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ARTICLE

Sequential one-pot multicomponent synthesis of bis-aminothiazols and evaluation of their antibacterial and antioxidant activities

Jafar Parvizi[1] | Nosrat O. Mahmoodi[2] | Fateme Ghanbari Pirbasti[2]

[1]Department of Chemistry, University campus2, University of Guilan, Rasht, Iran

[2]Department of Chemistry, Faculty of Sciences, University of Guilan, Rasht, Iran

Correspondence
Nosrat O. Mahmoodi, Faculty of Sciences, Department of Organic Chemistry, University of Guilan, PO Box 41335-1914, Rasht, Iran.
Email: mahmoodi@guilan.ac.ir; nosmahmoodi@gmail.com

Funding information
the University of Guilan

A series of novel bis-thiazoles were synthesized through a one-pot semi-five-component reaction of the prepared α-bisbromo ketones, aldehydes, and thiosemicarbazide in the presence of *p*-TsOH under reflux condition. Products were obtained in reasonable yields via an efficient, convenient, and simple setup. The inhibitory activity on bacterial growth of the products was studied against Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive bacterial strains (*Micrococcus luteus*, *Staphylococcus aureus*) at different concentrations (25, 50, 100, and 200 μg/mL at 600 nm). Most of the products showed inhibitory activity at the concentration of 200 μg/mL. In addition, bis-thiazoles showeed high to moderate antioxidant activity using the diphenylpicrylhydrazyl (DPPH) method. Bis-thiazoles **6i** and **6j** showed higher antioxidant activity than vitamin C and vitamin E.

KEYWORDS

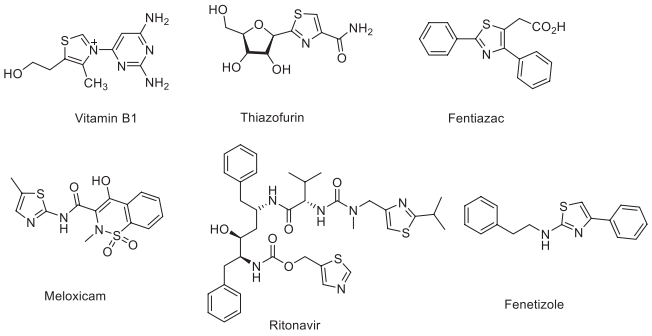
antibacterial, antioxidant, bis-aminothiazol, bis-ketones, multicomponent synthesis

1 | INTRODUCTION

Heterocyclic compounds are a diverse family of chemical compounds with many important biological activities. Thiazoles are one of the important members of heterocyclic compounds with various properties and applications. The thiazole ring as an interesting building block is found in many natural and medicinal compounds with potential biological activities: for example, urukthapelstatin A is a cyclic compound isolated from Thermoactinomycetaceae bacteria showing anticancer activity against human lung cancer A549 cells.[1] Cyclic hexapeptides and venturamides A and B, which were isolated from marine *Cyanobacterium oscillatoria* sp., possess antimalarial activity.[2] These diverse biological activities of thiazoles have attracted great attention of researchers in the synthesis and investigation of their biological activities such as antimycobacterial antibiotics,[3] pin1 inhibitor,[4] α-glucosidase inhibitor,[5] antioxidant,[6] anti-liver cancer,[7] antibacterial,[8,9] antiplatelet,[10] anti-inflammatory,[11] anti-Candida activity[12] activities, and so on. Also, thiamine or vitamin B1 is one of the most important natural thiazoles. Moreover, many commercial drugs contain the thiazole moiety and have various clinical applications such as the anticancer drug tiazofurin, the non-steroidal anti-inflammatory drugs fentizac and meloxicam, the anti-HIV drug ritonavir, and the immunoregulating drug fanetizole (Scheme 1).

In addition, some thiazole-containing compounds have physical applications, for example, thiophene-thiazole-functionalized conjugated oligomers have been used for the fluorescent and colorimetric sensing of Cu^{2+} and Fe^{2+} from water and thiazole-based iridium(III) complexes for organic light-emitting diode (OLED) applications.[13,14] Among the thiazole derivatives, hydrazinyl thiazoles are found to be associated with different biological activities such as antimalarial,[15] antimycobacterial,[16] β-glucuronidase inhibitory,[17] antibacterial, and antitubercular.[18]

Finding new tools for saving energy, eco-friendliness, atom economy, and saving time in synthetic organic chemistry has gained much attention of researchers, and this challenge has led to innovative and sustainable one-pot multicomponent reactions (MCRs). A large to complex



SCHEME 1 Structure of commercial drugs that possess the thiazole moiety with various clinical applications

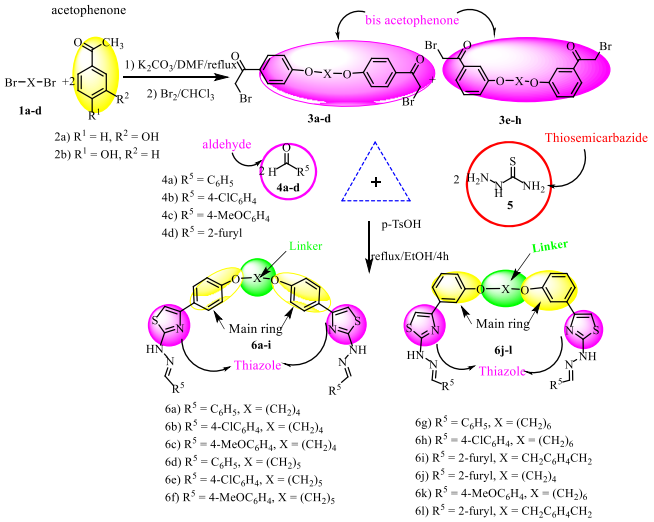
library of compounds without isolation of any intermediate can be synthesized using simple procedures and in high yields. Moreover, recently MCRs of hydrazinyl thiazoles have been reported.[19–21]

Encouraged by all of the above, as well as the limited studies on the synthesis of bis-thiazoles in the literature,[22–24] and in continuation of our ongoing research program on the synthesis of mono- and bis-thiazoles and screening for their biological activities,[25–33] we report in this paper the one-pot semi-five-component, efficient, and rapid method for the synthesis of new bis-thiazoles and screening otheir antibacterial and antioxidant activities.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Bis-bromo ketones **3a–h** were prepared according to the literature[34] and were applied in one-pot semi-five-component reaction of 2 equiv of aldehydes **4a–d** with thiosemicarbazide **5** in EtOH in the presence of *p*-TsOH (10 mol%) under reflux condition (Scheme 2). According to Table 1, suitable reaction condition for the synthesis of bis-thiazole **6a** as model reaction was considered. According to entry 1, in the absence of a catalyst at r.t., the product **6a** was obtained in 55% yield during 12 hr. The same was performed with a slightly higher yield and shorter reaction time under reflux condition (entry 2). However, the yield of **6a** increased to 70% in the presence of 5 mol% of the catalyst during 8 hr (entry 3). Moreover, increasing the amount of catalyst led to the formation of product **6a** in higher yield in a shorter reaction time (entry 4). Although products **6a** was obtained in high yield (80%) in 4 hr in CH_3CN as solvent (entry 7), using EtOH as green solvent (entry 4) was a better choice. The reaction proceeded through the condensation of aldehydes **4a–d** with thiosemicarbazide **5** followed by nucleophilic addition to bromo-ketones **3a–h** through Hantzsch reaction and subsequent intramolecular cyclization. Under the optimized condition, bis-products **6a–l** were obtained in reasonable yields, through a simple, eco-friendly, convenient



SCHEME 2 Synthesis procedure of bis-thiazoles **6a–h**

work-up and straightforward method not involving chromatographic purification.

The structure of the products was elucidated by their FT-IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. The IR spectra of products **6a–l** showed characteristic absorption bands at 3,450–3,414 and 1,628–1,603 cm^{-1} due to N–H and C=N stretches, respectively.

Also, in the ^{1}H and ^{13}C NMR spectra of **6a–l**, the expected number, chemical shifts, and coupling constants of various protons appeared. The N-H signal appeared as exocyclic at 12.68–11.27 ppm, which is incomplete agreement with the literature (Table 2).[35]

In addition, the presence of a signal at 7.62–6.71 confirmed the presence of thiazole ring (C=H). Signals due to the aromatic and aliphatic protons appeared at 8.32–6.83 and 5.22–1.25 ppm, respectively. The expected number and types of carbons appeared in the ^{13}C NMR spectra. Aromatic and aliphatic carbons appeared in range 178.40–96.68 and 70.09–19.04 ppm, respectively.

2.2 | Biology

2.2.1 | Antibacterial activity

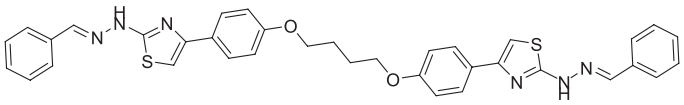
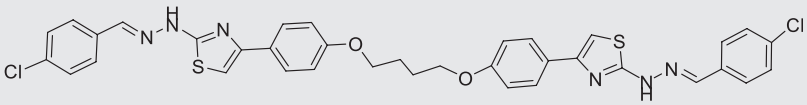
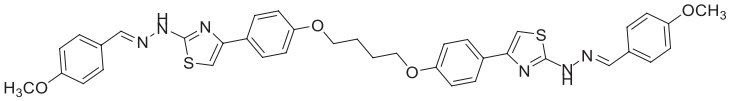
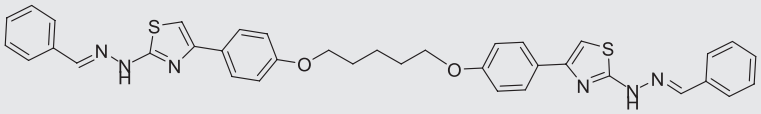
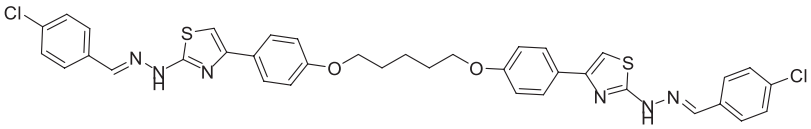
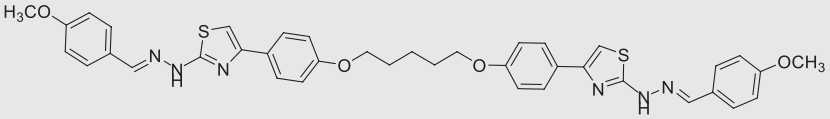
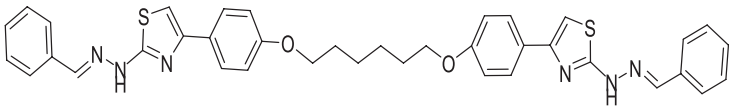
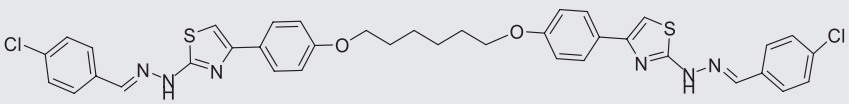
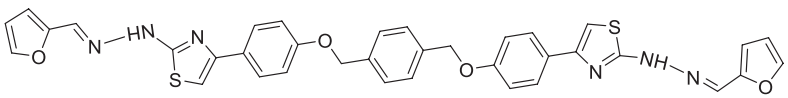
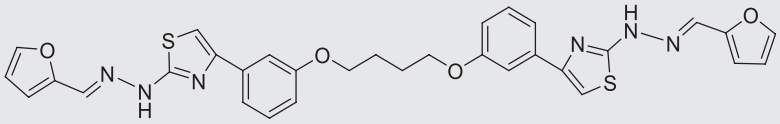
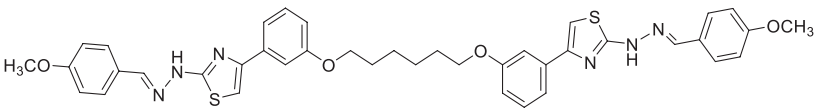
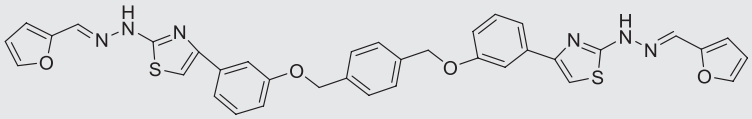
Pathogenic bacteria have an important role in the creation of unknown diseases; also, bacterial resistance to available antimicrobial drugs has become a challenge nowadays.[36] So, exploring new, cheaper, and effective antibacterial compounds is highly required. *In vitro* antibacterial activity of bis-thiazoles **6a–l** was investigated against Gram-positive bacteria strains including *Micrococcus luteus* and *Staphylococcus aureus* and Gram-negative bacteria strains including *Escherichia coli* and *Pseudomonas aeruginosa.* Bacterial inhibition percentages of the products at different concentrations of 25, 50, 100, and 200 μg/mL in DMSO were studied at 600 nm. Penicillin was used as positive control.

According to Figure 1, only products **6h** and **6i** inhibited the growth of *P. aeruginosa* by 85 and 72%, respectively, at

TABLE 1 Optimization of the synthesis of **6a**

Entry	Catalyst	Amount of catalyst (Mol%)	Solvent	Condition	Time (hr)	Yield (%)
1	—	—	EtOH	r.t.	12	55
2	—	—	EtOH	Reflux	10	57
3	*p*-TsOH	5	EtOH	Reflux	8	70
4	*p*-TsOH	10	EtOH	Reflux	4	80
5	*p*-TsOH	10	EtOH:H_2O	Reflux	6	60
6	*p*-TsOH	10	DMF	Reflux	6	70
7	*p*-TsOH	10	CH_3CN	Reflux	4	80
8	*p*-TsOH	10	MeOH	Reflux	5	70

TABLE 2 Structure and physical properties **6a-l**

Compound	Product structure	Color	Melting point	Yield (%)
6a		Brown	225–229	80
6b		Dark yellow	228–231	80
6c		Brown	222–226	80
6d		Cream	232–235	75
6e		Brown	227–231	77
6f		Dark brown	224–228	85
6g		Dark	214–217	80
6h		Dark brown	215–219	83
6i		Brown	230–232	85
6j		Dark yellow	227–230	83
6k		Cream	230–233	90
6l		Cream	225–229	85

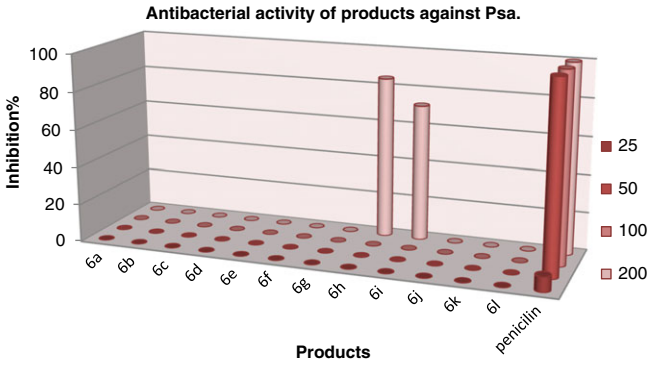


FIGURE 1 Inhibition percentages of products against *P. aeruginosa*

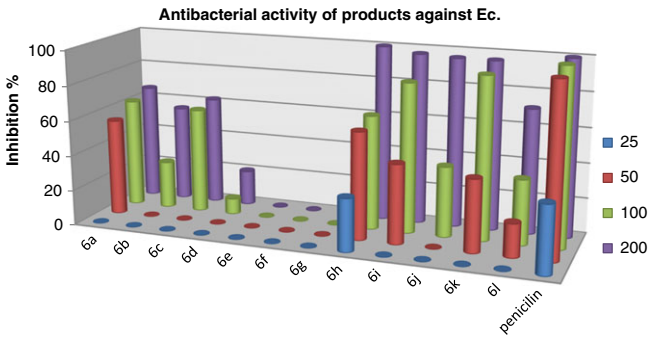


FIGURE 2 Inhibition percentages of products against *E. coli*

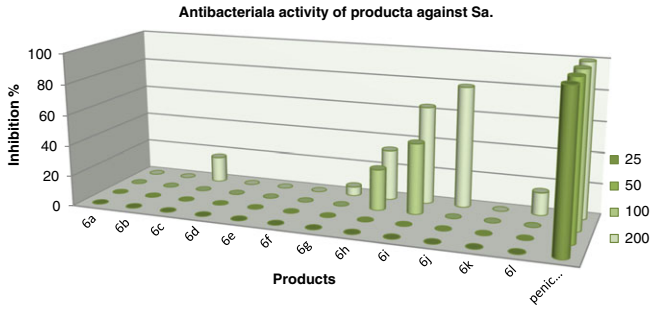


FIGURE 3 Inhibition percentages of products against *S. aureus*

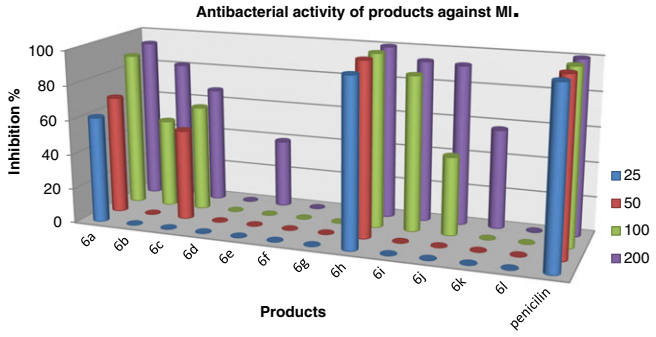


FIGURE 4 Inhibition percentages of products against *M. luteus*

the concentration of 200 μg/mL. Also, penicillin inhibited 100% growth of *P. aeruginosa* at the concentrations of 50, 100 and 200 μg/mL.

Moreover, most of the products showed inhibition against *E. coli.* Product **6h** inhibited the growth of *E. coli* completely at the concentration of 200 μg/mL; also, the products **6i–k** inhibited over 90% of bacterial growth at the concentration of 200 μg/mL. Furthermore, product **6h** showed antibacterial activity at all tested concentrations from 30 to 100%. However, products **6e–g** showed no antibacterial activity against *E. coli.* Also, at the concentration of 100 μg/mL, product **6k** showed the highest inhibitory activity (85%). Furthermore, penicillin inhibited the growth of *E. coli* completely at the concentration of 100 and 200 μg/mL and by 97 and 38% at the concentrations of 50 and 25 μg/mL, respectively (Figure 2).

Products **6d**, **6g–j,** and **6l** showed inhibitory activity against *S. aureus.* Products **6h–i** possessed inhibitory activity at higher concentrations: for example, 100 and 200 μg/mL. Furthermore, product **6j** had the highest inhibitory activity (79%) at the concentration of 200 μg/mL. Penicillin as a positive control inhibited the growth of *S. aureus* completely (Figure 3).

According to Figure 4, most of the products possessed antibacterial activity against *M. luteus.* Product **6a** inhibited the growth of *M. luteus* completely at the concentrations of 50, 100, and 200 μg/mL and by 96% at the concentration of 50 μg/mL. Moreover, products **6a** and **6i–j** showed high antibacterial activity and inhibited the growth of *M. luteus* by more than 90% at the concentration of 200 μg/mL. Additionally, products **6a** and **6h** showed antibacterial activity against *M. luteus* at all tested concentrations. Also, all tested concentrations of penicillin inhibited the growth of *M. luteus* completely.

In our recent study, it was observed that benzyl linkage has a potent influence on the antibacterial activity. Similar results were observed in this study for products **6i** and **6l**.[28] Moreover, the only structural difference between these isomers (**6i** and **6l**) is the linkage position on the benzyl ring, namely para and meta connections, respectively. However, this tiny difference had a major effect on the antibacterial activity: for example, **6i** with the para-substituted linkage showed antibacterial activity against all four bacterial strains, while **6l** with meta-substituted linkage showed antibacterial activity against *E. coli* and *S. aureus.* It can be suggested that the symmetry of **6i** has a positive effect on its antibacterial activity. In addition, **6j** showed good antibacterial activity, especially against *E. coli, S. aureus*, and *M. luteus*, which may be due to incorporation of the heterocyclic furyl moiety. Also, **6i** and **6l** with good antibacterial activity possess the furyl moiety. Recently it was shown that the presence of Cl substituent has a positive effect on the antibacterial activity, and in this study the Cl-substituted product **6h** showed high antibacterial activity.[37]

Interestingly, most of the products possessed antibacterial activity against the Gram-negative bacterial strain *E. coli,* especially products **6h–k**. All bacteria have an inner cell membrane; however, this layer is unique in Gram-negative

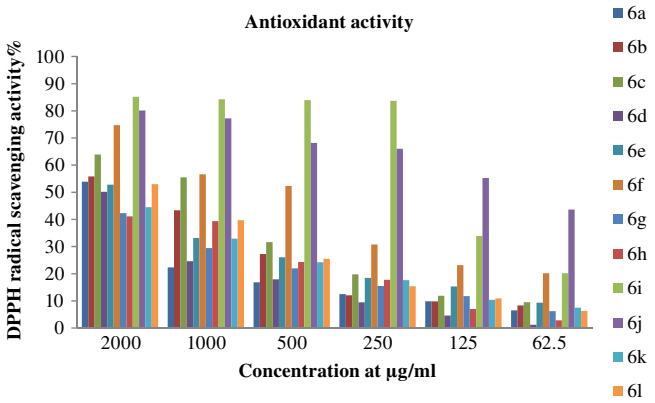


FIGURE 5 Antioxidant activity of **6a–l** using DPPH method

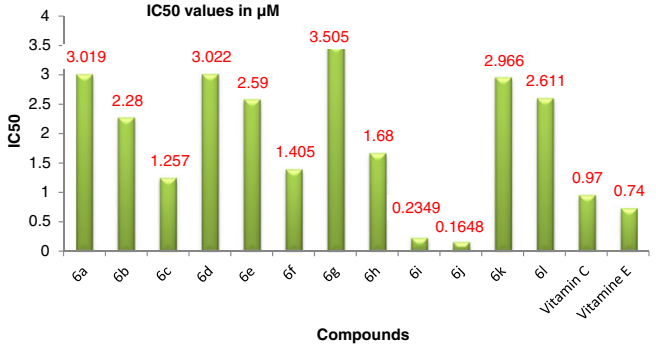


FIGURE 6 IC_{50} values of **6a–l** and standards

bacteria. A lipopolysaccharide layer (outer layer) is present in Gram-negative bacteria, and this outer layer excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why Gram-negative bacteria are generally more resistant to antibiotics than are Gram-positive bacteria. So, the synthesis and finding of new compounds with the ability to inhibit Gram-negative bacteria are important.

Recently, Singh and coworkers studied antibacterial activity of 2,4-disubstitued thiazoles.[38] According to their results, none of the products was active against *E. coli* while in our study most of the products were active against *E. coli.* Also, the above authors found a few products were active against *P. aeruginosa* like in our study. In another study, 3-(1-phenyl-4-((2-[4-arylthiazol-2-yl]hydrazono)methyl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one exhibited moderate to excellent antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa* with zones of inhibition of 8–22, 7–18, 8–22, and 8–20 mm and MICs of 50–200, 50–200, 125–200, and 50–200 µg/mL, respectively.[39] Also, these products showed good antibacterial activity against *E. coli* like our products. However, these compounds showed better antibacterial activity against *P. aeruginosa* and *S. aureus* than our products because of the presence of the coumarinyl moiety. Moreover, in our recent study,[26] 2,4-disubstituted hydrazinyl-thiazoles showed antibacterial activity against *S. aureus*, *M. luteus*, *E. coli*, *P. aeruginosa*, *B. subtilis*, and *A. hydrophila* with the zones of inhibition of 6–11, 7–10, 9–13, 7–17, 6–21, and 6–11 mm, respectively, and these products showed antibacterial activity against *E. coli.*

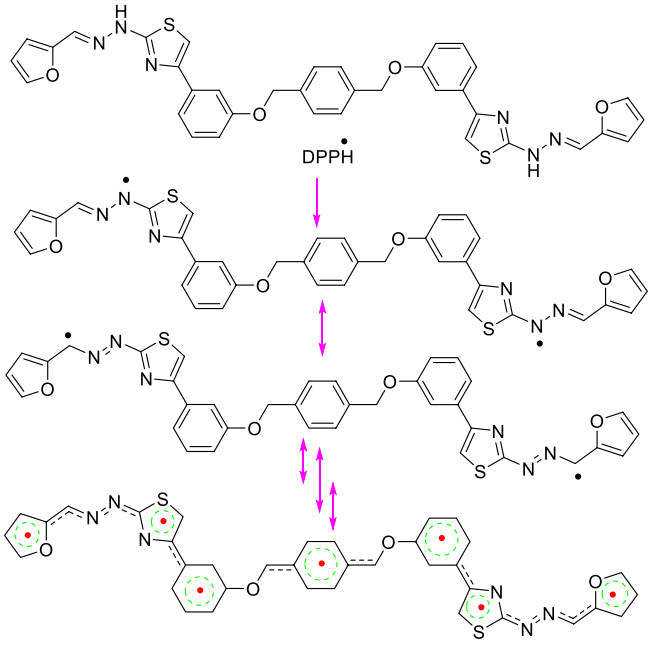
2.3 | Antioxidant activity

Sunlight, ultraviolet light, ionizing radiation, chemical reactions, and metabolic processes can produce free-radical species which can react and oxidize DNA, lipids, proteins, and nucleic acids in living systems and result in degenerative disease and health problems such as chronic diseases, cardiovascular diseases, metabolic syndrome, cancer, and some neurodegenerative diseases.[40] Antioxidants are a class of compounds that trap free radicals, so they can reduce the risk of diseases.[41]

Among various antioxidant assays, the diphenylpicrylhydrazyl (DPPH) assay is a fast and simple method. DPPH is a stable free radical of violet color and turns to yellow to colorless in the presence of an antioxidant compound on receiving a radical hydrogen atom. DPPH violet solution has a sharp absorption band at 517 nm, and this band decreases as the reduced form of DPPH increases. The radical scavenging activity of new bis-thiazoles **6a–l** was evaluated at a concentration of 2,000–62.5 µg/mL at 517 nm. Also, the IC_{50} values (i.e., the concentration of products to scavenge 50% of DPPH radical concentration) were calculated from a linear equation. Vitamin C (ascorbic acid) and vitamin E (α-tocopherol) were used as standards. According to Figure 5, all new bis-thiazoles revealed potent to moderate antioxidant activity. Bis-thiazoles **6i–j** possessed radical scavenging activity of >50% at concentrations of 250 and 125 µg/mL, respectively. Also, bis-thiazoles **6c** and **6f** showed potent antioxidant activity at concentrations of 1,000 and 500 µg/mL, respectively.

According to Figure 6, the higher antioxidant activity is reflected in lower IC_{50} values. Interestingly, bis-thiazoles **6i–j** had the lowest IC_{50} values (234.9 and 164.8 µM) and their antioxidant activity was higher than that of vitamin C (0.970 µM) and vitamin E (740 µM). The IC_{50} values of other products were higher than those of the standards. The antioxidant activity of bis-thiazoles can be ordered as follows: **6j**, **6i**, **6c**, **6f**, **6h**, **6b**, **6e**, **6l**, **6k**, **6a**, **6d,** and **6g**.

Recently, we discussed mechanism of the antioxidant activity of hydrazinylthiazoles and the important role of the *endo*- or *exo*-N-H of thiazole. Also, if the structure of compound stabilizes the formed radical through resonance, the antioxidant activity can be improved. Besides, N-H and N=C-C=NH moieties in other parts of compounds can affect the antioxidant activity. Some proposed radical structures and resonance of radical through the structure of bis-thiazole **6i** are depicted in Scheme 3. Ultimately, compounds **6a–l,** especially **6i–j,** can be introduced as potent antioxidant compounds similar to our recently synthesized hydrazinylthiazoles.[26,27]



SCHEME 3 Proposed mechanism of antioxidant activity of bis-thiazole **6i**

3 | CONCLUSIONS

In conclusion, a one-pot, multicomponent, efficient, eco-friendly, productive, and simple (setup and work-up) synthesis was applied for the synthesis of new bis-thiazoles. Also, the novel bis-thiazoles showed antibacterial activity against Gram-positive and Gram-negative bacterial strains. The antibacterial activity of product **6h** was comparable to that of penicillin at the concentration of 200 μg/mL against *E. coli* and *M. luteus.* Specifically, most of the products showed antibacterial activity against the Gram-negative *E. coli.* In addition, bis-thiazoles **6i** and **j** showed high antioxidant activity, even higher than those of vitamin C and vitamin E. Moreover, other bis-thiazoles showed good antioxidant activity. The results of antibacterial and antioxidant activities of bis-thiazoles should encourage the investigation of other biological activities.

4 | EXPERIMENTAL

4.1 | Materials and methods

Chemicals were purchased from Sigma and Merck chemical companies. Solvents were supplied from local manufacturers. FT- IR spectra were recorded with a Shimadzu 470 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker 400 DRX-Avance NMR spectrometer. Deuterated DMSO and TMS were used as solvent and internal standard, respectively. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. Elemental analysis was carried out using a Carlo-ErbaEA1110 CNNO-S analyzer. Absorbance of the products during antioxidant and antibacterial activity studies was measured on a visible spectrophotometer Unico 2100 and UV–vis spectrophotometer NANOCOLOR® UV/VIS Macherey Nagel, respectively. Bacterial strains were supplied generously by the Department of Biology, Faculty of Sciences, University of Guilan.

4.2 | General procedure for the synthesis of *bis*-thiazoles 6a–h

Compounds **3a–h** were prepared according to literature.[30,34]

The prepared α-bromo ketones **3a–h** (1 mmol), aldehydes **4a–d** (2 mmol), and thiosemicarbazide **5** (2 mmol) were added to a flask and refluxed in EtOH in the presence of *p*-TsOH (10 mol%) for 4 hr. After the required time, the reaction was cooled and filtered. The crude product was washed with warm EtOH.

4.2.1 | 1,4-Bis(4-(2-(2-([*E*]-benzylidene)hydrazinyl)thiazol-4-yl)phenoxy)butane (6a)

Brown solid, Yield: 80%; m.p.: 225–229°C, FT-IR (KBr cm^{-1}): 3,445 (stretch, N–H), 3,136 (stretch, C–H aromatic), 2,935 (stretch, C–H aliphatic), 1,604 (stretch, C=N), 1,569, 1,509, (stretch, C=C), 1463 (bending, C–H, CH_2), 1255, 1029 (stretch, C–O), 1171, 1119 (bending, C–N), 832, 653 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 12.04 (s, 2H, NH, H_f), 7.54 (s, 2H, H_g), 7.5 (d, J = 7.2 Hz, 4H, H_h), 7.35 (d, J = 8.0 Hz, 4H, H_d), 7.28–7.22 (m, 6H, H_i, H_J), 6.88 (s, 2H, H_e), 6.83 (d, J = 8.0 Hz, 4H, H_c), 3.58 (t, J = 6.8 Hz, 4H, H_b), 2.10–2.11 (m, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 176.13(C_4), 136.99 (C_1), 133.60 (C_3), 129.4, 127.35, 124.02, 123.86, 121.23, 120.36, 119.22, 118.52, 112.24, 68.07 (C_b), 31.84 (C_a) ppm. Anal.calcd for $C_{36}H_{32}N_6O_2S_2$: C, 67.06; H, 5.00; N, 13.03. Found: C, 67.10; H, 4.86; N, 13.07.

4.2.2 | 1,4-Bis(4-(2-(2-([*E*]-4-chlorobenzylidene)hydrazinyl) thiazol-4-yl)phenoxy)butane (6b)

Dark yellow solid, Yield: 80%; m.p.: 228–231°C, FT-IR (KBr, cm^{-1}): 3,447 (stretch, N–H), 3,015 (stretch, C–H aromatic), 2925, 2857 (stretch, C–H aliphatic), 1615 (stretch, C=N), 1593, 1504 (stretch, C=C), 1459 (bending, C–H and CH_2), 1270, 1070 (stretch, C–O), 1172 (stretch, C–N), 837, 814, 761 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 12.50 (brs, 2H, NH, H_f), 8.06 (s, 2H, H_g), 7.72 (d, J = 8.4 Hz, 4H, H_h), 7.53 (d, J = 8.6 Hz, 4H, H_d), 7.50 (d, J = 8.4, 4H, H_i), 7.14 (S, 2H, H_e), 7.22 (d, J = 8.6 Hz, 4H, H_c), 4.03 (t, J = 6.4 Hz, 4H, H_b), 1.70–1.54 (m, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 169.87 (C_4), 159.12 (C_1), 150.92 (C_3), 146.18 (C_g), 138.12 (C_6), 133.49 (C_5), 130.73, 129.46, 128.55, 125.98, 114.40, 110.00, 68.99 (C_b), 31.18 (C_a) ppm. Anal. calcd for $C_{36}H_{30}Cl_2N_6O_2S_2$: C, 60.58; H, 4.24;N, 11.78. Found: C, 60.50; H, 4.30; N, 11.71.

4.2.3 | 1,4-Bis(4-(2-(2-([*E*]-4-methoxybenzylidene)hydrazinyl) thiazol-4-yl)phenoxy)butane (6c)

Brown solid, Yield: 80%; m.p.: 222–226°C, FT-IR (KBr, cm^{-1}): 3,416 (stretch, N–H), 3061 (stretch, C–H aromatic),

2930, 2860 (stretch, C–H aliphatic), 1603 (stretch, C=N), 1503 (stretch, C=C), 1461–1386 (bending, C–H, CH_2), 1251, 1012 (C–O stretch), 1186 (C–N stretch), 830, 752 (OOP, C-H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.51 (s, 2H, NH, H_f), 7.50 (d, J = 7.2 Hz, 4H, H_d), 7.35 (s, 2H, H_g), 7.31 (d, J = 8.4 Hz, 4H, H_h), 7.18 (s, 2H, H_e), 6.86 (d, J = 8.4, 4H, H_i), 6.70 (d, J = 7.2 Hz, 4H, H_c), 4.15 (t, J = 6.0 Hz, 4H, H_b), 3.63 (s, 6H, H_j), 2.01–1.88 (m, 4H, H_a) ppm.. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 164.18 (C_4), 161.87 (C_6), 160.92 (C_1), 145.84 (C_3), 138.34 (C_g), 132.47, 130.09, 128.62, 126.33, 125.99, 123.41, 114.84 (C_e), 67.89 (C_b), 55.88 (C_j), 21.26 (C_a) ppm. Anal.calcd for $C_{38}H_{36}N_6O_4S_2$: C, 64.70; H, 5.15; N, 11.92. Found: C, 64.74; H, 5.21; N, 11.85.

4.2.4 | 1,5-Bis(4-(2-(2-([*E*]-benzylidene)hydrazinyl)thiazol-4-yl)phenoxy)pentane (6d)

Cream solid, Yield: 75%; m.p.: 232–235°C, FT-IR (KBr, cm^{-1}): 3,417 (stretch, N-H), 3064 (stretch, C–H aromatic), 2922, 2855 (stretch, C–H aliphatic), 1628 (stretch, C=N), 1491 (stretch, C=C), 1241, 1005 (stretch, C–O), 1119 (stretch, C–N), 815, 715 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 12.03 (s, 2H, NH, H_g), 7.99 (s, 2H, H_h), 7.86 (d, J = 7.2 Hz, 4H, H_i), 7.60 (d, J = 8.8 Hz, 4H, H_e), 7.42 (t, J = 7.6 Hz, 4H, H_j), 7.33–7.29 (m, 4H, H_k, H_f), 7.01 (d, J = 8.8 Hz, 4H, H_d), 4.06 (t, J = 6.4 Hz, 4H, H_c), 1.86–1.79 (m, 4H, H_b), 1.62–1.60 (m, 2H, H_a) ppm.^{13}C NMR (100 MHz, DMSO-d_6): δ; 178.4 (C_4), 168.82 (C_1), 159.07 (C_3), 142.79 (C_h), 138.63 (C_5), 134.66, 129.34, 128.73, 127.77, 126.03, 115.06, 102.33 (C_f), 67.94 (C_c), 28.90 (C_b), 21.26 (C_a) ppm. Anal. calcd For $C_{37}H_{34}N_6O_2S_2$: C, 67.45; H, 5.20; N, 12.80. Found: C, 67.40; H, 5.14; N, 12.72.

4.2.5 | 1,5-Bis(4-(2-(2-([*E*]-4-chlorobenzylidene)hydrazinyl) thiazol-4-yl)phenoxy)pentane (6e)

Brown solid, Yield: 77%; m.p.: 227–231°C, FT-IR (KBr, cm^{-1}): 3,414 (stretch, N–H), 3082 (stretch, C–H aromatic), 2922, 2867 (stretch, C–H aliphatic), 1615 (stretch, C=N), 1510, 1449, (stretch, C=C), 1449 (bending, C–H, CH_2), 1254, 1033 (stretch, C–O), 1187 (bending, C–N), 813, 754 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.45 (s, 2H, NH, H_g), 8.05 (s, 2H, H_h), 7.78 (d, J = 8.8 Hz, 4H, H_i), 7.68 (d, J = 7.2 Hz, 4H, H_e), 7.51–7.41 (m, 4H, H_j), 7.14 (d, J = 7.2 Hz, 4H, H_d,), 7.00 (s, 2H, H_f), 4.05 (t, J = 6.00 Hz, 4H, H_c), 2.1 (s, 4H, H_b), 1.83–1.80 (m, 2H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 172.65 (C_4), 160.82 (C_1), 152.33 (C_3), 145.68 (C_h), 138.43 (C_5), 136.68, 131.68, 129.87, 128.65, 125.98, 115.06, 106.87 (C_f), 56.50 (C_c), 21.27 (C_b), 19.04 (C_a) ppm. Anal. calcd for $C_{37}H_{32}Cl_2N_6O_2S_2$: C, 61.07; H, 4.43; N, 11.59 Found: C, 61.13; H, 4.34; N, 11.53.

4.2.6 | 1,5-Bis(4-(2-(2-([*E*]-4-methoxybenzylidene)hydrazinyl) thiazol-4-yl)phenoxy)pentane (6f)

Dark brown solid, Yield: 85%; m.p.: 224–228°C, FT-IR (KBr, cm^{-1}): 3,416 (stretch, N–H), 3061 (stretch, C–H aromatic), 2930, 2850 (stretch, C–H aliphatic), 1603 (stretch, C=N), 1567, 1505 (stretch, C=C), 1466 (bending, C–H, CH_2), 1243, 1029 (stretch, C–O), 1173 (bending, C–N), 834, 764 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.71 (s, 2H, NH, H_g), 8.06 (s, 2H, H_h), 8.01 (d, J = 7.4 Hz, 4H, H_i), 7.90 (d, J = 7.4 Hz, 4H, H_e), 7.84 (s, 2H, H_f), 7.61 (d, J = 7.4 Hz, 4H, H_j,), 7.50 (d, J = 7.4 Hz, 4H, H_d), 4.14 (t, J = 8.2 Hz 4H, H_c), 3.80 (s, 6H, H_k), 2.27–2.22 (m, 4H, H_b), 1.82 (s, 2H, H_a) ppm.. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 167.40 (C_4), 160.20 (C_6), 157.41 (C_1), 150.20 (C_3), 145.94 (C_h), 138.28, 132.47, 128.60, 125.99, 115.35, 114.85 (C_d or C_j), 102.73 (C_f), 65.70 (C_c), 55.74 (C_k), 28.60 (C_b),21.27 (C_a) ppm. Anal. calcd for $C_{39}H_{38}N_6O_4S_2$: C, 65.16; H, 5.33; N, 11.69, Found: C, 65.18; H, 5.34; N, 11.70.

4.2.7 | 1,6-Bis(4-(2-(2-([*E*]-benzylidene)hydrazinyl)thiazol-4-yl)phenoxy)hexane (6g)

Brown solid, Yield: 80%; m.p.: 214–217°C, FT-IR (KBr, cm^{-1}): 3,416 (stretch, N–H), 3062 (stretch, C–H aromatic), 2934, 2855 (stretch, C–H aliphatic), 1604 (stretch, C=N), 1553, 1489 (stretch, C=C), 1466 (bending, C–H, CH_2), 1247, 1008 (stretch, C–O), 1174, 1115 (bending, C–N), 823, 752 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 12.09 (brs, 2H, NH, H_g), 8.00 (s, 2H, H_h), 7.86 (d, J = 7.8 Hz, 4H, H_e), 7.60 (d, J = 8.8 Hz, 4H, H_i), 7.42 (t, J = 7.6, 4H, H_j), 7.33–7.29 (m, 4H, H_k, H_h,), 7.00 (d, J = 7.8 Hz, 4H, H_d), 4.03 (t, J = 6.4 Hz, 4H, H_c), 1.77–1.75 (m, 4H, H_b), 1.50 (s, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 170.60 (C_4), 156.13 (C_1), 150.89 (C_3), 146.13 (C_h), 133.62 (C_5), 129.46, 127.23, 123.89, 121.36, 119.22, 118.52, 102.79 (C_f), 68.00 (C_c), 29.22 (C_b), 25.73 (C_a) ppm. Anal. calcd for $C_{38}H_{36}N_6O_2S_2$: C, 67.77; H, 5.39; N, 12.41, Found: C, 68.84; H, 5.45; N, 12.50.

4.2.8 | 1,6-Bis(4-(2-(2-([*E*]-4-chlorobenzylidene)hydrazinyl) thiazol-4-yl)phenoxy)hexane (6h)

Dark brown solid, Yield: 83%; m.p.: 215–219°C, FT-IR (KBr, cm^{-1}): 3,415 (stretch, N–H), 3063 (stretch, C–H aromatic), 2927, 2858 (stretch, C–H aliphatic), 1614 (stretch, C=N), 1575, 1,476 (stretch, C=C), 1433 (bending,C–H, CH_2), 1216, 1005 (stretch, C–O), 1161, 1111 (bending, C–N), 869, 783, 753 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.27 (s, 2H, NH, H_g), 7.48 (s, 2H, H_h), 7.31 (d, J = 7.8 Hz, 4H, H_i), 7.26 (d, J = 6.8 Hz, 4H, H_e), 7.18 (d, J = 7.8, 4H, H_j), 6.88 (d, J = 6.8 Hz, 4H, H_d), 6.71 (s, 2H, H_f,), 4.00–3.95 (m, 4H, H_c), 3.56 (s, 4H, H_b), 1.31–1.28 (m, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 170.60 (C_4), 164.09 (C_1), 160.01 (C_3), 145.84 (C_h), 138.62 (C_6), 132.47, 130.49, 129.12, 128.62, 125.82, 115.32, 101.32 (C_f), 68.47 (C_c), 28.18 (C_b), 25.56 (C_a) ppm. Anal.

calcd for $C_{38}H_{34}Cl_2N_6O_2S_2$: C, 61.48; H, 4.68; N, 11.30, Found: C, 61.54; H, 4.58; N, 11.39.

4.2.9 | 1,4-Bis((4-(2-([*E*]-2-(furan-2-ylmethylene)hydrazinyl) thiazol-4-yl)phenoxy)methyl)benzene (6i)

Brown solid, Yield: 85%; m.p.: 230–232°C, FT-IR (KBr, cm^{-1}): 3,414 (stretch, N–H), 3064 (stretch, C–H aromatic), 2930, 2861 (stretch, C–H aliphatic), 1611 (stretch, C=N), 1486 (stretch, C=C), 1438 (bending, C–H, CH_2), 1216, 1005 (stretch, C–O), 1158, 1118 (bending, C–N), 873, 817, 787 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.039 (s, 2H, NH, H_f), 8.16 (s, 2H, H_g), 7.95 (d, J = 8.0 Hz, 2H, H_j), 7.70 (d, J = 6.8 Hz, 4H, H_d), 7.53 (s, 4H, H_a), 7.35 (s, 2H, H_e), 7.13 (d, J = 8.0 Hz, 4H, H_c), 6.47–6.41 (m, 4H, H_i, H_h), 5.24 (s, 4H, H_b) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 170.61 (C_5), 163.02 (C_2), 159.95 (C_4), 155.35 (C_6), 152.11, 147.93, 145.32, 142.69, 139.65, 136.66, 130.96, 127.79, 115.36, 100.98 (C_e), 68.26 (C_b) ppm. Anal. calcd for $C_{36}H_{28}N_6O_4S_2$: C, 64.33; H, 4.20; N, 12.49, Found: C, 64.27; H, 4.22; N, 12.31.

4.2.10 | 1,4-Bis(3-(2-(2-([*E*]-furan-2-ylmethylene)hydrazinyl) thiazol-4-yl)phenoxy)butane (6j)

Dark yellow solid, Yield: 83%; m.p.: 227–230°C, FT-IR (KBr, cm^{-1}): 3,447 (stretch, N–H), 3,160 (stretch,C–H aromatic), 2933, 2863 (stretch, C–H aliphatic), 1603 (stretch, C=N), 1568, 1510 (stretch, C=C), 1463 (bending, C–H, CH_2), 1252, 1026 (stretch, C–O), 1171, 1118 (bending, C–N), 833 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.88 (s, 2H, NH, H_f), 7.68 (s, 2H, H_g), 7.49 (d, J = 7.2 Hz, 2H, H_j), 7.31 (t, J = 6.4, 2H, H_d), 7.27–7.23 (m, 4H, H_l, H_e), 7.17 (s, 2H, H_k), 6.7 (d, J = 7.2 Hz, 2H, H_c), 6.89–6.85 (m, 4H, H_h, H_j), 3.99 (s, 4H, H_b), 2.27 (s, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 173.32 (C_4), 160.92 (C_1), 154.82 (C_3), 150.00 (C_5), 144.84, 139.12, 135.17, 130.09, 128.00, 121.65, 118.00, 111.82, 108.49, 96.68, 70.09 (C_b), 26.65, (C_a) ppm. Anal. calcd for $C_{32}H_{28}N_6O_4S_2$: C, 65.55; H, 5.47; N, 11.47, Found: C, 65.63; H, 5.51; N, 11.56.

4.2.11 | 1,6-Bis(3-(2-(2-([*E*]-4-methoxybenzylidene) hydrazinyl)thiazol-4-yl)phenoxy)hexane (6k)

Cream solid, Yield: 90%; m.p.: 230–233°C, FT-IR (KBr, cm^{-1}): 3,450 (stretch, N–H), 3070 (stretch, C–H aromatic), 2939, 2863 (stretch, C–H aliphatic), 1607 (stretch,C=N), 1571, 1509 (stretch, C=C), 1457 (bending, C–H, CH_2), 1250, 1029 (stretch, C–O), 1170, 1121 (bending, C–N), 875, 831, 783 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 11.71 (s, 2H, NH, H_g), 7.98 (s, 2H, H_h), 7.9 (d, J = 7.8 Hz, 4H, H_j), 7.73 (t, J = 7.0 Hz, 2H, H_e), 7.50 (d, J = 8.0 Hz, 2H, H_f), 7.25 (s, 2H, H_m), 7.14 (d, J = 7.6, 2H, H_d), 7.06 (d, J = 7.8 Hz, 4H, H_j), 7.00 (s, 2H, H_l), 3.81 (t, J = 6.8, 4H, H_c), 3.55 (s, 6H, H_k), 2.36–2.27 (s, 4H, H_b), 1.30–1.19 (m, 4H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 167.47 (C_4), 161.88, 160.74, 158.68, 152.87, 149.17, 146.06, 138.20, 132.20, 130.09, 129.65, 128.57, 125.99, 114.73, 67.89 (C_c), 55.78, (C_k), 30.28, (C_b), 21.26, (C_a) ppm. Anal. calcd for $C_{40}H_{40}N_6O_4S_2$: C, 61.52; H, 4.52; N, 13.45, Found: C, 61.61; H, 4.60; N, 13.51.

4.2.12 | 1,4-Bis((3-(2-(2-((*E*)-furan-2-ylmethylene)hydrazinyl) thiazol-4-yl)phenoxy)methyl)benzene (6l)

Cream solid, Yield: 85%; m.p.: 225–229°C, FT-IR (KBr, cm^{-1}): 3,415 (stretch, N–H), 3058 (stretch, C–H aromatic), 2925, 2860 (stretch, C–H aliphatic), 1620 (stretch, C=N), 1615 (stretch, C–C aromatic), 1442 (bending, C–H, CH_2), 1275, 1026 (stretch, C–O), 1140 (bending, C–N), 839, 766 (OOP, C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 12.03 (s, 2H, NH, H_f), 8.18 (s, 2H, H_g), 7.93 (d, J = 8.8 Hz, 2H, H_h), 7.75 (s, 4H, H_a), 7.04 (s, 2H, H_l), 6.98 (s, 2H, H_k), 6.95–6.92 m, 6H, H_c, H_d, H_e), 7.87–6.83 (m, 4H, H_i, H_j), 4.14 (s, 4H, H_b) ppm.^{13}C NMR (100 MHz, DMSO-d_6): δ; 169.87 (C_5), 159.12 (C_2), 157.46, 150.92, 146.18, 138.76, 136.29, 129.58, 126.66, 125.08, 124.20, 121.30, 119.70, 114.69, 113.39, 107.76 (C_k), 67.45 (C_b) ppm. Anal. calcd for $C_{36}H_{28}N_6O_4S_2$: C, 64.27; H, 4.20; N, 12.49, Found: C, 64.36; H, 4.28; N, 12.32.

4.3 | Antibacterial assay

In vitro antibacterial activity of bis-thiazoles was expressed as inhibition percentage against Gram-positive bacteria strains including *M. luteus* and *S. aureus* and Gram-negative bacteria strains including *E. coli* and *P. aeruginosa* at 600 nm. Nutrient agar and nutrient broth cultures were prepared according to manufacturer's instructions and were incubated at 37°C for appropriate times. The antibacterial activity of products was investigated at concentrations of 25, 50, 100, and 200 μg/mL in DMSO. Cultures were incubated at 37°C for 24 hr; after this time, the absorbance was recorded at 600 nm. DMSO was used as negative control and penicillin was used as positive control.

4.4 | Antioxidant assay

Antioxidant activity of bis-thiazoles was investigated using the DPPH method according to our recent research.[26] DPPH solution (3.9 mL, 6.25×10^{-5} M in MeOH) was added to bis-thiazole solution (0.1 mL at different concentrations of 2,000, 1,000, 500, 250, 125, and 62.5 μg/mL in MeOH) and was shaken vigorously. Samples were kept in darkness for 30 min and then their absorbance was measured at 517 nm. MeOH was used as blank. The absorbance of negative control (containing all reagents except test compounds) was also measured. DPPH radical scavenging activity was calculated as follows:

$$\text{Radical scavenging activity}\% = \frac{\text{A control} - \text{A sample}}{\text{A control}} \times 100.$$

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