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Synthesis, molecular docking, antibacterial & antifungal activity study of novel 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives

Pramod B. Guje,[1] Anil B. Chidrawar,[1] S.B. Patwari,[2] Balaji R. Madje,[3] Dhanji P. Rajani,[4] Jaiprakash N. Sangshetti,[5] Manoj Damale,[6] Rajkumar U. Pokalwar[1]*

[1]Department of Chemistry, Degloor College, Degloor, Nanded-431717 Maharashtra, India.
[2]Department of Chemistry, L.B.S. College, Dharmabad, Nanded, Maharashtra, India.
[3]Department of Chemistry, Vasantrao Naik College, Aurangabad-431003, Maharashtra, India.
[4]Microcare Laboratory and Tuberculosis Research Center, Surat-395003, Gujrat, India.
[5]Y. B. Chavan College of Pharmacy, Aurangabad 431001, Maharashtra, India.
[6]Srinath College of pharmacy, Aurangabad, 431136, Maharashtra, India
E-mail: rajupokalwar@rediffmail.com
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Abstract: A new and convenient method was developed for the synthesis of 3-(1H-benzo(d)imidazole-2-ylthio) methyl-2-chloroquinoline using 2-chloroquinolin-3-carbaldehydes in quantitative yield. The newly prepared compounds were characterized by ^{1}HNMR, IR and Mass spectroscopy. These newly synthesized compounds were studied for antifungal and antibacterial activities. Antibacterial activity study with S. aureus, E. coli, P. aeruginosa and S. pyogenes of compound **4e** was found good when compared with Ampicillin as standard. Molecular docking studies have been performed to rationalize the experimentally observed affinity 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives to gain insights of the mode of inhibition of MurD ligase enzyme. The molecular docking study revealed that derivatives **4e** and **4f** of 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline are the most active. Antifungal activity of compound **4e** was found good with C. Albicans, A. Niger and A. Clavatus when compared with standard Greseofulvin, remaining compounds **4a-d** and **4f** were not showed any good activities.

Keywords: 2-Chloroquinoline-3-carbaldehyde, antibacterial, antifungal, molecular docking, 3-(1H-benzo(d)imidazole-2-yithio) methyl-2-chloroquinoline.

Introduction

Quinoline ring system represents a very important and major class of heterocyclic compounds and is used as a key intermediate for many pharmacologically important compounds. [1-3] The derivatives of quinoline exhibits physiological and biological activities such as antimalarial, [4-11] anti-inflammatory, [12-17] antitumor, [18-20] DNA binding capacity, [21-

22] antibacterial,[23-26] antimicrobial,[27-33] anticancer[34-35] anti-tuberculosis[36] antihistamine,[37] antifungal,[38] anti-HIV,[39] antihypertensive[40] and antiparasitic properties.[41] Also quinoline is used in the study of bioorganic and bioorganometallic processes.[42]

The benzimidazole is also an important class of heterocyclic compounds, the derivatives of benzimidazole possesses biological activities such as antimicrobial,[43-44] antiviral,[45-46] anti-tumor,[47] anti-mutagens,[48] cardio-vascular,[49] anticalmodulin,[50] antiparkinsons,[51] anticancer,[52-54] anti-inflammatory,[55] antiulcer[56] and many other activities are well documented.[57] Benzimidazole ring has received attention when it is found one of the component of vitamin B12.[58] On the other hand, mercaptobenzimidazole is used for the synthesis of the wellknown proton pump inhibitors like pantoprazole,[59] omeprazole,[60] rabeprazole,[61] and lansoprazole[62] used in GERD as anti helicobacter agent.[63] Therefore benzimidazole acts as important core structure for the drug design.[64]

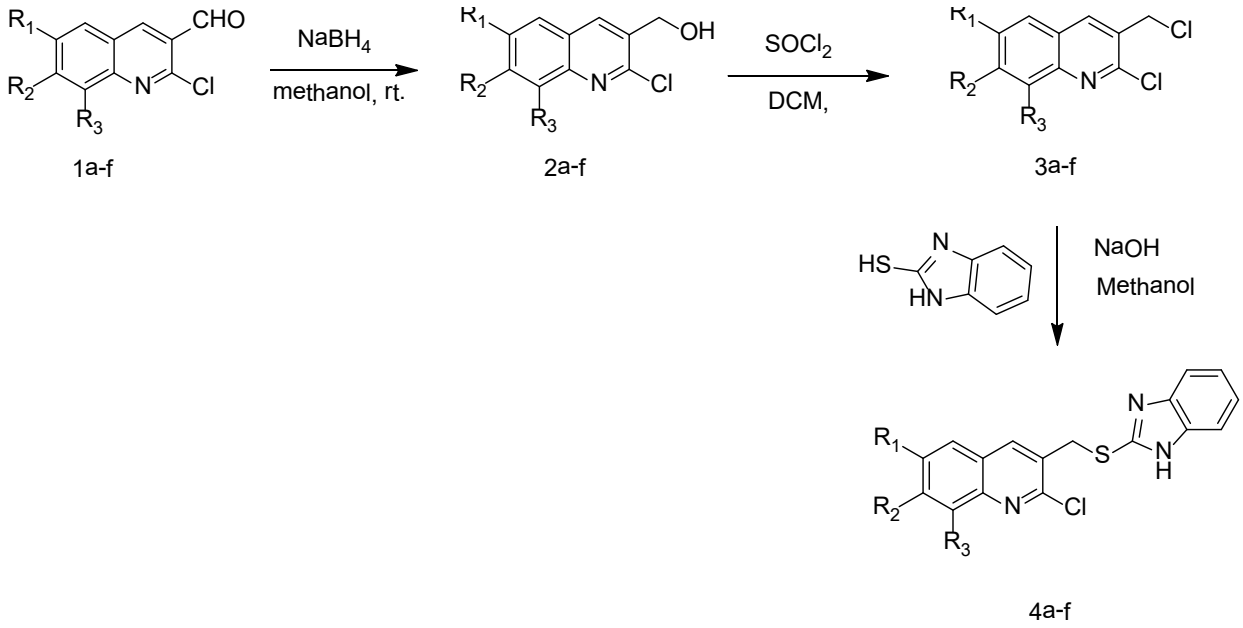
Literature search reveals that very little attention has been made to get the combo benefit of these two paharmacophores.[65] Our interest is to give some efforts in the direction to have synergic effects of the synthesized combo pharmacophore from quinoline and benzimidazole for antibacterial and antifungal activities.

Results and Discussion

Novel 3-((1H-benzo[d]imidazol-2-ylthio) methyl)-2-chloroquinoline derivatives were synthesized in quantitative yield **(Scheme-I).** The process includes reduction of 2-chloroquinoline-3-carbaldehyde **1a–f** with sodium borohydride at room temperature in methanol to afford the derivatives of (2-chloroquinolin-3-yl)methanol **2a–f** in 94–97% yields in shorter time (10 min) entries 1-6 are mentioned in Table-1. These obtained derivatives of (2-chloroquinolin-3-yl) methanol **2a–f** reacted with thionyl chloride in dichloromethane to form 2-chloro-3-(chloromethyl)quinoline derivatives **3a–f** in 95–98% yield and are entered in Table-1, entries 7-12. Above obtained derivatives of 2-chloro-3-(chloromethyl)quinoline **3a–f** were reacted with 1H-benzo[d]imidazole-2-thiol in methanol in the presence of base like sodium hydroxide. Progresses of the reactions were monitored on TLC using mobile phase (8:2) hexane: ethyl acetate. The reaction proceeded smoothly under basic condition and completed in 1 hr to afford the corresponding titled compounds having entries 13–18 in **Table -1** in high yields (85–95%). The chemical structures of the new compounds were confirmed by IR, ^{1}H NMR, mass spectroscopic data.

The newly prepared compound **4a-f** were studied for antibacterial activities using S. pyrogens, E. coli, S. aureus and P. aeruginosa with standard drug Ampicillin. The broth dilution technique was used for MIC values. **Table-2** shows the MIC values of synthesized compounds. When compared with the standard drug Ampicillin **(Table-4)**, the compound with substitution of methyl at the 8 th position of the quinoline ring **4b**, substitution of the methoxy at the 7 th position of the quinoline ring **4e** shows antibacterial activity with Gram +ve bacterial strains and Gram –ve strain.

The newly prepared compounds **4a-f** were studied for antifungal activity using C. albicans, A. Clavatus and A. Niger with standard drug Greseofulvin **Table-4** by broth dilution method and shown in **Table-3.** The compound **4a** and **4e** found active with C. albicans, A. Clavatus and A. Niger compared with Griseofulvin standard drug. On the contrary the compounds **4b**, **4d**



Scheme-1: Synthesis of 3-(1H-benzo(d)imidazol-2ylthio) methyl) -2-chloroquinoline

and **4f** were found to possess less activity.

Materials and methods

In laboratory 2-chloroquinoline-carbaldehyde[1] was prepared using reported method. Required solvents and reagents are purchased from spectrochem, Avra chemicals and S.D. fine chem. otherwise stated. Physical constants (melting point) were carried out in open capillaries at atmospheric pressure. Proton NMR was recorded on AVANCE in $CDCl_3$+DMSO and $CDCl_3$ at 300 MHz, 400 MHz using standard as TMS. Perkin- Elmer and Shimadzu FTIR were used for recording of IR spectra.Thermo exactive orbitrap methods (FTMS) used for mass spectra analysis, showing a molecular ion peak. Institute of Microbial Technology, Chandigarh, India provided strains.

Experimental Procedure

(2-Chloroquinoline-3-yl)methanol(2a)

In methanol 15 mL was added 2-chloroquinoline-3-carbaldehyde 1.9 gm, 10 mmol stirred for five minute then slowly sodium borohydride 0.5 gm, 13 mmol was added at room temperature with constant stirring. Continued stirring for further 10 minute and the reaction progress was checked on thin layer chromatography (TLC). After completion, reaction mixture was concentrated on rotary evaporator. Residue taken in ice water, filtered and cold water was used for washing to afford wet compound which was further dried on rotary evaporator by taking in round bottom flask to afford titled compound (1.85 gm, 95%). Similar procedure was applied for the preparation of compounds (**2b-f**) using an appropriate quantity of reagents.

2-chloro-3-(chloromethyl)quinoline(3a)

Thionyl chloride (2mL) in dichloromethane 5mLwas added dropwise in stirred solution of 2-chloroquinolin-3-yl- methanol 1.75 gm, 9 mmol in 10 mL dichloromethane. The reaction mixture stirred further 1 hr at atmospheric temperature and reaction progress was checked by thin layer chromatography using hexane ethyl acetate solvent system. After complete conversion of starting material, the reaction mass was concentrated on rotary evaporator to

obtain crude product 1.85 gm, 96%, which was enough pure and used directly for the next step. Similar procedure applied for preparation of compounds 3b-f using an appropriate quantity of reagents.

3-(1H-benzo(d)imidazole-2yl-thio) methyl-2-chloroquinoline (4a)

To the solution of 1H-benzo(d)imidazole-2thiol 1.48 gm,10 mmol in methanol 20 mL added sodium hydroxide 0.6 gm, 15 mmol. To this pre-stirred (10 min) solution 2-chloro-3-(chloromethyl)quinoline 1.75 gm, 9 mmol added at room temperature and stirred for 1 hr. The reaction progress checked on thin layer chromatography using Hexane and ethyl acetate as solvent system (8:2). After complete conversion of reaction mass, the solvent removed under vacuum on rota evaporator. To the obtained residue cold water 100 mL added, filtered solid and washed with water 50 mL to get product, which is dried on rotary evaporator. Dried compound purified on column chromatography by using hexane and ethyl acetate solvent to get the titled compound 2.4 gm, 89%.

IR (cm^{-1}): 3385(-NH); 3055 (-C-H); 1632 (-C=C); 737 (C-Cl);
^{1}H NMR ($CDCl_3$+ DMSO, δppm): 4.29 (s, 2H), 7.25 – 7.8 (m, 7H), 8.00 (s, 1H), 8.15 (s, 1H),
FTMS: 326.05 (m+1) m/z
Similar procedure was applied for the preparation of compounds (**4b-f**) using an appropriate quantity of reagents.
Compound (4b)
3-(1H-benzo(d)imidazol-2-ylthio) methyl)-2-chloro-8-methylquinoline
IR (cm^{-1}): 3448 (-NH), 3076 (-C-H), 1617 (-C=C), 752 (-C-Cl)
^{1}H NMR ($CDCl_3$, δppm): 2.72 (s, 3H), 4.79 (s, 2H), 7.20– 7.3 (m, 3H), 7.33– 7.6 (m, 4H), 8.25 (s, 1H),
FTMS: 340.06 (m+1) m/z
Compound (4c)
3-(1H-benzo(d)imidazol-2ylthio) methyl)-2-chloro-7-methylquinoline
IR (cm^{-1}): 3444 (-NH), 3052 (-C-H), 1621 (-C=C), 769 (-C-Cl)
^{1}H NMR ($CDCl_3$, δppm):2.62 (s, 3H), 4.84 (s, 2H), 7.3– 7.4 (m, 3H), 7.48– 7.6 (m, 4H), 8.18 (s, 1H),
FTMS: 340.06 (m+1) m/z
Compound (4d)
3-(1H-benzo(d)imidazol-2ylthio) methyl)-2-chloro-8-methylquinoline
IR (cm^{-1}): 3385 (-NH), 3076 (-C-H), 1617 (-C=C), 737 (-C-Cl)
^{1}H NMR ($CDCl_3$+DMSO, δppm): 2.62 (s, 3H), 4.84 (s, 2H), 7.3– 7.4 (m, 3H), 7.48– 7.6 (m, 4H), 8.25 (s, 1H),
FTMS: 340.06 (m+1) m/z
Compound (4e)
3-(1H-benzo(d)imidazol-2ylthio) methyl)-2-chloro-7-methoxyquinoline
IR (cm^{-1}): 3427 (-NH), 3078 (-C-H), 1620 (-C=C), 757 (-C-Cl)
^{1}H NMR ($CDCl_3$, δppm): 3.89 (s, 3H), 4.92 (s, 2H), 7.1– 7.35 (m, 5H), 7.58– 7.70 (m, 2H), 8.29 (s, 1H),
FTMS: 356.06 (m+1) m/z
Compound (4f)
3-(1H-benzo(d)imidazol-2ylthio) methyl)-2-chloro-6-methoxyquinoline
IR (cm^{-1}): 3444 (-NH), 3078 (-C-H), 1621 (-C=C), 751 (-C-Cl)
^{1}H NMR ($CDCl_3$+DMSO, δppm): 3.75 (s, 3H), 4.85 (s, 2H),6.9 (s, 1H), 7.26– 7.31 (m, 4H), 7.50– 7.75 (m, 3H), 8.23 (s, 1H),
FTMS: 356.06 (m+1) m/z

Antibacterial and Antifungal activity:

The study of antibacterial activity was carried out with p. aeruginosa (MTCC-1688), E. coli (MTCC-443), S. aureus (MTCC-96) and S. pyogenes (MTCC-442), and also the antifungal study wascarried out with A. Niger (MTCC-

282) C. albicans (MTCC-227), and A. Clavatus (MTCC-1323). Nutrient medium as Mueller Hinton Broth was used to grow and dilute drug suspension for test bacteria. This media sterilized in autoclaved at 120 °C for half hour, poured with uniform depth 5 mm and allowed to solidify. The microbial suspension 105 CFU/ mL was streaked over the surface using sterile cotton swab. The prepared compounds dissolved in dimethylsulphoxide to give the concentration 3.25–1000 µg/mL. Sterile filter paper discs of diameter 6.25 mm was previously soaked in known concentration of respective test compound in dimethylsulphoxide and placed on nutrient agar that was incubated microorganisms and incubated for 24 hr for bacteria and 72 hr for fungi at 37 °C. A control disc impregnated with an equivalent amount of dimethylsulphoxide without any sample was also used and did not produce any inhibition. Greseofulvin and Ampicillin were used for control drugs. MIC minimum bacterial inhibitory concentration of prepared compound determined by agar streak dilution method (Hawkey and Lewis 1994). Prepared stock solution in dimethylsulphoxide and graded quantities of the prepared compounds were incorporated in aspecified quantity of molten sterile agar for evaluation of antibacterial activity and Sabouraud dextrose agar for antifungal activity. In the petri dish the medium containing test compound was poured at depth of 4-5 mm and allowed to solidify for septic condition.The respective microorganism suspension of 105 CFU/mL prepared and applied on plates serially diluted compounds with concentrations in the range of 3.12–1000 µg/ml in dimethylsolphoxide and were incubated for 24 hr for bacteria and 72 hr for fungi at 37°C. Test run was triplicates; the lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC value.

Molecular Docking:

The binding conformations of the prepared compound was determined by Autodock Vina program and was used to dock 3-((1H-benzo[d] imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives to active sites of MurD ligase. For docking Auto Dock tools (ADT) 1.5.4 was used to prepare input files.[66] L-Glu containing sulphonamide inhibitor was retrieved with the structure of MurD ligase in complex.[67] Ions and water molecules were removed from protein crystallographic structures, partial atomic charges were assigned and polar hydrogens were added by Kollman united charges method.[68-69] In the enzyme the pKa values of the residues were calculated to determine if any of them likely to adopt nonstandard ionization states using PROPKA 2.0.[70] Lysine, histidine and arginine side chains residues protonated while glutamic acid, aspartic acid and carboxylic acid groups deprotonated. For each ligand, Gasteiger charges assigned, nonpolar hydrogens merged and rotatable bonds were setup. The structures saved in the file pdbqt by Autodoc. Grid box of 40×40×40 Å created around enzyme active pocket with spacing 1nm each dimension to determine ligand protein interactions. The average coordinates of crystallography ligand in the pdb structure has been set by the center of grid box. Other vina docking parameters were set by default.

Table-1: Data of newly synthesized compounds

Entry	Compound	R_1	R_2	R_3	Reaction Time (min)	Yield (%)	Melting Point (^{0}C)
1	**2a**	H	H	H	10	95	166-168
2	**2b**	H	H	CH_3	10	95	160-162
3	**2c**	H	CH_3	H	10	96	131-133
4	**2d**	CH_3	H	H	10	95	144-146
5	**2e**	H	OCH_3	H	10	95	122-124
6	**2f**	OCH_3	H	H	10	97	129-131
7	**3a**	H	H	H	30	96	----
8	**3b**	H	H	CH_3	30	95	----
9	**3c**	H	CH_3	H	30	96	----
10	**3d**	CH_3	H	H	30	97	----
11	**3e**	H	OCH_3	H	30	96	----
12	**3f**	OCH_3	H	H	30	95	----

13	**4a**	H	H	H	60	89	220-222
14	**4b**	H	H	CH_3	60	90	230-232
15	**4c**	H	CH_3	H	60	88	260-262
16	**4d**	CH_3	H	H	60	90	241-243
17	**4e**	H	OCH_3	H	60	90	238-240
18	**4f**	OCH_3	H	H	60	89	231-233

Table-2: Antibacterial Activity study of newly synthesized compounds

Sr. No.	Compounds	Minimal Bactericidal Concentration			
		E. Coli	P. Aeruginosa	S. Aureus	S. pyogenus
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442
		µg/mL			
1	4a	250	250	100	100
2	4b	62.5	500	125	250
3	4c	250	500	250	1000
4	4d	250	250	500	250
5	**4e**	**100**	**125**	**25**	**50**
6	4f	500	500	500	1000

Table-3: Antifungal activity study of newly synthesized compounds

Sr. No.	Compounds	Minimal Fungicidal Concentration		
		C. Albicans	A. Niger	A.Clavatus
		MTCC 227	MTCC 282	MTCC 1323
		µg/mL		
1	4a	>1000	500	1000
2	4b	> 1000	1000	>1000
3	4c	500	1000	1000
4	4d	1000	> 1000	> 1000
5	**4e**	**500**	**500**	**500**
6	4f	> 1000	> 1000	> 1000

Table-4: Antibacterial and antifungal activities of standard drugs

Drug	Minimal Bactericidal Concentration			
	E. Coli	P. Aeruginosa	S. Aureus	S. pyogenus
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
	µg/mL			
Erythromycin	2	5	0.25	0.5
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Drugs	Minimal Fungicidal Concentration		
	C. Albicans	A. Niger	A.Clavatus
	MTCC 227	MTCC 282	MTCC 1323
	µg/mL		
Nystatin	100	100	100
Greseofulvin	500	100	100

Molecular Docking:

The synthesized compounds **4a-4f** docked in active site of MurD ligase using Autodock vina docking tool and the results of docking are shown in table.

Table-5 Molecular docking of synthesized compounds in the study

Compound ID	Free Binding Energy (Kcal/mol) against 2JFH
4a	-4.96
4b	-4.41
4c	-4.22
4d	-3.98
4e	-5.78
4f	-5.66

All 3-(1H-benzo(d)imidazole-2-ylthio) methyl) -2-chloroquinoline derivatives efficiently bind in the active site of residues like LEU13, ARG37, SER71, PRO72, GLY73 and ASN138 of MurD ligase.

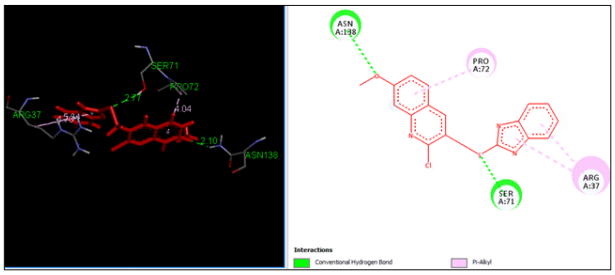


Fig.1 Binding Pose and molecular interactions of **4e** in the active site of MurD ligase.

Methoxy substitution **(4e, -5.78)** at the seventh position of the 3-(1H-benzo(d)imidazole-2-ylthio) methyl) -2-chloroquinoline ring interact with polar amino acid residues ASN138 where it interact with methoxyl oxygen atom of chloroquinoline ring with the distance of 2.10 Å to form conventional hydrogen bond interactions. The another polar amino acid of active site SER71 interact with bridged sulfur atoms of 2-chloroquinoline and benzimidazole

ring to forms conventional hydrogen bond interactions with the distance of 2.77 Å. The charged amino acid ARG37 and hydrophobic amino acid PRO72 interact with π electron cloud of aromatic ring and alkyl groups to form weak non covalent π-alkyl interactions of various distance shown in figure **Fig.1**.

Methoxy substitution at the sixth position of the 3-(1H-benzo(d)imidazole-2-ylthio) methyl) -2-chloroquinoline ring (**4f, -5.66)** interact with polar amino acid residues hydrophobic amino acid GLY73 and PRO72 interact with methoxyl hydrogen atoms of chloroquinoline ring with the distance of 2.02 and 2.11 Å to form carbon hydrogen bond interactions. The another hydrophobic amino acid of active site LEU13 interact with bridged sulfur atoms of 2-chloroquinoline and benzimidazole ring to forms carbon hydrogen bond interactions with the distance of 3.03 Å. The charged amino acid ARG37 and polar amino acid PRO72 interact with π-electron cloud of aromatic ring and alkyl groups to form weak non covalent π-alkyl interactions of various distance shown in figure **Fig.2**.

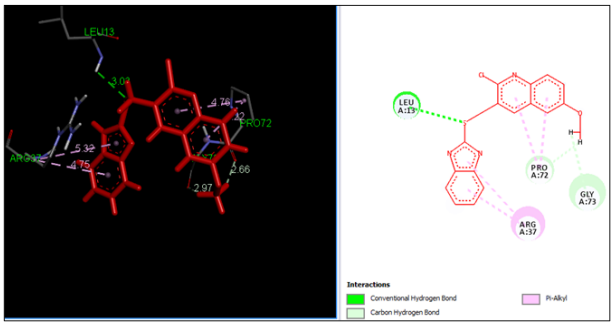


Fig.2 Binding Pose and molecular interactions of **4f** in the active site of MurD ligase.

Conclusion

In this study, new derivatives using 2-chloroquinolin-3-carbaldehyde were prepared as 3-(1H-benzo(d)imidazole-2-yithio) methyl-2-chloroquinoline. Docking study and preliminary evaluation for antimicrobial activity of the newly prepared compounds are performed. When compared with the standard drug Ampicillin the compound with substitution of methyl at the 8 th position of the quinoline ring **4b**, substitution of the methoxy at the 7 th position of the quinoline ring **4e** shows antibacterial activity with Gram +ve bacterial strains and Gram –ve strain.The newly prepared compounds were studied for antifungal activity using standard drug Greseofulvin**.** The compound **4a** and **4e** found active with C. albicans, A. Clavatus and A. Niger.

Antifungal and antibacterial activity study supported by molecular docking study using MurD ligase enzyme. The molecular docking study suggested that **4e** and **4f** are the most active among all the newly prepared 3-(1H-benzo(d) imidazole-2-yithio) methyl-2-chloroquinoline derivatives and will served as excellent lead in anti-microbial drug discovery.

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