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# SYNTHESIS OF SOME 2, 3-DIARYL-6-ISOXAZYL-QUINOLINE-4-CARBOXYLIC ACID DERIVETIVES

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**ABSTRACT:** A series of some new substituted quinolines were synthesized by Doebner reaction, a three component coupling of various aromatic amines with two aldehydes and phenyl pyruvic acid, the intermediate 2, 3-diary-6-acetyl-quinoline-4-carboxylic acids were reacted with various aromatic aldehydes in the presence of basic medium using Claisen-Schmidt condensation in order to afford the corresponding chalcones. The substituted chalcones, on condensation with hydroxylamine hydrochloride in ethanol furnished isoxazoles derivatives. Another quinolines derivative were synthesized in this study by using an aryl amines with acetylacetone as Combes reaction, Knorr reaction between an aryl amines and ethylacetoacetate with heating above 100 ºC, and Conrad-Limpach quinoline synthesis a thermal condensation of an aryl amines with ethylacetoacetate. The reaction progress for all synthesized compounds was checked by thin layer chromatography (TLC) and melting point techniques, the structure of synthesized compounds were confirmed using IR, $^{1}$HNMR, $^{13}$CNMR, and GCMS. All the compounds have been screened for their antibacterial and antifungal activity.

**INTRODUCTION:** Quinolines are receiving increasing importance due to their wide range of biological and pharmacological activities [1], a number of biological activities have been associated with quinoline containing compounds such as antimalarial [2, 3], especially those which containing chalcones [4], anti-inflammatory agent, anti-asthmatic, antibacterial [5, 6], antihyper tensive, anti cancer [7], tyrosine kinase inhibiting agent, and anti nuclear inhibitors of immuno deficiency virus [8].

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In addition, quinoline derivatives have been used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties [9].

## MATERIALS AND METHODS:

All the chemicals used in the work were of analytical grade, melting points were determined by Gallenkamp melting point apparatus and were uncorrected, IR spectrum (in KBr disk) is recorded using FTIR-8400s instrument (Shimadzu, Japan) and frequencies are expressed in $cm^{-1}$. The $^{1}$HNMR and $^{13}$CNMR recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using DMSO as solvent, the values is expressed in δ ppm. GCMS spectra performed on QP 2010 GC instrument (Shimadzu, Japan).

**General procedure for synthesis of 2,3-diaryl-quinoline – 4 - carboxylic acid (I, II, and $VII_{a-c}$):** In a 1 liter round bottom flask equipped with a reflux condenser were placed 0.236 mol of the required aromatic aldehydes, 0.25 mol of freshly distilled phenyl pyruvic acid and 200 ml of absolute ethanol. The mixture was heated on a boiling point water bath and a solution of 0.248 mol of the required amine in a 100 ml of absolute ethanol was added slowly with frequent shaking during 1hour. The mixture was refluxed on a water bath for 3 hours and left to stand overnight, filtered, washed with a little ether and recrystallized from ethanol.

**I: 2, 3-Diphenyl-6-acetyl-quinoline-4-carboxylic acid: Yield** 80.30%, **mp** 249-250C°. **IR (KBr, $cm^{-1}$):** 1452.30, 1512.09 (C=C), 1369.37 (C-N), 1660.00, 1679.88 (C=O), 3000.00-3437.50 (O-H). **$^1$HNMR (DMSO, ppm):** 7.86-7.92 (2H, m, Quinoline ring), 10.73 (1H, s, Quinoline ring), 7.08-7.44 (8H, m, H-Ar), 7.76 (2H, d, H-Ar), 2.50 (3H, s, $CH_3$). **MS (m/z):** 292, 246, 77.

**II: 2 – Furyl – 3 – phenyl – 6 – acetyl quinoline-4-carboxylic acids: Yield** 45%, **mp** 227-228C°. **IR (KBr, $cm^{-1}$):** 1512.09, 1600.81 (C=C), 1365.51 (C-N), 1672.17, 1687.60 (C=O), 1271 (C-O), 3187.50-3437.50 (O-H).

**$^1$HNMR (DMSO, ppm):** 6.90-7.77 (2H, 2H, 5H, m, Quinoline ring, Furyl ring, H-Ar), 7.95 (1H, s, Quinoline ring), 6.18 (1H, t, Furyl ring), 2.57 (3H, s, $CH_3$). **$^{13}$CNMR (DMSO, ppm):** 26.49 ($CH_3$), 115.00 (C, H-Ar), 121.00 (CH, Furyl ring), 126.97-128.99 (3CH, C, Quinoline ring, 5CH, H-Ar), 129.00-132.00 (4C, Quinoline ring), 139.00 (CH, Furyl ring), 142.95 (CH, Furyl ring), 143.11 (C, Quinoline ring), 148.74 (C, Quinoline ring, C, Furyl ring), 165.52 (C, Carboxylic acid), 196.66 (C, C=O).

**$VII_a$: 2, 3-Diphenyl-6-sulphamido-quinoline-4-carboxylic acid: Yield** 78%, **mp** 251-252C°. **IR (KBr, $cm^{-1}$):** 1498.59, 1593.09 (C=C), 1369.37 (C-N), 1685.67 (C=O), 3311.55, 3280.00 (N-H), 1311.50, 1159.14 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 7.89-7.92 (2H, m, Quinoline ring), 10.75 (1H, s, Quinoline ring), 7.09-7.44 (8H, 2H, m, H-Ar, $NH_2$), 7.75 (2H, d, H-Ar). **MS (m/z):** 207, 179, 77.

**$VII_b$: 2, 3-Diphenyl-6-(5-methyl-3-sulphamido-isoxazole)-quinoline-4-carboxylic acid: Yield** 37%, **mp** 266-267C°. **IR (KBr, $cm^{-1}$):** 1496.66, 1591.16 (C=C), 1367.44 (C-N), 1681.81 (C=O), 3259.47 (N-H), 1313.43, 1172.64 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 7.73-7.79 (2H, 2H, m, Quinoline ring, H-Ar), 7.92 (1H, d, Quinoline ring), 7.09-7.43 (8H, m, H-Ar), 10.76 (1H, s, NH), 6.62 (1H, s, Isoxazole ring), 2.29 (3H, s, $CH_3$), 11.36 (1H, s, OH). **MS (m/z):** 429, 281, 147.

**$VII_c$: 2, 3 – Diphenyl – 6 - (5, 6-dimethoxy-4-sulphamido-pyrimidine)-quinoline-4-carboxylic acid: Yield** 42.6%, **mp** 218-219C°. **IR (KBr, $cm^{-1}$):** 1483.16, 1595.02 (C=C), 1365.51 (C-N), 1704.96 (C=O), 3303.83 (N-H), 1311.50, 1157.21 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 8.10 (1H, s, Quinoline ring), 7.09-7.43 (2H, 8H, m, Quinoline ring, H-Ar), 7.73 (2H, d, H-Ar), 10.75 (1H, s, NH), 3.65 (3H, s, $OCH_3$), 3.90 (3H, s, $OCH_3$), 7.92 (1H, s, Pyrimidine ring), 11.09 (1H, s, OH). **MS (m/z):** 327, 178, 125.

**General procedure for synthesis of chalcones ($III_{a-d}$) and ($IV_{a-e}$):** A mixture of 0.01 mol of the required aromatic aldehydes and 0.01 mol of substituted quinoline was stirred in 30 ml of ethanol at room temperature in the presence of 10 ml of 20% sodium hydroxide solution. The mixture was stirred for 24 hour at RT and kept for overnight. The mixture was poured into crushed ice and acidified with dilute hydrochloric acid to neutral. The chalcones derivatives are precipitates out as solid, filtered, dried and recrystallized from ethanol.

**$III_a$: 2, 3-Diphenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 96%, **mp** 244-245C°. **IR (KBr, $cm^{-1}$):** 1450.00, 1496.66 (C=C), 1512.09 ($C=C_{olefin}$), 1369.37 (C-N), 1660.00, 1668.31 (C=O), 1217.00 (C-O). **$^1$HNMR (DMSO, ppm):** 7.81-7.96 (2H, 2H, m, Quinoline ring, H-Ar), 8.12 (1H, s, Quinoline ring), 7.08-7.47 (13H, 1H, m, H-Ar, H-C=), 7.69 (1H, d, =C-H). **MS (m/z):** 311, 207, 77.

**$III_b$: 2, 3-Diphenyl-6-(3-furyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 81.5%, **mp** 215-216C°. **IR (KBr, $cm^{-1}$):** 1496.66, 1508.23 (C=C), 1600.81 ($C=C_{olefin}$), 1369.37 (C-N), 1654.81, 1670.00 (C=O), 1222.79 (C-O). **$^1$HNMR**

**(DMSO, ppm):** 7.77-7.93 (2H, 2H, 1H, m, Quinoline ring, H-Ar, Furyl ring), 8.02 (1H, s, Quinoline ring), 7.09-7.52 (8H, 2H, 1H, m, H-Ar, HC=CH, Furyl ring), 6.68 (1H, t, Furyl ring). **MS (m/z):** 301, 208, 77.

**$III_c$: 2, 3-Diphenyl-6-(3-[2-phenyl ethylene]-prop -2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 93%, **mp** 204-205C°. **IR (KBr, $cm^{-1}$):** 1500.00, 1508.23 (C=C), 1598.88 ($C=C_{olefin}$), 1369.37 (C-N), 1652.88, 1668.31 (C=O), 1255.57 (C-O). **$^1$HNMR (DMSO, ppm):** 7.77-7.96 (2H, 2H, m, Quinoline ring, H-Ar), 9.52 (1H, s, Quinoline ring), 7.08-7.61 (13H, 4H, m, H-Ar, 2HC=CH). **MS (m/z):** 361, 105, 77.

**$III_d$: 2, 3 – Diphenyl – 6 - (3-[3-N, N - dimethylaminophenyl] – prop – 2 – en – 1 – one -1-yl)-quinoline-4-carboxylic acid: Yield** 88%, **mp** 198-199C°. **IR (KBr, $cm^{-1}$):** 1520.00, 1550.00 (C=C), 1596.95 ($C=C_{olefin}$), 1371.29 (C-N), 1647.10, 1670.24 (C=O), 1215.07 (C-O). **$^1$HNMR (DMSO, ppm):** 7.91 (1H, d, Quinoline ring), 7.86 (1H, d, Quinoline ring), 8.04 (1H, s, Quinoline ring), 7.17-7.47 (8H, 1H, m, H-Ar, H-C=), 7.69 (2H, d, H-Ar), 7.63 (1H, d, =C-H), 6.75 (1H, d, H-Ar), 7.06 (2H, m, H-Ar), 6.73 (1H, s, H-Ar), 3.05 (6H, s, $CH_3$). **MS (m/z):** 223, 120, 103.

**$IV_a$: 2 - Furyl-3-phenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 95.2%, **mp** 268-269C°. **IR (KBr, $cm^{-1}$):** 1496.66, 1512.09 (C=C), 1596.95 ($C=C_{olefin}$), 1365.51 (C-N), 1650.00, 1670.24 (C=O), 1218.93 (C-O). **$^1$HNMR (DMSO, ppm):** 7.69-7.82 (2H, m, Quinoline ring), 8.03 (1H, s, Quinoline ring), 7.36-7.42 (10H, 2H, 2H, m, H-Ar, Furyl ring, HC=CH), 6.20 (1H, t, Furyl ring).

**$IV_b$: 2 - Furyl-3-phenyl – 6 - (3-furyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 93%, **mp** 237-238C°. **IR (KBr, $cm^{-1}$):** 1500.00, 1550.00 (C=C), 1600.81 ($C=C_{olefin}$), 1367.44 (C-N), 1660.60, 1675.00 (C=O), 1230.50 (C-O). **$^1$HNMR (DMSO, ppm):** 7.50-7.88 (3H, 5H, 4H, 2H, m, Quinoline ring, H-Ar, Furyl ring, HC=CH), 6.49-6.68 (2H, m, Furyl ring). **$^{13}$CNMR (DMS, ppm):** 123.33 (CH, Ethylene group), 124.50-132.00 (5C, Quinoline ring), 127.43-129.83 (3CH, Quinoline ring, CH, Ethylene group, 5CH, H-Ar), 130.00 (C, H-Ar), 132.93 (C, Quinoline ring), 134.00, 136.00, 137.00, 139.00, 142.16, 143.00, 144.00, and 140.05 (6CH, 2C, Furyl ring), 186.95 (C, C=O), 188.00 (C, Carboxylic acid).

**$IV_c$: 2 – Furyl - 3 – phenyl – 6 - (3-[2-phenylethylene] – prop – 2 – en – 1 – one – 1 - yl)-quinoline-4-carboxylic acid: Yield** 92.3%, **mp** 225-226C°. **IR (KBr, $cm^{-1}$):** 1450.00, 1515.94 (C=C), 1598.88 ($C=C_{olefin}$), 1363.58 (C-N), 1652.88, 1683.74 (C=O), 1288.43 (C-O). **$^1$HNMR (DMSO, ppm):** 7.79 (1H, d, Quinoline ring), 7.69 (1H, d, Quinoline ring), 7.98 (1H, s, Quinoline ring), 7.01-7.49 (10H, 3H, 3H, m, H-Ar, Furyl ring, HC=CH, =CH), 6.20 (1H, d, H-C=). **$^{13}$CNMR (DMSO, ppm):** 119.00, 119.80 (2C, H-Ar), , 123.00-124.95 (CH, 3C, Quinoline ring, 2CH, Ethylene group), 125.43, 132.57, 136.04, and 142.45 (CH, 3C, Quinoline ring), 127.20-129.15 (10CH, H-Ar, CH, Quinoline ring, 2CH, Ethylene group), 138.00, 139.00, 141.35, and 142.00 (3CH, C, Furyl ring), 187.00 (C, C=O).

**$IV_d$: 2 – Furyl – 3 – phenyl - 6-(3-[3-N, N-dimethyl amino phenyl]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield** 87%, **mp** 204-205C°. **IR (KBr, $cm^{-1}$):** 1525.59, 1577.66 (C=C), 1596.95 ($C=C_{olefin}$), 1363.58 (C-N), 1652.88, 1674.10 (C=O), 1230.50 (C-O). **$^1$HNMR (DMSO, ppm):** 9.74 (1H, s, Quinoline ring), 7.53-7.98 (2H, 7H, 3H, 2H, m, Quinoline ring, H-Ar, Furyl ring, HC=CH), 6.70 (1H, d, H-Ar), 6.16 (1H, s, H-Ar), 3.09 (6H, s, $CH_3$). **$^{13}$CNMR (DMSO, ppm):** 40.09 (2CH, $CH_3$), 109.65, 137.00, 141.91, and 143.00 (3CH, C, Furyl ring), 111.71, 115.90, 138.00, and 151.87 (3CH, C, H-Ar), 122.00 (CH, Ethylene group), 121.00-122.12 (2C, H-Ar, C, Quinoline ring), 123.00, 124.00, and 132.82 (2CH, 2C, Quinoline ring), 144.41 (C, Quinoline ring, CH, Ethylene group), 127.43-128.87 (3CH, Quinoline ring, 6CH, H-Ar), 189.85 (C, C=O).

**$IV_e$: 2 - Furyl-3-phenyl- 6-(3-[2-hydroxyphenyl]-prop – 2 - en- 1 - one-1-yl) - quinoline – 4 - carboxylic acid: Yield** 84%, **mp** 184-185C°. **IR (KBr, $cm^{-1}$):** 1458.08, 1512.09 (C=C), 1598.88 ($C=C_{olefin}$), 1363.58 (C-N), 1660.00, 1679.88 (C=O), 1274.86 (C-O). **$^1$HNMR (DMSO, ppm):** 7.95 (1H, d, Quinoline ring), 7.75-7.80 (1H, 1H, m, Quinoline ring, =C-H), 8.01 (1H, s, Quinoline ring), 7.34-7.69 (8H, 3H, 1H, m, H-Ar, Furyl ring, H-C=), 6.20 (1H, d, H-Ar). **$^{13}$CNMR (DMSO,**

**ppm):** 110.26, 110.76, 141.00, and 142.67 (3CH, C, Furyl ring), 115.00-121.00 (3C, 2CH, H-Ar), 119.84 (CH, H-Ar), 119.94, 142.00 (2CH, Ethylene group), 123.00-129.13 (3CH, 6C, Quinoline ring, 7CH, H-Ar), 196.66 (C, C=O).

**General procedure for synthesis of isoxazoles ($V_{a-d}$) and ($VI_{a-e}$):** A mixture of 0.02 mol of the required chalcone, 0.02 mol of hydroxylamine hydrochloride and 0.05 mol sodium acetate in 25 ml ethanol was refluxed for 6hour. The mixture was concentrated by distilling out the solvent and poured into ice water. The precipitate was filtered, washed and recrystallized from ethanol.

**$V_a$: 2, 3-Diphenyl – 6 - (5-phenyl-oxazole-3-yl)-quinoline-4-carboxylic acid: Yield** 92.2%, **mp** 189-190C°. **IR (KBr, cm$^{-1}$):** 1515.94, 1602.74 (C=C), 1249.80 (C-O), 1369.37 (C-N), 1681.81 (C=O), 931.55 (N-O). **$^1$HNMR (DMSO, ppm):** 7.41-7.66 (2H, 15H, m, Quinoline ring, H-Ar), 8.01 (1H, s, Quinoline ring), 6.00 (1H, s, Isoxazole ring).

**$V_b$: 2, 3 – Diphenyl – 6 - (5-furyl-oxazole-3-yl) - quinoline-4-carboxylic acid: Yield** 95.8%, **mp** 181-182C°. **IR (KBr, cm$^{-1}$):** 1514.02, 1600.81 (C=C), 1215.07 (C-O), 1367.44 (C-N), 1681.81 (C=O), 931.56 (N-O), 2800.00-3520.00 (O-H). **$^1$HNMR (DMSO, ppm):** 7.17-7.72 (2H, 10H, 3H, m, Quinoline ring, H-Ar, Furyl ring), 7.96 (1H, s, Quinoline ring), 6.01 (1H, s, Isoxazole ring). **$^{13}$CNMR (DMSO, ppm):** 113.08, 114.00, 141.12, and 143.15 (3CH, C, Furyl ring), 123.27-131.50 (3CH, 5C, Quinoline ring, 11CH, H-Ar), 132.90 (C, Quinoline ring), 137.40 (C, H-Ar), 146.06, 149.00, and 151.18 (CH, 2C, Isoxazole ring), 166.14 (C, Carboxylic acid).

**$V_c$: 2, 3 - Diphenyl – 6 - (5-[2-phenylethylene] - oxazole-3-yl)-quinoline-4-carboxylic acid: Yield** 83.3%, **mp** 244-245C°. **IR (KBr, cm$^{-1}$):** 1448.44, 1512.09 (C=C), 1255.57 (C-O), 1363.58 (C-N), 1668.38 (C=O), 931.55 (N-O), 1598.88 (C=$C_{olefin}$). **$^1$HNMR (DMSO, ppm):** 7.31- 7.70 (2H, 15H, m, Quinoline ring, H-Ar), 7.92 (1H, s, Quinoline ring), 6.01 (1H, s, Isoxazole ring), 7.00 (2H, q, HC=CH). **$^{13}$CNMR (DMSO, ppm):** 123.53-133.08 (3CH, 6C, Quinoline ring, 15CH, C, H-Ar), 135.99-137.30 (2CH, Ethylene group, C, Quinoline ring, 2CH, H-Ar), 140.98, 143.89, and 150.00 (CH, 2C, Isoxazole ring).

**$V_d$: 2, 3-Diphenyl-6-(5-[3-N, N-dimethylamino phenyl] – oxazole – 3 - yl) – quinoline – 4 - carboxylic acid: Yield** 77.8%, **mp** 236-237C°. **IR (KBr, cm$^{-1}$):** 1523.66, 1577.66 (C=C), 1211.21 (C-O), 1367.44 (C-N), 1674.10 (C=O), 931.55 (N-O). **$^1$HNMR (DMSO, ppm):** 7.16-7.76 (2H, 13H, m, Quinoline ring, H-Ar), 7.94 (1H, s, Quinoline ring), 6.01 (1H, s, Isoxazole ring), 6.68 (1H, d, H-Ar), 3.04 (6H, s, $CH_3$). **$^{13}$CNMR (DMSO, ppm):** 40.10 (2CH, $CH_3$), 111.70, 115.87, 137.41, 140.00 (3CH, 2C, H-Ar), 122.04-133.81 (3CH, 5C, Quinoline ring, 11CH, 2C, H-Ar), 138.00 (C, Quinoline ring), 141.00, 144.69, and 151.90 (CH, 2C, Isoxazole ring), 165.88 (C, Carboxylic acid).

**$VI_a$: 2 - Furyl-3-phenyl-6-(5-phenyl-oxazole-3-yl) –quinoline-4-carboxylic acid: Yield** 84%, **mp** 204-205C°. **IR (KBr, cm$^{-1}$):** 1515.94, 1600.81 (C=C), 1200.00 (C-O), 1367.44 (C-N), 1683.74 (C=O), 931.55 (N-O). **$^1$HNMR (DMSO, ppm):** 7.35-7.80 (2H, 10H, 2H, m, Quinoline ring, H-Ar, Furyl ring), 8.03 (1H, s, Quinoline ring), 6.00-6.30 (1H, 1H, m, Furyl ring, Isoxazole ring).

**$VI_b$: 2-Furyl-3-phenyl-6-(5-furyl-oxazole-3-yl)-quinoline-4-carboxylic acid: Yield** 83.3%, **mp** 174-175C°. **IR (KBr, cm$^{-1}$):** 1514.02, 1602.74 (C=C), 1228.57 (C-O), 1365.51 (C-N), 1689.53 (C=O), 931.55 (N-O). **$^1$HNMR (DMSO, ppm):** 7.36-7.80 (2H, 5H, 5H, m, Quinoline ring, H-Ar, Furyl ring), 8.05 (1H, s, Quinoline ring), 6.19-6.72 (1H, 1H, m, Isoxazole ring, Furyl ring). **$^{13}$CNMR (DMSO, ppm):** 110.37, 111.40, 140.95, and 143.21 (6CH, 2C, Furyl ring), 120.22-133.02 (3CH, 5C, Quinoline ring, 6CH, H-Ar), 139.00 (C, Quinoline ring), 146.10, 148.78, and 151.18 (CH, 2C, Isoxazole ring), 165.64 (C, Carboxylic acid).

**$VI_c$: 2 – Fury l – 3 – phenyl – 6 - (5-[2-phenylethylene] – oxazole - 3 - yl) – quinoline - 4-carboxylic acid: Yield** 80.5%, **mp** 237-238C°. **IR (KBr, cm$^{-1}$):** 1446.51, 1512.09 (C=C), 1286.43 (C-O), 1363.58 (C-N), 1670.24 (C=O), 931.55 (N-O), 1598.88 (C=$C_{olefin}$). **$^1$HNMR (DMSO, ppm):** 7.69 (1H, d, Quinoline ring), 7.78 (1H, d, Quinoline ring), 7.98 (1H, s, Quinoline ring), 7.29-7.51 (10H, 2H, m, H-Ar, Furyl ring), 7.01-7.09 (1H, 2H, m, Furyl ring, HC=CH), 6.19 (1H, s,

Isoxazole ring). **$^{13}$CNMR (DMSO, ppm):** 110.38, 142.96, and 143.12 (2CH, C, Furyl ring), 111.43 (CH, Ethylene group, CH, Furyl ring), 120.22-133.17 (3C, 5C, Quinoline ring, 10CH, H-Ar), 136.00(C, Quinoline ring), 140.86 and 141.52 (2C, H-Ar), 146.75 (CH, Ethylene group), 143.95, 149.00, and 150.00 (CH, 2C, Isoxazole ring), 165.55 (C, Carboxylic acid).

**$VI_d$: 2 – Furyl – 3 – pheny l – 6 - (5-[3-N, N-dimethyl amino phenyl]-oxazole-3-yl)-quinoline-4-carboxylic acid: Yield** 75%, **mp** 231-232C°. **IR (KBr, cm$^{-1}$):** 1577.66, 1600.81 (C=C), 1228.57 (C-O), 1365.51 (C-N), 1676.03 (C=O), 933.48 (N-O). **$^1$HNMR (DMSO, ppm):** 7.69 (1H, d, Quinoline ring), 7.75 (1H, d, Quinoline ring), 8.01 (1H, s, Quinoline ring), 7.32-7.40 (7H, 2H, m, H-Ar, Furyl ring), 6.50-6.70 (1H, 2H, m, Furyl ring, H-Ar), 6.19 (1H, s, Isoxazole ring), 3.05 (6H, s, $CH_3$). **$^{13}$CNMR (DMSO, ppm):** 40.10 (2CH, $CH_3$), 110.36 (CH, Furyl ring, CH, H-Ar), 111.34, 111.71, and 144.74 (2CH, C, H-Ar), 119.72, 140.48, and 141.00 (CH, Furyl ring), 122.05-133.92 (3CH, 5C, Quinoline ring, 6CH, 2C, H-Ar), 139.00 (C, Quinoline ring), 147.00, 148.86, and 151.94 (CH, 2C, Isoxazole ring), 165.54 (C, Carboxylic acid).

**$VI_e$: 2 - Furyl-3-phenyl-6- (5- [2-hydroxyphenyl] -oxazole-3-yl)-quinoline-4-carboxylic acid: Yield** 80.6%, **mp** 177-178C°. **IR (KBr, cm$^{-1}$):** 1515.94, 1600.80 (C=C), 1215.07 (C-O), 1367.44 (C-N), 931.55 (N-O), 2400.00-3520.00 (O-H). **$^1$HNMR (DMSO, ppm):** 7.35-7.79 (2H, 6H, 2H, m, Quinoline ring, H-Ar, Furyl ring), 8.03 (1H, s, Quinoline ring), 6.82-6.93 (1H, 2H, m, Furyl ring, H-Ar), 6.19 (1H, s, Isoxazole ring), 6.97 (1H, t, H-Ar), 8.22 (1H, s, OH). **$^{13}$CNMR (DMSO, ppm):** 110.34, 111.13, 142.98, and 143.45 (3CH, C, Furyl ring), 116.26, 118.84, and 143.07 (CH, 2C, H-Ar), 121.42-137.10(3CH, 5C, Quinoline ring, 8CH, C, H-Ar), 139.05 (C, Quinoline ring), 148.00, 149.13, and 152.33 (CH, 2C, Isoxazole ring), 165.37 (C, Carboxylic acid).

**General procedure for synthesis of 2,4-dimethyl quinoline-6-sulphamide (VIII):** A mixture of 2.00g (0.012 mol) of sulphanilamide, 3ml (0.029 mol) of acetyl acetone and 4g of drierite was refluxed for 4hour, the precipitate obtained on elution with ether, and it was filtered, washed and recrystallized from benzene petroleum ether [10].

**2, 4-Dimethyl quinoline-6-sulphamide: Yield** 91.2%, **mp** 176 - 177C°. **IR (KBr, cm$^{-1}$):** 1515.94, 1627.81 (C=C), 3332.76, 3242.12 (N-H), 1330.79, 1151.42 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 7.36 (2H, m, Quinoline ring), 7.79 (1H, s, Quinoline ring), 5.35 (1H, s, Quinoline ring), 6.91 (2H, s, $NH_2$), 2.14 (3H, s, $CH_3$), 2.04 (3H, s, $CH_3$). **MS (m/z):** 156, 92, 65.

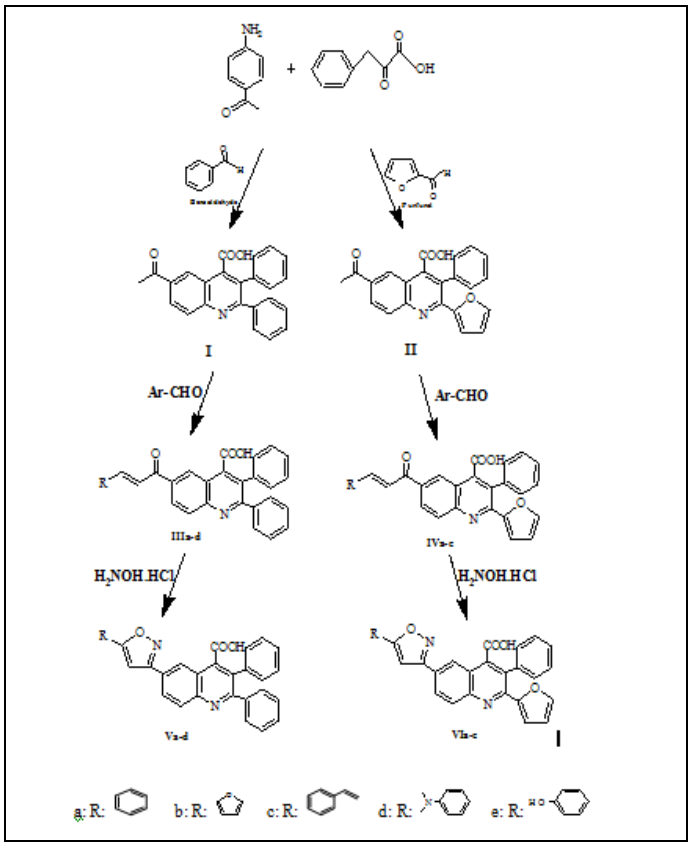
**General procedure for synthesis of 4-methyl-2-hydroxy quinoline-6-sulphamide (IX):** A mixture of 1.72g (0.01mol) of sulphanilamide, 1.26ml (0.01mol) of ethylacetoacetate was refluxed for 5minutes. The precipitate was filtered, concentrated sulphuric acid was added to the precipitate and refluxed on a water bath for 15minutes, cooled, and poured into saturated solution of sodium carbonate. The precipitate was filtered, washed and recrystallized from acetic acid and water then from ethanol and water [11].

**4 – Methyl – 2 – hydroxyquinoline – 6 - sulphamide: Yield** 79.8%, **mp** dec at 298C°. **IR (KBr, cm$^{-1}$):** 1598.88, 1629.74 (C=C), 3375.20, 3274.90 (N-H), 1313.43, 1149.50 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 6.58 (2H, d, Quinoline ring), 7.44 (1H, s, Quinoline ring), 6.90 (2H, s, $NH_2$), 5.82 (1H, s, Quinoline ring), 2.51 (3H, s, $CH_3$). **MS (m/z):** 183, 155.

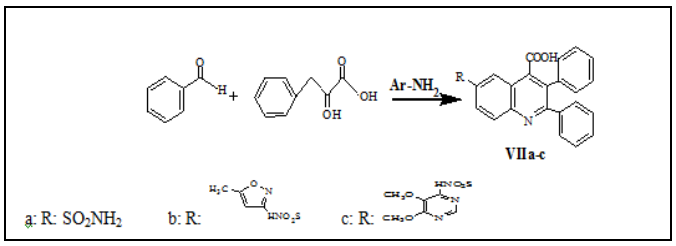
**General procedure for synthesis of 2-methyl-4-hydroxy quinoline-6-sulphamide (X):** To a mixture of 1.72g (0.01 mol) of sulphanilamide, 1.26ml (0.01 mol) of ethylacetoacetate was added 3.5ml of absolute ethanol, about 3.5g of drierite, and four drops of glacial acetic acid, the resulting mixture was refluxed for 4hour. The drierite was filtered and the ethanol was distilled, the mixture poured into petry dish to dried and recrystallized from water.

**2 - Methyl - 4-hydroxyquinoline – 6 - sulphamide: Yield** 86.1%, **mp** 168-169C°. **IR (KBr, cm$^{-1}$):** 1575.73, 1627.81 (C=C), 3319.26, 3240.19 (N-H), 1309.58, 1153.35 ($SO_2$). **$^1$HNMR (DMSO, ppm):** 6.06-6.58 (2H, m, Quinoline ring), 7.46 (1H, s, Quinoline ring), 5.82 (1H, s, Quinoline

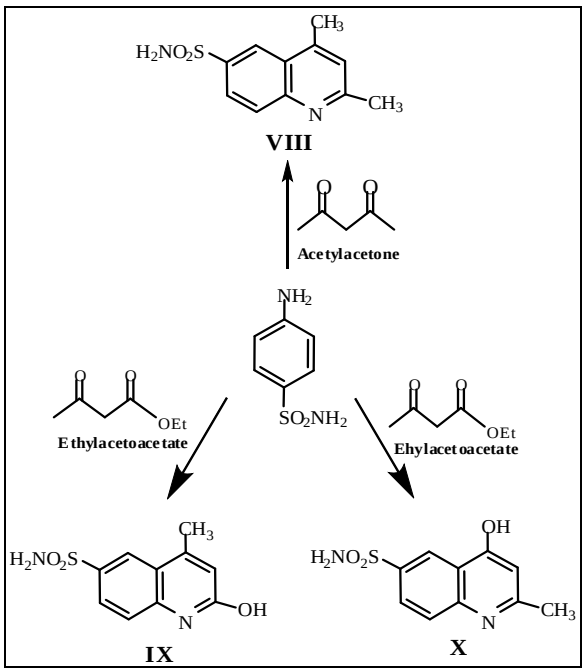
ring), 6.91 (2H, s, $NH_2$), 2.51 (3H, s, Quinoline ring). **MS (m/z):** 172, 156, 92.



**SCHEME-1: CHEMICAL STRUCTURE OF 2, 3-DIPHENYL- AND 2-FURYL-3-PHENYL-6-ISOXAZOLYL-QUINOLINE-4-CARBOXYLIC ACID**.



**SCHEME-2: CHEMICAL STRUCTURE OF 2, 3-DIPHENYL-6-SULPHANILAMIDE-QUINOLINE-4-CARBOXYLIC ACID**.



**SCHEME-3: CHEMICAL STRUCTURE OF PRODUCTS UNDER COMBES, KNORR, CONRAD-LIMPACH CONDITIONS**

## Antimicrobial activity:

All the newly synthesized compounds were screened for their in-vitro antimicrobial activity by employing disk diffusion method. The antimicrobial activity was carried out against *Proteus vulgaris*, *Escherichia coli* (gram-negative), *Bacillus subtillis*, *Staphylococus aureus* (gram-positive) and for antifungal activity against *Aspergillus niger* and *Candida albicans* by measuring the zone of inhibition in mm. The activities were performed at a conc. of 5 mg/ml in propylene glycol. The antimicrobial activity data is reported in **Table 1**.

**TABLE 1: ANTIMICROBIAL AND ANTIFUNGAL DATA OF COMPOUNDS**

| Comp | *P. vulgaris* | *E.coli* | *B. subtillis* | *S. aureus* | *Aspergillus niger* | *Candida albicans* |
|---|---|---|---|---|---|---|
| ***I*** | *7.00* | - | *8.00* | - | - | - |
| **II** | 9.00 | 14.00 | - | - | - | 6.00 |
| **$III_a$** | - | - | - | 12.00 | - | 5.00 |
| **$III_b$** | - | - | - | 11.00 | - | - |
| **$III_c$** | - | - | - | 9.00 | - | 9.00 |
| **$III_d$** | - | - | - | 10.00 | - | 6.00 |
| **$IV_a$** | - | - | - | - | - | 8.00 |
| **$IV_b$** | 10.00 | - | - | - | - | 5.00 |
| **$IV_c$** | - | - | - | - | - | - |
| **$IV_d$** | - | - | - | - | - | - |
| **$IV_e$** | 10.00 | - | 15.00 | 12.00 | - | 11.00 |
| **$V_a$** | - | - | - | 10.00 | - | 7.00 |
| **$V_b$** | - | - | - | - | - | 11.00 |
| **$V_c$** | - | - | - | - | - | 8.00 |
| **$V_d$** | - | - | - | - | - | 10.00 |
| **$VI_a$** | 8.00 | - | 7.00 | 13.00 | - | - |
| **$VI_b$** | 9.00 | - | - | 7.00 | - | 9.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **$VI_c$** | 6.00 | - | - | 8.00 | - | - |
| **$VI_d$** | - | - | - | - | - | - |
| **$VI_e$** | 12.00 | 11.00 | - | 6.00 | - | - |
| **$VII_a$** | 10.00 | 13.00 | 13.00 | - | - | 10.00 |
| **$VII_b$** | - | - | 11.00 | 10.00 | - | - |
| **$VII_c$** | 10.00 | - | 13.00 | 8.00 | - | - |
| **VIII** | 16.00 | 11.00 | 10.00 | - | - | - |
| **IX** | 9.00 | 15.00 | - | - | - | 7.00 |
| **X** | 13.00 | 13.00 | 8.00 | - | - | 7.00 |

**RESULT AND DISCUSSIONS:** The structural core of quinoline in this study has been synthesized by Doebner reaction which is a condensation reaction between primary aryl amines, aldehydes, and phenyl pyruvic acid to form 3-phenyl-quinoline-4-carboxylic acids, Combes synthesis is a formation of dialkyl quinoline by the condensation of primary aryl amines with β – diketones followed by an acid catalyzed ring closure of the schiff base intermediate, Knorr synthesis to prepare 2-hydroxy quinolines[12] from β – ketoesters and aryl amines the reaction requires heating above 100°, and Conrad-limach cyclization which is a thermal condensation of primary aromatic amines with β – ketoesters, followed by the cyclization of schiff base intermediate to form 4-hydroxy quinolines [13]. The synthesized 2, 3-diaryl-quinoline-4-carboxylic acid condensed with various aromatic aldehydes by Claisen-Schmidt condensation to form corresponding chalcones [14], which on condensation with hydroxylamine hydrochloride afforded isoxazoles. The structure of newly synthesized compounds were identified by performing TLC, melting points, and elucidated on the basis of spectral data by IR, $^1$HNMR, $^{13}$CNMR and GCMS, the reaction sequence for the synthesis of the title compounds is outlined in **Scheme 1, 2, 3**.

All the compounds have been screened for their *in-vitro* biological activity using disk diffusion method against various gram positive, gram negative bacteria and fungal stains, all compounds did not show activity against *Aspergillus niger,* the most active compound against *P.vulgaris* are VIII, X, $VI_e$, against *E.coli* are IX, II, $VII_a$, against *B.subtillis* are $IV_e$, $VII_a$, $VII_c$, against *S.aureus* are $VII_a$, $III_a$, $IV_e$, and against *Candida albicans* are $IV_e$, $V_b$, $V_d$.

## REFERENCES:


1. Revanasiddappa C. B, Subrahmanyan S. V. E, Satyanarayana D, and Thomas J: Synthesis and biological studies of some novel SCHIFF base and hydrazones derived from 8-hydroxy quinoline moiety. International J. Chem. Tech. Res 2009; 1(4):1100-1104.
2. Iniyavan P, Sarveswari S and Vijayakumar V: Ultrasound promoted oxidation of 2-chloroquinoline based 1,4-dihydropyridine and poly hydroquinolines to its pyridines. Canadian chemistry transactions 2014; 2(3):286-295.
3. Bawa S, Kumar S, Drabu S and Kumar R: Structural modifications of quinoline-based antimalarial agents: Recent developments. J Pharm Bioallied Sci 2010; 2(2):64-71.
4. Kirandeep K, Meenakshi J, Ravi P and Rahul J: Quinoline and structurally related heterocycles as antimalarials. European Journal of medicinal chemistry 2010; 45: 3245-3264.
5. Amir M, Javed A. S and Hassan Z. M: Synthesis and antimicrobial activity of pyrazolinone and pyrazole analogues containing quinoline moiety. Indian Journal of chemistry 2013; 52B:1493-1499.
6. Ramjith U. S, Radhika G, Muhammed Shakeel K. V, Nabeel C. K and Ayda C: Conventional and microwave assisted synthesis of novel quinoline derivatives and their antimicrobial and antioxidant potential. Int J Pharm Pharm Sci 2013; 5 suppl 4:521-524.
7. Balaji P.N, Sai Sreevani M, Harini P, Johnsi Rani P, Prathusha K and Chandu T. J: Antimicribial activity of some novel synthesized heterocyclic compounds from substituted chalcones. J. Chem. Pharm. Res 2010; 2(4): 754-758.
8. Pritam N. D: HIV-1 Integrase inhibitors: Update and perspectives. JCBPSC 2014; 4(2):1152-1170.
9. Xiao C, Cai Z. M, Sheng R. S, Hu S. Q and Zhan L. X: Microwave-assisted Friedlander synthesis of poly substituted quinolines based on poly (ethylene glycol) bound acetoacetate. J. Chin. Chem. Soc 2011; 58: 18-23.
10. Johnson S. W and Mathews J. F: Cyclization studies in the benzoquinoline series. J. Am. Chem. Soc 1944; 66 (2): 210-215.
11. Hauser R. C and Reynolds A. G: Reaction of β-keto esters with aromatic amines. Synthesis of 2-and 4-hydroxyquinoline derivatives. J. Am. Chem. Soc 1948; 70(7):2402-2404.
12. Pitchai P, Uvarani C, Gengan M. R, and Mohan S.P: A one pot microwave assisted synthesis of 3-acyl-2, 4-dihydroxyquinoline followed by synthesis of 7-methyldibenzo[c,f][2,7] naphthyridin-6(5H)-ones via three routes. Indian Journal of chemistry 2013; 52B:776-786.
13. Brouet C. L, Gu S, Peet P. N and Williams D. J: A survey of solvents for the Conrad-Limpach synthesis of 4-hydroxy quinolines. Syn. Commun 2009; 39(9): 5193-5196.
14. Rayees M. A, Girija V. S, and Nasreen B: Antibacterial and antioxidant activity of some novel chalcones derivatives. Journal of Pharmacy Research 2011; 4(7):2347.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