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# Synthesis and Microbial Studies of New Pyrazoline/Isoxazoline Derivatives Bearing Quinoline Moiety using Ultrasound Irradiation

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***ABSTRACT***

*A new series having quinoline, pyrazoline/isoxazoline, and benzotriazole moiety in a single molecule frame have been synthesized by mixture of 2-(1H benzo[d][1,2,3]triazol-1-yl)-6-substituted quinoline-3-carbaldehyde 1 and substituted acetophenone 2 in ethanolic sodium hydroxide using ultrasound irradiated for 10-20 min at 50°C. After that add hydroxylamine hydrochloride/hydrazine hydrate and further irradiated for 5-15 min at 50°C to form desired compounds 3a-r. The synthesized compounds confirmed by IR, $^{13}$C NMR, $^{1}$H NMR, and mass spectroscopic methods. All the synthesized compounds were evaluated for antimicrobial activity. From all the compounds, 3b, 3h, and 3n have shown more activity as compared to standard drugs.*

***Key words:*** *Quinoline, Benzotriazole, Pyrazoline/isoxazoline, Ultrasound irradiation, Antimicrobial activity.*

## 1. INTRODUCTION

Microorganisms are becoming resistant to conventional antimicrobial therapy, so it is necessary to discover and development of new antimicrobial agents. This is achieving by designing and testing new heterocyclic derivatives which have a broad range of biological activity. Quinoline derivatives have wide applications in medicinal chemistry such as antimalarial, antibacterial, antifungal, and anticancer agents [1-5]. A wide range of biological activity also shows by 2-pyrazoline derivatives such as antimicrobial, analgesic agent, anticancer agent, and antitubercular agent [6-10], which stimulate the research activity in this field. Isoxazoline derivatives have been reported in the literature to possess antibacterial, antifungal, and antiviral [11-13] activities.

In recent years, it is expected that combining features of more than one biologically active segment in a single molecule may result in pronounced biological activity [14]. Simultaneously, the way by which hybrid compounds are synthesized is very important for the organic chemist. The conventional procedures are not found to be satisfactory with regard to operational simplicity, effectiveness, and yield. An alternative synthetic approach is ultrasound irradiation [15,16]. Encouraged by these points and in continuation of our research work on the synthesis of new heterocyclic derivatives containing quinoline moiety with potential biological activities [3], we synthesized new pyrazoline/isoxazoline derivatives bearing quinoline moiety. According to the literature survey, there are no reports on the designing of pyrazoline/isoxazoline derivatives via two steps one pot way under ultrasound irradiation. Furthermore, we investigate the antimicrobial activity of a new synthesized compounds 3a-r.

## 2. EXPERIMENTAL

Ultrasonication was performed in D-Compact ultrasonic cleaner with a frequency of 50 kHz and power of 250 W (EIE Inst. Pvt. Ltd, Ahmadabad, Gujarat). The reaction flask was suspended at the center of the ultrasonic bath, so as the surface of the reactants remained slightly lower than the level of water in the bath. All the reagents and solvents were obtained commercially and used without further purification. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA), only the characteristic peaks are reported in $cm^{-1}$. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA); all compounds are within 0.4% of theory specified. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as an internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass

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spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

### *2.1. Screening of Catalyst under Conventional and Ultrasonic Irradiation*

In this research work, we examined the model reaction in the absence and presence of catalyst. When the reaction was carried out without addition of catalyst, no product was isolated. When we were used acid catalysts (10%) such as acetic acid (AcOH) can push the reaction toward the formation of product in yields of 20% (Table 1). The yield was improved when basic catalysts (10%) used. The best results were obtained when NaOH was used, which provided a yield of 74% (No. 6). According to data in Table 1, it revealed that using sodium hydroxide as basic catalyst under ultrasound irradiation give high yield in minimum time than conventional method. To study the effect of the amount of the catalyst, the reactions were carried out with different amounts of NaOH, ranging from 10 to 40 mol%. It was found that when the amount of NaOH was 20% than the yield was increased. However, there was no significant change in reaction yield when the amount of catalyst was increased up to 40 mol% (Table 2).

### *2.2. Effect of Temperature on Reaction under Ultrasonic Irradiation*

To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from 30°C to 60°C using different catalysts (20%) under ultrasonic irradiation Table 3. It revealed that the yield was improved and the reaction time was shortened (94% in 15 min) when the temperature was increased to 50°C in case of NaOH use as base. No significant changes in the yield were observed when the temperature was further increased.

**Table 1:** The effect of catalyst on % yield of 3 h at 70°C.

| No. | Cat. (10%) | Sonication | | Conventional | |
|---|---|---|---|---|---|
| | | Time (min) | Yield (%) | Time (h) | Yield (%) |
| 1 | None | 130 | - | 9 | - |
| 2 | AcOH | 80 | 20 | 8.3 | 10 |
| 3 | $Et_3N$ | 60 | 47 | 8.1 | 38 |
| 4 | Piperidine | 80 | 30 | 7 | 24 |
| 5 | $K_2CO_3$ | 35 | 34 | 8 | 30 |
| 6 | NaOH | 15 | 74 | 5 | 40 |

**Table 2:** The effect of % of NaOH on % yield of 3 h at 70°C under ultrasound irradiation.

| Entry | Catalyst (%) | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | NaOH (10) | 15 | 74 |
| 2 | NaOH (20) | 16 | 77 |
| 3 | NaOH (30) | 20 | 69 |
| 4 | NaOH (40) | 18 | 69 |

### *2.3. General Procedure for the Synthesis of Targeted Compounds (3a-r)*

#### *2.3.1. Conventional heating method*

In a 20% ethanolic sodium hydroxide solution, take a mixture of 2-(1*H* benzo[*d*] [1,2,3]triazol-1-yl)-6-substitutedquinoline-3-carbaldehyde 1 (0.01 mol), substituted acetophenone 2 (0.01 mol) refluxed it for 3-4 h. The synthesis of chalcone is determined by monitories thin-layer chromatography (TLC) (ethyl acetate:ether). In this mixture, add hydroxylamine hydrochloride/hydrazine hydrate (0.01 mol) and reflux for 1-3 h progress of reaction was monitories by TLC (ethyl acetate/ether). After completion of reaction cool and filter it. The crud product recrystallized by methanol to got final pure product.

#### *2.3.2. Ultrasound irradiation method*

A mixture of 2-(1*H* benzo[d] [1,2,3]triazol-1-yl)-6-substitutedquinoline-3-carbaldehyde 1 (0.01 mol), substituted acetophenone 2 (0.01 mol) ethanolic sodium hydroxide solution ultrasound irradiated for 10-20 min. Here, according to Aldol condensation, chalcone is synthesize and it is monitories by TLC (ethyl acetate/ether). After completion of reaction, add hydroxylamine hydrochloride/hydrazine hydrate (0.01 mol) and again ultrasound irradiated for 5-15 min. The progress of the reaction was monitored by TLC (ethyl acetate/ether). After completion of the reaction, the precipitate was separated by filtration, washed with cold water, and crystallized from methanol. The targeted compounds yield, time required to complete reaction are summarized in Table 4.

2.3.2.1. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)quinoline (3a)

Mp: 230-233°C; IR (KBr) $V_{max}$: 3420, 3051, 2978, 1588, 1443; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 5.31 (t, 1H, CH), 3.1 ($H_A$) (1H, dd), 3.5 ($H_B$) (1H, dd), 7.28-8.96 (m, 15H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 44.5, 60.8, 113.1, 115.3, 119.5, 125.2, 127.0, 128.1, 129.4, 130.2, 131.2, 132.3, 133.6, 136.4, 137.8, 140.2, 141.4, 142.4, 143.7, 145.6; LC-MS: 391(M)$^+$; Anal. Calcd for $C_{24}H_{18}N_6$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.55; H, 4.88; N, 21.67%.

2.3.2.2. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-(3-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)quinoline (3b)

Mp: 229°C; IR (KBr) $V_{max}$: 3317, 3047, 2955, 1597, 1443, 748; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 5.41 (t, 1H, CH), 3.2 ($H_A$) (1H, dd) 3.6 ($H_B$) (1H, dd), 7.19-8.91 (m, 14H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 45.0, 59.6, 113.8, 115.8, 119.4,

**Table 3:** The effect of reaction temperature on the synthesis of compound 3 h using different catalysts (20%).

| Entry | Cat. (20%) | Temp °C | Sonication | | Entry | Cat. (20%) | Temp °C | Sonication | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Time (min) | Yield (%) | | | | Time (min) | Yield (%) |
| 1 | NaOH | 30 | 40 | 35 | 9 | $Et_3N$ | 30 | 90 | - |
| 2 | | 40 | 26 | 63 | 10 | | 40 | 85 | - |
| 3 | | 50 | 15 | 94 | 11 | | 50 | 80 | 10 |
| 4 | | 60 | 15 | 78 | 12 | | 60 | 70 | 30 |
| 5 | Acetic acid | 30 | 80 | - | 13 | $K_2CO_3$ | 30 | 75 | - |
| 6 | | 40 | 75 | 5 | 14 | | 40 | 70 | - |
| 7 | | 50 | 70 | 11 | 15 | | 50 | 85 | 15 |
| 8 | | 60 | 80 | 25 | 16 | | 60 | 85 | 22 |

**Table 4:** Synthesis of new pyrazoline/isoxazoline derivatives 3a-r at 50°C using NaOH as base.

| Compounds | $R_1$ | $R_2$ | X | Ultrasound method | | Conventional method | |
|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield (%) | Time (h) | Yield (%) |
| 3a | H | H | NH | 30 | 90 | 5.5 | 77 |
| 3b | H | F | NH | 19 | 80 | 5.0 | 65 |
| 3c | H | $CH_3$ | NH | 26 | 88 | 5.3 | 74 |
| 3d | H | H | O | 27 | 84 | 6.2 | 64 |
| 3e | H | F | O | 21 | 80 | 6.0 | 70 |
| 3f | H | $CH_3$ | O | 30 | 79 | 6.5 | 73 |
| 3g | $CH_3$ | H | NH | 20 | 91 | 4.8 | 83 |
| 3h | $CH_3$ | F | NH | 15 | 94 | 4.0 | 77 |
| 3i | $CH_3$ | $CH_3$ | NH | 28 | 87 | 5.0 | 81 |
| 3j | $CH_3$ | H | O | 18 | 78 | 5.6 | 72 |
| 3k | $CH_3$ | F | O | 23 | 87 | 4.7 | 65 |
| 3l | $CH_3$ | $CH_3$ | O | 25 | 88 | 6.5 | 75 |
| 3m | $OCH_3$ | H | NH | 30 | 75 | 7.0 | 67 |
| 3n | $OCH_3$ | F | NH | 29 | 90 | 4.1 | 81 |
| 3o | $OCH_3$ | $CH_3$ | NH | 35 | 81 | 4.4 | 70 |
| 3p | $OCH_3$ | H | O | 33 | 83 | 5.8 | 65 |
| 3q | $OCH_3$ | F | O | 29 | 77 | 5.5 | 61 |
| 3r | $OCH_3$ | $CH_3$ | O | 32 | 76 | 6.0 | 59 |

125.7, 127.1, 128.1, 128.7, 129.5, 129.9, 131.4, 133.3, 136.6, 137.1, 139.6, 141.7, 142.7, 143.6, 145.7, 148.07; LC-MS: 409(M)$^+$; Anal. Calcd for $C_{24}H_{17}FN_6$: C, 70.58; H, 4.20; N, 20.58. Found: C, 70.68; H, 4.2; N, 20.21%.

2.3.2.3. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-(3-p-tolyl-4,5-dihydro-1*H*-pyrazol-5-yl)quinoline (3c)
Mp: 234°C; IR (KBr) $V_{max}$: 3380, 3067, 2930, 1578, 1502; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.29 (s, $CH_3$), 5.2 (t, 1H, CH), 3.2 ($H_A$) (1H, dd), 3.6 ($H_B$) (1H, dd), 6.97-8.81 (m, 14H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 20.4, 45.4, 59.0, 113.3, 119.8, 126.0, 127.0, 1276.6, 128.4, 128.8, 129.6, 129.8, 131.2, 133.8, 136.9, 137.4, 139.2, 140.3, 141.5, 142.7, 143.3, 145.7, LC-MS: 405(M)$^+$; Anal. Calcd for $C_{25}H_{20}N_6$: C, 74.24; H, 4.98; N, 20.78. Found: C, 74.41; H, 4.99; N, 20.67%.

2.3.2.4. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl) quinolin-3-yl)-3-phenyl-4,5-dihydroisoxazole (3d)
Mp: 227°C; IR (KBr) $V_{max}$: 3039, 2932, 1602, 1435; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 6.38 (t, 1H, CH), 3.60 ($H_A$) (1H, dd), 3.98 ($H_B$) (1H, dd), 6.94-8.80 (m, 15H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 41.3, 78.6, 110.8, 114.1, 120.9, 124.2, 125.4, 126.0, 127.2, 128.1, 128.5, 128.8, 129.4, 129.7, 130.2, 131.6, 134.3, 137.2, 144.3, 146.0, 155.6; LC-MS: 392(M)$^+$; Anal. Calcd for $C_{24}H_{17}N_5O$: C, 73.64; H, 4.38; N, 17.89. Found: C, 73.33; H, 4.3; N, 17.71%.

2.3.2.5. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)quinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (3e)
Mp: 236°C; IR (KBr) $V_{max}$: 3064, 3001, 1614, 1443, 864; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 6.41 (t, 1H, CH), 3.57 ($H_A$) (1H, dd), 4.03 ($H_B$) (1H, dd), 7.11-8.83 (m, 14H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 41.7, 78.3, 110.2, 115.2, 120.8, 124.1, 125.6, 126.4, 127.0, 128.1, 128.6, 128.9, 129.2, 129.7, 130.3, 134.1, 136.9, 145.6, 146.3, 156.0, 164.4; LC-MS: 410(M)$^+$; Anal. Calcd for $C_{24}H_{16}FN_5O$: C, 70.41; H, 3.94; N, 17.11. Found: C, 70.52; H, 4.11; N, 17.31%.

2.3.2.6. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl) quinolin-3-yl)-3-(p-tolyl)-4,5-dihydroisoxazole (3f)
Mp: 231°C; IR (KBr) $V_{max}$: 3101, 2993, 1576, 1443; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.31 (s, 3H, $CH_3$), 6.40 (t, 1H, CH), 3.58 ($H_A$) (1H, dd), 3.95 ($H_B$) (1H, dd), 7.23-8.76 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 20.4, 42.5, 77.9, 109.9, 114.7, 119.9, 124.5, 125.9, 126.6, 127.2, 128.3, 128.5, 128.8, 129.6, 129.8, 131.7, 133.1, 137.8, 140.5, 145.7, 146.5, 156.7; LC-MS: 406(M)$^+$; Anal. Calcd for $C_{25}H_{19}N_5O$: C, 74.06; H, 4.72; N, 17.27. Found: C, 74.56; H, 4.22; N 17.5%.

2.3.2.7. 2-(1*H*-benzo*[d*][1,2,3]triazol-1-yl)-6-methyl-3-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl) quinoline (3g)
Mp: 224°C; IR (KBr) $V_{max}$: 3379, 3095, 2935, 1612, 1458; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.17 (s, 3H, $CH_3$), 5.47 (t, 1H, CH), 3.98 ($H_A$) (1H, dd), 4.69 ($H_B$) (1H, dd), 6.81-8.75 (m, 11H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75MHz) δ: 22.4, 45.6, 59.9, 114.5, 116.2, 120.1, 124.3, 126.5, 127.3, 128.0, 128.4, 130.5, 131.4, 132.5, 132.9, 135.3, 137.0, 140.7, 141.1, 142.6, 143.6, 145.3; LC-MS: 405(M)$^+$; Anal. Calcd for C25H20N6: C, 74.24; H 4.98; N, 20.78. Found: C, 74.74; H, 4.99; N 20.89%.

2.3.2.8. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-(3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-6 methylquinoline (3h)
Mp: 226°C; IR (KBr) $V_{max}$: 3325, 3055, 2919, 1605, 1497, 825; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.21 (s, 3H, $CH_3$), 4.56 (t, 1H, CH), 3.68 ($H_A$) (1H, dd), 4.55 ($H_B$) (1H, dd), 6.69-8.92 (m, 13H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 22.9, 40.5, 60.4, 114.5, 116.7, 119.2, 127.4, 127.9, 128.4, 128.6, 129.3, 130.4, 131.4, 134.1, 136.4, 137.2, 139.2, 139.7, 144.3, 145.0, 146.9, 148.4; LC-MS: 423(M)$^+$; Anal. Calcd for $C_{25}H_{19}FN_6$: C, 71.08; H, 4.50; N, 19.89. Found: C, 74.51; H, 4.65; N, 20.13%.

2.3.2.9. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methyl-3-(3-p-tolyl-4,5-dihydro-1*H*-pyrazol-5-yl) quinoline (3i)
Mp: 230°C; IR (KBr) $V_{max}$: 3412, 3067, 2923, 1598, 1476; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.25 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 4.3 (t, 1H, CH), 3.52 ($H_A$) (1H, dd), 4.68 ($H_B$) (1H, dd), 6.80-8.83 (m, 13H, Ar-H and NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 21.8, 41.3, 60.4, 114.1, 120.3, 126.3, 127.3, 127.6, 127.9, 128.2, 128.6, 129.5, 130.1, 130.3, 131.1, 132.6, 136.4, 136.9, 139.7, 140.0, 143.3, 146.6, 149.2; LC-MS: 419(M)$^+$; Anal. Calcd for $C_{26}H_{22}N_6$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.11; H, 5.5; N, 20.22%.

2.3.2.10. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methylquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazole (3j)
Mp: 223°C; IR (KBr) $V_{max}$: 3073, 2978, 1641,1456; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.45 (s, 3H, $CH_3$), 6.56 (t, 1H, CH), 4.15 ($H_A$) (1H, dd), 4.89 ($H_B$) (1H, dd), 7.23-8.96 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 22.1, 40.7, 77.1, 113.3, 118.6, 124.9, 126.3, 128.8, 128.1, 128.7, 129.3, 129.7, 129.9, 131.5, 133.2, 137.0, 137.5, 139.2, 139.5, 145.1, 147.8, 154.1; LC-MS: 406(M)$^+$; Anal. Calcd for $C_{25}H_{19}N_5O$: C, 74.06; H, 4.72; N, 17.27. Found: C, 74.5; H, 4.98; N, 16.89%.

2.3.2.11. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methylquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (3k)
Mp: 220°C; IR (KBr) $V_{max}$: 3032, 2995, 1589, 1423, 867; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.37 (s, 3H, $CH_3$), 6.61 (t, 1H, CH), 4.07 ($H_A$) (1H, dd), 4.91 ($H_B$) (1H, dd), 6.82-8.79 (m, 12H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 23.4, 39.1, 74.6, 113.6, 116.1, 120.2, 126.8, 127.5, 128.7, 129.6, 130.3, 131.7, 132.5, 133.8, 135.6, 138.1, 139.6, 139.8, 145.4, 148.2, 153.9, 164.1; LC-MS: 424(M)$^+$; Anal. Calcd for $C_{25}H_{18}FN_5O$: C, 70.91; H, 4.28; N, 16.54. Found: C, 70.89; H, 4.44; N, 16.42%.

2.3.2.12. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methylquinolin-3-yl)-3-p-tolyl-4,5-dihydroisoxazole (3l)
Mp: 218°C; IR (KBr) $V_{max}$: 3102, 2987, 1624, 1432; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.35 (s, 3H, $CH_3$), 2.45 (s, 3H, $CH_3$), 6.22 (t, 1H, CH), 4.13 ($H_A$) (1H, dd), 4.82 ($H_B$) (1H, dd), 6.75-8.83 (m, 10H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 21.3, 22.0, 40.2, 78.2, 114.2, 120.1, 126.3, 127.3, 127.3, 127.5, 128.8, 129.9, 130.5, 130.8, 131.1, 132.6, 136.2, 136.8, 139.8, 140.1, 145.4, 148.1,155.3; LC-MS: 420(M)$^+$; Anal. Calcd for $C_{26}H_{21}N_5O$: C, 74.44; H, 5.05; N, 16.70. Found: C, 74.25; H, 4.79; N, 16.51%.

2.3.2.13. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methoxy-3-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl) quinoline (3m)
Mp: 241°C; IR (KBr) $V_{max}$: 3324, 3021, 2957, 1612, 1447, 1231; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 3.98 (s, 3H, $OCH_3$), 5.31 (t, 1H, CH), 3.1($H_A$) (1H, dd), 3.5 ($H_B$) (1H, dd), 6.79-8.96 (m, 14H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 43.3, 49.4, 56.2, 106.6, 113.5, 117.2, 120.0, 124.4, 125.4, 125.7, 126.0, 126.4, 129.1, 129.3, 129.6, 130.6, 133.3, 138.18, 139.1,

142.5, 145.9, 159.1; LC-MS: 421(M)$^+$; Anal. Calcd for $C_{25}H_{20}N_6O$: C, 71.41; H, 4.79; N, 19.99. Found: C, 71.6; H, 4.87; N, 19.63%.

2.3.2.14. 2-(1H-benzo[d][1,2,3]triazol-1-yl)-3-(5-(4-fluorophenyl)-2,3-dihydro-1H-pyrazol-3-yl)-6-methoxyquinoline (3n)
Mp: 237°C; IR (KBr) $V_{max}$: 3432, 3071, 2988, 1618, 1454, 1245, 778; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 4.03 (s, 3H, $OCH_3$), 5.26 (t, 1H, CH), 3.20 ($H_A$) (1H, dd), 3.48 ($H_B$) (1H, dd), 6.96-8.91 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 43.6, 49.3, 56.5, 106.3, 113.7, 116.8, 118.1, 120.6, 123.8, 125.7, 125.8, 126.2, 126.6, 127.4, 128.3, 133.3, 138.1, 139.1, 142.5, 145.9, 159.1, 164.4; LC-MS: 439(M)$^+$; Anal. Calcd for $C_{25}H_{19}FN_6O$: C, 68.48; H, 4.37; N, 19.17. Found: C, 68.18; H, 4.65; N, 19.38%.

2.3.2.15. 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methoxy-3-(3-p-tolyl-4,5-dihydro-1*H*-pyrazol-5-yl) quinoline (3o)
Mp: 235°C; IR (KBr) $V_{max}$: 3429, 3081, 2945, 1611, 1494, 1254; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.23 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 5.28 (t, 1H, CH), 3.25 ($H_A$) (1H, dd), 3.53 ($H_B$), (1H, dd), 7.11-8.95 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 22.4, 43.7, 50.5, 56.6, 106.6, 114.3, 117.5, 120.7, 124.3, 125.3, 125.8, 126.1, 126.6, 127.4, 129.5, 131.3, 134.5, 138.4, 139.7, 142.8, 146.6, 158.2; LC-MS: 435(M)+; Anal. Calcd for C26H22N6O: C, 71.87; H, 5.10; N, 19.34. Found: C, 71.33; H, 4.95; N, 19.45%.

2.3.2.16. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methoxyquinolin-3-yl)-3-phenyl-4,5-dihydroisoxazole (3p)
Mp: 227°C; IR (KBr) $V_{max}$: 3105, 2956, 1578, 1436, 1302; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 3.87 (s, 3H, $CH_3$), 6.42 (t, 1H, CH), 3.60 ($H_A$) (1H, dd), 3.98 ($H_B$) (1H, dd), 6.68-8.80 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 41.1, 57.2, 76.5, 106.2, 112.5, 121.3, 122.1, 127.7, 128.6, 129.1, 129.6, 129.8, 131.2, 133.7, 137.2, 137.7, 139.5, 139.8, 146.1, 148.4, 155.5, 156.6; LC-MS: 422(M)$^+$; Anal. Calcd for $C_{25}H_{19}N_5O_2$: C, 71.25; H, 4.54; N, 16.62. Found: C, 71.69; H, 4.85; N, 16.77%.

2.3.2.17. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methoxyquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (3q)
Mp: 239°C; IR (KBr) $V_{max}$: 3029, 2987, 1587, 1430, 1254,846; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 3.82 (s, 3H, $OCH_3$), 6.37 (t, 1H, CH), 3.58 ($H_A$) (1H, dd), 4.01 ($H_B$) (1H, dd), 6.92-8.83 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 40.3, 56.8, 76.4, 105.5, 114.1, 116.1, 119.2, 122.2, 125.4, 126.7, 128.1, 128.3, 128.5, 129.4, 131.4, 134.6, 139.6, 140.1, 145.2, 148.2, 153.4, 156.4, 163.7; LC-MS: 440(M)$^+$; Anal. Calcd for $C_{25}H_{18}FN_5O_2$: C, 68.33; H, 4.13; N, 15.94. Found: C, 68.23; H, 3.93; N, 15.86%.

2.3.2.18. 5-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-methoxyquinolin-3-yl)-3-p-tolyl-4,5-dihydroisoxazole (3r)
Mp: 218°C; IR (KBr) $V_{max}$: 3065, 2975,1617, 1467, 1237; $^1$H NMR (400 MHz, DMSO-$d_6$) δ/ppm 2.27 (s, 3H, $CH_3$), 3.92 (s, 3H, $CH_3$), 6.21 (t, 1H, CH), 3.57 ($H_A$) (1H, dd), 4.03 ($H_B$) (1H, dd), 7.13-8.83 (m, 12H, Ar-H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 41.2, 56.2, 77.3, 106.2, 114.1, 120.8, 127.3, 127.7, 127.9, 128.3, 129.3, 130.6, 131.5, 132.5, 133.3, 136.7, 136.9, 140.6, 140.9, 145.4, 147.5, 156.6, 157.6; LC-MS: 436(M)$^+$; Anal. Calcd for $C_{26}H_{21}N_5O_2$: C, 71.71; H, 4.86; N, 16.08. Found: C, 71.78; H, 5.09; N, 16.31%.

## 3. BIOLOGICAL ACTIVITY

Antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method [17,18]. Each synthesized compound was diluted with DMSO so as to have the stock solution of 2000 g/mL concentration as a stock solution. The results were recorded in the form of primary and secondary screening. The compounds 3a-r were screened for their antibacterial activity against *Streptococcus pneumonia* (SP) (MTCC 1936), *Clostridium tetani* (CT) (MTCC 449), *Bacillus subtilis* (BS) (MTCC 441), *Salmonella typhi* (ST) (MTCC 98), *Vibrio cholera* (VC) (MTCC 3906), and *Escherichia coli* (EC) (MTCC 443) as well as for antifungal activity against *Aspergillus fumigatus* (AF) (MTCC 3008) and *Candida albicans* (CA) (MTCC 227). The lowest concentration, which showed no visible growth (turbidity) after spot subculture, was considered as the minimum inhibitory concentration (MIC) for each compound. In the present study, ampicillin, ciprofloxacin, and chloramphenicol were used as standard antibacterial drugs, whereas griseofulvin and nystatin were used as a standard antifungal drug. The values of MIC are summarized in Table 5.

## 4. RESULT AND DISCUSSION

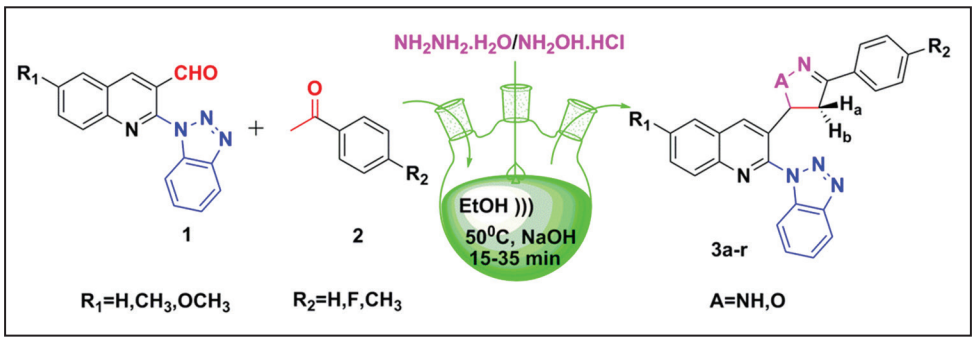
### *4.1. Chemistry*

The title compounds 3a-r synthesized by ultrasound irradiating as shown in general Scheme 1. To justify the use of ultrasound, we carried out this reaction by the conventional way, and results are presented in Table 4. In the conventional method, the time required for completion of these reactions increased with a decrease in product yield. Ultrasound enhances the reactivates of chemical reactions via acoustic cavitations process. Thus, ultrasound method has been superior to the traditional method with respect to yield, reaction time, and simplicity. Here, without isolating intermediates, changing reaction conditions, or adding reagents, we get desired compounds in a single pot. Compounds 1 confirmed by Beilstein test. Regarding the structure of 3a-r, the assignment of 3b was described. In $^1$H NMR of 3b, two double doublet signal observed at 3.1($H_A$)

**Table 5:** The *in vitro* antimicrobial activity of compounds 3a-r.

| Compound | Minimum inhibitory concentration in µg/Ml | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gram-positive bacteria | | | Gram-negative bacteria | | | Fungi | |
| | BS | CT | SP | EC | ST | VC | CA | AF |
| | MTCC441 | MTCC449 | MTC1936 | MTCC443 | MTCC98 | MTCC3906 | MTCC227 | MTCC3008 |
| 3a | 250 | 100 | 125 | 250 | 250 | 250 | 500 | >1000 |
| 3b | 62.5 | 50 | 100 | 200 | 200 | 200 | 100 | 200 |
| 3c | 250 | 250 | 200 | 250 | 250 | 250 | 250 | 1000 |
| 3d | 200 | 500 | 250 | 500 | 200 | 500 | 1000 | 500 |
| 3e | 100 | 250 | 200 | 500 | 250 | 100 | 500 | >1000 |
| 3f | 500 | 500 | 500 | 250 | 500 | 500 | 1000 | 1000 |
| 3g | 200 | 100 | 200 | 100 | 250 | 250 | 250 | 1000 |
| 3h | 100 | 62.5 | 125 | 200 | 100 | 500 | 500 | 1000 |
| 3i | 500 | 500 | 250 | 500 | 200 | 100 | 1000 | >1000 |
| 3j | 250 | 250 | 250 | 250 | 250 | 200 | 1000 | 1000 |
| 3k | 125 | 200 | 200 | 500 | 200 | 125 | 500 | 1000 |
| 3l | 500 | 500 | 500 | 500 | 500 | 500 | 1000 | 250 |
| 3m | 250 | 250 | 100 | 200 | 500 | 250 | 250 | 1000 |
| 3n | 62.5 | 200 | 200 | 200 | 100 | 200 | 250 | 1000 |
| 3o | 500 | 250 | 250 | 250 | 250 | 500 | 1000 | 500 |
| 3p | 100 | 200 | 500 | 500 | 500 | 200 | 1000 | 1000 |
| 3q | 250 | 125 | 50 | 250 | 250 | 100 | 500 | 250 |
| 3r | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 1000 |
| Ampi. | 100 | 100 | 250 | 250 | 250 | 100 | - | - |
| Chlo. | 50 | 50 | 50 | 50 | 50 | 50 | - | - |
| Cipro. | 25 | 25 | 25 | 50 | 100 | 50 | - | - |
| Nyst. 7 | - | - | - | - | - | - | 100 | 100 |
| Gri. | - | - | - | - | - | - | 500 | 100 |

SP: *Streptococcus pneumoniae*, CT: *Clostridium tetani*, BS: *Bacillus subtilis*, ST: *Salmonella typhi*, VC: *Vibrio cholera*, EC: *Escherichia coli*, CA: *Candida albicans*, AF: *Aspergillus fumigatus*, Ampi.: Ampicillin; Cipr.: Ciprofloxacin; Chlo.: Chloramphenicol; Gri.: Griseofulvin; Nyst.: Nystatin. MTCC: Microbial type culture collection bolt value indicates compounds are more potent than standard drug, -: Not tested




**Scheme 1:** Synthetic route for the title compounds 3a-r

and 3.5($H_B$) for -$CH_2$ proton of pyrazoline, triplet at 5.31 for -CH of pyrazoline. The $^{13}C$ spectra show signal at 40.2 for pyrazoline -$CH_2$, 59.61 for (-CH), and 113.82-163.2 for aromatic carbon atoms. Mass spectra of compound 3b gave molecular ion peak at m/z 409 ($M^{+1}$) corresponding to molecular formula $C_{24}H_{17}FN_6$. The IR spectra of 3b showed the presence of a characteristic absorption band corresponding to the -NH stretching in the region 3317 $cm^{-1}$, C-F stretching at 748 $cm^{-1}$ (Supplementary Infromation).

### *4.2. Antimicrobial Activity*

*4.2.1. Gram-positive bacteria*

The antibacterial screening data in Table 5 revealed that compounds 3n and 3b (MIC=62.5 µg/mL) which were more potent than standard drug ampicillin (MIC=100 µg/mL) against BS. Compound 3b (MIC=50 µg/mL) was more potency than standard drug ampicillin (MIC=100 µg/mL) while equally potent as standard drug chloramphenicol (MIC=50 µg/mL) toward CT. Compounds 3b, 3m (MIC=100 µg/mL), 3a, 3h (MIC=125 µg/mL), 3c, 3e, 3g, 3k, and 3n (MIC=200 µg/mL) are more active against SP than slandered drug ampicillin and 3q (MIC=50 µg/mL) was more potent than ampicillin while equally potent as chloramphenicol (MIC=50 µg/mL) toward SP.

*4.2.2 Gram-negative bacteria*

Compounds 3g (MIC=100 µg/mL) 3b, 3h, 3m, and 3n (MIC=200 µg/mL) were posses more potency against EC, whereas 3b, 3d, 3i, 3k (MIC=200 µg/mL), 3h and 3n (MIC=100 µg/mL) compounds were more active toward ST than standard drug ampicillin. No one member of this series was more active toward VC than standard drugs. Compounds 3c, 3g, 3m, 3n, 3n (MIC=250 µg/mL), 3q (MIC=100 µg/mL), and 3b are more potent than griseofulvin against CA. Compounds 3b, 3d, 3i, 3k (MIC=200 µg/mL) and 3h, 3n (MIC=100 µg/mL) have more potency than standard drug ampicillin toward ST

*4.2.3. Fungi*

Data in Table 5 revealed that compounds 3b (MIC=100 µg/mL) 3c, 3g, 3m, and 3n (MIC=250 µg/mL) are more active against CA than standard drug nystatin. Single member of this series is not active against AF According to analysis of Table 4 data, we have shown that compounds having fluorine substitution and pyrazoline moiety are more biologically active than another member of the series.

## 5. CONCLUSION

We have developed a convenient, new, and efficient protocol for the synthesis of new compounds 3a-r. The results clearly demonstrate that the application of the ultrasonic system markedly enhances the efficiency of the chemical processes of interest here and this type of approach decrease reaction time, one step of reaction and increase yield of desired products. Compounds 3b, 3n, and 3h are highly active toward antimicrobial bacteria than rest of the series compounds.

## 6. ACKNOWLEDGMENT

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***Bibliographical Sketch**

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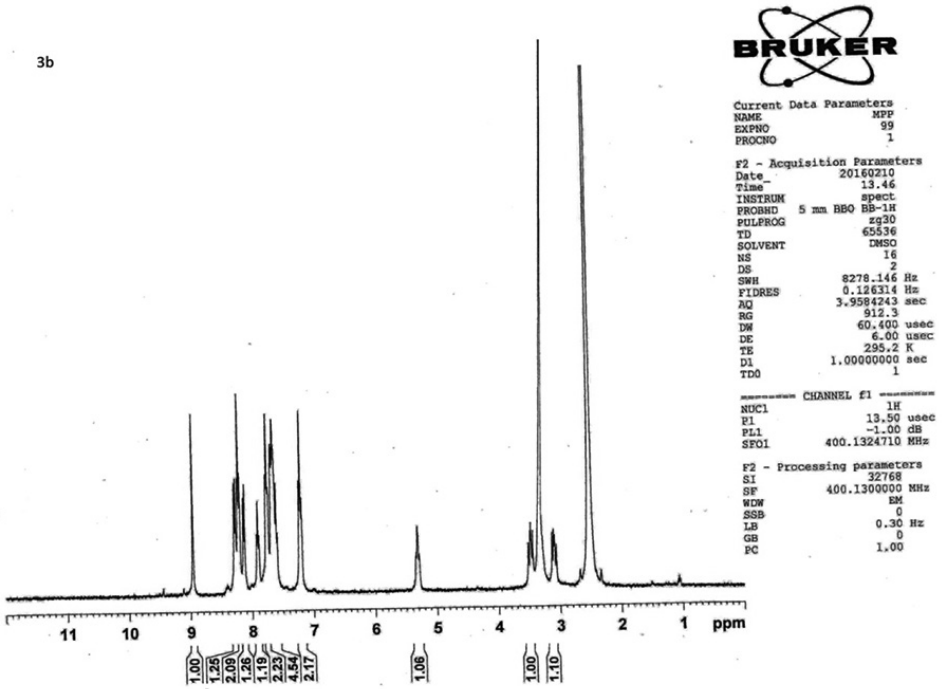
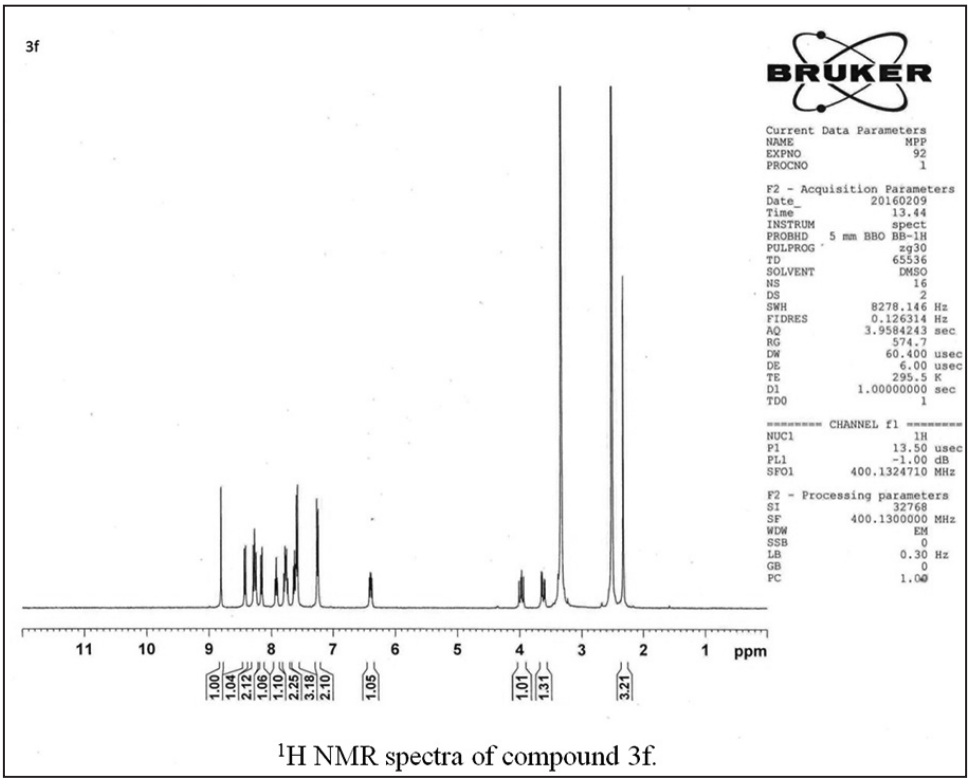
## SUPPLEMENTARY INFORMATION




$^1$H NMR spectra of compound 3b.

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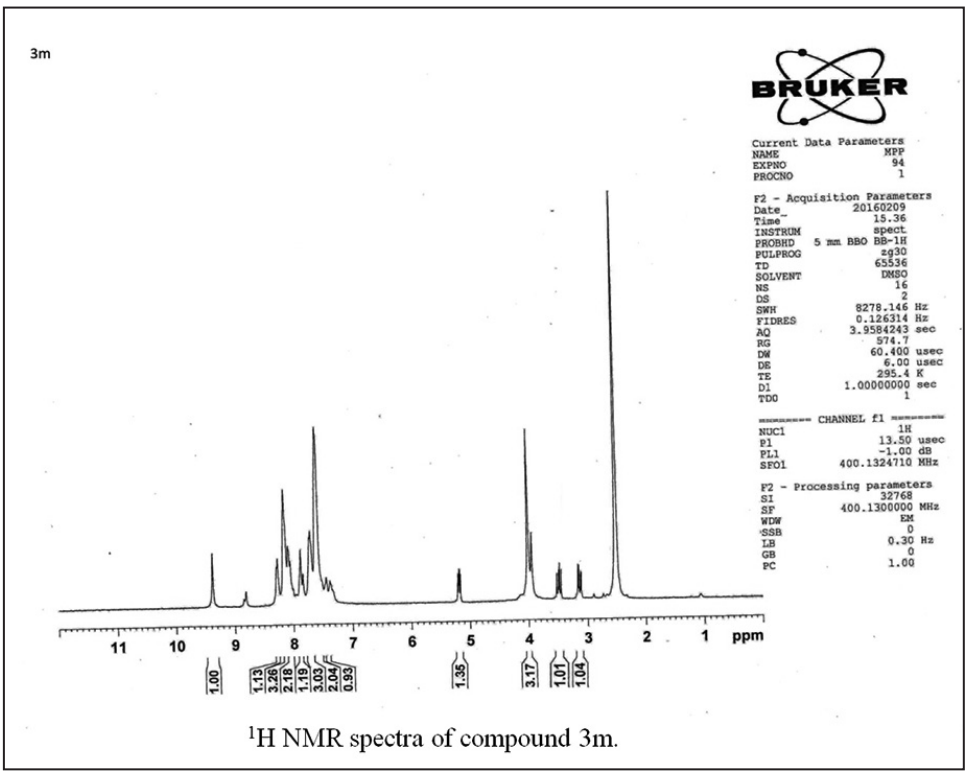
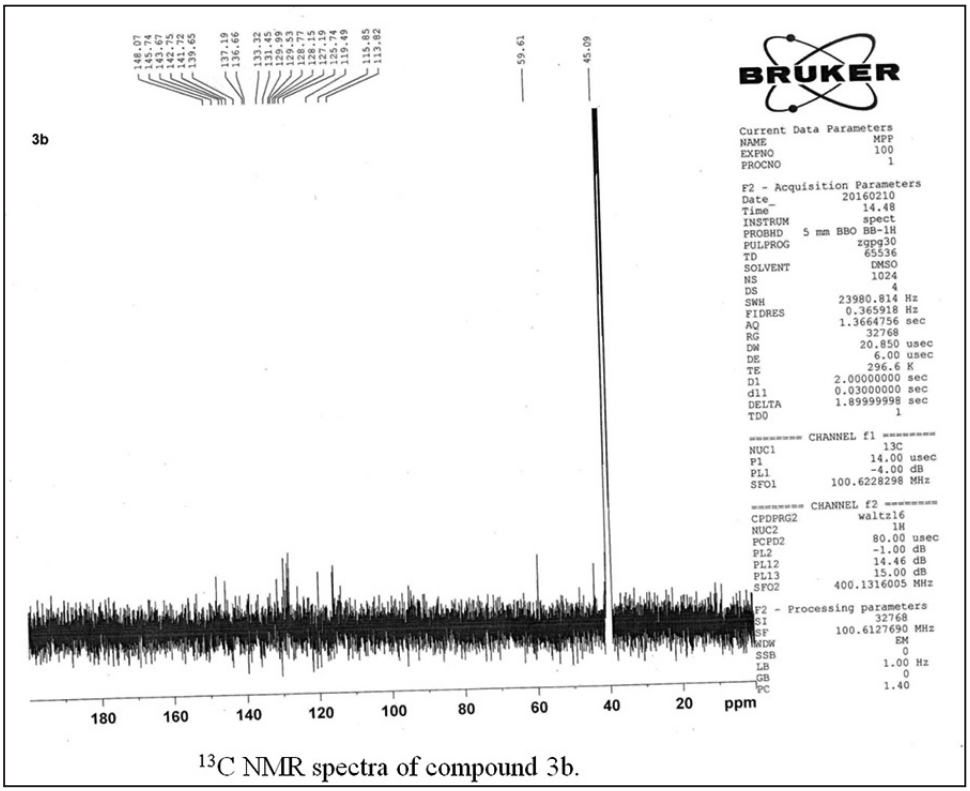



$^1$H NMR spectra of compound 3m.

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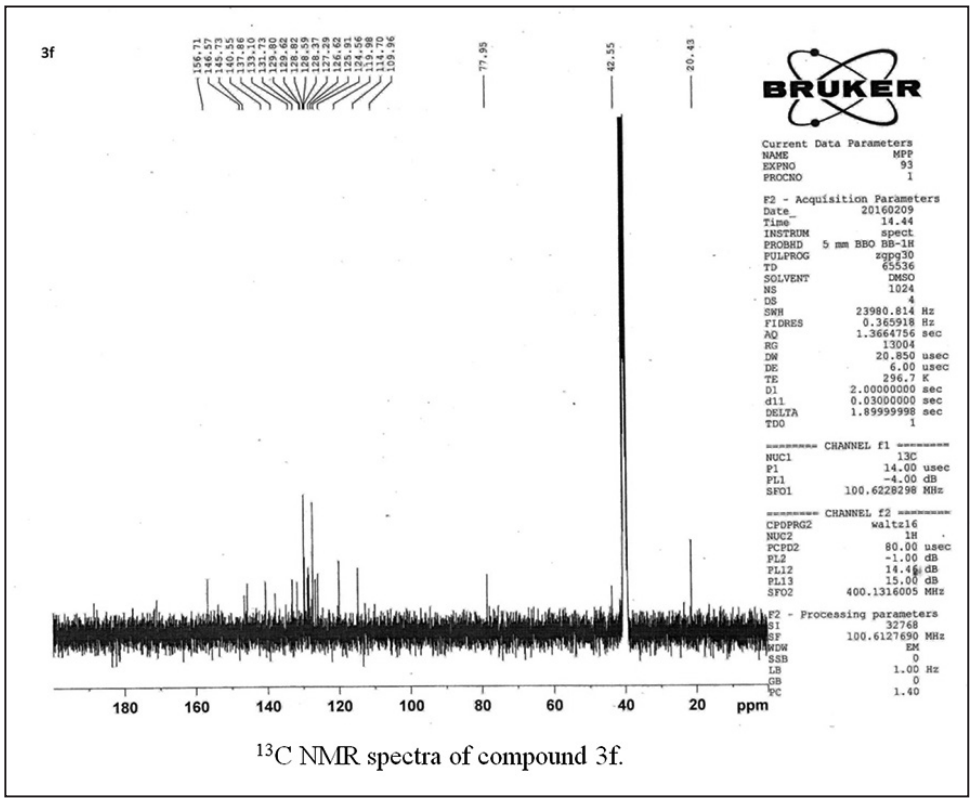


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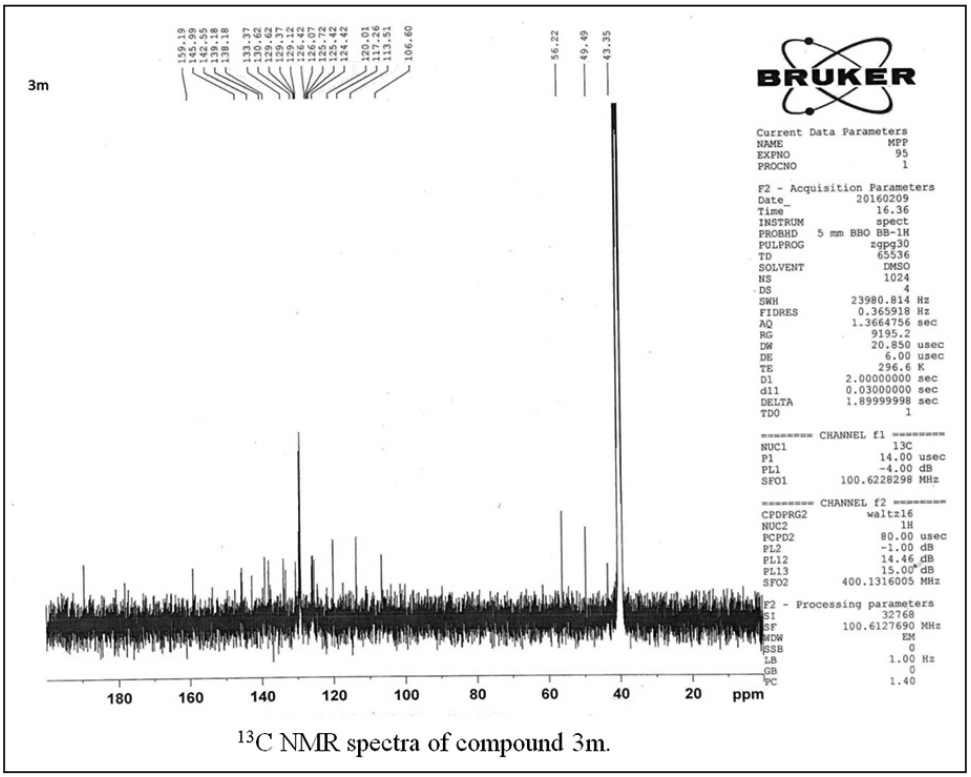


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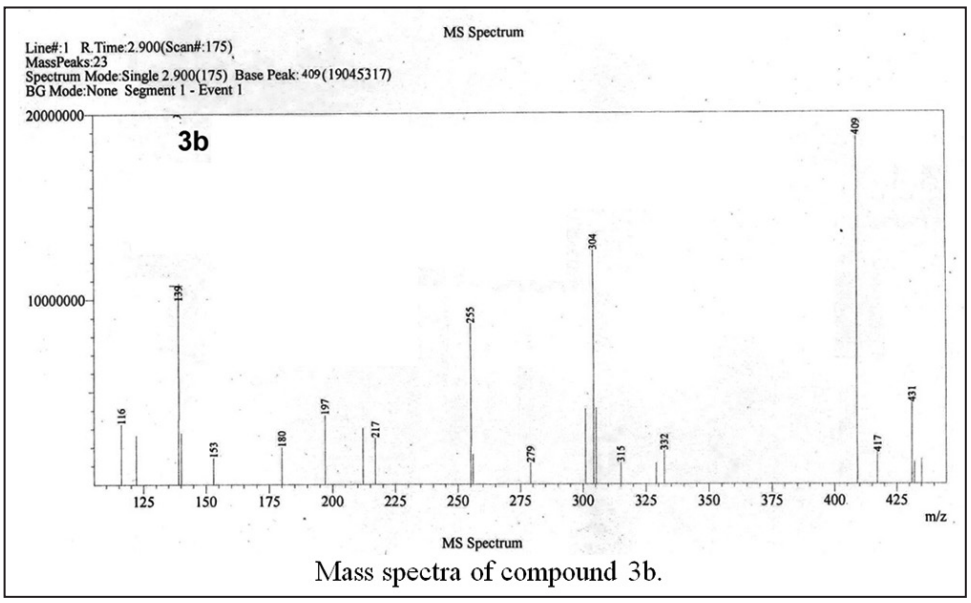


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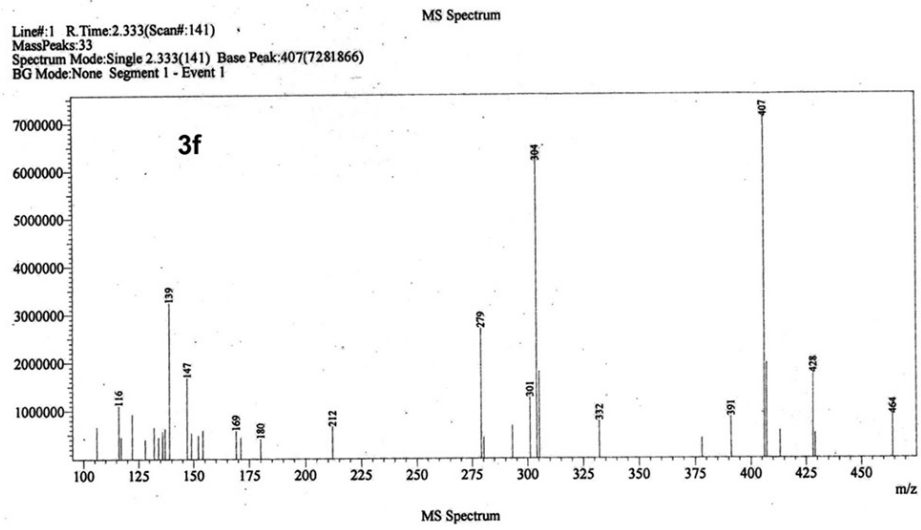


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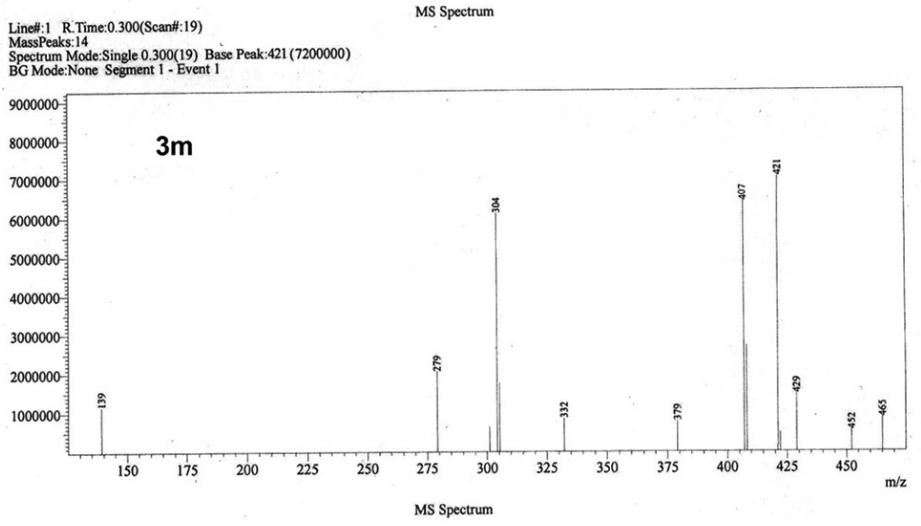


Mass spectra of compound 3m.