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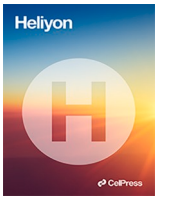

Research article

Novel hybrid thiazoles, bis-thiazoles linked to azo-sulfamethoxazole: Synthesis, docking, and antimicrobial activity

Mostafa E. Salem [a,b], Ismail A. Abdelhamid [b,**], Ahmed H.M. Elwahy [b,*], Mohamed A. Ragheb [c], Arwa sultan Alqahtani [a], Magdi E.A. Zaki [a], Faisal K. Algethami [a], Huda Kamel Mahmoud [b]

[a] Department of Chemistry, College of Science, Imam Mohammad Ibn Saud Islamic University(IMSIU), P.O. Box, 90950, Riyadh, 11623, Saudi Arabia
[b] Department of Chemistry, Faculty of Science, Cairo University, Giza, 12613, Egypt
[c] Department of Chemistry (Biochemistry Division), Faculty of Science, Cairo University, Giza, 12613, Egypt

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ABSTRACT

The reaction of sulfamethoxazolehydrazonoyl chloride with thiosemicarbazones, bis-thiosemicarbazones, or 4-amino-3-mercapto-1,2,4-triazole in dioxane in the presence of triethylamine as a basic catalyst at reflux resulted in the regioselective synthesis of thiazoles and bis-thiazoles linked to azo-sulfamethoxazole as novel hybrid molecules. The structures of the new compounds were confirmed using a range of spectra. Each compound's antibacterial properties were evaluated using the agar well-diffusion technique, and most of them demonstrated significant potency. In silico investigations revealed that the described compounds had strong interactions with the binding sites of MurE ligase, tyrosyl-tRNA synthetase, and dihydropteroate synthase, demonstrating inhibitory activity.

1. Introduction

Infections due to bacteria are growing more frequent over the world, and they have the potential to have a significant impact on health and become the primary cause of disease [1–3]. Public health is severely threatened globally by the emergence of new microbial strains that are resistant to contemporary antibiotics [4,5]. One of the biggest shortcomings in the management of bacterial infections is that the antimicrobial treatments currently being developed are inadequate to address the growing threat of antibiotic resistance, according to the annual pipeline report by the World Health Organization. Several approaches have been proposed to address this issue, including the development and introduction of novel medications capable of eliminating multidrug resistance. Furthermore, decreasing the propagation of resistant infections and reducing the speed of resistance growth are key aims in this respect [6].

Various heterocyclic rings have piqued the interest of researchers as antimicrobial agents with novel modes of action in recent decades [7,8]. Sulfamethoxazole was one of the most used antimicrobial compounds, with good activity against a wide range of

* Corresponding author.
** Corresponding author.
E-mail addresses: ismail_shafy@yahoo.com, ismail_shafy@cu.edu.eg (I.A. Abdelhamid), aelwahy@hotmail.com, aelwhy@cu.edu.eg (A.H.M. Elwahy).

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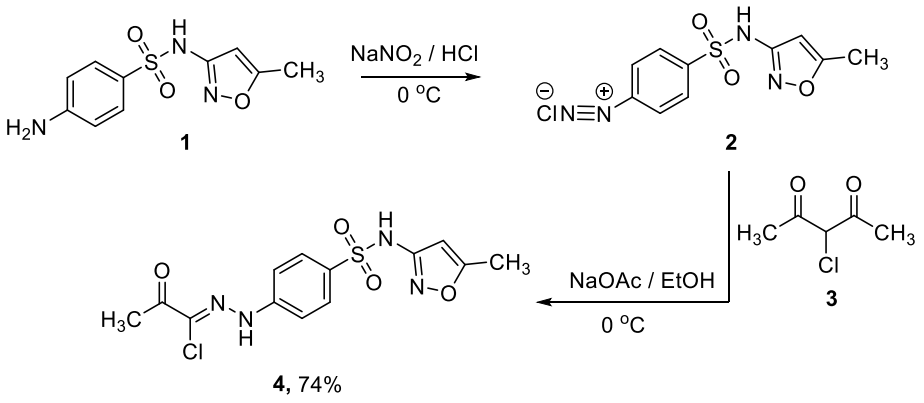
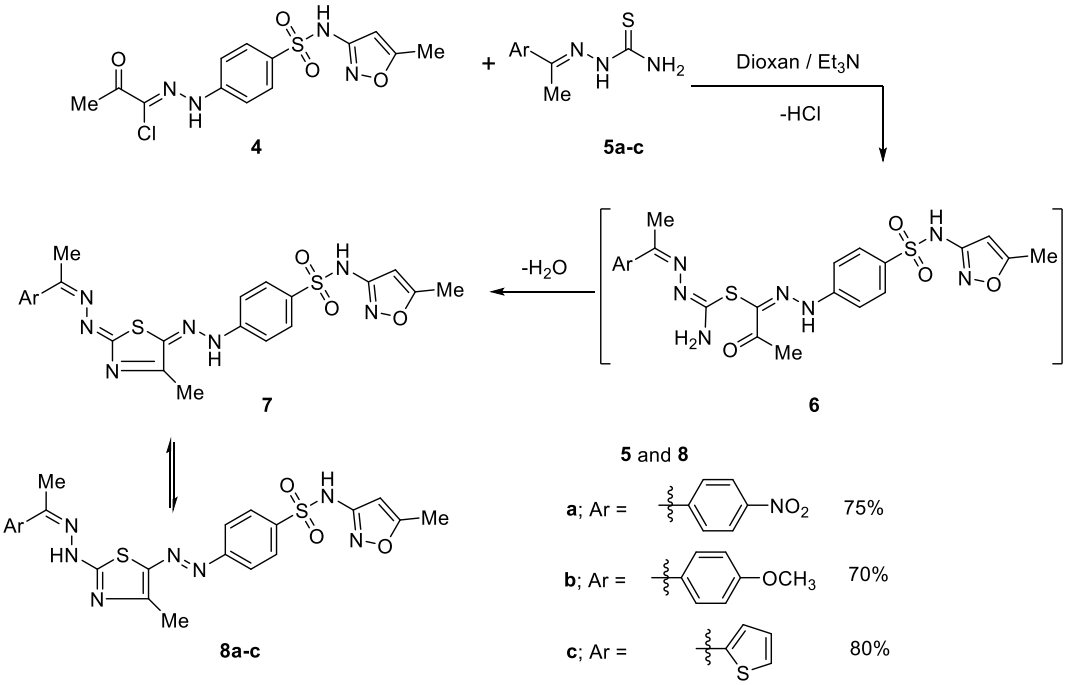
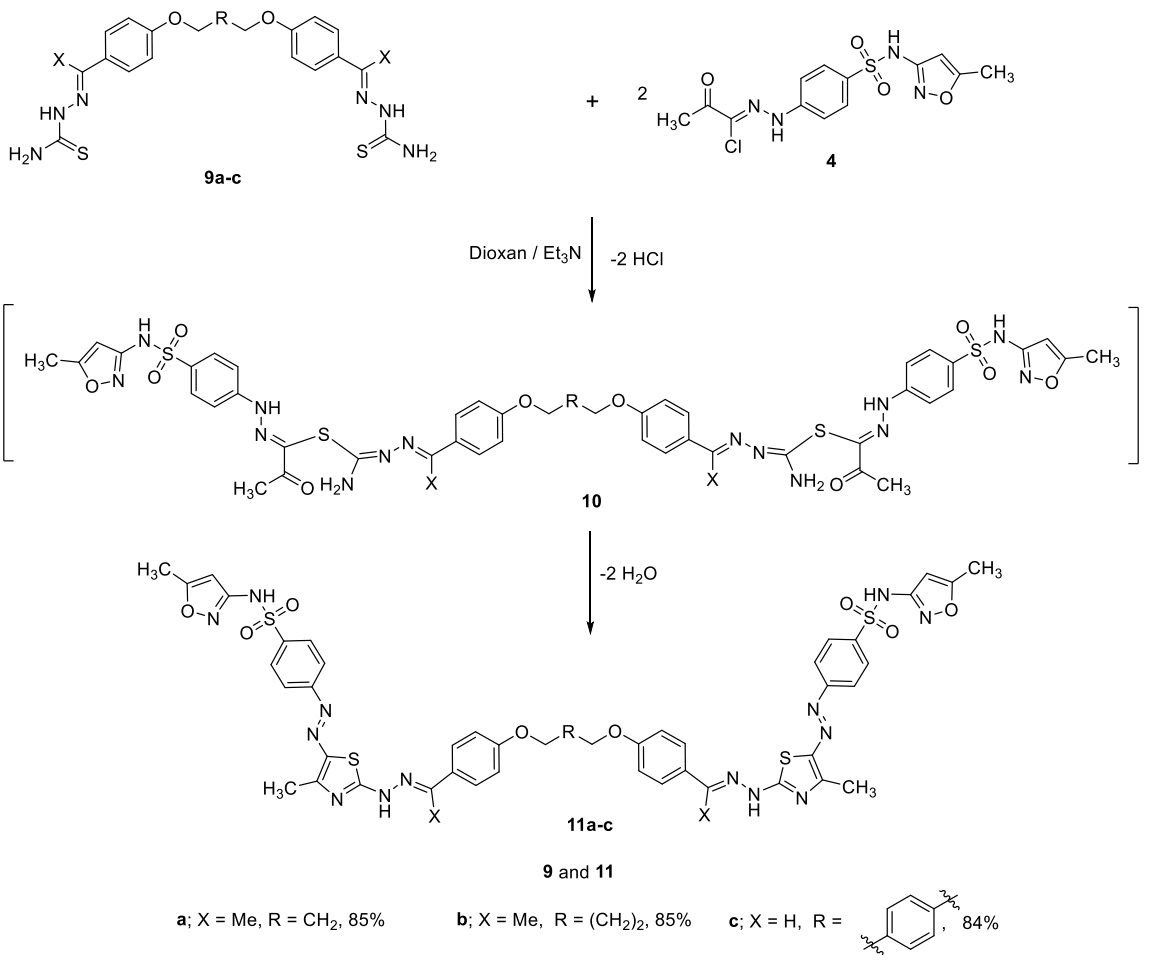


Scheme 1. Synthesis of *N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-2-oxopropanehydrazonoyl chloride **4**.

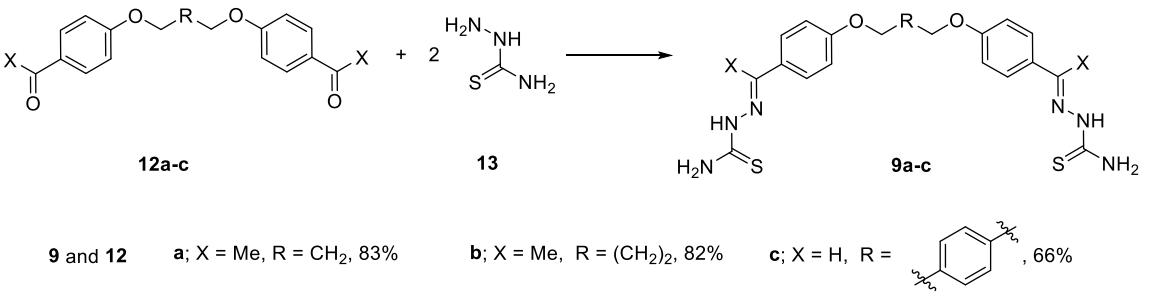


Scheme 2. Synthesis of (hydrazineyl)thiazol-5-yl)diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide **8a-c**.

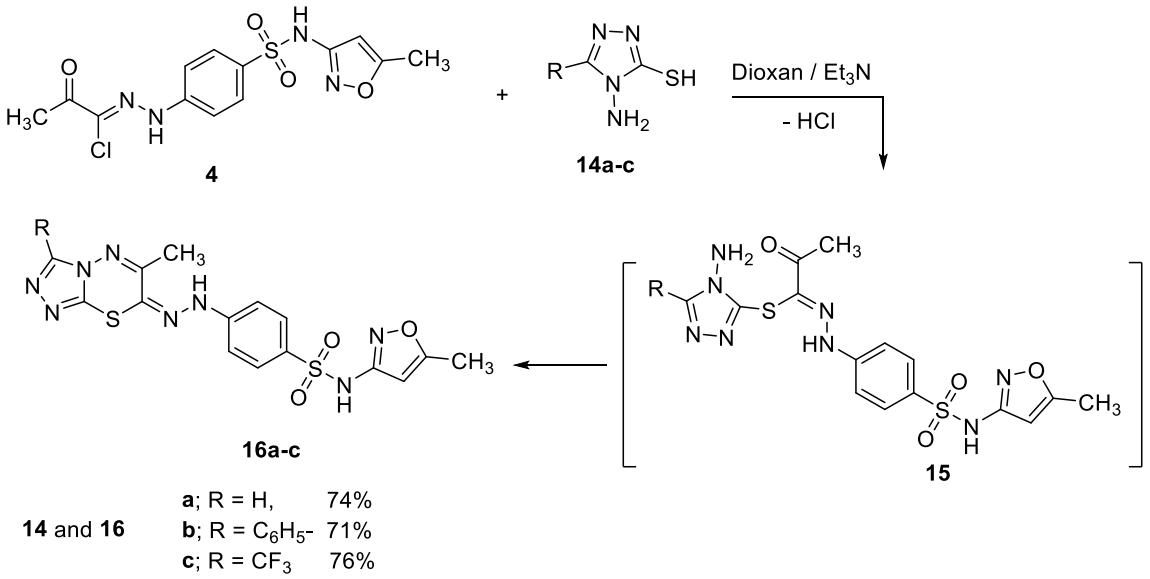
bacteria. It has been reported that it inhibits folic acid production in bacteria, which is necessary for nucleic acid production [9–11]. Nonetheless, the emergence of widespread resistance has severely compromised their once-critical role in managing bacterial infections [12]. Furthermore, thiazoles and their derivatives have been identified as important scaffolds in medicinal chemistry among the most diverse heterocyclic compounds. They showed significant antibacterial activity against a wide range of bacteria and pathogens, as well as a variety of biological activities [13–25]. Many powerful drugs contain a thiazole ring, including sulfathiazole (an antimicrobial) and abafungin (an antifungal drug). Moreover, compounds containing 1,2,4-triazole [26–35] and/or 1,3,4-thiadiazines [32,36,37] are well-known for their broad biological activities and have attracted attention primarily as potent antibacterial agents. In addition, over the past few decades, the idea of molecular hybridization has generated a great deal of attention in the realm of drug creation. A new and effective synthetic technique for combining two or more different entities into a single molecule with unique biological features is the hybrid approach. The resulting scaffolds may be capable of overcoming drug resistance while also increasing activity and binding affinity [38–41]. Based on the aforementioned hypotheses and our continued endeavor towards the synthesis of heterocycles [42–72] we report herein the synthesis of some thiazoles, bis(thiazoles), and [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazines linked to hydrazinyl-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide moiety as novel hybrid molecules and evaluation their bioactivities against different bacterial strains and fungal strains; in an attempt to conquer sulfonamide resistance and find novel



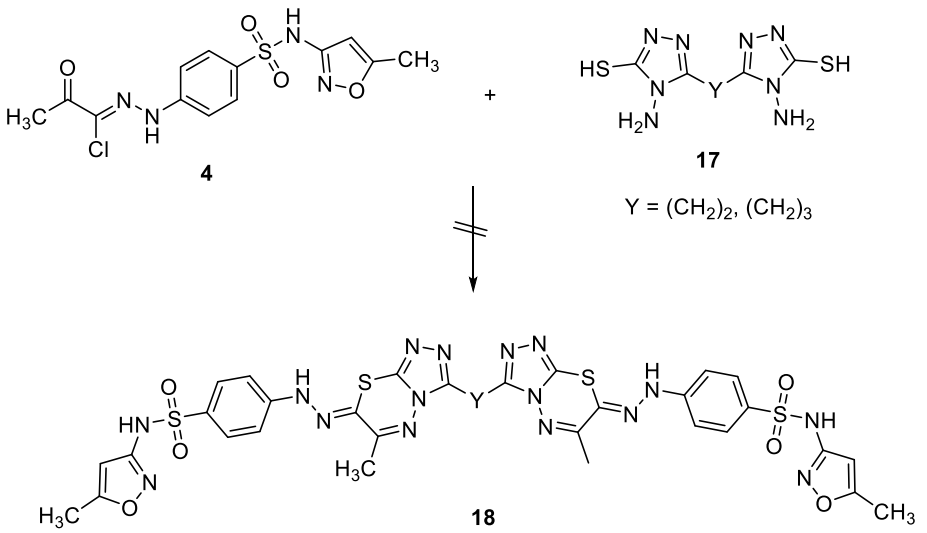
Scheme 3. Synthesis of bis-(hydrazineyl)thiazol-5-yl)diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamides **11**.



Scheme 4. Synthesis of bis-thiosemicarbazones **9a-c**.



Scheme 5. Synthesis of [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazin-7-ylidene)hydrazineyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide **16a-c**.



Scheme 6. Attempted synthesis of bis-thiadiazoles **18**.

therapeutic options. Furthermore, the potential binding interactions of the novel compounds with the active sites of different target enzymes were investigated using molecular docking simulations.

2. Results and discussion

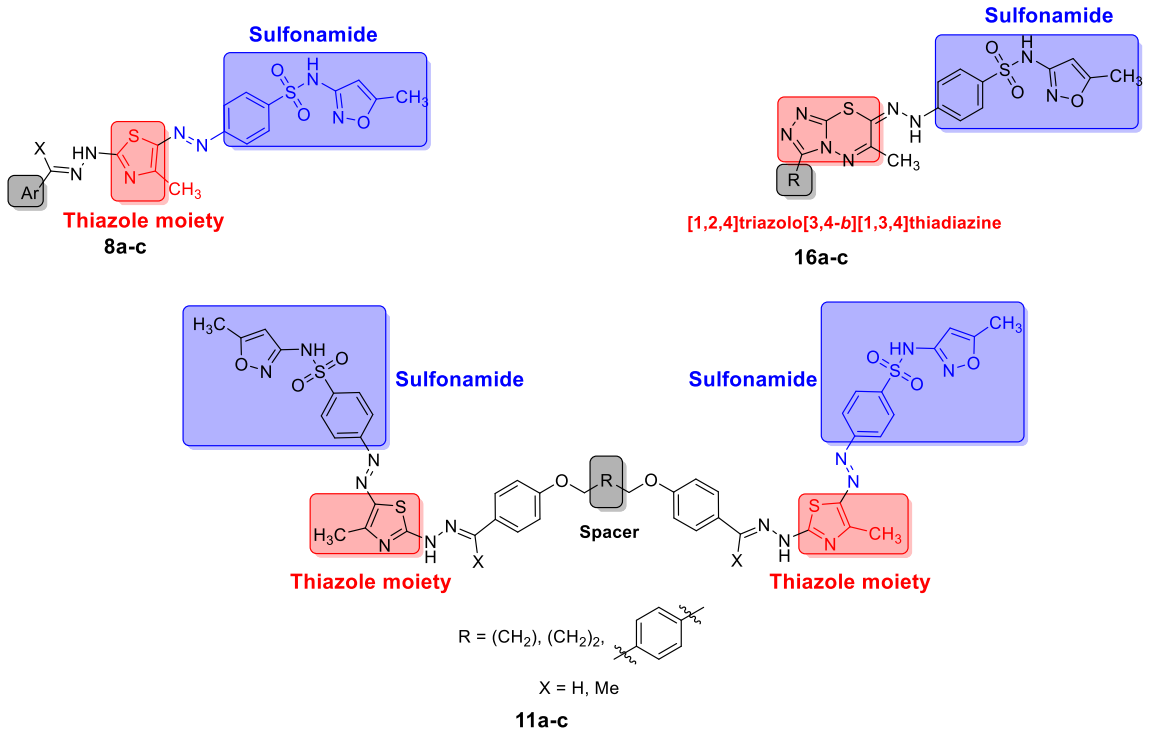
The *N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-2-oxopropanehydrazonoyl chloride **4** was chosen as an interesting synthon for a variety of valuable bioactive heterocyclic compounds.

In the first step, sulfamethoxazole diazonium chloride **2** is prepared from the corresponding sulfamethoxazole **1** and the appropriate quantities of both HCl and sodium nitrite. In the second step, the coupling reaction of **2** with 3-chloropentane-2,4-dione **3** in a basic KOH solution afforded the corresponding sulfamethoxazolehydrazonoyl chloride **4** (see Scheme 1). The constitution of compound **4** was confirmed based on the spectral analysis. Thus, the ^{1}H NMR spectrum revealed three characteristic singlets at 2.29, 2.51, and 6.12 ppm for the two methyl groups and isoxazole-H, respectively. It also indicated the presence of characteristic two broad exchangeable signals at 11.01 and 11.28 for the two NH groups. The aromatic multiplet appeared at its expected position at 7.8–7.83

Table 1
Antibacterial and antifungal activities of the newly synthesized compounds.

Tested microorganisms	*Sample No.*									
	8a	8b	8c	11a	11b	11c	16a	16b	16c	Control
Fungi										*Ketoconazole*
Aspergillus fumigatus	NA	NA	NA	NA	NA	NA	NA	NA	NA	17
Candida albicans	NA	NA	NA	NA	NA	NA	NA	NA	NA	20
Gram-positive Bacteria										*Gentamycin*
Staphylococcus aureus	14	16	15	10	9	NA	13	NA	15	24
Bacillus subtilis	12	17	16	NA	NA	NA	NA	8	10	26
Gram-negative Bacteria										*Gentamycin*
Escherichia coli	10	15	14	11	10	NA	10	NA	12	30
Proteus vulgaris	13	17	15	14	8	NA	15	NA	13	25
Pseudomonas aeruginosa	12	13	13	10	11	NA	11	10	11	32

"Mean zone of inhibition in mm beyond well diameter (6 mm) produced on a range of microorganisms".
"The test was done using the diffusion agar technique, well diameter: 6.0 mm (100 μL was tested).
Positive control for fungi (Ketoconazole, 100 μg/mL) and Positive control for bacteria (Gentamycin, 4 μg/mL)".
NA: No activity. The sample was tested at 10 mg/ml concentration.



Scheme 7. Design strategy of compounds **8**, **11**, and **16**.

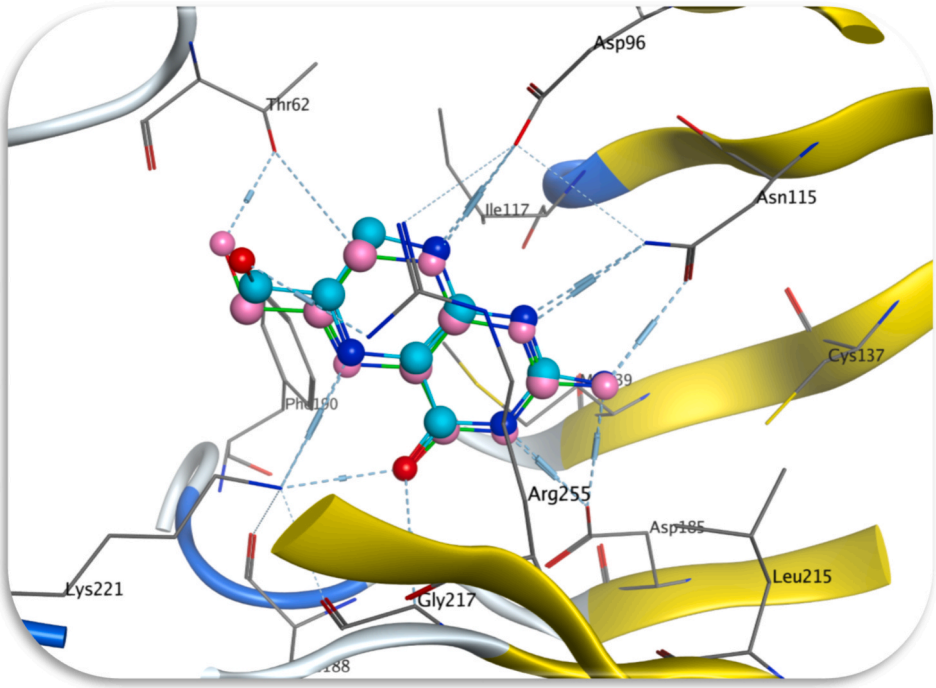


Fig. 1. Superimposition of the re-docked (carbon atoms with cyan color) and the co-crystallized ligand (carbon atoms with green color) within the active site of its protein receptor (dihydropteroate synthase, PDB ID: 1AJ0). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

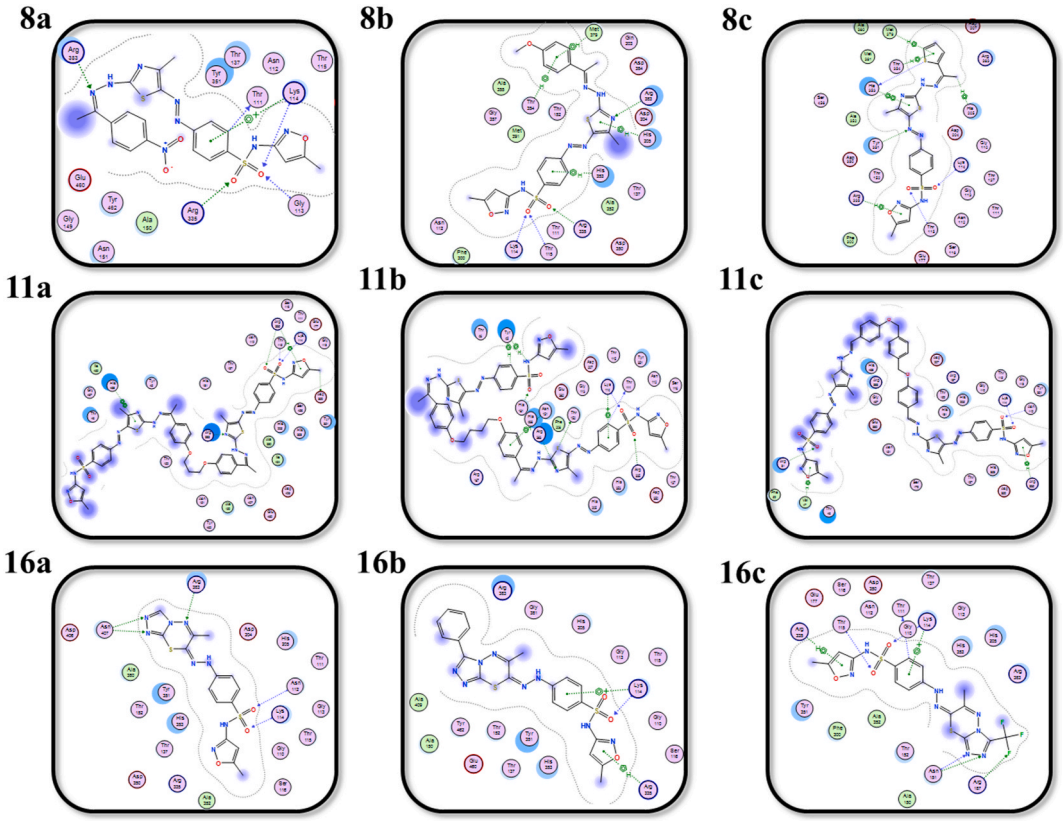


Fig. 2. 2D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives (**8a-c**, **11a-c,** and **16a-c)** against MurE ligase (PDB ID: 4C13) active site residues.

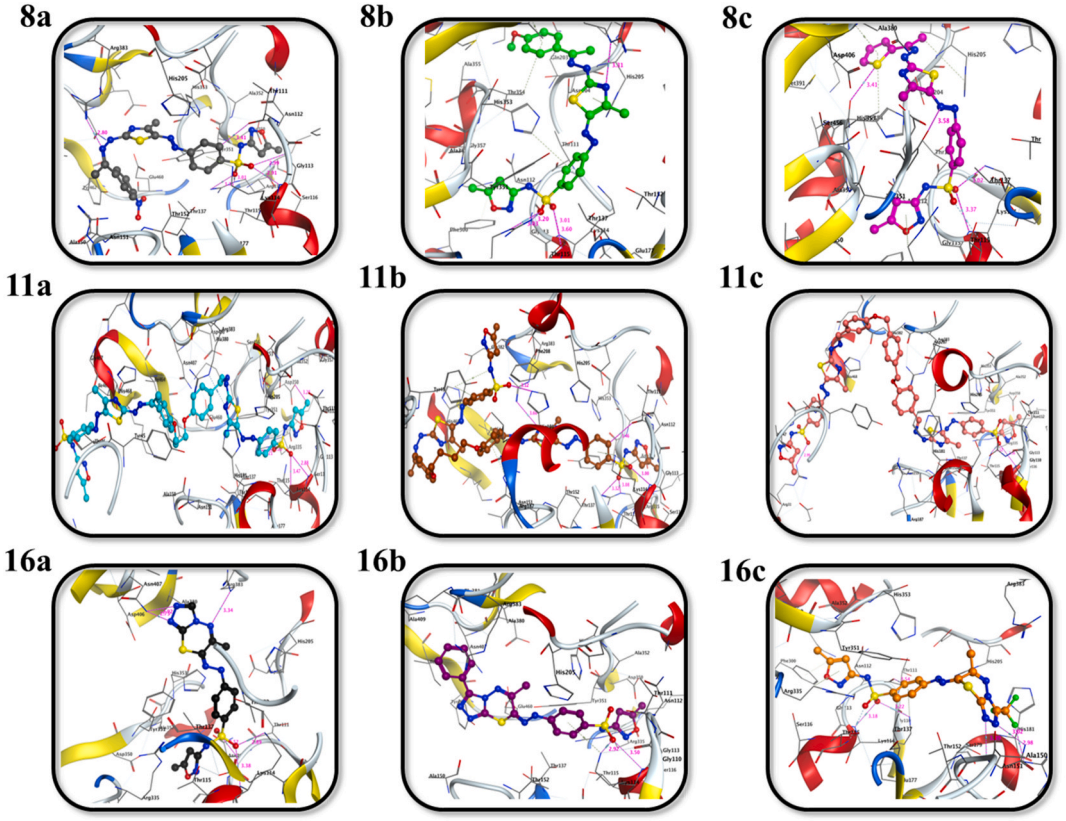


Fig. 3. 3D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives **(8a-c**, **11a-c,** and **16a-c)** against MurE ligase (PDB ID: 4C13) active site residues.

ppm.

The reactivity of the novel sulfamethoxazolehydrazonoyl chloride towards thiosemicarbazone was then investigated. High yields were obtained when the reaction was conducted at reflux in dioxane with triethylamine acting as a basic catalyst. The reaction was carried out in several solvents, including EtOH, CH_3CN, H_2O, dioxane, and DMF. While H_2O may be used as a green solvent to carry out the reaction, other substrates' intrinsic insolubility has limited their use. The reactions continue in the absence of a solvent, but regretfully with extremely low yields. The use of chitosan in our reactions makes the isolation and purification of some derivatives time-consuming, even though it is an inexpensive, non-toxic base, eco-friendly, and highly reactive catalyst for building organic frameworks. Even after a considerable period, no residues of the products were found at room temperature, despite the reactions producing excellent yields of the products at the solvent's refluxing temperature. The findings demonstrated that, in terms of reaction yields, MW heating did not significantly outperform conventional heating.

Thus, the reaction of sulfamethoxazolehydrazonoyl chloride **4** with 1-(aryl)ethanone thiosemicarbazone **5a**, **5b,** and 1-(2-thienyl) ethanone thiosemicarbazone **5c** in dioxane at reflux in the presence of few drops of TEA afforded (hydrazineyl)thiazol-5-yl)diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide **8a-c** in 70–80 % yields. The reaction occurs *via* an initial S-alkylation reaction of **5** with **4** to yield **6**. Removal of water affords intermediate **7** that could tautomerize into the final isolable product **8** (Scheme 2).

Based on spectral data, the structures of compounds **8a-c** were supported. Thus, the ^{1}H NMR spectrum of **8a** indicated four characteristic singlets at 2.29, 2.56, 2.61, and 6.11 ppm for the three methyl groups and isoxazole-4-H, respectively. It also indicated the presence of a characteristic broad exchangeable signal at 11.19 for the NH group. The aromatic multiplet appeared at their expected position at 7.45–8.34 ppm.

Stimulated by these results and in a trial to expand the scope of this reaction, we also investigated the cyclo-condensation reactions of bis-thiosemicarbazones with the sulfamethoxazolehydrazonoyl chloride (Scheme 3). Thus, a series of bis-(hydrazineyl)thiazol-5-yl) diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamides that are linked to propane **11a**, butane **11b**, or benzene **11c** core *via*

Table 2
Molecular docking reports of the synthesized sulfonamide derivatives (**8a-c**, **11a-c,** and **16a-c)** with bacterial protein MurE ligase (PDB ID: 4C13).

Protein (PDB ID)	Compd. No.	Docking score (kcal/mol)	Ligand	Receptor	Type of interaction	Distance	E (kcal/mol)
4C13	**8a**	−9.46	C 2	O THR 111	H-donor	3.41	−0.7
			O 12	N GLY 113	H-acceptor	2.99	−0.5
			O 12	N LYS 114	H-acceptor	2.91	−1.0
			O 13	NE ARG 335	H-acceptor	3.01	−3.9
			O 13	NH2 ARG 335	H-acceptor	3.35	−0.9
			N 31	NH2 ARG 383	H-acceptor	2.80	−1.6
			6-ring	NZ LYS 114	pi-cation	4.04	−0.9
	8b	−10.15	O 12	N LYS 114	H-acceptor	3.01	−0.7
			O 12	N THR 115	H-acceptor	3.60	−0.5
			O 13	NE ARG 335	H-acceptor	3.03	−3.7
			O 13	NH2 ARG 335	H-acceptor	3.20	−2.0
			N 26	NE ARG 383	H-acceptor	3.31	−1.5
			5-ring	CE1 HIS 205	pi-H	3.93	−0.6
			6-ring	CE1 HIS 353	pi-H	4.18	−0.5
			6-ring	CG2 THR 354	pi-H	4.53	−0.5
			6-ring	CE MET 379	pi-H	3.78	−0.7
	8c	−9.89	S 40	O HIS 353	H-donor	3.41	−1.3
			O 12	N LYS 114	H-acceptor	3.37	−1.0
			O 12	NZ LYS 114	H-acceptor	3.02	−5.3
			O 13	N THR 115	H-acceptor	3.43	−1.0
			N 23	OH TYR 351	H-acceptor	3.58	−0.5
			C 45	5-ring HIS 205	H-pi	4.68	−0.5
			5-ring	CD ARG 335	pi-H	4.36	−0.8
			5-ring	CG2 THR 354	pi-H	4.45	−0.5
			5-ring	CE MET 379	pi-H	3.74	−0.9
			5-ring	5-ring HIS 353	pi-pi	3.98	−0.0
	11a	−12.12	C 96	OD2 ASP 350	H-donor	3.28	−0.5
			O 12	N LYS 114	H-acceptor	2.88	−0.7
			O 12	N THR 115	H-acceptor	3.47	−1.0
			O 13	NE ARG 335	H-acceptor	3.20	−2.5
			O 13	NH2 ARG 335	H-acceptor	3.21	−2.0
			N 26	NE ARG 383	H-acceptor	3.65	−1.5
			5-ring	CD ARG 335	pi-H	4.34	−1.0
			5-ring	5-ring HIS 468	pi-pi	3.94	−0.0
	11b	−11.98	C 2	O THR 111	H-donor	3.46	−0.7
			S 24	OG1 THR 152	H-donor	4.06	−0.7
			O 12	NE ARG 335	H-acceptor	3.08	−3.4
			O 12	NH2 ARG 335	H-acceptor	3.32	−1.3
			O 13	N LYS 114	H-acceptor	3.00	−0.9
			N 26	NH2 ARG 383	H-acceptor	3.60	−1.5
			O 89	NE2 HIS 181	H-acceptor	3.12	−0.8
			C 81	6-ring TYR 45	H-pi	4.04	−1.0
			N 91	6-ring TYR 45	H-pi	4.37	−1.1
			6-ring	NZ LYS 114	pi-cation	4.02	−0.9
			6-ring	ND2 ASN 151	pi-H	3.73	−0.5
	11c	−11.53	O 13	NH1 ARG 31	H-acceptor	2.99	−4.5
			O 95	N LYS 114	H-acceptor	3.36	−0.9
			O 95	NZ LYS 114	H-acceptor	3.12	−3.8
			O 96	CA ASN 112	H-acceptor	3.45	−0.7
			5-ring	CG2 VAL 47	pi-H	4.08	−0.5
			5-ring	CD ARG 335	pi-H	3.78	−1.1
	16a	−8.28	O 12	CA ASN 112	H-acceptor	3.52	−0.6
			O 13	N LYS 114	H-acceptor	3.38	−1.1
			O 13	NZ LYS 114	H-acceptor	2.89	−6.9
			N 28	NE ARG 383	H-acceptor	3.34	−1.3
			N 31	ND2 ASN 407	H-acceptor	2.92	−0.5
			N 32	ND2 ASN 407	H-acceptor	2.75	−0.7
	16b	−8.07	O 13	N LYS 114	H-acceptor	3.50	−0.5
			O 13	NZ LYS 114	H-acceptor	2.92	−5.4
			6-ring	NZ LYS 114	pi-cation	4.23	−0.6
			5-ring	CD ARG 335	pi-H	3.88	−0.7
	16c	−8.31	C 2	O THR 111	H-donor	3.54	−0.6
			O 12	N LYS 114	H-acceptor	3.18	−2.1
			O 12	NZ LYS 114	H-acceptor	3.22	−4.0
			O 13	N THR 115	H-acceptor	3.25	−2.0
			N 31	ND2 ASN 151	H-acceptor	3.02	−0.6
			N 32	CA ASN 151	H-acceptor	3.39	−0.9
			F 35	NH1 ARG 187	H-acceptor	2.98	−0.7
			6-ring	NZ LYS 114	pi-cation	4.05	−0.5
			5-ring	CD ARG 335	pi-H	4.37	−0.9

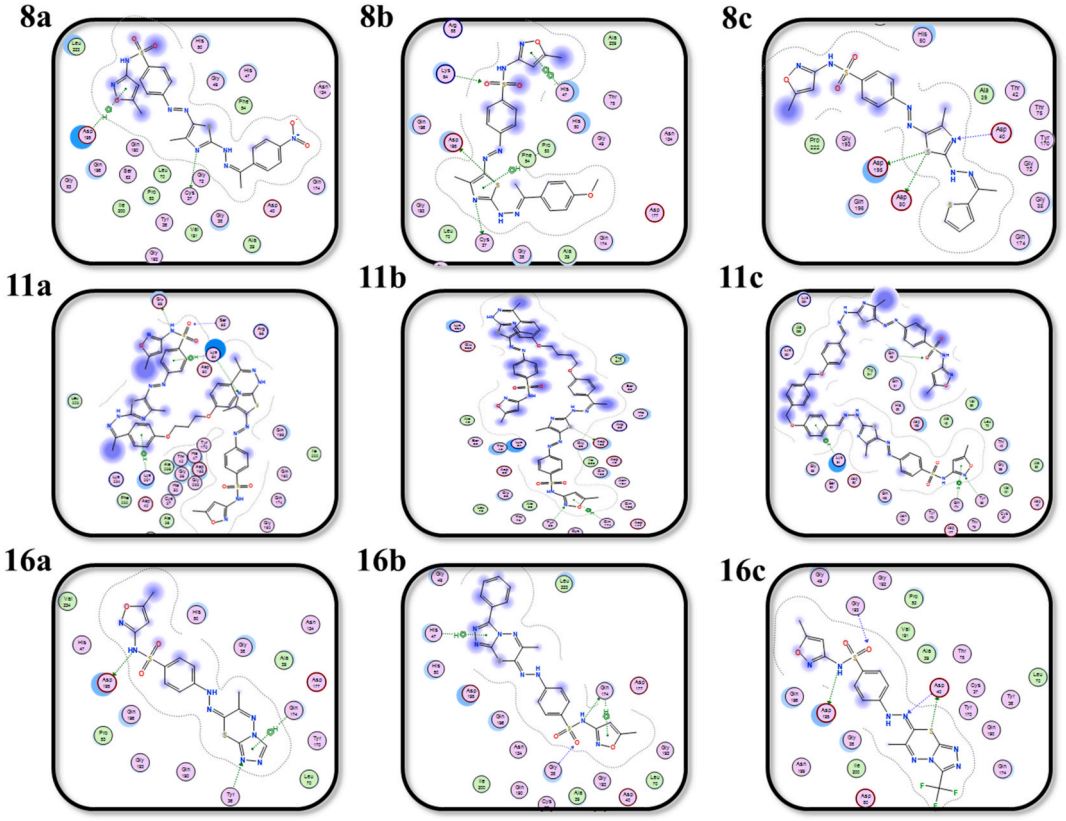


Fig. 4. 2D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives **(8a-c**, **11a-c,** and **16a-c)** against tyrosyl-tRNA synthetase (PDB ID: 1JIJ) active site residues.

phenoxymethyl linkage were prepared in good yields *via* the reaction of the corresponding bis-thiosemicarbazones **9a-c** with sulfamethoxazolehydrazonoyl chloride **4** in ethanolic – triethylamine solution. The reaction occurs *via* an initial bis-S-alkylation reaction of **9** with **4** to yield intermediate **10** that loses two water molecules to give **11** (Scheme 2).

It is worth noting that bis-thiosemicarbazones **9a-c** were prepared *via* the condensation of acetophenones **12a** and **12b** or bis-aldehydes **12c** with thiosemicarbazide **13** (Scheme 4) [73–75].

Furthermore, the reaction of sulfamethoxazolehydrazonoyl chloride **4** with 4-amino-3-mercapto-1,2,4-triazole derivatives **14a-c** in ethanol in the presence of few drops of triethylamine as a catalyst at reflux produced the novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-ylidene)hydrazineyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide **16a-c** (Scheme 5). The reaction pathway may involve S-alkylation to yield *S*-alkyl-aminotriazole intermediates **15** that undergo intramolecular cyclocondensation to afford the target products **16a-c** in good yields (Scheme 5).

On the other hand, repeated attempts to prepare bis-thiadiazoles **18**, by the reaction of 1 mol of bis(4-amino-4*H*-1,2,4-triazole-3-thiols) **17** with 2 mol of sulfamethoxazolehydrazonoyl chloride **4** were unsuccessful. Instead, the reaction yielded a combination of non-isolable compounds that could not be purified at this time (see Scheme 6).

2.1. In vitro antimicrobial activity

In this study, the synthesized compounds **8a-c**, **11a**–**c**, and **16a-c** have been evaluated *in vitro* for their inhibitory action on the growth of five bacterial strains "(Gram-positive bacterial species (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacterial species (*Escherichia coli*, *Proteus vulgaris,* and *Pseudomonas aeruginosa*)) in addition to two fungal strains (one filamentous fungus (*Aspergillus fumigatus*) and one yeast species (*Candida albicans*))". Table 1 lists the antibacterial activity results, that were acquired through the measurement of the inhibition zone (mm) with the classical agar well diffusion method [76]. Gentamycin and ketoconazole have been utilized as the standard antibacterial and antifungal drugs, respectively, with remarkable inhibition zone diameters against the examined microorganisms. Overall, the investigated derivatives exhibited remarkable antibacterial activities with variable potencies. The antibacterial properties of the (hydrazineyl)thiazol-5-yl)diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide derivatives **8a-c** (ranged from 10 to 17 mm) was greater than their corresponding bis-(hydrazineyl)thiazol-5-yl)diazenyl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide derivatives **11a-c** (from no activity to 14 mm) and [1,2,4]triazolo[3,4-*b*][1,3,4]

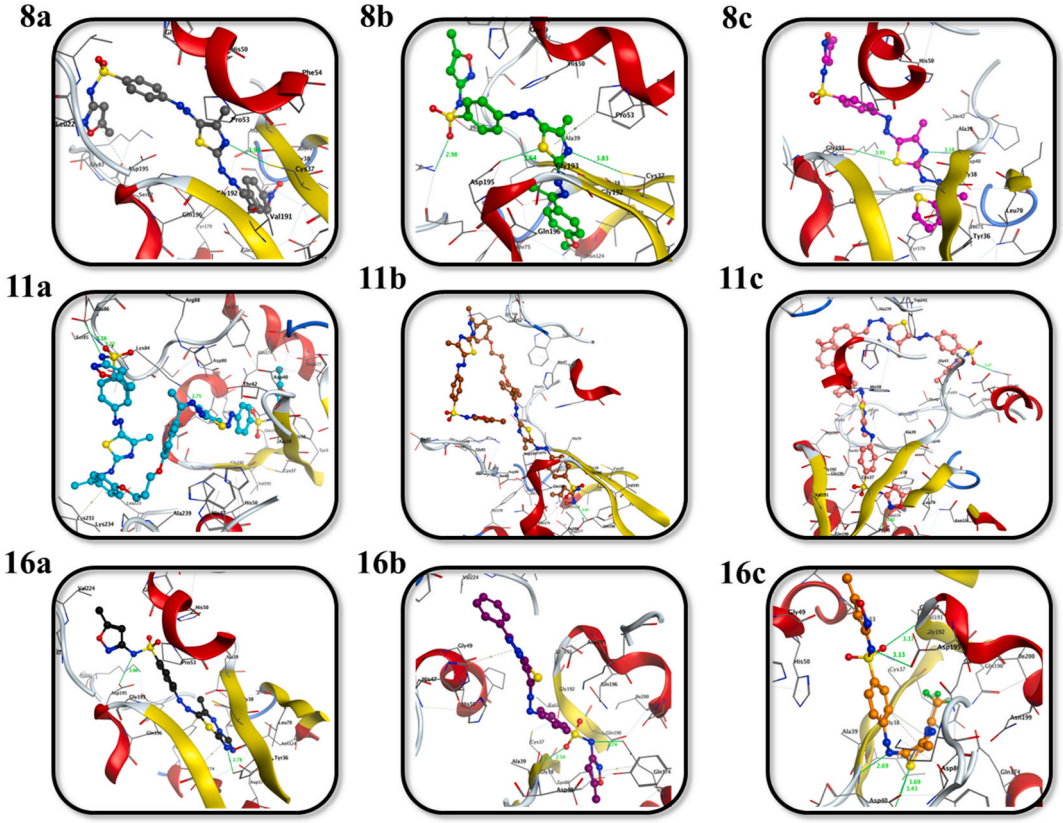


Fig. 5. 3D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives **(8a-c**, **11a-c,** and **16a-c)** against tyrosyl-tRNA synthetase (PDB ID: 1JIJ) active site residues.

thiadiazin-7-ylidene)hydrazineyl)-*N*-(5-methylisoxazol-3 yl)benzenesulfonamide derivatives **16a-c** (from no activity to 15 mm). In addition, the synthesized derivatives were non-toxic against the fungus *C. albicans*.

2.2. Structure-activity relationship

The structure-activity relationship (SAR) investigations could serve as a valuable tool for the subsequent rational design of the studied compounds and contribute to assessing numerous areas of drug discovery, from primary screening to lead optimization. Sulphonamide, sulfamethazine, and sulfadiazine drugs are a significant family of antibiotics with a broad spectrum of activity that is particularly potent against several bacterial and fungal infections, such as *Staphylococcus aureus*, *Escherichia coli*, *Pneumocystis carinii*, *Klebsiella*, *Salmonella*, and *Enterobacter* species [77]. As illustrated in the current work (Scheme 7 and Table 1), sulfonamide derivatives **8a-c** have been determined to be the most potent of the three investigated series of synthesized derivatives. It was noted that compound **8b** bearing 4-methoxyphenyl group, with electron-donating methoxy group attached to phenyl ring, exhibited higher antibacterial properties than thienyl-containing derivative **8c** and 4-nitrophenyl group bearing derivative **8a**, with electron-withdrawing nitro group attached to phenyl ring, with the inhibition zone in the range of 17 to 13 mm, 16 to 13 mm, and 14 to 10 mm, respectively, against the different tested bacterial strains. On the other side, investigating the bis-sulfonamide derivatives **11a-c** antibacterial activities, compound **11a** (inhibition zone: no activity-14 mm) with a propyl-linker exhibited good antimicrobial activity, whereas compound **11b** (inhibition zone: no activity-11 mm) having a butyl-linker exhibited weaker activity. Replacing the aforementioned aliphatic linkers with the 1,4-dimethylphenyl linker in derivative **11c** remarkably abolished the compound **11c** activity. In the SAR analysis of the third sulfonamide derivatives, **16a-c**, **16c** with strong electron-withdrawing trifluoromethyl moiety revealed good antibacterial potency (inhibition zone: 10–15 mm), nevertheless, **16a** with H-atom had a reduced activity (inhibition zone: no activity-15 mm). While **16b** bearing phenyl moiety displayed almost no activity except for *B. subtilis* and *P. aeruginos*a with 8 and 10

Table 3
Molecular docking reports of the synthesized sulfonamide derivatives (**8a-c**, **11a-c,** and **16a-c)** with bacterial protein tyrosyl-tRNA synthetase (PDB ID: 1JIJ).

Protein (PDB ID)	Compound	Docking score (kcal/mol)	Ligand	Receptor	Type of interaction	Distance	E (kcal/mol)
1JIJ	**8a**	−8.15	N 26	SG CYS 37	H-donor	3.93	−1.4
			5-ring	CB ASP 195	pi-H	4.54	−0.5
	8b	−8.72	S 24	OD2 ASP 195	H-donor	3.64	−1.0
			N 26	SG CYS 37	H-donor	3.83	−0.9
			O 12	NZ LYS 84	H-acceptor	2.98	−6.9
			5-ring	CG PRO 53	pi-H	4.33	−0.9
			5-ring	5-ring HIS 47	pi-pi	3.91	−0.0
	8c	−8.30	S 24	OD2 ASP 80	H-donor	4.00	−0.6
			S 24	OD1 ASP 195	H-donor	3.95	−3.0
			N 26	N ASP 40	H-acceptor	3.18	−4.1
	11a	−10.65	N 14	OE2 GLU 86	H-donor	3.16	−1.1
			O 13	N SER 85	H-acceptor	3.22	−1.7
			N 70	NZ LYS 84	H-acceptor	2.75	−8.2
			6-ring	CA LYS 84	pi-H	4.46	−0.7
			6-ring	CB LYS 231	pi-H	3.95	−1.0
	11b	−10.44	S 24	OD1 ASP 195	H-donor	4.06	−0.8
			N 17	OH TYR 36	H-acceptor	2.83	−1.4
			5-ring	CG GLN 174	pi-H	4.25	−1.1
	11c	−10.25	O 13	NE2 GLN 95	H-acceptor	3.27	−1.7
			N 100	OH TYR 36	H-acceptor	2.82	−1.6
			6-ring	CE LYS 84	pi-H	4.64	−0.7
			5-ring	CG GLN 174	pi-H	4.25	−1.1
	16a	−6.96	N 14	OD2 ASP 195	H-donor	3.06	−6.4
			N 32	OH TYR 36	H-acceptor	2.78	−1.6
			5-ring	CG GLN 174	pi-H	3.86	−0.7
	16b	−7.19	N 14	OE1 GLN 174	H-donor	2.74	−0.5
			O 13	N GLY 38	H-acceptor	2.54	−1.7
			5-ring	CE1 HIS 47	pi-H	4.10	−0.8
			5-ring	CG GLN 174	pi-H	3.71	−0.7
	16c	−7.19	N 14	OD1 ASP 195	H-donor	3.13	−4.2
			S 25	OD1 ASP 40	H-donor	3.69	−0.5
			S 25	OD2 ASP 40	H-donor	3.43	−1.5
			O 12	N GLY 193	H-acceptor	3.17	−1.3
			N 24	N ASP 40	H-acceptor	2.69	−2.5

mm inhibition zones, respectively.

2.3. Molecular docking study

Chemotherapeutic drugs such as antibiotics are used to either suppress or eradicate pathogens. According to Zessel et al., sulfonamides function as structural mimics and competitive antagonists of *p*-aminobenzoic acid (PABA) in the formation of folic acid, which is necessary for the bacteria to continue replicating DNA and survive (10.1016/j.chemosphere.2013.11.038). Thus, molecular docking has been utilized to give additional insight into the potential molecular mechanism of the synthesized compounds. Molecular docking has greatly contributed to the pursuit of potentially new compounds of therapeutic interest as an innovative approach for rationalizing, forecasting the affinities of compounds at a molecular basis, and assessing the suitable orientations and binding of compounds under study at pockets of receptor proteins [78–80]. The primary objective is to investigate how our novel sulfonamides will interact with different bacterial proteins, namely MurE ligase (PDB ID: 4C13), tyrosyl-tRNA synthetase (PDB ID: 1JIJ), and dihydropteroate synthase (PDB ID: 1AJ0), that are considered as crucial targets for finding broad-spectrum antibiotics [81–87].

Docking results were first validated by self-docking of the reference co-crystallized ligand (2-amino-6-hydroxymethyl-7,8-dihydro-3*H*-pteridin-4-one) with its corresponding receptor (PDB ID: 1AJ0). RMSD value was found to be less than 1 Å and a remarkable superimposition of the re-docked and co-crystallized ligand within the active site was exhibited. In addition, the docking protocol was successful and reproduced the majority of the key interactions between the ligand (re-docked (cyan) and co-crystalized (green)) and the amino acids of its corresponding protein active site, as illustrated in Fig. 1.

MurE ligase is involved in the peptidoglycan biosynthesis of the bacterial cell wall through the addition of *m*-DAP to UDP-MurNAc-L-Ala-D-Glu [81,82], and it is a highly attractive drug target due to it being unique in bacteria and absent in human cells [88,89]. Fig. 2, Fig. 3, and Table 2 revealed significant interaction profiles (binding affinities) of the sulfonamide derivatives (**8a-c**, **11a**–**c**, and **16a-c**)

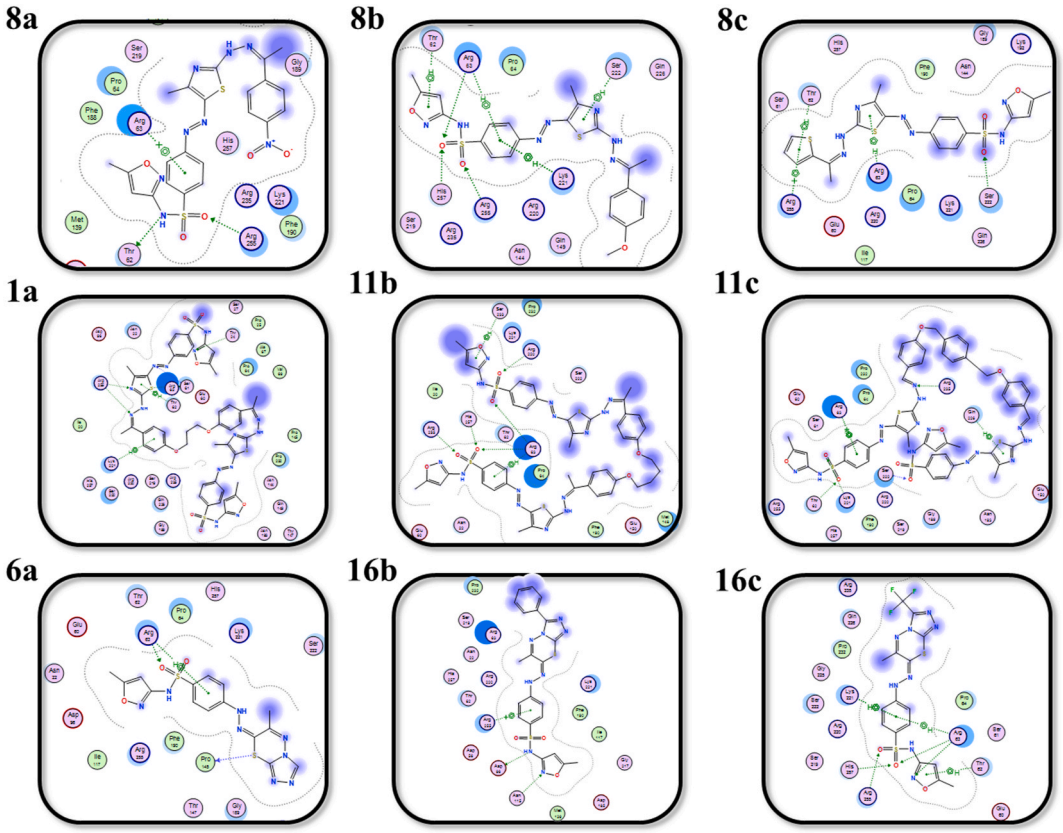


Fig. 6. 2D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives **(8a-c**, **11a-c,** and **16a-c)** against dihydropteroate synthase (PDB ID: 1AJ0) active site residues.

with the binding cavity of MurE ligase (Pdb ID: 4C13) with significant docking scores ranging from −8.07 to −12.12 kcal mol^{-1}. Sulfonamides **8b, 11a,** and **16c** were found to be the most potent among the synthesized derivatives **8a-c**, **11a–c,** and **16a-c**, as evidenced by their binding scores of −10.15, −12.12, and −8.31 kcal mol^{-1}, respectively. Analogue **8b** formed nine non-covalent interactions with Lys114, Thr115, NE and NH2 of Arg335, Arg383, His205, His353 Thr354 and Met379 residues. Seven non-covalent interactions were observed for **11a** with Asp350, Lys114, Thr115, NE, CD, and NH2 of Arg335, Arg383, and His468 residues. Furthermore, **16c** established nine non-covalent interactions with Thr111, N, and NZ of Lys114, Thr115, ND2, and CA of Asn151, Arg187, and Arg335 residues.

Furthermore, the bacterial enzyme tyrosyl-tRNA synthetase (TyrRS) contributes to the process of amino acids binding to their corresponding tRNAs that are required for the production of bacterial proteins [83,84]. TyrRS is selected as an emerging druggable target because of its essentiality for bacterial survival. As illustrated in Fig. 4, Fig. 5, and Table 3, all of the synthesized sulfonamides were efficiently docked into the TyrRS pocket, with binding energies in the range of −6.96 to −10.65 kcal mol^{-1}. With binding scores of −8.72, −10.65, and −7.19 kcal mol^{-1}, the investigation of the docking data revealed that **8b, 11a,** and **16c** had significant binding affinities among the synthesized derivatives. Notably, the sulfonamide compounds **8b, 11a,** and **16c** interacted with TyrRS pocket amino acid residues through five non-covalent interactions. Compound **8b** associated with Asp195, Cys37, Lys84, Pro53 and His47 residues, **11a** had its interaction with Glu86, Ser85, NZ and CA of Lys84, and Lys231 residues, whereas **16c** bound to OD1, OD2 and N of Asp40, Asp195 and Gly193 residues.

Eventually, dihydropteroate synthase (DHPS) has a prominent role in bacterial folate biosynthesis required for amino acids and nucleic acids production through the formation of dihydropteroate from *para*-aminobenzoic acid and dihydropterin pyrophosphate [85–87]. The most frequently utilized DHPS inhibitors are a family of synthetic compounds known as sulfonamides, which function as competitive inhibitors [10.1006/bbrc.1999.0695]. Sulfonamide derivatives (**8a-c**, **11a–c**, and **16a-c**) exhibited good binding scores of

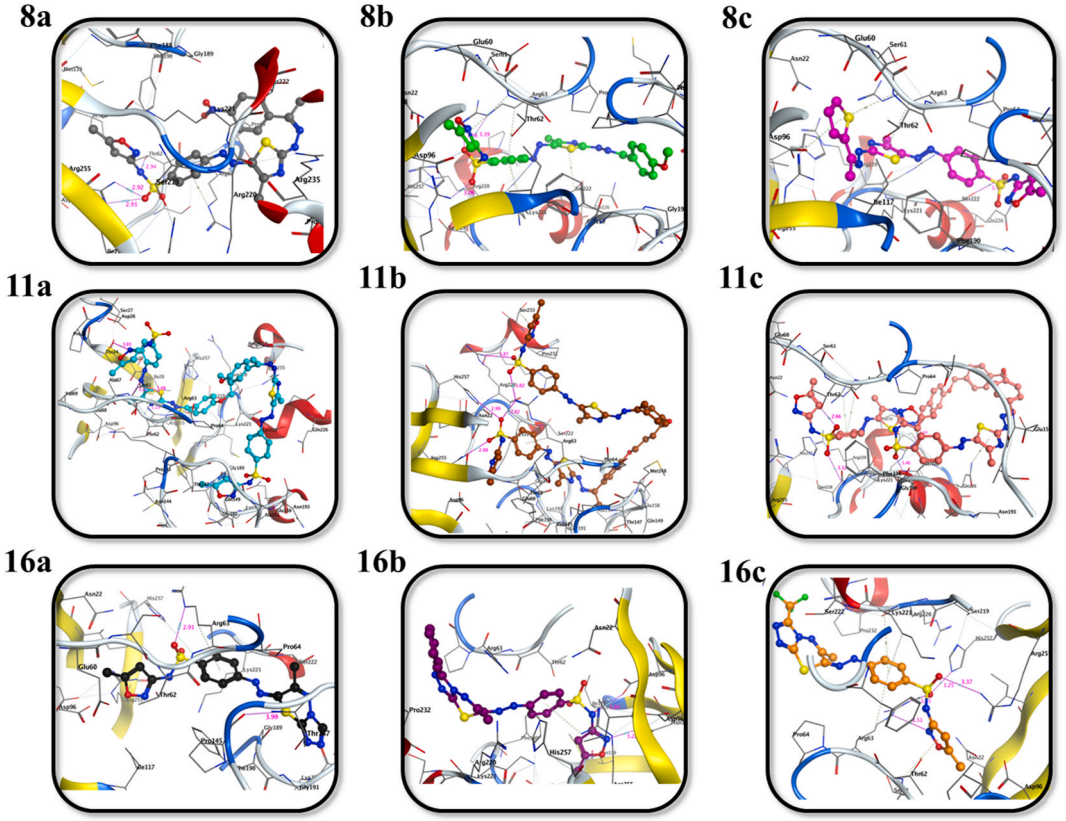


Fig. 7. 3D representations of the putative intermolecular interaction of the synthesized sulfonamide derivatives **(8a-c**, **11a-c,** and **16a-c)** against dihydropteroate synthase (PDB ID: 1AJ0) active site residues.

−6.45 to −10.75 kcal mol^{-1} against DHPS (PDB ID: 1AJ0) active site, as depicted in Fig. 6, Fig. 7 and Table 4. Compound **8b** had good binding affinity among sulfonamides **8a-c** with a binding score of −8.05 kcal mol^{-1} through nine non-covalent interactions with NE, NH_2, and CG of Arg63, His257, Arg255, Thr62, CA, and CG of Lys221 and Ser222 residues. Compounds **11a** and **16c** displayed binding scores of −10.75 and −6.92 kcal mol^{-1} compared to their groups **11a-c** and **16a-c**. Compound **11a** established seven interactions with OG and CA of Ser61, NH1, and NH2 of Arg255, Thr24, Thr62, and Lys221 residues, and compound **16c** had eight interactions with NH2, NE and CG of Arg63, His257, Arg255, Thr62, and CA and CG of Lys221 residues.

Collectively, the aforementioned molecular docking findings for the synthesized derivatives demonstrated that **8b**, **11a**, and **16c** were the most potent against the pocket of the investigated druggable proteins, including MurE ligase, tyrosyl-tRNA synthetase, and dihydropteroate synthase, with lower binding energy among their corresponding synthesized derivatives. This led to increased compatibility with the experimental antibacterial activities.

2.4. Toxicological properties

The potential safety/toxicity parameters of the most potent antibacterial derivative **8b** were evaluated using the ProTox-II online server (https://tox-new.charite.de/protox_II). Based on ProTox-II prediction, **8b** was found to belong to class V with a predicted half-lethal dose (LD50) of 3471 mg/kg. As illustrated in Fig. 8 and Table 5, compound **8b** was found to be non-neurotoxin, non-nephrotoxic, non-cardiotoxic, non-immunotoxin, non-mutagenic, non-cytotoxic, and non-ecotoxic with probability ranging from 0.54 to 0.99, nonetheless, it exhibited hepatotoxicity, respiratory toxicity, carcinogenicity, and nutritional toxicity with probability ranged from 0.5 to 0.61. Additionally, **8b** exhibited no effect against numerous proteins involved in nuclear receptor signaling pathways, including aryl hydrocarbon receptor, androgen receptor, androgen receptor ligand binding domain, aromatase, oestrogen receptor alpha, oestrogen receptor ligand binding domain, and peroxisome proliferator-activated receptor gamma. Additionally, **8b** was inactive against several proteins involved in the stress response pathway, including nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element, heat shock factor response element, mitochondrial membrane potential, phosphoprotein (tumour suppressor) p53, and ATPase family AAA domain-containing protein 5. Compound **8b** exhibited inactivity towards several molecular initiating events, including Thyroid hormone receptor alpha, Thyroid hormone receptor beta, Transtyretrin, Ryanodine receptor, GABA receptor, Glutamate N-methyl-D-

Table 4
Molecular docking reports of the synthesized sulfonamide derivatives (**8a-c**, **11a-c,** and **16a-c)** with bacterial protein dihydropteroate synthase (PDB ID: 1AJ0).

Protein (PDB ID)	Compound	Docking score (kcal/mol)	Ligand	Receptor	Type of interaction	Distance	E (kcal/mol)
1AJ0	**8a**	−7.80	N 14	OG1 THR 62	H-donor	2.94	−1.2
			O 13	NH1 ARG 255	H-acceptor	2.92	−4.0
			O 13	NH2 ARG 255	H-acceptor	2.93	−3.9
			6-ring	NE ARG 63	pi-cation	3.74	−0.7
	8b	−8.05	O 12	NE ARG 63	H-acceptor	3.39	−0.7
			O 12	NH2 ARG 63	H-acceptor	3.08	−3.6
			O 12	NE2 HIS 257	H-acceptor	3.33	−0.8
			O 13	NH1 ARG 255	H-acceptor	3.06	−3.0
			5-ring	N THR 62	pi-H	4.12	−0.6
			6-ring	CG ARG 63	pi-H	4.39	−0.7
			6-ring	CA LYS 221	pi-H	4.79	−0.5
			6-ring	CG LYS 221	pi-H	3.93	−0.7
			5-ring	CB SER 222	pi-H	3.97	−0.6
	8c	−7.89	O 13	OG SER 222	H-acceptor	3.17	−1.0
			5-ring	N THR 62	pi-H	4.06	−1.2
			5-ring	CG ARG 63	pi-H	4.06	−1.0
			5-ring	NH2 ARG 255	pi-cation	3.66	−1.8
	11a	−10.76	S 68	OG SER 61	H-donor	3.88	−0.8
			N 65	NH1 ARG 255	H-acceptor	2.96	−6.2
			N 70	NH2 ARG 255	H-acceptor	3.19	−0.7
			N 73	CA SER 61	H-acceptor	3.22	−1.0
			N 91	OG1 THR 24	H-acceptor	3.01	−1.7
			5-ring	N THR 62	pi-H	4.10	−0.5
			6-ring	CG LYS 221	pi-H	3.66	−0.5
	11b	−10.55	O 12	NH1 ARG 255	H-acceptor	2.88	−4.8
			O 13	NH2 ARG 63	H-acceptor	2.82	−4.7
			O 13	NE2 HIS 257	H-acceptor	2.99	−0.8
			O 89	NH2 ARG 63	H-acceptor	3.02	−3.4
			O 90	NH1 ARG 220	H-acceptor	3.07	−1.6
			6-ring	CG ARG 63	pi-H	3.77	−0.8
			5-ring	CB SER 233	pi-H	4.66	−0.6
	11c	−8.93	O 12	N SER 222	H-acceptor	3.46	−0.9
			N 74	NH2 ARG 235	H-acceptor	3.04	−4.5
			O 95	OG1 THR 62	H-acceptor	2.66	−1.7
			O 96	NZ LYS 221	H-acceptor	3.12	−1.2
			6-ring	CG ARG 63	pi-H	4.37	−0.6
			6-ring	NE ARG 63	pi-cation	3.81	−0.6
			5-ring	NE2 GLN 226	pi-H	3.89	−0.6
	16a	−6.83	S 25	O PRO 145	H-donor	3.99	−0.5
			O 13	NE ARG 63	H-acceptor	2.91	−4.4
			6-ring	CG ARG 63	pi-H	4.36	−0.5
	16b	−6.46	N 14	OD2 ASP 96	H-donor	2.89	−10.3
			N 17	ND2 ASN 115	H-acceptor	3.22	−3.0
			6-ring	NH1 ARG 255	pi-cation	3.66	−0.5
	16c	−6.92	O 12	NH2 ARG 63	H-acceptor	3.15	−3.0
			O 12	NE2 HIS 257	H-acceptor	3.25	−0.6
			O 13	NH1 ARG 255	H-acceptor	3.37	−0.8
			N 17	NE ARG 63	H-acceptor	3.51	−0.6
			5-ring	N THR 62	pi-H	4.13	−1.4
			6-ring	CG ARG 63	pi-H	4.51	−0.5
			6-ring	CA LYS 221	pi-H	4.58	−0.8
			6-ring	CG LYS 221	pi-H	3.95	−0.5

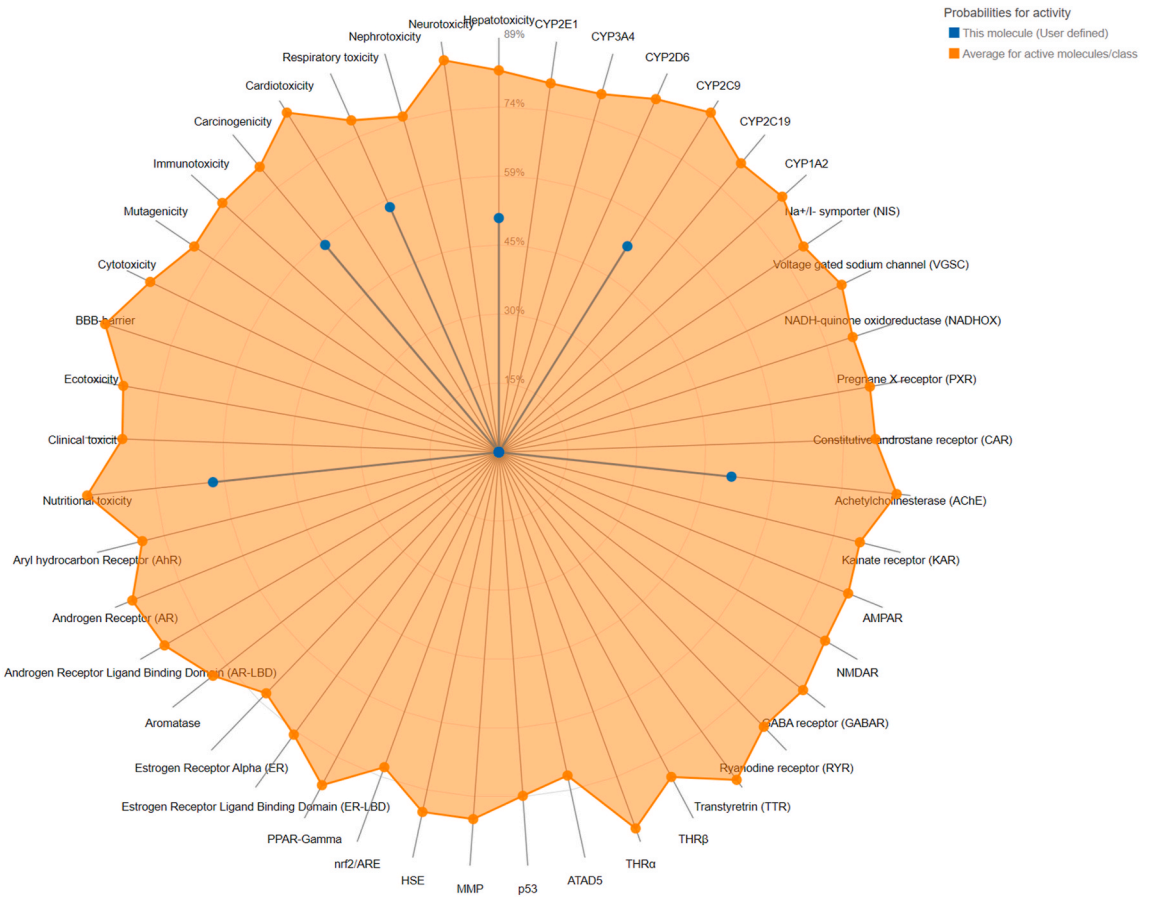


Fig. 8. Toxicity radar for derivative **8b**.

aspartate receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor, Kainate receptor, Acetylcholinesterase, Constitutive androstane receptor, Pregnane X receptor, NADH-quinone oxidoreductase, Voltage-gated sodium channel, and Na+/I-symporter. In addition, **8b** was found to be inactive against different cytochrome P450 proteins that are implicated in drug metabolism, such as CYP1A2, CYP2C19, CYP2D6, CYP3A4, and CYP2E1, except activity against CYP2C9.

3. Conclusion

We devised a new method for producing novel hybrid compounds including thiazoles or bis-thiazoles coupled to azo-sulfamethoxazole. We attempted to apply green chemistry to the design of synthetic protocols while minimizing environmental impact. The synthetic process in use has gentle reaction conditions, is straightforward to operate, has a large structural diversity, and tolerates functional groups well. We believe that combining these heterocyclic systems with adaptable structural motifs in a single molecule will improve the biological activities of the resultant heterocyclic systems. The antibacterial screening of the produced compounds revealed that several of the new derivatives displayed exceptional activity, with compounds **8b**, **11a**, and **16c** remaining the most powerful among the three series. The molecular docking data were inconsistent with the antibacterial experimental results, but they could provide useful information about a potential mechanism of action by illustrating the thermodynamic associations that formed when these compounds bound to the crucial proteins' active sites. Our future research will focus on improving the structure of our compounds by including solubilizing groups into the primary core of compounds, to improve their pharmacokinetic characteristics.

Table 5
The predicted toxicity for compound **8b** using ProTox-II.

Classification	Target	Prediction	Probability
Organ toxicity	Hepatotoxicity	Active	0.50
	Neurotoxicity	Inactive	0.82
	Nephrotoxicity	Inactive	0.54
	Respiratory toxicity	Active	0.57
	Cardiotoxicity	Inactive	0.70
Toxicity endpoints	Carcinogenicity	Active	0.58
	Immunotoxicity	Inactive	0.99
	Mutagenicity	Inactive	0.61
	Cytotoxicity	Inactive	0.92
	BBB-barrier	Inactive	0.56
	Ecotoxicity	Inactive	0.75
	Clinical toxicity	Inactive	0.58
	Nutritional toxicity	Active	0.61
Tox21-Nuclear receptor signaling pathways	Aryl hydrocarbon Receptor	Inactive	0.95
	Androgen Receptor	Inactive	0.95
	Androgen Receptor Ligand Binding Domain	Inactive	0.99
	Aromatase	Inactive	0.98
	Estrogen Receptor Alpha	Inactive	0.96
	Estrogen Receptor Ligand Binding Domain	Inactive	0.98
	Peroxisome Proliferator-Activated Receptor Gamma	Inactive	0.96
	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element	Inactive	0.98
	Heat shock factor response element	Inactive	0.98
	Mitochondrial Membrane Potential	Inactive	0.77
	Phosphoprotein (Tumor Suppressor) p53	Inactive	0.96
	ATPase family AAA domain-containing protein 5	Inactive	0.97
Molecular Initiating Events	Thyroid hormone receptor alpha	Inactive	0.90
	Thyroid hormone receptor beta	Inactive	0.78
	Transtyretrin	Inactive	0.97
	Ryanodine receptor	Inactive	0.98
	GABA receptor	Inactive	0.96
	Glutamate N-methyl-D-aspartate receptor	Inactive	0.92
	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor	Inactive	0.97
	Kainate receptor	Inactive	0.99
	Acetylcholinesterase	Active	0.50
	Constitutive androstane receptor	Inactive	0.98
	Pregnane X receptor	Inactive	0.92
	NADH-quinone oxidoreductase	Inactive	0.97
	Voltage-gated sodium channel	Inactive	0.95
	Na+/I- symporter (NIS)	Inactive	0.98
Metabolism	Cytochrome CYP1A2	Inactive	0.87
	Cytochrome CYP2C19	Inactive	0.63
	Cytochrome CYP2C9	Active	0.52
	Cytochrome CYP2D6	Inactive	0.82
	Cytochrome CYP3A4	Inactive	0.65
	Cytochrome CYP2E1	Inactive	0.99

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Mostafa E. Salem: Writing – original draft, Methodology, Data curation. **Ismail A. Abdelhamid:** Writing – review & editing, Conceptualization. **Ahmed H.M. Elwahy:** Writing – review & editing, Conceptualization. **Mohamed A. Ragheb:** Writing – original draft, Software, Formal analysis, Data curation. **Arwa sultan Alqahtani:** Methodology, Formal analysis. **Magdi E.A. Zaki:** Methodology, Formal analysis. **Faisal K. Algethami:** Methodology, Data curation. **Huda Kamel Mahmoud:** Writing – original draft, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31082.

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