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Original Article

# SYNTHESIS OF QUINOLINYL-OXADIAZOLE AS A POTENT ANTIBACTERIAL AGENT AND SA-FABI INHIBITOR

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**ABSTRACT**

**Objective:** Microbial resistance to currently marketed drugs is a serious problem worldwide and there is a vital need to develop novel antibiotics. Enoyl-ACP reductase (FabI) is essential for fatty acid biosynthesis and hence serves as an appealing target for antibacterials against methicillin resistant *S. aureus*. The present study focuses on the synthesis, antibacterial and saFab1 docking studies of three new series of quinoline derivatives: 5-[(quinolin-8-yloxy) methyl]-1,3,4-oxadiazole-2(3*H*)-thiones, N-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2oxyacetamides and 2-(oxyacetyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-ones with integrated ether linkages.

**Methods:** Three different substituted hydrazides were synthesized from substituted quinolinols. These hydrazides were allowed to undergo further reactions with carbon disulphide, 2,5-hexanedione and ethyl acetoacetate respectively to prepare 1,3,4-oxadiazole-2-thiones, N-substituted pyrrole acetamides and pyrazol-3-ones. The synthesized hydrazide derivatives were subjected to antimicrobial studies against *Staphylococcus aureus*. Docking studies were carried out using enoyl-ACP reductase crystal structure complexed with NADPH.

**Results:** 5-{[(2-methylquinolin-8-yl) oxy] methyl}-1, 3, 4-oxadiazole-2(3*H*)-thione (2b) with a methyl substituent on the quinoline ring was found to display significant antibacterial potential against *S. aureus.* Good binding interactions were observed in subsequent docking studies via formation of Fab1-$NAD^+$-2b ternary complex through hydrogen bonding and stacking interactions.

**Conclusion:** 1, 3, 4-oxadiazole-2(3*H*)-thione (2b) was found to exhibit promising antibacterial potential against *S. aureus*.

**Keywords:** Oxadiazole, Antibacterial, saFab1, Triclosan.

## INTRODUCTION

Antibiotics have turned the tide in terms of the treatment of various types of infectious diseases. But the evolution of antibiotic-resistant strains is of principally severe concern due to the biochemical fickleness of several bacteria and the over use of many of these antibiotics. Multidrug resistant bacteria have become a major public health crisis because existing antibiotics are no longer effective in many cases. Considering the rapid advance of multidrug resistance to the existing variety of marketed antibiotics, new approaches are immediately needed. In recent times very few novel antibiotics have been reported. Hence it is essential to discover antibiotics that act through the disruption of a novel target.

*Staphylococcus aureus* is a dangerous gram-positive pathogen that is readily transferred to immune-compromised patients [1, 2]. Methicillin-resistant *S. aureus* (MRSA) strains are unfortunately widespread [3] and the well-recognized resistance among *S. aureus* strains against penicillins is apparently totally because of the production of an inducible β-lactamase. The severity of this problem has been further added by the fact that antibiotics that have usually been drugs of last resort like vancomycin are becoming the first line of treatment of resistant infections [4, 5]. Thus, there is an urgent requirement for newer antibiotics to combat these continually adapting pathogens.

One strategy that targets the bacterial cell envelope involves the selective inhibition of the type II fatty acid biosynthesis pathway (FAS II) which consists of individual mono functional enzymes that are responsible for the endogenous production of lipids to be incorporated into the bacterial cell membrane. The final reduction in this pathway is catalyzed by the NAD (P) H-dependant trans-2-enoyl-ACP reductase (FabI), which plays a vital regulatory role. The *S. aureus* enoyl-ACP reductase (saFabI) is the only known FabI which has a determinant role in completing cycles of elongation in type II fatty acid synthase systems with a clear preference for NADPH that has garnered the most attention as an antibacterial target. The clinical success of FabI inhibitors, such as isoniazid and triclosan validates this enzyme as a striking dug target [6, 7]. Triclosan binds at the FabI active site and the replacement of the ether linkage in triclosan by a carbon bridge prevents the formation of a stable FabI-NAD (P)1-drug ternary complex which is a key factor for the antibacterial activity of FabI inhibitors.

The oxadiazole group has been demonstrated to bear an important application in medicinal chemistry with anticancer, antiinflammatory, antituberculosis, antimalarial and anti schistosomiasis properties [8]. A number of therapeutic agents such as HIV integrase inhibitor raltagravir [9], nitrofuran antibacterial furamizole [10], a potent peptide deformylase inhibitor BB-83698 [11], antihypertensive agents tiodazosin [12] and nesapidil [13] are based on 1,3,4-oxadiazole moiety. Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry with biological importance [14, 15]. The presence of pyrazole moiety in organic molecules has proved to play ubiquitous role in the field of pharmaceutical chemistry [16-22]. In the present study, we explore few quinoline derivatives with an incorporated ether linkage for their antibacterial and Sa-FabI inhibitory potential.

## MATERIALS AND METHODS

### General

Thin layer chromatography was performed using pre coated aluminium sheets with Aluchrosep silica Gel 60/UV254 and spots were visualized in UV chamber. The elemental analysis of the newly synthesized compounds was carried out in Flash thermo 1112 series CHN analyser.

The IR spectra in KBr pellets and $^1$H-NMR and $^{13}$C-NMR spectra with TMS as internal standard and DMSO-$d_6$ as solvent were recorded in a Schimadzu FTIR 8400S spectrophotometer and 400 MHz AV500 NMR spectrometer respectively. The mass spectrum was taken in a Schimadzu GCMS-QP5050 mass spectrometer. Melting points were determined by open capillary method and were uncorrected.

**Synthesis**

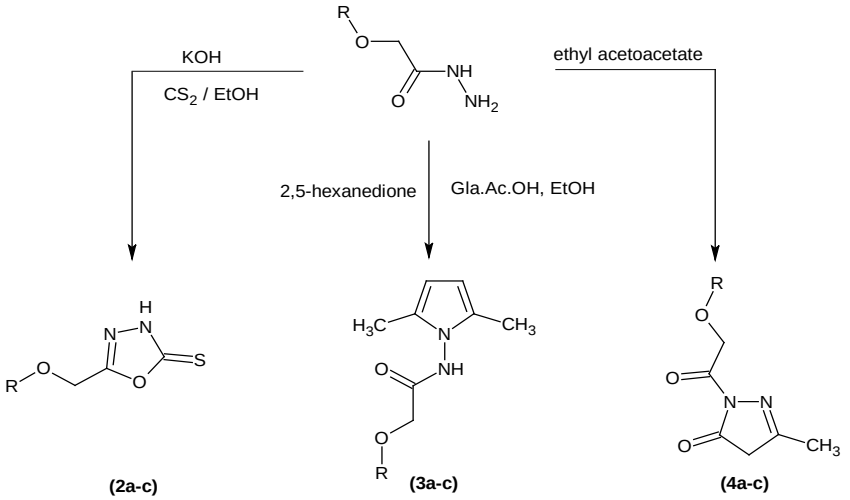
Three different substituted hydrazides were synthesized from substituted quinolinols by multistep reactions. Equimolar quantitities of substituted quinolinols and ethylchloroacetate was allowed to react in the presence of potassium carbonate for 18 h in dry acetone medium to give the ester. The ester obtained was further refluxed with hydrazine hydrate to give the corresponding hydrazides. The hydrazides were allowed to undergo further reactions to prepare 1, 3, 4-oxadiazole-2-thiones, N-substituted pyrrole acetamides and pyrazol-3-ones (Scheme-1).

**Synthesis of 5-[(substitutedquinolin-8-yloxy) methyl]-1, 3, 4-oxadiazole-2(3*H*)-thiones [2a-c]**

About 0.0038 mole of hydrazide was dissolved in a solution of 0.006 mol of KOH in 2 mL of water and 20 mL ethanol. To the above reaction mixture 2 mL carbon disulphide was added with stirring and refluxed for 8 h. Solvents were removed and the residue obtained was treated with water, filtered, dried and recrystallized from ethanol.

**5-[(quinolin-8-yloxy) methyl]-1, 3, 4-oxadiazole-2(3*H*)-thione [2a]**

Cream solid (53 %) m. p. 260 °C; $R_f$ = 0.225; IR (KBr) [$cm^{-1}$]: 3402 (N-H str.), 3055 (Ar. C-H str.), 1604 (C=N str.), 1180 (C=S str.), 1581 (Ar. C=C str.), 1257 (Ar. C-O-C asym. str.), 1103 (Ar. C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400 MHz: 5.23 (s, 2H, $OCH_2$), 7.31-8.21 (6H, Ar. H), 11.21 (brs, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 87.15, 114.90, 121.53, 123.72, 124.85, 128.24, 129.58, 135.67, 142.33, 142.24, 144.27, 155.20; MS ($FAB^+$): m/z (%): 259 $M^+$(100 %); Anal. Calcd. For $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.47; N, 16.22; found: C, 55.78; H, 3.48; N, 16.27.




| Comp. No. | R |
|---|---|
| **1a, 2a, 3a, 4a** | 8-quinolinyl |
| **1b, 2b, 3b, 4b** | 2-methyl-8-quinolinyl |
| **1c, 2c, 3c, 4c** | 5,7-dichloro-8-quinolinyl |

**Scheme 1**: **Synthesis of compounds (2a-c), (3a-c) and (4a-c)**

**5-{[(2-methylquinolin-8-yl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione [2b]**

Cream solid (63 %) m. p. 264 °C; $R_f$ = 0.61; IR (KBr) [$cm^{-1}$]: 3456 (N-H str.), 3062 (Ar. C-H str.), 2916 ($CH_3$ asym. str.), 2831 ($CH_3$ sym. str.), 1612 (C=N str.), 1180 (C=S str.), 1573 (Ar. C=C str.), 1226 (Ar. C-O-C asym. str.), 1110 (Ar. C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400 MHz: 2.66 (s, 3H, $CH_3$), 5.24 (s, 2H, $OCH_2$), 7.29-8.21 (5H, Ar. H), 11.21 (brs, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 20.03, 87.35, 115.29, 121.65, 122.94, 123.43, 128.24, 130.88, 136.50, 142.58, 144.67, 152.63, 153.29; MS ($FAB^+$): m/z (%): 273 $M^+$(100 %); Anal. Calcd. For $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.03; N, 15.38; found: C, 57.35; H, 4.04; N, 15.41.

**5-{[(5,7-dichloro-2-methylquinolin-8-yl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione [2c]**

Cream solid (66 %) m. p. 270 °C; $R_f$ = 0.48; IR (KBr) [$cm^{-1}$]: 3421 (N-H str.), 3139 (Ar. C-H str.), 1635 (C=N str.), 1184 (C=S str.), 1581 (Ar. C=C str.), 1218 (Ar. C-O-C asym. str.), 1103 (Ar. C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400 MHz: 5.29 (s, 2H, $OCH_2$), 7.45-8.29 (4H, Ar. H), 11.22 (brs, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 87.24, 121.93, 123.35, 129.03, 129.58, 130.43, 135.75, 138.18, 142.47, 144.25, 153.65, 154.28; MS ($FAB^+$): m/z (%): 328 $M^+$(100 %); Anal. Calcd. For $C_{12}H_7N_3O_2SCl_2$: C, 43.90; H, 2.13; N, 12.80; found: C, 44.05; H, 2.14; N, 12.84.

**Synthesis of N-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2 substitutedoxy acetamides [3a-c]**

About 0.0038 mol hydrazide in 10 ml ethanol was added to a mixture of 0.006 mol of acetonyl acetone and 1 mL glacial acetic acid. The reaction mixture was refluxed for 4 h, concentrated to half its volume and poured into 50 g crushed ice. Solid separated was filtered, washed with water and recrystallized from ethanol.

**N-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-(8-quinolinoloxy)acetamide [3a]**

White solid (66 %) m. p. 112 °C; $R_f$ = 0.46; IR (KBr) [$cm^{-1}$]: 3517 (N-H str.), 2916 ($CH_3$ asym. str.), 2846 ($CH_3$ sym. str.), 1689 (C=O str.), 1512 (Ar. C-C str.), 1249 (C-O-C asym. str.), 1118 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.95 (6H, $CH_3$), 5.07 (s, 2H, $OCH_2$), 5.63 (s, 2H, pyrrole), 7.31-8.89 (6H, Ar. H), 11.18 (s, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 19.96, 86.72, 93.90, 121.02, 123.14, 128.96, 129.35, 130.31, 132.55, 135.29, 138.20, 142.24, 153.38, 172.64; MS ($FAB^+$): m/z (%): 295 $M^+$(100 %); Anal. Calcd. For $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24; found: C, 69.40; H, 5.78; N, 14.28.

**N-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-(2-methyl-8-quinolinoloxy) acetamide [3b]**

White solid (72 %); m. p. 108-110 °C; $R_f$ = 0.48; IR (KBr) [$cm^{-1}$]: 3521 (N-H str.), 2908 ($CH_3$ asym. str.), 2854 ($CH_3$ sym. str.), 1695

(C=O str.), 1604 (Ar. C-C str.), 1257 (C-O-C asym. str.), 1106 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.94 (s, 6H, $CH_3$), 2.61 (s, 3H, $CH_3$), 5.09 (s, 2H, $OCH_2$), 5.64 (s, 2H, pyrrole), 7.33-8.89 (5H, Ar. H), 11.19 (s, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 19.82, 20.09, 87.03, 93.81, 114.57, 121.51, 121.89, 123.35, 128.20, 128.22, 129.55, 132.62, 133.04, 137.50, 143.09, 172.73; MS (FAB$^+$): m/z (%): 309 M$^+$(100 %); Anal. Calcd. For $C_{18}H_{19}N_3O_2$: C, 69.90; H, 6.15; N, 13.59; found: C, 70.17; H, 6.16; N, 13.65.

**N-(2,5-dimethyl-1H-pyrrol-1-yl)-2-(5,7-dichloro-8-quinolinoloxy) acetamide [3c]**

Yellowish brown solid (62 %); m. p. 158-160 °C; $R_f$ = 0.71; IR (KBr) [cm$^{-1}$]: 3509 (N-H str.), 2931 ($CH_3$ asym. str.), 2868 ($CH_3$ sym. str.), 1766 (C=O str.), 1581 (Ar. C-C str.), 1266 (C-O-C asym. str.), 1103 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.95 (s, 6H, $CH_3$), 5.09 (s, 2H, $OCH_2$), 5.64 (s, 2H, pyrrole), 7.31-8.79 (4H, Ar. H), 11.21 (s, N-H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 19.98, 87.12, 93.97, 121.82, 123.32, 129.05, 129.52, 130.44, 132.65, 135.71, 138.25, 142.37, 153.68, 172.75; MS (FAB$^+$): m/z (%): 364 M$^+$(100 %); Anal. Calcd. For $C_{17}H_{15}N_3O_2Cl_2$: C, 56.04; H, 4.12; N, 11.54; found: C, 56.23; H, 4.13; N, 11.58.

**Synthesis of 2-(substitutedoxyacetyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-ones [4a-c]**

About 0.0038 mol hydrazide was refluxed with 0.0038 mol of ethyl acetoacetate for 1 h with stirring. The resultant solution was allowed to cool to room temperature, washed thoroughly with ether to remove colored impurities, solid separated out was recrystallized from ethanol.

**5-methyl-2-[(quinolin-8-yloxy)acetyl]-2,4-dihydro-3*H*-pyrazol-3-one [4a]**

White solid (54 %); m. p. 156-158 °C; $R_f$ = 0.5; IR (KBr) [cm$^{-1}$]: 3155(Ar. C-H str.), 2977 (C-H asym. Str.), 2916 (C-H sym. str.), 1749, 1704 (C=O str.), 1242 (C-O-C asym. str.), 1118 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.85 (s, 3H, $CH_3$), 5.10 (s, 2H, $OCH_2$), 5.54 (s, 2H, pyrrole), 7.21-8.68 (6H, Ar. H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$) δ = 19.82, 46.00, 71.86, 117.76, 121.22, 125.1, 129.66, 130.78, 139.13, 142.02, 151.76, 155.5, 159.66, 172.70, 173.42; MS (FAB$^+$): m/z (%): 283 M$^+$(100 %); Anal. Calcd. For $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.59; N, 14.84; found: C, 63.84; H, 4.60; N, 14.89.

**5-methyl-2-{[(2-methylquinolin-8-yl) oxy] acetyl}-2,4-dihydro-3*H*-pyrazol-3-one [4b]**

Cream solid (84 %); m. p. 138-140 °C; $R_f$ = 0.44; IR (KBr) [cm$^{-1}$]: 3147 (Ar. C-H str.), 2977 (C-H asym. Str.), 2916 (C-H sym. str.), 1757, 1705 (C=O str.), 1250 (C-O-C asym. str.), 1119 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.86 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 5.12 (s, 2H, $OCH_2$), 5.55 (s, 2H, pyrrole), 7.33-8.68 (5H, Ar. H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$ δ = 19.82, 27.36, 45.89, 71.66, 117.36, 121.12, 126.06, 129.68, 130.58, 139, 142.09, 155.5, 159.61, 163.06, 172.79, 173.36; MS (FAB$^+$): m/z (%): 297 M$^+$(100 %); Anal. Calcd. For $C_{16}H_{15}N_3O_3$: C, 60.61; H, 5.05; N, 14.14; found: C, 60.81; H, 5.06; N, 14.20.

**2-{[(5,7-dichloroquinolin-8-yl)oxy]acetyl}-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one [4c]**

Cream solid (68 %); m. p.120-124 °C; $R_f$ = 0.46; IR (KBr) [cm$^{-1}$]: 3139 (Ar. C-H str.), 2985 (C-H asym. Str.), 2870 (C-H sym. str.), 1748, 1698 (C=O str.), 1296 (C-O-C asym. str.), 1103 (C-O-C sym. str.); $^1$H NMR [ppm] DMSO-$d_6$, 400MHz: 1.86 (s, 3H, $CH_3$), 5.18 (s, 2H, $OCH_2$), 5.54 (s, 2H, pyrrole), 7.36-8.67 (4H, Ar. H); $^{13}$C NMR, 400 MHz, DMSO-$d_6$) δ = 19.86, 46.09, 71.75, 125.17, 125.94, 128.34, 132.80, 133.26, 136.24, 142.02, 151.76, 156.29, 159.66, 172.7, 173.40; MS (FAB$^+$): m/z (%): 352 M$^+$(100 %); Anal. Calcd. For $C_{15}H_{11}N_3O_3Cl_2$: C, 51.14; H, 3.13; N, 11.93; found: C, 51.25; H, 3.14; N, 11.96.

**Antimicrobial studies**

The antimicrobial activity of synthesized compounds was examined by Disc Diffusion Method. Nutrient agar media was prepared and plated on petriplates. Plates were inoculated by swab culturing using stock culture. Different discs were dipped in the solution of hydrazide derivatives and placed in inoculated plates using sterile forceps and were gently pressed. Plates were further incubated for 24 h at 37 °C for Gram+ve *Staphylococcus aureus*. The experiments were performed in duplicates. After incubation, diameter of an inhibition zone was measured. Tetracycline (500 µg/ml) was used as the standard drug.

**Docking studies**

The enoyl-ACP reductase crystal structure complexed with NADPH (Dihydro-Nicotinamide-Adenine-Dinucleotide Phosphate) with a corresponding entry code 4CUZ was recovered from the PDB database (www. pdb. org). Surflex dock module of sybyl ver 1.7 was used (Tripos Inc. St. Louis, USA) and protomol were generated based on already complexed ligand residues (*i.e.*1-(3-amino-2-methylbenzyl)-4-hexylpyridine-2(1*H*)-one) for carrying out docking studies. The proprietary software is licensed to Manipal Institute of Technology, Manipal University, India. The best favorable conformation in terms of highest docking score was chosen [23].

**RESULTS AND DISCUSSION**

The formation of cyclized product 5-[(substitutedquinolin-8-yloxy)methyl]-1,3,4-oxadiazole-2(3*H*)-thiones (2a-c) were confirmed by the IR absorption peaks observed at 1604 cm$^{-1}$ and 1180 cm$^{-1}$ due to C=N and C=S stretching vibrations. The $^1$HNMR spectra showed a singlet at 5.23 ppm corresponding to $OCH_2$ protons and a broad peak at 11.21 ppm due to proton attached to nitrogen. The carbonyl stretch in the IR spectra of compounds 3a-c was observed at around 1690 cm$^{-1}$.

The formation of pyrrole ring was confirmed by the singlet observed at 5.6 ppm in the $^1$HNMR spectra. The six identical protons of the methyl groups attached to the pyrrole ring were found to resonate at 1.9 ppm. The formation of pyrazol-3-ones was confirmed by the appearance of two carbonyl stretching vibrations in the IR spectra at 1700 cm$^{-1}$ and 1750 cm$^{-1}$. The $^1$HNMR spectra displayed the three methyl protons and the 2 protons in the pyrrole ring as singlets at 1.8 and 5.5 ppm respectively. The $^{13}$ C NMR spectra of all the synthesized compounds accounted for the respective number of carbon atoms. The mass spectra of the compounds were in agreement with the molecular weights of the compounds.

All the oxadiazole thione derivatives (2a-c) were found to show good antibacterial activity against *S. aureus*. The compound 2b with methyl substituent on the quinoline ring was found to be the most sensitive among the three oxadiazole thiones. Neither the pyrrole nor pyrazolone derivatives, exhibited any sensitivity towards the bacterial strain studied. The results of antimicrobial studies of the hydrazide derivatives expressed as mean value of the duplicates against *S. aureus* are given in table 1.

**Table 1: Zone of inhibition and docking scores of quinoline derivatives**

| Comp. No. | Zone of inhibition[a] (mm) | 4cuz(FabI)-docking score | Comp. No. | Zone of inhibition (mm) | 4cuz(FabI)-docking score |
|---|---|---|---|---|---|
| 2a | 16 | 5.45 | 3c | - | 5.58 |
| 2b | 20 | 6.67 | 4a | - | - |
| 2c | 11 | 6.34 | 4b | - | - |
| 3a | - | 6.34 | 4c | - | - |
| 3b | - | 6.58 | Tetracycline | 37 | - |

[a]Inhibition zone expressed as mean of two replicas

The similarities in the structures of synthesized compounds and triclosan and its proposed mechanisms of action prompted us to determine whether the oxadiazoles were also FabI inhibitors. To investigate the suitability of saFabI as a drug target, we have structurally characterized this enzyme with respect to inhibitor binding and conformational flexibility and further compared with triclosan-saFabI complex structure. The results of the docking studies are presented in table 1. The docked conformer of 2b is depicted in fig. 1A. Triclosan is a particularly effective FabI inhibitor due to the slow formation of a stable, ternary FabI-NAD$^+$-triclosan ternary complex, and this property of triclosan is responsible for its antibacterial activity through the formation of H-bond between oxygen attached to quinoline ring of 2b and NDP1258 of NADPH. The two nitrogen atoms of oxadiazole ring of 2b were also found to engage in H-bonds with Tyrosine 157 which is much similar to the sandwiched binding mode between triclosan, the protein and the cofactor. Hydrogen bond network and stacking interactions from the bridge that connects triclosan, protein and NAD$^+$ [24]. Compound 2b also demonstrates the formation of ternary complexes with FabI. The ternary FabI-NAD$^+$-2b complex formation is represented in fig. 1B.

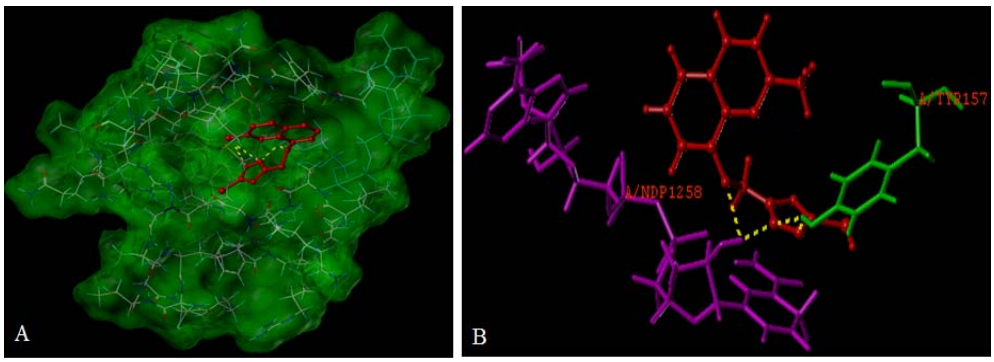



**Fig. 1: A) Docked conformer of 2b with the active residue of Fab1 and the substrate NADPH, B) FabI-NAD$^+$-2b complex formation; Red-ligand, Green-Tyrosine 157 of Fab1 and Purple-NADPH**

The ether linkage in tri closan is a structural feature that is essential for the formation of the inhibitory ternary complex. The substitution of a carbon bridge for the ether oxygen in triclosan results in a compound that cannot orient itself to optimally participate in this network. This is most likely attributed to the different angle of the carbon bridge compared with the ether bridge, preventing the molecule from forming hydrogen bond connections and the stacking interactions with NAD$^+$ [25]. It is also proposed that the ether oxygen of triclosan is part of a hydrogen bond network that also includes the hydroxyl groups of Tyr-156, triclosan, and the NAD$^+$ribose [26]. Thus, the presence of the ether oxygen is clearly important in promoting tight drug binding and the ensuing conformational change that leads to essentially irreversible FabI inhibition and potent antibacterial activity. Thus the presence of ether linkage and the ability to form ternary bonding might have made 2b the most potential antibacterial agent among all the compounds studied.

## CONCLUSION

In the present study three new series of hydrazide derivatives incorporating bioactive quinoline moiety were synthesized and were characterized by spectral techniques. Antimicrobial activity of oxadiazole thione, pyrrole and pyrazolone derivatives of hydrazides was studied by disc diffusion method. All the oxadiazole thione derivatives showed good antibacterial activity against *S. aureus*.

Increased opportunities for hydrogen bond formation between the nitrogens and oxygen and the protein is one possible explanation for understanding the potency of 2b as a FabI inhibitor. Molecular modeling of the energy-minimized docked FabI-NAD1-2b structure indicated the formation of ternary bond formation. The ether linkage is an essential feature for ternary complex formation and ensuing conformational changes that can promote its interaction with FabI with potent antibacterial activity. Oxygen bridge in 2b which is critical to the formation of a ternary complex, similar to triclosan might have added to the structural features that determine inhibitory activity.

## CONFLICT OF INTERESTS

Declared None

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