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Synthesis, Antibacterial and Cytotoxic Activities of New Thiazole Based Pyrrolidine Derivatives

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Abstract: In this study, some thiazole-based pyrrolidine derivatives were synthesized, characterized by FT-IR and ^{1}H NMR spectroscopic techniques, and evaluated as potential antibacterial agents. Their antibacterial activities were evaluated by broth microdilution method and expressed as minimum inhibitory concentration; against *Escherichia coli*, *Salmonella typhimurium*, *Bacillus cereus*, and *Staphylococcus aureus*. Cytotoxicity studies of synthesized compounds were also conducted to minimize the toxic effects on healthy mammalian cells. From synthesized compounds, 4-F-phenyl derivative compound (11) has been found to inhibit Gram-positive bacteria with minimum toxicity selectively.

Keywords: thiazole; pyrrolidine; antibacterial activity; cytotoxicity.

1. Introduction

Although existing for centuries, infectious diseases are still a severe human health problem [1]. Among organisms that cause infectious diseases, bacteria has become one of the most challenging issues in the treatment because the widespread application of antibiotics has caused multidrug-resistant bacteria [2-3]. This drives researchers around the World to work on discovering or develop new and different potent antibacterial compounds. While developing new compounds, besides the antibacterial activity, the toxicity towards healthy mammalian cells is a key factor [4]. Despite all tremendous studies about this area, humans suffer from a lack of effective and safe medicines [5].

Thiazole is part of a class of five-membered heterocyclic compounds with a sulfur and nitrogen atom and has been the subject of many different research types to date [6]. Thiazole derivatives can be seen in nature as thiamine (vitamin-B_1), penicillin, and luciferin [7]. It has been reported many times in the literature that thiazole and its derivatives possess a broad range of biological activities [8], such as antibacterial, anticancer9, antifungal [10], anti-inflammatory [11], anti-tubercular [12], antioxidant [13] activities. In addition to these, pyrrolidine is also a five-membered heterocyclic compound present in alkaloids such as

nicotine [14] and hygrine [15]. Pyrrolidine derivatives have a variety of biological activities such as antimicrobial [16], anti-HIV [17], anticancer [18], and many more [19].

Keeping these facts in mind, we decided to combine two heterocyclic compounds for antibacterial activity. We synthesized some thiazole derivatives and combined them with pyrrolidine derivatives. After characterizing their structure with FT-IR and 1H NMR techniques, their antibacterial activity was evaluated against Staphylococcus aureus, Bacillus cereus, Salmonella typhimurium, and Escherichia coli. Also, cytotoxicity studies were also conducted with L929 cells to minimize the toxic effects on healthy cells.

2. Materials and Methods

2.1. Synthesis.

Unless otherwise noted, chemicals were obtained from global suppliers (Merck or Aldrich) and were used without further purification. Solvents were of HPLC or analytical grade, and they were dried with molecular sieves (3 Å). All melting points were determined with EZ-Melt Automated Melting Point Apparatus. FT-IR spectra were recorded on Thermo Nicolet İS5. ^{1}H NMR spectra were measured on a Varian 400 MHz in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as δ ppm.

2.1.1. General procedure for the synthesis of 1,3-thiazole derivatives.

In a 50 ml single necked flask, 0,005 mol phenacylbromide and 0,02 mol sodium acetate were added to the solution of 0,005 mol thiosemicarbazide in 10 mL ethanol. The reaction mixture was heated under reflux for 6 h, concentrated, and left to cool. The solid was filtered and recrystallized using appropriate solvent mixtures.

4- (4-bromophenyl) -2-hydrazinylthiazole (1).

$CHCl_3$/Hexane; Yellow powder; Yield 68%; m.p.: 117-119 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,45 (s, 1H, NH); 8,80 (s, 2H, NH_2); 7,60-7,85 (m, 4H, Ar–H); 7,10 (s, 1H, CH thiazole). FT-IR: 3310 (-NH_2), 3256 (-NH), 1606 (-C=N), 1537, 1471, 1317, 1200, 1070, 903. 814.

4- (4-chlorophenyl) -2-hydrazinylthiazole (2).

$CHCl_3$/Hexane; Yellow powder; Yield 70%; m.p.: 120-122 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,40 (s, 1H, NH); 8,85 (s, 2H, NH_2); 7,50-7,80 (m, 4H, Ar–H); 7,20 (s, 1H, CH thiazole). FT-IR: 3307 (-NH_2), 3255 (-NH), 1608 (-C=N), 1539, 1476, 1417, 1321, 1175, 1113, 969.

2-hydrazinyl-4- (3-nitrophenyl) thiazole (3).

Ethanol; Orange powder; Yield 65%; m.p.: 138-140 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,50 (s, 1H, NH); 8,75 (s, 2H, NH_2); 7,60-7,90 (m, 4H, Ar–H); 7,15 (s, 1H, CH thiazole). FT-IR: 3365 (-NH_2), 3165 (-NH), 1615 (-C=N),1575, 1511, 1405, 1337, 1259, 1120, 935.

2-hydrazinyl-4- (4-nitrophenyl) thiazole (4).

Ethanol; Orange powder; Yield 70%; m.p.: 143-145 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,45 (s, 1H, NH); 8,70 (s, 2H, NH_2); 7,55-8,15 (m, 4H, Ar–H); 7,25 (s, 1H, CH thiazole). FT-IR: 3353 (-NH_2), 3236 (-NH), 1627 (-C=N), 1595, 1558, 1410, 1331, 1106, 959.

4- (4-fluorophenyl) -2-hydrazinylthiazole (5).

Ethanol; Red-brown powder; Yield 60%; m.p.: 116-118 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,40 (s, 1H, NH); 8,85 (s, 2H, NH_2); 7,65-8,10 (m, 4H, Ar–H); 7,15 (s, 1H, CH thiazole). FT-IR: 3338 (-NH_2), 3207 (-NH), 1630 (-C=N), 1599, 1531, 1489, 1407, 1280, 1116, 917.

3- (2-hydrazinylthiazol-4-yl) -2H-chromen-2-one (6).

Ethanol; Brown powder; Yield 75%; m.p.: 178-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,50 (s, 1H, NH); 8,70 (s, 2H, NH_2); 7,60-7,90 (m, 4H, Ar–H); 7,20 (s, 1H, CH thiazole). FT-IR: 3340 (-NH_2), 3236 (-NH), 1604 (-C=N), 1560, 1485, 1433, 1376, 1150, 927.

2.1.2. General procedure for the synthesis of pyrrolidine derivatives of 1,3-thiazoles.

1,3-thiazole derivative (0.05 mol) and L-(+)-tartaric acid (0.05 mol) were refluxed in xylene for 8 hours with a Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature, and the resulting crystalline product was filtered off. After washing the crude product with hexane several times, it was recrystallized with ethanol solvent.

(3S-4S) -1 - ((4- (4-bromophenyl) thiazol-2-yl) amino) -3,4-dihydroxypyrrolidine-2,5-dione (7).

Light yellow powder; Yield 62%; m.p.: 188-190 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,40 (s, 1H, NH), 7,60-8,30 (m, 4H, Ar–H), 7,25 (s, 1H, CH thiazole), 6,30 (br,2H, OH), 5,00 (d, 2H, CH). FT-IR: 3234 (-OH), 3150 (-NH), 2965, 1667 (-C=O), 1552, 1474, 1397, 1262, 1200, 1132, 1071, 833.

(3S-4S) -1 - ((4- (4-chlorophenyl) thiazol-2-yl) amino) -3,4-dihydroxypyrrolidine-2,5-dione (8).

Light yellow powder; Yield 63%; m.p.: 196-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,30 (s, 1H, NH), 7,55-8,30 (m, 4H, Ar–H), 7,20 (s, 1H, CH thiazole), 6,28 (br,2H, OH), 5,10 (d, 2H, CH). FT-IR: 3235 (-OH), 3148 (-NH), 2967, 1666 (-C=O), 1550, 1403, 1352, 1260, 1076, 865.

(3S-4S) -3,4-dihydroxy-1 - ((4- (3-nitrophenyl) thiazol-2-yl) amino) -pyrrolidine-2,5-dione (9).

Yellow powder; Yield 58%; m.p.: 201-203 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,45 (s, 1H, NH), 7,50-8,30 (m, 4H, Ar–H), 7,25 (s, 1H, CH thiazole), 6,36 (br,2H, OH), 5,20 (d, 2H, CH). FT-IR: 3324 (-OH), 3120 (-NH), 1730 (-C=O), 1555, 1412, 1343, 1260, 1082, 876.

(3S-4S) -3,4-dihydroxy-1 - ((4- (4-nitrophenyl) thiazol-2-yl) amino) -pyrrolidine-2,5-dione (10).

Yellow powder; Yield 60%; m.p.: 207-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,50 (s, 1H, NH); 7,60-8,30 (m, 4H, Ar–H); 7,40 (s, 1H, CH thiazole); 6,35 (br,2H, OH); 5,30 (d, 2H, CH). FT-IR: 3320 (-OH), 3115 (-NH), 1732 (-C=O), 1597, 1564, 1507, 1333, 1284, 1108, 851.

(3S-4S) -1 - ((4- (4-fluorophenyl) thiazol-2-yl) amino) -3,4-dihydroxyprolidine-2,5-dione (11).

Light yellow powder; Yield 63%; m.p.: 193-195 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,55 (s, 1H, NH); 7,65-8,35 (m, 4H, Ar–H); 7,23 (s, 1H, CH thiazole); 6,26 (br,2H, OH); 5,05 (d, 2H, CH). FT-IR: 3323 (-OH), 3234 (-NH), 2870, 1674 (-C=O), 1508, 1417. 1223. 1169, 993.

(3S,4S)-3,4-dihydroxy-1-((4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)pyrrolidine-2,5-dione (12).

Brown powder, Yield 66%; m.p.: 211-213 °C. 1H NMR (400 MHz, DMSO-d_6, 25 ºC), (δ: ppm): 10,45 (s, 1H, NH); 7,55-8,35 (m, 4H, Ar–H); 7,42 (s, 1H, coumarin); 7,20 (s, 1H, CH thiazole); 6,26 (br,2H, OH); 5,15 (d, 2H, CH). FT-IR: 3252 (-OH), 3236 (-NH), 1753 (-C=O ester), 1706 (-C=O), 1567, 1487, 1452, 1258, 1010, 926.

2.2. Antibacterial activity.

Antibacterial activity of synthesized samples was evaluated by the agar well diffusion method [20]. Both gram-positive *Bacillus cereus* (ATCC 11778) and *Staphylococcus aureus* (ATCC 25923), and gram-negative *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028) bacteria were used in the study. Lyophilized cultures of bacteria were obtained from Microbiologics Inc. (Saint Cloud, MN, USA). Then, stock cultures of bacteria were prepared in Nutrient Broth containing 20% glycerol and stored at -18°C.

Each microorganism's stock cultures were incubated on Nutrient agar, and then were transferred to tubes containing Mueller Hinton Broth medium and left for 18-24 hours incubation at 37 °C. Then, the bacterial suspensions were adjusted to 0.5 McFarland turbidity representing approximately 1.5 x 108 colony forming units (CFU / mL). McFarland Standards were prepared by using 1% H_2SO_4 and 1.175% $BaCl_2.2H_2O$ stock solutions. The inoculum was spread on Mueller Hinton Agar plates and air-dried at room temperature. A well of approximately 7 mm diameter was created on the Muller-Hinton Agar plate with the aid of a gel piercing tool. Dimethyl sulfoxide (DMSO) was used to prepare stock solutions of the samples. Furthermore, 50 µL aliquots of the compounds with 160 and 400 µg concentrations were added to the wells and the substance. Then the diameters of the inhibition zones (mm) around the wells were measured at the end of the 24-hour incubation at 35 ° C. Antibacterial activity of the compounds was determined in comparison to gentamicin (Oxoid, 10 µg/sensidisc antibiotic disc, and the experiments were repeated three times.

2.3. Cytotoxicity assay.

L929 cells were used for cytotoxicity experiments. Cells were cultured in T25 flasks with DMEM/F12 medium supplemented with Fetal Bovine Serum 10% (FBS) and PEST (0.5% from 10,000 unit/mL Penicillin − 10 mg/mL Streptomycin) and incubated at 37°C. After the culture became confluent, the medium was poured, and 400 µl of the trypsin-EDTA enzyme was added. Then cells were incubated at 37°C for 5 minutes. After incubation, 5 ml of medium was added, and the cells were centrifuged at 1000 rpm for 5 minutes. Cell number was counted via hemocytometer before experiments.

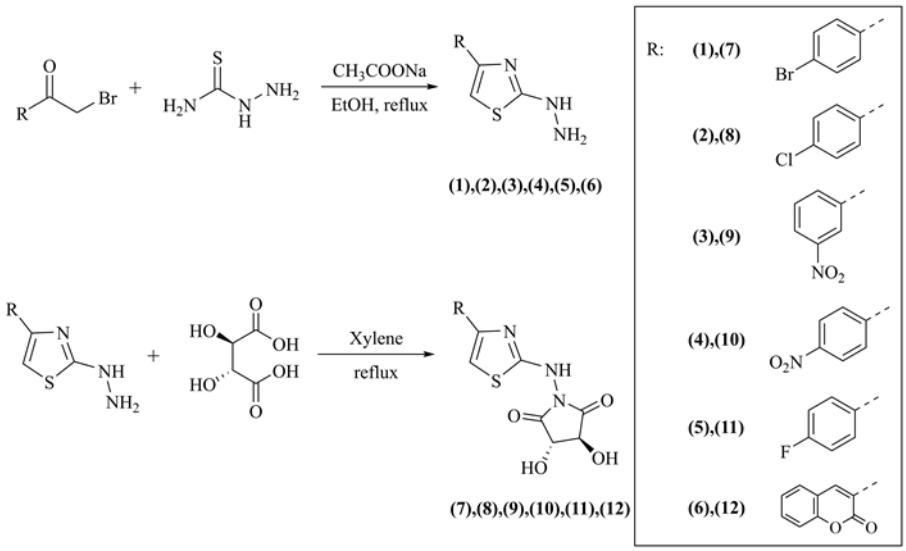
The toxic effect of compounds on L929 cells was determined by the 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2 H-tetrazolium-5-carboxanilide (XTT) method [21]. XTT is a method that measures metabolic activity. The results obtained in the form of absorbance are directly proportional to cell viability. L929 cells with a concentration of 104 cells/well were seeded in sterile flat-bottom 96-well plates. After 24 hours of incubation at 37°C, the media was removed, and a fresh medium containing different concentrations of compounds (0.125, 0.25, 0.5, 1, 2 mg/mL) was added to the cells. Cells were exposed to the substances for 24 hours. Then the medium was replaced with 100 µL of 0.5 mg/ mL XTT solution (supplemented with 7.5 µg/mL phenazine methosulfate) in fresh medium. Cells were incubated for 4 h at 37

°C in 5% CO_2 incubator, and optical density was measured at 450 nm (Lab-Line multiplate reader).

3. Results and Discussion

3.1. Chemistry.

Synthesis studies began with the preparation of 1,3-thiazoles via condensation of thiosemicarbazide with acetophenone derivatives as described in the literature [22]. After recrystallization of thiazole derivatives, compounds (1)-(6) obtained. Pyrrolidine derivatives of synthesized thiazole compounds were prepared via their reaction with L-(+)-tartaric acid[23]. Several times, washing of crude product with hexane gave Pyrrolidine derivatives (7)-(12) in moderate yields. The synthetic procedures adopted to obtain the target compounds are given in Scheme 1. The conversion of acetophenone derivatives to thiazoles was depicted in FT-IR spectra by the disappearance of strong carbonyl stretching vibrations around 1700cm^{-1}. The bands for -NH_2 stretching and C=N stretching were observed around 3365-3310cm^{-1} and 1630-1604cm^{-1} regions, respectively. Pyrrolidine derivatives were characterized by 1753-1666 cm-1 bands that indicate C=O groups that come from tartaric acid. The ^{1}H NMR spectra of all compounds displayed singlet signals between δ 7.25 and 7.10 ppm assignable to the C-H proton of the thiazole ring as expected. The successful ring closure of thiazole derivatives to pyrrolidine was confirmed with the absence of δ 8,80-8,70 -NH_2 singlet. All compounds showed singlet signals between δ 10.50–10.30 ppm, which correspond to -NH proton near thiazole ring.



Scheme 1. Synthesis of compounds (1)-(12).

3.2. Antibacterial activity.

Table 1. Inhibition zones (diameter) in mm of the compounds against tested bacterial strains.

Compounds	Microorganisms			
	E. coli	***S. typhimurium***	***B. cereus***	***S. aureus***
(11) 160 ug	–	–	8.97 ± 0.31	–
(11) 400 µg	–	–	21.70 ± 0.36	30.53 ± 0.42
Gentamicin 10ug	21.57 ± 0.32	24.53 ± 0.35	22.65 ± 0.21	22.17 ± 0.47

[1] The individual data points were expressed in the form of mean ± standard deviation (mean ± SD).
– Denotes no antibacterial activity.

In vitro susceptibilities of selected microorganisms against the compounds were determined by the agar well diffusion method and given in Figure 1. The diameter of the inhibition zone (mm) formed by the compounds as shown in Table 1. The results revealed that the compound (11) exhibited antibacterial activity against *S. aureus* and *B. cereus* but did not develop a zone of inhibition against the Gram-negative bacteria *E. coli* and *S. typhimurium*. Herein the compound (11) at 400 µg concentrations exhibited an inhibition value of 30.53 ± 0.42 and 21.70 ± 0.36 mm against *S. aureus* and *B. cereus*, respectively. The compound (11) at 160 µg concentration showed an inhibition zone with 8.97 ± 0.31 mm against *B. cereus*. On the other hand, other samples did not show any antibacterial activity.

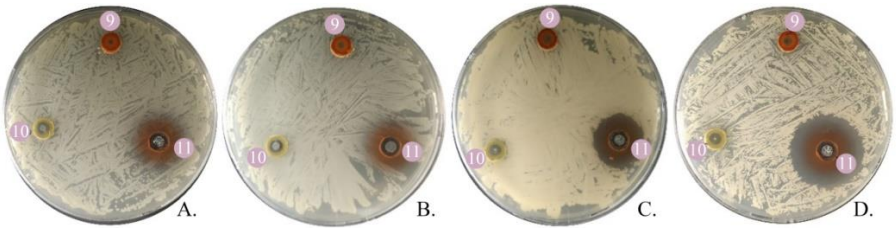


Figure 1. *In vitro* agar well diffusion studies of compounds (9), (10), (11) against A.) *E. coli*, B) *S. typhimurium*, C) *B. cereus*, D) *S. aureus*.

3.3. Cytotoxic activity.

Figure 2 shows the effects of different compounds on the viability of L929 cells. Absorbance values are directly proportional to increasing viability. As seen in the graph, the toxic effect increased with increasing concentrations of the compounds. There are no toxic effects observed at 0.125 and 0.25 mg/ml (7), (8). The concentration of 0.125 mg/ml, (11) and (12) did not show any toxicity. For other compounds and concentrations, there were proportionately reductions in viability at higher concentrations.

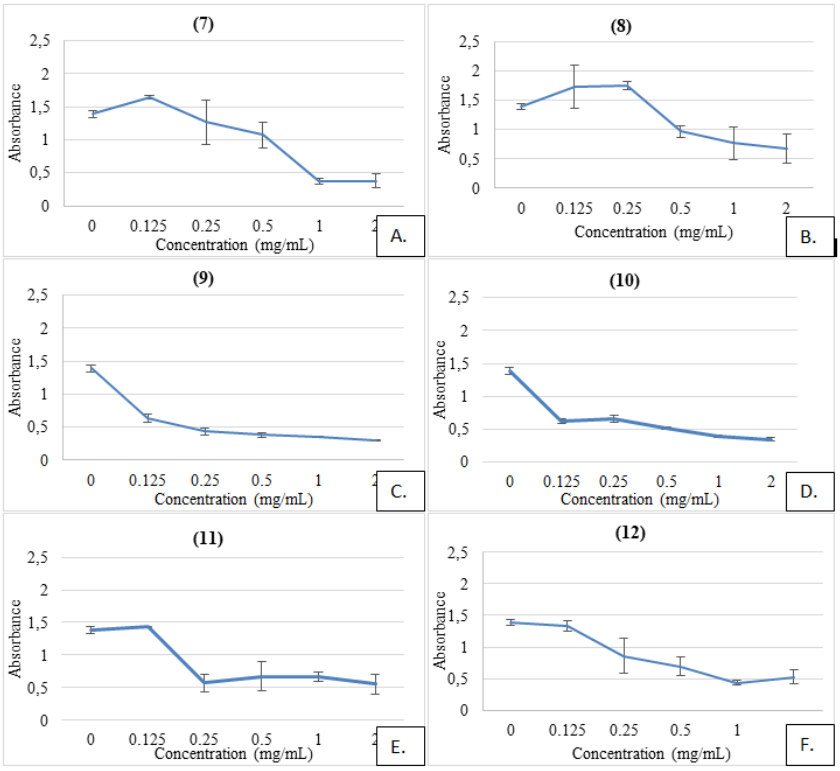


Figure 2. Viability of L929 cells exposed to A.) (7), B.) (8), C.) (9), D.) (10), E.) (11) and F.) (12) with different concentrations.

4. Conclusions

In conclusion, the present study's objective was to synthesize and investigate some thiazole-pyrrolidine derivatives' antibacterial and cytotoxic activities that can serve as promising antibacterial agents. We found that the compound (11) has antibacterial activity against only Gram-positive bacteria. This may be caused by bacteria's structural features, such as different cell wall structures of Gram-negative bacteria and Gram-positive bacteria. As we observed in our previous studies and known in the literature, the outer membrane of Gram-negative bacteria acts as a barrier. It provides for increased tolerance to antimicrobial compounds[24]. Besides, no toxicity effects were observed for compounds (7), (11) at given concentrations. The above results confirmed that combining thiazole and pyrrolidine derivatives as new antibacterial agents were appropriate. Therefore, synthesized compounds in this study will be subjected to further derivatizations for further antimicrobial evaluation.

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Conflicts of Interest

The authors declare no conflict of interest.

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