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Design, Synthesis, Molecular Docking Studies and Antimicrobial Profiling of 7-Nitroquinazoline Derivatives against *Staphylococcus aureus* (MRSA)

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The alarming increase in antibiotic resistance contributes to the growing risk posed by *Staphylococcus aureus* (MRSA) in the worldwide healthcare sector. To address the challenge, this study designed, synthesized and evaluated novel quinazoline derivatives, specifically 7-nitroquinazolines, for their antimicrobial efficacy against *Staphylococcus aureus* (MRSA). Molecular docking studies revealed that compounds **8a** and **8b** exhibited superior binding affinity to the protein 1T2W, with binding energies of -9.6 kcal/mol and -8.8 kcal/mol, surpassing ciprofloxacin. The derivatives demonstrated favourable pharmacokinetic properties, including moderate lipophilicity, optimal polarity and good water solubility. Compound **8b** shows a potent minimum inhibitory concentration (MIC) of 31.1 µg/mL against *S. aureus* (MRSA ATCC6538), outperforming ciprofloxacin. These findings indicate that compound **8b** and related derivatives hold promise as novel therapeutic agents against MRSA, warranting further research to combat the growing issue of antibiotic resistance.

Keywords: 7-Nitro-quinazoline derivatives, Docking, ADME, Antimicrobial activity.

INTRODUCTION

The rapid emergence of antimicrobial-resistant bacteria (AMR) has recently become a pressing public health concern. The alarming rise of drug-resistant strains of microbes, fungi, viruses and parasites has significantly compromised the efficacy of existing antimicrobial treatments, creating a critical need for innovative solutions. This highlights the imperative for a sustained and intensive search for novel antimicrobial agents to combat the growing threat of AMR and restore the effectiveness of antimicrobial therapies [1,2].

The potentially dangerous bacterium *Staphylococcus aureus* is a common cause of methicillin resistance, which causes significant pain for individuals all around the world [3-5]. Despite being inherently treatable, the management of these illnesses has been severely impacted by the swift emergence of multi-drug resistance, rendering traditional treatments increasingly ineffective [6,7]. The WHO has recently classified MRSA as a high risk due to its significant threat, ranking it among the 12 critical bacteria that pose a danger to human health [8-10]. The escalating resistance of pathogens to current treatments and the surge in hospital-acquired and community-based infections have created a vital need to identify and develop novel antibiotics for use in clinical and community settings [11-23].

The diverse structural landscape and versatile chemical reactivity of heterocyclic compounds have made them an attractive and promising class of molecules to design and develop novel antimicrobial agents [24]. Quinazolinones have emerged as a promising class of compounds in our relentless quest for new antibiotics. Owing to their remarkable spectrum of biological activities, which encompass antimicrobial, antifungal, anticancer, anti-HIV and analgesic properties, making them versatile and attractive scaffolds for drug development [25-30], Recently, there has been a surge in focus on leveraging the quinazolinone core to design and synthesize new antimicrobial drugs [31,32].

Quinazolin-4(3*H*)-one, a derivative of quinazoline, has been identified as a potent antimicrobial agent, effective against a broad spectrum of pathogens, including fungi and bacteria. Its mechanism of action involves disrupting cellular membrane integrity, inhibiting protein synthesis, Interfering with DNA replication and repair and restricting biofilm formation [33].

Sortase A, a crucial enzyme, plays a significant role in the infection of various infections from bacteria in the breathing pathway, circulation, epidermis and tissues, primarily caused by *S. aureus* (MRSA) (Gram-positive) bacteria. Sortase A facilitates the anchoring of virulence-associated proteins to the bacterial cell surface. Due to its essential role in bacterial virulence, Sortase A has been a promising drug target for several decades. Inhibiting Sortase A activity disrupts the attachment of MRSA to host cells, ultimately alleviating infection. In this study, we utilized newly synthesized new substituted 7-nitro quinazoline derivatives to investigate the binding cavity of *S. aureus* Sortase A using the Autodock Vina docking software to elucidate the molecular mechanisms of Sortase A inhibition and identify potential therapeutic leads [34].

EXPERIMENTAL

The melting points of synthesized compounds were determined by employing the open capillary method and are uncorrected. ^{1}H and ^{13}C NMR spectra of the synthesized derivatives were acquired in Agilent technologies (Bruker Advance Neo 400 MHz Spectrometer) using solvent DMSO. A Shimadzu GCMS-QP 1000 EX mass spectrometer was used to record the mass spectra at 70 eV.

Synthesis of (2Z)-2-benzylidenehydrazine-1-carboxamide (3): A mixture of hydrazide carboxamide (**2**, 0.01 M) and sodium acetate (0.02 M) in 15-20 mL distilled water was stirred in a flat-bottomed flask followed by the addition of benzaldehyde (**1**, 0.01 M). The resulting precipitate product was filtered and recrystallized from hot ethanol. The product was obtained as a white or off-white powder with 86.90% yield.

Synthesis of 5-phenyl-1,3,4-oxadiazol-2-amine (4): Compound **3** (0.01 M) and sodium acetate (0.02 M) in 30-40 mL of glacial acetic acid was stirred continuously. Bromine (0.7 mL) was taken in 5 mL of glacial acetic acid and then added slowly, with the mixture stirred for 1 h. The reaction mixture was then poured onto crushed ice and the resulting solid product was separated and recrystallized from hot ethanol. The product was obtained as a white or off-white powder with 86% yield.

Synthesis of 2-methyl-7-nitro-4*H*-3,1-benzoxazin-4-one (6): 2-Amino-4-nitrobenzoic acid (**5**, 0.01 M, 1.8 g) was refluxed in acetic anhydride under anhydrous conditions for 4 or 3 h. The excess acetic anhydride was removed upon completion resulting in the desired product.

Synthesis of 2-methyl-7-nitro-3-(5-phenyl-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one (7): A mixture of compounds **4** and **6** (0.01 M) in 10 mL of glacial acetic acid was refluxed for 4 h. After cooling, the mixture was poured onto crushed ice, filtered, thoroughly washed with cold distilled water and recrystallized from hot ethanol. The product was obtained as a yellow powder with a yield of 78%. ^{1}H NMR (400 MHz, DMSO) δ ppm: 2.49 (3H, s), 7.25-7.46 (3H, s), 7.43 (dddd, *J* = 7.8, 7.4, 1.1, 0.4 Hz), 7.52 (tt, *J* = 7.4, 1.5 Hz), 7.74 (4H, s), 7.89 (dd, *J* = 8.2, 0.4 Hz), 7.90 (dtd, *J* = 7.8, 1.5, 0.4 Hz), 7.98 (dd, *J* = 8.2, 1.8 Hz), 9.14 (1H, dd, *J* = 1.8, 0.4 Hz). ^{13}C NMR (400 MHz, DMSO) δ ppm: 25.2 (s, 1C), 114.3 (s, 1C), 117.0 (s, 1C), 122.0 (s, 1C), 124.6 (s, 1C), 125.4 (s, 1C), 127.8 (s, 1C), 129.5 (s, 1C), 130.8 (s, 2C), 132.8 (s, 1C), 138.5 (s, 1C), 141.5 (s, 1C), 150.3 (s, 1C), 168.4 (s, 1C), 169.6 (s, 1C). Purity: 49.80%. Mass $C_{17}H_{11}N_5O_4$ *m/z* (%), calcd. (found): 349.30 (348.30, M-1).

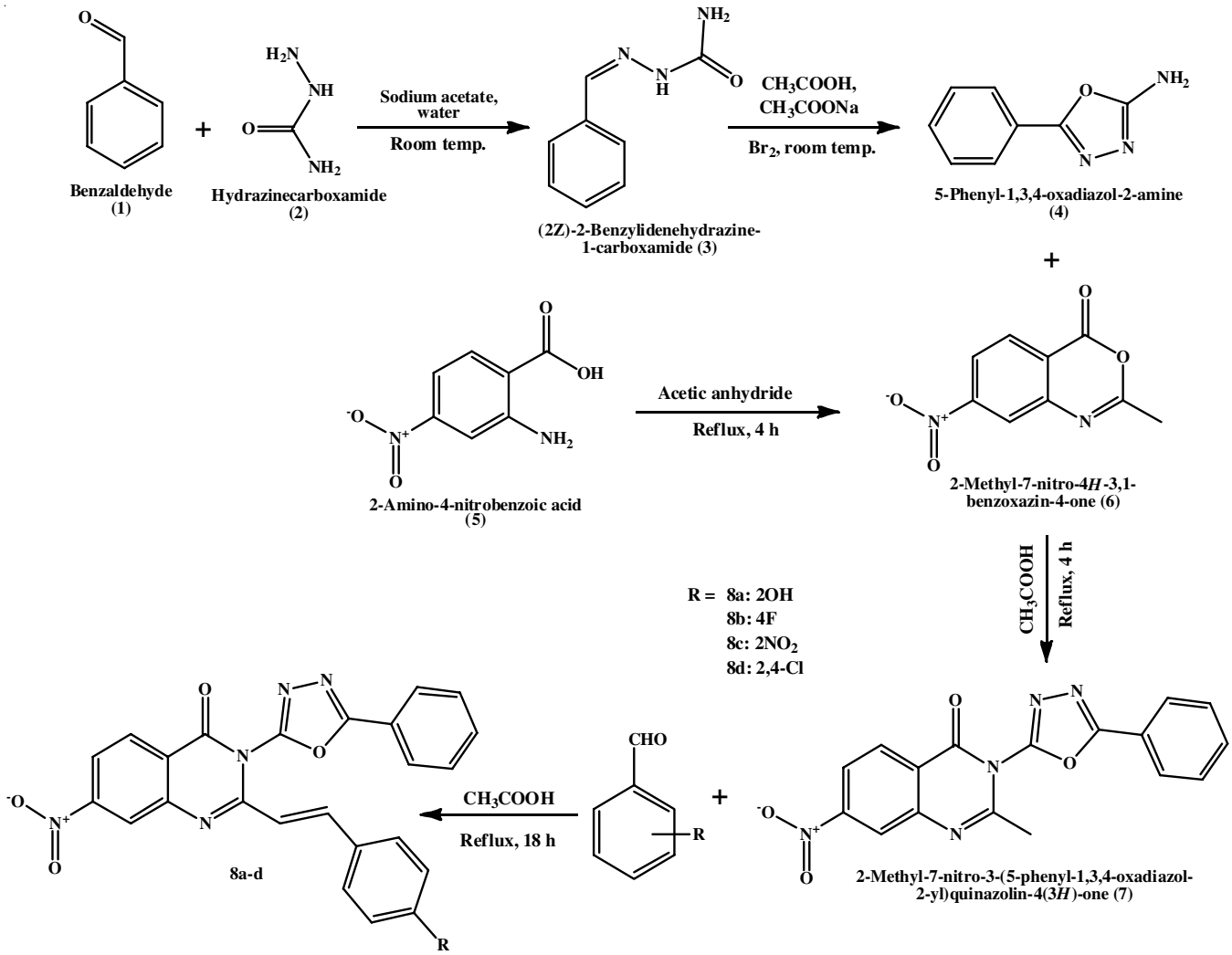
Synthesis of 7-nitroquinazoline derivatives (8a-d): An equimolar mixture of compound **7** (0.003 M) and aromatic aldehyde was refluxed in 1.3 mL of glacial acetic acid for 18 h, resulting in a formation of solid residue. The solid was recrystallized from hot ethanol (**Scheme-I**).

2-[(*E*)-2-(2-Hydroxyphenyl)ethenyl]-7-nitroquinazoline (8a): Light yellow, yield: 52%. ^{1}H NMR (400 MHz, DMSO) δ ppm: 6.84 (1H, ddd, *J* = 8.0, 1.1, 0.4 Hz), 7.02 (1H, d, *J* = 15.8 Hz), 7.25 (1H, ddd, *J* = 7.7, 7.6, 1.1 Hz), 7.36-7.58 (5H, s), 7.43 (dddd, *J* = 7.8, 7.4, 1.1, 0.4 Hz), 7.47 (d, *J* = 15.8 Hz), 7.47 (ddd, *J* = 8.0, 7.6, 1.4 Hz), 7.52 (tt, *J* = 7.4, 1.5 Hz), 7.92 (2H, s), 7.68 (dd, *J* = 8.2, 1.8 Hz), 7.76 (ddd, *J* = 7.7, 1.4, 0.4 Hz), 8.16-8.19 (3H, s), 7.90 (dtd, *J* = 7.8, 1.5, 0.4 Hz), 7.94 (dd, *J* = 8.2, 0.5 Hz)), 9.12 (1H, dd, *J* = 1.8, 0.5 Hz). ^{13}C NMR (400 MHz, DMSO) δ ppm: 114.7 (s, 1C), 114.8 (s, 1C), 117.3 (s, 1C), 122.6 (s, 1C), 123.8 (s, 1C), 126.3 (s, 1C), 126.7 (s, 2C), 126.9 (s, 1C), 127.8 (s, 1C), 128.1 (s, 1C), 128.3 (s, 1C), 128.5-128.7 (4C, s), 128.8-133.0 (s, 1C), 141.4 (s, 1C), 145.0 (s, 1C), 146.8 (s, 1C), 150.5 (s, 1C), 150.4 (s, 1C), 168.3 (s, 1C), 169.6 (s, 1C). Purity: 99.7%. Mass $C_{24}H_{15}N_5O_5$ *m/z* (%), calcd. (found): 453.40 (452.30, M-1).

2-[(*E*)-2-(4-fluorophenyl)ethenyl]-7-nitro-quinazoline (8b): Dark brown, yield: 58%. ^{1}H NMR (400 MHz, DMSO) δ ppm:7.00 (1H, d, *J* = 15.7 Hz), 7.36 (6H, s), 7.43 (dddd, *J* = 7.8, 7.4, 1.1, 0.4 Hz), 7.47 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.52 (d, *J* = 15.7 Hz), 7.52 (tt, *J* = 7.4, 1.5 Hz), 7.73 (dd, *J* = 8.5, 0.5 Hz), 7.74 (dd, *J* = 8.5, 1.8 Hz), 7.83 (ddd, *J* = 8.1, 1.5, 0.5 Hz), 7.88 (6H, s), 7.90 (dtd, *J* = 7.8, 1.5, 0.4 Hz), 9.14 (1H, dd, *J* = 1.8, 0.5 Hz). ^{13}C NMR (400 MHz, DMSO) δ ppm: 114.5 (s, 1C), 117.1 (s, 1C), 122.2 (s, 1C), 123.8 (s, 1C), 125.7 (s, 1C), 126.3 (s, 1C), 126.9 (s, 1C), 127.8 (s, 1C), 128.1 (s, 1C), 128.2 (s, 1C), 128.4 (s, 3C), 128.5 (s, 1C), 128.6 (1C, s), 133.1 (s, 1C), 138.1 (s, 1C), 141.6 (s, 1C), 146.8 (s, 1C), 155.2 (s, 1C), 161.3 (s, 1C), 168.4 (s, 1C), 169.5 (s, 1C). Purity: 97.4%. Mass $C_{24}H_{14}FN_5O_4$ *m/z* (%), calcd. (found): 455.39 (456.5, M+1).

2-[(*E*)-2-(2-nitrophenyl)ethenyl]-7-nitro-quinazoline (8c): Pale yellow, yield: 48%. ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.25 (1H, d, *J* = 15.7 Hz), 7.3 (3H, s), 7.43 (dddd, *J* = 7.8, 7.4, 1.1, 0.4 Hz), 7.52 (tt, *J* = 7.4, 1.5 Hz)), 7.70 (8H, s), 7.77 (ddd, *J* = 8.0, 7.9, 1.6 Hz), 7.80 (dd, *J* = 8.5, 0.5 Hz), 7.85 (ddd, *J* = 8.7, 7.9, 1.8 Hz), 7.90 (dtd, *J* = 7.8, 1.5, 0.4 Hz), 7.91 (ddd, *J* = 8.0, 1.8, 0.5 Hz), 8.04 (d, *J* = 15.7 Hz), 8.05 (ddd, *J* = 8.7, 1.6, 0.5 Hz), 8.12-8.14 (2H, s), 8.32 (dd, *J* = 1.8, 0.5 Hz), 9.23 (dd, *J* = 8.5, 1.8 Hz). ^{13}C NMR (400 MHz, DMSO) δ ppm: 114.6 (s, 1C), 117.1 (s, 1C), 122.2 (s, 1C), 124.7 (s, 1C), 124.8 (s, 1C), 125.4 (s, 2C),126.9 (s, 1C), 127.8 (s, 1C), 128.1 (s, 1C), 128.3 (s, 1C), 128.5-130.1 (4C, s), 132.2 (s, 1C), 132.5 (s, 1C), 135.0 (s, 1C), 145.0 (s, 1C), 146.8 (s, 1C), 148.0 (s, 1C), 150.4 (s, 1C), 168.4 (s, 1C), 169.5 (s, 1C). Purity: 71.8%. Mass $C_{24}H_{14}N_6O_6$ *m/z* (%), calcd. (found): 482.40 (481.3, M-1).

2-[(*E*)-2-(2,6-dichlorophenyl)ethenyl]-7-nitroquinazoline (8d): Pale yellow, yield: 52%. ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.09 (1H, d, *J* = 15.7 Hz), 7.56 (7H, s), 7.43 (dddd, *J* = 7.8, 7.4, 1.1, 0.4 Hz), 7.43 (dd, *J* = 8.2, 1.4 Hz), 7.49 (t, *J* = 8.2 Hz), 7.52 (tt, *J* = 7.4, 1.5 Hz), 7.58 (d, *J* = 15.7



Scheme-I: Synthetic scheme of 7-nitroquinazoline derivatives (**8a-d**)

Hz), 7.89 (4H, s), 7.90 (dtd, *J* = 7.8, 1.5, 0.4 Hz), 7.94 (dd, *J* = 8.5, 0.6 Hz), 7.95 (dd, *J* = 8.5, 1.8 Hz), 9.25 (1H, dd, *J* = 1.8, 0.6 Hz). ^{13}C NMR (400 MHz, DMSO) δ ppm:114.6 (s, 1C), 117.6 (s, 1C), 123.8 (s, 1C), 126.3 (s, 1C), 126.7 (s, 2C), 126.9 (s, 1C), 127.8 (s, 1C), 128.1 (s, 1C), 128.6 (s, 1C), 130.4 (s, 1C), 130.7 (s, 1C), 132.2 (s, 1C), 132.9 (s, 1C), 135.5 (s, 2C), 138.1 (s, 1C), 141.5 (s, 1C), 146.8 (s, 1C), 150.4 (s, 1C), 168.4 (s, 1C), 169.5 (s, 1C). Purity: 68.4%. Mass $C_{24}H_{13}Cl_2N_5O_4$ *m/z* (%), calcd. (found): 506.29 (507.31, M+1).

***In silico* Docking study:** Docking experiments were conducted using Auto Dock Vina to assess quinazoline derivatives' binding patterns and affinities. The crystal structure of the target protein, Sortase A (PDB ID: 1T2W), was obtained from the PDB [35]. LPETG peptide and water molecules were removed from the protein structure. Auto Dock Vina was used with default parameters to conduct the molecular docking simulations. Ligands were designed using Chemdraw software and the docking results were analyzed based on binding affinity (kcal/mol) and binding pose. The binding interactions between the ligands and Sortase A were examined and the critical residues involved in these interactions were identified to evaluate the potential of the ligands as Sortase A inhibitors [36].

ADMET prediction: ADME analysis of the synthesized compounds **8a-d** was conducted using the Swiss ADME web tool to evaluate their drug-likeness based on physico-chemical properties like lipophilicity, size, polarity, solubility, flexibility and saturation. These properties support the bioavailability radar, thoroughly assessing the compounds' potential for oral bioavailability and drug-like behaviour. The structures of synthesized compounds were sketched by Chemdraw and converted to SMILES format for prediction [37,38].

***In vitro* antimicrobial evaluation:** The synthesized molecules were screened for their antimicrobial potential against *S. aureus* (MRSA ATCC6538) by employing resazurin assay method [39]. The studies were conducted in a 96-well plate using sterile conditions. The hygienic plates with 96-wells were labeled and set up for the assay. In this, 100 mL of the test specimen at various concentrations 7.8, 15.6, 31.2, 62.5, 125, 250, 500 and 1000 µg/mL in DMSO followed by 50 µL of diluted nutrient broth and ciprofloxacin was used as the standard control. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of sample, showing a colour change. Absorbance was then measured at 600 nm using the ELISA method reader [40].

The following formula was used to calculate the inhibition (%):

$$\text{Inhibition (\%)} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

RESULTS AND DISCUSSION

Novel 7-nitroquinazoline derivatives was successfully synthesized, characterized and evaluated for antimicrobial activity. The synthesis began with the condensation of benzaldehyde with semicarbazide in the presence of sodium acetate to obtain (2Z)-2-benzylidenehydrazine-1-carboxamide (**3**). This was followed by its reaction with acetic acid and sodium acetate and subsequent bromination at room temperature for 1 h, yielding 2-amino-oxadiazole (**4**) through cyclization and tautomeric rearrangement. In this step, benzoxazine (**6**) was synthesized by cyclizing an appropriate precursor with acetic anhydride under reflux conditions for 4 or 3 h, which served as the dehydrating agent; in the subsequent step, 2-amino-oxadiazole (**4**) was refluxed in acetic acid for 4 h, resulting in the formation of 7-nitroquinazoline (**7**) through cyclization and condensation reactions. Finally, The final step involved refluxing subsituted benzaldehyde and 7-nitroquinazoline (**7**) in acetic acid for 18 h by following the condensation and cyclization reactions. The title compounds **8a-d** exhibited aromatic protons at δ 7.0-8.42 ppm and the -CH=CH shows the δ 6.92-7.34 ppm.

Molecular docking study: Molecular docking studies using Auto Dock Vina revealed that quinazoline derivatives exhibited high binding affinity towards Sortase A, surpassing ciprofloxacin, with binding capacity ranging from -8.5 to -10.2 kcal/mol. Binding pose analysis showed that the ligands interacted with critical active site residues, including Arg A197, Glu A105 and Ile A199 and 182, forming hydrogen bonds and hydrophobic interactions (Table-1, Figs. 1 and 2). These findings indicate the binding solid interactions between the quinazoline derivatives and Sortase A suggesting the potential inhibitory activity against the enzyme.

***In silico* prediction of physico-chemical properties, pharmacokinetics and drug-likeness profiles**: The ADME profile of the synthesized derivatives **8a-d** was evaluated using the Swiss ADME web-based tool, which predicted their physicochemical properties. The bioavailability radar (Fig. 3) indicated that the optimal ranges for these properties are lipophilicity (iLOGP3) between 2.24 and 3.25, polarity (TPSA) between 70-170 Å, moderate water solubility (Table-2) and no more than six rotatable bonds, all of which fall within the desirable "pink area" of the bioavailability radar, suggesting that the derivatives possess favourable drug-like properties.

Antimicrobial assay: The antimicrobial activity of compound **7** and its derivatives **8a-d** were evaluated against *S. aureus* (MRSA ATCC6538). The results revealed compound **7** and its derivatives (**8a-d**) manifest minimum inhibitory concentrations (MIC) between 62.5 µg/mL and 31.2 µg/mL. Compound

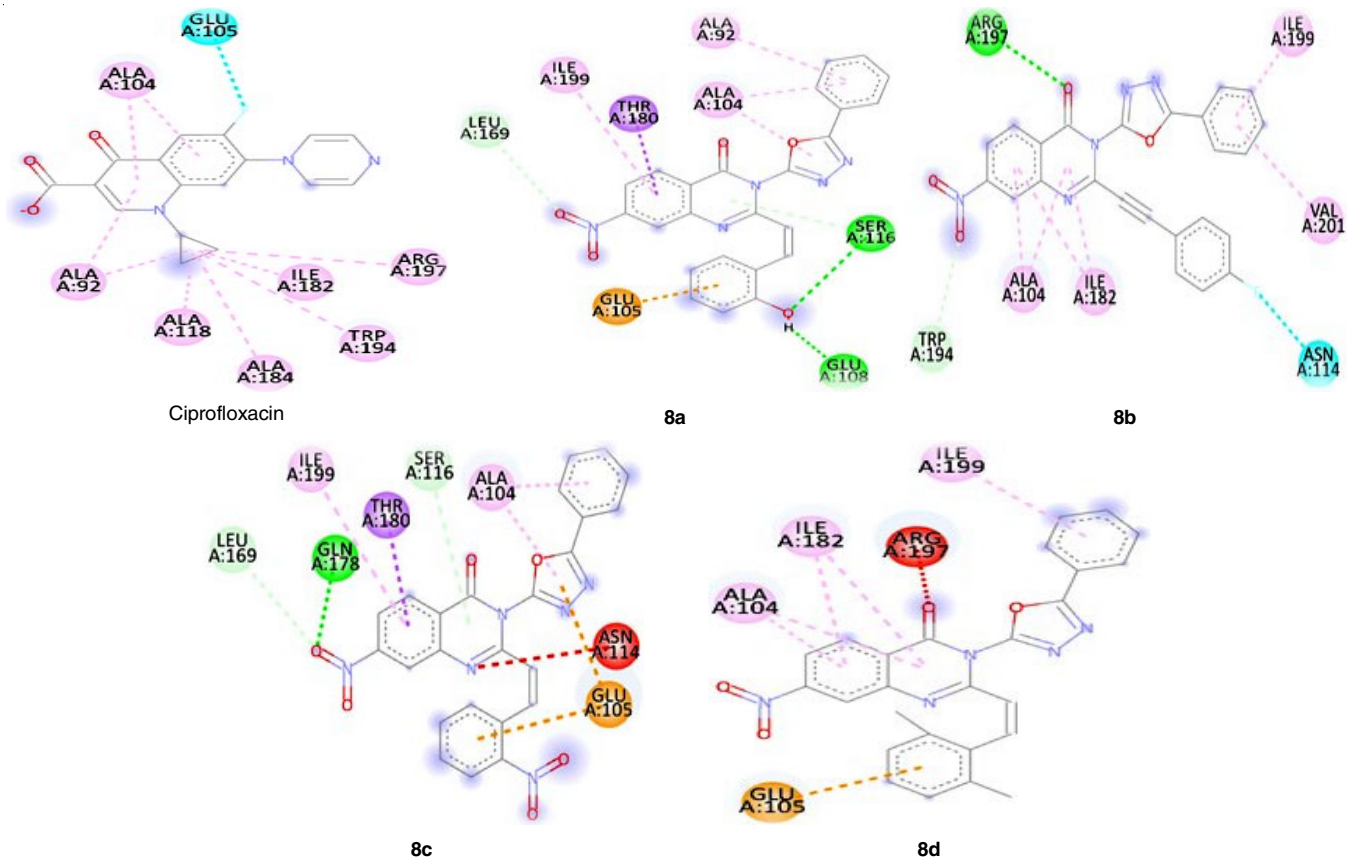


Fig. 1. Binding capacity of the newly synthesized compounds within the target receptor's binding pocket, highlighting the 2D interactions predicted by Autodock Vina docking simulations

TABLE-1
DOCKING SCORES AND INTERACTIONS OF COMPOUNDS (DERIVATIVES)
COMPARED WITH REFERENCE (STANDARD) DRUG CIPROFLOXACIN

Compound	Docking score (Kcal/mol)	Hydrogen bond interaction	Electrostatic interaction	Hydrophobic interaction
8a	-9.6	SER A:116, GLU A:108	LEUA:169, GLUA:105	ILE A:199, THR A:180, ALA A:104, ALA A:92
8b	-8.8	ARG A:197	TRP A:194, ASN A:114	ALA A:104, ILE A:182, VAL A:201, ILE A:199
8c	-8.7	GLN A:178	LEUA:169, GLUA:105, SER A:116	ILE A:199, THR A:180, ALA A:104, ASN A:114
8d	-8.4	–	GLUA:105	ILE A:199, ILE A:182, ALA A:104, ARG A:197
Ciprofloxacin	-6.7	–	GLUA:105, TRP A:194	ALA A:104, ALA A:92, ALA A:118, ILE A:182, ARG A:197, ALA A:184

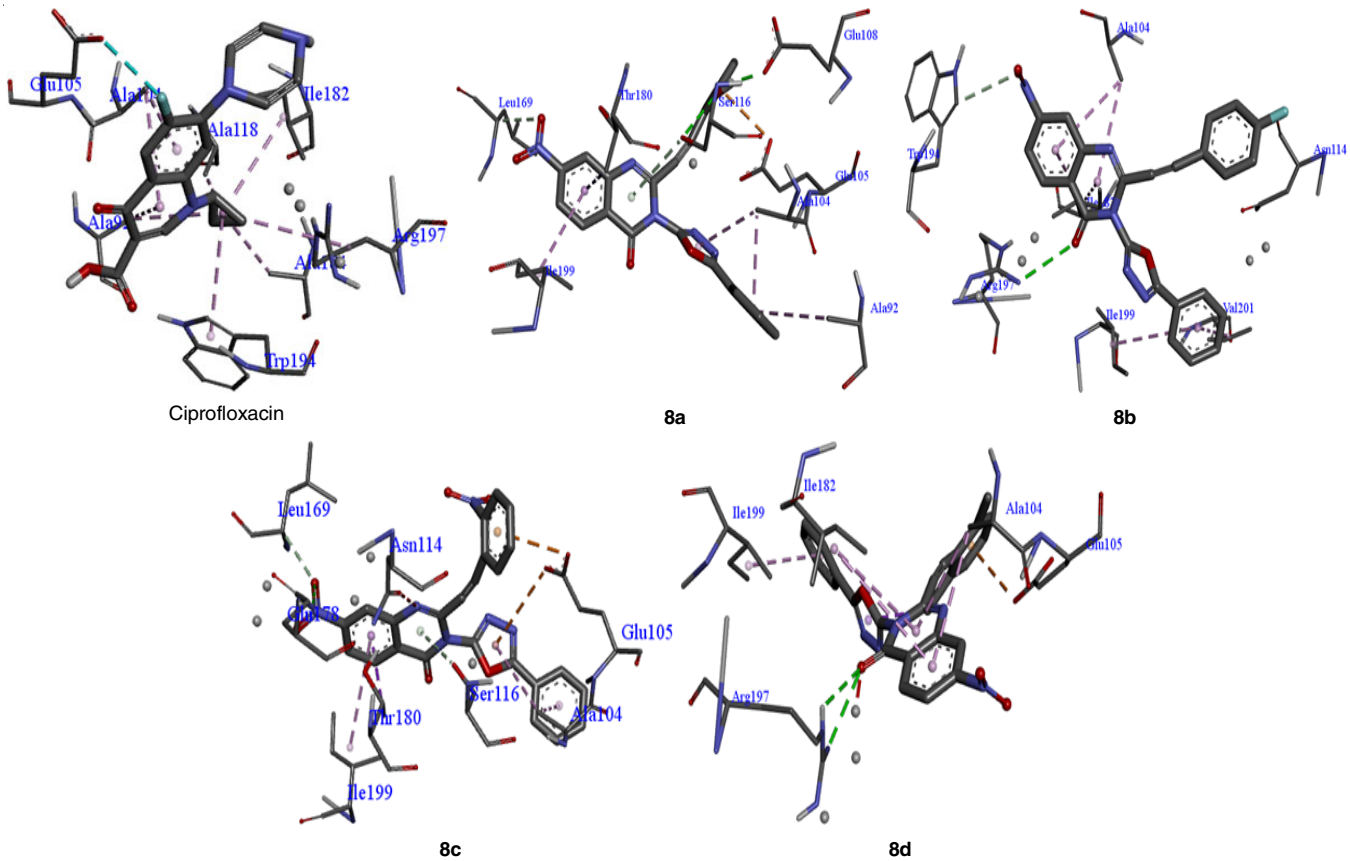


Fig. 2. 3D docking pose of the newly synthesized compounds at the target receptor's binding site, highlighting the predicted interactions with the binding pocket using Autodock Vina

TABLE-2
ADME PROPERTIES OF DESIRED COMPOUNDS (DERIVATIVES) AND STANDARD (CIPROFLOXACIN)

Compound	Lipophilicity (logo)	TPAS (Å^2)	G.I. absorption	B.B.B. Permeant	Water solubility
8a	2.73	139.8	Low	No	Moderately soluble
8b	3.10	119.6	Low	No	Moderately soluble
8c	2.51	165.4	Low	No	Moderately soluble
8d	3.23	119.6	Low	No	Poorly soluble
Ciprofloxacin	2.24	74.57	High	No	Very soluble

8b demonstrated the most potent antimicrobial activity, with a MIC value of 31.2 µg/mL, comparable to the standard antibiotic ciprofloxacin (Table-3). The results demonstrated that compound **8b** shows promise as a lead molecule for further research and development, highlighting the quinazoline derivative's potential as a new treatment agent against MRSA.

Conclusion

This study presents a novel series of 7-nitroquinazoline derivatives (**8a-d**) with antimicrobial activity against methicillin resistant *Staphylococcus aureus* (MRSA). Molecular docking studies revealed a high binding affinity of compounds **8a** and **8b** towards the 1T2W protein, with binding energies of -9.6

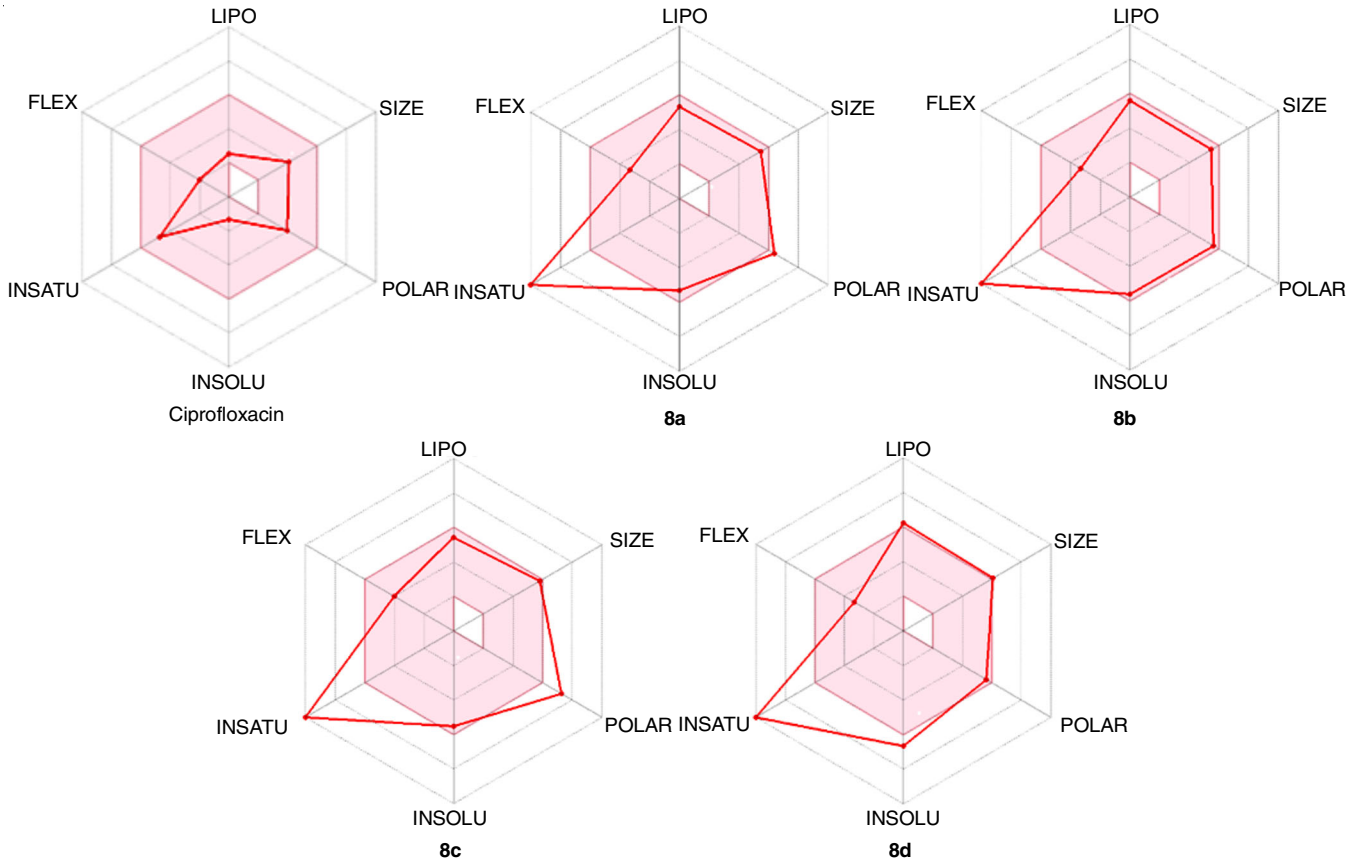


Fig. 3. ADME profile of synthesized derivatives (**8a-d**) and ciprofloxacin

TABLE-3
MIC (mg/mL) OF 7-NITRO-QUINAZOLINE DERIVATIVES AGAINST MRSA

Compound	*Staphylococcus aureus* (MRSA ATCC6538); % of Growth inhibition at different conc.							
	7.8 µg/mL	15.6 µg/mL	31.2 µg/mL	62.5 µg/mL	125 µg/mL	250 µg/mL	500 µg/mL	1000 µg/mL
7	–	–	–	8.92	6.23	55.27	53.71	64.50
8a	–	–	–	7.29	12.35	17.71	33.93	62.32
8b	–	–	8.73	16.34	12.72	12.91	41.35	62.94
8c	–	–	–	7.29	8.85	7.11	7.11	90.39
8d	–	–	–	5.55	6.11	7.04	7.79	9.85
Ciprofloxacin	–	–	11.35	12.85	47.97	61.88	66.87	73.67

kcal/mol and -8.8 kcal/mol, respectively, surpassing ciprofloxacin. The synthesized compounds exhibited favourable ADME properties, including moderate lipophilicity, acceptable polarity, moderate water solubility and fewer than six rotatable bonds. The biological evaluation showed that compound **8b** demonstrated a lower MIC of 31.1 µg/mL against MRSA, comparable to ciprofloxacin. These findings suggest that the synthe-*sized compounds, particularly **8b**, possess potential as novel therapeutic agents against MRSA.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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