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Synthesis and Antimicrobial Evaluation of New Quinoline Derivatives

Jonny Kumar*, Arvind Kumar

Abstract

Introduction: Heterocyclic compound quinoline, a very important category of heterocyclic compounds, and its derivatives have medicine properties. Quinoline contains element heterocyclic aromatic ring. It's additionally referred to as benzopyridine or 1-aza-napthalene and chemical formula of quinoline is chemical formula C9H7N. **Methods:** Synthesis of quinoline derivative from 4-Methoxy-acetophenon and 1H-Indole-2,3-dione after that reaction between 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid and using excess of dry methanol in the presence con. H2SO4 for the synthesis of 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid methyl ester and this intermediate product react with hydrazine hydrate in methanol and 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide derivative collated and react with five deferent substituted acetophenone. Five quinoline derivatives were synthesis and were synthesis, characterization and evaluated antimicrobial activity against standard drug. **Results:** Some new substituted quinoline derivative 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-phenyl-ethylidene) hydrazide (M1), 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid [1-(4-amino-phenyl)-ethylidene]-hydrazide (M2), 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid [1-(4-bromo-phenyl)-ethylidene] hydrazide (M3), 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid [1-(4-chloro-phenyl)-ethylidene]-hydrazide (M4) and 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid [1-(4-hydroxyphenyl) ethylidene]-hydrazide (M5). All derivatives were found the active against different microorganism. Some compounds show the good antifungal activity. **Conclusion:** Some new substituted quinoline derivative synthesis and evaluated antimicrobial activity against the Gram-positive and Gram-negative bacterial stain and fungal stain. All derivatives were shown the antimicrobial activity.

Keywords: Anticonvulsant activity, Antitumor activity, Anti-inflammatory, Antimicrobial activity, Antitumor, Enzyme inhibiter activity, Quinoline

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Introduction

Heterocyclic compound quinoline, a very important category of heterocyclic compounds, and its derivatives have medicine properties.[1] The quinoline ring used for the look of the many artificial compounds.[2] In many manmade, quinoline is found and natural product shown to exhibit a good form of medicine activities antimicrobial activity,[3-8] anti-inflammatory drug activity,[9-13] malignant tumor activity,[14-18] and inhibitor activity.[19-21] It's lead compound and acts as a major pharmacophore for varies medicine activities.[22] Quinoline contains element heterocyclic aromatic ring. It's additionally referred to as benzopyridine or 1-aza-napthalene and chemical formula of quinoline is chemical formula C_9H_7N.[23-26] According to this investigation, quinoline derivatives a very important category of heterocyclic compounds for synthesize and to evaluate their biological activity for the antimicrobial activity.

Materials and Methods

All borosilicate glassware use for the synthesis. All chemical and solvent used after dry and chemical purchased from the S.D. Fine, Merck (India), Central Drug House (India). Open capillary method use for the determination of melting point determined melting point is uncorrected. Reaction progress monitored by previously cleaned and silica gel G coated TLC plate with thickness of about 0.3 mm. Mobile phases were selected according to polarity of compound. Hot air oven uses for the dry and activation of TLC and dry of all glassware. FTIR spectra were recorded on spectra; potassium bromide (KBr) was on a Perkin-Elmer using KBr discs, Bruker 300 MHz spectrometer use for recorded H^1-NMR spectra was using $CDCl_3$ as solvent and TMS as internal reference (Chemical shifts in δ, ppm). The mass spectra were recorded on a Waters Micromass ZQ 2000 mass spectrophotometer.

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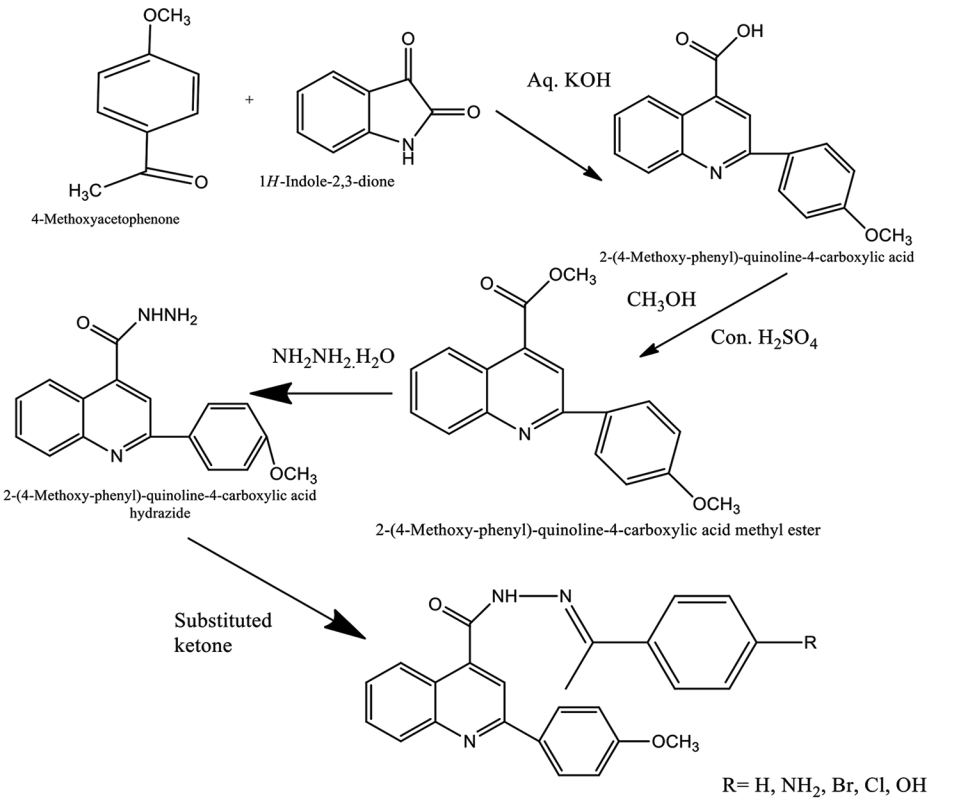
General Procedure

Synthesis of quinoline derivative

Synthesis of 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid was synthesized from 4-Methoxy-acetophenon (01.mol) and 1H-Indole-2,3-dione (0.1 mol) in the presence 25 *g* potassium hydroxide in 5 ml ethanol water was stirred at room temperature for 15–30 min and reflux for 12 *h*, 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid methyl ester was synthesis from 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (0.01 mol) using excess of dry methanol in the presence con. H_2SO_4 Reaction mixture reflux for 24 h after completion of reaction remove excess solvent and product was collected, 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide was synthesized from the reaction between 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid methyl ester (0.01 mol) and hydrazine hydrate (0.01 mol) in methanol reflux for 36 h. Solid product collected after completion of reaction by filtration and recrystallization, and substituted 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid



Substituted 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide derivative

hydrazide derivative was synthesis reaction between 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide (0.001 mol) and substituted acetophenone in the glacial acetic acid and ethanol reflux for 45 *min* and after the completion of reaction product collected by the filtration and recrystallization.

Synthetic scheme

Synthesis of new quinoline derivative from Methoxy-acetophenon and 1H-Indole-2,3-dione according to the following given synthetic scheme and five deferent new derivative synthesized from five substituted acetophenone.

Pharmacology

The *in vitro* antimicrobial activity evaluation of all synthesized compounds was carried out at S.D. College of pharmacy and vocational studies Muzaffarnagar following the procedure**.**

In vitro Antimicrobial Screening

The *in vitro* antimicrobial screenings of synthesized derivative evaluated against the standard bacterial strains, *Pseudomonas aeruginosa*, *Micrococcus luteus*, *Staphylococcus aureus*, and *Escherichia coli*. For antifungal evaluation, *Aspergillus niger* and *Penicillium chrysogenum* were used. Bacterial cultures obtained from the culture collection center, were used for antimicrobial test organisms. The bacteria were maintained in nutrient broth (NB) at 37°C and fungus was maintained on potato dextrose agar (PDA) at 28°C. The Gram-positive *S. aureus* and *M. luteus*, and Gram-negative bacteria *E. coli* and *P. aeruginosa* were pre-cultured in NB overnight in a rotary shaker at 37°C, centrifuged at 10,000 rpm for 5 min, pellet was suspended in double distill. Water and the cell density were standardized spectrophotometrically (A 610 nm). The fungal *P. chrysogenum* and *A. niger* were prepared from 5- to 10-day-old culture grown on PDA medium. The Petri dishes were flooded with 8–10 ml of distilled water and the conidia were scraped using sterile spatula.[27-31]

A definite volume of the microbial suspension (inoculums) was poured into the sterilized nutrient agar media (cooled at 40°C) and mixed thoroughly. About 20 ml of this suspension was poured aseptically in the Petri plates and kept till the solidification. The surface of agar plates was pierced using a sterile cork borer. The prepared wells were filled with equal volume of a solution of synthesized compounds and standard drugs; separately. After a period of pre-incubation diffusion, the plates were incubated face up for a definite time.[32-35]

Results and Discussion

A series of structurally diverse substituted 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide derivative were synthesized according to general synthetic route as illustrated in scheme. All the final products were confirmed using various analytical and spectral techniques.

2-(4-Methoxy-phenyl)-quinoline-4-carboxylic Acid (1-phenyl-ethylidene) Hydrazide (M1)

Chemical Formula: $C_{25}H_{21}N_3O$, Mol. Wt.: 379.45, Melting Point: 194-202°C, Rf value: 0.53

IR (KBr, cm^{-1}) ν 1571.02 (C=C), 1646.01 (C_6H_5), 1656.60 (C=O),1446.39 (-C-H), 2989.90 (-CH_3) 755.75 (Ar C-H) 1328.27 (Ar-$NH_{2)}$ 853.78 (R2-NH), ^{1}H-NMR (400 MHz, Solvent) δ ppm 2.16 (s, 3

H) 3.89 (s, 3 H) 7.04–7.07 (m, 2 H) 7.25–7.29 (m, 1 H) 7.41–7.45 (m, 2 H) 7.55 (ddd, *J* = 8.70, 7.17, 1.83 Hz, 1 H) 7.72–7.81 (m, 3 H) 7.99 (dd, *J* = 7.39, 1.89 Hz, 1 H) 8.10 (dd, *J* = 8.24, 1.28 Hz, 2 H) 8.33 (dd, *J* = 8.61, 1.53 Hz, 1 H) 8.69 (s, 1 H), Mass m/e: 395.16

Elemental analysis: C, 79.13; H, 5.58; N, 11.07; O, 4.22

2-(4-Methoxy-phenyl)-quinoline-4-carboxylic Acid [1-(4-amino-phenyl)-ethylidene]-Hydrazide (M2)

Molecular formula: $C_{25}H_{22}N_4O_2$, Mol. Wt.: 410.47, melting point: 192–198°C, Rf value: 0.53

IR (KBr, cm^{-1}) ν 1622.37(C=C), 1564.49 (C_6H_5), 1666.90 (C=O), 1446.72 (-C-H), 294454 ($-CH_3$) 853.78 (Ar C-H) 1343.13 (Ar-NH_2) 741.57 (R2-NH), ^{1}H-NMR (400 MHz, Solvent) δ ppm 2.13 (s, 3 H) 3.89 (s, 3 H) 6.62–6.65 (m, 2 H) 7.04–7.07 (m, 2 H) 7.39–7.41 (m, 2 H) 7.55 (ddd, *J* = 8.70, 7.17, 1.83 Hz, 1 H) 7.72–7.81 (m, 3 H) 7.99 (dd, *J* = 7.39, 1.89 Hz, 1 H) 8.33 (dd, *J* = 8.61, 1.53 Hz, 1 H) 8.69 (s, 1 H), mass m/e: 410.17 elemental analysis - C, 73.15; H, 5.40; N, 13.65; O, 7.80

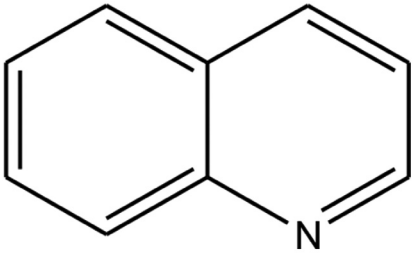
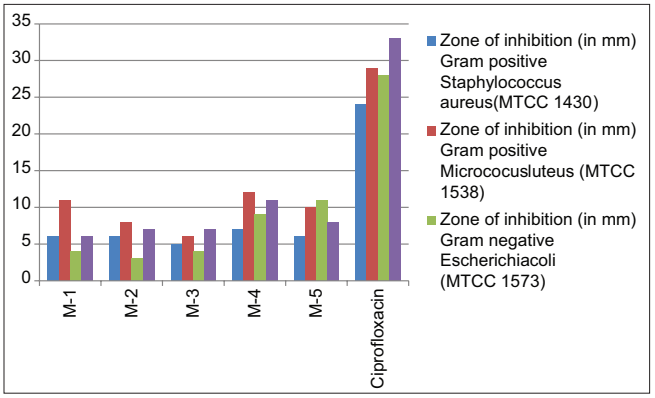
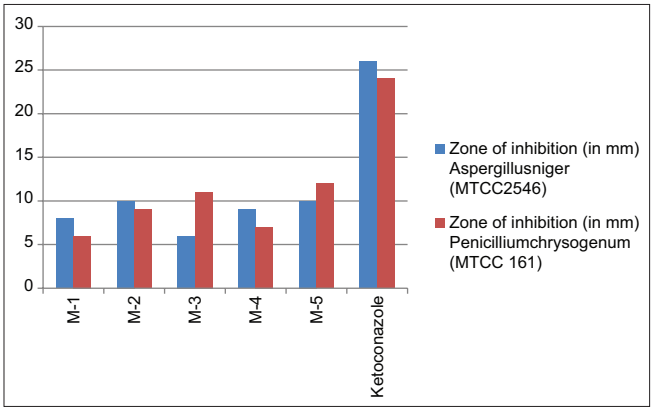


Figure 1: Quinoline



Graph 1: Graphical reparations in vitro antibacterial activity of substituted quinoline derivative



Graph 2: Graphical reparations of in vitro antifungal activity of substituted quinoline derivative

2-(4-Methoxy-phenyl)-quinoline-4-carboxylic Acid [1-(4-bromo-phenyl)-ethylidene] Hydrazide (M3)

Molecular formula: $C_{25}H_{20}BrN_3O_2$, Mol. Wt.: 474.35, melting point: 210–215°C, Rf value: 0.48

IR (KBr, cm^{-1}) ν 1589.3(C=C), 1511.7 (C_6H_5), 1674.8(C=O), 1462.0 (-C-H), 2976.2 ($-CH_3$) 892.2 (Ar C-H) 981.2(Ar-Br). 740.2 (R2-NH), ^{1}H-NMR (400 MHz, Solvent) δ ppm 2.17 (s, 3 H) 3.89 (s, 3 H) 7.04–7.07 (m, 2 H) 7.30–7.33 (m, 2 H) 7.50–7.57 (m, 3 H) 7.72–7.81 (m, 3 H) 7.99 (dd, *J* = 7.39, 1.89 Hz, 1 H) 8.33 (dd, *J* = 8.48, 1.40 Hz, 1 H) 8.69 (s, 1 H) mass - m/e: 473.07 elemental analysis- C, 63.30; H, 4.25; Br, 16.84; N, 8.86; O, 6.75

2-(4-Methoxy-phenyl)-quinoline-4-carboxylic Acid [1-(4-chloro-phenyl)-ethylidene]-Hydrazide (M4)

Molecular formula: $C_{25}H_{20}Cl\ N_3O_2$, Mol. Wt.: 429.90, melting point: 185-195°C, Rf value: 0.58

IR (KBr, cm^{-1}) ν 1588.9 (C=C), 1511.6 (C_6H_5), 1674.5 (C=O), 1462.3 (-C-H), 2960.1 ($-CH_3$) 981.2 (Ar C-H) 737.9 (Ar-Cl). 759.1(R2-NH), ^{1}H-NMR (400 MHz, Solvent) δ ppm 2.17 (s, 3 H) 3.89 (s, 3 H) 7.04–7.07 (m, 2 H) 7.30–7.33 (m, 2 H) 7.53–7.59 (m, 3 H) 7.72–7.81 (m, 3 H) 7.99 (dd, *J* = 7.39, 1.89 Hz, 1 H) 8.31–8.32 (m, 1 H) 8.32–8.35 (m, 1 H) 8.69 (s, 1 H) mass - m/e: 429.12, elemental analysis- C, 69.85; H, 4.69; Cl, 8.25; N, 9.77; O, 7.44

2-(4-Methoxy-phenyl)-quinoline-4-carboxylic Acid [1-(4-hydroxyphenyl)ethylidene]-Hydrazide (M5)

Molecular formula: $C_{25}H_{21}N_3O_3$, Mol. Wt.: 411.45, melting point: 198-205°C, Rf value:0.71

Table 1: *In vitro* antibacterial activity of substituted quinoline derivative (zone of inhibition)

Compounds	*Zone of inhibition (in mm)*			
	Gram positive		*Gram negative*	
	S. aureus (MTCC 1430)	*M. luteus (MTCC 1538)*	*E. coli (MTCC 1573)*	*P. aeruginosa (MTCC 424)*
M–1	6	11	4	6
M–2	6	8	3	7
M–3	5	6	4	7
M–4	7	12	9	11
M–5	6	10	11	8
Ciprofloxacin	24	29	28	33

S. aureus: Staphylococcus aureus, M. luteus: Micrococcus luteus, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa

Table 2: *In vitro* antifungal activity of substituted quinoline derivative (zone of inhibition)

Compounds	*Zone of inhibition (in mm)*	
	A. niger (MTCC 2546)	*P. chrysogenum (MTCC 161)*
M–1	8	6
M–2	10	9
M–3	6	11
M–4	9	7
M–5	10	12
Ketoconazole	26	24

A. niger: Aspergillus niger, P. chrysogenum: Penicillium chrysogenum

IR (KBr, cm^{-1}) ν 1582.8 (C=C), 1465.8 (C_6H_5), 1687.8 (C=O), 1500.0 (-C-H), 2913.9 (-CH_3) 834.7 (Ar C-H) 1305.1 (Ar-0H). 744.0 (R2-NH), ^{1}H-NMR (400 MHz, Solvent) δ ppm 2.17 (s, 3 H) 3.89 (s, 3 H) 7.04–7.07 (m, 2 H) 7.17–7.20 (m, 2 H) 7.45–7.48 (m, 2 H) 7.55 (ddd, *J* = 8.70, 7.17, 1.83 Hz, 1 H) 7.72–7.81 (m, 3 H) 7.99 (dd, *J* = 7.39, 1.89 Hz, 1 H) 8.33 (dd, *J* = 8.61, 1.53 Hz, 1 H) 8.69 (s, 1 H)) mass - m/e: 411.16, elemental analysis- C, 72.98; H, 5.14; N, 10.21; O, 11.67

The newly synthesized substituted 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid hydrazide derivative was evaluated for their zone of inhibition the standard bacterial strains, *P. aeruginosa*, *M. luteus*, *S. aureus,* and *E. coli*. For antifungal evaluation, *A. niger* and *P. chrysogenum*, ciprofloxacin, and ketoconazole were used as a standard drug. The newly synthesized derivative shows the zone of inhibition against bacterial and fungal growth data shown in Tables 1 and 2 and graphical reparations of data in Graphs 1 and 2.

Conclusion

Some new substituted quinoline derivative synthesis and evaluated antimicrobial activity against the Gram-positive and Gram-negative bacterial stain and fungal stain. All derivatives were shown the antimicrobial activity. Compound 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-[4-chloro-phenyl]-ethylidene)-hydrazide (M4) shows significant activity against Gram-positive and Gram-negative bacteria and compound 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-[4-amino-phenyl]-ethylidene)-hydrazide (M2), 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-[4-bromo-phenyl]-ethylidene) hydrazide (M3) gives the good activity against Gram-positive and Gram-negative bacterial against stains. All compounds show the good antifungal activity and compound 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-[4-amino-phenyl]-ethylidene)-hydrazide (M2), 2-(4-Methoxy-phenyl)-quinoline-4-carboxylic acid (1-[4-bromo-phenyl]-ethylidene) hydrazide (M3) shows the significant activity antifungal activity against fungal stains.

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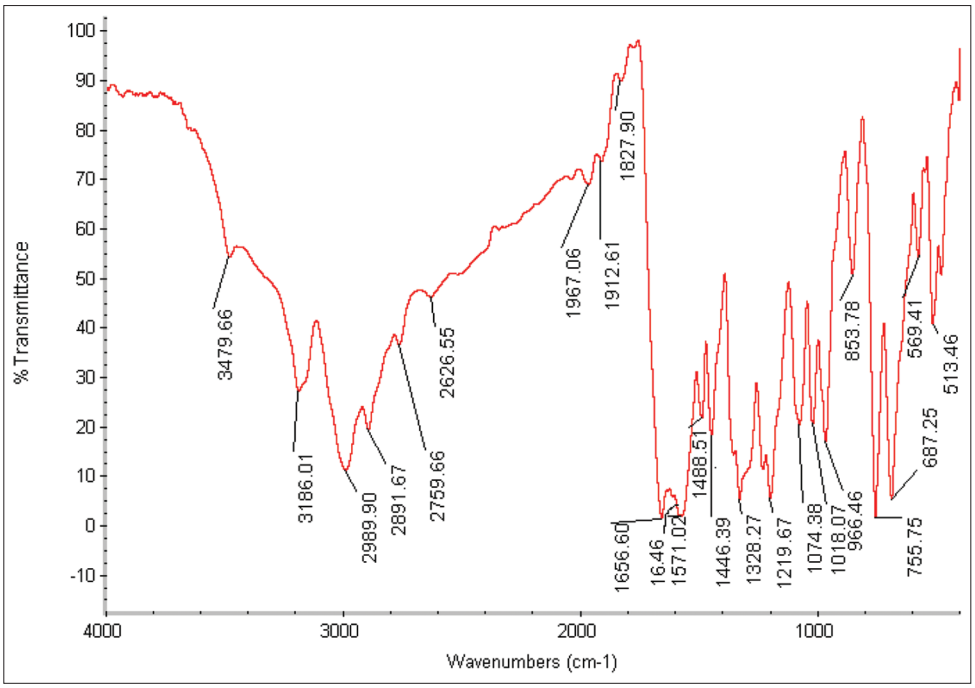

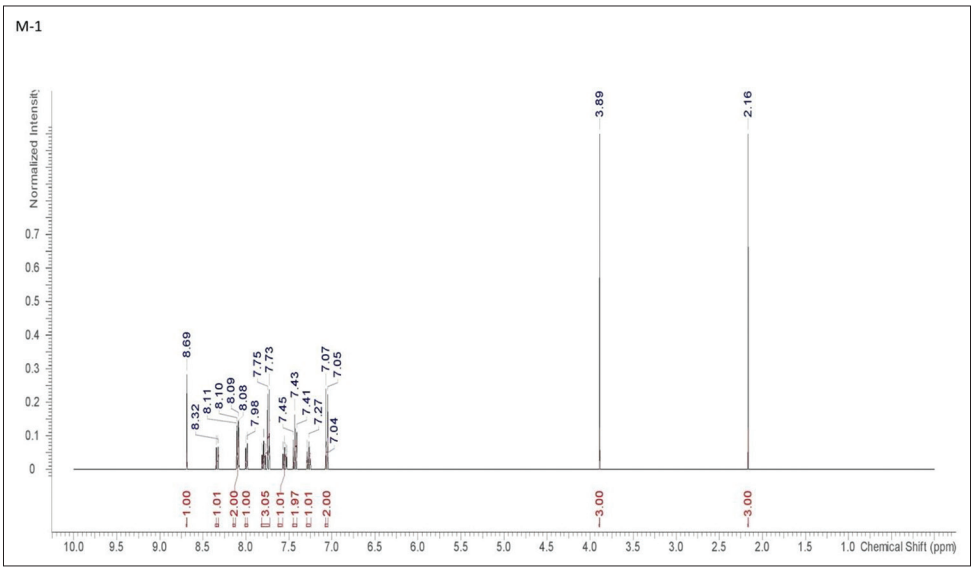

Figure 2: Fourier transform infrared and ^{1}H-NMR spectra for M-1

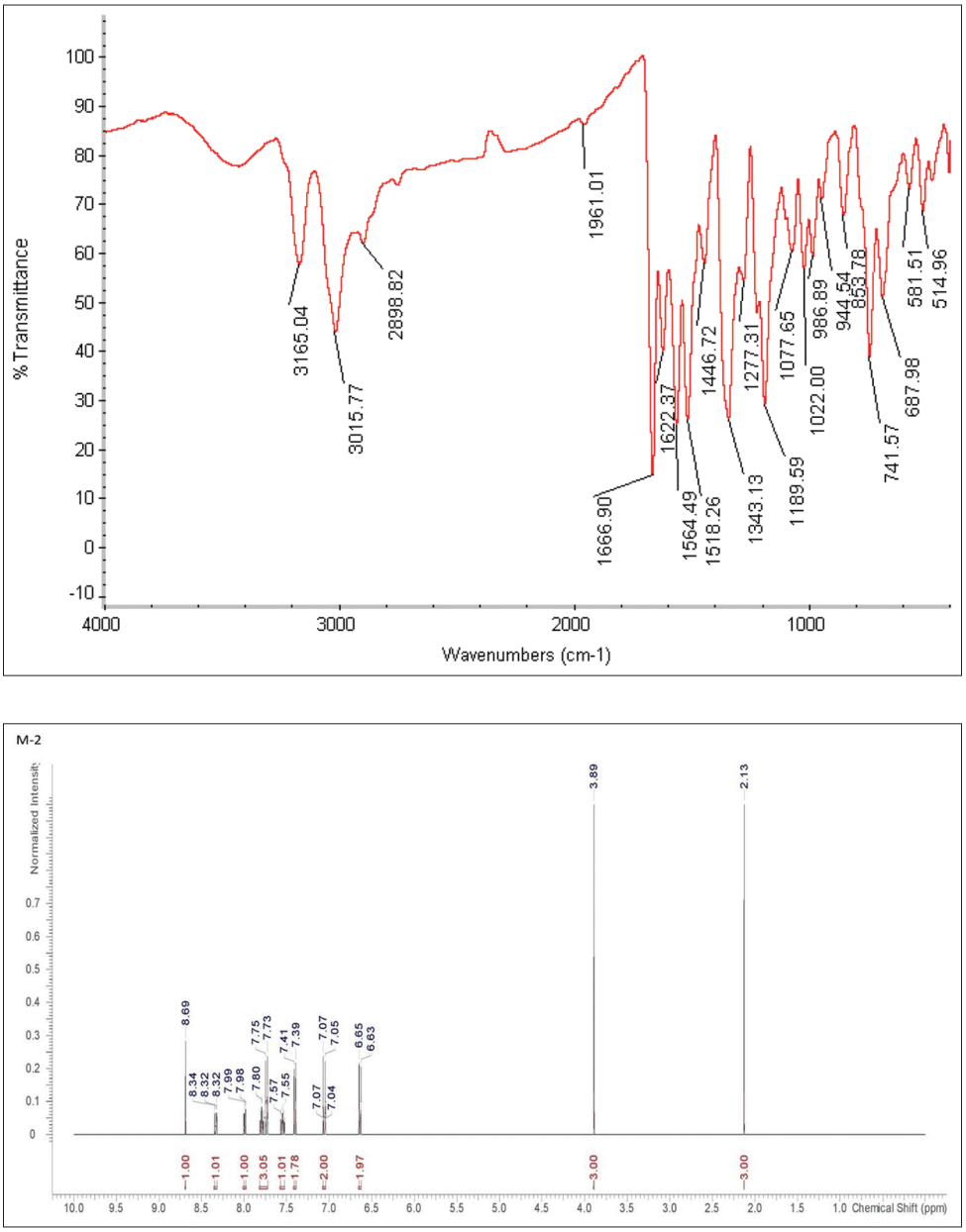

Figure 3: Fourier transform infrared and ^{1}H-NMR spectra for M-2

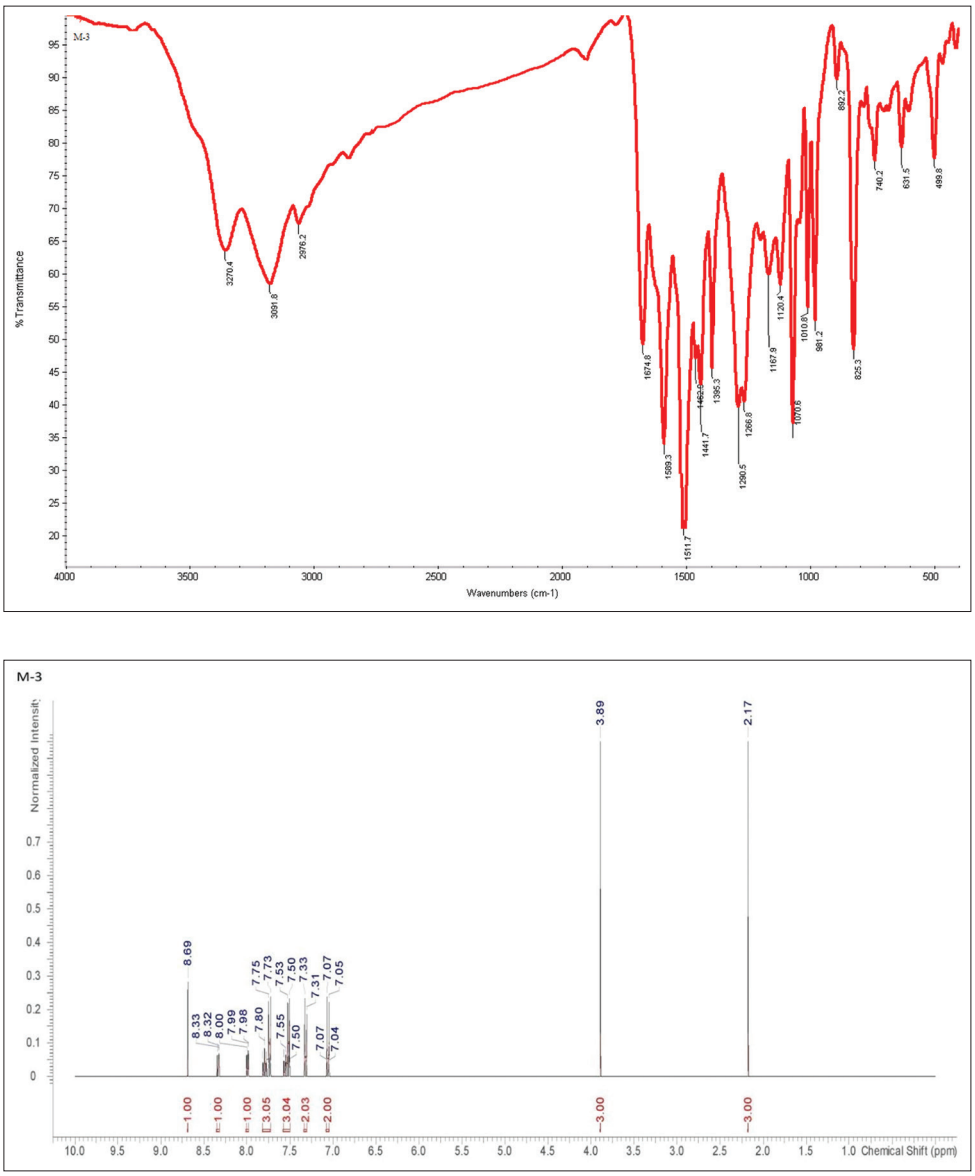

Figure 4: Fourier transform infrared and ^{1}H-NMR spectra for M-3

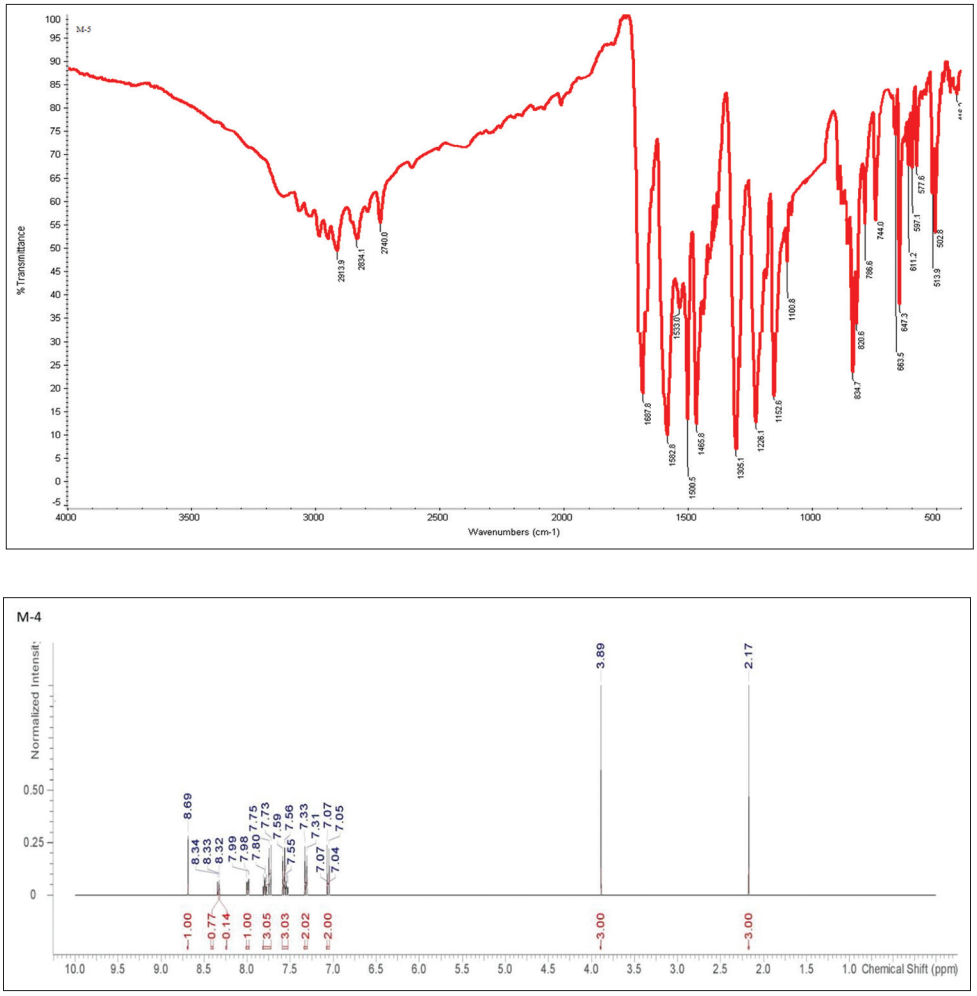

Figure 5: Fourier transform infrared and ^{1}H-NMR spectra for M-4

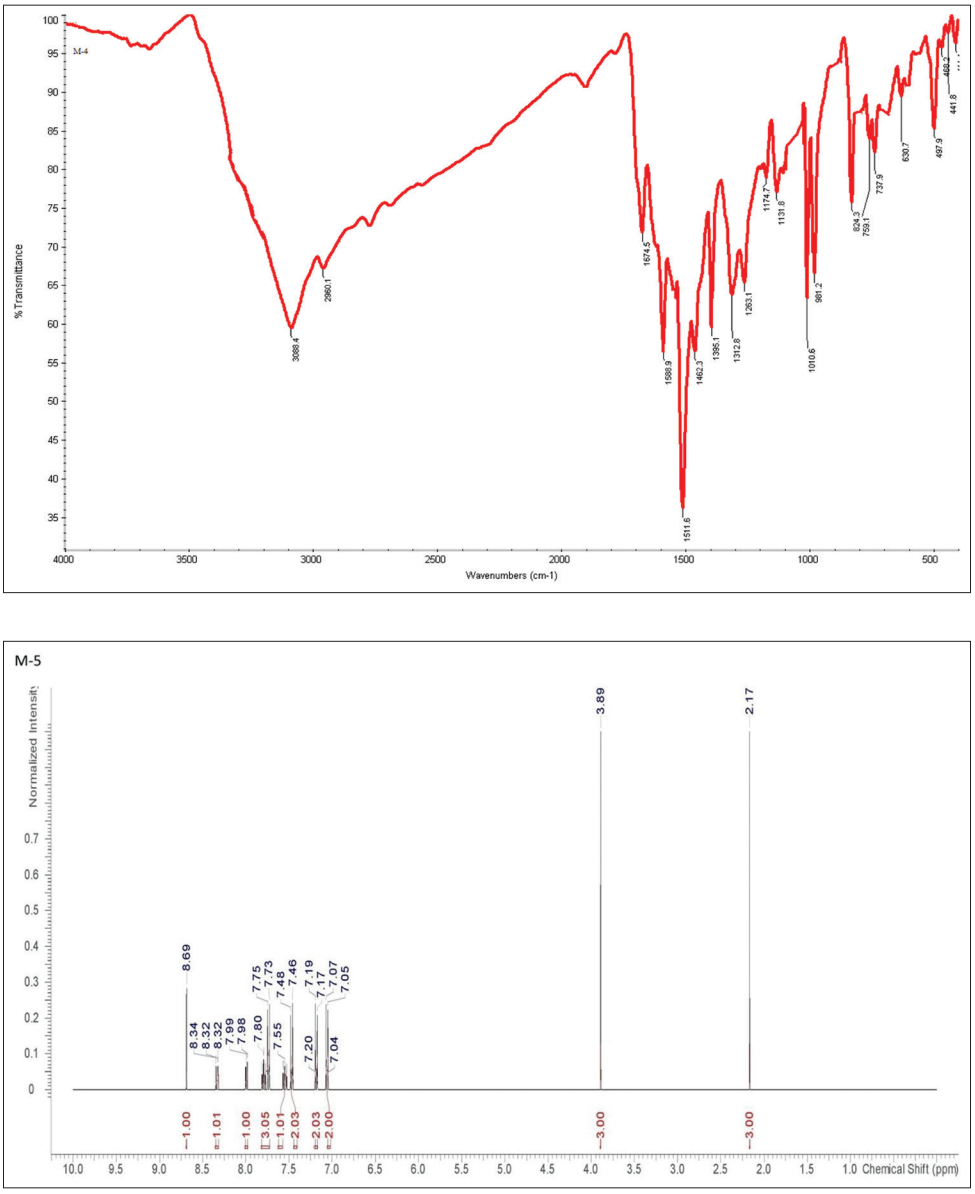

Figure 6: Fourier transform infrared and ^{1}H-NMR spectra for M-5