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Original article

Synthesis and Antimicrobial Activity of Some Piperazine Dithiocarbamate Derivatives

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Nine new dithiocarbamic acid ester derivatives, including thiazole moiety, were synthesized and investigated for their antimicrobial activity. The structures of the obtained final compounds (**6a-i**) were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The antimicrobial activity of the compounds was determined (**6a-i**) by using the microbroth dilution method. Antimicrobial activity results revealed that synthesized compounds exhibited moderate antimicrobial activity against to *E. faecalis* (ATCC 51922) and *P. aeruginosa* (ATCC 27853).

Key words: Thiazole, Dithiocarbamate, Antimicrobial activity

Bazı Piperazin Ditiyokarbamat Türevlerinin Sentezi ve Antimikrobiyal Aktiviteleri

Tiyazol halkası içeren dokuz yeni ditiyokarbamik asit esteri türevinin sentezi gerçekleştirilmiş ve antimikrobiyal aktiviteleri incelenmiştir. Sonuç bileşiklerinin (**6a-i**) yapıları spektral veriler (IR, , ^{1}H-NMR, ^{13}C-NMR ve MS) yardımıyla aydınlatılmıştır. Bileşiklerin (**6a-i**) antimikrobiyal aktiviteleri mikrobroth dilüsyon yöntemi kullanılarak belirlenmiştir. Antimikrobiyal aktivite sonuçlarına göre sentezlenen bileşiklerin *E. faecalis* (ATCC 51922) ve *P. aeruginosa* (ATCC 27853)'ya karşı orta düzeyde antimikrobiyal etkinlik gösterdiği tespit edilmiştir.

Anahtar kelimeler*:* Tiyazol, Ditiyokarbamat, Antimikrobiyal aktivite

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INTRODUCTION

From the past bacterial infection and, more recently fungal and viral infection have benefited from therapeutic substances of synthetic drugs in addition all causative micro-organism have revealed a remarkable ability to adapt themselves to survive by developing a great resistance to every synthetic agent administered. So antibacterial drug resistance is a clinically important and emerging subject especially in human medicines. For this reason the workers in pharmaceutical industry, pharmacists and even chemists must take a responsibility in order to overcome this problem by trying to synthesize new drugs with a little or even without any bacterial resistance (1-4). So a possible key for bacterial resistance is to design small heterocyclic molecules which are similar to biologically active compounds and provided a good pharmacophore of medicinally active agents (5, 6).

N-mono and N,N-di substituted dithiocarbamate derivatives show antibacterial, antiviral and antifungal activities (7-13). The structure-activity relationship study showed that the antibacterial activity on thiocarbonyl aromatic compounds was greatly affected by the lipophilicity, that is obtained by thiocarbonyl moiety, especially the calculated log P value and the balance between hydrophilic substituent and hydrophobic substituent on the aromatic

compounds. In addition, sulfur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. Penicillins containing a thiazole ringsystem (thiazolidine) (14) are also important naturally occurring products. In this respect it is not surprising for thiazoles and their deravatives to have many biological activities such as antibacterial and antifungal (15-20). Piperazine is a unique heterocyclic m constituent of several biologically active compounds. The polar nitrogen atoms in the piperazine ring considered bioactive molecule and enhance favorable interaction with macromolecules, piperazine residue containing compounds have been reported to have antibacterial activity (21-23). In our study we try to collect all these three components which are thiazole, dithiocarbamate and piperazine in one strong, bio labile and magic structure according to our expection or aspiration.

EXPERIMENTAL

Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO). All melting points (m.p.) were determined by Electrothermal 9100 digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: IR, Shimadzu 8400S spectrophotometer (Shimadzu, Tokyo, Japan); ^{1}H-NMR, Bruker DPX 500 NMR spectrometer (Bruker Bioscience, Billerica, MA, USA), ^{13}C-NMR Bruker DPX 125 NMR spectrometer (Bruker Bioscience, Billerica, MA, USA), in DMSO-d_6 using TMS as internal standard; M+1 peaks were determined by AB Sciex-3200 Q-TRAP LC/MS/MS system (AB Applied Biosystems Co., MA, USA).

General procedure for synthesis of compounds 2-[[4-(2-Methyl-4-thiazolyl)-phenyl]amino]-2-oxoethyl 4-substituted-piperazine-1-carbodithioate (6a-6i)

Compound **5** was stirred with appropriate sodium salts of dithiocarbamic acids (0.01 mol) in acetone for 3 h. The precipitated product was filtered and washed with water.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-(2-hydroxyethyl)piperazine-1-carbodithioate (6a)

Yield: %82; M.p. 157-158 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 3312 (amide N-H), 1679 (amide C=O), 1310-1018 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.44 (t, *J*=6.10 Hz, 4H, piperazine CH_2), 2.70 (s, 3H, CH_3), 3.53 (q, 2H, *J*: 8.55 Hz, $\underline{CH_2}OH$, 3.95 (brs, 2H, piperazine CH_2), 4.22 (brs, 2H, piperazine CH_2), 4.29 (s, 2H, CH_2S), 4.52 (t, *J*=5.20 Hz, 1H, OH), 7.66 (d, *J*=8.70 Hz, 2H, Ar-H), 7.79 (s, 1H, thiazole C_5-H), 7.88 (d, *J*=8.65 Hz, 2H, Ar-H), 10.39 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 39.87, 49.80, 52.51, 58.46, 59.46, 112.46, 119.14, 126.39, 129.39, 138.63, 153.52, 165.32, 165.36, 194.23. MS (ES+) : m/z 437.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-[2-(N,N-dimethylamino)ethyl] piperazine-1-carbodithioate (6b)

Yield: %78. M.p. 110-112 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 3289 (amide N-H), 1676 (amide C=O), 1352-1018 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.35 (t, 2H, *J*=6.67 Hz, CH_2), 2.43 (t, 2H, *J*=6.70 Hz, CH_2), 2.44 (t, *J*=6.20 Hz, 4H, piperazine CH_2), 2.71 (s, 3H, CH_3), 3.41 (s, 6H, $N(CH_3)_2$), 3.94 (brs, 2H, piperazine CH_2), 4.20 (brs, 2H, piperazine CH_2), 4.28 (s, 2H, CH_2S), 7.65 (d, *J*=8.65 Hz, 2H, Ar-H), 7.80 (s, 1H, thiazole C_5-H), 7.88 (d, 2H, *J*=8.65 Hz, Ar-H), 10.39 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 39.88, 45.46, 49.76, 52.43, 55.0, 56.53, 112.46, 119.12, 126.39, 129.39, 138.63, 153.52, 165.29, 165.34, 194.23. MS (ES+) : m/z 464.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-[3-(N,N-dimethylamino)propyl] piperazine-1-carbodithioate (6c)

Yield: %81. M:p. 153-154 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 3290 (amide N-H), 1677 (amide C=O), 1337-1025 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53-1.58 (m, 2H, CH_2),

2.20 (t, 2H, *J*=7.15 Hz, CH_2), 2.32 (t, 2H, *J*=7.35 Hz, CH_2), 2.45 (brs, 4H, piperazine CH_2), 2.71 (s, 3H, CH_3), 3.40 (s, 6H, $N(CH_3)_2$), 3.95 (brs, 2H, piperazine CH_2), 4.21 (brs, 2H, piperazine CH_2), 4.28 (s, 2H, CH_2S), 7.65 (d, *J*=8.60 Hz, 2H, Ar-H), 7.80 (s, 1H, thiazole C_5-H), 7.88 (d, *J*=8.55 Hz, 2H, Ar-H), 10.39 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 24.43, 41.29, 45.17, 51.12, 52.17, 55.33, 57.13, 112.45, 119.12, 126.39, 129.39, 138.64, 153.53, 165.30, 165.33, 194.23. MS (ES+) : m/z 478.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-cyclohexylpiperazine-1-carbodithioate (6d)

Yield: %85. M.p. 194-196 °C. IR (KBr) ν_{max} (cm^{-1}): 3298 (amide N-H), 1678 (amide C=O), 1356-1023 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06-1.23 (m, 5H, cyclohexyl CH_2), 1.56-1.76 (m, 5H, cyclohexyl CH_2), 2.27-2.29 (m, 1H, cyclohexyl CH_2), 2.58 (brs, 4H, piperazine CH_2), 2.71 (s, 3H, CH_3), 3.92 (brs, 2H, piperazine CH_2), 4.19 (brs, 2H, piperazine CH_2), 4.27 (s, 2H, CH_2S), 7.65 (d, *J*=8.50 Hz, 2H, Ar-H), 7.80 (s, 1H, thiazole C_5-H), 7.88 (d, *J*=8.50 Hz, 2H, Ar-H), 10.39 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 25.20, 25.77, 28.25, 39.88, 39.96, 40.05, 41.22, 62.23, 112.46, 119.10, 126.38, 129.38, 138.63, 153.53, 165.34, 194.02. MS (ES+) : m/z 475.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-phenylpiperazine-1-carbodithioate (6e)

Yield: %84. M.p. 190-193 °C. IR (KBr) ν_{max} (cm^{-1}): 3299 (amide N-H), 1674 (amide C=O), 1356-1014 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.71 (s, 3H, CH_3), 3.26 (brs, 4H, piperazine CH_2), 4.13 (brs, 2H, piperazine CH_2), 4.29 (s, 2H, CH_2S), 4.37 (brs, 2H, piperazine CH_2), 6.82 (t, 1H, *J*=7.28 Hz, Ar-H), 6.96 (d, 2H, *J*=8.10 Hz, Ar-H), 7.25 (t, 2H, *J*=7.98 Hz, Ar-H), 7.66 (d, *J*=8.70 Hz, 2H, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.88 (d, *J*=8.65 Hz, 2H, Ar-H), 10.42 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 39.89, 39.97, 40.06, 41.27, 47.56, 112.49, 115.45, 119.13, 119.26, 126.40, 129.03, 129.41, 138.63, 149.99, 153.52, 165.27, 165.36, 194.02. MS (ES+) : m/z 469.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-(4-fluorophenyl)piperazine-1-carbodithioate (6f)

Yield: %78. M.p. 188-189 °C. IR (KBr) ν_{max} (cm^{-1}): 3315 (amide N-H), 1672 (amide C=O), 1367-1010 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.71 (s, 3H, CH_3), 3.21 (brs, 4H, piperazine CH_2), 4.12 (brs, 2H, piperazine CH_2), 4.32 (s, 2H, CH_2S), 4.36 (brs, 2H, piperazine CH_2), 7.44 (2H, d, *J*=8.02 Hz, Ar-H), 7.66 (d, *J*=8.70 Hz, 2H, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.89 (d, *J*=8.60 Hz, 2H, Ar-H), 8.12 (2H, d, *J*=8.12 Hz, Ar-H), 10.42 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 39.88, 39.96, 40.05, 41.29, 48.47, 50.74, 112.48, 115.32, 115.49, 117.39, 117.45, 117.77, 119.14, 126.40, 129.41, 138.63, 146.91, 165.26, 165.36, 194.65. MS (ES+) : m/z 487.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-(4-nitrophenyl)piperazine-1-carbodithioate (6g)

Yield: %75. M.p. 210-212 °C. IR (KBr) ν_{max} (cm^{-1}): 3305 (amide N-H), 1671 (amide C=O), 1345-1018 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.71 (s, 3H, CH_3), 3.73 (brs, 4H, piperazine CH_2), 4.17 (brs, 2H, piperazine CH_2), 4.33 (s, 2H, CH_2S), 4.37 (brs, 2H, piperazine CH_2), 6.94 (d, 2H, *J*=9.50 Hz, Ar-H), 7.66 (d, 2H, *J*=8.70 Hz, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.88 (d, *J*=8.60 Hz, 2H, Ar-H), 8.10 (d, 2H, *J*=9.35 Hz, Ar-H), 10.42 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.89, 39.88, 39.96, 41.21, 44.64, 111.79, 112.49, 119.13, 125.76, 126.40, 129.41, 138.62, 153.51, 153.65, 165.22, 165.36, 194.72. MS (ES+) : m/z 514.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-(4-methoxyphenyl)piperazine-1-carbodithioate (6h)

Yield: % 80. M.p. 195-196 °C. IR (KBr) ν_{max} (cm^{-1}): 3325 (amide N-H), 1675 (amide C=O), 1363-1016 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.71 (s, 3H, CH_3), 3.15 (s, 3H, OCH_3), 3.69 (brs, 4H, piperazine CH_2), 4.11 (brs, 2H, piperazine CH_2), 4.32 (s, 2H, CH_2S), 4.37 (brs, 2H, piperazine CH_2), 6.85 (d, 2H, *J*=9.05 Hz, Ar-H), 6.93 (d, 2H, *J*=9.05 Hz, Ar-H), 7.67 (d, 2H, *J*=8.70 Hz, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.89 (d,

J=8.65 Hz, 2H, Ar-H), 10.42 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.90, 39.89, 39.97, 49.32, 55.15, 112.48, 114.31, 117.88, 119.14, 126.41, 129.41, 138.64, 144.37, 153.38, 153.53, 165.28, 165.36, 194.72. MS (ES+) : m/z 499.

2-[[4-(2-Methyl-4-thiazolyl)phenyl]amino]-2-oxoethyl 4-(4-methylbenzyl)piperazine-1-carbodithioate (6i)

Yield: %82. M.p. 140-141 °C. IR (KBr) ν_{max} (cm^{-1}): 3318 (amide N-H), 1674 (amide C=O), 1355-1024 (C-N and C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 3.46 (brs, 4H, piperazine CH_2), 3.95 (brs, 2H, piperazine CH_2), 4.22 (brs, 2H, piperazine CH_2), 4.29 (s, 2H, CH_2S), 7.11 (d, 2H, *J*=8.10 Hz, Ar-H), 7.18 (d, 2H, *J*=7.90 Hz, Ar-H), 7.67 (d, 2H, *J*=8.70 Hz, Ar-H), 7.80 (s, 1H, thiazole C_5-H), 7.89 (d, *J*=8.65 Hz, 2H, Ar-H), 10.42 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.90, 20.69, 41.35, 49.79, 51.82, 61.02, 112.46, 119.14, 126.40, 128.79, 128.92, 129.41, 134.30, 136.16, 138.65, 153.54, 165.30, 165.33, 194.29. MS (ES+) : m/z 497.

Antimicrobial Activity

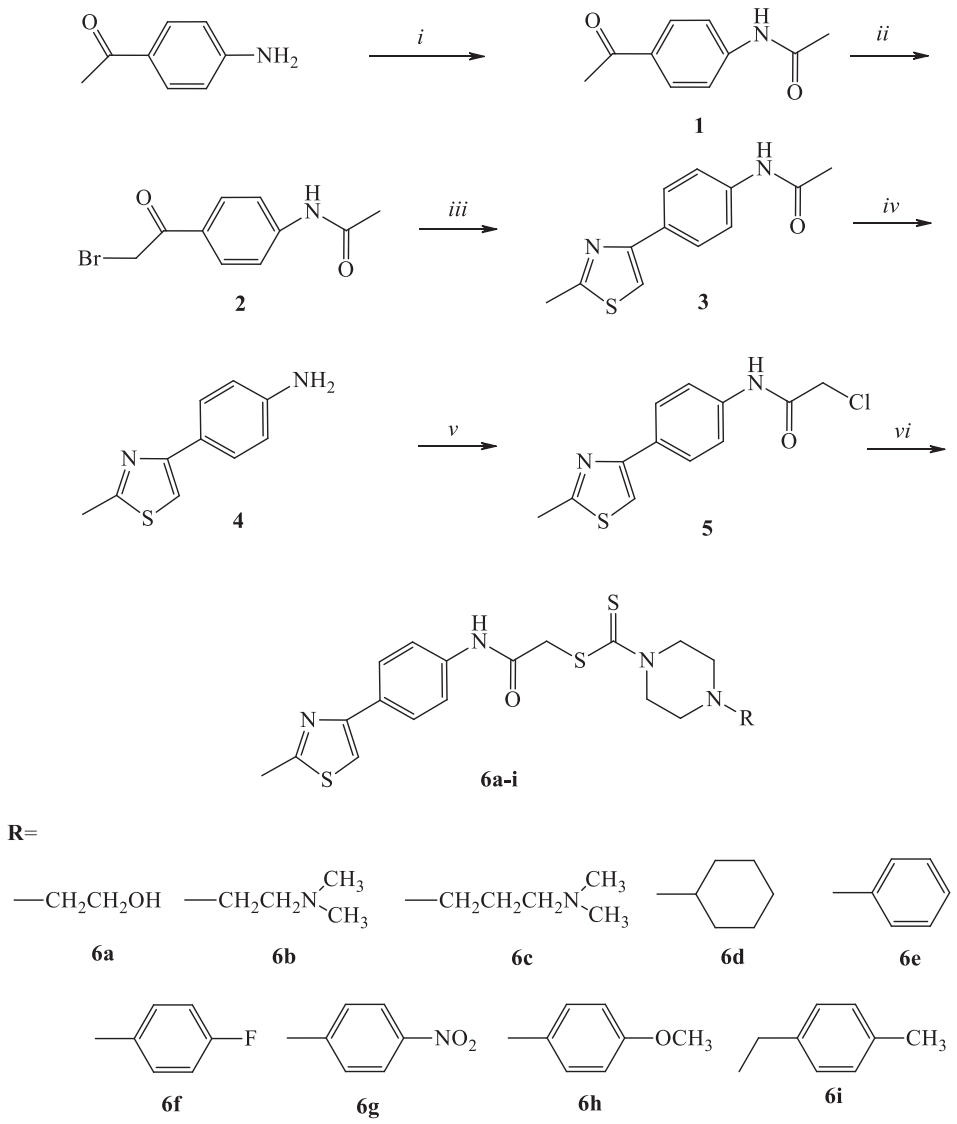
The study was designed to compare MICs obtained by the CLSI reference M7–A7 broth microdilution method (24). MIC readings were performed twice for each chemical agent. Final products were tested for their *in vitro* growth inhibitory activity against human pathogenic as Gram-positive bacteria; *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212) and *E. faecalis* (ATCC 51922) as Gram-negative bacteria; *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 700603), *Escherichia coli* (ATCC 35218), *E. coli* (ATCC 25922) and and yeast as *Candida albicans* (10231), *Candida glabrata* (ATCC 90030) and *Candida krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 7330). Chloramphenicol and Ketoconazole were used as control drugs.

Broth Microdilution Assay

The cultures were obtained from Mueller–Hinton broth (Difco) for the bacterial strains after overnight incubation at 35 ± 1 °C. The yeasts were maintained in Sabouroud Dextrose Broth (Difco) after overnight incubation 35 ± 1 °C. The inocula of test microorganisms adjusted to match the turbidity of a Mac Farland 0.5 standard tube as determined with a spectrophotometer and the final inoculum size was 0.5-2.5 × 10^5 cfu/mL for antibacterial and antifungal assays. Testing was carried out in Mueller–Hinton broth and Sabouroud Dextrose Broth (Difco) at pH 7 and the two-fold serial dilutions technique was applied. The last well on the microplates containing only inoculated broth was kept as controls and the last well with no growth of microorganism was recorded to represent the MIC expressed in μg/mL. For both the antibacterial and antifungal assays the compounds were dissolved in DMSO. Further dilutions of the compounds and standard drugs in test medium were prepared at the required quantities of 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.13 and 1.63 μg/mL concentrations with Mueller–Hinton Broth and Sabouroud Dextrose Broth (25). Each experiment in the antimicrobial assays was replicated twice in order to define the MIC values given in Table 1.

RESULTS AND DISCUSSION

Nine new 2-[[4-(2-methyl-4-thiazolyl) phenyl]amino]-2-oxoethyl 4-(substituted) piperazine-1-carbodithioate derivatives were synthesized in a similar way in our earlier study (26). The thiazole ring was synthesized with a well-known reaction between haloketones (*N*-[4-(2-bromoacetyl)phenyl] acetamide-**2**) and thioamide (thioacetamide) called Hantzsch reaction. Then acetylated compound (2-chloro-*N*-[4-(2-methyl-4-thiazolyl)phenyl]acetamide-**5**) was reacted with carbon disulphide, sodium hydroxide and appropriate secondary amines to give final compounds (**6a-i**) (Scheme 1).



Scheme 1. The synthesis of the compounds (**6a-j**)

Reagents: (*i*) acetyl chloride, TEA, THF, 0-5 ^{o}C; (*ii*) Br_2, AcOH; (*iii*) thioacetamide, EtOH, r.t. (*iv*) 10 % HCl , EtOH, reflux; (*v*) chloroacetyl chloride, TEA, THF, r.t.; (*vi*) appropriate sodium salts of *N,N*-disubstituted dithiocarbamic acids, K_2CO_3, acetone, reflux.

The structures of the synthesized compounds were elucidated by spectral data. In the IR spectra of the compounds characteristic stretching bands for C=O and N-H groups were observed at 1671-1679 cm^{-1} and at 3289-3325 cm^{-1}, respectively. In the ^{1}H-NMR spectra of the compounds, methyl protons at the second position of the thiazole ring and N-H protons belonging to amide moiety were observed at about 2.70-2.71 ppm and 10.39-10.42 ppm. In aromatic region C_5-H of the thiazole ring was observed at about 7.79-7.81 ppm as singlet peaks. Protons of the -CH_2 group linked to sulphur atom were assigned at 4.27-4.33 ppm as singlets and protons of the piperazine ring were seen at the range of 2.44 ppm and 4.22 ppm as broad singlets, commonly. In the ^{13}C-NMR spectra of the compounds, characteristic signals were determined at about 18.90 and 194.65 ppm belonging to CH_3 and C=S carbons. Peaks which were seen at about 39-61 ppm assigned

for piperazine carbons. The mass spectra of the compounds showed (M+1) peaks in agreement with their molecular weight.

Final products (**6a-i**) were tested for their *in vitro* growth inhibitory activity against human pathogens. As gram-positive bacteria; *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212) and *Enterococcus faecalis* (ATCC 51922); as gram-negative bacteria; *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 700603), *Escherichia coli* (ATCC 35218), and *Escherichia coli* (ATCC 25922) and as yeasts *Candida albicans* (ATCC 90028), *Candida glabrata* (ATCC 90030), *Candida krusei* (ATCC 6258) and *Candida parapsilosis* (ATCC 7330) were used in antimicrobial activity tests. The antimicrobial activity of the compounds (**6a-i**) was evaluated compared with standard drugs Chloramphenicol and Ketoconazole. The observed antimicrobial data of the compounds and the reference drugs are given in Table 1.

Table 1 demonstrates that synthesized compounds have more potency to inhibit gram-negative bacteria than gram positive ones. Among the bacteria strains, *E. faecalis* (ATCC 51922) and *P. aeruginosa* (ATCC 27853) were found as the most susceptible bacterial strains Four final compounds (**6a-d**) including alkyl groups in their structure have shown same potency such as chloramphenicol against *E. faecalis* (ATCC 51922). Furthermore, compound **6f** including 6-fluorophenyl moiety displayed better activity than Chloramphenicol against same microorganism. Against *P. aeruginosa* (ATCC 27853), all compounds showed same potency with standard drug, except **6h**. Compound **6h** containing 4-methoxyphenyl exhibited same potency compared with Chloramphenicol. Anticandidal activity results revealed that synthesized compounds have no influence to inhibit *Candida* species.

Table 1. Antimicrobial activity of the compounds **6a-6i** (μg/mL)

Comp.	6a	6b	6c	6d	6e	6f	6g	6h	6i	Ref
A	800	800	800	800	800	800	800	800	800	25
B	200	200	200	200	800	200	400	200	400	6.25
C	200	200	200	200	800	50	400	400	400	200
D	400	400	400	400	400	400	400	400	400	100
E	400	400	400	400	400	400	400	200	400	200
F	800	400	800	800	800	800	800	800	800	200
G	800	800	800	400	400	800	400	400	400	1.63
H	200	200	200	200	200	400	200	200	200	12.50
I	400	400	400	400	400	400	400	400	400	25
J	200	400	200	200	200	400	200	200	200	1.63
K	200	200	200	200	200	400	200	200	200	1.63

Reference: Chloramphenicol for bacterial strains and Ketoconazole for fungal strains, **A**: *S. aureus* (ATCC 25923), **B***: E. faecalis* (ATCC 29212), **C**: *E. faecalis* (ATCC 51922), **D**: *K. pneumonia* (ATCC 700603)*,* **E**: *P. aeruginosa* (ATCC 27853), **F**: *E. coli (*ATCC 35218), **G:** *E. coli* (ATCC 25922), **H**: *C. albicans* (ATCC 90028), **I:** *C. glabrata* (ATCC 90030), **J**: *C. krusei* (ATCC 6258), **K**: *C. parapsilosis* (ATCC 7330).

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REFERENCES

1. Sarkar A, Kumar KA, Dutta NK, Chakraborty P, Dastidar SG, Evaluation of *in vitro* and *in vivo* antibacterial activity of dobutamine hydrochloride, Indian J Med Microbiol 21, 172-178, 2003.
2. Gold HS, Moellering RC, Engl N, Antimicrobial-drug resistance, J Med Chem 335, 1445-1453, 1996.
3. Bossche HV, Marichal P, Odds FC, Molecular mechanisms of drug resistance in fungi Trends Microbiol 10, 393-400, 1994.
4. Cohen ML, Epidemiology of drug resistance: implications for a post-antimicrobial era, Science 257, 1050-1055, 1992.
5. Silverman RB, Organic Chemistry of Drug Design and Drug Action, Academic Press, San Diego, pp. 13-15, 1992.
6. Thompson LA, Ellman JA, Synthesis and Applications of Small Molecule Libraries, Chem Rev 96, 555-600, 1996.
7. Noguer T, Marty JL, High sensitive bienzymic sensor for the detection of dithiocarbamate fungicides, Anal Chim Acta 347, 63-70, 1997.
8. Kaplancikli ZA, Turan-Zitouni G, Revial G, Iscan G, Synthesis of some dithiocarbamate derivatives and their antimicrobial activity, Phosphorus Sulfur 179, 1449-1454, 2004.
9. Turan-Zitouni G, Ozdemir A, Guven K, Synthesis of some 1-[(N,N-disubstituted thiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives and investigation of their antibacterial and antifungal activities, Arch Pharm Chem Med Chem 338, 96-104, 2005.
10. Turan-Zitouni G, Ozdemir A, Kaplancikli ZA, Synthesis and antimicrobial activities of some 1-[(N,N-disubstitutedthiocarbamoylthio) acetyl]-3,5-diaryl-2pyrazolines, Phosphorus Sulfur 180, 2717-2727, 2005.
11. Kumar STVSK, Kumar L, Sharma V, Jain LA, Jain RK, Maikhuri JP, Kumar MP, Shukla K, Gupta G, Carbodithioic acid esters of fluoxetine, a novel class of dual-function spermicides, Eur J Med Chem 43, 2247-2256, 2008.
12. Tokuyama R, Takahashı Y, Tomıta Y, Tsubouchı M, Yoshıda T,Iwasakı N, Kado N, Okezakı E, Nagata O, Structure–Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 2. Relationship between Lipophilicity and Antibacterial Activity in 5-Thiocarbonyl Oxazolidinones, Chem Pharm Bull 49, 353-360, 2001.
13. Karaburun AÇ, Kaplancikli ZA, Gundogdu-Karaburun N, Demirci F, Synthesis, Antibacterial and Antifungal Activities of Some Carbazole Dithiocarbamate Derivatives, Lett Drug Des Discov 8, 811-815, 2011.
14. Gupta RR, Kumar M, Gupta V, Heterocyclic Chemistry Five-membered Heterocycles, Springer, New York, pp. 416, 1999.
15. Jpn H, Patent No. 87841; Chem Abstr 121, 205336, 1994.
16. Fhamy HT, Synthesis and antimicrobial screening of some novel thiazoles, dithiazoles and thiazolylpyridines, Pharmazie, 52, 750-753, 1997.
17. Bondock S, Pandeya N, Sriram DNath G, Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl)thiazol-2-yl] thiosemicarbazide, Eur J Pharm Sci 9, 25-31, 1999.
18. Fadaly SW, Metwally MA, Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety, Eur J Med Chem 45, 3692-3701, 2010.
19. Kaplancikli ZA, Turan-Zitouni G, Revial G, Güven, K, Synthesis and Study of Antibacterial and Antifungal Activities of Novel 2-[[(Benzoxazole/benzimidazole-2-yl)sulfanyl]acetylamino]thiazoles, Arch Pharm Res 27, 1081-1085, 2004.
20. Turan-Zitouni G, Demirayak S, Ozdemir A, Kaplancikli ZA, Yıldız MT, Synthesis of some 2-[(benzazole-2-yl)thioacetylamino] thiazole derivatives and their antimicrobial activity and toxicity, Eur J Med Chem 39, 267-272, 2004.
21. Jang SY, Ha YH, Ko SW, Lee W, Lee J, Kim S, Kim YW, Lee WK, Ha H, Synthesis and antibacterial activity of arylpiperazinyl oxazolidinones with diversification of the N-substituents, J Bioorg Med Chem Lett 15, 3881-3883, 2004.
22. Singh KK, Joshi SC, Mathela CS, Synthesis and invitro antibacterial activity of N-alkyl and N-aryl piperazine derivatives, Indian J Chem 50, 196-200, 2011.
23. Pancechowska-Ksepko D, Spalińsk KFoks H, Kędzi A, Wierzbowska M, Kwapisz E, Janowiec M, Zwolska Z, Augustynowicz-

Kopeć E, Synthesis and Antibacterial Activity of New 1,4-Disubstituted Piperazine Derivatives, Phosphorus Sulfur 183, 1252-1263, 2008.
24. CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically Approved Standard, CLSI Document M7-A7, seventhed. ISBN1-56238-587-9, 2006.
25. Yurttaş L, Özkay Y, Karaca H, Tunalı Y, Kaplancıklı ZA, Synthesis and Antimicrobial Evaluation of Some 2,5-Disubstituted Benzimidazole Derivatives, Lett Drug Des Discov 10, 486-491, 2013.
26. Yurttaş L, Kaplancıklı ZA, Özkay Y, Design, synthesis and evaluation of new thiazole-piperazines as acetylcholinesterase inhibitors, J Enzym Inhib Med Chem 28, 1040-1047, 2013.

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