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RESEARCH ARTICLE

ONE-POT GREENSTRATEGY FOR THE SYNTHESIS OF POLY-HYDROQUINOLINE DERIVATIVES AND MOLECULAR DOCKING STUDY

***Pinta Chouhan, Dr. Ritu Tomar and Dr. Renu Rathore**

Department of Chemistry, Bhupal Nobles' University, Udaipur

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ABSTRACT

Rapid expansion of antimicrobial-resistant pathogens has intensified the demand for chemotypes that are both potent and environmentally sustainable. We describe a green one-pot strategy for constructing a small library of polyhydroquinoline derivatives (4a–4e) starting from 5-methyl-2-aminopyridine and aromatic aldehydes in ethanol under catalytic HCl. Antimicrobial activity was assessed by agar well diffusion against *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*. Lead compound 4a produced inhibition zones of 30–31 mm for Gram-positive, 27–28 mm for Gram-negative bacteria and 24–26 mm for fungal strains, closely matching or surpassing the reference drugs streptomycin and fluconazole. Further, SwissADME predicted full Lipinski compliance and high GI absorption, while AutoDock Vina gave strong binding to S. aureus and E. coli (4a: –11.9/–9.9 kcal mol^{-1}). These findings showed a promising broad-spectrum antimicrobial derived via a sustainable synthesis.

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INTRODUCTION

Antimicrobial resistance (AMR) continues to escalate at a rate that outpaces the discovery of new drugs, threatening to undermine the efficacy of first-line antibiotics and antifungals worldwide [1]. Heteroaromatic scaffolds able to disrupt essential microbial enzymes are therefore a priority in contemporary medicinal chemistry. Polyhydroquinolinesfused 1,4-dihydropyridine frameworks often described as "privileged" because a single core accommodates diverse bioactivitieshave gained particular attention for their antibacterial, antifungal, antimalarial and anticancer properties [2-4]. Structure–activity-relationship (SAR) studies show that electronic tuning at the 4-oxo, 1-aryl and 8-heteroaryl positions can markedly enhance target affinity, yet conventional step-wise syntheses rely on multiple protection–deprotection operations, toxic solvents and high-temperature cyclisations that conflict with green-chemistry principles. [5-7]. One-pot multicomponent methodologies (MCRs) provide an attractive route to chemical diversity while maximising atom- and step-economy. [8-10] Acid-catalysed condensation of 2-aminopyridines with aldehydes, for example, delivers polyhydroquinoline analogues in a single flask, but most protocols still employ mineral acids in refluxing polar aprotic media [11-12]. Here we report a green, one-pot synthesis of polyhydroquinoline derivatives 4a–4e with in-vitro antibacterial and antifungal evaluation against four bacterial and two fungal strains. Further, SwissADME-guided assessment of Lipinski compliance and gastrointestinal absorption; and molecular docking studies were performed to rationalise observed SAR trends.

****Corresponding author:*** *Pinta Chouhan*
Department of Chemistry, Bhupal Nobles' University, Udaipur

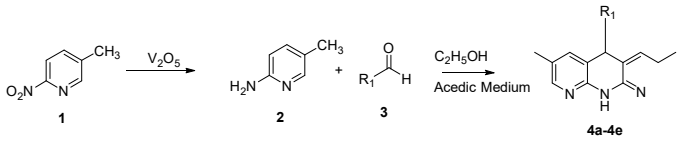
MATERIAL AND METHODS

Chemistry: General Methods of Synthesis of polyhydroquinoline and its analogues

Procedure of synthesis of 5-methylpyridin-2-amine (2): To a 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer, 1.22 g (10 mmol) of 5-methyl-2-nitropyridine (1) is dissolved in 30 mL of ethanol. To this solution, 0.18 g (1 mmol) of vanadium pentoxide (V_2O_5) is added as a catalyst. Then, 1.5 mL (30 mmol) of hydrazine hydrate (80%) is added dropwise under continuous stirring. The reaction mixture is heated to reflux (approximately 75–80°C) and maintained at that temperature with constant stirring for 5 hours. The progress of the reaction is monitored using thin-layer chromatography (TLC). After completion, the mixture is allowed to cool to room temperature, and the catalyst is removed by filtration. The filtrate is concentrated under reduced pressure using a rotary evaporator to remove the solvent. The crude residue is dissolved in 20 mL of ethyl acetate, washed with water (2 × 10 mL), and then with brine (1 × 10 mL). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The resulting crude product is purified by recrystallization from ethanol to afford 5-methylpyridin-2-amine as a pale-yellow solid in 70-85% yield.

Procedure of synthesis of polyhydroquinoline derivatives (4a-4e): A mixture of 5-methylpyridin-2-amine (2) (1 mmol) and substituted aromatic aldehyde (1 mmol) is dissolved in 10 mL of absolute ethanol in a 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer. To this solution, 1–2 drops of concentrated hydrochloric acid (HCl) are added to provide the acidic medium necessary for the condensation reaction. The reaction mixture is then

heated under reflux with constant stirring for 6–8 hours, during which time the progress of the reaction is monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture is allowed to cool to room temperature, and the resulting precipitate is filtered under vacuum. The solid is washed with cold ethanol and dried in a vacuum desiccator. The crude product is purified by recrystallization from ethanol.



Scheme 5.1: Synthesis of polyhydroquinoline derivatives (4a-4e)

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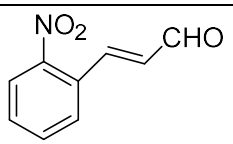
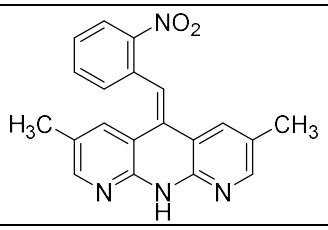
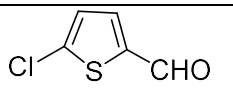
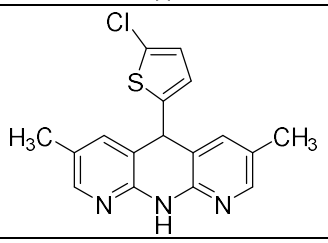
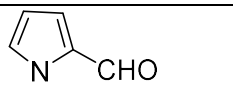
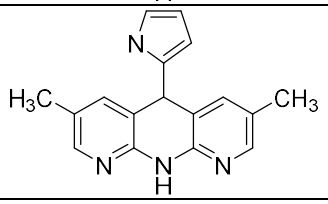
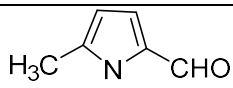
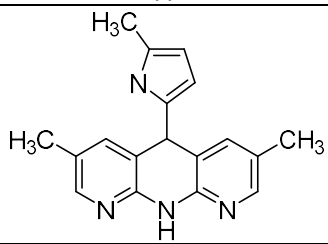
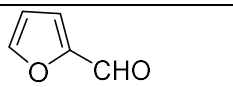
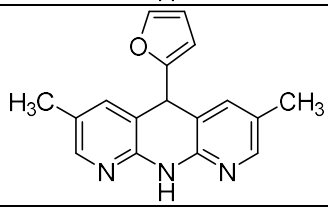
4a		
4b		
4c		
4d		
4e		

Biological Activity

In vitro Antibacterial activityand Antifungal activity: The synthesized compounds (4a-4e) were screened for antimicrobial activity and cup plate method was used for the determination zone of inhibition."Two-gram positive bacterial strains *Staphylococcus aureus, Bacillus anthracis,* two-gram negative bacterial strains *Pseudomonas aeruginosa and Escherichia coli* were used for determination of antibacterial activity. Two fungal strains *C. albicans* and *A. niger* were used for determination of antifungal activity. Streptomycin and Fluconazole were used as standard for antibacterial and antifungal activity respectively. DMSO was used as solvent control. Nutrient broth and Sabourd dextrose broth were used as Culture Media for bacteria and fungi respectively".

"Sterile nutrient broth/ sabourd dextrose broth plates were prepared, by pouring the sterile agar into petri dishes in aseptic conditions. 0.1 ml of each standardized test organism were spreaded into agar plates. Holes were prepared by using a sterile borer of diameter 6 mm. The test drug as well as the standard drug and the solvent control were placed in each hole separately. Then the plates were maintained at 4 °C for 1 h to allow the diffusion of solution into the medium. All the bacterial plates were incubated at 37 °C for 24 h and fungal plates at 25°C for 48 h. The zone of inhibition was measured in mm" [37-41].

In-silico **prediction of absorption and drug likeness:** To perform an in silico SwissADME analysis, one must begin by accessing the SwissADME web tool, which is freely available online athttps://www.swissadme.ch/. This tool, developed by the Swiss Institute of Bioinformatics, is designed to predict a wide range of pharmacokinetic properties, drug-likeness parameters, and medicinal chemistry features of small molecules. Before initiating the analysis, it is essential to have the chemical structure of the compound of interest, preferably in the form of a SMILES (Simplified Molecular Input Line Entry System) notation. Swiss ADME processes the molecular data and returns a comprehensive report including physicochemical properties (such as molecular weight, topological polar surface area, number of rotatable bonds, etc.), lipophilicity (LogP values from various predictive models), water solubility, and pharmacokinetic parameters including gastrointestinal absorption, blood-brain barrier penetration, and P-glycoprotein substrate or inhibitor prediction. "Lipinski rule or rule of five is like that to be drug-like, a candidate should have less than five hydrogen bond donors (HBD), less than 10 hydrogen bond acceptors (HBA), a molecular weight of less than 500 Da, and a partition coefficient log P of less than 5. The aim of the *rule of five* is to highlight possible bioavailability problems if two or more properties are violated" [42-44].

Molecular Docking Study

Hardware and Software: Windows 10 (64-bit) operating systems with 4 GB RAM and 2.50 GHz Intel(R) Core(TM) i5-7200U processor was used for executing the docking process. PyRx version 0.8, available at https://pyrx.sourceforge.io/ was used to perform the docking in Auto Dock Vina Wizard. Autodock Tools 4.2.6 which is made accessible by the Scripps Research Institute at https://autodock.scripps.edu/, was used for preparing the proteins and for grid generation, Ligands were processed using Open babel and PyRx 0.8 and interaction poses of ligands were visualized and analysed using Discovery Studio Visualizer.

Selection of Target Proteins: The molecular docking studies were carried out on two microbial proteins for assessing antimicrobial potential. Targets S. aureus (PDB ID: 1JIJ) [43-44] and E. coli (PDB ID: 1KZN) were chosen [47-49].

Protein and ligand processing for docking

Protein Preparation: The crystal structures of target proteins (PDB ID 1JIJ - topoisomerase II, PDB ID 1KZN - E. coliwere downloaded from the RCSB-Protein Data Bank and the proteins were prepared using Autodock Tools 4.2.6. In this step, attached water molecules and bound heteroatoms/ligand were removed, polar hydrogens and Kollman charges were added, the charge was spread equally over all atoms and residues were checked for missing atoms if any. The prepared PDB files were then converted to the PDBQT format for executing the next step.

Ligand Processing: Ligands in smiles format were converted to sdf files and 3D coordinates for all ligands were generated using Open Babel using command line. The 3D structure data files were processed in PyRx using UFF energy minimization and then converted to PDBQT format (autodock detectable format).

Grid Generation: The grid box was first set over attached ligands using AutoDock Tools and then manually adjusted to desired

dimensions in PyRx. The grid dimensions were set as -11.857 x 13.512 x 87.379 $Å^3$ keeping number of points as 25 in X, Y, Z direction for PDB ID: 1KZN and 20.562 x 30.804 x 35.946 $Å^3$ keeping number of points as 25 in X, Y, Z direction for PDB ID:5D6P.

Docking and visualization of results: The docking was implemented in Vina Wizard of PyRx Tool, using exhaustiveness of 8 and the resultant out files were split into individual pose files. These files and the protein structure were then taken for visualization of interactions using Maestro Visualizer academic version [50-53].

RESULTS AND DISCUSSION

The one-pot synthesis of polyhydroquinoline derivatives was successfully carried out via a multicomponent reaction strategy involving substituted 2-aminopyridines, and aldehydes in the presence of alcohol and under optimized reaction conditions. The structures of the synthesized polyhydroquinoline derivatives were confirmed by spectroscopic techniques such as ^1H NMR and LCMS. Elemental analysis (C, H, N) was in good agreement with the theoretical values, further supporting the proposed structures.

was assessed through agar well diffusion assay at a concentration of 1000 µg/mL. The zone of inhibition (measured in mm) against a panel of microbial strains including *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger*was compared with standard drugs streptomycin (antibacterial) and fluconazole (antifungal). The results are summarized below. Among all synthesized compounds, compound 4a demonstrated the most potent antibacterial activity, particularly against *B. anthracis* (31 mm) and *S. aureus* (30 mm), closely approaching the inhibition zones exhibited by streptomycin (34 mm and 33 mm, respectively). The efficacy of 4a against *P. aeruginosa* (28 mm) and *E. coli* (27 mm) was also notable, indicating a broad-spectrum antibacterial potential. Compounds 4b to 4e showed a gradual decline in antibacterial activity, correlating with the molecular docking results which showed a decrease in binding affinity from 4a to 4e. Compound 4b maintained good activity (zones between 24–29 mm), whereas 4c, 4d, and 4e displayed moderate to mild activity (zones ≤ 23 mm), suggesting a structure-activity relationship (SAR) trend influenced by specific substitutions on the polyhydroquinoline core. These results indicate that the polyhydroquinolinederivatives synthesized in this study have promising potential for the development of novel antimicrobial

Table 5.1. Antimicrobial Activity of Title compounds (4a-4e)

Compound (1000 µg/ml)	Zone of Inhibition (mm)					
	S. aureus	*B. anthracis*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*
Streptomycin	33	34	31	30	-	-
Fluconazole	-	-	-	-	28	30
4a	30	31	28	27	24	26
4b	27	29	25	24	20	22
4c	23	23	21	19	19	18
4d	24	23	21	19	17	20
4e	21	22	19	18	16	18

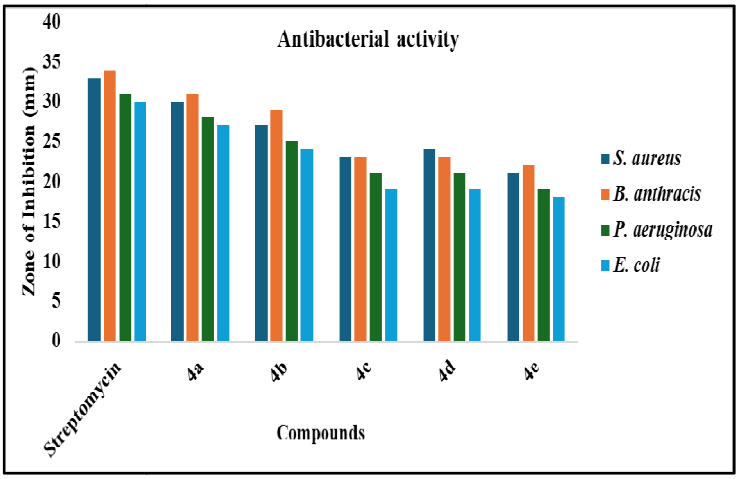


Figure 5.1. Antibacterial activity (4a-4e)

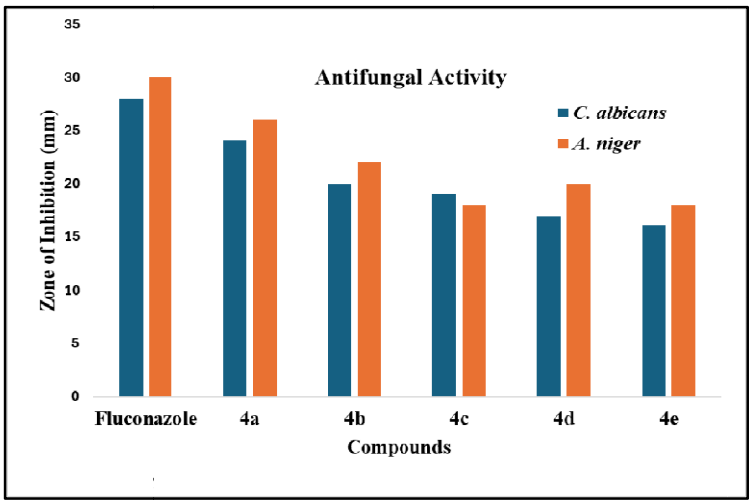


Figure 5.2. Antifungal activity (4a-4e)

agents, especially against resistant bacterial strains. Future studies, including ADMET testing and experimental antimicrobial assays, will be necessary to fully evaluate the therapeutic potential of these compounds.

ADME analysis: The synthesized polyhydroquinoline derivatives (4a–4e) were evaluated for their drug-likeness using computational tools to predict physicochemical properties, gastrointestinal (GI) absorption, and Lipinski's rule of five compliance. All compounds exhibited molecular weights within the acceptable range for oral drug candidates (≤500 Da). Compound 4a had the highest molecular weight (344.37 Da), indicating the presence of bulkier substituents, while compound 4c had the lowest (276.34 Da), suggesting a comparatively lighter framework. The number of rotatable bonds ranged from 1 to 2, indicating limited molecular flexibility which may enhance receptor binding specificity. Hydrogen bonding capacity, crucial for solubility and molecular interactions, was assessed through the number of H-bond donors and acceptors. All compounds contained one hydrogen bond donor and 2–4 acceptors, which align well with Lipinski's criteria, promoting favorable pharmacokinetic behavior. TPSA values ranged between 50.17 Å² and 87.39 Å². Values below 140 Å² generally predict good intestinal absorption, and indeed, all compounds showed high GI absorption in silico. Compound 4a, with the highest TPSA (87.39 Å²), remained well within the optimal range, while compounds 4c–4e exhibited lower TPSA values (~50 Å²), which may enhance passive membrane permeability. Log Po/w (iLOGP), an indicator of lipophilicity, ranged from -3.79 to 2.89. Most compounds showed moderate lipophilicity, which is favorable for oral bioavailability. Compound 4d exhibited a notably negative log Po/w value (-3.79), suggesting a highly hydrophilic nature, which may affect membrane permeability and bioavailability but can be advantageous for solubility and reduced nonspecific binding. Importantly, all five compounds fully complied with Lipinski's Rule of Five, with zero violations, indicating excellent drug-likeness and a high probability of oral bioavailability. This compliance underscores their potential as viable drug candidates.

Molecular docking study*:* To evaluate the potential inhibitory interactions of the synthesized polyhydroquinoline derivatives (4a–4e), molecular docking studies were performed against the crystal structure of the target protein (PDB ID: 1JIJ and 1KZN). In docking with 1JIJ, Compound 4a exhibited the most favourable binding affinity (-11.9 kcal/mol), significantly surpassing streptomycin (-8.0 kcal/mol) and other derivatives. This suggests a stronger interaction and potentially higher inhibitory efficiency of compound 4a against the target protein. Compounds 4b, 4d, and 4c also showed good binding affinities, with values ranging from -8.7 to -9.3 kcal/mol, indicating moderate binding potential. Compound 4e, while showing a slightly lower binding energy (-8.5 kcal/mol), still performed better than the standard drug streptomycin. All compounds formed numerous hydrophobic contacts with essential residues such as TYR170, GLY38, GLN174, ARG88, and ASP80indicating strong anchoring within the active site of the target. Notably, compound 4a interacted with a wider range of key amino acids, including THR42, GLN190, and ASP195, which are critical for the functional modulation of the target. Hydrogen bonding further contributed to ligand-receptor stability. Compound 4a formed a hydrogen bond with residue TPT75 (possibly a structural or ligand residue within the pocket), enhancing its specificity and orientation. Other compounds, especially 4b–4e, consistently formed hydrogen bonds with ASP40, a conserved active site residue, suggesting a common binding mode. Compound 4e uniquely formed dual hydrogen bonds with ASP40 and LYS84, reinforcing its potential despite its lower binding affinity. Streptomycin, used as a standard, showed moderate interaction energy (-8.0 kcal/mol) and formed multiple hydrogen bonds with residues such as ASP40, GLY38, GLN196, and ASP195. However, compared to the synthesized ligandsparticularly 4aits lower affinity suggests that polyhydroquinoline derivatives may offer improved binding potential and possibly better inhibitory profiles.

Table 5.2. *In silico* Drug Likeness and absorption

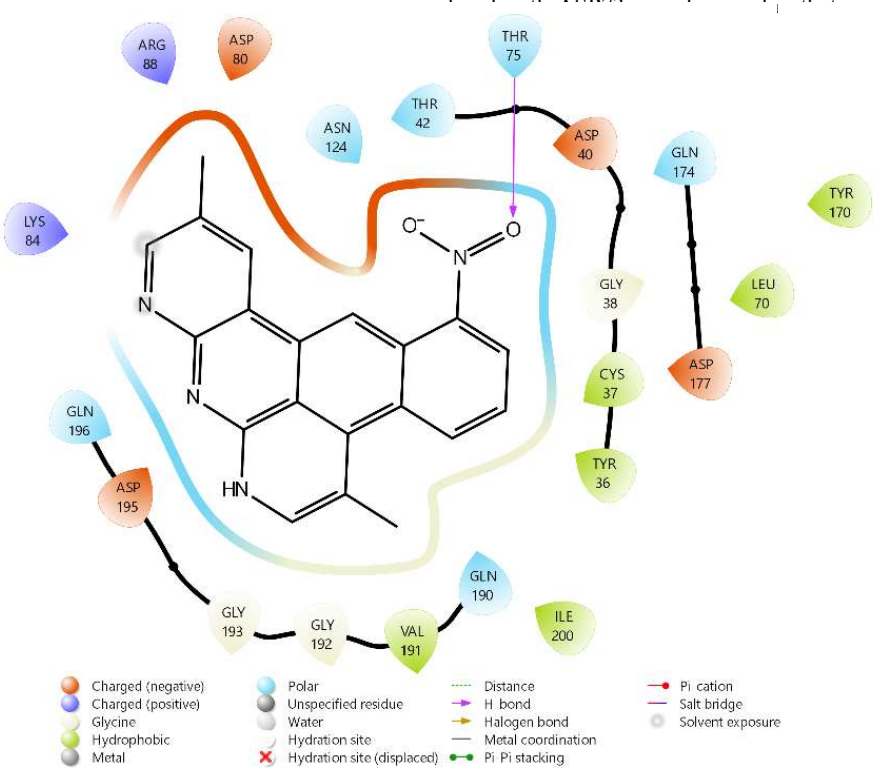
Comp	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	TPSA (Å²)	Log Po/w (iLOGP)	GI Absorption	Lipinski Violations
4a	344.37	2	4	1	87.39	2.73	High	0
4b	327.83	1	2	1	66.05	2.89	High	0
4c	276.34	1	3	1	50.17	2.22	High	0
4d	289.35	1	3	1	50.70	-3.79	High	0
4e	277.32	1	3	1	50.95	2.50	High	0

Table 5.3. Molecular Docking Study of Compounds 4a-4e with PDB id 1JIJ

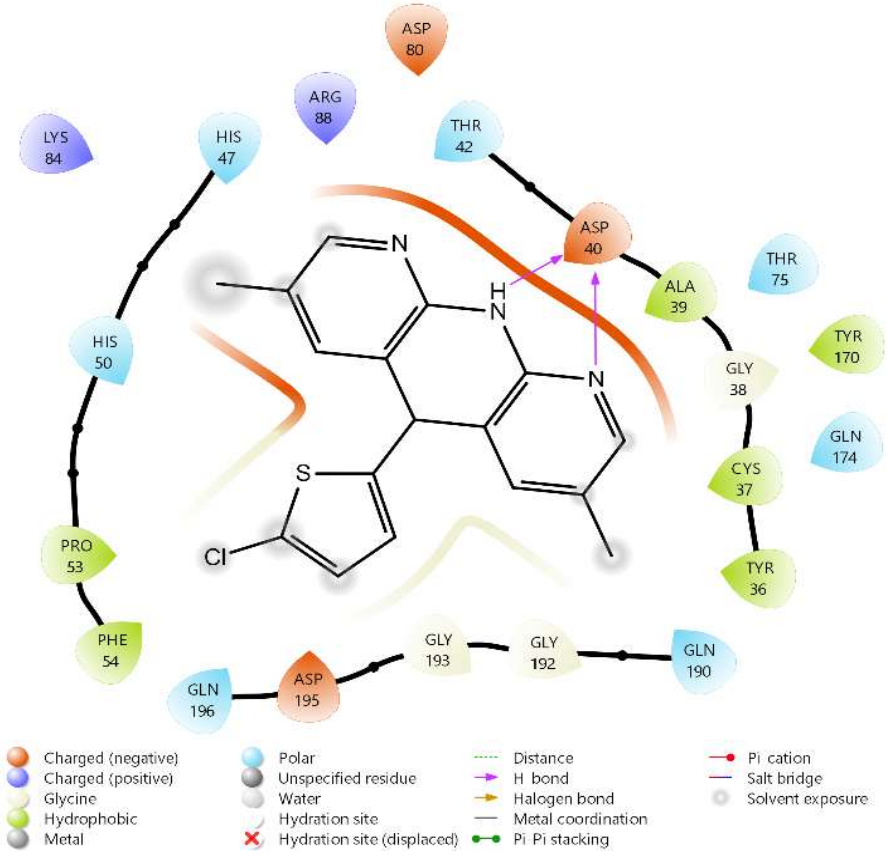
Ligand	Binding Affinity	Hydrophobic Interactions	H-bond
4a	-11.9	ASP40, GLY38, CYS37, TYR36, GLN174, ASP177, LEU70, TYR170, THR42, ILE200, GLN190, VAL191, GLY192, GLY193, ASP195, GLN196, LYS84, ARG88, ASP80, ASN124.	TPT75
4b	-9.1	THR42, ALA39, GLY38, CYS37, TYR36, THR75, TYR170, GLN174, GLN190, GLY192, GLY193, ASP195, GLN196, PHE54, PRO53, HIS50, LYS84, HIS47, ARG88, ASP80.	ASP40
4c	-8.7	ALA39, GLY38, CYS37, TYR36, GLN190, GLN174, GLY192, GLY193, ASP195, GLN196, LYS84, ARG88, THR42, HIS47, ASP80, PRO53, TYR170, THR75.	ASP40
4d	-9.3	ALA39, THR75, GLY38, TYR170, GLY38, CYS37, TYR36, GLN190, GLN174, GLY192, GLY193, APS195, GLN196, PHE54, PRO53, HIS50, LYS84, HIS47, ARG88, THR42.	ASP40
4e	-8.5	ARG88, HIS47, HIS50, THR42, ALA39, GLY38, ASN124, TYR170, THR75, TYR36, ASP177, GLN190, LEU70, GLN174, ASP80.	ASP40, LYS84
Streptomycin	-8	HIS50, PRO53, THR42, ALA39, CYS37, SER82, GLY83, LYS84, SER194, GLY193, ILE221, PRO222, LEU223, VAL224, PHE232, HIS47.	GLY49, ASSP40, GLY38, TYR170, ASP80, GLN196, ASP195

In docking with 1KZN, among all the tested compounds, compound 4a showed the highest binding affinity (-9.9 kcal/mol), suggesting the strongest interaction with the active site of the 1KZN protein. The affinity of 4a was significantly better than that of streptomycin (-7.0 kcal/mol), indicating potential for stronger biological activity. The binding affinities of compounds 4b to 4e ranged between -8.1 and -8.4 kcal/mol. Although lower than 4a, they still demonstrated better or comparable binding strength than the reference compound.

These values suggest the polyhydroquinoline derivatives, especially compound 4a, could serve as promising lead molecules for further biological evaluation. All compounds exhibited substantial hydrophobic interactions with key residues within the binding pocket, including VAL43, ALA47, GLU50, ARG76, GLY77, ILE78, PRO79, VAL120, THR165, and ARG136. These interactions stabilize the ligand within the active site and contribute significantly to overall binding energy. Compound 4a stood out due to its unique hydrogen



4a



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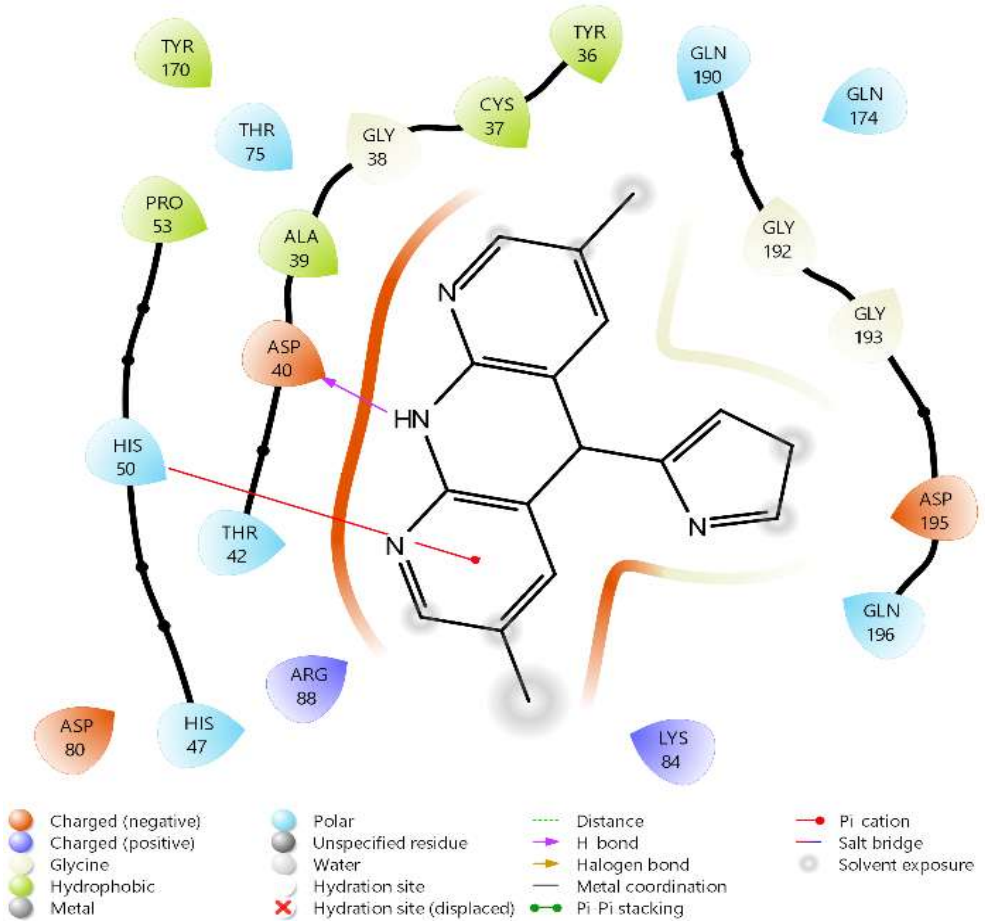
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ASP 40
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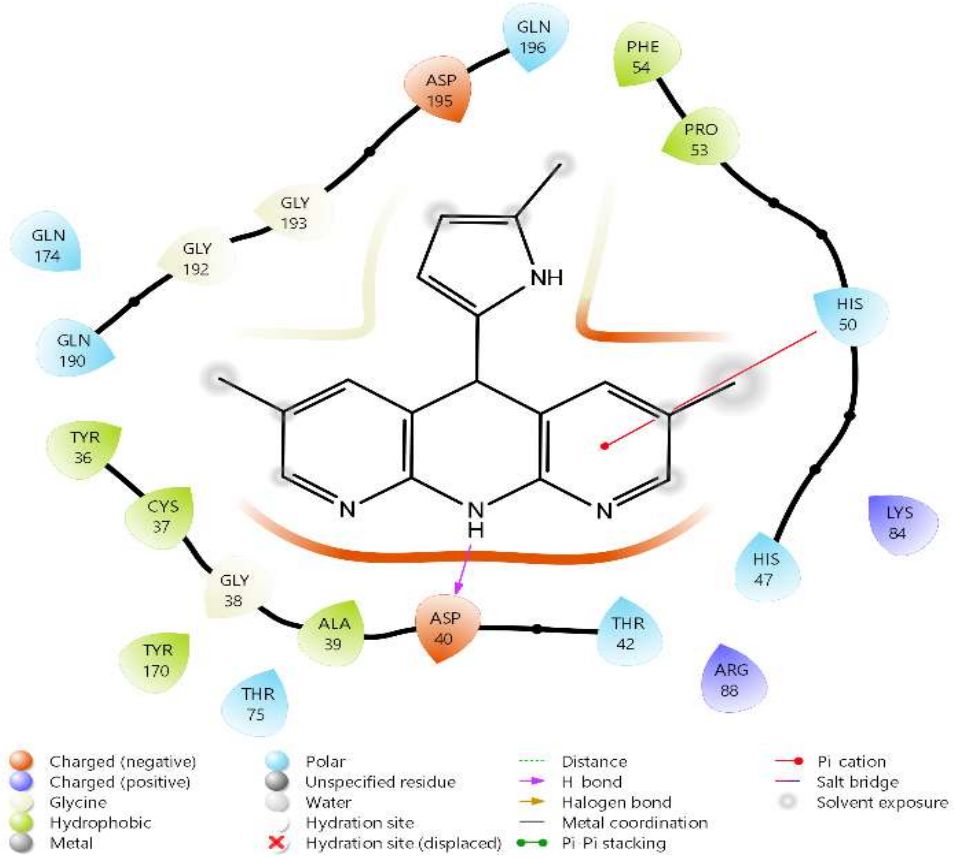
ASP 195
THR 42
GLN 196
ARG 88
ASP 80
HIS 47
LYS 84
Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H bond
Halogen bond
Metal coordination
Pi Pi stacking
Pi cation
Salt bridge
Solvent exposure

4c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ASP 40
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THR 75
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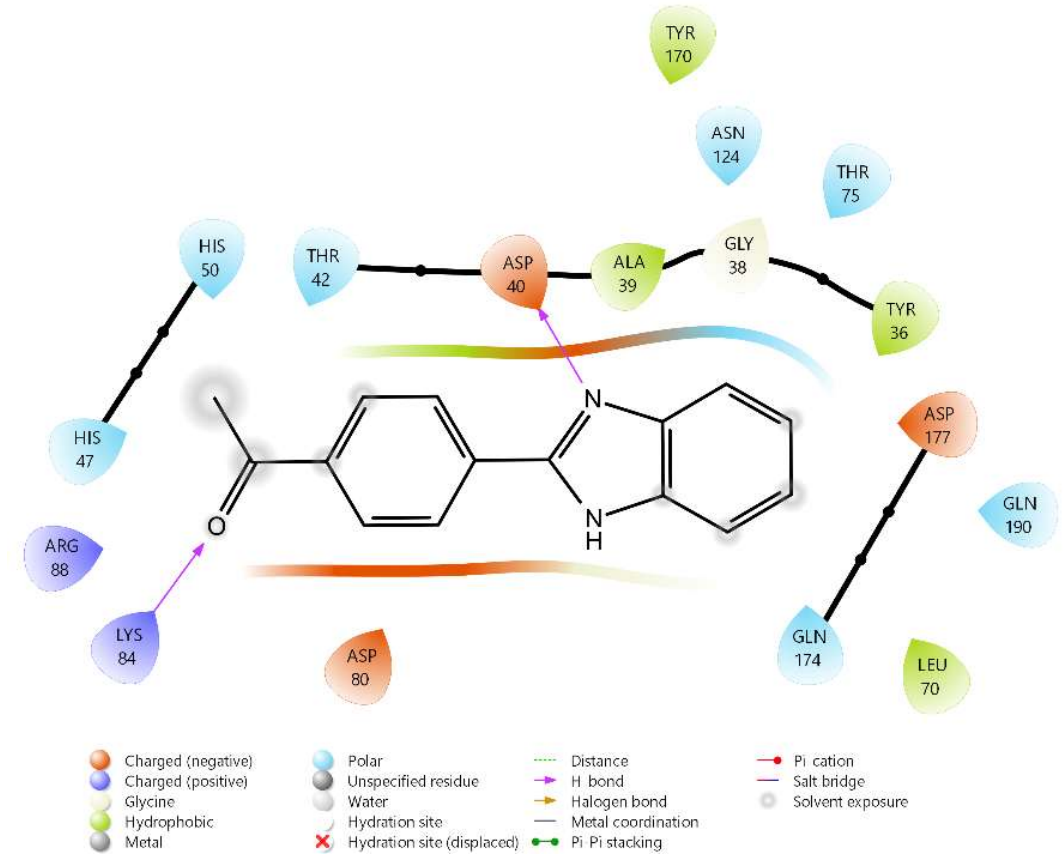
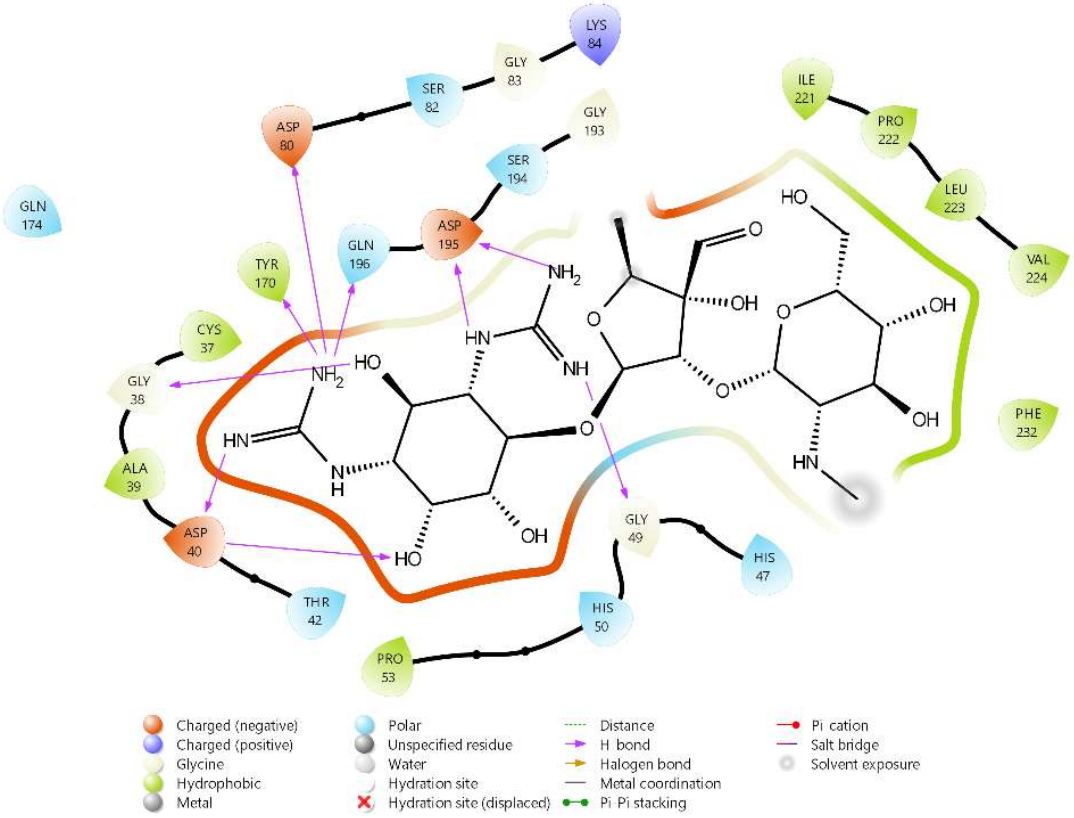
Pi cation
Salt bridge
Solvent exposure

4d



4e

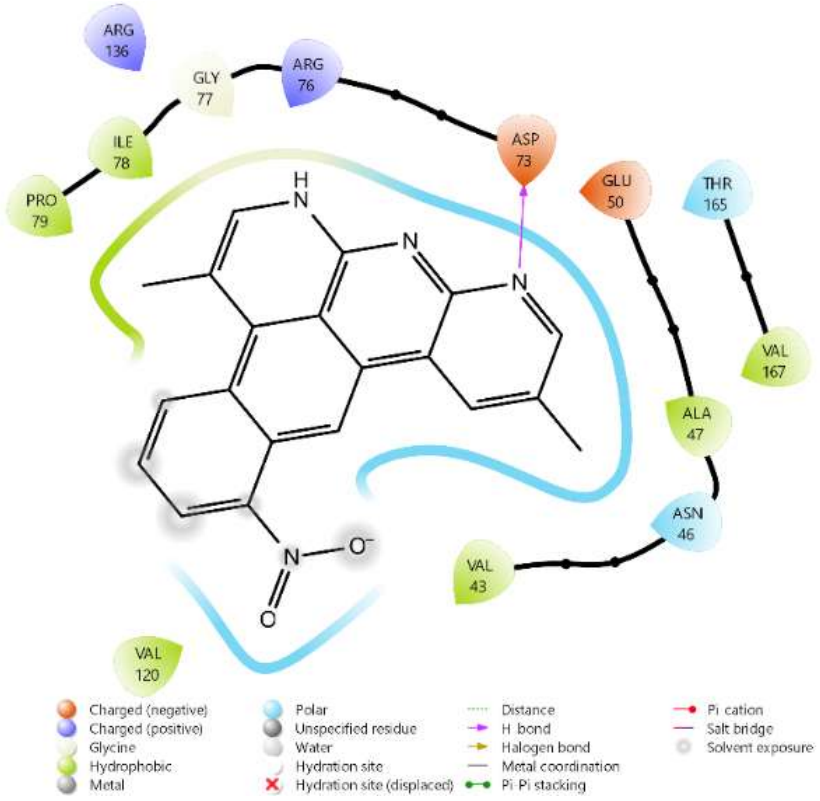


Streptomycin

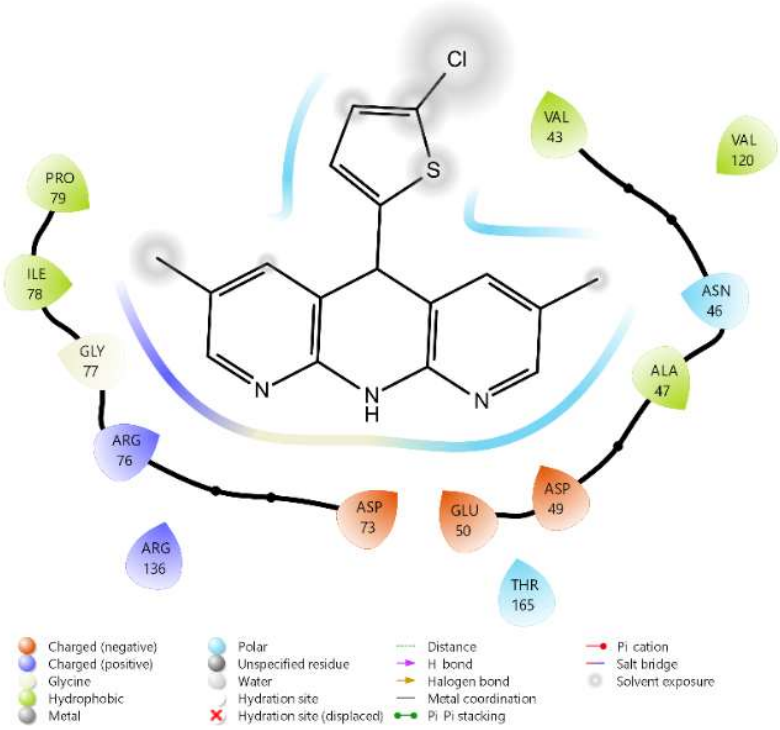
Figure 5.3. Binding Interactions of Compounds 4a-4e with PDB id 1JIJ

Table 5.4: Molecular Docking Study of Compounds 4a-4e with PDB id 1KZN

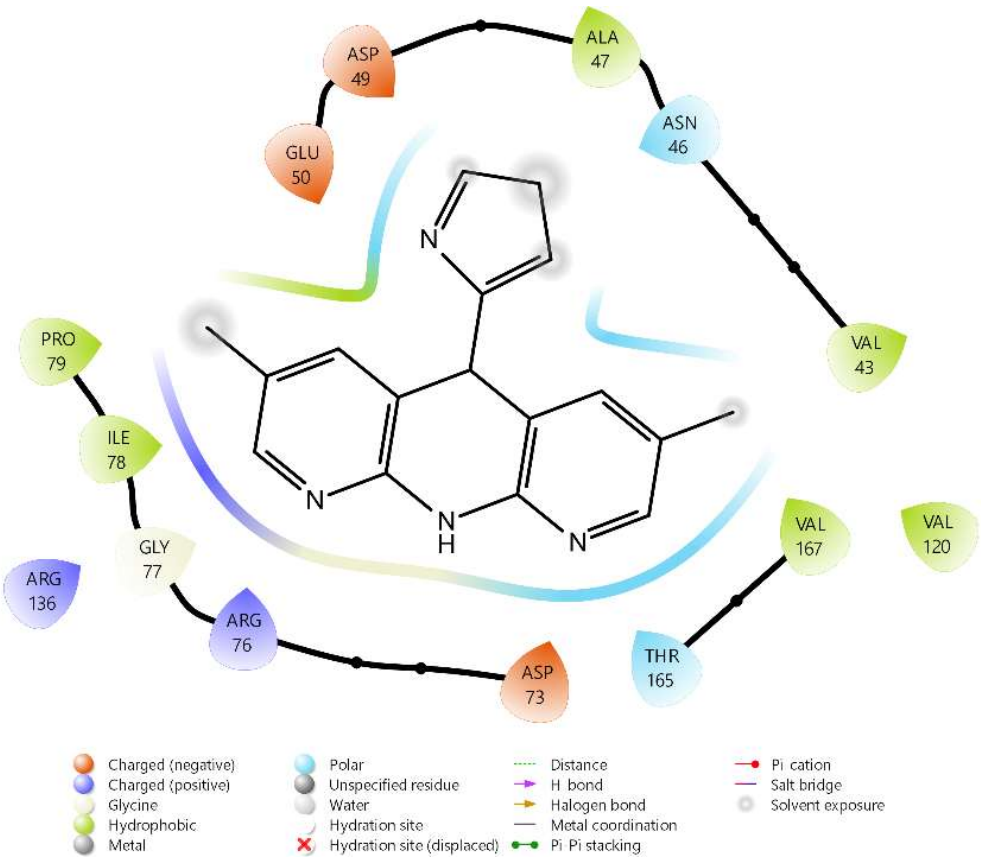
Ligand	Binding Affinity	Hydrophobic Interactions	H-bond
4a	-9.9	ARG136, THR165, VAL167, VAL120, VAL43, ASN46, ALA47, GLU50, ARG76, GLY77, ILE78, PRO79.	ASP73
4b	-8.4	PRO79, ILE78, GLY77, ARG76, ASSP73, GLU50, ASP49, ALA47, ASN46, VAL43, VAL120, THE165, ARG136.	
4c	-8.3	PRO79, ILE78, GLY77, ARG76, ASP73, GLU50, ASP49, ALA47, ASN46, VAL43, VAL120, ARG136, THR165, VAL167.	
4d	-8.2	VAL43, ASN46, ALA47, ASP49, GLU50, ARG76, GLY77, ILE78, PRO79, VAL120, ARG136, THR165, VAL167.	ASP73
4e	-8.1	VAL43, ASN46, ALA47, ASP49, GLU50, ASP73, ARG76, GLY77, ILE78, PRO79, VAL120, ARG136, THR165, VAL167.	
Streptomycin	-7	GLU42, ASP45, ALA47, ASP49, GLU50, ALA53, ARG76, ILE78, GLY117, GLY119, VAL120, SER121, THR165.	ASN46



4a



4b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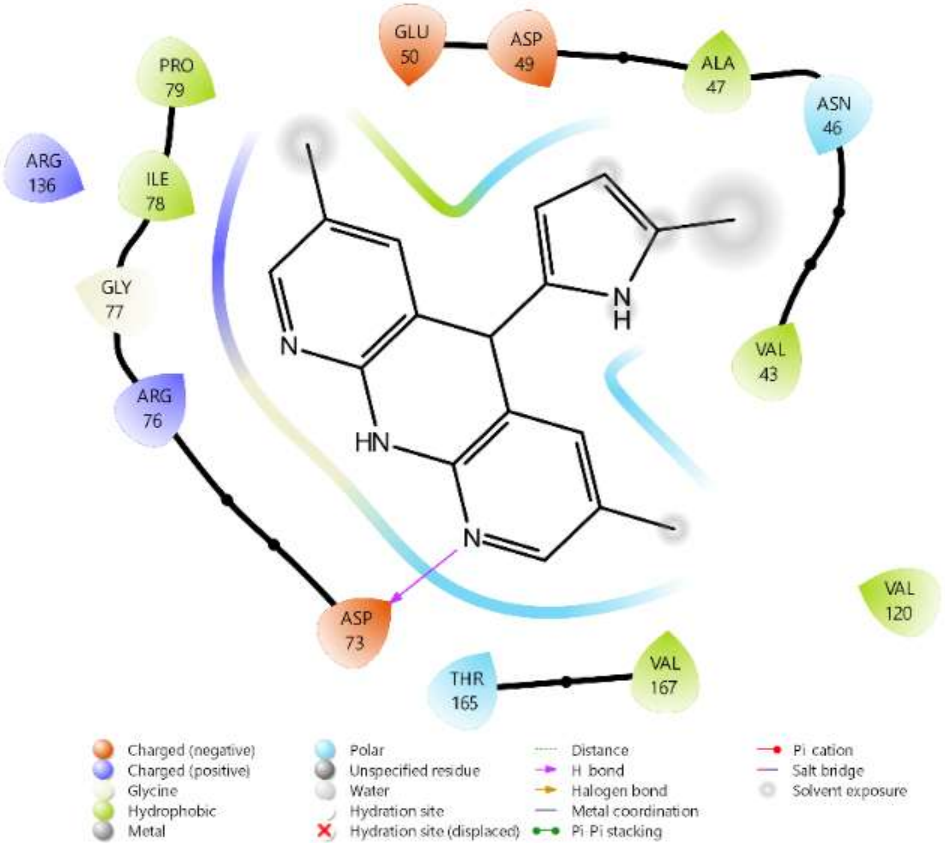
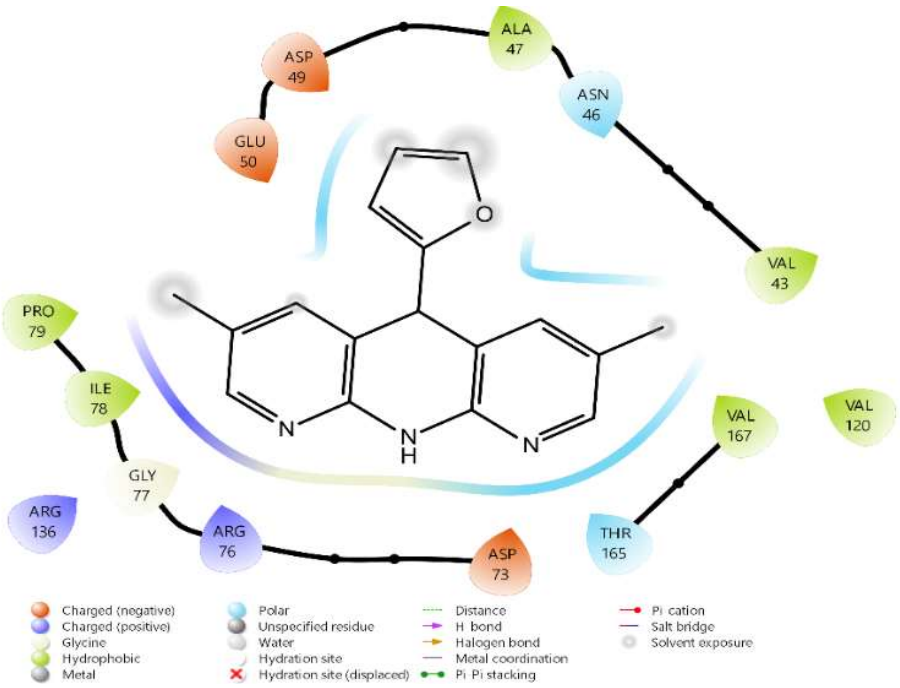
ALA 47
GLU 50
ASN 46
PRO 79
VAL 43
ILE 78
VAL 167
VAL 120
GLY 77
ARG 136
ARG 76
THR 165
ASP 73
N
N
H
N
Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H bond
Halogen bond
Metal coordination
Pi Pi stacking
Pi cation
Salt bridge
Solvent exposure

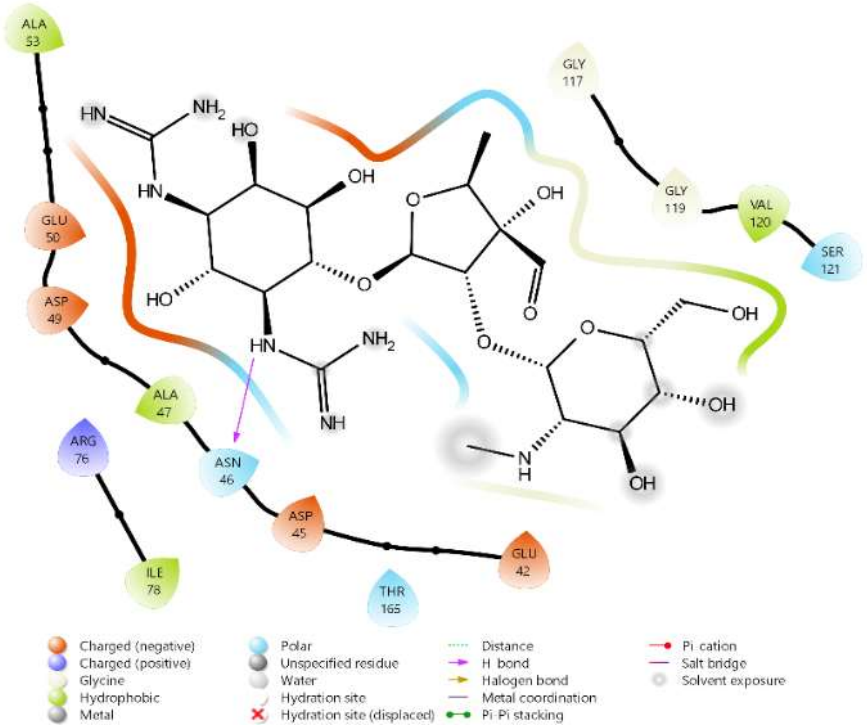
4c


GLU 50
ASP 49
ALA 47
PRO 79
ASN 46
ARG 136
ILE 78
GLY 77
VAL 43
ARG 76
N
H
HN
N
ASP 73
VAL 120
THR 165
VAL 167
Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H bond
Halogen bond
Metal coordination
Pi Pi stacking
Pi cation
Salt bridge
Solvent exposure

4d



4e



Streptomycin

Figure 5.4. Binding Interactions of Compounds 3a-3i with PDB id 1KJN

Overall, compound 4a, combines favourable physicochemical properties, excellent docking results, and strong antimicrobial activity, emerges as the most promising lead compound for further drug development.

CONCLUSION

In this study, a series of novel polyhydroquinoline derivatives (4a–4e) were synthesized using a one-pot green synthetic approach. The synthesized compounds were characterized and The in vitro antimicrobial screening further confirmed the computational predictions, with compound 4a demonstrating the most potent activity against both bacterial (*S. aureus*, *B. anthracis*, *P. aeruginosa*, *E. coli*) and fungal (*C. albicans*, *A. niger*) strains. Further synthesised compounds are subjected to in silico molecular docking studies against selected bacterial and fungal protein targets (PDB IDs: 1JIJ and 1KZN). Among the tested derivatives, compound 4a exhibited the highest binding affinity and strong molecular interactions with key amino acid residues, indicating significant binding efficiency and target specificity. These findings highlight the therapeutic potential of the polyhydroquinoline scaffold as a lead pharmacophore for the development of broad-spectrum antimicrobial agents.

Future Work: Overall, this research demonstrates the potential of green synthetic strategies in generating pharmacologically relevant molecules. The combined computational and experimental findings suggest that Schiff base derivatives, especially compound 4a, are

promising candidates for future development as antimicrobial agents. Further pharmacological and mechanistic studies are warranted to explore their full therapeutic potential.

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Gurjar VK, Pal DI. Recent developments and multiple biological activities available with 1, 8-polyhydroquinoline derivatives: a review. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2019;11(1):17-37.

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