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Novel Scaffolds Based on Bis-thiazole Connected to Quinoxaline or Thienothiophene through 2-Phenoxy-*N*-arylacetamide Groups as New Hybrid Molecules: Synthesis, Antibacterial Activity, and Molecular Docking Investigations

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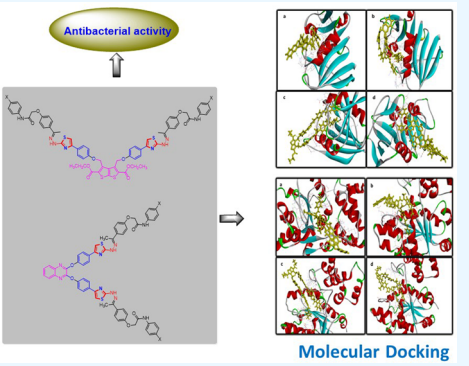
ABSTRACT: The resistance of microorganisms to antimicrobials has endangered the health of many people across the world. Overcoming the resistance problem will require the invention of molecules with a new mechanism of action so that no cross-resistance with existing therapies occurs. Because of their powerful antibacterial activity against a wide spectrum of Gram-positive and Gram-negative bacterial strains, heterocyclic compounds are appealing candidates for medicinal chemists. In this regard, as unique hybrid compounds, we synthesized a novel family of bis-thiazoles linked to quinoxaline or thienothiophene via the 2-phenoxy-*N*-arylacetamide moiety. The target compounds were synthesized by reacting the relevant bis(*α*-haloketones) with the corresponding thiosemicarbazones in EtOH at reflux with a few drops of TEA. Under comparable reaction conditions, the isomeric bis(thiazoles) were synthesized by reacting the appropriate bis(thiosemicarbazone) with the respective *α*-haloketones. The structures of the novel compounds were confirmed using elements and spectral data. All of the synthesized compounds were tested for antibacterial activity in vitro. With an inhibitory zone width of 12 mm, compound **12a** had the same activity as the reference medication tobramycin against *Staphylococcus aureus*. Compound **12b** showed 20 mg/mL as a minimum inhibitory concentration (MIC) against *Bacillus subtilis*. Some of the synthesized compounds were tested via molecular docking against two bacterial proteins (dihydrofolate reductase and tyrosyl-tRNA synthetase).



1. INTRODUCTION

The creation of novel antimicrobial medicines has become a hot issue and one of the most difficult problems, while multidrug-resistant bacteria threaten all fields of human medicine worldwide. This involves creating analogues of existing antibacterial medication classes with novel modes of action aiming at increasing potency, reducing resistance, and reducing toxicity.[1] The problem of bacterial infection management cannot be dismissed simply by discussing the diseases caused, the bacteria involved, and the benefits and drawbacks of the various antibacterial agents now available, especially since the latter still have certain definite shortcomings. A deeper knowledge of how humans fight and harbor germs, as well as some of the mechanisms by which bacteria create negative consequences, can help with the management of more complex and resistant bacterial illnesses.[2] Extensive research has been carried out over the years in the hunt for effective and safe antimicrobial drugs based on heterocyclic scaffolds, particularly to combat the ever-increasing microbial resistance and to minimize the high late-stage attrition rate in the drug development process. In this regard, thiazole derivatives have been shown to exhibit antiviral, antibacterial, antifungal, antidiabetic, antioxidant, anti-inflammatory, anticancer, and analgesic properties.[3−9] They are also found in 18 clinically approved drugs (FDA-approved), including antitumor drugs (epothilone and tiazofurin), anti-inflammatory drugs (meloxicam), antifungal drugs (isavuconazole), antiparasitic drugs (thiabendazole and nitazoxanide), antigout drugs (febuxostat), antithrombotic drugs (edoxaban), antiulcer drugs (nizatidine and famotidine), and antibacterial drugs (aztreonam, sulfathiazole, cefepime, and ceftriaxone) (Figure 1).[10−12] Because of the simplicity of chemical achievement as well as structural optimization, thiazole-based scaffolds are the most attractive heterocycles in synthetic medicinal chemistry.[6,13,14] Furthermore, phenoxyacetamide and its derivatives are pharmacolog-

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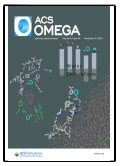

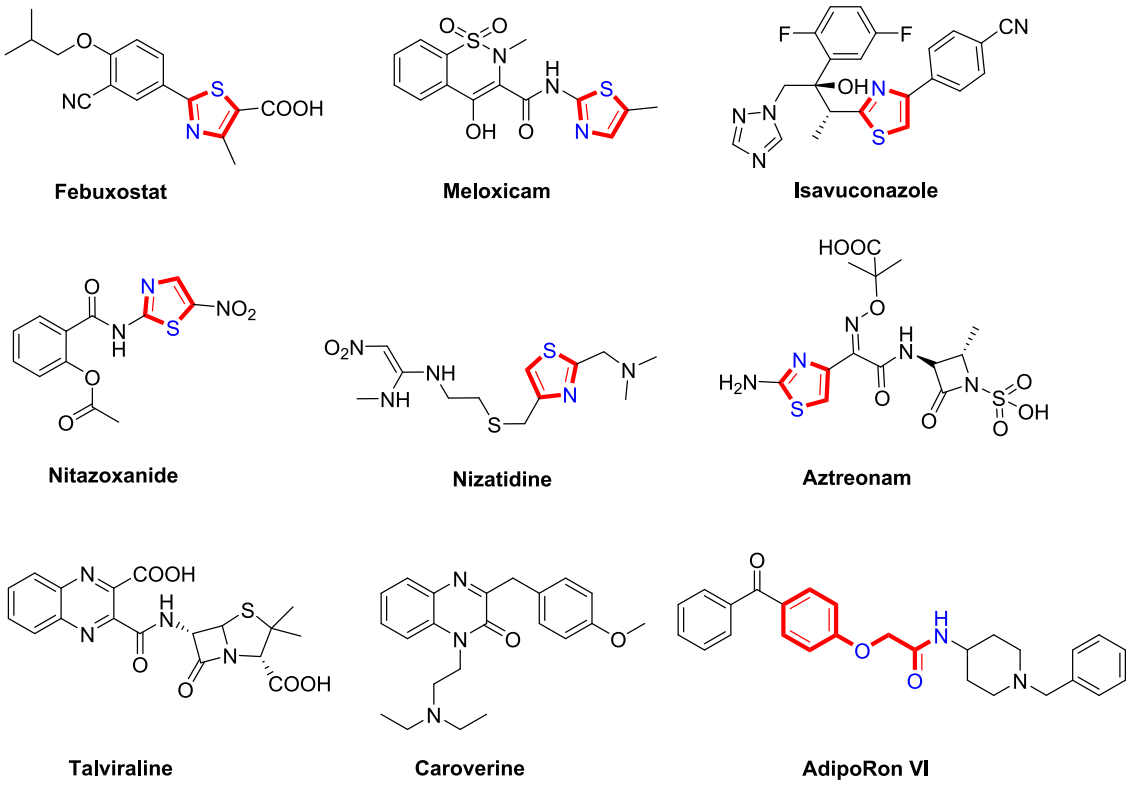

Figure 1. Some clinically approved drugs (FDA-approved) include the thiazole ring, quinoxline, or the phenoxyacetamide moiety.

ically active molecules with anticancer, antiviral, antioxidant, anti-inflammatory, antiparasitic, antibacterial, and antihyperglycemic effects, as well as antituberculosis and MAO-A inhibitor activity.[15−23] AdipoRon VI (Figure 1), a phenoxyacetamide medication, has received a lot of interest in this respect as a potential therapy for obesity, cardiovascular disease, diabetes, and nonalcoholic fatty liver disease. Moreover, quinoxaline derivatives have been the focus of substantial investigation since they have emerged as an important heterocyclic moiety with a varied spectrum of physicochemical and biological functions including antibacterial, antitubercular, antimalarial, antiviral, anti-inflammatory, antifungal, anticancer, antiproliferative, antitumor, and anticonvulsant properties.[24−34] They have a wide variety of biological actions. Figure 1 depicts the quinoxaline core structure of several pharmacological compounds.[35] In addition to the prospective applications of thieno[2,3-*b*]thiophene derivatives in optical and electrical systems, they have also sparked significant medicinal interest due to their diverse biological properties, which include antibacterial, antiviral, anticancer, and antiglaucoma properties.[36−45] Furthermore, bis-heterocyclic compounds are widely used as scaffolds in drugs and pharmaceutically relevant substances. Many bis-heterocycles have been shown to have anticancer, antibacterial, antiallergic, and other disease-fighting characteristics when linked properly.[46,47] Molecular hybridization is the process of combining at least two pharmacophore fragments from different bioactive chemicals to create hybrids that outperform the original drugs. The pharmacophore scaffolds of several compounds are combined to create hybrid molecules. In this regard, anticancer drugs that are safer and more effective than those presently on the market may benefit from hybridization.[48,49] In light of these findings, as well as our continuing interest in the synthesis of heterocycles[50−62] and their bis(heterocycles),[63−77] we sought to incorporate *N*-arylacetamide units into the backbone of thiazole to obtain a novel series of bis-thiazole derivatives linked through biologically active quinoxaline or thienothiophene cores using a "hybrid conjugation of bioactive ligands" approach. Our synthetic strategy employs 2-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenoxy)-*N*-(aryl)-acetamides, 2-(4-(2-bromoacetyl)phenoxy)-*N*-(aryl)-acetamides, bis(4,1-phenylene)bis(2-bromoethan-1-ones) **7**, bis(*α*-bromoketone), and bis(thiosemicarbazone) as precursors (Figure 2).

2. RESULTS AND DISCUSSION

2.1. Synthesis. In boiling DMF, the potassium salt of 4-hydroxyacetophenone (**2**) reacts with the corresponding 2-chloro-*N*-arylacetamide derivatives (**1a,b**) to give the corresponding 2-(4-acetylphenoxy)-*N*-(aryl)acetamides **3a,b**. Bromoacetyl derivatives **6a,b** were produced by treating the corresponding **3a,b** with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid (*p*-TsOH). Thiosemicarbazone precursors **5a,b** were produced when **3a,b** was condensed with one equivalent of thiosemicarbazide (**4**) in refluxing ethanol acidified with acetic acid (Scheme 1).

Utilizing thiosemicarbazones **5a,b**, we investigated the synthesis of bis(thiazoles) **7a,b** that are linked to the quinoxaline core to achieve the concept of molecular hybridization. Thus, the reaction of bis(*α*-bromoketone) **7**[78] with the corresponding thiosemicarbazones **5a,b** in EtOH at reflux with a few drops of TEA as a catalyst resulted in the novel bis-thiazoles **8a,b** in 74 and 76% yields, respectively (Scheme 2).

The novel isomeric bis(thiazoles) **10a** and **10b** were successfully synthesized in 77 and 79% yields, respectively, by reacting bis(thiosemicarbazone) **9**[78] with the appropriate *α*-

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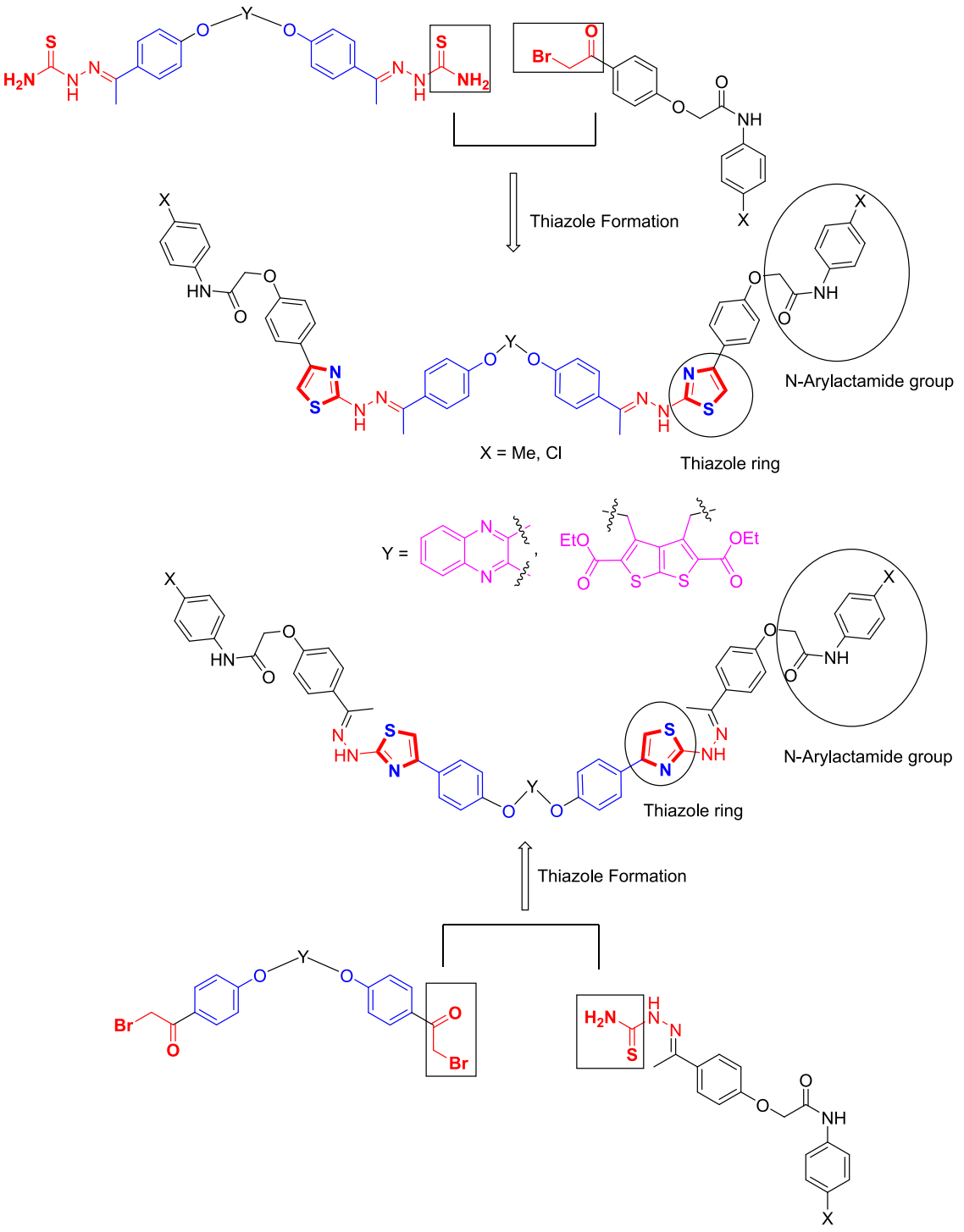

Figure 2. Design concept of bis-thiazole derivatives.

bromoketones **6a** and **6b** in ethanol at reflux with a few drops of TEA (Scheme 3).

Our investigation was expanded to include the synthesis of novel bis(thiazole) **12a,b** linked to the thienothiophene core, in addition to their prospective applications in optical and electrical systems. Thus, the reaction of bis(α-bromoketone) **11**[79] with the corresponding thiosemicarbazones **5a,b** in refluxing ethanol and a catalytic amount of triethylamine yielded the expected bis-thiazole derivatives **12a,b** in good yields (Scheme 4).

Similarly, the reaction of bis(thiosemicarbazone) **13**[79] with the appropriate α-bromoketones **6a** and **6b** in ethanol at reflux with catalytic trimethylamine as a basic catalyst yielded bis-thiazoles **14a** and **14b** in 69 and 73% yields, respectively (Scheme 5).

We postulated in Scheme 6 that the reaction that culminates in the production of thiazole derivatives begins with the creation of nonisolable intermediates **I**. Following the loss of water molecules under experimental circumstances, the latter underwent sequential in situ cyclization to yield the appropriate nonisolable intermediates **II**, which gave the

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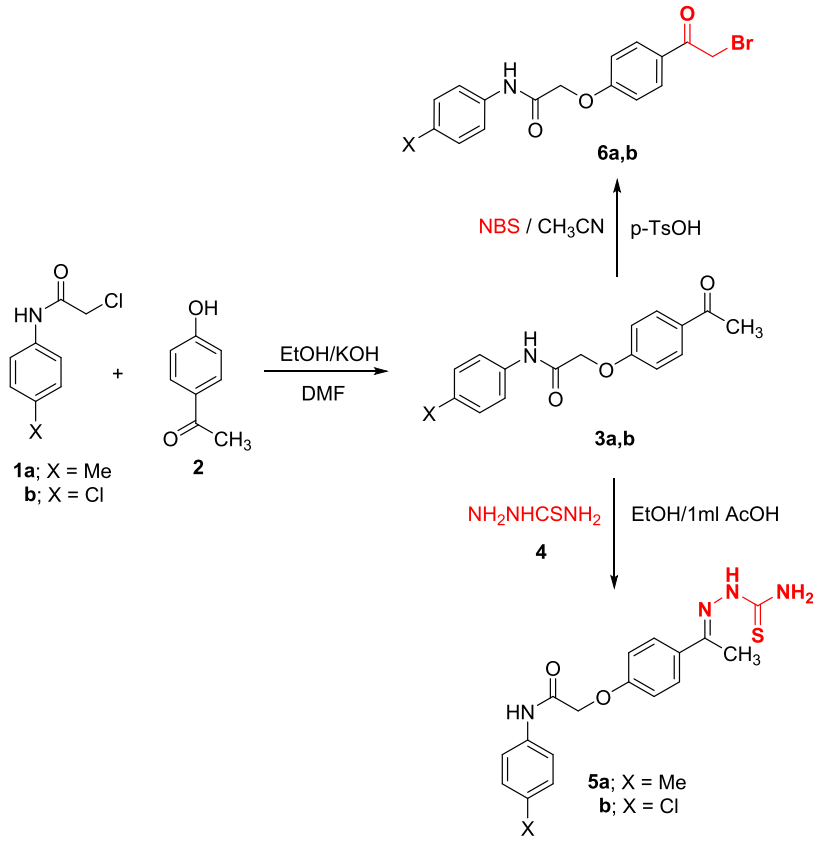
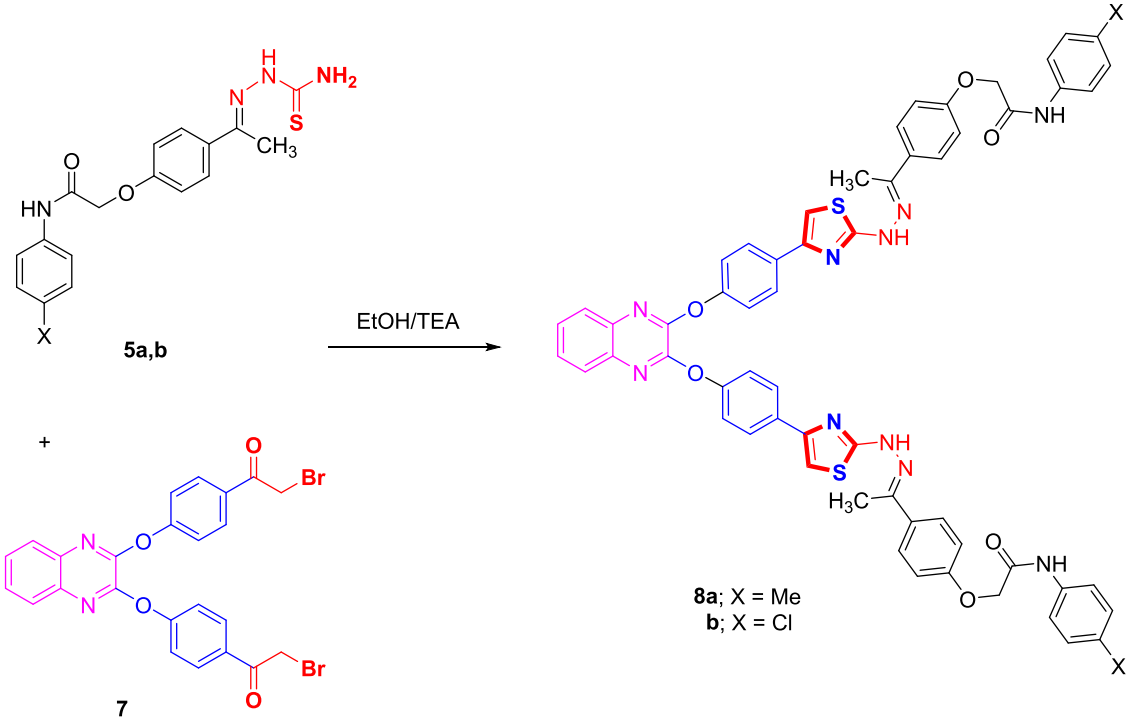
Scheme 1. Synthesis of Acetyl-, Bromoacetyl-, and Thiosemicarbazone Derivatives



Scheme 2. Synthesis of Bis-thiazoles 8a,b Linked to the Quinoxaline Core



required bis-thiazoles as end condensation products (Scheme 6).

2.2. Spectroscopy. The proposed structures of the newly synthesized compounds are supported by elemental analyses as well as spectral data. The ^{1}H NMR spectra of **6a** revealed the disappearance of the methyl group and the presence of CH_2–Br protons, which resonated at 4.82 ppm as singlet signals integrating two protons. Spectroscopic data, such as IR, ^{1}H NMR, and ^{13}C NMR, supported the structure confirmation of thiosemicarbazones **5a,b**. C═N stretching was observed in the

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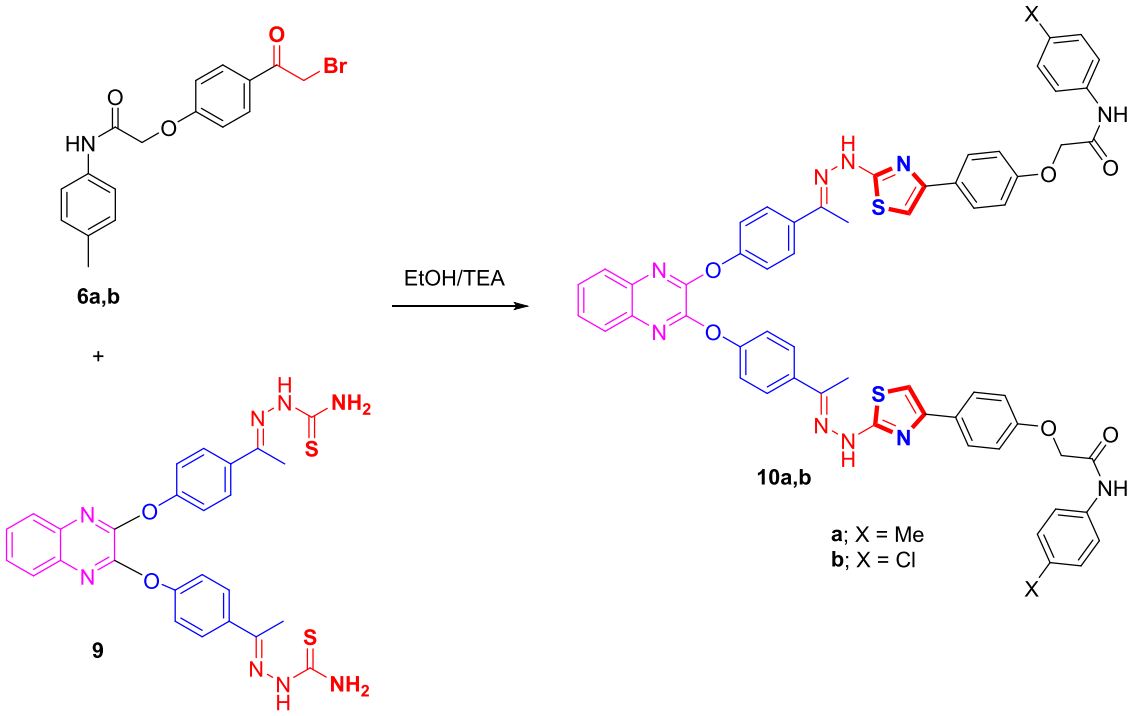
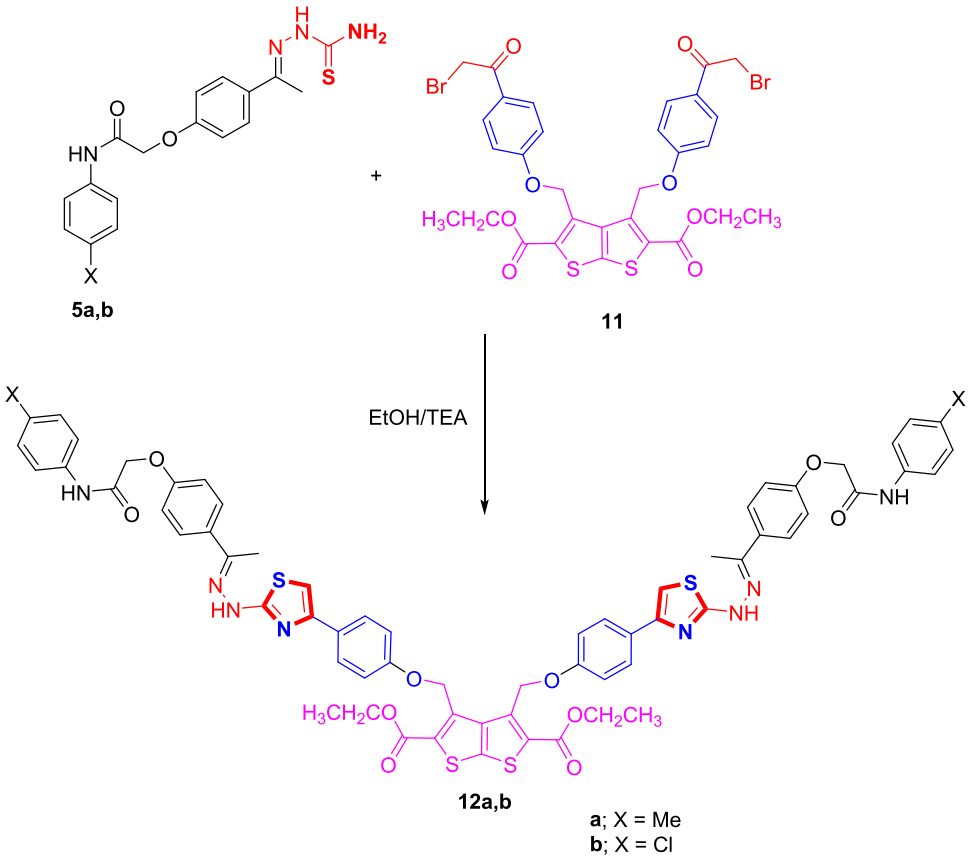
Scheme 3. Synthesis of Isomeric Bis-thiazoles 10a,b Linked to the Quinoxaline Core



Scheme 4. Synthesis of Bis-thiazoles 12a,b Linked to the Thiophene Core



FTIR range of 1540−1565 cm^{-1}, while the C═S band was discovered between 1212 and 1256 cm^{-1}. C═O stretching was detected between 1710 and 1670 cm^{-1}, and NH stretching was detected between 3225 and 3320 cm^{-1}. As an example, in ^{1}H NMR of **5a**, CH_2 appeared as a singlet in the range of 4.72−4.74 ppm, while the NH−N signal appeared at 9.98 ppm. At 10.09, however, a broad singlet was observed for NH−C═S. The abovementioned analysis also confirmed the spectral

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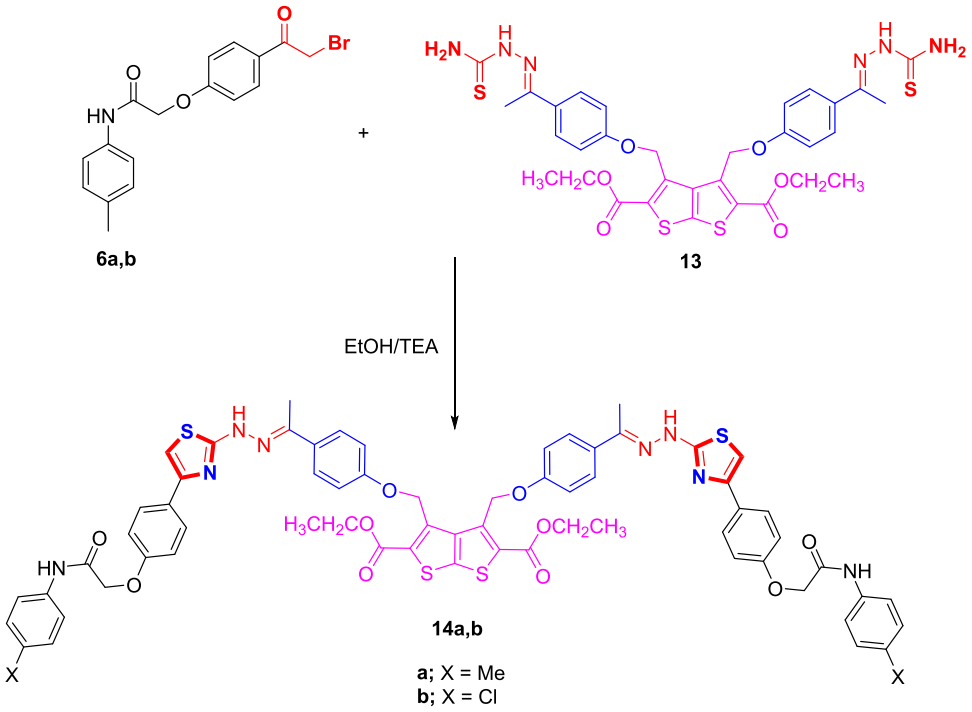
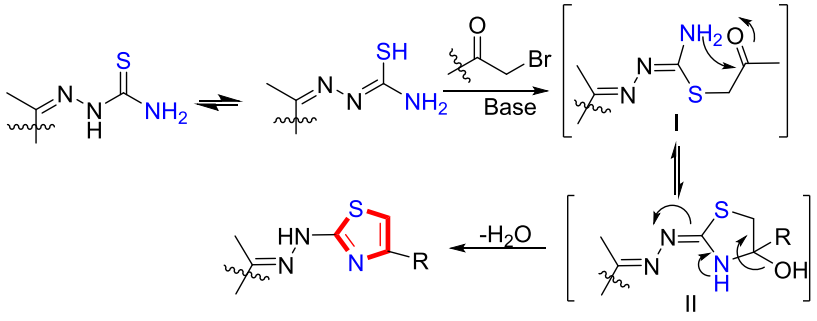
Scheme 5. Synthesis of Isomeric Bis-thiazoles 14a,b Linked to the Thiophene Core



Scheme 6. Plausible Mechanism for the Formation of Targeted Thiazoles



data of the remaining protons, which were found to be in good agreement with the predicted structure. The IR spectrum of **10b** revealed an absorption band caused by NH and C═O at 3275 and 1673 cm^{-1}, respectively. Due to D_2O-exchangeable NH protons, its ^1H NMR spectrum revealed two signals at 10.24 and 11.14 ppm. Furthermore, three distinct singlet signals appear at 2.31, 4.76, and 7.36 ppm, which are attributed to the methyl, methylene ether linkage OCH_2CO, and the thiazole ring's C-5 proton. The chemical shifts and integral values of the remaining protons were all as expected. The mass spectrum of compound **10b** revealed a molecular ion peak at *m*/*z* 1112 corresponding to its molecular formula.

The IR spectrum of compound **14a** revealed the presence of a −NH group absorption band at 3275 cm^{-1}. Furthermore, it displayed C═O values at 1705 and 1681 cm^{-1}. The ^1H NMR spectrum of **14a** revealed the presence of two singlet signals at 2.25 and 2.80 ppm, which corresponded to four CH_3. It also showed ethyl ester as a triplet signal at 1.28 ppm and a quartet signal at 4.34 ppm. It also revealed the OCH_2 linkage as a singlet signal at 5.64 ppm. At 10.20 and 11.90 ppm, the two −NH groups appeared as broad signals. The aryl protons were assigned multiplets at 6.91−7.74 ppm.

2.3. Antibacterial Activity. The antibacterial activity of the synthesized compounds was tested against four bacterial strains: two Gram-positive bacteria (*Bacillus subtilis* (DSM 1088) and *Staphylococcus aureus* (ATCC 6538) and two Gram-negative bacteria (*Pseudomonas aeruginosa* (ATCC 10145) and *Escherichia coli* (ATCC 8739). The antibacterial activity data are shown in Table 1. Compound **12a** had a comparable action against *S. aureus* as the conventional antibiotic tobramycin, with an inhibition zone of 12 mm. Compounds **8a** and **12b** inhibited *S. aureus* with an inhibition zone of 11 mm, which was highly similar to tobramycin. When compared to the reference antibiotic clindamycin (the diameter of the inhibition zone was 27 mm), compounds **12a** and **12b** had modest action against *B. subtilis* (the diameters of the inhibition zone were 10 and 15 mm, respectively). With a diameter of the inhibition zone of 10 mm, compound **8b** had comparable activity to tobramycin (13 mm) and moderate activity to ofloxacin (17 mm) against *E. coli*. All of the substances tested demonstrated no efficacy against *P. aeruginosa*. The microdilution technique was performed to determine the minimum inhibitory concentration (MIC) for the most effective compound (**12b**) which had the highest activity against *B. subtilis*. MIC is the lowest concentration that inhibits 100% of the bacterial

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Table 1. Antibacterial Activity of the Prepared Compounds at a Concentration of 20 mg/mL[a]

	diameter of the zone of inhibition (mm) at 20 mg/mL			
sample	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*E. coli*
8a	NA	11	NA	NA
8b	NA	NA	NA	10
10a	NA	NA	NA	NA
10b	NA	NA	NA	NA
12a	10	12	NA	NA
12b	15	11	NA	NA
14a	NA	NA	NA	NA
14b	NA	NA	NA	NA
tobramycin[80]		12		13
ofloxacin[81]			20	17
clindamycin	27	23		
DMSO	0.0	0.0	0.0	0.0

[a]Standard antibiotic tobramycin (10 μg) for *S. aureus* and *E. coli*, ofloxacin (2 μg/disk) for Gram-negative bacteria, and clindamycin (2 μg/disk) for Gram-positive bacteria. NA: no activity.

growth. As shown in Figure 3, the MIC was 20 mg/mL for compound **12b**.

2.4. Structure–Activity Relationship. The location of the bis-thiazoles from the quinoxaline core in derivatives **8a, 8b, 10a**, and **10b** had a significant influence on activity, according to the structure–activity relationship. Because of the closeness of the bis-thiazoles to the quinoxaline core in derivatives **8a** and **8b**, they showed promising efficacy against *S. aureus* and *E. coli* when compared to tobramycin, respectively. While the presence of bis-thiazoles farther away from the quinoxaline core decreased antibacterial activity in derivatives **10a** and **10b**, the inclusion of the electron-donating group (methyl) and the electron-withdrawing moiety (Cl) in derivatives **8a** and **8b**, respectively, had no discernible effect on activity. Similarly, in derivatives **12a** and **12b**, the presence of bis-thiazoles close to the thiophene core resulted in promising action against *S. aureus* and slight activity against *B. subtilis* when compared to tobramycin and clindamycin, respectively. The presence of bis-thiazoles distant from the thienothiophene core in derivatives **14a** and **14b** reduced activity. The activity of derivatives **12a** and **12b** differed little depending on whether the methyl group or the Cl atom was present.

2.5. Molecular Docking. The molecular docking study was carried out to evaluate the potential mechanism of action of compounds **8a, 8b, 12a**, and **12b** as antibacterial agents. For this investigation, bacterial dihydrofolate reductase (DHFR) and tyrosyl-tRNA synthetase (TyrRS) were used. The enzyme DHFR is involved in the folic acid pathway.[82] It converts dihydrofolate to tetrahydrofolate, boosting thymidylate production, DNA replication, RNA transcription, protein translation, and cell development.[83] Other tetrahydrofolate metabolites are also involved in the conversion of single-carbon units into pyrimidines, purines, and amino acids.[82] As a result, DHFR suppression can result in a lack of protein and nucleic acid components, resulting in a halt in DNA synthesis and programmed cell death. Aminoacyl-tRNA synthetases (aaRSs) are a class of enzymes that promote the transfer of amino acids to their matching tRNAs during protein synthesis.[84] Since the identification of this information, which includes the structures of the amino acids and the coinciding tRNA molecules, it is critical to transform the coded information into protein structures in nucleic acids.[85] TyrRS belongs to the aaRSs family, which is found in all living organisms and has two highly conserved sequence motifs at the active site, HIGH and KMSKS.[84] Compounds **8a, 8b, 12a**, and **12b** fit in the active site of DHFR with comparable binding energies (−40.8, −37.14, −39.7, and −37.9 kcal/mol) relative to the cocrystallized ligand (−16.2 kcal/mol), as shown in Table 2. Binding energies of our compounds were found to be more negative than those of the standard, implying that they fit with higher stability than the standard. The binding energies for TyrRS were likewise extremely comparable (−36, −36.6, −37.1, and −40 kcal/mol, respectively) and were more negative than the standard (−18.6 kcal/mol) (Table 2). Figure 3 depicts the modes of interaction of the investigated compounds with the DHFR active site. It was found that compound **8a** interacted through 11 interactions, one hydrogen bond between the nitrogen of quinoxaline ring and LYS: 144 with bond distance 5.68 A0; two alkyl hydrophobic interactions with VAL: 6 and LYS: 45; seven π-alkyl

Table 2. Binding Energy Values for Compounds 8a, 8b, 12a, and 12b and Standard Ligands with Bacterial Dihydrofolate Reductase and Tyrosyl-tRNA Synthetase Proteins

	Gibbs free energy (*S*) (kcal/mol)	
sample	bacterial dihydrofolate reductase	bacterial tyrosyl-tRNA synthetase
8a	−40.8	−36
8b	−37.14	−36.6
12a	−39.7	−37.1
12b	−37.9	−40
cocrystallized ligand (standard)	−16.2	−18.6

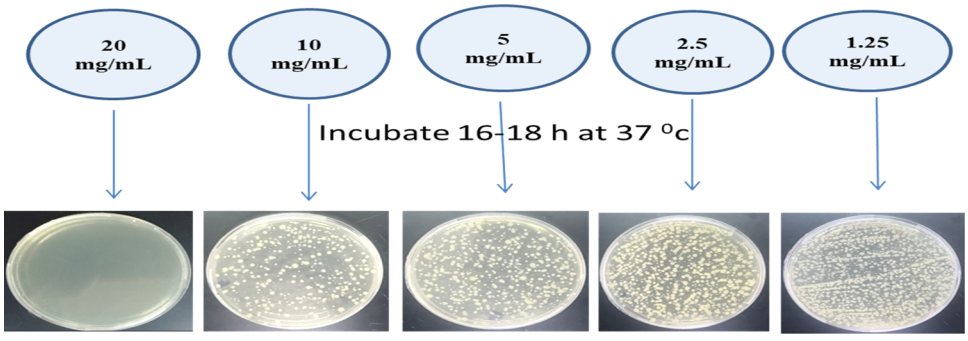

Figure 3. Microdilution assay for compound **12b** against *B. subtilis*.

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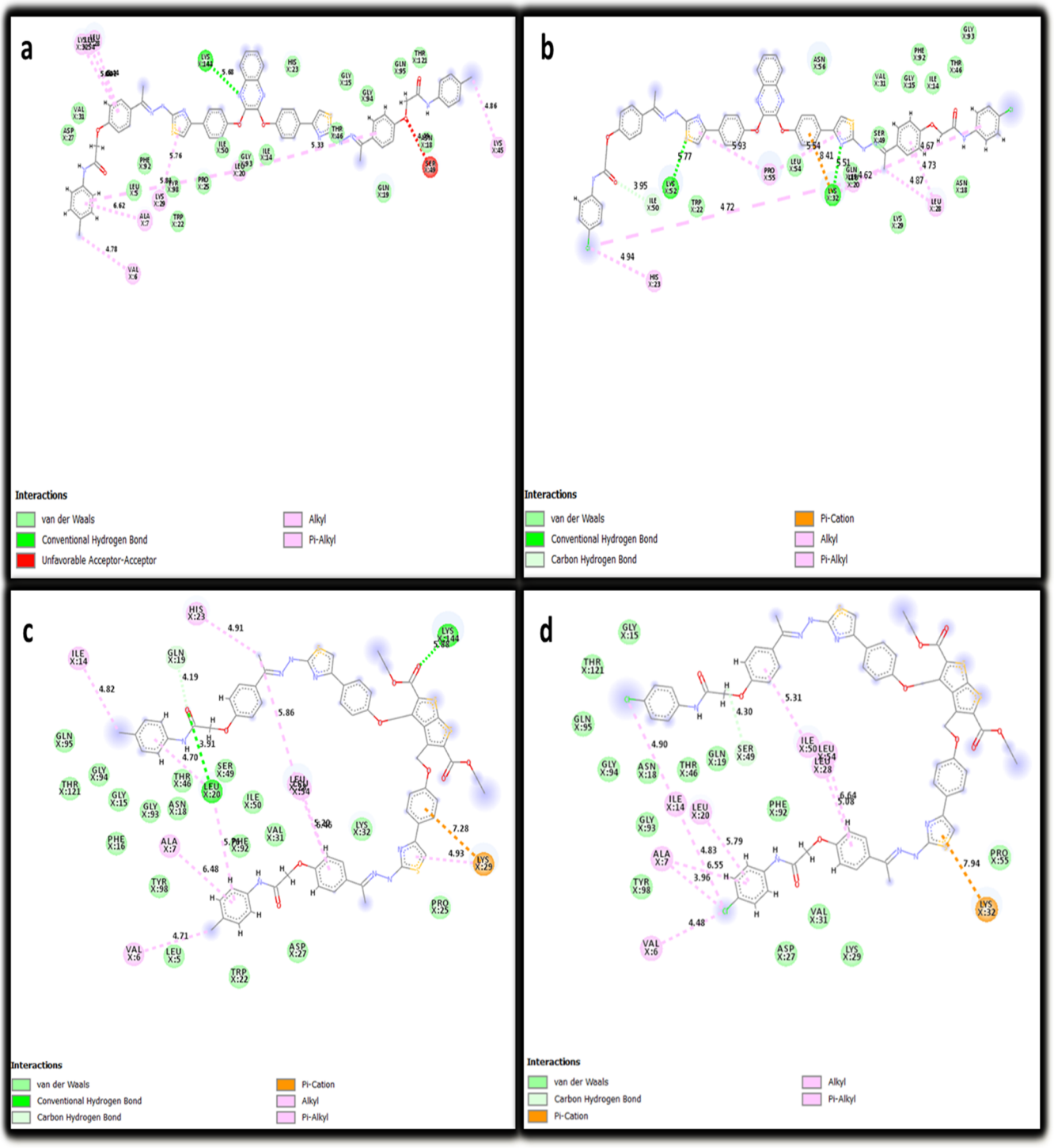

Figure 4. Two-dimensional (2D) representation of (a) compound **8a**, (b) compound **8b**, (c) compound **12a**, and (d) compound **12b** with bacterial dihydrofolate reductase.

hydrophobic with ALA: 7, LYS: 29, LEU: 20, LEU: 28, LEU: 54, and LYS: 32 residues; and one unfavorable acceptor−acceptor with SER: 49 (Figures 4a and 5a). Compound **8b** was able to fit into the active site of DHFR via 12 interactions, including three hydrogen bonds with LYS: 32, ILE: 50, and LYS: 52; one π-cation electrostatic with LYS: 32; and eight π-alkyl hydrophobic with HIS: 23, PRO: 55, LEU: 28, and LYS: 32 residues (Figures 4b and 5b). Compound **12a** had 14 interactions: three hydrogen bonds with GLN: 19, LEU: 20, and LYS: 144; one π-cation electrostatic interaction with LYS: 29; and 10 alkyl and π-alkyl hydrophobic interactions with LYS: 29, LEU: 28, LEU: 54, HIS: 23, LEU: 20, ALA: 7, VAL: 6, and ILE: 14 residues (Figures 4c and 5c). Figures 4d and 5d reveal 11 contacts for compound **12b**, including one hydrogen bond with SER 49; one π-cation electrostatic interaction with LYS 23; and nine π-alkyl hydrophobic interactions with VAL 6, ALA 7, ILE 14, LEU 20, ILE 50, LEU 54, and LEU 28 residues. Compound **8a** was found to match TyrRS through

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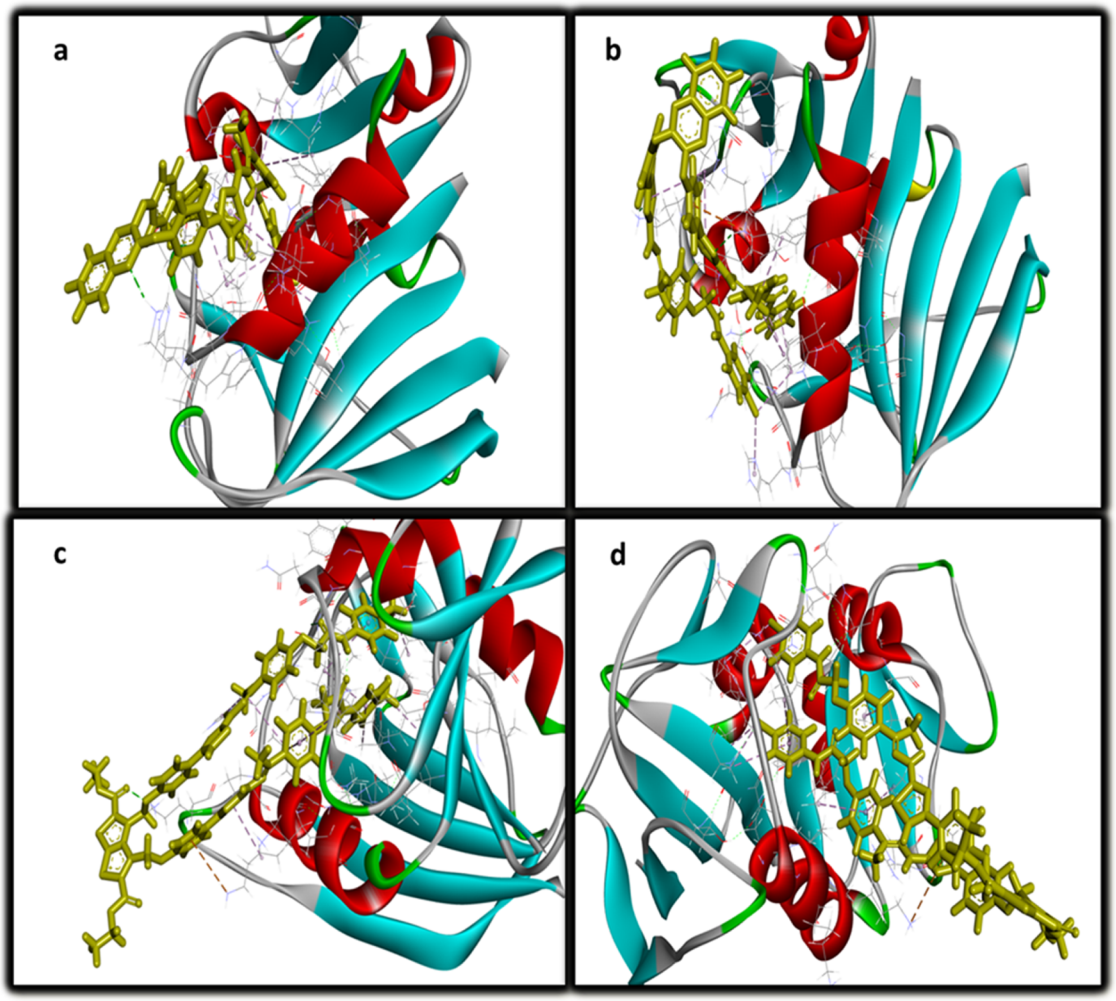

Figure 5. Three-dimensional representation (3D) of the molecular interaction of (a) compound **8a**, (b) compound **8b**, (c) compound **12a**, and (d) compound **12b** with bacterial dihydrofolate reductase.

nine interactions (Figures 6a and 7a). Two hydrogen bonds were formed with LYS: 84 and ASP: 195; five alkyl hydrophobic contacts were formed with ALA: 43, HIS: 47, HIS: 50, TRP: 241, and VAL: 224; one $\pi-\pi$ stacked with HIS: 47; and one $\pi-\sigma$ with LEU: 223. Figures 6b and 7b show five hydrogen bonds with GLY: 49, ASP: 40, and LYS: 84; two alkyl hydrophobic with CYS: 37 and LEU: 70; two π-alkyl hydrophobic with PRO: 53 and LYS: 84; one π-sulfur between the benzene ring and CYS: 37; and one π-cation electrostatic between the benzene ring and LYS: 84. Compound **12a** also had 11 interactions, including three hydrogen bonds with LYS: 84 and ASP: 195; three electrostatic interactions with ASP: 80, LYS: 84, and TRP: 241; and five hydrophobic interactions with HIS: 47, PRO: 53, LEU: 223, ALA: 239, and TRP: 241 residues (Figures 6c and 7c), while compound **12b** fitted via 12 interactions, including four hydrogen bonds with HIS: 50 and ASP: 40; two π-cation electrostatic with LYS: 84 and LYS: 234; four alkyl hydrophobic with CYS: 37, LEU: 70, LYS: 84, and LYS: 231; one $\pi-\pi$ T-shaped with HIS: 47; and one π-alkyl hydrophobic interaction with LYS: 234 (Figures 6d and 7d). As a result, compounds **8a, 8b, 12a**, and **12b** may have antibacterial action by inhibiting the bacterial DHFR and TyrRS enzymes.

3. CONCLUSIONS

Bis-thiazoles connected to quinoxaline or thienothiophene via 2-phenoxy-*N*-arylacetamide were synthesized as novel hybrid compounds. Condensation of bis-thiosemicarbazones or bis(α-haloketones) with a suitable reagent is the key step in our synthetic strategy. The mechanistic routes and chemical structures of all synthesized derivatives were described and validated by using spectrum data. The products were produced in high yields using easily accessible starting ingredients and a straightforward method. Compound **12a** had promising antibacterial activity when compared to tobramycin and moderate activity when compared to clindamycin. Compound **12b** exerted the highest activity against *B. subtilis* with a diameter of the inhibitory zone and MIC equaled to 15 mm and 20 mg/mL, respectively. The molecular docking simulation demonstrated that compounds **8a**, **8b**, **12a**, and **12b** could fit in the active site of bacterial DHFR and TyrRS with binding energies lower than those of the standard.

4. EXPERIMENTAL SECTION

4.1. General. *4.1.1. Synthesis of Target Molecules.* Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

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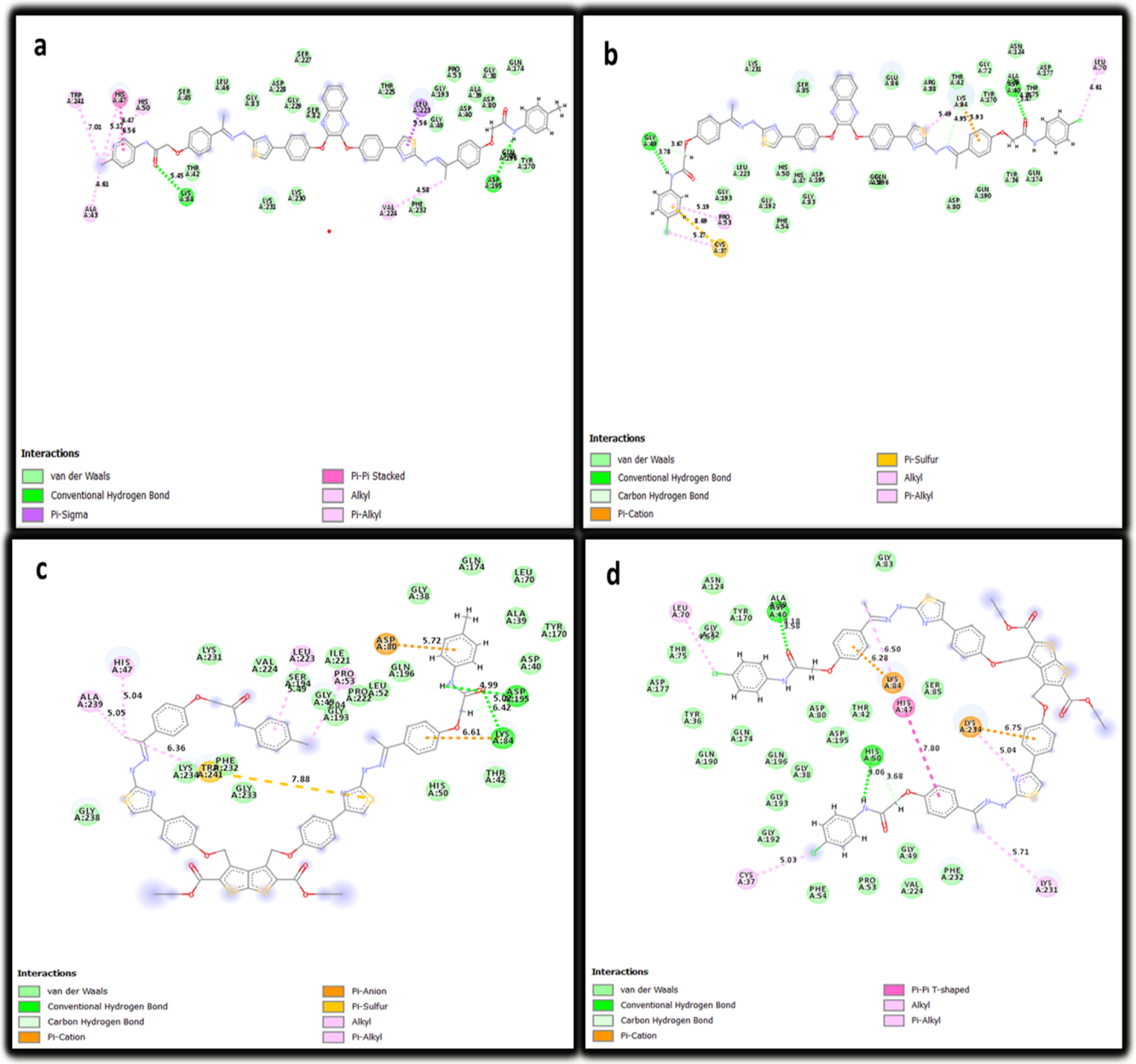

Figure 6. Two-dimensional representation of (a) compound **8a**, (b) compound **8b**, (c) compound **12a**, and (d) compound **12b** with bacterial tyrosyl-tRNA synthetase.

The infrared spectra were recorded as potassium bromide disks on a PyeUnicam SP 3-300 and Shimadzu FTIR 8101 infrared spectrophotometer. NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) using DMSO-d_6 as solvent Chemical shifts were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. Compounds **6a** and **6b** were prepared as described.[86]

*4.1.2. Synthesis of 2-(4-(1-(2-Carbamothioylhydrazineylidene)ethyl)phenoxy)-N-(aryl)-acetamide (**5a,b**).* To a solution of the acetyl compounds **3a,b** (10 mmol) in absolute ethanol (25 mL) containing 1 mL of acetic acid, thiosemicarbazide (**4**) (10 mmol) was added. The reaction mixture was heated under reflux for 3 h and then allowed to cool. The solid formed was collected by filtration and recrystallized from ethanol/DMF to give **5a,b** as a yellow powder.

*4.1.3. 2-(4-(1-(2-Carbamothioylhydrazineylidene)ethyl)-phenoxy)-N-(p-tolyl)acetamide (**5a**).* Pale yellow powder, (81% yield), mp. 215−217 °C; IR: (potassium bromide) 3421, 3366 (NH_2), 3251 (NH), 1675 (C═O) cm^{-1}; ^{1}H NMR: δ 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.72 (s, 2H, OCH_2C═O), 6.99 (d, 2H, J = 7.2 Hz, ArH), 7.11 (d, 2H, J = 7.5 Hz, ArH), 7.51 (d, 2H, J = 7.2 Hz, ArH), 7.88−7.91 (m, 2H, ArH), 8.18 (s, 2H, NH_2), 9.98 (s, 1H, NH), 10.09 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.0, 21.5, 67.3, 114.6, 120.3, 127.3, 128.6, 129.4, 130.6, 136.8, 142.5, 161.1, 162.3, 179.9; MS: m/z (%) 356 (M^+). Anal. Calcd. for

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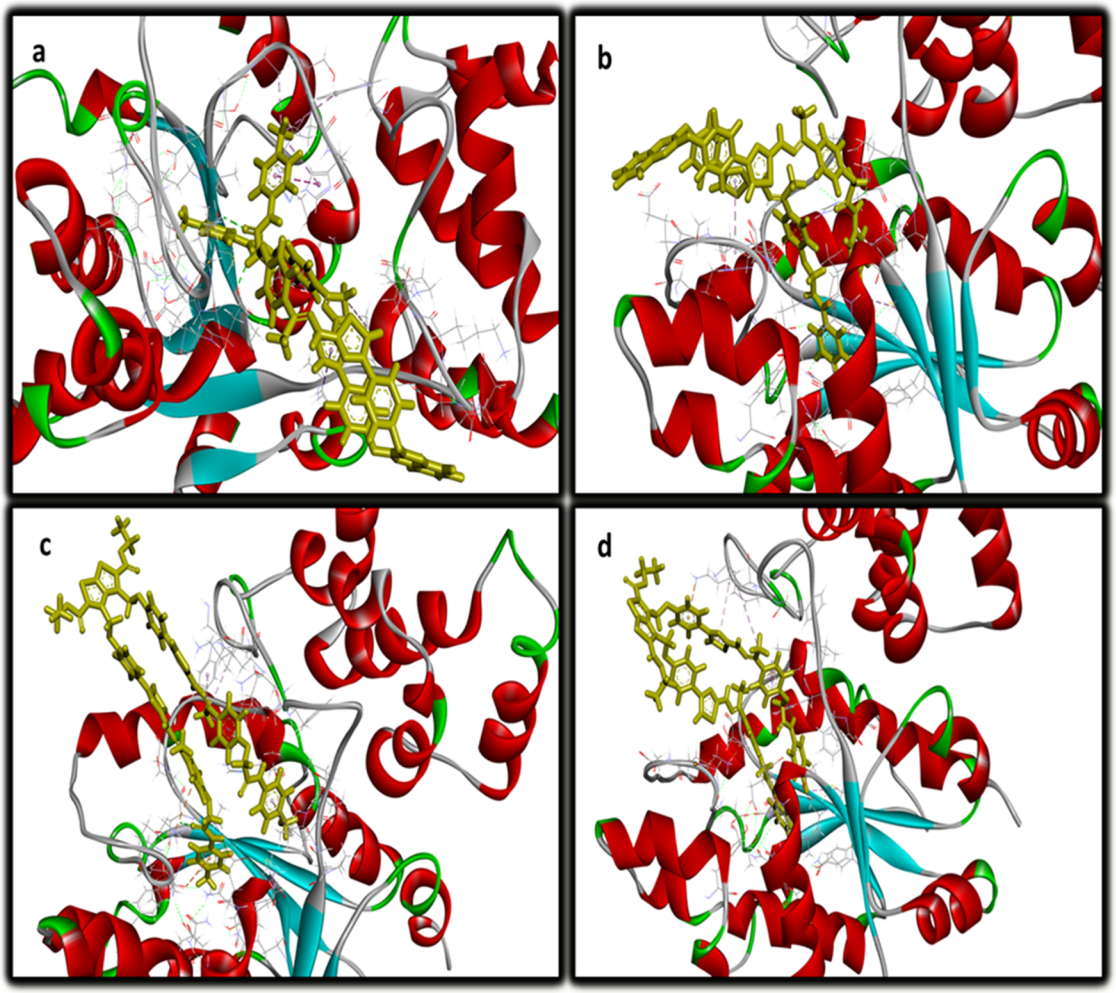

Figure 7. Three-dimensional representation of the molecular interaction of (a) compound **8a**, (b) compound **8b**, (c) compound **12a**, and (d) compound **12b** with bacterial tyrosyl-tRNA synthetase.

$C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72; S, 8.99. Found: C, 60.62; H, 5.69; N, 15.75; S, 8.96.

*4.1.4. 2-(4-(1-(2-Carbamothioylhydrazineylidene)ethyl)-phenoxy)-N-(4-chlorophenyl)acetamide (**5b**).* Pale yellow powder, (80% yield), mp. 220−222 °C; IR: (potassium bromide) 3433, 3361 (NH_2), 3257 (NH), 1681 (C═O) cm^{-1}; ^1H NMR: δ 2.26 (s, 3H, CH_3), 4.74 (s, 2H, OCH_2C═O), 6.98 (d, 2H, J = 8.4 Hz, ArH), 7.36 (d, 2H, J = 8.4 Hz, ArH), 7.67 (d, 2H, J = 7.8 Hz, ArH), 7.89 (d, 2H, J = 7.8 Hz, ArH), 8.18 (s, 2H, NH_2), 10.06 (s, 1H, NH), 10.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.8, 67.7, 114.2, 121.7, 126.3, 129.7, 133.2, 137.3, 142.1, 158.1, 166.1, 172.7; MS: m/z (%) 376 (M^+). Anal. Calcd. for $C_{17}H_{17}ClN_4O_2S$: C, 54.18; H, 4.55; Cl, 9.41; N, 14.87; S, 8.51. Found: C, 54.12; H, 4.59; N, 14.85; S, 8.56.

*4.1.5. Synthesis of Bis(thiazoles) Linked to Heteroaromatic Cores **8a,b** and **12a,b**.* A mixture of the appropriate bis-2-bromoethanone derivatives **7** or **11** (1 mmol) and the thiosemicarbazone **5a,b** (2 mmol) was dissolved in ethanol (25 mL), TEA (0.2 mL) was added, and the reaction mixture was heated at reflux for 3−5 h. The reaction mixture was then left to cool, and the solid product was filtered off and recrystallized from ethanol/DMF, to afford compounds **8a,b** and **12a,b.**

*4.1.6. 2,2′-(((((((Quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(4,1-phenylene))bis-(oxy))bis(N-(p-tolyl)acetamide) (**8a**).* Brown powder, (74% yield); mp 259−261 °C; IR (KBr): 3311 (NH), 1673 (C═O), 1555 (C═N) cm^{-1}; ^1H NMR: δ 2.26 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 4.73 (s, 4H, OCH_2C═O), 7.06 (d, 4H, J = 8.7 Hz, ArH), 7.13 (d, 4H, J = 8.1 Hz, ArH), 7.35 (s, 2H, thiazol-5-H), 7.45 (d, 4H, J = 8.4 Hz, ArH), 7.53 (d, 4H, J = 8.1 Hz, ArH), 7.58−7.78 (m, 8H, ArH), 8.01 (d, 4H, J = 8.4 Hz, ArH), 10.00 (s, 2H, NH), 11.14 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.3, 20.0, 68.1, 102.4, 114.5, 120.6, 121.6, 121.9, 127.1, 127.4, 128.7, 129.5, 134.1, 137.0, 141.1, 145.8, 147.4, 152.3, 155.7, 160.5, 161.3, 167.9, 172.1; MS: m/z (%) 1070 (M^+). Anal. Calcd. for $C_{60}H_{50}N_{10}O_6S_2$: C, 67.27; H, 4.70; N, 13.08; S, 5.99. Found: C, 67.24; H, 4.71; N, 13.05; S, 5.97.

*4.1.7. 2,2′-(((((((Quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(thiazole-4,2-diyl))bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))bis(4,1-phenylene))bis-(oxy))bis(N-(4-chlorophenyl)acetamide) (**8b**).* Brown powder, (78% yield); mp 253−255 °C; IR (KBr): 3275 (NH), 1673 (C═O), 1551 (C═N) cm^{-1}; ^1H NMR: δ 2.31 (s, 6H, CH_3), 4.76 (s, 4H, OCH_2C═O), 7.05 (d, 4H, J = 9 Hz, ArH), 7.36 (s, 2H, thiazol-5-H), 7.38 (d, 4H, J = 9 Hz, ArH), 7.45 (d, 4H, J = 8.7 Hz, ArH), 7.55−7.70 (m, 8H, ArH), 7.76 (d, 4H, J = 8.7 Hz, ArH), 8.01 (d, 4H, J = 8.7 Hz, ArH), 10.24 (s, 2H, NH), 11.14 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ

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14.1, 67.1, 103.9, 114.6, 121.3, 122.0, 126.6, 127.0, 127.2, 127.4, 127.9, 128.7, 131.2, 132.4, 137.0, 137.4, 146.4, 149.3, 149.9, 151.9, 158.4, 166.6, 170.1; MS: m/z (%) 1110 (M^+). Anal. Calcd. for $C_{58}H_{44}Cl_2N_{10}O_6S_2$: C, 62.64; H, 3.99; N, 12.60; S, 5.77. Found: C, 62.62; H, 3.99; N, 12.61; S, 5.75.

*4.1.8. Diethyl 3,4-Bis((4-(2-(2-(1-(4-(2-oxo-2-(p-tolylamino)ethoxy)phenyl)ethylidene)hydrazineyl)thiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**12a**).* Brown powder, (71% yield); mp 240−242 °C; IR (KBr): 3275 (NH), 1712 (C═O), 1671 (C═O), 1553 (C═N) cm^{-1}; ^1H NMR: δ 1.28 (t, 6H, J = 6.9, CH_3), 2.25 (s, 6H, CH_3), 2.29 (s, 6H, CH_3), 4.34 (q, 4H, J = 6.9, CH_2), 4.71(s, 4H, OCH_2C═O), 5.66 (s, 4H, OCH_2), 6.90 (d, 4H, J = 8.4 Hz, ArH), 7.02 (d, 4H, J = 8.1 Hz, ArH), 7.10−7.53 (m, 10H, ArH and thiazol-5-H), 7.66 (d, 4H, J = 8.4 Hz, ArH), 7.71 (d, 4H, J = 8.4 Hz, ArH), 9.98 (s, 2H, NH), 11.00 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 19.7, 28.2, 61.3, 67.2, 104.2, 113.2, 114.6, 116.3, 126.3, 126.5, 126.8, 128.2, 128.6, 129.9, 130.2, 134.3, 135.9, 146.9, 152.6, 156.8, 157.6, 160.4, 167.3, 169.7, 173.5; MS: m/z (%) 1252 (M^+). Anal. Calcd. for $C_{66}H_{60}N_8O_{10}S_4$: C, 63.24; H, 4.82; N, 8.94; S, 10.23. Found: C, 63.22; H, 4.81; N, 8.95; S, 10.21.

*4.1.9. Diethyl 3,4-Bis((4-(2-(2-(1-(4-(2-((4-chlorophenyl)-amino)-2-oxoethoxy)phenyl)ethylidene)hydrazineyl)thiazol-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**12b**).* Brown powder, (71% yield); mp 234−236 °C; IR (KBr): 3275 (NH), 1710 (C═O), 1675 (C═O), 1553 (C═N) cm^{-1}; ^1H NMR: δ 1.28 (t, 6H, J = 6.9, CH_3), 2.29 (s, 6H, CH_3), 4.34 (q, 4H, J = 6.9, CH_2), 4.74(s, 4H, OCH_2C═O), 5.66 (s, 4H, OCH_2), 6.90 (d, 4H, J = 8.4 Hz, ArH), 6.95−7.09 (m, 6H, ArH and thiazol-5-H), 7.37 (d, 4H, J = 8.4 Hz, ArH), 7.65−7.70 (m, 8H, ArH), 7.74 (d, 4H, J = 9 Hz, ArH), 10.22 (s, 2H, NH), 11.01 (brs, 2H, NH); MS: m/z (%) 1292 (M^+). Anal. Calcd. for $C_{64}H_{54}Cl_2N_8O_{10}S_4$: C, 59.39; H, 4.21; N, 8.66; S, 9.91. Found: C, 59.37; H, 4.23; N, 8.64; S, 9.88.

*4.1.10. Synthesis of Isomeric Bis(thiazoles) Linked to Heteroaromatic Cores **10a,b**, and **14a,b**.* To a solution of the appropriate bis(thiosemicarbazone derivatives) **9** or **13** (1 mmol) was added the α-bromoketone **6a,b** (2 mmol) in ethanol (25 mL) containing TEA (0.2 mL). The reaction mixture was heated at reflux for 4 h. The obtained solid products upon cooling were filtered off and then recrystallized from ethanol/DMF to afford compounds **10a,b**, and **14a,b**.

*4.1.11. 2,2′-(((((((Quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-2,4-diyl))bis(4,1-phenylene))bis(oxy))-bis(N-(p-tolyl)acetamide) (**10a**).* Brown powder, (77% yield); mp 270−271 °C; IR (KBr): 3315 (NH), 1693 (C═O), 1551 (C═N) cm^{-1}; ^1H NMR: δ 2.26 (s, 6H, CH_3), 2.80 (s, 6H, CH_3), 4.71 (s, 4H, OCH_2C═O), 7.04 (d, 4H, J = 9 Hz, ArH), 7.12 (d, 4H, J = 7.8 Hz, ArH), 7.18 (s, 2H, thiazol-5-H), 7.47−7.82 (m, 20H, ArH), 9.97 (s, 2H, NH), 12.18 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0, 20.5, 67.2, 101.8, 114.8, 119.8, 121.5, 122.9, 126.8, 129.2, 130.5, 132.7, 135.2, 135.8, 135.9, 141.1, 142.1, 150.6, 155.6, 157.3, 161.3, 166.3, 168.0; MS: m/z (%) 1070 (M^+). Anal. Calcd. for $C_{60}H_{50}N_{10}O_6S_2$: C, 67.27; H, 4.70; N, 13.08; S, 5.99. Found: C, 67.25; H, 4.71; N, 13.06; S, 5.95.

*4.1.12. 2,2′-(((((((Quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazin-1-yl-2-ylidene))bis(thiazole-2,4-diyl))bis(4,1-phenylene))bis(oxy))-bis(N-(4-chlorophenyl)acetamide) (**10b**).* Brown powder, (79% yield); mp 273−275 °C; IR (KBr): 3280 (NH), 1683 (C═O), 1546 (C═N) cm^{-1}; ^1H NMR: δ 2.95 (s, 6H, CH_3), 4.74 (s, 4H, OCH_2C═O), 7.04 (d, 4H, J = 9 Hz, ArH), 7.18 (s, 2H, thiazol-5-H), 7.37−7.71 (m, 20H, ArH), 7.95 (d, 4H, J = 8.7 Hz, ArH), 10.21 (s, 2H, NH), 12.19 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.5, 66.3, 105.6, 114.8, 119.8, 126.8, 127.0, 127.8, 128.3, 129.1, 129.4, 129.9, 132.7, 135.8, 141.2, 146.1, 150.2, 153.1, 157.3, 159.6, 166.3, 168.3, 172.3; MS: m/z (%) 1110 (M^+). Anal. Calcd. for $C_{58}H_{44}Cl_2N_{10}O_6S_2$: C, 62.64; H, 3.99; N, 12.60; S, 5.77. Found: C, 62.61; H, 3.97; N, 12.61; S, 5.75.

*4.1.13. Diethyl 3,4-Bis((4-(1-(2-(4-(4-(2-oxo-2-(p-tolylamino)ethoxy)phenyl)thiazol-2-yl)hydrazineylidene)-ethyl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**14a**).* Brown powder, (69% yield); mp 269−271 °C; IR (KBr): 3297 (NH), 1705 (C═O), 1681 (C═O), 1551 (C═N) cm^{-1}; ^1H NMR: δ 1.27 (t, 6H, J = 6.9, CH_3), 2.25 (s, 6H, CH_3), 2.80 (s, 6H, CH_3), 4.33 (q, 4H, J = 6.9, CH_2), 4.70 (s, 4H, OCH_2C═O), 5.63 (s, 4H, OCH_2), 6.91 (d, 4H, J = 8.7 Hz, ArH), 7.99−7.13 (m, 10H, ArH and thiazol-5-H), 7.46 (d, 4H, J = 8.1 Hz, ArH), 7.52 (d, 4H, J = 8.1 Hz, ArH), 7.74 (d, 4H, J = 8.7 Hz, ArH), 9.97 (s, 2H, NH), 11.92 (brs, 2H, NH); MS: m/z (%) 1252 (M^+). Anal. Calcd. for $C_{66}H_{60}N_8O_{10}S_4$: C, 63.24; H, 4.82; N, 8.94; S, 10.23. Found: C, 63.21; H, 4.80; N, 8.95; S, 10.22.

*4.1.14. Diethyl 3,4-Bis((4-(1-(2-(4-(4-(2-((4-chlorophenyl)-amino)-2-oxoethoxy)phenyl)thiazol-2-yl)hydrazineylidene)-ethyl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**14b**).* Brown powder, (73% yield); mp 261−263 °C; IR (KBr): 3295 (NH), 1711 (C═O), 1671 (C═O), 1550 (C═N) cm^{-1}; ^1H NMR: δ 1.28 (t, 6H, J = 6.9, CH_3), 2.95 (s, 6H, CH_3), 4.34 (q, 4H, J = 6.9, CH_2), 4.73 (s, 4H, OCH_2C═O), 5.64 (s, 4H, OCH_2), 6.91 (d, 4H, J = 8.7 Hz, ArH), 7.00 (m, 4H, J = 8.7 Hz, ArH), 7.03 (s, 2H, thiazol-5-H), 7.37 (d, 4H, J = 8.7 Hz, ArH), 7.46 (d, 4H, J = 8.7 Hz, ArH), 7.68 (d, 4H, J = 8.7 Hz, ArH), 7.73 (d, 4H, J = 8.7 Hz, ArH), 10.20 (s, 2H, NH), 11.90 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0, 18.1, 61.7, 65.1, 109.1, 112.7, 120.5, 120.6, 120.7, 122.2, 122.3, 122.4, 123.5, 125.0, 126.4, 130.8, 134.4, 138.1, 144.6, 149.1, 153.5, 156.5, 150.2, 162.5, 168.1, 173.2; MS: m/z (%) 1292 (M^+). Anal. Calcd. for $C_{64}H_{54}Cl_2N_8O_{10}S_4$: C, 59.39; H, 4.21; N, 8.66; S, 9.91. Found: C, 59.36; H, 4.23; N, 8.64; S, 9.89.

4.2. Antibacterial Assay. The antibacterial activity of the synthesized compounds was tested by using the agar well diffusion technique. *B. subtilis* (DSM 1088) and *S. aureus* (ATCC 6538) were used as Gram-positive bacteria, whereas *P. aeruginosa* (ATCC 10145) and *E. coli* (ATCC 8739) were used as Gram-negative bacteria. Dimethyl sulfoxide (DMSO) was used as a carrier to create a solution for each synthesized compound (20 mg/mL). Bacterial centrifuged pellets from overnight culture with about 1×10^6 colony forming unit CFU per mL were cultivated on nutritional agar plates (yeast extract 0.5%, peptone 1%, NaCl 0.5%, agar 1.5%, distilled water 1 L, pH 7.2). Before use, the nutritional agar was autoclaved for at least 20 min at 121 °C. The nutrient agar plates were then allowed to cool to 45 °C. Following that, sterile metallic bores were used to create 6 mm wells in nutritional media. The activity was then evaluated by measuring the diameter of the inhibitory zone in millimeters. 20 L of the investigated chemicals (20 mg/mL) was poured into the plates' prepared wells. As a negative control, a DMSO vehicle was added. As a positive control for *S. aureus* and *E. coli*, standard tobramycin[80] (10 μg) was employed. For gram-positive and gram-negative

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bacteria, conventional clindamycin (2 g/disk) and ofloxacin[81] (2 g/disk) were employed as positive controls, respectively. The plates were incubated at 37 °C for 24 h before the inhibitory zone diameter was measured in millimeters using a caliper.

4.3. Microdilution Assay. The microdilution technique was used to determine the MIC for compound **12b** against *B. subtilis* (DSM 1088) established by CLSI.[87] Briefly, (5 mg/mL) stock solution of compound **12b** in DMSO was diluted in nutrient broth media to different concentrations (20, 10, 5, 2.5, 1.25, 0.625, and 0.3125 mg/mL). The DMSO final concentration was ≤2.5%, which does not affect the bacterial growth. The bacterial strain was transferred to fresh nutrient broth agar 1 day before the test. An overnight inoculum was prepared 12−16 h before the test and incubated overnight on a reciprocal shaker at 37 °C. 180 μL portion of the prepared bacterial suspension was then added to 20 μL of the tested compound which was present in every well of the micro-titration plate. An eight-channel pipet was used to perform this procedure. The first well of the plate was taken as blank and contained 200 μL of liquid broth medium with 1% DMSO. The OD was read at a wavelength of 600 nm. Finally, the minimum concentration at which 100% of bacterial growth was inhibited (MIC) was determined.

4.4. Molecular Docking. The Molecular Operating Environment (MOE) version 2009.10 was used for the molecular docking simulation research. The program builder interface was used to draw the structures of the target compounds **8a, 8b, 12a**, and **12b**. Then, using the integrated MOPAC, they were subjected to local energy reduction. The compounds were then subjected to global energy reduction by systematic conformational search, with RMS distance and RMS gradient set to 0.1 Å and 0.01 kcal/mol, respectively. The protein database was used to derive the X-ray crystallographic structures of the bacterial dihydrofolate reductase and tyrosyl-tRNA synthetase proteins complexed with their cocrystallized ligands (PDB ID: 3FRA and 1JIJ, respectively). 5-[(2S)-2-Cyclopropyl-7,8-dimethoxy-2H-chromen-5-yl]-methylpyrimidine-2,4-diamine and 2-amino-3-(4-hydroxy-phenyl)-propionylamino-(1,3,4,5-tetrahydroxy-4-hydroxymethyl-piperidine-2-yl)-acetic acid were the cocrystallized ligands. The proteins were modified in the following ways: first, the proteins with their standard ligands were protonated. Following that, the target proteins' undesirable water chains and cocrystallized ligands were eliminated. The MOE α site finder was then used to locate the active site of the chosen proteins, and fake atoms were created from the α spheres. Finally, the changed proteins were docked with the target molecules following self-docking with their cocrystallized ligands. Using BIOVIA Discovery Studio software V6.1.0.15350, the protein−ligand interactions were identified in the active domain and visualized in 2 and 3 dimensions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c07125.

^{1}H NMR spectrum of compound **5a**; ^{13}C NMR spectrum of compound **5a**; IR spectrum of compound **5a**; mass spectrum of compound **5a**; ^{1}H NMR spectrum of compound **5b**; ^{13}C NMR spectrum of compound **5b**; IR spectrum of compound **5b**; mass spectrum of compound **5b**; ^{1}H NMR spectrum of compound **8a**; ^{13}C NMR spectrum of compound **8a**; IR spectrum of compound **8a**; mass spectrum of compound **8a**; ^{1}H NMR spectrum of compound **8b**; ^{13}C NMR spectrum of compound **8b**; IR spectrum of compound **8b**; mass spectrum of compound **8b**; ^{1}H NMR spectrum of compound **10a**; ^{13}C NMR spectrum of compound **10a**; IR spectrum of compound **10a**; mass spectrum of compound **10a**; ^{1}H NMR spectrum of compound **10b**; ^{13}C NMR spectrum of compound **10b**; IR spectrum of compound **10b**; mass spectrum of compound **10b**; ^{1}H NMR spectrum of compound **12a**; ^{13}C NMR spectrum of compound **12a**; IR spectrum of compound **12a**; mass spectrum of compound **12a**; ^{1}H NMR spectrum of compound **12b**; IR spectrum of compound **12b**; mass spectrum of compound **12b**; ^{1}H NMR spectrum of compound **14a**; IR spectrum of compound **14a**; mass spectrum of compound **14a**; ^{1}H NMR spectrum of compound **14b**; ^{13}C NMR spectrum of compound **14b**; IR spectrum of compound **14b**; and mass spectrum of compound **14b** (PDF)

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Notes

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