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Insilco Molecular Docking studies of series of Pyridines

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Abstract

A series of structurally diverse compounds (2a–h, 3a–h, 4a–h, and 5a–h) (Fig:1, Table:1,2,3,4) bearing substituted pyridine rings were evaluated for their binding affinity toward *Staphylococcus aureus* DNA gyrase B (PDB ID: 4URM) using molecular docking studies. The docking analysis revealed binding energies ranging from −6.26 to −8.08 kcal/mol, indicating favorable interactions with the enzyme active site. Compound 2f exhibited the highest binding affinity (−8.08 kcal/mol) with a low inhibition constant of 1.19 µM, followed by 3f (−7.95 kcal/mol) and 4f (−7.72 kcal/mol). Hydrogen-bond interactions with key catalytic residues including SER128, LYS111, ASP81, GLY109, ALA108, and VAL126 significantly contributed to complex stabilization. Halogen-substituted analogues, particularly bromo- and chloro-containing derivatives, displayed superior docking scores compared with methyl-substituted analogues, demonstrating the importance of electronic effects in receptor binding. These findings suggest that halogenated derivatives represent promising lead molecules for the development of novel antibacterial agents targeting DNA gyrase B.

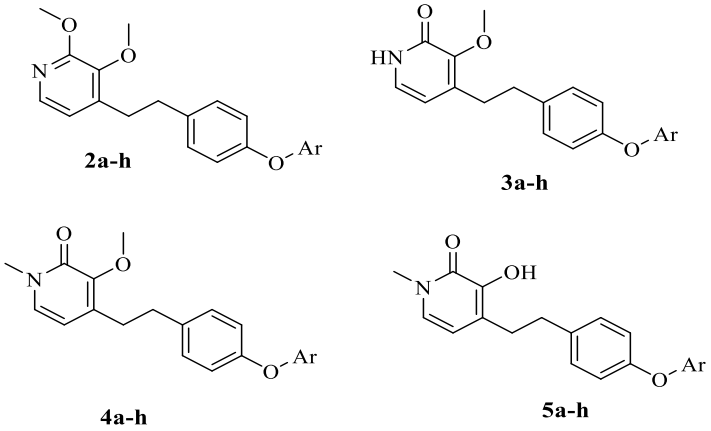
Introduction

The rapid emergence of multidrug-resistant (*MDR*) *Staphylococcus aureus* has become a major global healthcare challenge, necessitating the development of new antibacterial agents with novel mechanisms of action.[1] DNA gyrase B, an ATP-dependent bacterial topoisomerase, plays an essential role in DNA replication and has emerged as an attractive antibacterial target.[2–3] Molecular docking has become an indispensable computational tool for predicting ligand–protein interactions and accelerating antibacterial drug discovery.[4]

Heterocyclic compounds containing pyridine, pyridone, quinolone, and related pharmacophores exhibit diverse biological activities including potent antibacterial properties.[5] Halogen substitution often enhances lipophilicity, membrane permeability, and binding affinity toward biological targets through favorable hydrophobic and halogen-bond interactions.[6]

Previous studies have demonstrated that amino acid residues such as SER128, LYS111, ASP81, and GLY109 are crucial for inhibitor recognition within the ATP-binding pocket of DNA gyrase B.[7] Therefore, structural optimization of heterocyclic scaffolds with suitable electronic substituents can significantly improve antibacterial activity.[8] In the present work, four structurally related series (2a–h, 3a–h, 4a–h, and 5a–h) were investigated by molecular docking against *S. aureus* DNA gyrase B to establish

structure–activity relationships and identify promising lead molecules.[9,10] Herein, we describe the series of structurally diverse compounds (2a–h, 3a–h, 4a–h, and 5a–h) (Fig:1, Table:1,2,3,4)



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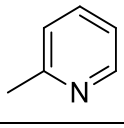
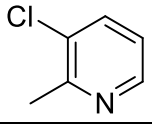
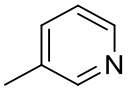
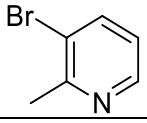
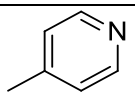
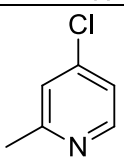
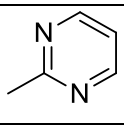
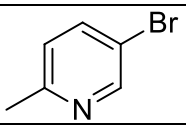
a:		e:	
b:		f:	
c:		g:	
d:		h:	

Fig:1

Results and Discussion

Molecular docking Studies

Molecular docking studies were carried out to investigate the binding affinity and interaction profile of the synthesized compounds 2a–2h, 3a–3h, 4a–4h, and 5a–5h against *Staphylococcus aureus* DNA gyrase B (PDB ID: 4URM), a well-established antibacterial target involved in DNA replication [11-15]. The docking results demonstrated that all compounds exhibited moderate to excellent binding affinity toward the active site of the target protein, with binding energies ranging from -6.26 to -8.08 kcal/mol and predicted inhibition constants (Ki) from 25.65 to 1.19 µM.

Among all the docked compounds, compound 2f displayed the highest binding affinity, with a docking score of -8.08 kcal/mol and the lowest inhibition constant (Ki = 1.19 µM). This compound also

formed one hydrogen bond with SER128, with a bond length of 1.85 Å, indicating a strong and favorable interaction within the active site. The excellent docking score and low Ki value suggest that 2f is the most promising inhibitor among the entire series. The second-best binding affinity was observed for compound 3f, which showed a docking score of -7.95 kcal/mol and a Ki value of 1.49 µM, along with one hydrogen bond involving SER128 at 1.98 Å. This result indicates that 3f also possesses excellent binding potential toward DNA gyrase B. Similarly, compound 4f demonstrated a highly favourable docking score of -7.72 kcal/mol and a Ki value of 2.18 µM, although it did not form any hydrogen bonds. The strong binding of 4f in the absence of hydrogen bonding suggests that hydrophobic interactions, π–π stacking, van der Waals forces, and steric complementarity may play a dominant role in stabilizing this ligand within the active site.

Likewise, compound 3e exhibited a docking score of -7.65 kcal/mol with a Ki value of 2.46 µM, while compound 5h showed an identical docking score of -7.65 kcal/mol and a Ki value of 2.47 µM. Among these, 5h formed one strong hydrogen bond with ALA108, having a bond length of 1.69 Å, indicating efficient stabilization inside the receptor cavity. In contrast, 3e did not form any hydrogen bond, again emphasizing that non-bonded interactions can also significantly contribute to docking affinity.

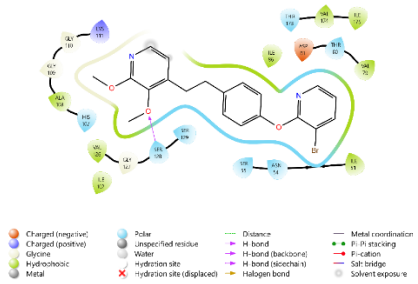
The compounds 4b, 3h, 3g, 2h, 3a, 5g, 5f, 4h, and 2b also displayed good docking scores in the range of -7.06 to -7.32 kcal/mol, indicating appreciable inhibitory potential. Notably, compound 4b showed a docking score of -7.32 kcal/mol with a Ki value of 4.29 µM, and formed two hydrogen bonds with SER128 (2.15 Å) and LYS111 (2.21 Å). Similarly, compound 2h formed two hydrogen bonds with LYS111 (1.87 Å) and SER128 (2.57 Å), corresponding to a docking score of -7.18 kcal/mol and a Ki value of 5.45 µM. These interactions indicate that dual hydrogen bonding with key active site residues contributes significantly to ligand stabilization.

Among the series 3 derivatives, compound 3d formed two hydrogen bonds with SER128 (1.92 Å) and GLY109 (2.20 Å), although its docking score (-6.79 kcal/mol) was comparatively moderate. This suggests that while hydrogen bonding is important, the overall binding affinity is also influenced by ligand orientation, hydrophobic contacts, and steric fit within the binding pocket.

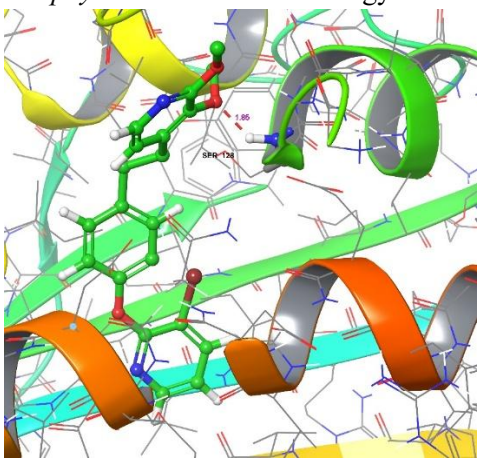
A particularly interesting observation was made for compound 5e, which formed the highest number of hydrogen bonds (three) among all the tested compounds. It interacted with LYS111 (1.97 Å), VAL126 (2.20 Å), and SER128 (1.14 Å). However, despite these multiple interactions, its docking score was only -6.76 kcal/mol with a Ki value of 11.02 µM, indicating that a higher number of hydrogen bonds does not necessarily guarantee superior binding affinity. This highlights the importance of overall molecular fit and non-polar interactions in the docking process.

Several compounds such as 2e, 3e, 3g, 4f, and 4h exhibited good docking scores despite lacking hydrogen-bonding interactions, suggesting that their binding is likely governed by hydrophobic and aromatic interactions within the active site.

In contrast, compounds such as 2d, 2a, 4e, and 5c showed comparatively weaker docking scores and higher Ki values, indicating relatively lower inhibitory potential. (Fig:1, Table:1,2,3,4)



2D interaction of the compound **2f** with *Staphylococcus aureus* DNA gyrase B



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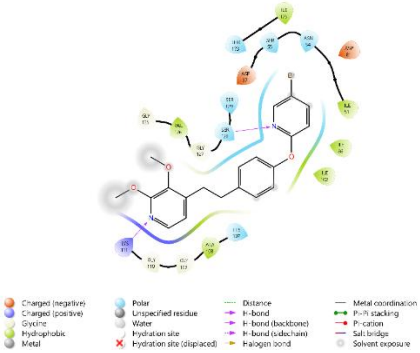

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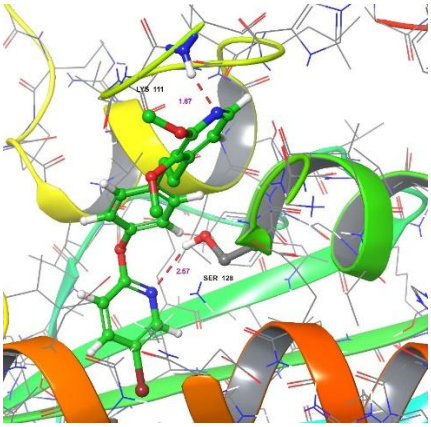
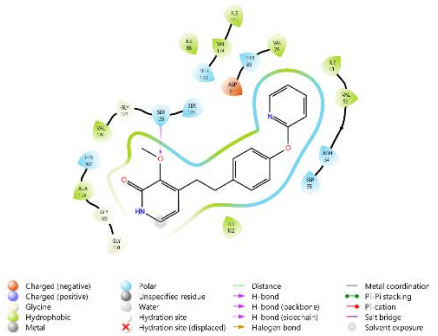
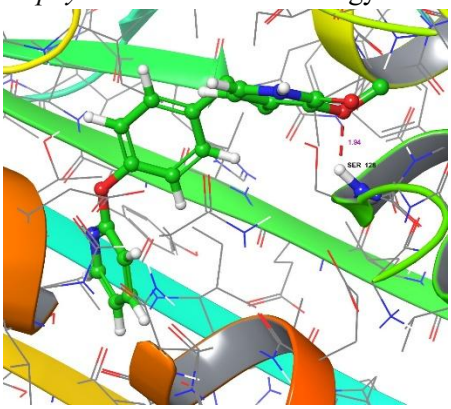


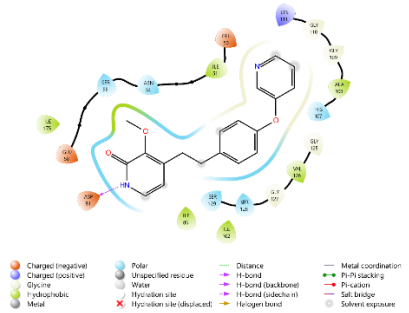
3D interaction of the compound **2h** with *Staphylococcus aureus* DNA gyrase B



2D interaction of the compound **3a** with *Staphylococcus aureus* DNA gyrase B



3D interaction of the compound **3a** with *Staphylococcus aureus* DNA gyrase B



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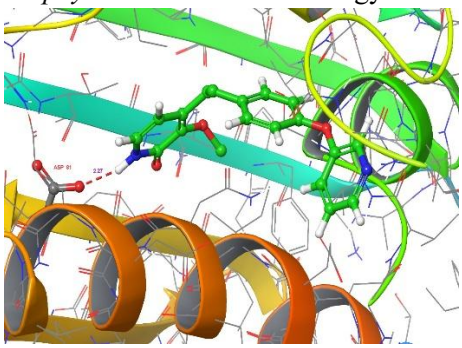
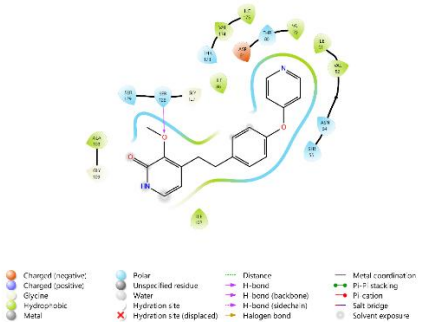


3D interaction of the compound **3b** with *Staphylococcus aureus* DNA gyrase B



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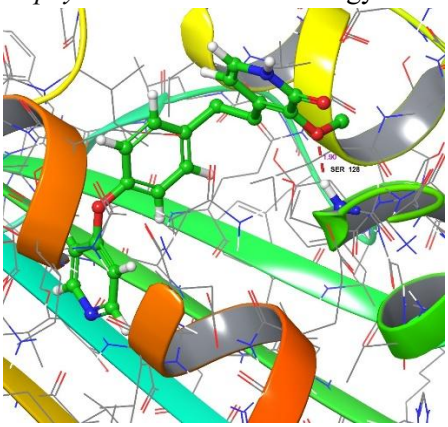

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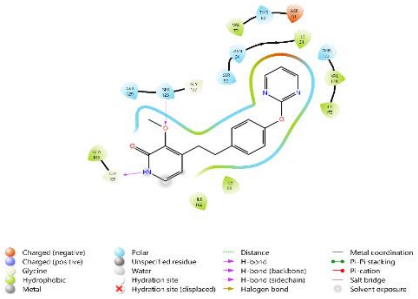

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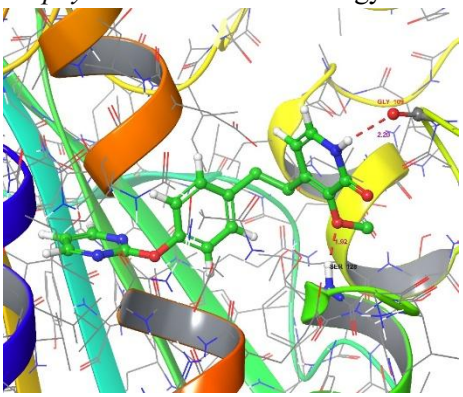
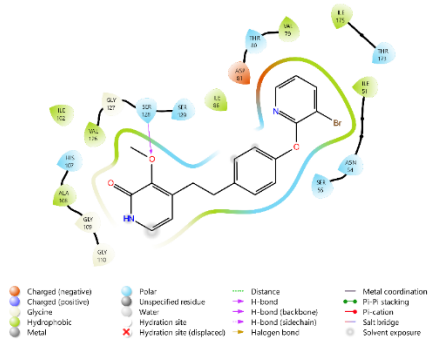


3D interaction of the compound **3d** with *Staphylococcus aureus* DNA gyrase B



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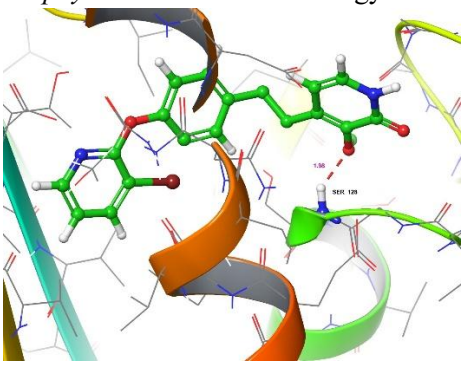

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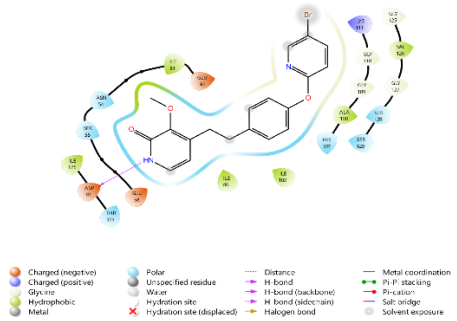

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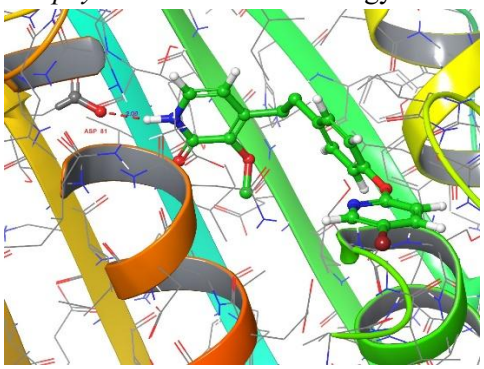
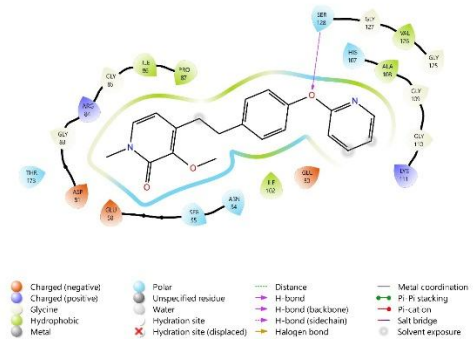


3D interaction of the compound **3h** with *Staphylococcus aureus* DNA gyrase B



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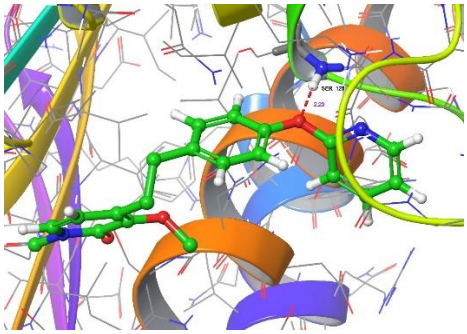

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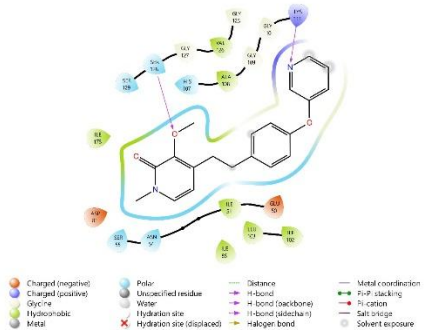

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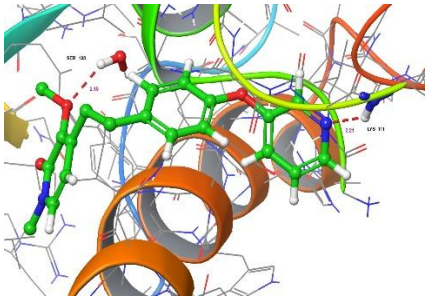

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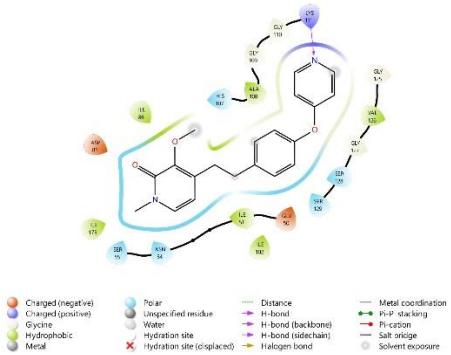

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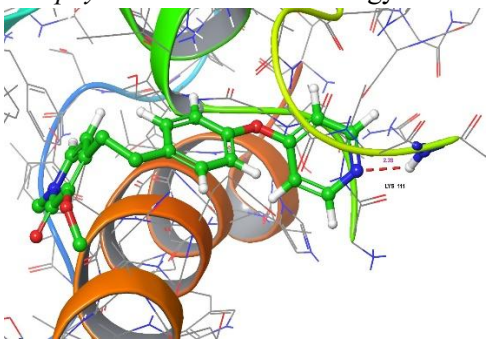

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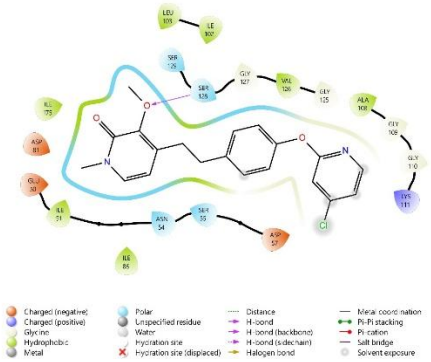

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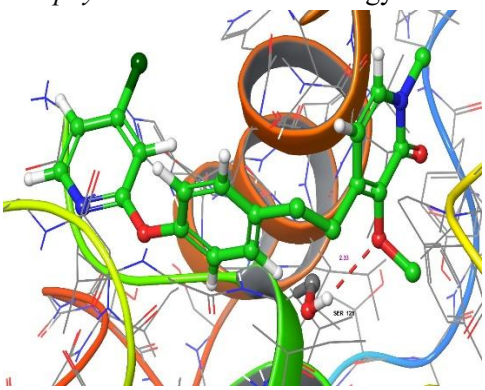

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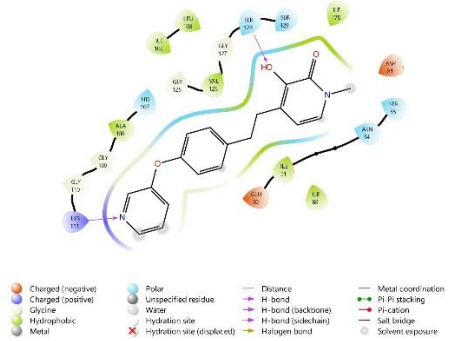

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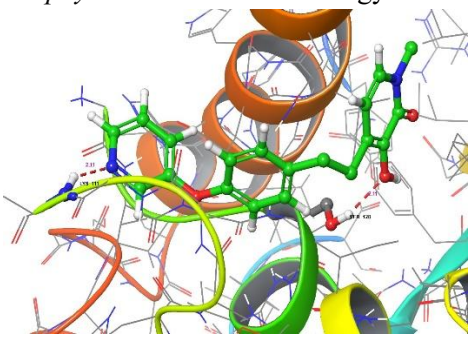

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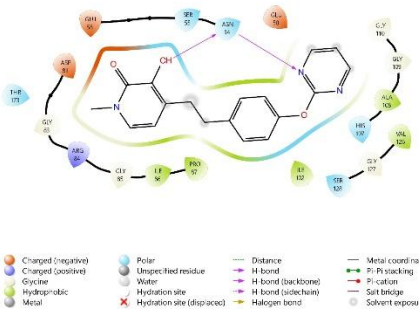

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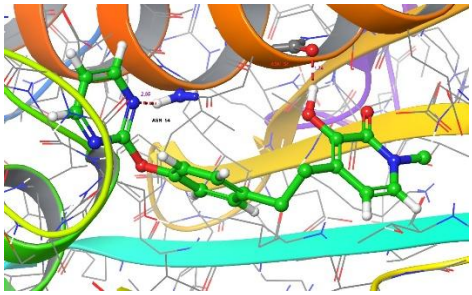

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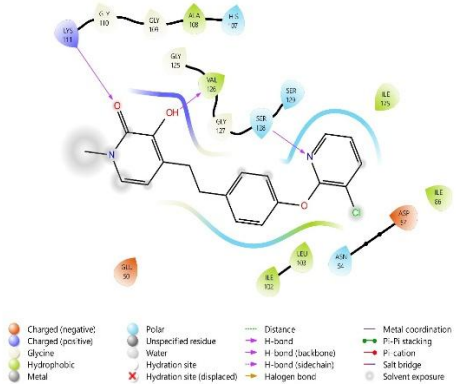

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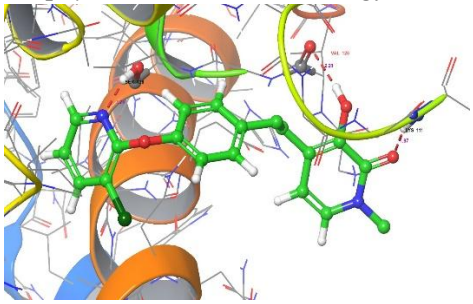

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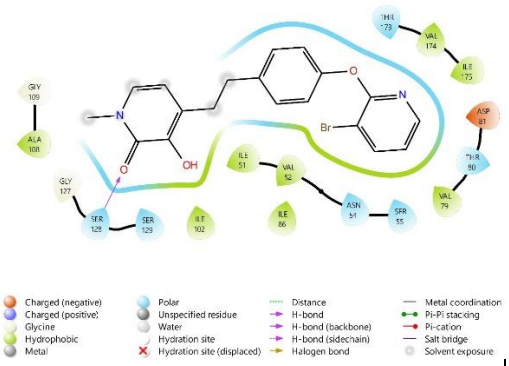

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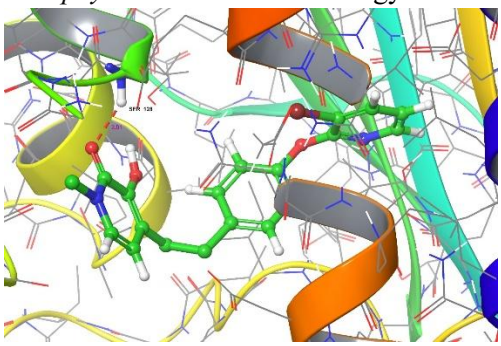
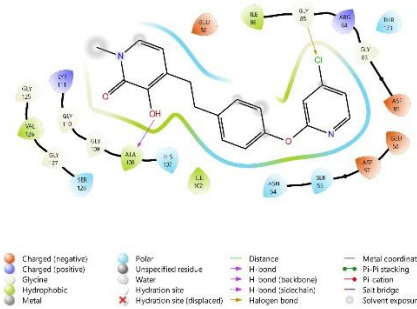
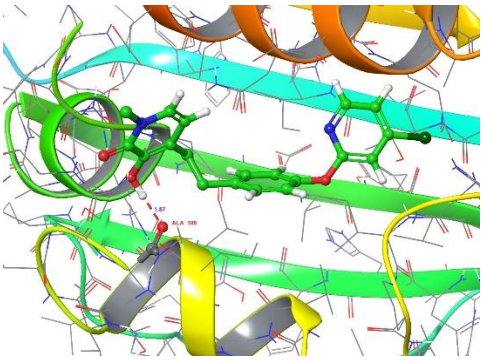


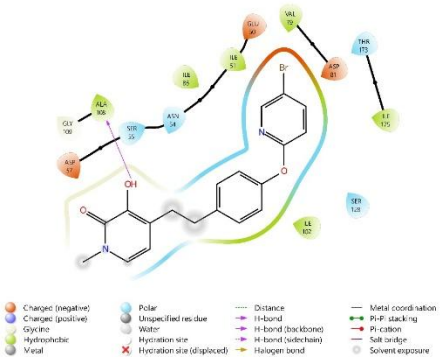
3D interaction of the compound **5f** with *Staphylococcus aureus* DNA gyrase B



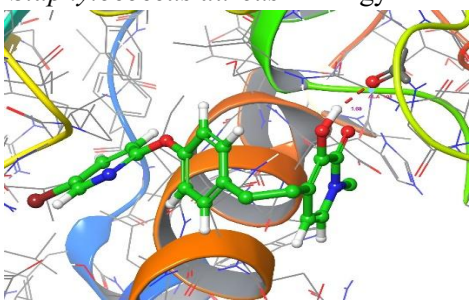
2D interaction of the compound **5g** with *Staphylococcus aureus* DNA gyrase B



3D interaction of the compound **5g** with *Staphylococcus aureus* DNA gyrase B



2D interaction of the compound **5h** with *Staphylococcus aureus* DNA gyrase B



3D interaction of the compound **5h** with *Staphylococcus aureus* DNA gyrase B

Conclusion

The molecular docking study demonstrated that all synthesized derivatives possess appreciable affinity toward *Staphylococcus aureus* DNA gyrase B. Among them, compound 2f emerged as the most promising inhibitor with the highest binding affinity and lowest inhibition constant. Bromine- and chlorine-substituted derivatives consistently exhibited superior docking performance compared with methyl analogues. Hydrogen-bond interactions with SER128 and LYS111 were identified as the major contributors to binding stabilization. The observed structure–activity relationship indicates that halogen substitution enhances

antibacterial target recognition. These findings provide valuable insights for the rational design of potent DNA gyrase B inhibitors as prospective antibacterial agents. Overall, the docking results establish that halogen substitution, particularly bromine, together with hydrogen bonding to SER128 and LYS111, plays a decisive role in enhancing inhibitory potential against DNA gyrase B.

Entry	Binding Energy (kcal/mol)	Inhibition Constant	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
2a	-6.50	17.10 µM	-	-
2b	-7.06	6.71 µM	1	LYS111(2.14)
2c	-6.71	12.12 µM	-	-
2d	-6.26	25.65 µM	-	-
2e	-7.34	4.14 µM	-	-
2f	-8.08	1.19 µM	1	SER128(1.85)
2g	-7.01	7.32 µM	-	-
2h	-7.18	5.45 µM	2	LYS111(1.87), SER128(2.57)

Table 1. Molecular docking results of compounds **2a-2h** with *Staphylococcus aureus* DNA gyrase B (PDB ID-4URM).

Table 2. Molecular docking results of compounds **3a-3h** with *Staphylococcus aureus* DNA gyrase B (PDB ID-4URM).

Entry	Binding Energy (kcal/mol)	Inhibition Constant	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
3a	-7.15	5.78 µM	1	SER128(1.94)
3b	-6.93	8.29 µM	1	ASP81(2.27)
3c	-7.02	7.17 µM	1	SER128(1.90)
3d	-6.79	10.61 µM	2	SER128(1.92), GLY109(2.20)
3e	-7.65	2.46 µM	-	-
3f	-7.95	1.49 µM	1	SER128(1.98)
3g	-7.24	4.91 µM	-	-
3h	-7.30	4.43 µM	1	ASP81(2.09)

Entry	Binding Energy (kcal/mol)	Inhibition Constant	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
4a	-6.92	8.51 µM	1	SER128(2.23)
4b	-7.32	4.29 µM	2	SER128(2.15), LYS111(2.21)
4c	-6.77	10.92 µM	1	LYS111(2.33)
4d	-6.74	11.43 µM	-	-
4e	-6.60	14.41 µM	-	-
4f	-7.72	2.18 µM	-	-
4g	-6.88	9.00 µM	1	SER128(2.33)
4h	-7.11	6.14 µM	-	-

Table 3. Molecular docking results of compounds **4a-4h** with *Staphylococcus aureus* DNA gyrase B (PDB ID-4URM).

Entry	Binding Energy (kcal/mol)	Inhibition Constant	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
5a	-6.74	11.46 µM	-	-
5b	-6.74	11.46 µM	2	LYS111(2.11), SER128(2.11)
5c	-6.68	12.66 µM	-	-
5d	-6.90	8.76 µM	2	ASN(1.74, 2.35)
5e	-6.76	11.02 µM	3	LYS111(1.97), VAL126(2.20), SER128(1.14)
5f	-7.08	6.42 µM	1	SER128(2.01)
5g	-7.10	6.27 µM	1	ALA108(1.87)
5h	-7.65	2.47 µM	1	ALA108(1.69)

Table 4. Molecular docking results of compounds **5a-5h** with *Staphylococcus aureus* DNA gyrase B (PDB ID-4URM).

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