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SYNTHESIS AND MOLECULAR DOCKING STUDY OF BIOACTIVE QUINOLINO-BENZIMIDAZOLE DERIVATIVES

N. J. Deshmukh [1], J. T. Deshmukh [*2] and M. C. Mandewale [2]

Department of Chemistry [1], Vivekanand College, Kolhapur- 416003, Maharashtra, India.
Department of Chemistry [2], Government of Maharashtra's Ismail Yusuf College of Arts, Science and Commerce, Jogeshwari (East) - 400060, Mumbai, India.

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Correspondence to Author:
Dr. J. T. Deshmukh

Assistant Professor, Department of Chemistry, Government of Maharashtra's Ismail Yusuf College of Arts, Science and Commerce, Jogeshwari (East) - 400060, Mumbai, India.

E-mail: iycmustapha@gmail.com

ABSTRACT: A series of some quinolino-benzimidazole/thiazole derivatives (3a-3h) have been synthesized from2-hydroxyquinoline-3-formaldehyde derivatives (1a-1d) and 1, 2-phenylenediamines/2-aminothiophenols (2a-2c). The synthesized compounds were characterized by FTIR, ^{1}H-NMR and Mass Spectrometry. All the compounds were screened *in-vitro* for their antibacterial activity against *Mycobacterium tuberculosis* (H37 RV strain) ATCC No-27294. Among the compounds tested, compounds 3e showed potent antitubercular activity against *M. tuberculosis* at MIC 6.25 µg/mL. We extended our study to explore the inhibition mechanism by conducting molecular docking analysis by using Schrödinger.

INTRODUCTION: Heterocyclic chemistry is one of the largest classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often heteroaromatic derivatives. Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole.

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The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} [1]. Benzimidazole nucleus is an important heterocyclic ring because of its synthetic utility and broad range of pharmacological activities. Some benzimidazole derivatives with different pharmacological effects, including antifungal [2], anti-helminthic [3], anti-HIV [4], antihistaminic [5, 6, 7], antiulcer [8, 9], cardiotonic [10], antihypertensive [11, 12] and neuroleptic [13] are in clinical use.

Extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. Based on recent literature and in continuation of our research [14, 15, 16, 17, 18, 19, 20, 21] for more potent antibacterial agents, we synthesized and screened quinolinobenzimidazole derivatives (3a-3h). The compounds (3a-3h) were prepared using reported methodology [22] by using o-phenylene diamines and various substituted quinolone aldehydes in presence of catalytic NH_4Cl in ethanol.

EXPERIMENTAL:

Materials and Methods: All required chemicals and solvents were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and used without further purification. The NMR spectra were recorded on a Bruker Avance 300 apparatus in DMSO-d_6. The chemical shifts are measured on the δ (ppm) scale using TMS (Tetramethylsilane) as the internal standard reference. Infrared (IR) spectra measured on an FTIR-7600 Lambda Scientific Pty. Ltd. using KBr disk for the range 4000-400 cm^{-1}. Mass spectra obtained on BRUKER ESQUIRE HCT spectrometer.

General Procedure of Preparation: Compound 2a-2c (1 mmol) was dissolved in 4 ml ethanol in 20 ml round flask. Then, with constant stirring, 1 mmol of 1a-1e was slowly added followed by NH_4Cl (30 mol %). The resulting reaction mixture was stirred for 2 h at 80 °C. The reaction progress was checked with TLC. After completion of the reaction, it was poured in ice-cold water. The precipitates were then collected by filtration, washed with distilled water and purified by recrystallization from ethanol to give the pure product.

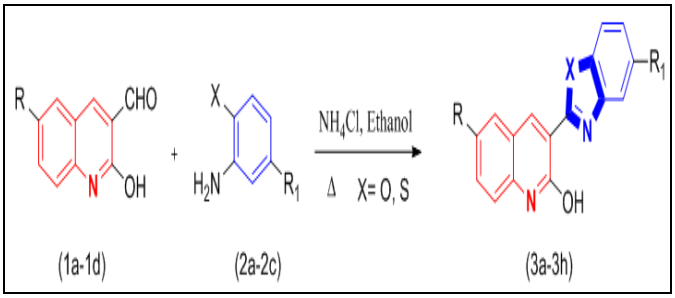

FIG. 1: SCHEME OF PREPARATION OF COMPOUNDS 3a-3h

Synthesis of 3-(1*H*-benzimidazol-2-yl)quinolin-2-ol [3a]: Yield 86%, ^{1}HNMR (300 MHz, DMSO-d_6) δ:6.31-6.58 (m, 2H),7.05-7.45 (m, 3H), 7.58-7.73 (m, 2H), 7.81–7.96 (m, 1H), 9.11 (m, 1H), 11.89 (s, 1H, -NH), 12.18 (s, 1H, -OH); Mass Spectra: [M^{+1}] 262.53, IR (KBr, ν, cm^{-1}): 3426 (-OH), 1612, 1406, 1038, 721. Anal. Calc. For $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found. C, 73.80; H, 4.03; N, 16.47.

Synthesis of 3-(1,3-benzothiazol-2-yl)quinolin-2-ol [3b]: Yield 83%, ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.24-6.25(m, 1H), 6.39-6.44(m, 1H), 6.56-6.61(m, 1H), 6.71-6.76(m, 1H), 6.87-7.19(m, 1H), 7.31-7.34(m, 1H), 7.46-7.51(m, 1H), 7.67-7.69(m, 1H), 7.83(s, 1H), 12.02(s, 1H); Mass Spectra: [M+1] 281.35; IR (KBr, ν, cm^{-1}): 3415, 1604, 1328, 1034, 760. Anal. Calc. For $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.07. Found. C, 68.85; H, 3.76; N, 10.13.

TABLE 1: STRUCTURES OF THE COMPOUNDS 3a-3h

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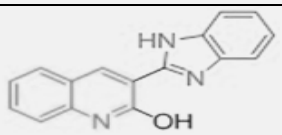
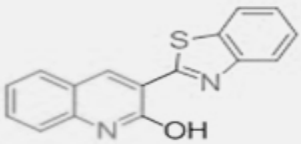
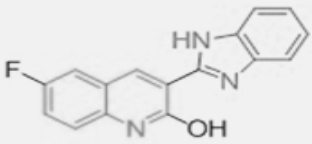
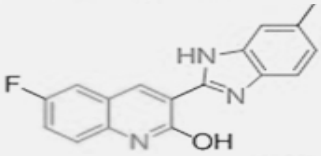
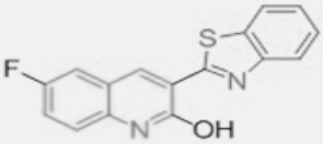
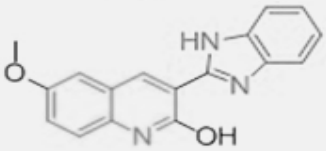
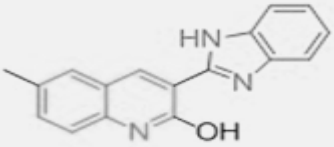
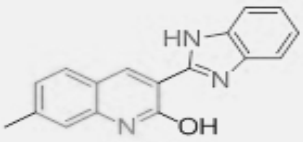
3a	
3b	
3c	
3d	
3e	
3f	
3g	
3h	

Synthesis of 3-(1*H*-benzimidazol-2-yl)-6-fluoro-quinolin-2-ol [3c]: Yield 89%, ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.22 (m,2H), 7.47-7.53 (m, 2H), 7.63-7.72 (m, 2H), 7.83-7.86 (m, 1H), 9.12 (s, 1H), 12.54 (s, 1H), 12.67 (s, 1H). Mass Spectra: [M^{+1}] 280.85; IR (KBr, ν, cm^{-1}): 3450, 1612, 1341, 738; Anal. Calc. For $C_{16}H_{10}FN_3O$: C, 68.81; H, 3.61; N, 15.05. Found. C, 68.93; H, 3.48; N, 14.92.

Synthesis of 6-fluoro-3-(6-methyl-1*H*-benz-imidazol-2-yl) quinolin-2-ol [3d]: Yield 90%, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H), 7.03-7.05 (m, 1H), 7.33 (m, 1H), 7.47-7.57 (m,3H), 7.82-7.85 (m, 1H), 9.08 (s, 1H), 11.98 (s, 1H), 12.53 (s,1H); Mass Spectra: [M^{+1}] 294.42; IR (KBr, ν, cm^{-1}): 3428, 1611, 1331, 736. Anal. Calc. For $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found. C, 69.97; H, 4.08; N, 14.20.

Synthesis of 3-(1,3-benzothiazol-2-yl)-6-fluoro-quinolin-2-ol[3e]: Yield 86%, ^{1}HNMR (300 MHz, DMSO-d_6) δ 6.98-7.13 (m, 2H), 7.44 (m, 1H), 7.46-7.63 (m, 1H), 7.91-7.94 (m, 1H), 8.06-8.17 (m, 2H), 9.20 (s, 1H), 12.61 (s, 1H); Mass Spectra: [M^{+1}] 297.87; IR (KBr, ν, cm^{-1}): 3398, 1602, 1347, 742. Anal. Calc. For $C_{16}H_9FN_2OS$: C, 64.85; H, 3.06; N, 9.45. Found. C, 65.11; H, 3.21; N, 9.40.

Synthesis of 3-(1H-benzo[d]imidazol-2-yl)-6-methoxyquinolin-2-ol [3f]: Yield 78%, ^{1}HNMR (300 MHz, DMSO-d_6) δ3.74 (s, 1H, -OCH_3), 7.12-7.20 (m, 2H), 7.37-7.40 (m, 1H), 7.52 (m, 1H), 7.69-7.77 (m, 3H), 9.08 (m, 1H), 11.77 (s, H, -NH), 12.38 (S, 1H, -OH); Mass Spectra: [M^{+1}] 292.57; IR (KBr, ν, cm^{-1}): 3428, 1614, 1368, 764. Anal. Calc. For $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found. C, 70.27; H, 4.38; N, 14.29.

Synthesis of 3-(1H-benzo[d]imidazol-2-yl)-6-methylquinolin-2-ol [3g]: Yield 76%, ^{1}HNMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H), 7.20-7.50 (m, 3H), 7.70 (m, 4H), 9.01 (s, 1H), 11.78 (s,1H), 12.38(s, 1H); Mass Spectra: [M^{+1}] 276.57; IR (KBr, ν, cm^{-1}): 3422, 1608, 1340, 1026, 762; Anal. Calc. For $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found. C, 74.52; H, 4.81; N, 15.33.

Synthesis of 3-(1H-benzo[d]imidazol-2-yl)-7-methylquinolin-2-ol [3h]: Yield 79%, ^{1}HNMR (300 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.06-7.22 (m, 2H), 7.50 (m, 1H), 7.70 (m,4H), 9.01 (s, 1H), 11.78 (s,1H), 12.38(s, 1H); Mass Spectra: [M^{+1}] 276.41; IR (KBr, ν, cm^{-1}): 3430, 1609, 1360, 1024, 762; Anal. Calc. For $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found. C, 73.97; H, 4.29; N, 15.40.

RESULTS AND DISCUSSION:

Chemistry: The target compounds Quinolino-benzimidazole / thiazole derivatives (3a-3h) successfully synthesized from 1a-1d and 2a-2c. For structure identification of these compounds 3a-3h we have utilized advanced techniques like NMR, MASS, FTIR and Elemental analysis.

The FTIR spectrum of compound 3d showed strong absorption peak at 3428 and 1611 corresponding to -OH group of quinoline ring and -C=N- group of benzimidazole group respectively. In addition to expected aromatic signals ^{1}H-NMR spectra of compound 3d show four singlets at 2.42 (-CH_3, benzimidazole), 9.08 (C-H, quinoline ring), 11.98 (-N-H, imidazole ring) and 12.53 ppm (-OH, quinoline ring). Moreover, the Mass spectrum of 3d revealed a molecular ion peak at m/z 294.42 (M+H) corresponding to the molecular formula [$C_{17}H_{12}FN_3O$]. In a similar manner, compounds 3a–3h were prepared and characterized.

Molecular Docking Studies: The molecule 3e was found to be best docked among the compound series having docking score of -9.128 as compared to native cocrystallized one (-10.208) for the Enoyl-Acyl Carrier Protein Reductase protein (PDB ID: 2X22). It also had a good binding energy of -72.299. The compound 3e was also found to better docked than those for std. drugs like Bedaquiline and Ciprofloxacin (-6.389 and -5.932 Kcal/mol respectively).

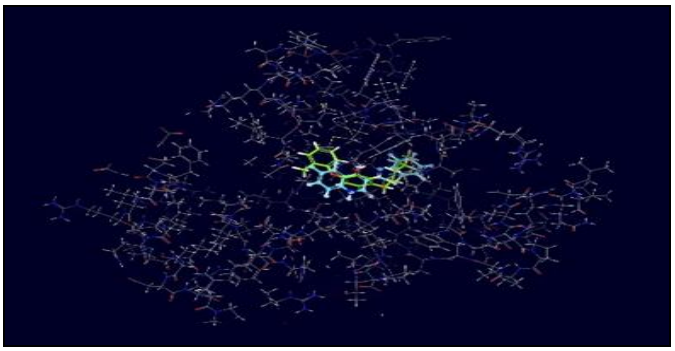


FIG. 2: SUPERIMPOSITION OF BEST DOCKED LIGAND SKY BLUE WITH THE NATIVE ONE FOR PROTEIN 2×22

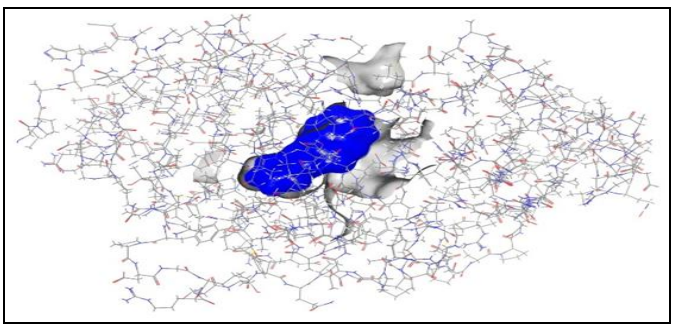


FIG. 3: BINDING POCKET OF HIGHDOCK MOLECULE (FOR PS PROTEIN PDB ID: 3ivx)

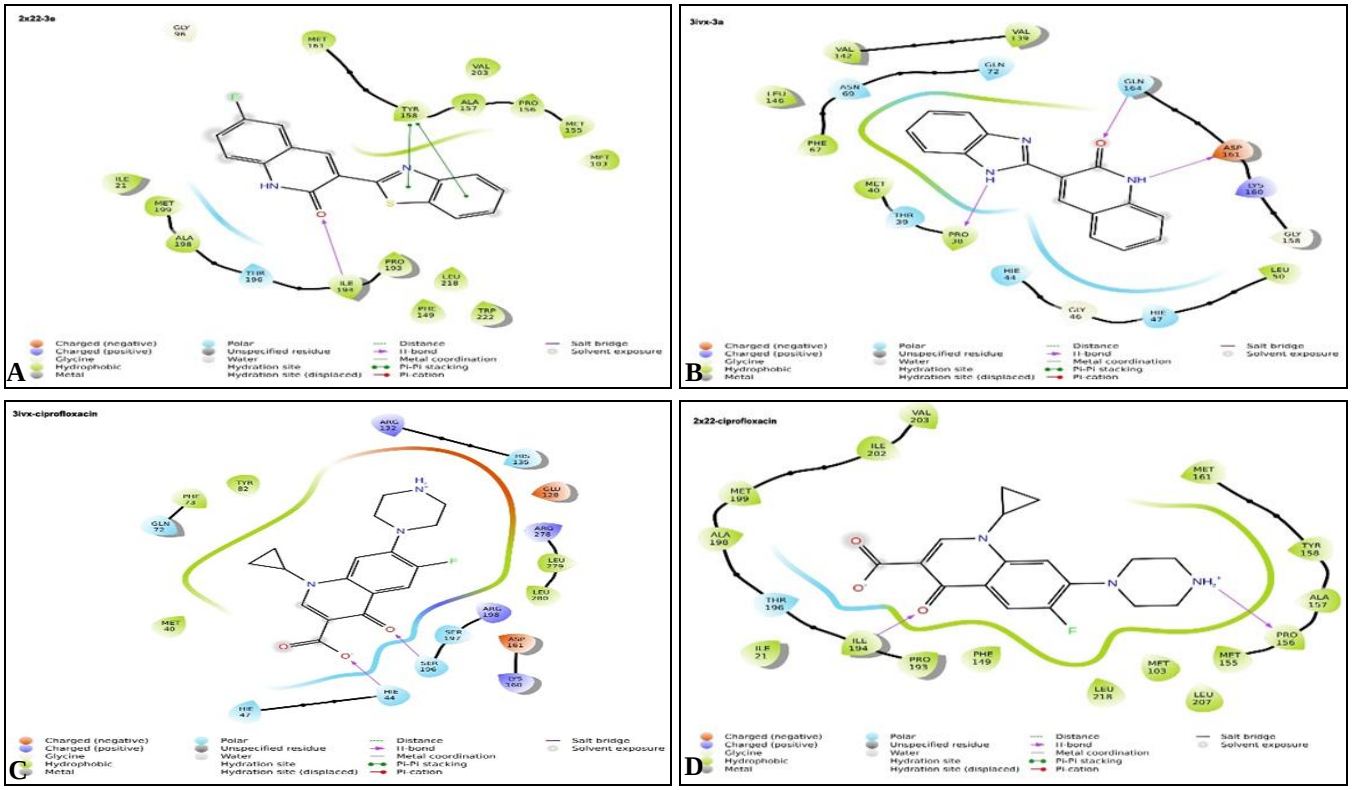


FIG. 4: A] 2D INTERACTIONS OF BEST DOCK COMPOUND 3e WITH TARGET PROTEINS 2×22 B] 2D INTERACTIONS OF BEST DOCK COMPOUND 3a WITH TARGET PROTEINS 3ivx C] 2D INTERACTIONS OF CIPROFLOXACIN WITH TARGET PROTEINS 3ivxd] 2D INTERACTIONS OF BEST DOCK CIPROFLOXACIN WITH TARGET PROTEINS 2×22

TABLE 2: ADME PREDICTIONS FOR COMPOUNDS (3a-3h) by QikProp

Entry	MW	#stars	dipole	volume	QPlogPo/w	QPPCaco	#metab	% HumanOral Absorption	Rule of Five	PSA
3a	261.282	1	8.367	842.283	3.05	1038.369	0	100	0	64.593
3b	278.328	0	4.918	863.08	3.043	1606.077	1	100	0	51.468
3c	279.273	1	5.772	858.436	3.286	1038.537	0	100	0	64.589
3d	293.3	0	5.683	918.314	3.596	1038.486	1	100	0	64.594
3e	296.318	0	2.283	879.232	3.286	1606.283	1	100	0	51.466
3f	291.309	0	8.608	917.202	3.152	1037.426	1	100	0	72.882
3g	275.309	0	8.859	902.246	3.36	1038.082	1	100	0	64.596
3h	275.309	0	8.764	902.319	3.361	1037.814	1	100	0	64.595

TABLE 3: MOLECULAR DOCKING STUDY FOR COMPOUND (3a-3h) ALONG WITH PrimeMMGBSA dG BIND ENERGY VALUES

Comp. ID	PDB ID:2x22 (RMSD=0.089)			PDB ID:3ivx (RMSD=0.083)		
	Docking score (Kcal/mol)	Residues involved	MMGBSA dG Bind energy	Docking score (Kcal/mol)	Residues involved	MMGBSA dG Bind energy
Native ligand	-10.208	TYR158(H-BOND)	-98.343	-9.746	SER196, SER197, HIE44, VAL187, HIE47, MET40(H-BOND), HIE44 (PI-PI STACKING), LYS160 (SALT BRIDGE)	-52.067
3a	-8.337	ILE194 (H-BOND), TYR158 (PI-PI STACKING)	-56.002	-8.557 (BEST DOCK)	GLY164 (H-BOND), ASP161(H-BOND), PRO38(H-BOND)	-43.836
3b	-8.722	ILE194 (H-BOND), TYR158 (PI-PI STACKING)	-71.085	-5.961	LYS160(PI-CATION), SER197, HIE44(H-BOND), HIE44 (PI-PI STACKING)	-59.733
3c	-8.568	ILE194 (H-BOND), TYR158 (PI-PI STACKING)	-56.929	-6.252	HIE44(PI-PI STACKING), HIE47, MET40 (H-BOND)	-48.655
3d	-8.904	ILE194(H-BOND),	-56.35	-3.689	HIE47, ASP161(H-BOND), HIE44	-55.168

		TYR158 (PI-PI STACKING)		(LEAST DOCK)	(PI-PI STACKING)	
3e	-9.128 (BEST DOCK)	ILE194(H-BOND), TYR158 (PI-PI STACKING)	-72.299	-6.326	SER197, HIE44(H-BOND), HIE44(PI-PI STACKING), LYS160 (PI-CATION)	-60.368
3f	-8.372	LYS165 (H-BOND), ILE194 (H-BOND), TYR158 (PI-PI STACKING)	-60.927	-6.733	MET195,HIE47,VAL187(H-BOND),HIE44 (PI-PI STACKING)	-59.272
3g	-8.538	ILE194(H-BOND), TYR158 (PI-PI STACKING)	-55.616	-7.108	GLY164(H-BOND)	-46.936
3h	-8.15 (LEAST DOCK)	ILE194(H-BOND), TYR158 (PI-PI STACKING)	-58.758	-7.036	HIE47(H-BOND)	-52.757
Bedaquiline	-6.389	TYR158 (H-BOND).	-79.099	-6.623	GLN164, ASP161(H-BOND); ASP(SALT BRIDGE); TYR82, PHE73 (PI-PI STACKING)	-53.623
Ciprofloxacin	-5.932	PRO156 (H-BOND), ILE194 (H-BOND)	-58.72	-3.879	SER196, HIE44(H-BOND)	-52.535

In the case of pantothenate synthetase Protein (PDB ID: 3IVX), molecule 3a was found to be the best dock having docking score of -8.557 as compared to native one (-9.746). The molecule 3a was also found to have good docking score than those of std. drugs like Bedaquiline and Ciprofloxacin (-6.623 and -3.879 Kcal/mol respectively). There was no violation of Lipinski's rule for all the compound prepared **Table 2**. The percent Human oral absorption values, as well as the caco cell permeability values, were found to be good.

Anti-tuberculosis Study: The anti-tubercular activity of the compounds 3a-3h evaluated against *Mycobacterium tuberculosis* (H37 RV strain) ATCC No.-27294. The method applied is similar to that reported by Lourenco *et al.* [23]

TABLE 4: ANTITUBERCULAR ACTIVITY RESULTS

Test Sample	Sample concentration in µg/mL (MIC)
3a	25.00
3b	12.50
3c	25.00
3d	12.50
3e	06.25
3f	12.50
3g	50.00
3h	25.00
Ciprofloxacin	3.12
Pyrazinamide	3.12
Streptomycin	6.25

CONCLUSION: The target compounds (3a-3h) successfully synthesized and characterized. This synthetic strategy allows for the incorporation of the imine, quinoline, and benzimidazole in a single scaffold. The anti-tubercular activity evaluated using blue Alamar method to identify the more effective compound. The compounds under study show moderate to good anti-tubercular potency. Compound 3e was found most active against *M. tuberculosis* with 6.25 µg/mL. These results are in good agreement with molecular docking results.

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CONFLICTS OF INTEREST: No conflict of interest.

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