Original Article

Anti-Tuberculosis Activity and Synthesis of 3-((1*H*-Benzo[*d*]Imidazol-2-Ylthio)Methyl)-2-Chloroquinoline Derivatives by Using Copper Nanoparticles Grafted on Carbon Microspheres

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ABSTRACT

The copper nanoparticles grafted on carbon microsphere (Cu-NP/C) catalyst was used to create a convenient and efficient synthesis of 3-(1*H*-benzo(*d*)imidazole-2-yithio) methyl-2-chloroquinoline (4a-f) from 2-Chloroquinoline-3-carbaldehyde (1a-f) and 1H-benzo[d]imidazole-2-thiol (Scheme 1 and Table 2). The synthesis was placed under mild reaction conditions, resulting in an excellent yield (92-97%, Table 2) of the appropriate compounds. The prepared compounds were characterized by H1NMR, IR, and Mass spectroscopy. These synthesized compounds were studied for anti-tuberculosis activities (Tables 3 and 4a-f) against the standard drug isoniazid and rifampicin and showed the moderate activity.
To explain the experimentally discovered affinity for 3-((1*H*-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives, molecular docking studies were conducted. A molecular docking study reveals the 4e and 4f derivatives of 3-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-2-chloroquinoline to be the most active ones.

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Introduction

A highly prominent and significant class of heterocyclic compounds is the quinoline ring system, because of their wide range of uses in organic synthesis, coordination chemistry, and drug design and development which includes antibacterial [1], anti-inflammatory [2], antifungal [3], antimalarial [4], anti-HIV [5], anti-hypertensive [6], antiviral [7], anticancer [8], DNA binding capacity [9], anti-tuberculosis [10], and Antihistamine [11]. Also, quinoline is used in the study of bioorganic and bio-organometallic processes [12]. Benzimidazole is also an important class of heterocyclic compounds, the benzimidazole derivatives exhibit biological activity like antimicrobial [13], antiviral [14], antimicrobial activity [15], cardio-vascular [16], anti-Parkinson's [17], anticancer [18], anti-inflammatory [19], and antiulcer [20]. Mercaptobenzimidazole, on the other hand, is employed in the synthesis of well-known proton pump inhibitors like pantoprazole [21], omeprazole [22], rabeprazole [23], and lansoprazole [24]. Copper nanocatalysts are significant nanoparticles [25]. Compared with the traditional metal-catalyzed processes, copper nanoparticle catalyzed reactions have advantages in terms of low catalyst loading, high atom economy, improved yields, affordability, faster reaction times, and the catalyst's capacity to be recycled. Nanoparticles self-assemble and are challenging to remove from the reaction mixture. By securing them to a few supports, this restriction can be removed. These newly created catalytic metallic nanoparticles are cheap, neither entirely nor very hazardous, extremely active, stable, and simple to be separated from the reaction mixture.

A survey of the literature reveals that very little effort has been made to maximize the combined benefit of these two pharmacophores Quinoline and Benzimidazole. Our goal is to make some attempts in the direction of having synergistic, Anti-tuberculosis properties of the produced combination pharmacophore from quinoline and benzimidazole. In this paper, we offer a straightforward and practical approach to the synthesis of 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline, under the catalysis of copper nanoparticles grafted on carbon microspheres (Cu-NP/C) (Scheme 1) by using Cu-NP/C reaction proceeded smoothly with an excellent yield.

Experimental

Materials and methods

The 2-chloroquinoline-carbaldehyde was synthesized in the lab by using the reported method. S.D. fine chem, Avra chemicals, and spectrochem are the providers for the solvents and reagents. The recommended procedure was used to synthesize the Cu-NP/C catalyst [26-27]. Physical constants (such as the melting point) were determined in open capillaries at the atmospheric pressure. AVANCE was subjected to proton NMR experiments in CDCl3+DMSO and CDCl3 at 300 and 400 MHz with TMS serving as a reference. FTIR systems from Perkin-Elmer and Shimadzu were used to capture IR spectra. Analysis of mass spectra using thermo exactive orbitrap methods (FTMS) reveals a molecular ion peak.

Experimental Procedure

Synthesis of Cu-NP/C Catalyst

A styrene-based commercial cation exchange resin containing divinylbenzene crosslinker

(7%), acrylonitrile modifier (2%), and iminodiacetate (-$CH_2N(CH_2COOH)_2$) functional groups (binding capacity of 1 mol divalent metal cation per 1 dm3 resin, VARIONBIM-7) was used as the starting material. Initially, the resin was saturated with copper (II) ions by using an aqueous copper sulfate solution. The exchanged resin was dried in the air followed by in a drying box at 120 ºC for 1 day. The dried resin was carbonized for 4 h in dry nitrogen.

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

2-Chloroquinoline-3-carbaldehyde (1.9 g, 10 mmol) was added to 15 mL of methanol, stirred for five minutes, and then it was slowly added sodium borohydride (0.5 g, 13 mmol) while stirring at room temperature. After another 10 minutes of stirring, the reaction's progress was analyzed by using thin layer chromatography (TLC). As soon as it was finished, the reaction mixture was concentrated on a rotary evaporator. The product was filtered and washed in cold water to afford the titled compound (**2b-f**) (1.85 gm, 95%).

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

Thionyl chloride (2 mL) in dichloromethane (5 mL) were added dropwise to the stirring mixture containing 1.75 g of 2-chloroquinolin-3-yl methanol and 9 mmol in 10 mL of dichloromethane. The reaction was stirred for an additional hour at room temperature, and the progress of the reaction was monitored by using thin layer chromatography with a hexane-ethyl-acetate solvent system. After the starting material had been completely converted, the reaction mass was concentrated on a rotary evaporator to produce a crude product that was 1.85 gm (96% pure), which was sufficient and could be utilized right away for the following stage.

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

To the solution of 1H-benzo(d)imidazole-2 thiol 1.48 gm, 10 mmol in methanol 20 mL added a catalytic amount of Cu-NP/C. To this pre-stirred (10 min) solution 2-chloro-3-(chloromethyl) quinoline 1.75 gm, 9 mmol added at room temperature and stirred for 40 min. The reaction progress was checked on thin layer chromatography by using hexane and ethyl acetate as a solvent system (8:2). After the complete conversion, the reaction mass was filtered to separate the catalyst. The solvent was removed under vacuum on a rota evaporator. To the obtained residue, the cold water 100 mL was added, filtered solid, and washed with water 50 mL to get a product, which is dried. Yield 2.6 gm, 92%.

Anti-tubercular activity

By using isoniazid and rifampicin as a reference medication, all synthesized compounds were screened for anti-tubercular efficacy against M. tuberculosis H37RV. By preparing various concentrations, the mycobacteria growth indicator tubes (MGIT) containing 4 mL of modified Middle brook 7H9 broth base were examined for anti-tuberculosis efficacy in this approach. After centrifuging the tubes for 15 minutes at 3000 rpm, the suspension was allowed to sit for 20 minutes. Following that, a prepared suspension of the M. tuberculosis strain H37Rv (104 to 107 CFU/mL) and 0.1 mL of egg-based medium (Lowenstein and Jensen, L.J.) were added to the medium to be incubated. When a positive result was seen, the MGIT tubes were then tightly closed, thoroughly mixed, and incubated in the BACTEC MGIT apparatus at 371 °C. The readings were measured daily starting from the second day of incubation. Positive cultures were usually detected within 10 days.

The MGIT tubes were taken out of the incubator and put in the UV light beside a positive control tube and an un-inoculated tube to read the results (negative control). The bright orange color and an orange reflection on the meniscus were both signs of bright fluorescence that the associated MGIT tube had observed. In a BACTEC MGIT system, the primary screening was done by using doses of 1000, 500, and 250 µg/mL against M. tuberculosis H37Rv.

The most powerful compounds were those that showed 99% inhibition in the initial screen. The L.J. MIC method was used to check each of the remaining compounds three times for their true MIC. The lowest concentration preventing 99% of the inoculum from growing was called the MIC.

By using the L.J. MIC technique, test compounds were subjected to the secondary screening against M. tuberculosis H37Rv. The liquid L.J. medium was then added to stock solutions of the primary 1000, 500, and the secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, and 3.12 µg/mL dilutions of each test agent in DMSO, and the media were sterilized by using the inspissations procedure. A M. tuberculosis H37Rv culture that was developing on L.J. media was collected and stored in bijou bottles containing 0.85% saline. After 24 hours of incubation at 37±1 °C, M. tuberculosis H37Rv was streaked in these tubes (5 X 10^4 bacilli per tube). Then, these tubes were incubated once again at 37±1 °C. After 12, 22, and finally 28 days of incubation, bacilli began to grow. Compound-containing tubes were compared with control tubes that only had medium and M. tuberculosis H37Rv incubated in them. The MIC concentration of the test substance was determined to be the concentration at which no colonies developed or < 20 colonies appeared. The well-known medication isoniazid was tested against the common strain of M. tuberculosis, H37Rv.

Molecular Docking

The Autodock Vina program was used to determine the binding conformations of the synthesized compound, which were then used to dock 3-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives to active sites of MurD ligase.

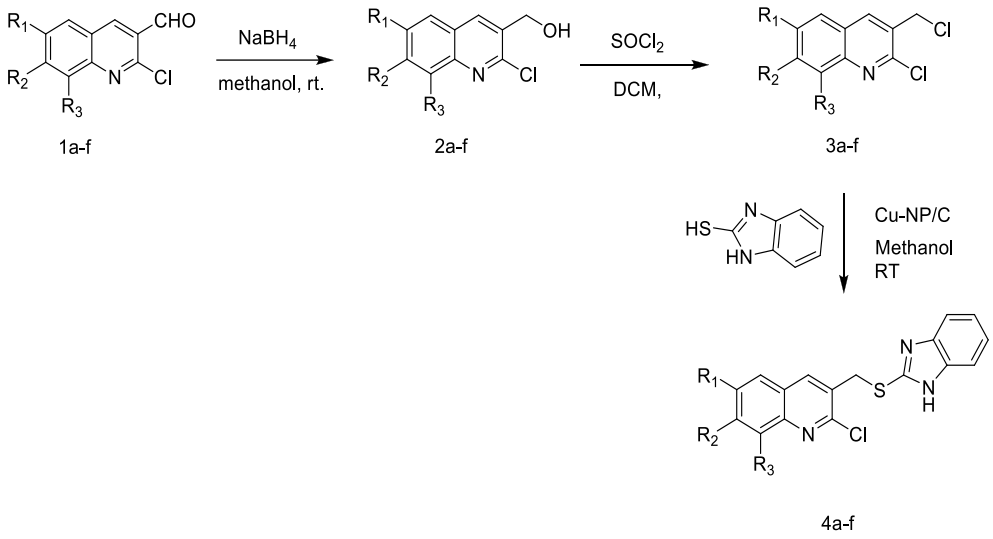
Input files for docking were prepared by using Auto Dock Tools (ADT) 1.5.4. The structure of MurD ligase was recovered together with the L-Glu containing sulphonamide inhibitor. [28-30] Ions and water molecules were taken out of the protein. By using the Kollman unified charges approach, the partial atomic charges were assigned to crystallographic structures and polar hydrogen was added. By using PROPKA 2.0, the pKa values of the residues in the enzyme were determined to see if any of them were likely to adopt non-standard ionization states. While glutamic acid, aspartic acid, and carboxylic acid groups were deprotonated, the side chains of lysine, histidine, and arginine residues were protonated.

Gasteiger charges were assigned, nonpolar hydrogen was combined, and rotatable bonds were made up for each ligand.

Autodoc stores the structures in the file pdbqt.

To identify ligand-protein interactions, a grid box of 40 ×40 ×40 was made around the active site of the enzyme, with 1 nm between each dimension. The center of a grid box has been used to get the average coordinates of the crystallographic ligand in the pdb structure.

Other vina docking options were pre-configured.



Scheme 1. Synthesis of 3-(1*H*-benzo(*d*)imidazol-2ylthio) methyl) -2-chloroquinolin

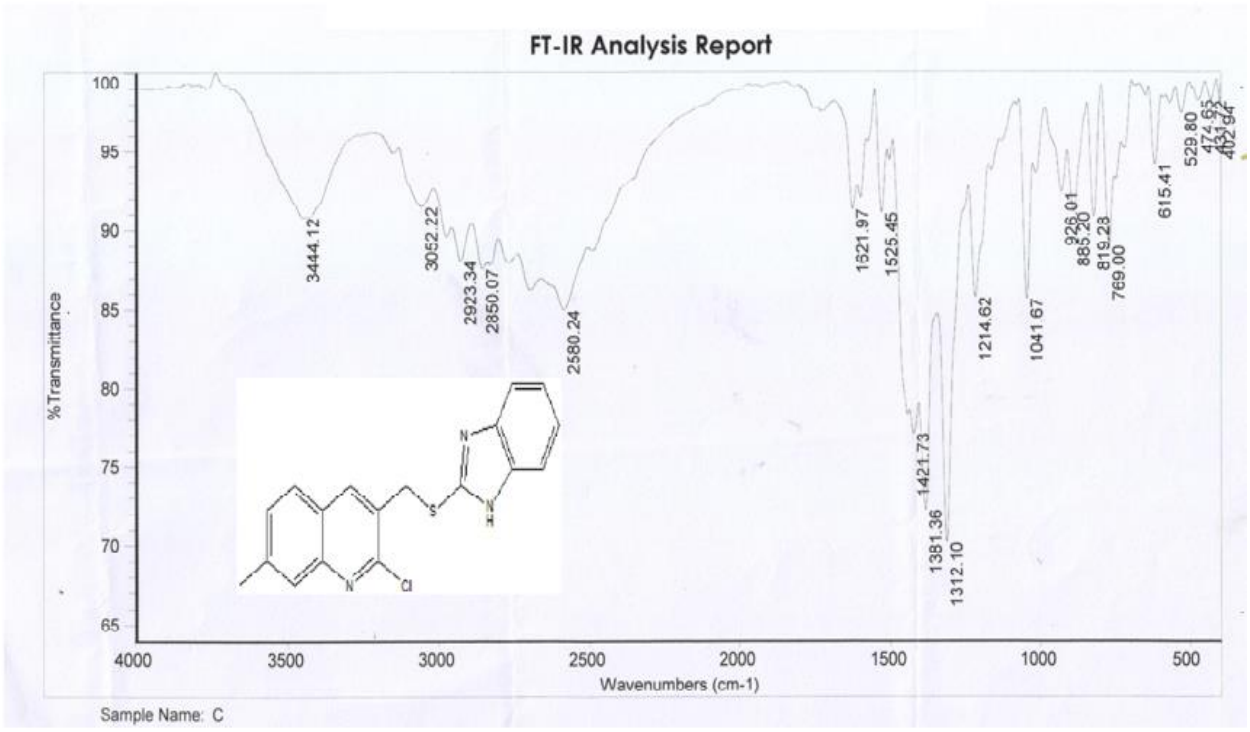


Figure 1. IR Spectra

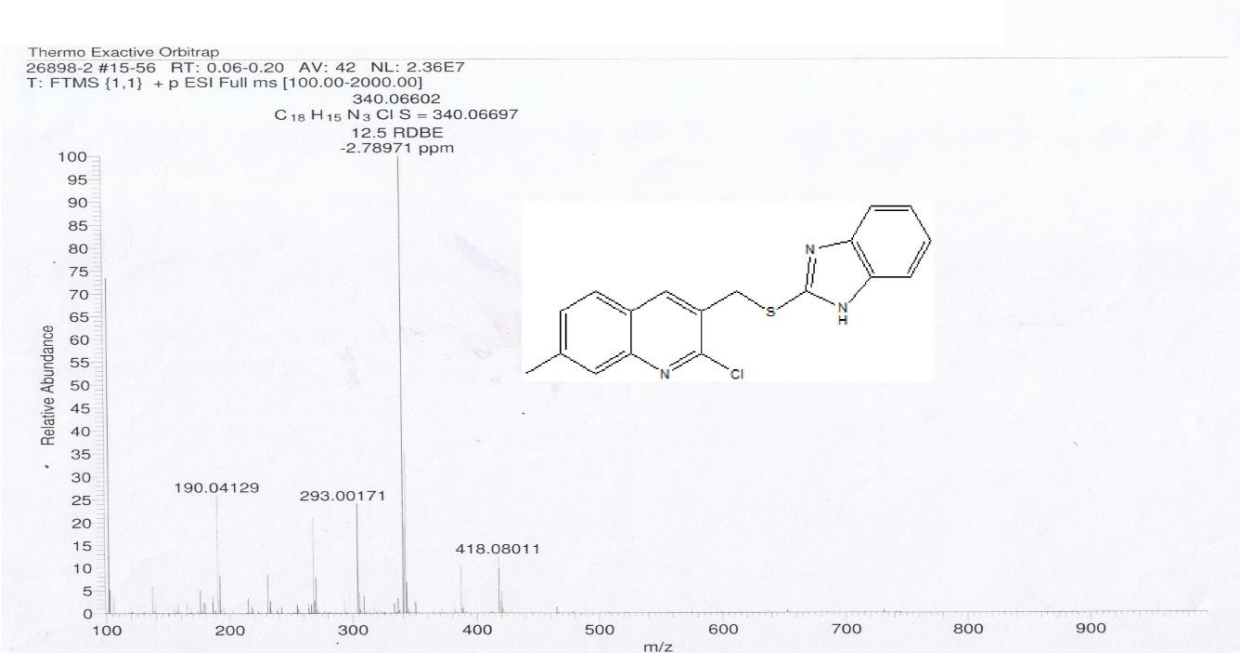


Figure 2. MASS Spectra

Figure 3. ^{1}H NMR Spectra

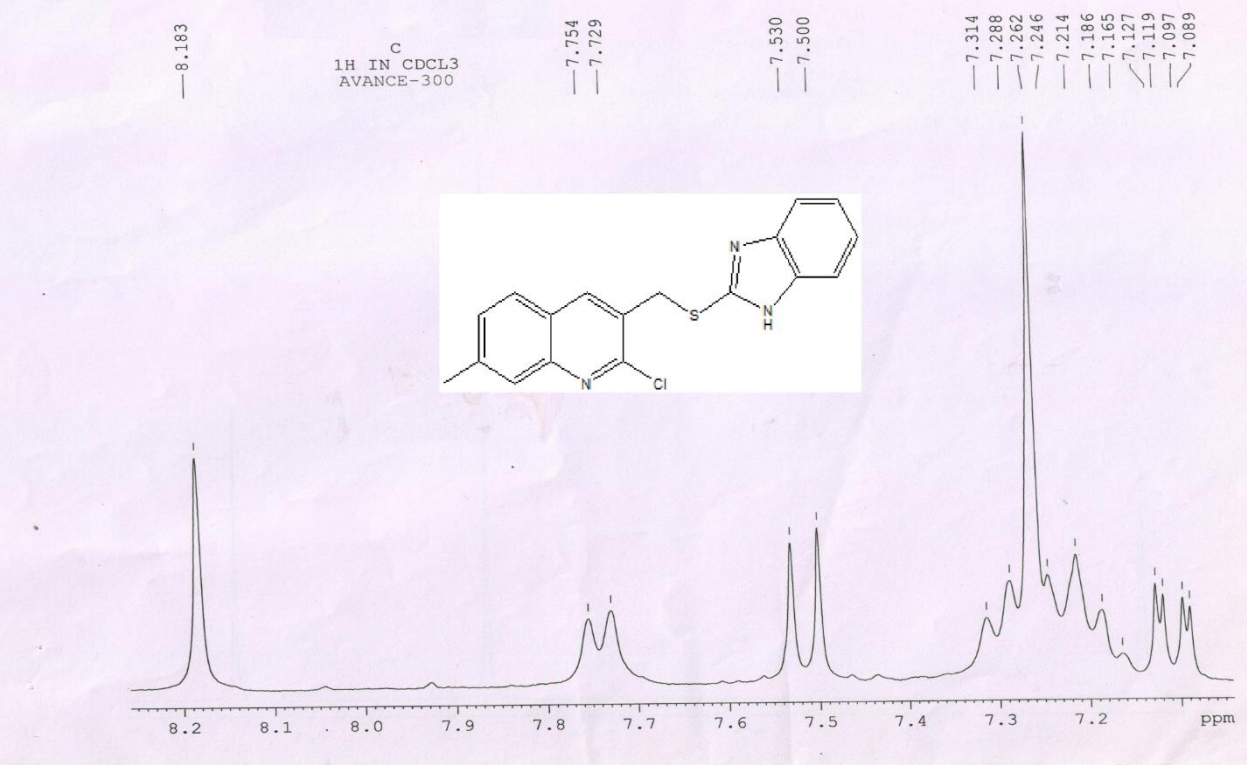


Figure 4. ^{1}H NMR Spectra

Results and Discussion

We describe an effective and simple procedure for the synthesis of 3-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives from 2-chloroquinoline-3-carbaldehyde and 1*H*-benzo[*d*]imidazole-2-thiol by using Cu NP/C as a reusable and secure catalyst. Due to the growing interest in solid catalysts for the heterocycles synthesis, the recommended procedure was used to synthesize the Cu-NP/C catalyst [30-31] and could be recycled for multiple times without significantly losing its catalytic activity.

The procedure involves reducing 2-chloroquinoline-3-carbaldehyde 1a-f with sodium borohydride in methanol at room temperature to generate derivatives of (2-chloroquinolin-3-yl)methanol 2a-f in 94-97% yields with less time (10 min). Table 2 refers to the entries 1-6. These 2-chloroquinolin-3-yl)methanol derivatives 2a-f were reacted with thionyl chloride in dichloromethane to give 2-chloro-3-(chloromethyl)quinoline derivatives 3a-f in 95-98% yield, entries 7-12. These obtained derivatives of 2-chloro-3-(chloromethyl)quinoline 3a–f were reacted with 1*H*-benzo[*d*]imidazole-2-thiol in methanol in the presence of copper nanoparticles grafted on carbon microspheres as a catalyst. The progress of the reactions was monitored on TLC by using mobile phase (8:2) hexane: ethyl acetate. The reaction proceeded smoothly under catalytic conditions and completed in 1 hour to afford the corresponding titled compounds with entries 13–18 in Table 2 in high yields (90–97%).

Initially, a series of reactions involving 2-chloro-3-(chloromethyl)quinoline and 1*H*-benzo[*d*]imidazole-2-thiol were conducted in different solvents and catalysts to optimize the reaction conditions at various temperatures (Table 1).

An essential feature of a catalyst is its reusability. The catalyst was discovered to work effectively in successive runs without significantly losing its catalytic activity. Therefore, Cu-NP/C can be easily separated and successfully recycled numerous times without suffering a major loss of activity.

The chemical structures of the new compounds were confirmed by IR, ^{1}H NMR, and mass spectroscopic data. The synthesized compounds underwent anti-tubercular activity screening against M. tuberculosis H37Rv by using isoniazid and rifampicin as a reference medication. By using the broth dilution assay by the L.J. agar method, the MIC of the investigated substances was identified. The utilized diluent was DMSO. Table 3 provides the MIC values of the examined substances. Compared the majority of the produced compounds with the isoniazid and rifampicin as a standard drug, they all showed a moderate activity.

To explain the experimentally discovered affinity for 3-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives, the molecular docking studies were conducted. A molecular docking study reveals the 4e and 4f derivatives of 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline to be the most active ones.

Table 1. Optimization of the reaction conditions

Entry	Solvent	Catalyst	Temperature (°C)	Time (min.)	Yield (%)
1	CH_3COCH_3	NaOH	RT	60	81
2	CH_3COCH_3	Cu-NP/C	RT	55	78
3	CH_3OH	K_2CO_3	RT	60	85
4	CH_3OH	NaOH	RT	60	89
5	CH_3OH	Cu-NP/C	RT	40	92
6	C_2H_5OH	K_2CO_3	RT	55	78
7	C_2H_5OH	NaOH	RT	60	80
8	C_2H_5OH	Cu-NP/C	RT	60	83
9	CH_3OH	K_2CO_3	40	50	76
10	CH_3OH	Cu-NP/C	40	50	82
11	CH_3OH	NaOH	40	52	84
12	C_2H_5OH	NaOH	40	60	73

Table2. 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	40	92	220-222
14	**4b**	H	H	CH_3	45	95	230-232
15	**4c**	H	CH_3	H	40	96	260-262
16	**4d**	CH_3	H	H	45	94	241-243
17	**4e**	H	OCH_3	H	40	97	238-240
18	**4f**	OCH_3	H	H	45	95	231-233

Table 3. Anti-tuberculosis activity

Anti Tuberculosis activity		
Method	L.J. Medium [Conventional Method]	
Sr No.	Compound	H37RV (MIC µg/mL)
1	4a	125
2	4c	125
3	4d	250
4	4f	100
Standard Drug		
Isoniazid		0.20 µg/mL
Rifampicin		0.25 µg/mL

Molecular docking

The results of the docking of the produced compounds 4a–4f in the active site of MurD ligase are presented in Table 4.

Methoxy substitution (4e, -5.78) at the seventh position of the 3-(1*H*-benzo(*d*)imidazole-2-ylthio)methyl)-2-chloroquinoline ring interacts with the polar amino acid residues in ASN138, where it interacts with the methoxyl oxygen atom of the chloroquinoline ring at a distance of 2.10 to form conventional hydrogen bond interactions. With a distance of 2.77, another polar amino acid of the active site SER71 interacts with the bridging sulfur atoms of the 2-chloroquinoline and benzimidazole rings to form typical hydrogen bond interactions.

The weak non-covalent-alkyl interactions of various distances between the charged amino acid ARG37 and the hydrophobic amino acid PRO72 and the aromatic ring and alkyl groups are seen in Figure 5.

Hydrophobic amino acids GLY73 and PRO72 interact with the methoxyl hydrogen atoms of the chloroquinoline ring at a distance of 2.02 and 2.11 to form carbon-hydrogen bond interactions. Methoxy substitution at the sixth position of the 3-(1H-benzo(d)imidazole-2-ylthio) methyl) -2-chloroquinoline ring (4f, -5.66) interacts with polar amino acid residues. Another hydrophobic amino acid of the active site LEU13 forms carbon-hydrogen bond interactions with the 2-chloroquinoline and benzimidazole rings at a distance of 3.03.

The weak noncovalent-alkyl interactions of various distances formed by the charged amino acid ARG37 and the polar amino acid PRO72 with the aromatic ring and alkyl groups are depicted in Figure 6.

Table 4. Molecular docking of synthesized compounds

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

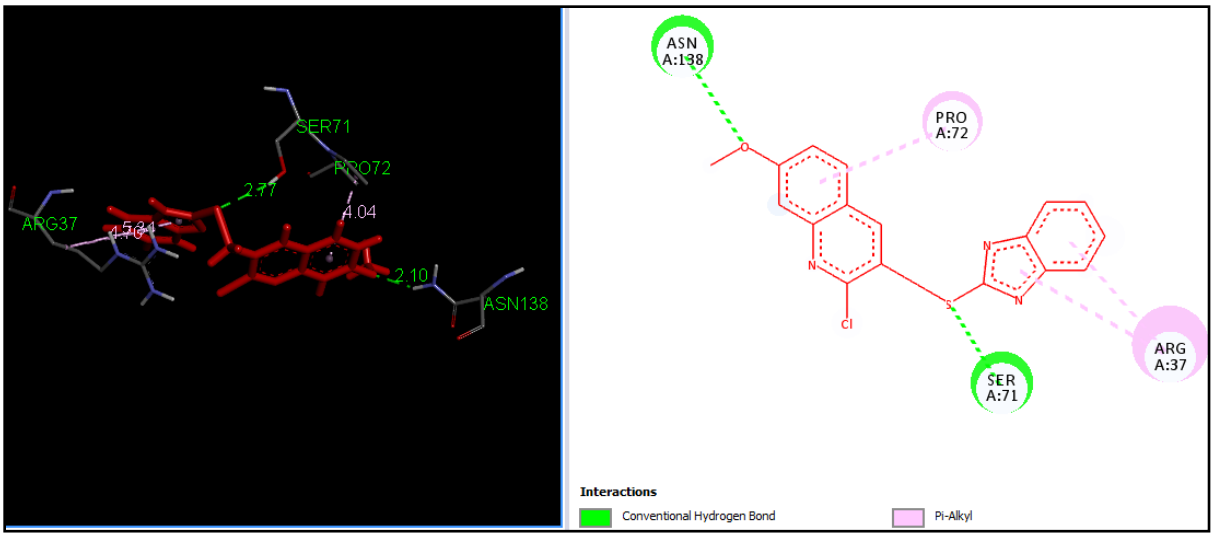


Figure 5. Binding pose and molecular interactions of **4e** in the active site of MurD ligase

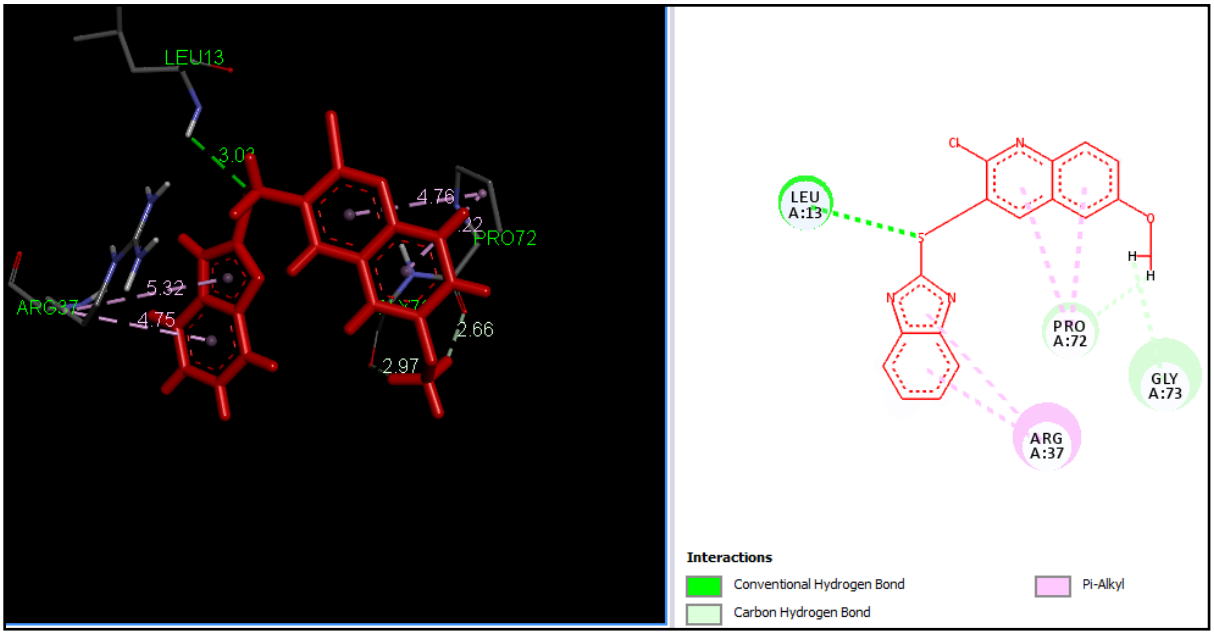


Figure 6. Binding pose and molecular interactions of **4f** in the active site of MurD ligase

Spectral Analysis: Compound (4a)

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

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.
Elemental analysis: C: 62.52%, H: 3.60%, N: 12.81%.

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.
Elemental analysis: C: 63.52%, H: 4.05%, N: 12.25%.

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.
Elemental analysis: C: 63.55%, H: 4.09%, N: 12.29%.

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.
Elemental analysis: C: 63.54%, H: 4.07%, N: 12.28%.

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.
Elemental analysis: C: 60.69%, H: 3.92%, N: 11.72%.

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.
Elemental analysis: C: 60.65%, H: 3.90%, N: 11.70%.

Conclusion

In this particular work, the 3-(1*H*-benzo(*d*)imidazole-2-yithio)methyl-2-chloroquinoline is synthesized from 2-chloroquinoline-3-carbaldehyde and 1*H*-benzo[*d*]imidazole-2-thiol by using a reusable heterogeneous catalyst made of carbon microspheres bonded with copper

nanoparticles, use of a readily separable catalyst (Cu-NP/C), risk-free settings for the reaction, and clean reaction conditions. The current procedure for the synthesis of 3-(1*H*-benzo(*d*)imidazole-2-yithio)methyl-2-chloroquinoline is environmentally friendly and green.

Likewise, the synthesized compound was characterized and evaluated for anti-tuberculosis activity. And the analyzed compound showed the moderate activity. It might be beneficial for future testing, designing, and creating more effective anti-tuberculosis agents. The anti-tuberculosis activity study was supported by using a molecular docking analysis employing the enzyme MurD ligase.

According to the molecular docking analysis, the most active 3-(1*H*-benzo(*d*)imidazole-2-yithio)methyl-2-chloroquinoline derivatives are 4e and 4f.

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