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Synthesis of new thiazole derivatives and evaluation of their antimicrobial and cytotoxic activities

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ABSTRACT

Novel 2-heteroaryl-*N*-[4-(substituted aryl)thiazol-2-yl]propanamide derivatives **(7a–7o)** were synthesized and investigated for their antimicrobial activity. Among the tested compounds, 2-[(1H-Benzimidazol-2-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide **(7e)** and N-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[(1-methyl-1H-tetrazol-5-yl)thio]propanamide (**7f**) showed the highest antibacterial activity, whereas 2-[Benzothiazol-2-ylthio]-N-[4-(4-chlorophenyl)thiazol-2-yl]propanamide (**7i**) and 2-[(1H-Benzimidazol-2-yl)thio]-N-[4-(4-chlorophenyl)thiazol-2-yl]propanamide (**7j**) displayed anticandidal effect against *C. parapsilosis* and *C. glabrata*. The cytotoxic activity of the compounds **(7a–7o)** was also tested against HL-60 human leukemia cells, THP-1 human monocytic leukemia cells, and NIH/3T3 mouse embryonic fibroblast cells. Compound N-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[(1-methyl-1H-imidazol-2-yl)thio]propanamide (**7 g)** and compound **7j** exhibited high cytotoxicity against HL-60; and compounds 2-[(1-Methyl-1H-imidazol-2-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (**7b)**, **7 g** and N-[4-(4-Methoxyphenyl)thiazol-2-yl]-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]propanamide (**7 m)** also had cytotoxic activity against THP-1 compared with standard drug with selective profile. Additionally, *in silico* physicochemical properties of the compounds were described.

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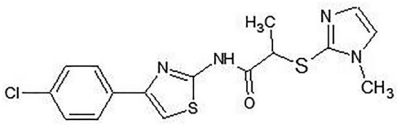
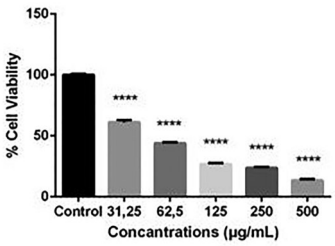
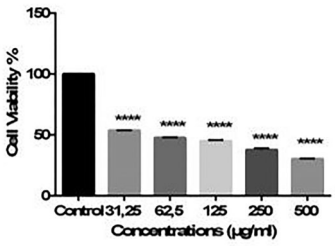
Thiazole; antibacterial; antifungal; cytotoxicity; anticancer; THP-1; HL-60

GRAPHICAL ABSTRACT





THP-1 Cells



HL-60 Cells

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Introduction

Despite the extensive studies in the field of medicinal chemistry, definitive and radical treatments have not been reached in dealing with infectious and neoplastic diseases. The main reasons for this situation are the development of drug resistance and the severe side effects of drugs.[1–3] Heterocyclic chemistry is a key science, which can present appreciable solutions when applied to new drug design and discovery. It is of great importance to develop new, active molecules with few side effects. Five membered heterocyclic rings are essential to certain drugs' activities with a wide range of pharmaceutical and industrial applications.[4,5]

Thiazole ring is a ring system known for having various biological activities including antibacterial, antifungal, anticancer, antitumor, antimalarial, antiviral, antidiabetic, anticonvulsant, antioxidant, antiallergic, analgesic, anti-inflammatory, and anti-hypolipidemic properties.[2,6–12] The ring is also found in the structure of many natural bioactive molecules. It is found in compounds having actions in certain metabolic process such as the vitamin thiamin.[13] Certain penicillins, cephalosporins, and other antibiotics also have a ring as part of their structures.[14,15] Epothilone metabolite and tubulin modulator used as an antineoplastic agent,[16] bleomycin antitumor antibiotic,[17] bacitracin, which is a cyclic peptide produced by organisms of the licheniformis group of *Bacillus subtilis*,[18] and many other compounds of therapeutic activity have a thiazole ring.[19,20] These activities occur through toxophoric unit transport[21] by blocking the biosynthesis of certain bacterial lipids and other mechanisms.[22] Among thiazole derivatives, 2-aminothiazole scaffold was investigated and its efficacy was proven by numerous studies.[23–26] 2-aminothiazole scaffold has a similarity in its chemical structural to that of the antibacterial thiolactomycin.[27] Molecules carrying this residue show high antibacterial activity.[28–33] Additionally, 2,4-disubstituted derivatization is beneficial in biological activity.[34,35] Compounds having a 2,4-disubstituted thiazole ring were reported to have anticancer activity as well as antimicrobial activity.[36–42] Clinically available thiazole-containing anticancer drugs act as inosine 5′-monophosphate (IMP) dehydrogenase inhibitor (tiazofurin), tyrosine kinase inhibitor (dasatinib), inhibitor of proto-oncogene B-Raf enzyme (dabrafenib), microtubule stabilization (ixabepilone), or microtubule function inhibitor, epothilone.[43]

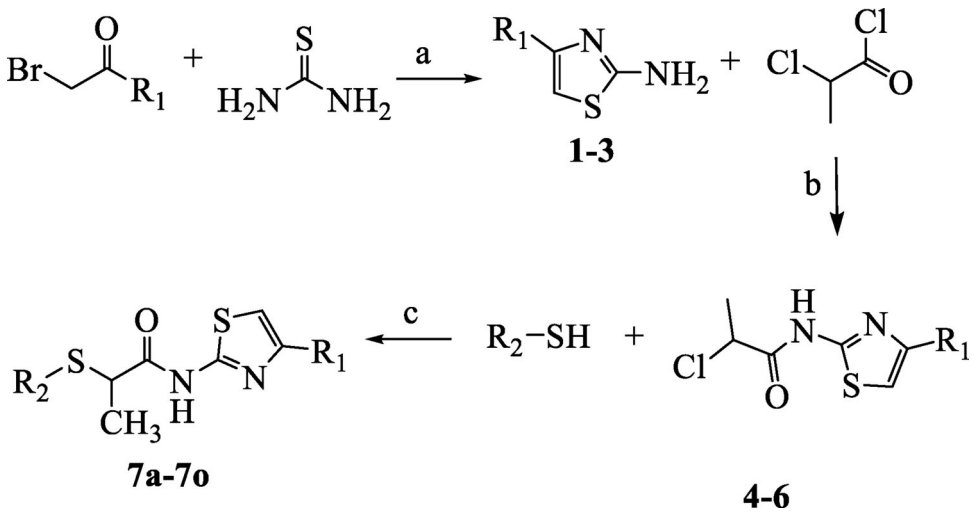
Based on the above information and considering the need to discover and develop new active agents, new thiazole derivatives were synthesized and investigated for their antibacterial, antifungal, and cytotoxic activities.

Results and discussion

Chemistry

The target 2-(heteroaryl)-*N*-[4-(substituted aryl)thiazol-2-yl]propanamide derivatives (**7a–7o**) were obtained in three steps as shown in Scheme 1 and Table S 1. The final compounds were purified by recrystallization from ethanol. Purity determination and structure elucidation were achieved by melting point analysis, proton nuclear magnetic resonance (^{1}H NMR) spectrometry, ^{13}C nuclear magnetic resonance (^{13}C NMR) spectrometry, elemental analysis, and high-resolution mass spectrometry (HRMS).

Aliphatic CH_3 (C-3 of propanamide) resonated as doublets in the range of 1.44–1.73 ppm. The chemical shifts of this methyl group among the compounds studied were affected by the azole substituent used. This effect of azole derivatives can be concluded when comparing compounds using the same derivatives, e.g., **7a**, **7f**, **7k**, where their methyls' chemical shifts were almost identical. Three of the azole rings used had side methyl substituents. Tetrazole-CH_3 peaks of compounds **7a**, **7f**, and **7k** appeared as singlets around 3.96 ppm, while the peaks of imidazole-CH_3 and triazole-CH_3 were observed at around 3.58 and 3.57 ppm, respectively. The methine's (C-2 of propanamide) hydrogen showed quartet peaks at the range of 4.15–4.91 ppm where the difference was owed to the different azole substituents used. The aromatic region at the range 6.5–8.5 ppm of the spectra showed all the aromatic hydrogens of the synthesized products. It is noteworthy that some of the aromatic hydrogens could be assigned perfectly to their peaks in the



Scheme 1. Synthesis plan of the targeted compounds. **(a)** EtOH, rt, 1 h; **(b)** THF, TEA, 0°C; **(c)** acetone, K_2CO_3, rt, overnight.

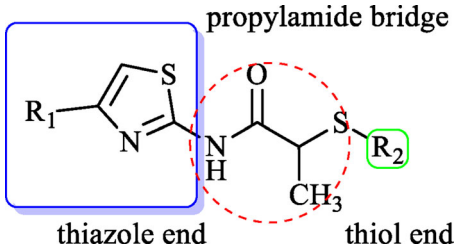


Figure 1. The core structure of the final compounds.

spectra as the peaks were shifted well. For example, hydrogens of phenyl-3,5 of compounds **7f–7g** were observed as doublets at 7.49 ppm, while those of compounds **7k–7o** appeared around 6.97 ppm. Likewise, hydrogens of phenyl-2,6 of compounds **7f–7j** were observed as doublets around 7.91 ppm, whereas those of compounds **7k–7o** were seen around 7.81 ppm. The different chemical shifts of the phenyl hydrogens among **7f–7j** and **7k–7o** series were due to the Cl and OCH_3 substituents, respectively. A complex pattern of multiplet peaks was observed frequently in the aromatic region from which the number of the remaining aromatic hydrogens could be determined. The hydrogen of the amidic group resonated at about 12.50 ppm where it could be observed as a broad singlet but in some cases as a very weak singlet.

In ^{13}C NMR spectra, the aliphatic-CH_3 (C-3 of propanamide) showed signals in the range of 17.62–19.64 ppm, differing by the effect of the azole side group. The methine's carbon (C-2 of propanamide) showed signals at the range 44.80–48.18 ppm affected by the azole side groups too. The methyl groups bonded to the azole rings showed different chemical shifts. Tetrazole-CH_3 showed signals around 34.30 ppm, while imidazole-CH_3 and triazole-CH_3 showed signals around 33.70 and 31.50 ppm, respectively. Methoxy group of compounds **7k–7o** was observed around 55.60 ppm. The aromatic region in the range 100–170 ppm showed the carbons of the aromatic cycles. The amidic carbonyl group was observed around 170 ppm.

HRMS and elemental analyses confirmed the structural backbone of the designed compounds. The analysis results of the final compounds are displayed in the Supplemental data.

Calculations of the ADME parameter values

Molecular weights were calculated between 374.48 and 447.60. Log P values that indicate the lipophilicity *via* partition coefficient between octanol and water were found between 2.25 and 5.51. Water solubility (Log S) and skin permeation (Log Kp) were calculated in the ranges −3.80 to −7.10 and −4.20 to −6.77, respectively. Drug-likeness model scores (DLMS) were found between 0.05 and 1.29. The number of hydrogen bond donors (HBD) differed between 1 and 2 among the targeted compounds, whereas the number of hydrogen bond acceptors (HBA) was between 3 and 6. Molecular volumes were calculated between 317.39 and 392.58 $Å^3$. Topological polar surface areas (TPSA) were determined between 113.35 and 148.36 $Å^2$. Therefore, according to ADME prediction, all compounds can be used orally. All findings are shown in Table S 2.

Antimicrobial activity evaluation

The synthesized compounds were tested against five bacteria and four fungi strains. The results are shown in Table S 3. To explain better, we grouped the main structure of the molecules as a thiazole end, linker/bridge, and thiol end as shown in Figure 1.

Generally, although all compounds showed antibacterial activity, none of them showed good antimicrobial activity like that of chloramphenicol or ketoconazole; therefore, no further investigation was carried out, e.g., enzyme or docking studies. Gondru et al.[44] reported the synthesis of thiazole–triazole derivatives that showed antimicrobial activity to certain fungal strains but the antibacterial activity was modest. Their work involved the synthesis of thiazole bound to a bicyclic system in position 4 and triazole derivatives bound to position 2. The designed compounds in our study were intended to have thiazole core bound to various pharmacophoric rings and groups at positions 2 and 4. In addition to thiazole, the compounds were composed of azole rings, which are known for their contribution to the antimicrobial and antiparasitic activities of various drugs. Drugs that contain azole rings as an effective pharmacophore include albendazole and mebendazole as anthelminthic agents, ketoconazole and fluconazole as antifungal agents, and metronidazole as antibacterial drug. Despite the compounds were expected to have antimicrobial activity, they displayed activity less than that of the standard used in the study.

Although the biological activity herein this study was modest, the most effective compounds were **7d**, **7e**, and **7i** against *Enterococcus faecalis*; **7e**, **7f**, **7i, 7j, 7k, and 7l** against *Klebsiella pneumoniae*; **7e** and **7f** against *Pseudomonas aeruginosa*. No selectivity against *Escherichia coli* species (ATCC35218 and ATCC25922) was determined among the compounds, but their effects were lower than chloramphenicol. However, all compounds were found sensitive to *E. coli* (ATCC25922) as they act at twofold concentration of chloramphenicol. **7e**, **7f**, and **7i** had impact on three different bacteria. But **7e** (MIC:100 µg/mL) was identified as a valuable compound since it showed an antibacterial effect against four species at twofold concentration over chloramphenicol (MIC:50 µg/mL). Moreover, when the substitutions at the thiol end were bulky groups such as benzothiazole (**7d, 7i**) or benzimidazole (**7e**), it was observed that the antibacterial effect was increased against *E. faecalis*. Also, naphthalene substitution on thiazole enhanced the activity against the same bacteria. On the other hand, 4-chlorophenyl derivatives were found to be more active than the others against *K. pneumoniae*. Additionally, the benzimidazole on the left (**7e, 7j**) showed activity at low doses. It was observed that the antibacterial effect was independent on substitutions of the thiol side when the thiazole had the naphthyl substitution, probably due to the high-volume area of the compounds, except for compound **7e**. There was no success to gain antibacterial activity as much as chloramphenicol against *P. aeruginosa*. Only **7e** (naphthalene-

benzimidazole) and **7f** (4-chlorophenyl-tetrazole) displayed antibacterial activity close to that of chloramphenicol.

Anticandidal activity was also observed for the final compounds (**7a–7o**). Some *Candida* species displayed more susceptibility against compounds **7a, 7c, 7e, 7i,** and **7j**. Interestingly, the antifungal activity against *Candida albicans* and *Candida krusei* was determined as low since the MIC values of the compounds were eightfold more than ketoconazole. In fact, **7i, 7j,** and **7m** showed higher activity than other analogs against *C. krusei*. Also, the naphthalene derivatives did not exhibit antifungal activity, and this might be related to its bulkiness. Naphthalene (**7a, 7c, 7e**) and 4-chlorophenyl (**7i, 7j**) derivatives were found to be more effective than 4-methoxyphenyl derivatives against *Candida parapsilosis*. Similarly, compounds **7i** and **7j** showed antifungal activity against *Candida glabrata* at twofold concentration of ketoconazole (MIC: 100 µg/mL). Briefly, **7i** and **7j** are more worthy compounds than the others against *Candida* species, but their activity was not enough to proceed for further tests. The graphs of the results are provided in the Supplemental data.

It was observed that the substituents on position 4 of thiazole should have had a polar property and avoid bulkiness to offer antimicrobial activity.[44,45] The naphthyl group hence impeded the compounds to act properly. We also think that the aromatic functionality at position 4 might halt the antimicrobial activity unless it has a prominent polar or electron-donating groups.[45,46]

Anticancer activity evaluation

The cytotoxicity of the compounds (**7a–7o**) was tested against HL-60 human leukemia cells, THP-1 human monocytic leukemia cells, and NIH/3T3 mouse embryonic fibroblast cells as shown in Table S 4. According to the results, the most active compounds against HL-60 cells were determined as **7g** (IC_{50}: 45.00 µg/mL) and **7j** (IC_{50}:61.33 µg/mL) because their IC_{50} values were lower than IC_{50} value of doxorubicin. (IC_{50}: 58.16 µg/mL), and their selectivity index (SI) in comparison with NIH/3T3 cells were 8.94 and >8.15, respectively. The anticancer activity of the remaining compounds was not powerful as much as doxorubicin. Because the final compounds did not show cytotoxicity against the NIH/3T3 healthy cells generally, the SI calculation surprisingly displayed that **7a, 7b, 7c, 7f, 7h, 7l, 7n,** and **7o** were highly selective. It was observed that the non-condensed ring substituents on the thiazole side, independent of the substituent on the thiazole, provided an increased activity. Also, the most powerful effect was provided with the 4-chlorophenyl substitution on the thiol end.

The activity against THP-1 cells was appreciated where all the final compounds showed anticancer activity against them. All compounds have lower IC_{50} values than doxorubicin except compounds **7j** and **7o**. Compounds **7d** and **7k** were determined as cytotoxic to both tumor and healthy cells. Among the substitutions on the thiazole end, the benzimidazole group decreased the activity. Generally, pentagonal rings increased the anticancer effect, and the benzothiazole moiety was also effective. Considering the most active compounds, **7d** and **7m**, and their analogs (**7i, 7n** and **7c, 7 h**), benzothiazole and *N*-methyl triazole moieties were responsible for the maximum effect, and the thiol end increased or decreased the activity potency. Regarding the selectivity against THP-1, compounds **7a, 7b, 7c, 7f, 7g, 7h, 7j, 7l, 7n,** and **7o** were found highly selective. Although the activity against THP-1 cells seems to be independent on the thiazole end, and the best substitutions were determined as triazole and benzothiazole, it is concluded that the electron-withdrawing group decreased the activity. Thus, there were no meaningful differences between the bulky and small groups regarding the activity. Briefly, it was determined that the most effective compounds against HL-60 were **7g** and **7j** and those effective against THP-1 were **7b, 7g,** and **7m**. The graphs of the results are provided in the Supplemental data.

The anticancer activity of the designed compounds could have been better if a ring substituent was bonded to carbon 5 of the thiazole ring.[47] Regardless of the size of the group on position 2 of thiazole ring, the acetamide functionality is well known for its inhibitory activity against cancer cells. Comparable designed compounds with some similarity in targeting the activity to that of our design were reported with the promising results.[43,48]

Materials and methods

Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Columbus, OH, USA) and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA). Spectroscopic data were recorded using the following instruments: ^{1}H-NMR and ^{13}C-NMR (nuclear magnetic resonance) Bruker DPX- 300 FT-NMR spectrometer (Bruker Bioscience, Billerica, MA, USA); M + 1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan). The Supplement data contain sample ^{1}H and ^{13}C NMR spectra and high-resolution mass spectra of the products 7 (Figures S 1 – S 45).

General synthesis of 4-(substituted aryl)thiazol-2-amine (1, 2, 3)

2-bromo-1-(naphthalen-2-yl)ethan-1-one (3.0 g, 12.043 mmol) was reacted with thiourea (0.917 g, 12.043 mmol) in ethanol (20 mL) for 1 h at room temperature to obtain 4-(naphthalen-2-yl)-1,3-thiazol-2-amine (**1**). Likewise, with the same reaction conditions, 2-bromo-1-(4-chlorophenyl)ethan-1-one (3.0 g, 13.096 mmol) was reacted with thiourea (0.997 g, 13.096 mmol) to obtain 4-(4-chlorophenyl)-1,3-thiazol-2-amine (**2**); and 2-bromo-1-(4-methoxyphenyl)ethan-1-one (3 g, 13.096 mmol) with thiourea (0.997 g, 13.096 mmol) to obtain 4-(4-methoxyphenyl)-1,3-thiazol-2-amine (**3**). The reaction was monitored using TLC. The mixture was filtered after the reaction was finished, and the residue was recrystallized using ethanol.

General synthesis of 2-chloro-N-[(4-(substituted aryl)thiazol-2-yl]propanamide (4, 5, 6)

Compounds **1, 2,** and **3** (3.173 g, 14.021 mmol; 3.744 g, 17.771 mmol; and 2.199 g, 10.661 mmol, respectively) were placed in separate flasks followed by the addition of tetrahydrofuran (20 mL, THF) as a solvent then triethylamine (TEA) (2 equivalents) as a basic catalyst. The flasks were placed in an ice bath over magnetic stirrer, and 2-chloropropionyl chloride (1.2 equivalents for each) was dissolved in THF and added dropwise into the reaction mixtures. Compounds **4, 5,** and **6** were obtained from compounds **1, 2,** and **3**, respectively. The reactions were monitored using TLC. They needed about 24 h to finish after which the solvent was evaporated. The dried residues were washed thoroughly using water and separated by filtration. The obtained product residues were recrystallized from ethanol.

General synthesis of 2-mercapto-N-[4-(substituted aryl)thiazol-2-yl]propanamide derivatives (7a–7o)

The final products were obtained by reacting compounds **4, 5,** and **6** (0.30 g, 0.947 mmol, 0.30 g, 0.996 mmol, 0.30 g, 1.011 mmol, respectively) with the appropriate thiol derivatives (1: 1 equivalent ratio). The required thiol derivative was dissolved in acetone (30 mL) to which potassium carbonate (2 equivalents) was added. The mixture was stirred for 5 min followed by the addition of compounds **4, 5,** or **6**. The reaction was carried out in room temperature overnight. The reaction end point was monitored using TLC. Then, the solvent was evaporated, and the target product residue was washed using water and the obtained product after filtration was recrystallized from ethanol.

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (7a)

Physical properties: Melting point (m.p.): 217–218 °C, color: brown, yield: 61%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.65 (d, $J = 6.96$ Hz, 3H, aliphatic CH_3), 3.98 (s, 3H, tetrazole-CH_3), 4.62 (q, $J1 = 6.82$ Hz, $J2 = 13.86$ Hz, H, CO-CH-S), 7.51–7.53 (m, 2H, Ar-H), 7.81 (s, H, Ar-H), 7.91–7.98 (m, 3H, Ar-H), 8.07 (m, H, Ar-H), 8.44 (s, H, Ar-H), 12.77 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.80 (aliphatic-CH_3), 34.38 (tetrazole-CH_3), 46.41 (CO-CH-S), 109.75, 124.45, 124.77, 126.66, 127.01, 128.08, 128.66, 128.77, 132.08, 133.02, 133.60, 149.42, 151.98, 158.37, 169.74 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 397.0900; found: 397.0905.

2-[(1-Methyl-1H-imidazol-2-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (7b)

Physical properties: M.P.: 139–142 °C, color: reddish brown, yield: 84%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.47 (d, $J = 7.00$ Hz, 3H, aliphatic-CH_3), 3.61 (s, 3H, imidazole-CH_3), 4.19 (q, $J1 = 6.95$ Hz, $J2 = 14.04$ Hz, H, CO-CH-S), 7.04–7.06 (m, H, Ar-H), 7.35 (d, $J = 1.14$ Hz, H, Ar-H), 7.49–7.57 (m, 2H, Ar-H), 7.79 (s, H, Ar-H), 7.91–7.98 (m, 3H, Ar-H), 8.04–8.08 (m, H, Ar-H), 8.44 (s, H, Ar-H), 12.70 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 17.77 (aliphatic-CH_3), 33.72 (imidazole-CH_3), 45.76 (CO-CH-S), 109.47, 114.50, 119.90, 124.48, 124.82, 126.62, 126.99, 128.08, 128.73, 129.59, 132.17, 132.99, 133.61, 137.68, 149.32, 158.64, 170.79 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 395.0995; found: 395.1000.

2-[(4-Methyl-4H-1,2,4-triazol-3-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (7c)

Physical properties: M.P.: 210–211 °C, color: white, yield: 72%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.55 (d, $J = 7.01$ Hz, 3H, aliphatic CH_3), 3.59 (s, 3H, triazole-CH3), 4.36 (q, $J1 = 7.02$ Hz, $J2 = 14.01$ Hz, H, CO-CH-S), 7.50–7.54 (m, 2H, Ar-H), 7.79 (s, H, Ar-H), 7.90–7.98 (m, 3H, Ar-H), 8.02–8.06 (m, H, Ar-H), 8.42 (s, H, Ar-H), 8.62 (s, H, triazole-5) 12.55 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.10 (aliphatic-CH_3), 31.54 (triazole-CH_3), 45.36 (CO-CH-S), 109.68, 124.45, 124.76, 126.67, 127.02, 128.09, 128.65, 128.77, 132.07, 133.02, 133.59, 146.99, 147.22, 149.41, 158.17, 170.20 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 396.0947; found: 396.0957.

2-(Benzothiazol-2-ylthio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (7d)

Physical properties: M.P.: 177–179 °C, color: white, yield: 94%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.73 (d, $J = 7.05$ Hz, 3H, aliphatic-CH_3), 4.91 (q, $J1 = 6.86$ Hz, $J2 = 13.86$ Hz, H, CO-CH-S), 7.35–7.41 (m, H, Ar-H), 7.45–7.56 (m, 3H, Ar-H), 7.75 (s, H, Ar-H), 7.85–7.97 (m, 4H, Ar-H), 8.03–8.08 (m, 2H, Ar-H), 8.44 (s, H, Ar-H), 12.84 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 19.24 (aliphatic-CH_3), 47.37 (CO-CH-S), 109.27, 112.30, 121.79, 122.39, 124.52, 124.67, 125.21, 126.53, 126.94, 128.07, 128.63, 132.38, 132.95, 133.65, 135.36, 149.20, 153.06, 170.57 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 448.0607; found: 448.0612.

2-[(1h-Benzimidazol-2-yl)thio]-N-[4-(naphthalen-2-yl)thiazol-2-yl]propanamide (7e)

Physical properties: M.P.: 159–161 °C, color: grayish white, yield: 87%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.67 (d, $J = 7.11$ Hz, 3H, aliphatic-CH_3), 4.85 (q, $J1 = 7.05$ Hz, $J2 = 14.16$ Hz, H, CO-CH-S), 7.13–7.19 (m, 2H, Ar-H), 7.48–7.57 (m, 4H, Ar-H), 7.78 (s, H, Ar-H), 7.90–7.97 (m, 3H, Ar-H), 8.04–8.07 (m, H, Ar-H), 8.44 (s, H, Ar-H), 12.85 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.90 (aliphatic-CH_3), 45.02 (CO-CH-S), 109.44, 109.93, 114.58, 122.14, 122.77, 124.48, 124.72, 126.60, 126.99, 128.09, 128.63, 128.72, 132.19, 132.99, 133.61, 139.91, 149.05, 149.29, 158.87, 170.85 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 431.0995; found: 431.0997.

N-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[(1-methyl-1H-tetrazol-5-yl)thio]propanamide (7f)

Physical properties: M.P.: 195–197 °C, color: white, yield: 66%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.63 (d,

$J = 7.05$ Hz, 3H, aliphatic-CH_3), 3.96 (s, 3H, tetrazole-CH3), 4.60 (q, $J1 = 6.99$ Hz, $J2 = 14.04$ Hz, H, CO-CH-S), 7.49 (d, $J = 8.58$ Hz, 2H, phenyl-3,5), 7.73 (s, H, thiazole-5), 7.91 (d, $J = 8.61$ Hz, 2H, phenyl-2,6), 12.57 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.73 (aliphatic-CH_3), 34.32 (tetrazole-CH3), 46.30 (CO-CH-S), 109.83, 116.55, 127.86, 128.20, 129.26, 132.81, 133.47, 148.28, 151.95, 158.31, 169.71 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 381.0354; found: 381.0357.

N-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[(1-methyl-1H-imidazol-2-yl)thio]propanamide (7g)

Physical properties: M.P.: 168–170 °C, color: dark red, yield: 79%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.44 (d, $J = 7.02$ Hz, 3H, aliphatic-CH_3), 3.58 (s, 3H, imidazole-CH_3), 4.16 (q, $J1 = 6.99$ Hz, $J2 = 14.04$ Hz, H, CO-CH-S), 7.02 (d, $J = 1.17$ Hz, H, imidazole-4), 7.33 (d, $J = 1.17$ Hz, H, imidazole-5), 7.49 (d, $J = 8.58$ Hz, 2H, phenyl-3,5), 7.71 (s, H, thiazole-5), 7.91 (d, $J = 8.58$ Hz, 2H, phenyl-2,6), 12.54 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 17.62 (aliphatic-CH_3), 33.70 (imidazole-CH_3), 45.50 (CO-CH-S), 109.60, 109.62, 124.83, 127.84, 129.23, 129.56, 132.77, 133.51, 137.58, 148.21, 158.32, 170.66 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 379.0449; found: 379.0452.

N-[4-(4-Chlorophenyl)thiazol-2-yl]-2-((4-methyl-4H-1,2,4-triazol-3-yl)thio]propanamide (7h)

Physical properties: M.P.: 230–232 °C, color: white, yield: 52%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.51 (d, $J = 6.99$ Hz, 3H, aliphatic-CH_3), 3.57 (s, 3H, triazole-CH_3), 4.32 (q, $J1 = 6.98$ Hz, $J2 = 14.04$ Hz, H, CO-CH-S), 7.49 (d, $J = 8.58$ Hz, 2H, phenyl-3,5), 7.72 (s, H, thiazole-5), 7.90 (d, $J = 8.58$ Hz, 2H, phenyl-2,6), 8.63 (s, H, triazole-5), 12.58 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.10 (aliphatic-CH_3), 31.50 (triazole-CH_3), 45.37 (CO-CH-S), 109.69, 109.62, 127.85, 129.25, 132.78, 133.50, 147.05, 147.19, 158.37, 170.26 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 380.0401; found: 380.0406.

2-[Benzothiazol-2-ylthio]-N-[4-(4-chlorophenyl)thiazol-2-yl]propanamide (7i)

Physical properties: M.P.: 183–185 °C, color: gray, yield: 87%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.44 (d, $J = 6.99$ Hz, 3H, aliphatic-CH_3), 4.83 (q, $J1 = 6.94$ Hz, $J2 = 13.98$ Hz, H, CO-CH-S), 7.34–7.39 (m, H, Ar-H), 7.43–7.49 (m, 3H, Ar-H), 7.57 (s, H, thiazole-5), 7.85 (d, $J = 7.95$ Hz, H, benzothiazole-7), 7.91 (d, $J = 8.58$ Hz, 2H, phenyl-2,6) , 8.02 (d, j = 7.90 Hz, H, benzothiazole-4), 12.63 (brs, H, N-H). ^{13}C NMR (300 MHz) (DMSO-d_6) δ (ppm): 19.64 (aliphatic-CH_3), 48.18 (CO-CH-S), 108.76, 121.71, 122.32, 125.08, 126.86, 127.76, 129.08, 132.29, 134.16, 135.28, 147.80, 153.12, 165.86, 171.21 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 432.0060; found: 432.0070.

2-[(1h-Benzimidazol-2-yl)thio]-N-[4-(4-chlorophenyl)thiazol-2-yl]propanamide (7j)

Physical properties: M.P.: 199–200 °C, color: white, yield: 85%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.66 (d, $J = 7.02$ Hz, 3H, aliphatic-CH_3), 4.87 (q, $J1 = 6.81$ Hz, $J2 = 13.74$ Hz, H, CO-CH-S), 7.15-7.18 (m, 2H, Ar-H), 7.47–7.51 (m, 4H, Ar-H), 7.72 (s, H, thiazole-5), 7.92 (d, $J = 8.58$ Hz, 2H, phenyl-2,6) , 12.80 (brs, 2H, N-H, benzimidazole-1). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.84 (aliphatic-CH_3), 44.80 (CO-CH-S), 109.70, 111.53, 117.86, 121.75, 122.24, 127.84, 129.25, 132.79, 133.48, 148.21, 148.76, 158.26, 170.57 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 415.0449; found: 415.0449.

N-[4-(4-Methoxyphenyl)thiazol-2-yl]-2-[(1-methyl-1H-tetrazol-5-yl)thio]propanamide (7k)

Physical properties: M.P.: 234–236 °C, color: white, yield: 57%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.62 (d, $J = 6.96$ Hz, 3H, aliphatic-CH_3), 3.78 (s, 3H, OCH_3), 3.96 (s, 3H, tetrazole-CH_3), 4.53 (q, $J1 = 6.95$ Hz, $J2 = 13.92$ Hz, H, CO-CH-S), 6.96 (d, $J = 8.91$ Hz, 2H, phenyl-3,4), 7.33 (s, H, thiazole-5), 7.81 (d, $J = 8.85$ Hz, 2H, phenyl-2,6), 12.68 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 19.59 (aliphatic-CH_3), 34.23 (tetrazole-CH_3), 48.14 (CO-CH_2-S), 55.59 (OCH_3), 99.77, 105.99, 114.25, 127.36, 128.16, 148.93, 152.87, 159.19, 159.36, 170.75 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 377.0849; found: 377.0856.

N-[4-(4-Methoxyphenyl)thiazol-2-yl]-2-[(1-methyl-1H-imidazol-2-yl)thio]propanamide (7l)

Physical properties: M.P.: 142–144 °C, color: white, yield: 52%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.44 (d, $J = 6.99$ Hz, 3H, aliphatic-CH_3), 3.58 (s, 3H, imidazole-CH_3), 3.79 (s, 3H, OCH_3), 4.15 (q, $J1 = 6.96$ Hz, $J2 = 14.01$ Hz, H, CO-CH-S), 6.97–7.02 (m, 3H, Ar-H), 7.34 (s, H, Ar-H), 7.48 (s, H, Ar-H), 7.81 (d, $J = 8.58$ Hz, 2H, phenyl-2,6), 12.56 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 17.67 (aliphatic-CH_3), 33.70 (imidazole-CH_3), 45.52 (CO-CH-S), 55.63 (OCH_3), 106.84, 114.56, 124.84, 127.48, 129.57, 137.56, 144.61, 149.33, 157.95, 159.47, 170.49 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 375.0944; found: 375.0949.

N-[4-(4-Methoxyphenyl)thiazol-2-yl]-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]propanamide (7m)

Physical properties: M.P.: 193–194 °C, color: white, yield: 42%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.51 (d, $J = 6.99$ Hz, 3H, aliphatic-CH_3), 3.57 (s, 3H, triazole-CH_3), 3.79 (s, 3H, OCH_3), 4.31 (q, $J1 = 6.96$ Hz, $J2 = 13.98$ Hz, H, CO-CH-S), 6.99 (d, $J = 8.79$ Hz, 2H, phenyl-3,4), 7.49 (s, H, thiazole-5), 7.82 (d, $J = 8.76$ Hz, 2H, phenyl-2,6), 8.64 (s, H, triazole-5), 12.52 (brs, H, N-H). ^{13}C NMR (300 MHz) (DMSO-d_6) δ (ppm): 18.10 (aliphatic-CH_3), 31.50 (triazole-CH_3), 45.33 (CO-CH-S), 55.62 (OCH3), 99.78, 106.94, 114.26, 114.58, 127.28, 127.48, 147.01, 147.19, 149.40, 157.84, 159.49, 170.04 (carbonyl). HRMS (m/z): $[M+1]^+$ calculated: 376.0896; found: 376.0904.

2-(Benzothiazol-2-ylthio]-N-[4-(4-methoxyphenyl)thiazol-2-yl]propanamide (7n)

Physical properties: M.P.: 182–184 °C, color: white, yield: 75%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.71 (d, $J = 6.99$ Hz, 3H, aliphatic-CH_3), 3.78 (s, 3H, OCH_3), 4.86 (q, $J1 = 6.88$ Hz, $J2 = 13.80$ Hz, H, CO-CH-S), 6.97 (d, $J = 8.82$ Hz, 2H, phenyl-3,5), 7.34–7.39 (m, 2H, Ar-H), 7.43–7.49 (m, H, Ar-H), 7.81–7.86 (m, 3H, Ar-H), 8.01 (d, $J = 7.86$ Hz, H, benzothiazole-4), 12.50 (brs, H, N-H). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 19.56 (aliphatic-CH_3), 47.95 (CO-CH-S), 55.59 (OCH_3), 106.13, 114.25, 114.45, 121.72, 122.32, 125.10, 126.87, 127.39, 128.06, 135.30, 149.01, 153.11, 159.23, 161.14, 165.72, 170.81 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 428.0556; found: 428.0556.

2-[(1h-Benzimidazol-2-yl)thio]-N-[4-(4-methoxyphenyl)thiazol-2-yl]propanamide (7o)

Physical properties: M.P.: 177–178 °C, color: white, yield: 85%. ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 1.66 (d, $J = 7.08$ Hz, 3H, aliphatic-CH_3), 3.79 (s, 3H, OCH_3), 4.85 (q, $J1 = 7.05$ Hz, $J2 = 14.19$ Hz, H, CO-CH-S), 6.99 (d, $J = 8.88$ Hz, 2H, phenyl-3,5) 7.13–7.18 (m, 2H, Ar-H), 7.43–7.55 (m, 3H, Ar-H), 7.83 (d, $J = 8.82$ Hz, 2H, phenyl-2,6), 12.77 (brs, 2H, N-H, benzimidazole-1). ^{13}C NMR (75 MHz) (DMSO-d_6) δ (ppm): 18.88 (aliphatic-CH_3), 44.82 (CO-CH-S), 55.63 (OCH_3), 106.90, 114.57, 122.23, 127.46, 148.80, 149.34, 157.90, 159.48, 170.40 (carbonyl). HRMS (m/z): $[M + 1]^+$ calculated: 411.0944; found: 411.0944.

Antimicrobial activity

Compounds were evaluated for their *in vitro* growth inhibitory activity against bacteria and fungi species including *E. faecalis* (ATCC51299), *E. coli* (ATCC35218), *K. pneumoniae* (ATCC700603), *P. aeruginosa* (ATCC27853) *E. coli* (ATCC25922), *C. krusei* (ATCC 6258), *C. albicans* (ATCC90028), *C. parapsilosis* (ATCC 222019), and *C. glabrata* (ATCC 90030).

Microbiological studies were performed according to the following guides: CLSI reference M07-A9 broth microdilution method.[49] The yeasts were maintained in Sabouraud dextrose broth, and the bacteria were maintained in Mueller Hinton Broth after overnight incubation at 37 °C. The inocula of test microorganisms were adjusted to match the turbidity of a McFarland 0.5 standard tube as determined with spectrophotometer, and the final inoculum size was $0.5–2.5 \times 10^{5}$ CFU/mL for antimicrobial assays. Testing was carried out in Sabouroud dextrose broth (DIFCO) and Mueller Hinton Broth at pH 7 and the twofold 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 antibacterial and antifungal assays, the compounds were dissolved in dimethyl sulfoxide (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 Sabouraud dextrose broth and Mueller Hinton Broth. Each experiment in the antimicrobial assays was replicated twice in order to define the MIC values. Chloramphenicol was used for bacteria and ketoconazole was used for yeast as standard drug.

MTT cell viability assay

HL-60 acute promyelocytic leukemia (ATCC number CCL-240^{TM}), THP-1 acute monocytic leukemia (ATCC number TIB-202^{TM}), and NIH3T3 mouse healthy fibroblast cells (ATCC number CRL-1658^{TM}) were obtained from the American Type Culture Collection. All cells were grown in RPMI 1640 medium supplemented with 2 mM L-glutamine, 10% fetal bovine serum, and 1% penicillin/streptomycin at 37 °C in a humidified incubator with a 5% CO_2 atmosphere.

Compounds were dissolved in DMSO and diluted to working concentrations with fresh medium. Control group (solvent control) was prepared with medium containing 0.1% DMSO. Doxorubicin was used as a reference drug.

The viability of the cells was assessed by MTT [(3,4,5-dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide] assay, which is based on the reduction of yellow-colored MTT by the mitochondrial dehydrogenase of intact cells to a purple formazan product. This reduction takes place only when mitochondrial reductase enzymes are active, and therefore, the conversion can be directly related to the number of viable (living) cells.

Briefly, cells were grown in 96-well plates at a density of 5×10^{3} cells per well and subjected to different compound concentrations (500, 250, 125, 62.5, and 31.25 µg/mL). After 24-h incubation, MTT solution was added to wells to reach a final concentration of 0.5 mg/mL. The cells were incubated for another 4 h, and then, current medium was removed and 100 µL of DMSO solution was added. The absorbance values were measured at 540 nm using a Cytation 3 Cell Imaging Multi-Mode Reader (BioTek, USA). Cell survival rates were expressed as the percentage of the DMSO (0.1%) solvent control and IC_{50} concentrations were calculated according to the analysis result. The absorbance values obtained were accepted as cell viability, and the data were created in the form of % calculation in Microsoft Office Excel program. In the results of the experiments performed three times independently from each other, the control group was accepted as 100, and the % values of all other concentrations were calculated according to this value. The data obtained were analyzed statistically using GraphPad Prism 6.0 program and their graphs were created.[50]

ADME parameters

In the study, the main aim was to determine the structure–activity relationship. As a part of this process, the researchers calculated the physicochemical properties, and then, the relationship between molecular structure and their properties could be concluded accordingly.[51,52] ADME

properties of the target compounds **7a–7o** were calculated by the Molsoft software[53] and SwissADME program.[54–56]

Conclusion

Fifteen new 2-heteroaryl-*N*-[4-(substituted aryl)thiazol-2-yl]propanamide derivatives **(7a–7o)** were synthesized and tested for antibacterial, antifungal, and cytotoxic activity. Among five bacteria and four Candida species, compounds **7e** and **7f** exhibited antibacterial activity, while **7i** and **7j** showed anticandidal activity. 4-Chlorophenyl substitution at fourth position of thiazole ring was noted in three of these compounds (**7f, 7i,** and **7j**). Compounds **7g** and **7j** displayed higher cytotoxic activity than reference drug against HL-60 cell line. Against THP-1 cell line, compounds **7a, 7b, 7c, 7e, 7f, 7 g, 7 h, 7i, 7k, 7l,** and **7n** showed cytotoxic activity higher than doxorubicin with selective profile. According to the predicted physicochemical properties, all compounds are expected to be administrable orally.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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