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Design and synthesis of new 4-methylthiazole derivatives: In vitro and in silico studies of antimicrobial activity

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ABSTRACT

The development of resistance against antimicrobial drugs has become a world-wide issue. It is predicted that some or perhaps all the antimicrobial drugs used in clinics will be out of the treatment protocols soon. Therefore, researchers pay more attention to the development of new antimicrobial drugs. For this purpose, we designed and synthesized new 4-methylthiazole-(benz)azole derivatives. The structural elucidation of the compounds was performed by ^{1}H-NMR, ^{13}C-NMR, HSQC, NOESY, HMBC and LC/MS-IT-TOF spectral and elemental analyses. Then, their antimicrobial activity against bacteria and fungi strains was tested. The antibacterial effect of the compounds was found valuable as compared with their anticandidal activity. By combining the findings with molecular docking results, structure-activity relationship (SAR) was explained. Thus, in the development of new antimicrobial agents which can be used as DNA gyrase inhibitors, SAR showed that the products might be used in the discovery of new antimicrobials where their activity is owed to the allosteric effect. Although the effect of compound **3f** was modest compared to the reference compound, it was better than the other synthesized compounds. Also, compound **3f** has a better allosteric effect and might be a good lead candidate to synthesize new and better active hits. In addition, it was observed that all the synthesized compounds showed half potency against *P. aeruginosa* compared to the reference drug. On the other hand, no significant difference was seen between compounds against gram-positive or gram-negative bacteria. Briefly, meaningful data to correlate the SAR with thiazole-(benz)azole hybridized compounds were presented in this study. In future projects, the mentioned ideas can be used to synthesize new compounds having better antibacterial activity, particularly against resistant organisms.

1. Introduction

Thiazole ring is a five-membered aromatic heterocycle containing sulfur and nitrogen atoms at 1st and 3rd positions. This liquid substance is slightly soluble in water and possesses moderately basic chemical character with a pKa value of 2.5 [1] Thiazole and their derivatives exist as part of the structure of molecules of great importance such as penicillines [2], cephalosporines [3], thiamine [4] and various natural bioactive compounds [5]. Thiazole containing natural antibiotics (bleomycins etc.) are produced mainly from secondary metabolites sourced from Actinomycetes and gram-positive mycelial sporulating bacteria, pretty much the genus Streptomyces [6]. Many synthetic drugs in use today such as abafungin, aminitrozole, amiphenazole, aztreonam, dasatinib, febuxostat, fentiazac, fanetizole, lurasidone, meloxicam, nitazoxanide, nizatidine, pramipexazole, ritonavir, ruvaconazole, sudoxicam, sulfathiazole, tenonitrozole, tiazofurin, thiabendazole, voreloxin, zopolrestat carry thiazole ring [7-11]. Additionally, substituted thiazole derivatives and analogous rings are also widely involved as building blocks in the structure of numerous newly designed molecules due to their diverse bioactivity reported in many

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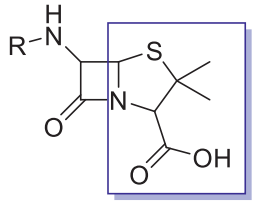


Fig. 1. The main structure of penicillins.

studies including antibacterial, anticancer, anticonvulsant, antifilarial, antifungal, anthelmintic, anti-inflammatory, antiulcer, antiviral, immunosuppressant action [12-19].

Among thiazole compounds, 2,4-disubstituted thiazole derivatives have been included in numerous studies regarding their antimicrobial activities [20]. In particular, 2-amino-1,3-thiazole pharmacophore presents as a privileged structure due to its prevalence of antibacterial activity [21]. On the other hand, aryl sulfide function is an important moiety that provides diverse biological activity to the compounds it is part of [22]. In fact, the core structure of the penicillin group antibiotics includes 5,5-dimethyl thiazolidine-4-carboxylic acid (as shown Fig. 1). Therefore, we designed our compounds to base the penicillin structure.

Today, resistance against antimicrobial drugs is a major concern. It is predicted that the drugs currently used in clinics cannot be used in the future. In fact, lists have been even created for some bacteria [23]. Despite the procedures applied clinically to reduce the resistance i.e. rational drug use and decreased antibiotic misuse, it is important to fight the resistance using different mechanisms including the development of new active molecules [24,25].

In the way of the above literature and based on the need to develop new and effective antimicrobial agents, novel 2,4-disubstituted thiazole derivatives were synthesized and evaluated for their antibacterial and antifungal activity.

2. Experimental

2.1. Chemistry

All chemicals used in the syntheses were purchased either from Merck Chemicals (Merck KGaA, Darmstadt, Germany) or Sigma-Aldrich Chemicals (Sigma-Aldrich Corp., St. Louis, MO, USA). The reactions and the purities of the compounds were observed by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum sheets obtained from Merck (Darmstadt, Germany). Melting points of the synthesized compounds were recorded by the MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were presented as uncorrected. ^{1}H NMR and ^{13}C NMR spectral analyses were achieved using a Bruker 300 MHz and 75 MHz digital FT-NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d_6. In the NMR spectra, splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; m: multiplet. Coupling constants (J) were reported as Hertz. High resolution mass spectrometric (HRMS) analyses were performed using a LC/MS-IT-TOF system (Shimadzu, Kyoto, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA).

2.1.1. Synthesis of 4-methylthiazole-2-amine (**1**)

Chloroacetone (39.77 mmol, 3.20 mL) and its equivalent thiourea (39.77 mmol, 3.028 g) were dissolved in ethanol and stirred at room temperature 4h. The reaction control was checked by thin-layer chromatography (TLC). After the completion of the reaction, the crude product was obtained by filtration and then recrystallized from ethanol.

2.1.2. Synthesis of 2-chloro-N-(4-methylthiazole-2-yl) propanamide (**2**)

Compound 1 was solved in tetrahydrofuran (THF), triethylamine was used as a catalyst. The final mixture was cooled in an ice bed, then 2-chloropropionyl chloride diluted in tetrahydrofuran was cautiously added dropwise to the solution. The mixture was stirred at room temperature for further 1h after the addition of 2-chloropropionyl chloride. The reaction was controlled by TLC. After completion of the reaction, the solvent was evaporated, and the solid product was washed with water and filtered. Subsequently, the crude product was recrystallized from ethanol.

2.1.3. General synthesis of N-(4-methylthiazol-2-yl)-2-(substituted mercapto)propanamide (**3a-3i**)

Mercapto derivatives (1.14 mmol) was dissolved in acetone (25 mL) and K_2CO_3 (0.23g, 1.71 mmol) was added to the solution followed by 2-chloro-*N*-(4-methylthiazole-2-yl)propanamide (2) (0.3 g, 1.14 mmol). The mixture was stirred at room temperature. The reaction was monitored with TLC. After the reaction was completed, acetone was evaporated, and the residue was washed with water.

2.1.4. 2-((1-Methyl-1H-tetrazol-5-yl)thio)-N-(4-methylthiazol-2-yl) propanamide (**3a**)

m. p. 188-190°C, yield 79 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.60 (d, J = 7.05 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 3.95 (s, 3H, tetrazole-$\underline{CH_3}$), 4.55 (q, J = 7.02 Hz, 1H, $\underline{H}$-C-S), 7.16 (s, 1H, Ar-H), 12.33 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.59 (thiazole-$\underline{CH_3}$), 18.90 (-$\underline{CH_3}$-C-S), 34.33 (tetrazole-$\underline{CH_3}$), 46.44 (H-$\underline{C}$-S), 127.27, 135.27, 152.02, 156.58, 169.12. For $C_9H_{12}N_6OS_2$ calculated: Elemental Analysis: %C, 38.01; %H, 4.25; %N, 29.55; found: %C, 38.03; %H, 4.24; %N, 29.56. HRMS (m/z): $[M+H]^+$ calculated 285.0587; found 285.0589.

2.1.5. 2-((1-Methyl-1H-imidazol-2-yl)thio)-N-(4-methylthiazol-2-yl) propanamide (**3b**)

m. p. 109–111 °C, yield 85 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.41 (d, J = 7.02 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 3.56 (s, 3H, imidazol-$\underline{CH_3}$), 4.11 (q, J = 6.99 Hz, 1H, $\underline{H}$-C-S), 7.01 (s, 1H, Ar-H), 7.13 (d, J = 1.23 Hz, 1H, Ar-H), 7.32 (d, J = 1.14 Hz, 1H, Ar-H), 12.29 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.55 (thiazole-$\underline{CH_3}$), 17.68 (-$\underline{CH_3}$-C-S), 33.67 (imidazole-$\underline{CH_3}$), 45.44 (H-$\underline{C}$-S), 124.75, 127.04, 129.48, 135.37, 137.79, 156.34, 170.00. For $C_{11}H_{14}N_4OS_2$ calculated: Elemental Analysis: %C, 46.79; %H, 5.00; %N, 19.84; found: %C, 46.81; %H, 4.98; %N, 19.85. HRMS (m/z): $[M+H]^+$ calculated 283.0682; found 283.0691.

2.1.6. 2-((4,5-Dihydrothiazol-2-yl)thio)-N-(4-methylthiazol-2-yl) propanamide (**3c**)

m. p. 181–183 °C, yield 82 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.51 (d, J = 7.11 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 3.46 (t, J = 7.62, 2H, dihydrothiazol), 4.14 (t, J = 8.25, 2H, dihydrothiazol), 4.66 (q, J = 7.11 Hz, 1H, $\underline{H}$-C-S), 7.15 (s, 1H, Ar-H), 12.16 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.57 (thiazole-$\underline{CH_3}$), 18.63 (-$\underline{CH_3}$-C-S), 35.81 (dihydrothiazol -$\underline{CH_3}$), 45.35 (H-$\underline{C}$-S), 64.51 (dihydrothiazol -$\underline{CH_3}$), 127.22, 135.37, 162.72, 169.46. For $C_{10}H_{13}N_3OS_3$ calculated: Elemental Analysis: %C, 41.79; %H, 4.56; %N, 14.62; found: %C, 41.77; %H, 4.59; %N, 14.60. HRMS (m/z): $[M+H]^+$ calculated 288.0294; found 288.0301.

2.1.7. 2-((5-Methyl-1,3,4-thiadiazol-2-yl)thio)-N-(4-methylthiazol-2-yl)propanamide (**3d**)

m. p. 187–189 °C, yield 79 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.57 (d, J = 7.05 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 2.69 (s, 3H, thiadiazole-$\underline{CH_3}$), 4.65 (q, J = 7.02 Hz, 1H, $\underline{H}$-C-S),

7.16 (s, 1H, Ar-H), 12.32 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.57 (thiazole-$\underline{CH_3}$), 15.71 (thiadiazole-$\underline{CH_3}$), 18.50 (-$\underline{CH_3}$-C-S), 46.44 (H-$\underline{C}$-S),127.26, 135.30, 156.37, 162.48, 167.36, 169.21. For $C_{10}H_{12}N_4OS_3$ calculated: Elemental Analysis: %C, 39.98; %H, 4.03; %N, 18.65; found: %C, 39.95; %H, 4.06; %N, 18.62. HRMS (m/z): $[M+H]^+$ calculated 301.0246; found 301.0246.

*2.1.8. N-(4-methylthiazol-2-yl)-2-((5-nitro-1H-benzimidazol-2-yl) thio)propanamide (**3e**)*

m. p. 199–201 °C, yield 80 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.64 (d, J = 7.08 Hz, 3H, -$\underline{CH_3}$-C-S), 2.33 (s, 3H, thiazole-$\underline{CH_3}$), 4.88 (q, J = 7.11 Hz, 1H, $\underline{H}$-C-S), 7.14 (s, 1H, Ar-H), 7.58 (d, J = 8.85 Hz, 1H, Ar-H) 8.03 (dd, J_1= 2.28Hz, J_2= 6.57 Hz, 1H, Ar-H), 8.29 (s, 1H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.57 (thiazole-$\underline{CH_3}$), 18.75 (-$\underline{CH_3}$-C-S), 44.47 (H-$\underline{C}$-S), 110.91, 114.10, 117.54, 127.14, 135.32, 142.14, 156.38, 156.92, 169.91. For $C_{14}H_{13}N_5O_3S_2$ calculated: Elemental Analysis: %C, 46.27; %H, 3.61; %N, 19.27; found: %C, 46.25; %H, 3.64; %N, 19.29. HRMS (m/z): $[M+H]^+$ calculated 364.0533; found 364.0534.

*2.1.9. 2-((5-Methoxy-1H-benzimidazol-2-yl)thio)-N-(4-methylthiazol-2-yl)propanamide (**3f**)*

m. p. 167–169 °C, yield 86 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.59 (d, J = 7.08 Hz, 3H, -$\underline{CH_3}$-C-S), 2.33 (s, 3H, thiazole-$\underline{CH_3}$), 3.77 (s, 3H, -$\underline{OCH_3}$), 4.68 (q, J = 7.02 Hz, 1H, $\underline{H}$-C-S), 6.77 (dd, J_1= 2.46Hz, J_2= 6.27 Hz, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 7.35 (d, J = 8.73 Hz, 1H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.65 (thiazole-$\underline{CH_3}$), 18.78 (-$\underline{CH_3}$-C-S), 44.85 (H-$\underline{C}$-S), 55.91 (-OCH_3), 97.36 (4 of benzimidazole), 111.23 (6 of benzimidazole), 115.52 (7 of benzimidazole), 126.85 (4 of thiazole), 135.28 (5 of thiazole), 148.07 (2 of benzimidazole), 155.89 (5 of benzimidazole), 157.01 (2 of thiazole), 170.23 (C=O). For $C_{15}H_{16}N_4O_2S_2$ calculated: Elemental Analysis: %C, 51.70; %H, 4.63; %N, 16.08; found: %C, 51.73; %H, 4.60; %N, 16.11. HRMS (m/z): $[M+H]^+$ calculated 349.0787; found 349.0794. Solubility: practically insoluble in water and anhydrous ethanol, soluble in hot ethanol, freely soluble in DMSO.

*2.1.10. 2-((5-Methyl-4H-1,2,4-triazol-3-yl)thio)-N-(4-methylthiazol-2-yl)propanamide (**3g**)*

m. p. 100–102 °C, yield 78 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.48 (d, J = 7.02 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 3.55 (s, 3H, triazol-$\underline{CH_3}$), 4.27 (q, J = 6.99 Hz, 1H, $\underline{H}$-C-S), 7.15 (s, 1H, Ar-H), 8.62 (s, 1H, Ar-H), 12.20 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.58 (thiazole-$\underline{CH_3}$), 18.17 (-$\underline{CH_3}$-C-S), 31.47 (triazol-$\underline{CH_3}$), 45.32 (H-$\underline{C}$-S), 127.23, 135.44, 147.06, 147.15, 156.15, 169.50. For $C_{10}H_{13}N_5OS_2$ calculated: Elemental Analysis: %C, 42.38; %H, 4.62; %N, 24.71; found: %C, 42.38; %H, 4.62; %N, 24.71. HRMS (m/z): $[M+H]^+$ calculated 284.0634; found 284.0637.

*2.1.11. 2-((1H-benzimidazol-2-yl)thio)-N-(4-methylthiazol-2-yl) propanamide (**3h**)*

m. p. 181–183 °C, yield 82 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.62 (d, J = 7.08 Hz, 3H, -$\underline{CH_3}$-C-S), 2.33 (s, 3H, thiazole-$\underline{CH_3}$), 4.82 (q, J = 7.08 Hz, 1H, $\underline{H}$-C-S), 7.13 – 7.18 (m, 3H, Ar-H), 7.45 – 7.48 (m, 2H, Ar-H), 12.60 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.57 (thiazole-$\underline{CH_3}$), 18.85 (-$\underline{CH_3}$-C-S), 44.65 (H-$\underline{C}$-S), 114.51, 122.20, 127.16, 135.33, 149.03, 156.35, 169.93. For $C_{14}H_{14}N_4OS_2$ calculated: Elemental Analysis: %C, 52.81; %H, 4.43; %N, 17.60; found: %C, 52.84; %H, 4.40; %N, 17.63. HRMS (m/z): $[M+H]^+$ calculated 319.0682; found 319.0691.

*2.1.12. 2-(Benzothiazol-2-ylthio)-N-(4-methylthiazol-2-yl) propanamide (**3i**)*

m. p. 194–196 °C, yield 82 %, ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ 1.67 (d, J = 7.05 Hz, 3H, -$\underline{CH_3}$-C-S), 2.34 (s, 3H, thiazole-$\underline{CH_3}$), 4.91 (q, J = 7.05 Hz, 1H, $\underline{H}$-C-S), 7.16 (s, 1H, Ar-H), 7.36 – 7.41 (m, 1H, Ar-H), 7.45 – 7.51 (m, 2H, Ar-H), 7.84 (d, J = 7.62 Hz, 1H, Ar-H), 8.04 (d, J = 7.95 Hz, 1H, Ar-H), 12.38 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 11.60 (thiazole-$\underline{CH_3}$), 18.94 (-$\underline{CH_3}$-C-S), 46.45 (H-$\underline{C}$-S), 121.80, 122.43, 125.30, 126.97, 127.31, 135.38, 152.94, 156.35, 164.75, 169.26. For $C_{14}H_{13}N_3OS_3$ calculated: Elemental Analysis: %C, 50.12; %H, 3.91; %N, 12.53; found: %C, 50.09; %H, 3.93; %N, 12.51. HRMS (m/z): $[M+H]^+$ calculated 336.0294; found 336.0296. Solubility: practically insoluble in water and anhydrous ethanol, soluble in hot ethanol, freely soluble in DMSO.

2.2. Antimicrobial activity

The antimicrobial activity of final compounds (**3a-3i**) compounds was screened on eight bacterial and three fungal strains according to the standard procedure of CLSI [26,27] as described in the previous study [28]. The antibacterial activities of the synthesized compounds were tested against *Escherichia coli* (ATCC 25922), *Serratia marcescens* (ATCC 8100), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 27853), *Enterococcus faecalis* (ATCC 2942), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29213), *and Staphylococcus epidermidis* (ATCC 12228). *Candida albicans* (ATCC 24433), *Candida krusei* (ATCC 6258), and *Candida parapsilopsis* (ATCC 22019) were used to test the antifungal activity of the same compounds. Tetracycline (against bacterial strains) and fluconazole (against candida strains) were used as standard reference drugs.

2.3. ADME parameters

The prediction of the physicochemical parameters of compounds (**3a-3i**) was calculated using the SwissADME web-based program [29-31].

2.4. Docking study

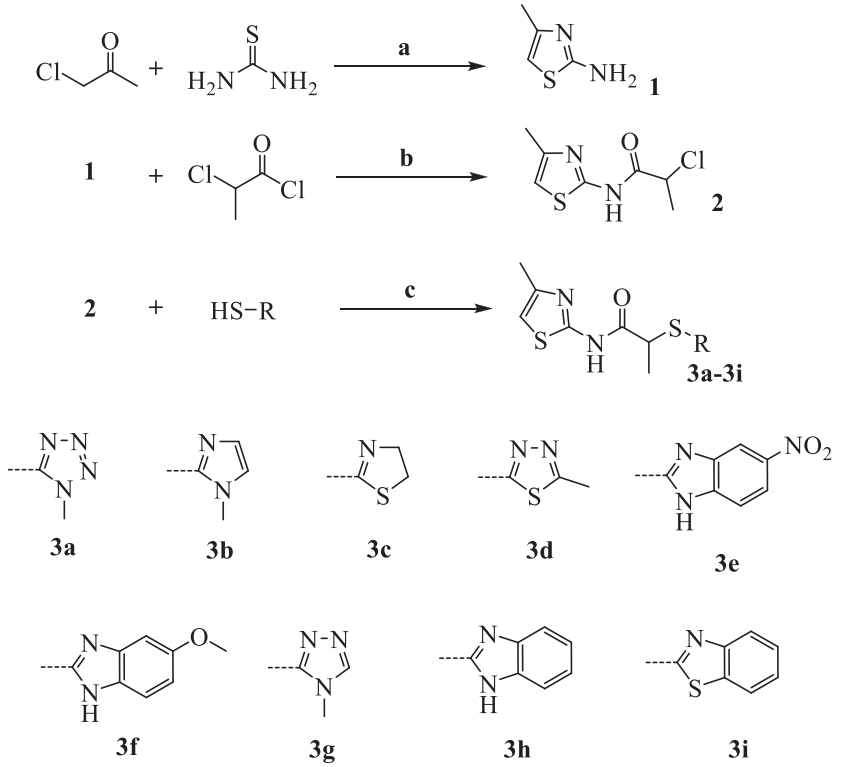
The crystal structure of the DNA gyrase enzyme was retrieved from the Protein Data Bank server (PDB code: 5NPK). The protein preparation process, ligand preparation process, grid generation, docking, and visualization studies were worked on Schrodinger's Maestro molecular modeling package [32].

The water molecules were removed from the crystal structure. Ligands were set to the physiological pH (pH = 7.4±1.0) at the protonation step. In molecular docking simulations: Glide/SP docking protocols were applied for the prediction of topologies of **3f** and **3i** at the allosteric pocket of the target structure [33], after the preparation steps, the molecules were docked to the allosteric pocket of 5NPK. The docking study was used here to predict the relationship between structure and inhibition of DNA gyrase enzyme. After determination of the best poses, strain energy calculation and rescoring function [34] was performed for the ligands with more than 4 kcal/mol energy difference between the docked and free conformations received to eliminate the calculation errors.

3. Results and discussion

3.1. Chemistry

The compounds **3a-3i** were synthesized as summarized in Scheme 1. Initially, the 4-methylthiazole-2-amine (**1**) resulted from the reaction of thiourea with 1-chloropropan-2-one. Then, the obtained compound **1** was acylated to gain 2-chloro-*N*-(4-methylthiazol-2-yl)propanamide (**2**). Lastly, the mercapto derivatives and compound **2** were reacted in acetone to obtain *N*-(4-methylthiazol-2-yl)propanamide derivatives as the core structure. The structures of synthesized compounds (**3a-3i**) were confirmed



Scheme 1. The synthesis diagram of the compounds **3a–3i**. *Reagents and conditions*: (**a**) EtOH, r.t., 24 h; (**b**) TEA, THF, $ClCOCH_2Cl$, 0–5 °C, then r.t 3 h; (**c**) Acetone, K_2CO_3, r.t.

by ^{1}H-NMR, ^{13}C-NMR, 2D-NMR (HSQC, NOESY, HMBC) and high-resolution mass spectroscopy (HRMS).

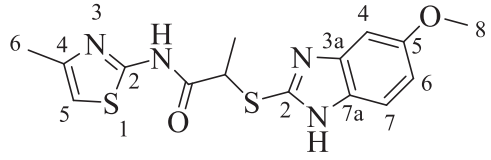
3.1.1. NMR spectrum

In the ^{1}H-NMR and ^{13}C-NMR spectra, the peaks were seen at estimated aromatic and aliphatic regions. The mass peaks [M+1] of the compounds were in agreement with their predicted molecular formula (**3a-3i**).

The ^{1}H-NMR spectra showed signals at δ 2.33–2.34 ppm (CH_3) for 4-methylthiazole protons which were singlet peaks. Propanamide protons were observed at δ 1.41–1.67 ppm (CH_3) as doublet and δ 4.11–4.91 ppm (CH) as quartet peaks. A broad singlet peak seen at δ 12.16–12.60 ppm indicated the propanamide N–H proton. The appearance of a pair of singlets, doublets, triplets, and/or multiplets δ 6.77–8.62 ppm were due to the aromatic protons of the aromatic rings. The ^{13}C-NMR spectra showed signals at δ 11.55–11.65 ppm for 4-methyl thiazole carbon (CH_3), while those at δ 17.68–18.94 ppm were for propanamide (CH_3), δ 44.47–46.45 ppm for propanamide (CH), δ 97.36–167.36 ppm for aromatic carbon and δ 169.12–170.23 ppm for carbonyl (C=O) carbon. M+1 peaks in LC-MS/MS spectra were in agreement with the calculated molecular weight of the target compounds (**3a–3i**). Elemental analysis results for C, H, and N elements agreed to the calculated values for the synthesized compounds.

3.1.2. Evaluation of 2D-NMR spectra

2D advanced NMR studies (HSQC, NOESY, HMBC) were carried out by taking compound **3f** (Scheme 2), which has the highest activity among the synthesized compounds. Firstly, the obtained data from the H^1-NMR and C^{13}-NMR spectrum was analyzed. Then, the HSQC spectrum was merged with H^1 and C^{13}-NMR spectrums to match the carbons that had hydrogen(s). Then, using the HMBC data, all carbons were marked. As a result, we exactly matched all



Scheme 2. As numbered the molecular structure of compound **3f**.

carbons and also found new two peaks that we could not observe in the C^{13}-NMR spectrum. These were belonging to 3a and 7a of the benzimidazole carbons observed at δ 135.10 and δ 139.8 ppm, respectively.

3.2. ADME parameters

The computational results were shown in Table 1. According to these results, there was no violation of Lipinski's rule of five [35]. Even if there is no exact finding in practice, these scores are in harmony with the activity potential of the compounds and these approximations would inspire drug design. In fact, it may be suggested that synthesized compounds may have a good pharmacokinetic profile. Thus, the drug-likeness issue of the compounds was tipped to positive.

3.3. Antimicrobial activity

Although there are numerous antimicrobial studies about substituted thiazoles from different positions, 2,4-disubstituted thiazoles are more attractive to eliminate the invasive microbes and have generally fewer side effects than other derivatives [11,36-39]. As a result, in this study, the core structure of the final compounds

Table 1
Physicochemical, pharmacokinetic and medicinal chemistry properties of the final compounds (by SwissAdme) **3a-3i**.

	Physicochemical Properties					Pharmacokinetics		Medicinal Chemistry	
	HBA	HBD	TPSA	Log $P_{o/w}$	Log S	GIA	Log K_p	RoF (V)	SA
3a	5	1	139.13	1.26	-4.01	High	-6.98	Yes (0)	3.26
3b	3	1	113.35	1.81	-3.93	High	-6.65	Yes (0)	3.15
3c	3	1	133.19	2.13	-4.79	High	-6.38	Yes (0)	3.64
3d	4	1	149.55	2.22	-5.47	Low	-6.23	Yes (0)	3.42
3e	5	2	170.03	2.06	-6.47	Low	-6.22	Yes (0)	3.39
3f	4	2	133.44	2.68	-5.85	Low	-6.03	Yes (0)	3.27
3g	4	1	126.24	1.38	-4.59	High	-7.08	Yes (0)	3.27
3h	3	2	124.21	2.80	-5.69	High	-5.83	Yes (0)	3.17
3i	3	1	136.66	3.53	-6.87	Low	-5.30	Yes (0)	3.32
RF- 1	9	6	181.62	-0.40	-3.64	Low	-8.83	Yes (1)	5.17
RF- 2	7	1	81.65	0.88	-1.63	High	-7.92	Yes (0)	2.91

HBA: H-bond acceptor, HBD: H-bond acceptor, TPSA: Topologic polar surface area (Å²) Log $P_{o/w}$: *Consensus* Log $P_{o/w}$ (Average of all five predictions), Log S: Water Solubility, GIA: Gastrointestinal absorption, Log K_p: skin permeation (cm/s) RoF (V): Rule of Five (violation number), SA: Synthetic accessibility from 1 (very easy) to 10 (very difficult). RF- 1: Tetracycline, RF-2: Fluconazole

Table 2
Antifungal activity of the compounds **3a-3i** as MIC values (µg/mL)

	A	B	C
3a	125.00	125.00	62.50
3b	125.00	125.00	62.50
3c	>250.00	>250.00	62.50
3d	125.00	125.00	15.63
3e	125.00	125.00	125.00
3f	250.00	250.00	250.00
3g	125.00	125.00	125.00
3h	125.00	125.00	125.00
3i	>250.00	125.00	>250.00
S. D.	7.81	7.81	3.91

A: *C. albicans* (ATCC 24433), **B:** *C. krusei* (ATCC 6258), **C:** *C. parapsilopsis* (ATCC 22019). **S.D:** Standard Drug= Fluconazole.

was synthesized according to this superiority and inspired also by ß-lactams.

3.3.1. Anticandidal activity

The final compounds (**3a-3i**) were tested against *Candida albicans* (ATCC 24433), *Candida krusei* (ATCC 6258), and *Candida parapsilopsis* (ATCC 22019). The results were showed in Table 2.

Based on the results, there was no compound worthy of note as an antifungal drug except **3d** (MIC: 15.63 µg/mL against *C. parapsilopsis*). The standard drug, fluconazole, was found 4-fold more active than compound **3d**. Therefore, the activity potential as anticandidal was found modest, yet it may be useful as a base to develop anticandidal drugs. 5-Methylthiadiazole moiety showed better activity than (benz)azoles, therefore our future studies for the development of anticandidal drugs would be in designing a linkage of thiazole-thiadiazole and modification of the substitutes.

3.3.2. Antibacterial activity

The final compounds (**3a-3i**) were tested against *Escherichia coli* (ATCC 25922), *Serratia marcescens* (ATCC 8100), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 27853), *Enterococcus faecalis* (ATCC 2942), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29213). The results were shown in Table 3.

According to the results of *in vitro* study, the final compounds showed modest potency. In general, the MIC values of the tested compounds were approximately 125.00 µg/mL. However, compound **3f** against *E. coli* (ATCC 25922) and S. *marcescens* (ATCC 8100) and compound **3i** against *S. marcescens* (ATCC 8100) and *E. faecalis* (ATCC 2942) were found active at 62.50 µg/mL. Also, the inhibition activity of compound **3f** (MIC:15.63 µg/mL) has an 8-fold or 16-fold higher potency than other compounds against *S. aureus* (ATCC 29213). It was found that all synthetic compounds show half-effect activity against *P. aeruginosa* compared to the reference drug.

The most active compound against *E. coli* was **3f**; against *S. marcescens* were **3f** and **3i**; against *E. faecalis* was **3i**. Also, against the rest of the strains, all compounds showed the same potency. There were no differences in potency between the tested compounds against gram-positive (+) and gram-negative(-) strains.

As a simple assertion about antimicrobial results, the final compounds, 2,4-disubstituted thiazole derivatives, showed modest activity at most against the invasive bacteria and fungus. According to previous studies by different groups [40-42] they used chalcone moiety, hydrazide, and several bulky groups at the 4th position, then they viewed the docking performance at the DNA gyrase active site. In those studies, although a significant antimicrobial activity was observed, DNA gyrase interactions were found just enough. However, 2,4-disubstituted thiazole moiety is an important motif to observe the antimicrobial activity. Alternatively, since the thiazole ring system allows for substitution diversity and also can be easily synthesized, it is important to make recommendations for future studies, namely structure-activity relationship (SAR).

Based on the above information, the focus was upon those two compounds to determine the mechanism of action. Since there was no enough concentration for effective inhibition to occur, either the binding energy between the compounds and the active pocket was low or the compounds could not fit well inside the pocket. But it is more logical to determine the shapes of interactions at the binding site and then discuss the structure-activity relationship (SAR) for developing new antimicrobial agents. Therefore, the common features of the compounds and bacteria strains were determined. First, the common feature of the gram (+) and the gram (-) strains, both have a DNA gyrase enzyme. *S. aureus* and *E. coli* are commonly used for the isolation of DNA gyrase [43,44]. Secondly, the active compounds have the thiazole-benzazole moieties, and designing with the bioisosteric replacement is fashion-

Table 3
Antibacterial activity of the compounds **3a-3i** as MIC values (μg/mL).

	A	B	C	D	E	F	G	H
3a	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3b	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3c	>250.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3d	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3e	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3f	62.50	62.50	125.00	125.00	125.00	125.00	15.63	125.00
3g	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3h	125.00	125.00	125.00	125.00	125.00	125.00	250.00	125.00
3i	>250.00	62.50	125.00	125.00	62.50	125.00	125.00	125.00
S. D.	7.81	3.91	7.81	62.50	15.63	7.81	<0.98	125.00

A: *E. coli* (ATCC 25922), **B:** *S. marcescens* (ATCC 8100), **C:** *K. pneumoniae* (ATCC 13883), **D:** *P. aeruginosa* (ATCC 27853), **E:** *E. faecalis* (ATCC 2942), **F:** *B. subtilis* (ATCC), **G:** *S. aureus* (ATCC 29213), **H:** *S. epidermidis* (ATCC 12228) **A-D:** Gram negative bacteria, **E-H:** Gram positive bacteria. **S.D:** Standard Drug=Tetracycline

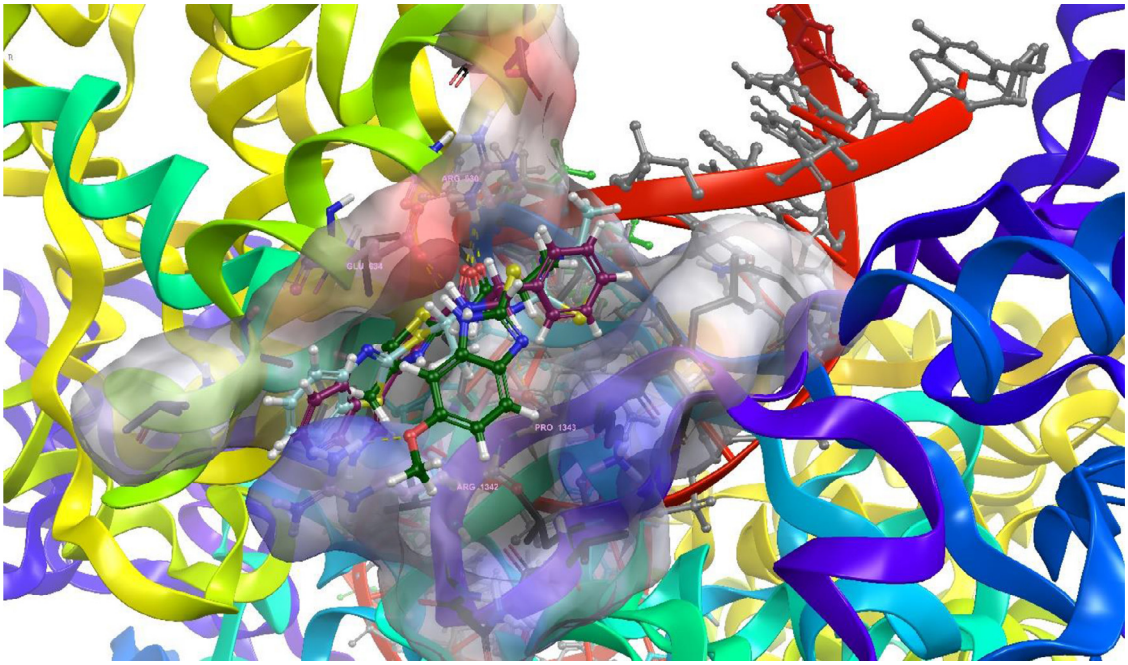


Fig. 2. Compounds 3f (green carbons) and 3i (turquoise carbons), and reference compound (maroon carbons) in DNA gyrase allosteric pocket (PDBID: 5NPK). The active site residues were draw in stick form (black carbons). If there is an interaction between ligand and residue, these residues were represented in a ball-stick form (plum carbons). Red line represents the DNA chain.

able to obtain active compounds since time immemorial. A previous study [33] has reported that compound 1 (reference compound: RF, include thiophene and pyrrolopyridine moieties as bioisosteres of thiazole and benzazoles, respectively) showed modest activity against DNA gyrase enzyme. Because of these reasons, we built up the docking study on DNA gyrase considering this work.

3.3.3. Molecular docking study

The aim of the DNA gyrase poisoning is simply based on the settling of the compound between the DNA and enzyme [45,46], however it was reported the discovering of a new pocket for thiophene analogs in 2017 [33]. It was observed that the compounds have no interaction with nucleotides in this pocket, albeit it showed modest activity by an allosteric mechanism. Accordingly, the products in our study were simulated in the allosteric pocket. The collected best poses were shown in Figs. 2–6, and the results of strain rescore was displayed in Table 4.

According to docking results, collected poses of **3f** and **3i** have not shown the strain penalty, therefore the results should be in harmony with the experimental study. Also, compound 3f showed three H-bonds with Arg630, Glu634, and Arg1342. On the other hand, compound **3i** displayed two H-bond with Arg630 and Pro1343, and one π- π stacking with Arg1342. Glutamic acid (634) and arginine (630) amino acids were described as important residues to obtain the inhibitor activity on the enzyme. Thus, the *in-silico* study supports the *in vitro* study due to differences in the interactions. The thiazole moiety of compound **3f** and thiophene moiety of the reference drug (RF) were in the same direction in the pocket which facilitates the interaction with significant residues. In spite of that compound **3i** was docked around the same coordinates as those of the reference compound, the thiazole moiety was unable to fit into the thiophene cavity, therefore, its inhibition activity against DNA gyrase was lower than **3f**.

Despite the bicyclics, pyrrolizidine (RF) and benzimidazole (**3f**), located in different areas, interacted with the same residue

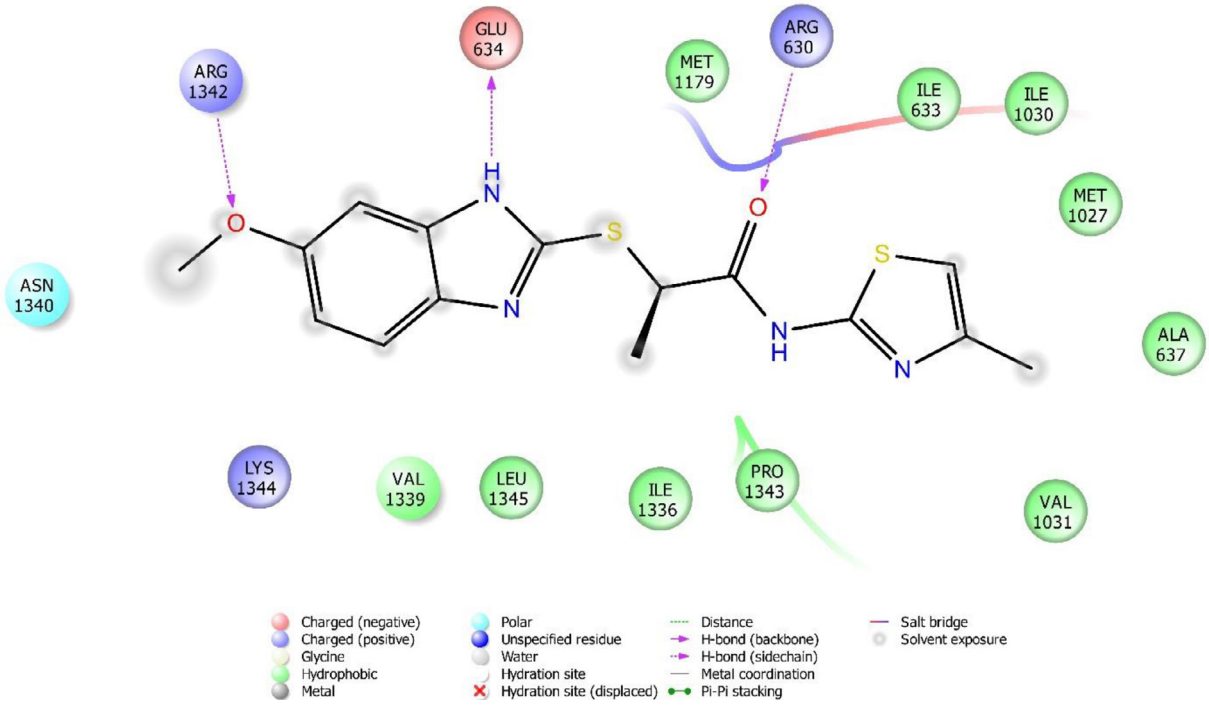


Fig. 3. 2D interaction diagram of **3f** in active site. (PDBID: 5NPK).

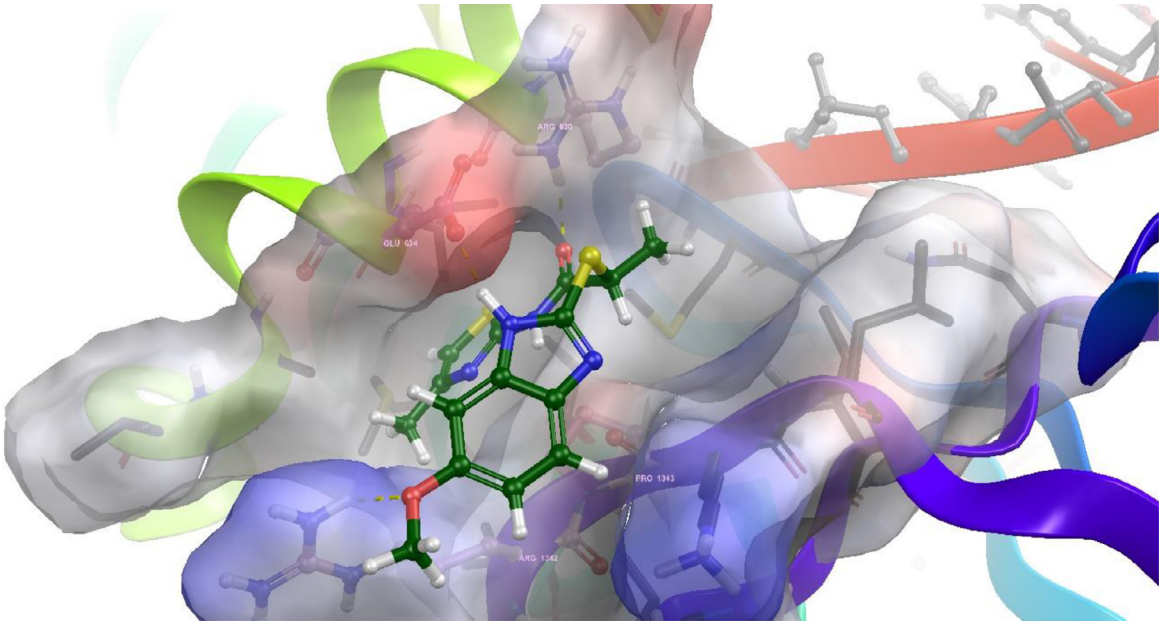


Fig. 4. Compound **3f** in active site as 3D pose. Red line represents the DNA chain. (PDBID: 5NPK).

(Arg1342) by approaching from a different side causing benzimidazole N_1 atom to form H-bond with this residue. Thus, it is thought that the benzimidazole ring was a better choice than benzothiazole ring for this activity. Additionally, each final compound can be useful according to its potential sites (N, O, S) for ligand-complex studies in the future, like one of the known antimicrobial elements, silver. Due to the silver(I) complexes for antimicrobial applications [47-49], the combination of the silver(I) and the compounds can improve the antimicrobial activity.

Briefly, because of the simple, cheap, and no time-consuming synthesis of 2,4-disubstituted thiazoles and their high potential chemotherapeutic effects, the following modifications recommended for designing new antibacterial molecules with better activity:

- 4-Methyl substituent can be replaced with small polar moieties such as chlorine, hydroxy, oxo, fluorine, and trifluoromethyl which may enable the interaction with Arg1342.
- The Propionamide chain can be enlarged between two-four carbons to reach the hydrophobic cavity.
- More than one substitution on benzimidazole, especially 5,6-disubstituted derivatives may be convenient to increase the activity allosterically.

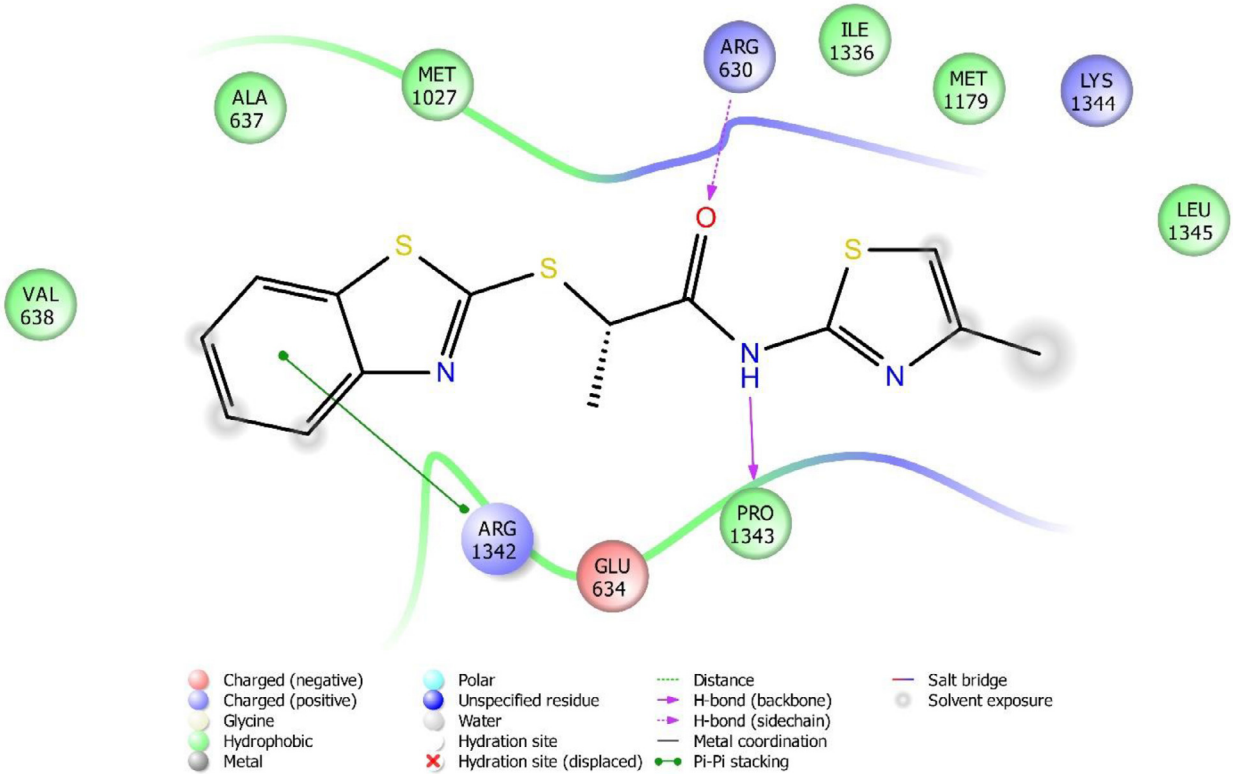


Fig. 5. 2D interaction diagram of compound **3i** in active site. (PDBID: 5NPK).

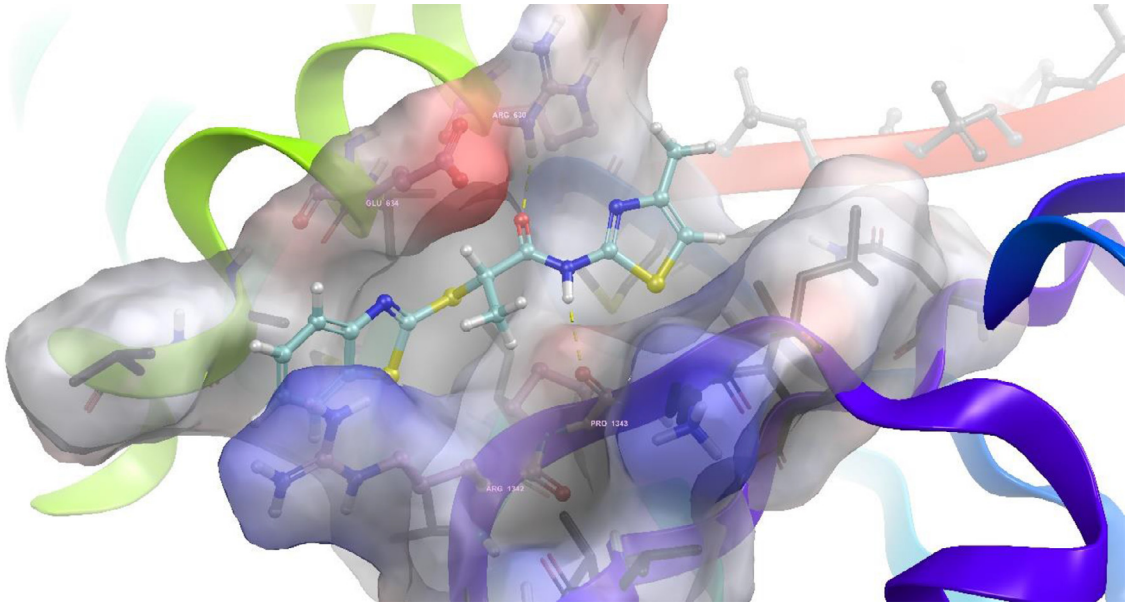


Fig. 6. Compound **3i** in active site as 3D pose. Red line represents the DNA chain.

Table 4
Strain rescore results.

Compound	Strain_Penalty	Strain_Energy	Bound_Energy	Unbound_Energy	Energy_Offset
3i	0.00	3.45	10.39	6.94	4.00
3f	0.00	4.02	12.27	8.26	4.00

strain penalty was calculated by the following calculation (=[(E{bound}-E{free}) - energy_offset] * scale_factor, if [E{bound}-E{free} - energy_offset] > 0).

4. Conclusion

In this study, novel (benz)azole derivatives including 4-methylthiazole were synthesized and investigated for their antimicrobial activity. The final compounds showed antibacterial activity between modest and good activity against gram(+) and gram-(-) strains. Compound **3f** had more attractive values against different strains. On the other hand, the results of the docking study gave the hope to fight against the development of antibacterial resistance, as well as the design of new compounds. But above all, since the antimicrobial agents used in clinics usually are applied through oral or semi-solid forms, ADME parameters should be considered at the beginning of the designing of new compounds. Briefly, meaningful data to correlate the SAR with thiazole-(benz)azole hybridized compounds were presented in this study. As a future project, the mentioned ideas will be used to synthesize new compounds having better antibacterial activity, particularly against resistant organisms.

5. Ethics approval and consent to participate

Not applicable.

6. Human and animal rights

Not applicable.

7. Consent for Publication

Not applicable.

8. Availability of DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available along with the manuscript.

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Declaration of Competing Interest

The author confirms that this article content has no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130692.

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