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

Hiba H. Mahgoub 1, Amna Bentwahab E. M. Hussein 2 and A. E. M. Saeed 1
Department of Chemistry 1, College of Science, Sudan University of Science and Technology, Khartoum, Sudan
Department of Chemistry 2, College of Science and Technology of Animal Production, Sudan University of Science and Technology, Khartoum, Sudan

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-diaryl-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, 1HNMR, 13CNMR, 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 tense, anti cancer 7, tyrosine kinase inhibiting agent, and anti nuclear inhibitors of immuno deficiency virus 8.

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 1HNMR and 13CNMR 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 VIIa-e):
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 1 hour. 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 249-250°C. 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).

1HNMR (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, CH₃). 13CNMR (DMSO, ppm): 26.49 (CH₃), 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).

VIIa: 2, 3-Diphenyl-6-(5-methyl-3-sulphamido-isoxazole)-quinoline-4-carboxylic acid: Yield 37%, mp 266-267°C. 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 (SO₂).

1HNMR (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, CH₃), 11.36 (1H, s, OH). MS (m/z): 429, 281, 147.

II: 2 – Furyl – 3 – phenyl – 6 - acetyl quinoline-4-carboxylic acids: Yield 45%, mp 227-228°C. 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 (N=), 3311.55, 3280.00 (N-H), 1681.81 (C=O), 1222.79 (C=S).

1HNMR (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, CH₃). MS (m/z): 292, 246, 77.

IIIa: 2, 3-Diphenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield 96%, mp 244-245°C. 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). 1HNMR (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.

VIIb: 2, 3-Diphenyl-6-(5-methyl-3-sulphamido-isoxazole)-quinoline-4-carboxylic acid: Yield 81.5%, mp 215-216°C. 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). 1HNMR
(DMSO, ppm): 7.77-7.93 (2H, 2H, 1H, m, Quinoline ring, H-Ar, Furl ring), 8.02 (1H, s, Quinoline ring), 7.09-7.52 (8H, 2H, 1H, m, H-Ar, HC=CH, Furl ring), 6.68 (1H, t, Furl ring). MS (m/z): 301, 208, 77.

IIIc: 2, 3-Diphenyl-6-(3-[2-phenyl ethylene]-prop -2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield 93%, mp 204-205°C. IR (KBr, cm⁻¹): 1500.00, 1508.23 (C=C), 1598.88 (C=O), 1369.37, 1652.88, 1668.31 (C=O), 1255.57 (C-O). ¹HNMR (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.

IIId: 2, 3 – Diphenyl – 6 - (3-[3-N, N - dimethylaminophenyl] – prop – 2 – en – 1 – one -1-yl)-quinoline-4-carboxylic acid: Yield 88%, mp 198-199°C. IR (KBr, cm⁻¹): 1520.00, 1550.00 (C=C), 1596.95 (C=O), 1371.29 (C=N), 1647.10, 1670.24 (C=O), 1215.07 (C-O). ¹HNMR (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, CH₃). MS (m/z): 223, 120, 103.

IVa: 2 - Furfyl-3-phenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield 95.2%, mp 268-269°C. IR (KBr, cm⁻¹): 1496.66, 1512.09 (C=C), 1596.95 (C=O), 1365.51 (C-N), 1650.00, 1670.24 (C=O), 1218.93 (C-O). ¹HNMR (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, Furl ring, HC=CH), 6.20 (1H, t, Furl ring).

IVb: 2 - Furfyl-3-phenyl – 6 - (3-furfyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield 93%, mp 237-238°C. IR (KBr, cm⁻¹): 1500.00, 1550.00 (C=C), 1600.81 (C=O), 1367.44 (C-N), 1660.60, 1675.00 (C=O), 1230.50 (C-O). ¹HNMR (DMSO, ppm): 7.50-7.88 (3H, 5H, 4H, 2H, m, Quinoline ring, H-Ar, Furl ring, HC=CH), 6.49-6.68 (2H, m, Furl ring). ¹³CNMR (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, Furl ring), 186.95 (C, C=O), 188.00 (C, Carboxylic acid).

IVc: 2 – Furfyl - 3 – phenyl – 6 - (3-[2-phenylethylene] – prop – 2 – en – 1 – one -1-yl)-quinoline-4-carboxylic acid: Yield 92.3%, mp 225-226°C. IR (KBr, cm⁻¹): 1450.00, 1515.94 (C=C), 1598.88 (C=O), 1363.58 (C-N), 1652.88, 1683.74 (C=O), 1288.43 (C-O). ¹HNMR (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, Furl ring, HC=CH, =C-H), 6.20 (1H, d, H=C=). ¹³CNMR (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, Furl ring), 187.00 (C, C=O).

IVd: 2 – Furfyl – 3 – phenyl - 6-(3-[3-N, N-dimethyl amino phenyl]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid: Yield 87%, mp 204-205°C. IR (KBr, cm⁻¹): 1525.59, 1577.66 (C=C), 1596.95 (C=O), 1363.58 (C-N), 1652.88, 1674.10 (C=O), 1230.50 (C-O). ¹HNMR (DMSO, ppm): 9.74 (1H, s, Quinoline ring), 7.53-7.98 (2H, 7H, 3H, 2H, m, Quinoline ring, H-Ar, Furl ring, HC=CH), 6.70 (1H, d, H-Ar, 6.16 (1H, s, H-Ar), 3.09 (6H, s, CH₃). ¹³CNMR (DMSO, ppm): 40.09 (2CH, CH₃), 109.65, 137.00, 141.91, and 143.00 (3CH, C, Furl ring), 111.71, 115.90, 138.00, and 151.87 (3CH, C, H-Ar), 122.00 (CH, Ethylene group), 121.00-122.12 (2CH, 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).

IVe: 2 - Furfyl-3-phenyl- 6-(3-[2-hydroxyphenyl]prop -2-en- 1 - one-1-yl) - quinoline - 4 - carboxylic acid: Yield 84%, mp 184-185°C. IR (KBr, cm⁻¹): 1458.08, 1512.09 (C=C), 1598.88 (C=O), 1363.58 (C-N), 1660.00, 1679.88 (C=O), 1274.86 (C-O). ¹HNMR (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, Furl ring, H-C=), 6.20 (1H, d, H-Ar). ¹³CNMR (DMSO,
ppm): 110.26, 110.76, 141.00, and 142.67 (3CH, C, Furfuryl 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 (Vₐ₋₄) and (VIₐ₋₄): 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 6 hour. The mixture was concentrated by distilling out the solvent and poured into ice water. The precipitate was filtered, washed and recrystallized from ethanol.

Vₐ: 2, 3-Dihenyl – 6 - (5-phenyl-oxazole-3-yl)-quinoline-4-carboxylic acid: Yield 92.2%, mp 189-190°C. 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). ¹HNMR (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).

VIₐ: 2 - 3-Diphenyl-6-(5-phenyl-oxazole-3-yl)-quinoline-4-carboxylic acid: Yield 84%, mp 174-175°C. 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). ¹HNMR (DMSO, ppm): 7.36-7.80 (2H, 10H, 2H, m, Quinoline ring, H-Ar, Furfuryl ring), 8.05 (1H, s, Quinoline ring), 7.00-6.30 (1H, 1H, m, Furfuryl ring, Isoxazole ring).

VIₐ: 2 - 3-Dihenyl-6-(5-phenyloxazole-3-yl)-quinoline-4-carboxylic acid: Yield 83.3%, mp 174-175°C. 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). ¹HNMR (DMSO, ppm): 7.36-7.80 (2H, 10H, 2H, m, Quinoline ring, H-Ar, Furfuryl ring), 8.05 (1H, s, Quinoline ring), 6.19-6.72 (1H, 1H, m, Isoxazole ring, Furfuryl ring). ¹³CNMR (DMSO, ppm): 110.37, 111.40, 140.54, and 143.21 (6CH, 2C, Furfuryl 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).

Vₐ: 2, 3 - Diphenyl – 6 - (5-[2-phenylethylene] -oxazole-3-yl)-quinoline-4-carboxylic acid: Yield 83.3%, mp 244-245°C. 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=Colefin). ¹HNMR (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). ¹³CNMR (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).

Vₐ: 2, 3-Diphenyl-6-(5-[3-N, N-dimethylamino phenyl] – oxazole – 3 - yl) – quinoline – 4 - carboxylic acid: Yield 77.8%, mp 236-237°C. 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). ¹HNMR (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, CH₃). ¹³CNMR (DMSO, ppm): 40.10 (2CH, CH₃), 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).
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).

**VIa:**  2 – Furfyl – 3 – phenyl – 6 - (5-[3-N, N-dimethyl amino phenyl]-oxazole-3-yl)-quinoline-4-carboxylic acid: *Yield 75%, mp 231-232ºC*. 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).

**VIb:**  2 - Furfyl-3-phenyl-6- (5- [2-hydroxyphenyl] -oxazole-3-yl)-quinoline-4-carboxylic acid: *Yield 80.6%, mp 177–178ºC*. 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 - 177ºC*. 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 ethylacetocacetate 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 - sulphanilamide: *Yield 79.8%, mp dec at 298ºC*. 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 ethylacetocacetate 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 - sulphanilamide: *Yield 86.1%, mp 168-169ºC*. 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), 2.14 (3H, s, CH$_3$), 2.04 (3H, s, CH$_3$). MS (m/z): 156, 92, 65.
(2H, s, \( \text{NH}_2 \)). 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 subtilis*, *Staphylococcus 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>
<thead>
<tr>
<th>Comp</th>
<th>P. vulgaris (mm)</th>
<th>E. coli (mm)</th>
<th>B. subtilis (mm)</th>
<th>S. aureus (mm)</th>
<th>Aspergillus niger (mm)</th>
<th>Candida albicans (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>9.00</td>
<td>14.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.00</td>
</tr>
<tr>
<td>IIIa</td>
<td>-</td>
<td>-</td>
<td>12.00</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>-</td>
<td>-</td>
<td>11.00</td>
<td>-</td>
<td>-</td>
<td>5.00</td>
</tr>
<tr>
<td>IIIc</td>
<td>-</td>
<td>-</td>
<td>9.00</td>
<td>-</td>
<td>-</td>
<td>9.00</td>
</tr>
<tr>
<td>IIId</td>
<td>-</td>
<td>-</td>
<td>10.00</td>
<td>-</td>
<td>-</td>
<td>6.00</td>
</tr>
<tr>
<td>IVa</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.00</td>
</tr>
<tr>
<td>IVb</td>
<td>10.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.00</td>
</tr>
<tr>
<td>IVc</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVd</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVe</td>
<td>10.00</td>
<td>-</td>
<td>15.00</td>
<td>12.00</td>
<td>-</td>
<td>11.00</td>
</tr>
<tr>
<td>Va</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.00</td>
<td>-</td>
<td>7.00</td>
</tr>
<tr>
<td>Vb</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11.00</td>
</tr>
<tr>
<td>Vc</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.00</td>
</tr>
<tr>
<td>Vd</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.00</td>
</tr>
<tr>
<td>VIa</td>
<td>8.00</td>
<td>-</td>
<td>7.00</td>
<td>13.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VIb</td>
<td>9.00</td>
<td>-</td>
<td>7.00</td>
<td>-</td>
<td>-</td>
<td>9.00</td>
</tr>
</tbody>
</table>
RESULT AND DISCUSSIONS: The structural core of quinoline in this study has been synthesized by Doeber reaction which is a condensation reaction between primary aryl amines, aldehydes, and phenyl pyruvic acid to form 3-phenylquinoline-4-carboxylic acids. Combes synthesis is a formation of dialky 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 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. The synthesized 2, 3-diaryl-quinoline-4-carboxylic acid condensed with various aromatic aldehydes by Claisen-Schmidt condensation to form corresponding chalcones, 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, 1HNMR, 13CNMR 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, VIe, against E.coli are IX, II, VIIa, against B.subtilis are IVc, VIIa, VIIc, against S.aureus are VIIa, IIIa, IVc, and against Candida albicans are IVc, Vb, Vd.

REFERENCES:


