to be active towards *S. typhimurium*, and *P. chrysogenum, F. oxysporum, C. Albicans* and *A. flavus*. The compound (**6j**) containing methyl-imidazole ring at the C2 position of the thiazolone moiety resulted in appearing of specific activity towards the Gram-positive bacteria *B. subtilis* and *S. aureus*. The compound (**6e**) with the terminal methylthio group is active toward.*B. subtilis, S. aureus* and *P. chrysogenum*, while compound (**6h**) with terminal mercapto group was proved to be inactive towards these bacterial and fungal strains.

CONCLUSION

The objective of our present study is to synthesize and investigation of the potent anticancer and antimicrobial activities of some new (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted organic acids.

This is the first reported synthesis of the (Z)-2-((5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted organic acids in water as solvent with excellent yields in shorter reaction time making the process economically lucrative for industrial application. Some derivatives were found to be more active against several bacteria and fungi strains than the common antimicrobial agents.

In vitro anticancer studies revealed that the compounds **6g**, **6i**, **6k** and **6l** are most active against MCF-7 and BT-474 human breast cancer cell lines.

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