FABAD J. Pharm. Sci., 47, 2, 231-240, 2022
Doi: 10.55262/fabadeczacilik.1134587
RESEARCH ARTICLE

Synthesis and Antibacterial Evaluation of Novel Benzimidazole, Benzothiazole, Benzofurane, and Naphtofurane Derivatives of Aminothiazoles

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SUMMARY

The thiazole ring is the core of bioactive molecules that generate broad activity. These activities include anticonvulsant, antimicrobial, antituberculosis, antiviral, etc. In this work, starting from seconder/cyclic amines, new compounds containing thiazole and benzimidazole/benzothiazole/benzofurane/naphtofurane rings were synthesized, and their antimicrobial effects were evaluated. 9 compounds were synthesized by converting the seconder and cyclic amines to thiourea, and continued by thiazole ring closure. Ring closure was achieved by methylene-carbonyl condensation except conventional methods. Compound characterization was realized by FT-IR, ^{1}H NMR and ^{13}C NMR and HRMS. Compounds did not show significant activity on bacterial strains. Nine aminothiazole derivatives have been synthesized successfully. Compounds did not show important antibacterial activity and thus were evaluated as inactive.

Key Words: *antibacterial, aminothiazole, benzothiazole, benzofurane, naphtofurane*

Aminotiyazollerin Benzimidazol, Benzotiyazol, Benzofuran ve Naftofuran Türevlerinden Yeni Bileşiklerin Sentezi Ve Antimikrobiyal Etkilerinin Değerlendirilmesi

ÖZ

Tiyazol halkası, birçok alanda biyolojik aktivite oluşturan moleküllerin çekirdeğidir. Bu aktiviteler arasında antikonvülsan, antimikrobiyal, antitüberküloz, antiviral vb. farmakolojik etkiler yer almaktadır. Bu çalışmada sekonder/siklik aminlerden yola çıkılarak tiyazol ve benzimidazol/benzotiyazol/benzofuran/naftofuran halkaları içeren yeni tiyazol türevleri sentezlenmiş ve antimikrobiyal etkileri değerlendirilmiştir. Bileşiklerin sentezinde, sekonder veya siklik aminler tiyoüreye dönüştürülerek 9 bileşik sentezlenmiş ve tiyazol halka kapanması ile devam edilmiştir. Halka kapatma, konvansiyonel yöntemler dışında metilen-karbonil kondenzassyonuyla gerçekleşmiştir. Bileşiklerin karakterizasyonu FT-IR, ^{1}H NMR ve ^{13}C NMR ve HRMS ile gerçekleştirilmiştir. Bileşikler, bakteri suşları üzerinde önemli aktivite göstermedi. 9 aminotiyazol türevi başarıyla sentezlenmiştir. Bileşikler önemli bir antibakteriyel etki göstermediğinden inaktif olarak tanımlanmıştır.

Anahtar Kelimeler: *antibakteriyel, aminotiyazol, benzotiyazol, benzofuran, naftofuran*

Received: 20.02.2022
Revised: 20.03.2022
Accepted: 29.03.2022

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INTRODUCTION

The discovery and clinical use of antibacterial drugs are one of the most outstanding achievements in the history of health (Gajdacs, 2019). Human lifespan has increased since the 1850s, which was manifested by the improvements that treated or prevented infectious diseases (Hayward, 2016). Today, however, bacterial resistance is growing with the decrease in the development of antibacterial drugs, and as a result, treatment options become more limited (Nambiar, 2014). Over the past few years, there has been increasing focus on the challenge of antimicrobial resistance. Despite discovering of new developments, there is still a long way to go to eliminate certain threats (Tomasi, 2018).

Individual infectious diseases usually have their specific bacterial strains. Among the microbial strains, *E. coli*, which causes diseases such as urinary tract infections, sepsis, meningitis, enteric, diarrhoeal (Kaper, 2004); *S. aureus*, which causes diseases such as bacteremia, infective endocarditis, pneumonia (Dayan, 2016; Oliveira, 2018); *Salmonella* species causes gastroenteritis, septicemia, and fever (Jajere, 2019).

Thiazole is the core of compounds with a wide range of activities (Rouf, 2015; Chhabria, 2016; Kashyap, 2018; Kumawat, 2018). These activities include anticonvulsant, antimicrobial, antituberculosis, antiviral, etc. (Parekh, 2012; Ayati, 2015; Althagafi, 2019; Singh, 2020; Borcea, 2021; Petrou, 2021). Previous research revealed that thiazole derivatives will be an essential basis for producing biologically active compounds. Also, the activity of compounds with a 2-aminothiazole nucleus is present (Makam, 2014; Wan, 2020; Elsadek, 2021). Besides, bicyclic heterocyclic rings are highly interested in drug discovery, with their potential of making hydrophobic and hydrogen bonding interactions. Benzimidazole, benzofurane, benzothiazole, and naphtofurane are among these rings, and they are present in drugs e.g., albendazole, pramipexole, amiodarone, and rubicordifolin, respectively. Conventional thiazole synthesis is realized by the Hantzsch method. However, there are also different ring synthesis methods. In one, benzoyl thioureas are reacting with bromoacetyl arenes, which include two mechanistic steps; the first, include the attack of sulfur to acyl bromide, and the second represents the carbonyl-methylene condensation (Ried, 1976; Sabbaghan, 2011; Belveren, 2017). Also, our group previously synthesized a series of compounds with this type of thiazole closure, and reported their acetylcholinesterase inhibitory activity (Sahin, 2018; Demirayak, 2019). In this study, cyclic and acyclic amines are converted to thiourea, then reacted with acyl bromides to obtain nine novel compounds. These compounds structures were elucidated and antibacterial activity was tested. A significant number of targets exist for antibacterial activity, including DNA gyrases, cell membrane disruption, protein synthesis, nucleic acid synthesis, biological metabolic compound synthesis inhibitors, secA inhibitors, etc. Screening of novel compounds such as in this study is essential to find their activity and then investigate their mechanism of action. However, as no significant activity is observed in the compounds (1-9), the mechanism of action is not investigated (Chen, 2010; Silver, 2016).

MATERIAL AND METHODS

Chemistry

Starting and intermediate compounds were supplied from Sigma-Aldrich, VWR, or Honeywell. Melting points (m.p.) were determined by Stuart MP90 digital melting point apparatus. Synthesis steps were checked by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates. Spectroscopy was measured with the following instruments: Fourier transform-infrared spectroscopy (FT-IR) (Perkin Elmer S, Shimadzu Affinity 1S spectrophotometer (Shimadzu, Tokyo, Japan); Nuclear magnetic resonance (NMR), Agilent 300 MHz NMR spectrometer (Agilent Technologies, California, USA), in dimethyl sulfoxide (DMSO)-d6. TMS was used as a standard. For high resolution mass spectroscopy, M+1 peaks were determined by Shimadzu 8040 Liquid Chromatography with tandem mass spectrometry (LC/MS/MS) system

(Shimadzu, Tokyo, Japan).

Bromination of 2-acetylbenzimidazole, 2-acetylbenzofurane and 2-acetylnaphtofurane

Heterocyclic methyl ketones were dissolved in acetic acid. An equal mole of bromine was diluted in AcOH, added dropwise, and refluxed until the reaction was complete. Then reaction left to cool, poured into cold water, and precipitation was collected, and recrystallized from ethanol. Checked for their melting point and compared with literature data.

Bromination of 2-acetylbenzothiazole

Heterocyclic methyl ketones were dissolved in ethyl acetate. An equal mole of copper (II) bromide ($CuBr_2$) were diluted in ethyl acetate, added dropwise, and refluxed until the reaction was complete. Then reaction left to cool, filtered off, and the liquid was evaporated. Obtained solid materials were recrystallized from ethanol. Checked for their melting point and compared with literature data.

Synthesis of benzoylthioureas

Amines (dimethylamine, pyrrolidine, piperidine, hexamethyleneimine, and morpholine) were treated with NH_4SCN and benzoyl chloride to obtain benzoylthioureas (Figure 1). Firstly, ammonium thiocyanate was dissolved in acetone. Benzoyl chloride (diluted in acetone) was added dropwise at room temperature. Then the equal mole of the corresponding amine is added and mixed for 10 min at room temperature and 1 h reflux. Washed with warm ethanol and used as it is for the next step.

Synthesis of tested compounds 1-9

Benzoylthioureas and bromoacetyl aryl derivatives were refluxed in ethanol to get final compounds 1-9 by a methylene-carbonyl condensation (Demirayak, 2019), as shown below (Figure 1). After the reaction was complete, mixture was left to cool, and precipitation was collected, and recrystallized from ethanol. Compound characterization has been made by IR, ^{1}HNMR, ^{13}CNMR, and HRMS spectra.

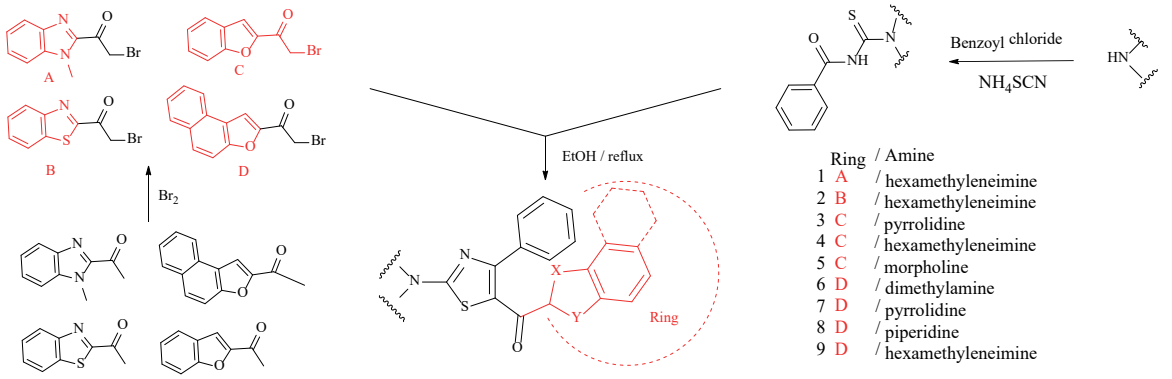


Figure 1. General synthesis of compounds

(2-(azepan-1-yl)-4-phenylthiazol-5-yl)(1-methyl-1H-benzo[d]imidazol-2-yl)methanone (Compound 1)

Yield 72%, light yellow, mp 230.3 °C. FT-IR ῡmax (cm^{-1}): 3041 to 2857 (C—H), 1620 (C═O), 1539 to 1330 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 1.56 (4H, brs, hexamethylene-CH_2), 1.80 (4H, brs, hexamethylene-CH_2), 3.69 (4H, brs, N(CH_2)$_2$), 3.96 (3H, s, N-CH_3), 7.25-7.67 (9H, m, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 27.47, 32.23 (Benzimidazole-CH_3), 111.57, 121.01, 123.49, 125.19, 127.78, 129.00, 129.81, 136.57, 136.72, 141.10, 148.22, 152.37, 164.13, 173.22 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{24}H_{24}N_4OS$: 416.1784; found: 416.1786.

(2-(azepan-1-yl)-4-phenylthiazol-5-yl)(benzo[d]thiazol-2-yl)methanone (Compound 2)

Yield 57%, light yellow solid, mp 176.1 °C. FT-IR ῡmax (cm^{-1}): 3050 to 2848 (C—H), 1602 (C═O), 1520 to 1280 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 1.58 (4H, brs, CH_2), 1.83 (4H,

brs, CH_2), 3.75 (4H, brs, $N(CH_2)_2$), 7.23-7.50 (3H, m, Ar-H), 7.51-7.80 (4H, m, Ar-H), 8.06-8.35 (2H, m, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 27.49($(CH_2)_3$), 54.55 ($N(CH_2)_2$), 123.42, 125.15, 127.66, 127.91, 129.43, 130.05, 136.24, 142.50, 144.29, 153.53, 169.92 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{23}H_{21}N_3OS_2$: 420.1199; found: 420.1199.

Benzofuran-2-yl(4-phenyl-2-(pyrrolidin-1-yl) thiazol-5-yl)methanone (Compound 3)

Yield 65.5%, orange solid, mp 166.8 °C. FT-IR ῡmax (cm^{-1}): 3108 to 2881 (C─H), 1542 (C═O), 1459 to 1299 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.02 (4H, t, J: 6.66 Hz, pyrrolidine-CH_2), 3.51 (4H, brs, $N(CH_2)_2$), 7.15-7.28 (4H, m, Ar-H), 7.30-7.39 (2H, m, Ar-H), 7.42-7.50 (2H, m, Ar-H), 7.53-7.60 (1H, m, Ar), 7.64 (1H, d, J: 7.72 Hz, Ar). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 25.67 ($(CH_2)_2$), 50.15 ($N(CH_2)_2$) 112.11, 113.38, 123.39, 124.20, 127.09, 127.94, 128.10, 128.36, 128.45, 129.07, 129.50, 131.99, 136.35, 152.47, 154.63, 161.41, 168.27, 174.59 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{22}H_{18}N_2O_2S$: 375.1162; found: 375.1167.

(2-(azepan-1-yl)-4-phenylthiazol-5-yl)(benzofuran-2-yl)methanone (Compound 4)

Yield 67.7%, yellow solid, mp 152.8 °C. FT-IR ῡmax (cm^{-1}): 3059 to 2925 (C─H), 1538 (C═O), 1464 to 1296 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 1.57 (4H, brs, hexamethylene-CH_2), 1.81 (4H, brs, hexamethylene-CH_2), 3.68 (4H, brs, $N(CH_2)_2$), 7.15-7.83 (8H, m, Ar), 7.89 (1H, d, J: 7.71 Hz, Ar), 8.15 (1H, d, J: 0.74 Hz, Ar). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 25.23, 27.47, 111.39, 111.96, 112.11, 112.82, 113.42, 115.12, 118.80, 122.91, 123.40, 124.20, 124.73, 127.94, 128.11, 129.09, 129.49, 136.30, 142.02, 179.17 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{24}H_{22}N_2O_2S$: 403.1475; found: 403.1480.

Benzofuran-2-yl(2-morpholino-4-phenylthiazol-5-yl)methanone (Compound 5)

Yield 69.8%, brown solid, mp 199.3 °C. FT-IR ῡmax (cm^{-1}): 3014 to 2870 (C─H), 1593 (C═O), 1519 to 1329 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 3.61 (4H, t, J:5.01 Hz, $N(CH_2)_2$), 3.75 (4H, t, J:5.76 Hz, $O(CH_2)_2$), 7.19-7.28 (4H, m, Ar-H), 7.33-7.49 (5H, m, Ar-H), 7.65 (1H, d, J:8.02 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 48.32($N(CH_2)_2$), 65.79($O(CH_2)_2$), 112.17, 114.01, 119.57, 123.53, 124.30, 127.05, 128.20, 129.20, 129.47, 136.0, 152.27, 154.75, 160.36, 175.0 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{22}H_{18}N_2O_3S$: 391.0507; found: 391.0508.

(2-(Dimethylamino)-4-phenylthiazol-5-yl) (naphtho[2,1-b]furan-2-yl)methanone (Compound 6)

Yield 71.3%, yellow solid, mp 181.7 °C. FT-IR ῡmax (cm^{-1}): 3055 to 2882 (C─H), 1583 (C═O), 1542 to 1302 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 3.20 (6H, s, $N(CH_3)_2$), 7.13-7.19 (3H, m, Ar-H), 7.39-7.55 (4H, m, Ar), 7.61-7.67 (1H, m, Ar-H), 7.90 (1H, d, J: 9.07 Hz, Ar-H), 8.01 (1H, d, J:7.76 Hz, Ar-H), 8.06 (1H, s, Ar-H), 8.26 (1H, d, J:8.03 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 41.5 ($N(CH_3)_2$), 112.72, 113.25, 113.28, 120.02, 122.87, 124.16, 125.91, 126.44, 127.21, 127.73, 127.93, 128.11, 129.01, 129.31, 129.48, 130.45, 131.02, 136.45, 151.96, 152.83, 160.66, 171.72, 174.36 (C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{24}H_{18}N_2O_2S$: 399.1162; found: 399.1158.

Naphtho[2,1-b]furan-2-yl(4-phenyl-2-(pyrrolidin-1-yl)thiazol-5-yl)methanone (Compound 7)

Yield 64.6%, brown solid, mp 186.3 °C. FT-IR ῡmax (cm^{-1}): 3054 to 2961 (C─H), 1541 (C═O), 1458 to 1311 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.02 (4H, brs, $(CH_2)_2$), 3.48 (4H, brs, $N(CH_2)_2$), 7.09-7.26 (3H, m, Ar-H), 7.40-7.74 (5H, m, Ar-H), 7.87 (1H, t, J:9.03 Hz, Ar-H), 7.98-8.02 (2H, m, Ar-H), 8.25 (1H, d, J: 8.04 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 25.68 ($(CH_2)_2$), 50.15 ($N(CH_2)_2$), 108.53, 112.17, 112.71, 113.10, 122.87, 124.14, 125.89, 128.09, 129.49, 130.45, 131.81, 136.54,

140.22, 152.03, 152.79, 160.93, 168.20, 174.28(C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{20}N_2O_2S$: 425.1318; found: 425.1321.

Naphtho[2,1-b]furan-2-yl(4-phenyl-2-(piperidin-1-yl)thiazol-5-yl)methanone (Compound 8)

Yield 83.9%, brown solid, mp 169.1 °C. FT-IR ῡmax (cm^{-1}): 3106 to 2857 (C—H), 1573 (C═O), 1541 to 1336 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 1.64 (6H, brs, $(CH_2)_3$), 3.62 (4H, brs, $N(CH_2)_2$), 7.08-7.20 (3H, m, Ar-H), 7.39-7.58 (4H, m, Ar-H), 7.64 (1H, t, J: 7.05 Hz, Ar-H), 7.89 (1H, d, J: 9.11 Hz, Ar), 8.0 (1H, d, J:8.08 Hz, Ar-H), 8.08 (1H, brs, Ar-H), 8.26 (1H, d, J: 7.91 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 23.81, 25.26, 49.44($N(CH_2)_2$), 112.72, 113.36, 119.40, 122.89, 124.16, 125.91, 127.74, 127.94, 128.11, 129.03, 129.30, 129.46, 129.52, 130.46, 136.39, 151.98, 152.88, 160.50, 171.39, 174.42(C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{22}N_2O_2S$: 439.1475; found: 439.1477.

(2-(Azepan-1-yl)-4-phenylthiazol-5-yl)(naphtho[2,1-b]furan-2-yl)methanone (Compound 9)

Yield 77.5%, yellow solid, mp 186.7 °C. FT-IR ῡmax (cm^{-1}): 3107 to 2877 (C—H), 1519 (C═O), 1475 to 1311 (C═C, C═N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 1.56 (4H, brs, hexamethylene-CH_2), 1.81 (4H, brs, $(CH_2)_2$), 3.68 (4H, brs, $N(CH_2)_2$), 7.07-7.22 (3H, m, Ar-H), 7.41 (1H, dd, J: 9.04 Hz, 0.60 Hz, Ar), 7.45-7.58 (3H, m, Ar-H), 7.64 (1H, t, J:7.05 Hz, Ar-H), 7.88 (1H, d, J: 9.08 Hz, Ar), 8.01 (1H, d, J: 9.03 Hz, Ar-H), 8.08 (1H, d, J: 0.74 Hz, Ar-H), 8.26 (1H, d, J:7.97 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 26.32, 27.49, 28.26, 51.20($N(CH_2)_2$), 112.70, 113.13, 119.33, 122.88, 124.16, 125.89, 127.71, 127.94, 128.08, 128.98, 129.29, 129.41, 129.50, 130.45, 136.50, 152.04, 152.79, 160.69, 170.98, 174.31(C=O). HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{24}N_2O_2S$: 453.1631; found: 453.1649.

Antimicrobial activity

Minimum inhibitory concentration assay

Gram-positive and gram-negative bacterial strains such as *E. coli* (ATCC8739), *S. aureus* (ATCC6538), *Salmonella* sp. (ATCC700623) were incubated and compounds were tested on these microorganisms. A previous procedure that was previously performed by this group is followed. Experiments were performed in triplicate (Giray, 2019).

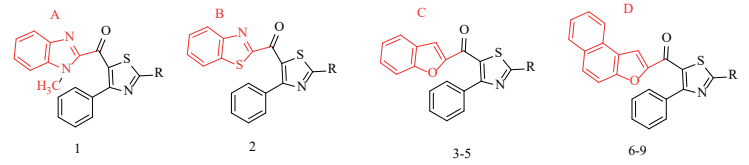
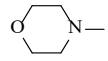
RESULTS AND DISCUSSION

Chemistry

Compounds were synthesized in a 55%-85% yield. Carbonyl peaks were observed around 1600 cm^{-1} and C-H stretchings were observed between 2800-3100 cm^{-1} in IR spectra. ^{1}H NMR and ^{13}C NMR spectral data were consistent with expectations. Compounds are consist of aromatic and aliphatic hydrogens. In the compound containing the 1-methylbenzimidazole structure, the hydrogens attached to the nitrogen attached to the methyl have a peak at 3.96 ppm in singlet form. Structures of the synthesized compounds are given below (Table 1).

Methylene hydrogens bound to the dialkylamine nitrogen have a peak around 3 ppm in ^{1}H NMR. The aromatic hydrogen peak in the five-membered regions of the benzofurane and naphthofurane rings is located between the peaks in the multiplet region, so the specific singlet is not separately observed. In ^{13}C NMR, the peak of the carbonyl carbon is observed between 173-175 ppm. The ^{13}C NMR peak of the methylene carbons adjacent to the dialkylamine nitrogen is observed at around 50 ppm. The methyl carbon attached to the 1st position of benzimidazole peaks was observed at 32.23 ppm. A carbon peak at the 2nd position of the thiazole was observed in the range of 164-171 ppm. Synthesized compounds are compatible with HRMS calculated data.

Table 1. Structures and some properties of the synthesized compounds

 1 2 3-5 6-9		Melting point °C	Yield	HRMS data (found)
1		230.3	72%	416.1786
2		176.1	57%	420.1199
3		166.8	65.5%	375.1167
4		152.8	67.7%	389.1318
5		199.3	69.8%	391.0508
6		181.7	71.3%	399.1158
7		186.3	64.6%	425.1321
8		169.1	83.9%	439.1477
9		186.7	77.5%	453.1649

Antibacterial activity

Antibacterial activity was tested by microdilution method against *E.coli*, *S.aureus,* and *Salmonella* species. Compounds did not show activity until 100 µM. Thus, compounds were evaluated as inactive. Antibacterial compounds generally have ionizable groups. In our tested compounds, amine groups are not good protonable groups as they are bound to aromatic thiazole ring. Besides, heterocyclic nitrogens are not protonable at medium pH's 4-9. These facts can be associated with the absence of the activity. For the other side of the molecules, in a former study, we have synthesized novel pyridine derivatives (Figure 2). Among them, 2 and 4- pyridyl derivatives showed low-moderate activity compared to chloramphenicol (Sahin, 2020). Following that, in this study, we have synthesized bicyclic heterocycles; however, this did not contribute to the activity. This can be the result of the blockade of the ring nitrogen hindrance by bicyclic structure, which would possibly interact with the probable target. Besides, in another study, Thomas et al. synthesized and tested similar structures. Similar to our study, they did not find activity on *S.aureus* and *E.coli*. They have discovered a close activity to penicillin for *B.subtilis* (Thomas, 2008a; Thomas 2008b).

In literature, antibacterial compounds are discussed for potential targets. There is numerous targets that change cell wall synthesis, protein synthesis, or some essential enzyme activities. Among these enzymes, compounds target the ATP binding site. ATP binding site ligands have amide, azomethine-NH, or protonable cyclic/acyclic moieties. In a detailed study performed on benzothiazoles mainly for *Mycobacterium tuberculosis*, potential antibacterial targets were evaluated with computational studies.

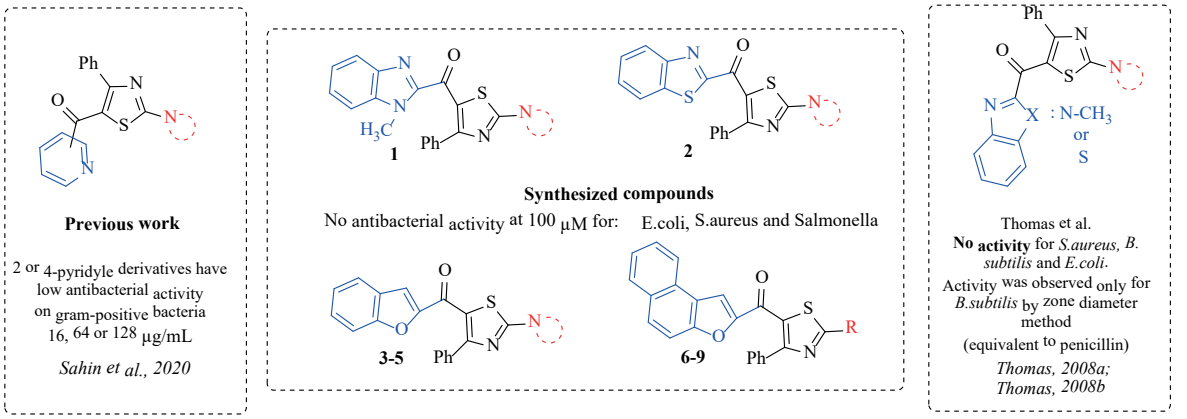


Figure 2. Summary of antibacterial activity

In this study, almost all of the active compounds bear carboxylic acid and/or amide moieties; thus, these or similar functional groups are essential for antibacterial activity (Gjorgjieva, 2018). Our synthesized structures do not have this kind of hydrophilic sites, which can also be the reason for the absence of antibacterial activity.

CONCLUSION

Consequently, nine novel thiazole derivatives were successfully synthesized and characterized. Although the similar compounds by this group were previously reported with different activities, this chemical group does not provide achievement in antibacterial drug development. Sidechains should be replaced and enriched with functional ionizable groups in the future.

ACKNOWLEDGEMENTS

This work is not funded by any organization.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Compounds were designed by S.D., and L.Y. Compounds were synthesized by Z.S., B.I.T., and E.A. Then structures were determined by L.Y., B.B., and Z.S. Antibacterial activity by microduliton method were made by A.C. Finally, manuscript preparation were realized by Z.S., E.A. and B.I.T.

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