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

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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 ¹H NMR, 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 Griseofulvin, 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-ylthio) 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.

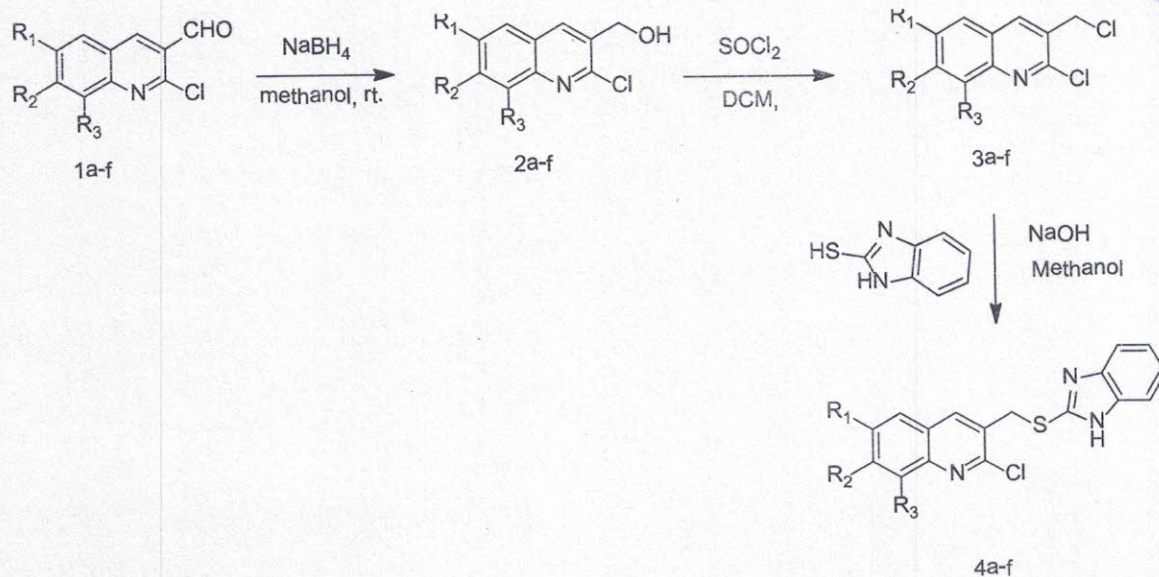
Results and Discussion

Novel 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives were synthesized in quantitative yield (**Scheme-1**). 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, ¹H 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 Griseofulvin **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** and **4f** were found to possess less activity.



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

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 $\text{CDCl}_3 + \text{DMSO}$ 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 5mL was 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-fusing an appropriate quantity of reagents.

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

To the solution of 1H-benzo(d)imidazole-2-thiol 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);

¹H NMR (CDCl₃+ 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)

¹H NMR (CDCl₃, 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-2-ylthio) methyl-2-chloro-7-methylquinoline

IR (cm⁻¹): 3444 (-NH), 3052 (-C-H), 1621 (-C=C), 769 (-C-Cl)

¹H NMR (CDCl₃, 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-2-ylthio) methyl-2-chloro-8-methylquinoline

IR (cm⁻¹): 3385 (-NH), 3076 (-C-H), 1617 (-C=C), 737 (-C-Cl)

¹H NMR (CDCl₃+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-2-ylthio) methyl-2-chloro-7-methoxyquinoline

IR (cm⁻¹): 3427 (-NH), 3078 (-C-H), 1620 (-C=C), 757 (-C-Cl)

¹H NMR (CDCl₃, 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-2-ylthio) methyl-2-chloro-6-methoxyquinoline

IR (cm⁻¹): 3444 (-NH), 3078 (-C-H), 1621 (-C=C), 751 (-C-Cl)

¹H NMR (CDCl₃+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 was carried 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 dimethylsulphoxide 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 (°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
ug/mL			
Nystatin	100	100	100
Greseofulvin	500	100	100

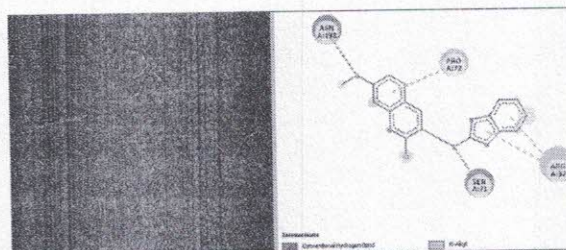
Molecular Docking:

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.

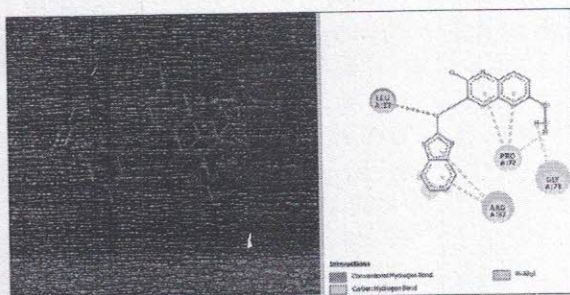


Fig.2 Binding Pose and molecular interactions of **4f** in the active site of MurD ligase.

Conclusion

In this study, new derivatives using 2-chloroquinolin-3-carbaldehyde were prepared as 3-(1H-benzo(d)imidazole-2-ylthio) 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 8th position of the quinoline ring **4b**, substitution of the methoxy at the 7th 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 Griseofulvin. 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-ylthio) methyl-2-chloroquinoline derivatives and will serve as excellent lead in anti-microbial drug discovery.

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