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Synthesis and biological evaluation of friedlander annulation approach for the diversity oriented of functionalized quinolines

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ABSTRACT

Synthesis, spectral analysis and bioactivity of new inexpensive and diversity oriented method for the synthesis of various polysubstituted quinolines through the condensation of o-amino aryl carbonyls with ketones containing an active methylene group. We have synthesized twenty Quinoline derivatives were synthesized in moderate to good yields. The structures of all the newly synthesized molecules were assigned by elemental analysis and spectral data. The synthesized compounds were screened for their antibacterial activities strains using Cup plate method.

Keywords: Click chemistry, functionalized quinolines, Suzuki coupling reaction, triethyl amine.

INTRODUCTION

Quinoline is a common structural unit found in many natural products with remarkable pharmacological properties. Members of this extraction have broad applications in medicinal chemistry. The classical methods for the synthesis of quinolines, such as the Skraup[1], Doebner-von Miller[2], Combes[3], Pfitzinger[4] Quinoline synthesis, require harsh reaction conditions and the yields are unsatisfactory in most cases. The Friedlander annulations is the simplest, most straightforward synthetic method for the synthesis of quinoline derivatives, to a great extent for the highly substituted 3-quinolinecarboxylic esters [5]. This method usually involves acid- or base-catalyzed or thermal (up to 250^{o}C) condensation between a 2-aminoaryl ketone or aldehyde and a second carbonyl compound possessing a reactive α-methylene group, followed by cyclodehydration.

Friedlander reported Quinoline synthesis in 1882 by the condensation of *o*-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide. Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and phosphoric acids are extensively used for this transformation[6]. However, many of these classical methods require high temperatures, lenghty reaction times and extreme conditions and the yields reported are unsatisfactory due to the formation of different side reactions. Therefore, produced catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness [7]. However in recent times iodine[8] , Lewis acids such as $ZnCl_2$ and $AuCl_3$-$3H_2O$[9], a combination of acidic catalysts [e.g., $NaAuCl_4$, $Bi(OTf)_3$, $Nd(NO_3)_3$ - $6H_2O$][10] , and microwave reactions[11]. Even some of these methods also suffer from harsh reaction conditions, low yields, high temperature, tedious work-up and the use of stoichiometric and relatively costly reagents[12]. Since Quinoline

derivatives are increasingly useful and important in drugs and pharmaceuticals, the development of easily understanding, suited and considerable yielding protocols are useful. As a part of our continuing efforts towards the development of useful synthetic activities[13], we planned to develop a new method for the synthesis of quinolines and its novel derivatives via Friedlander annulations approach catalyzed by copper sulphate. We observed the high efficiency of $CuSO_4.5H_2O$ (20 mol %) in sequential condensation / annulation reactions of *o*-amino aryl carbonyls and ketones containing an active methylene group for the synthesis of substituted quinolines.

MATERIALS AND METHODS

General Conditions: All the used reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR ($CDCl_3$,300 MHz) and ^{13}C NMR ($CDCl_3$,75 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

I. General procedure for the synthesis of 6-chloro-N-(4-methoxyphenyl)-4-phenyl-2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl) quinoline-3-carboxamide (3a-e)

To a solution of quinoline-3-carboxylic acid **1** (0.20 g, 0.454 mmol) in dry CH_2C1_2 (10 mL) was added EDCI (0.084 g, 0.545 mmol, dissolved in 3 mL) at 0^{o}C under nitrogen atmosphere and stirred for 20 min. To this well stirred solution *p*-methoxy aniline (0.055 g, 0.454 mmol, dissolved in 3 mL CH_2Cl_2) was added slowly over 5 min at the same temperature and reaction mixture was allowed to stir for 6-8 h (monitored by TLC). After completion of reaction, reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (2x30 mL), dried over sodium sulphate and solvent was evaporated under reduced pressure resulted crude product, which was purified by silica gel column chromatography to get triazole coupled quinoline-3-carboxamide **3a** (0.19 g, 78 %). m. p. 220-223^{o}C; IR (KBr): *V*max 3258, 3133, 3059, 3009, 2954, 2925, 2853, 1649, 1603, 1537, 1509, 1482, 1464, 1441, 1414, 1374, 1334, 1300, 1239, 1177, 1149, 1127, 1110, 1080, 1032, 960 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H), 5.97 (s, 2H), 6.66 (d, 2H, *J* = 8.87 Hz), 6.98 (d, 2H, *J* = 8.87 Hz), 7.28-7.48 (m, 4H), 7.47-7.57 (m, 3H), 7.61 (d, 1H, *J* = 2.07 Hz), 7.64-7.75 (m, 4H), 8.01 (d, 1H, *J* = 9.06 Hz), 8.05 (s, 1H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 54.44, 55.33, 113.92, 121.94, 122.80, 125.35, 125.65, 126.97, 128.09, 128.68, 128.92, 129.76, 129.23, 129.47, 130.22, 131.27, 131.53, 133.85, 134.27, 145.87, 146.01, 147.49, 151.02, 157.00, 164.97; ESI-MS: *m/z* 546 (M^++H); HRMS calculated for $C_{32}H_{25}N_5O_2Cl$ (M^++H) calculated 546.1691 found 546.1694.

This procedure was followed for the preparation of all triazole coupled quinoline-3-carboxamide 3**(b-e).**

6-chloro-4-phenyl-2-((4-phenyl-1*H*-1,2,3-triazol-l-yl)methyl)-N-(3-(trifluoromethyl)phenyl) quinoline-3-carboxamide (3b)

m.p. 231-233°C; IR (KBr): *V*max 3747, 3523, 3458, 3395, 3256, 3141, 3062, 3032, 2924, 2853, 1729, 1667, 1604, 1560, 1484, 1444, 1394, 1374, 1331, 1284, 1246, 1205, 1166, 1126, 1070, 1000, 961, 920 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.96 (s, 2H), 7.17-7.39 (m, 6H), 7.39-7.57 (m, 6H), 7.58-7.66 (m, 3H), 7.70 (dd, 1H, *J* = 9.06 Hz, 2.26 Hz), 7.98-8.04 (m, 2H), 8.13 (bs, 1H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 54.69, 113.97, 120.12, 120.39(7-C-Cl), 125.36, 125.57(-CF3), 125.69, 126.64, 126.85, 128.02, 128.56, 128.70, 129.02, 129.18, 129.28, 130.15, 130.35, 130.77, 131.48, 132.45, 133.42, 134.54, 145.74, 146.51, 147.93, 148.16, 150.05, 165.84; ESI-MS: *m/z* 606 (M^++Na), 584 (M^++H); HRMS calculated for $C_{32}H_{22}N_5OClF_3$ (M^++H) calculated 584.1459 found 584.1461.

6-chloro-4-phenyl-2-((4-phenyl-1*H*-l,2,3-triazol-1-yl)methyl)-*N*-(4-(trifluoromethoxy) phenyl) quinoline-3-carboxamide (3c)

m. p. 212-214 °C; IR (KBr): *V*max 3306, 3135, 3063, 3018, 2925, 2854, 1727, 1657, 1609, 1534, 1509, 1482, 1443, 1412, 1394, 1329, 1249, 1214, 1160, 1110, 1080, 1047, 1018, 957, 920 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.94 (s, 2H), 6.97 (d, 2H, *J* = 8.49 Hz), 7.18 (d, 2H, *J* = 8.49 Hz), 7.29-7.46 (m, 4H), 7.46-7.56 (m, 3H), 7.57-7.73 (m, 4H), 7.98 (d, 1H, *J*= 8.87 Hz), 8.02 (s, 1H), 8.27 (s, 1H); ^{13}CNMR (75 MHz, $CDC1_3$): δ 54.45, 121.43, 122.02, 121.91(-OCF_3), 125.38, 125.56, 126.95, 128.29, 128.55, 128.75, 128.91, 129.22, 129.32, 129.47, 129.92, 131.24, 131.66, 133.94, 134.11, 135.31, 145.89, 146.25, 147.50, 150.71, 165.26; ESI-MS: *m/z* 622 (M^++Na), 600 (M^++H); HRMS calculated for $C_{32}H_{22}N_5O_2C1F_3$ (M^++H) calculated 600.1408 found 600.1451.

6-chloro-*N*-(3-chloro-4-fluorophenyl)-4-phenyl-2-((4-phenyl-1*H*-l,2,3-triazol-1-yl)methyl)quinoline-3-carboxamide (3d)

m. p. 229-231 ^{o}C; IR (KBr): *V*max 3246, 3135, 3059, 3031, 2926, 2854, 1732, 1662, 1606, 1542, 1498, 1442, 1330, 1259, 1226, 1149, 1129, 1080, 1055, 1029, 961, 879, 834, 814 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.94 (s, 2H), 6.81-6.88 (m, 2H), 7.28-7.45 (m, 6H), 7.48-7.56 (m, 3H), 7.60-7.68 (m, 3H), 7.69-7.74 (m, 1H), 7.89 (s, 1H), 8.02 (s, 1H), 8.05 (d, 1H, *J* = 8.87 Hz); ^{13}CNMR (75 MHz, $CDCl_3$): δ 54.63, 116.28, 116.46, 120.24, 120.29, 120.90, 121.04(-Cl), 122.14, 122.73, 125.39, 125.53, 126.95, 128.31, 128.74, 128.93, 129.21, 129.31, 129.35, 129.80, 131.31, 131.71, 133.33, 133.99, 134.12, 145.92, 146.22, 147.47, 150.79, 154.13, 156.09(-F), 165.24; ESI-MS: *m/z* 568 (M^++H);HRMS calculated for $C_{31}H_{20}N_5OCl_2F$(M^++H) calculated 568.4325 found 568.4351.

6-chloro-*N*-(furan-2-ylmethyl)-4-phenyl-2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)quinoline-3-carboxamide (3e)

m. p. 213-214 ^{o}C; IR (KBr): *V*max 3269, 3138, 3060, 3014, 2924, 2853, 1726, 1648, 1607, 1563, 1482, 1465, 1442, 1375, 1327, 1215, 1149, 1077, 1049, 1010, 975, 919, 881, 834, 810, 750, 695, 665, 640, 599 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 4.24 (d, 2H, 5.28 Hz), *J* = 5.77-5.87 (m, 1H), 5.90 (s, 2H), 6.10-6.22 (m, 1H), 6.36-6.50 (m, 1H), 7.14 (s, 1H), 7.27-7.70 (m, 10H), 7.76 (d, 2H, *J* = 7.55 Hz), 7.94 (d, 1H, *J* = 9.06 Hz), 8.07 (s, 1H); ^{13}CNMR (75MHz, $CDCl_3$): δ 36.55, 54.09, 107.57, 110.16, 121.43, 121.70, 125.29, 125.60, 126.94, 128.13, 128.76, 128.97/129.11, 129.78, 130.28, 131.14, 131.40, 133.73, 133.88, 142.05, 145.74, 145.85, 147.37,'149.75, 150.95, 166.40; ESI-MS: *m/z* 542 (M^++Na), 520 (M^++H); HRMS calculated for $C_{30}H_{23}N_5O_2Cl$ (M^++H) calculated 520.1534 found 520.1543.

II. General procedure for the synthesis of ethyl 2-((4-benzoylpiperazin-1-yl) methyl)-6-chloro-4-phenylquinoline-3-carboxylate (6a-e).

To a mixture of Boc-deprotected product **4** (5.62 g, 25.5 mmol) and Et_3N (2.83 g, 28.0 mmol) in dry CH_2Cl_2 (20 mL) at 0^{o}C under nitrogen atm. was added catalytic amount of DMAP and stirred for 30 min. To this reaction mixture benzoyl chloride (taken in 5 mL CH_2Cl_2) was added dropwise over 10 min. The resulting reaction mixture was further stirred for 6 h at room temperature, diluted with CH_2Cl_2 (50 mL) and water. Organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, by eluting with 30% ethyl acetate/petroleum ether to afford 7.48 g of **6a** (98%) as a colorless solid, m.p. 239-241 ^{o}C; IR (KBr): *V*max 2976, 2928, 2865, 2809, 2312, 1723, 1691, 1637, 1565, 1481, 1457, 1423, 1365, 1340, 1315, 1285, 1259, 1241, 1222, 1163, 1103, 1082, 1071, 1001, 956, 645, 612, cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.98 Hz, CH_3), 2.35-2.68 (m, 4H, 2-CH_2), 3.22-3.42 (m, 2H, CH_2), 3.60-3.77 (m, 2H, CH_2), 3.91-4.06 (m, 4H, -$COCH_2$ + Ar-CH_2), 7.29-7.43 (m, 7H, ArH), 7.45-7.54 (m, 3H, ArH), 7.57 (d, 1H, ArH), 7.67 (dd, 1H, *J* = 8.87 Hz, *J* = 2.26 Hz, ArH), 8.04 (d, 1H, *J* = 8.87 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 13.46, 60.86, 63.35, 79.94, 125.26, 126.92, 127.42, 128.34, 128.64, 129.18, 129.60, 130.75, 131.08, 132.91, 134.95, 135.56, 145.36, 146.30, 154.59, 156.13, 167.82, 170.23; ESI-MS: *m/z* 536 (M^++Na), 514 (M^++H); HRMS calculated for $C_{30}H_{29}N_3O_3Cl$ (M^++H) calculated 514.1892 found 514.1873.

This procedure was followed for the preparation of all piperazinamides of quinolines **6(b-e).**

Ethyl 2-((4-(benzo[d][l,3]dioxole-5-carbonyl)piperazin-1-yl)methyl)-6-chloro-4-phenylquinoline-3-carboxylate (6b)

m.p. 219-221 ^{o}C; IR (KBr): *V*max 3061, 2982, 2922, 2811, 1721, 1632, 1565, 1482, 1458, 1441, 1400, 1342, 1315, 1281, 1247, 1221, 1169, 1141, 1103, 1081, 1070, 1037, 1000, 956, 931, 875, 833, 751, 701, 665, 646, 612, 570, cm^{-1} ; ^{1}HNMR (500 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 7.17 Hz, CH_3), 2.42-2.62 (m, 4H, 2-CH_2), 3.22 -3.72 (m, 4H, 2-CH_2), 3.93-4.04 (m, 4H, -$COCH_2$ + $ArCH_2$), 5.98 (s, 2H, OCH_2O), 7.79 (d, 1H, *J* = 7.93 Hz, ArH), 6.88 (d, 1H, *J* = 1.37 Hz, ArH), 6.90 (dd, 1H, *J* = 7.93 Hz, *J* = 1.37 Hz, ArH), 7.31-7.36 (m, 2H, ArH), 7.49-7.53 (m, 3H, ArH), 7.57 (d, 1H, *J* = 2.13 Hz, ArH), 7.67 (dd, 1H, *J* = 9.00 Hz, *J* = 2.88 Hz, ArH), 8.04 (d, 1H, *J* = 9.00 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 63.43, 60.92, 52.74, 52.70, 13.53, 101.36, 108.02, 108.12, 121.53, 125.32, 127.02, 127.49, 128.36, 128.67, 129.25, 130.84, 131.15, 132.97, 135.04, 145.45, 146.36, 147.54, 148.77, 156.18, 167.89, 169.78; ESI-MS: *m/z* 558 (M^++H); HRMS calculated for $C_{31}H_{29}N_3O_5Cl$ (M^++H) calculated 558.1790 found 558.1772.

Ethyl-6-chloro-4-phenyl-2-((4-(4-(trifluoromethyl) benzoyl) piperazin-1-yl) methyl) quinoline -3-carboxylate (6c)

m.p. 230-232 ^{o}C; IR (KBr): *V*max 3063, 2984, 2919, 2812, 1722, 1637, 1566, 1481, 1463, 1444, 1426, 1400, 1330, 1255, 1220, 1165, 1126, 1070, 1025, 999, 956, 917, 883, 834664, 647, 610 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.17 Hz, CH_3), 2.39-2.69 (m, 4H, 2 -CH_2), 3.22 -3.36 (m, 2H, CH_2), 3.64 -3.78 (m, 2H, CH_2), 3.94-4.05 (m, 4H, -$COCH_2$ + $ArCH_2$), 7.30-7.38 (m, 4H, ArH), 7.47-7.60 (m, 6H, ArH), 7.62-7.70 (m, 3H, ArH), 8.04 (d, 1H, *J* = 9.00 Hz, ArH); ^{13}CNMR (125 MHz, $CDCl_3$): δ 13.54, 42.18, 47.63, 52.41, 52.79, 60.94, 63.34, 124.02(-CF_3), 125.31, 126.45, 127.00, 127.43, 128.37, 128.70, 129.05, 129.22, 130.31, 130.83, 131.18, 133.01, 134.99, 136.40, 145.44, 146.43, 155.95, 167.87, 168.63; ESI-MS: *m/z* 582 (M^++H); HRMS calculated for $C_{31}H_{28}N_3O_3ClF_3$ (M^++H) calculated 582.1765 found 582.1750.

Ethyl-6-chloro-2-((4-(6-chlorobenzoyl)piperazin-l-yl)methyl)-4-phenylquinoline-3-carboxylate (6d)

m.p. 239-241^{o}C; ^{1}HNMR (300 MHz, $CDC1_3$): δ 0.87 (t, 3H, *J* = 7.17 Hz, CH_3), 2.41-2,69 (m, 4H, 2-CH_2), 3.25 -3.42 (m, 2H, CH_2), 3.61 -3.78 (m, 2H, CH_2), 3.93-4.01 (q, 2H, *J* = 7.17 Hz, CH_2), 4.02 (s, 2H, -$COCH_2$), 7.31-7.36 (m, 2H, ArH), 7.36-7.41 (m, 1H, ArH), 7.49-7.54 (m, 3H, ArH), 7.57 (d, 1H, *J* = 2.13 Hz, ArH), 7.68 (dd, 1H, *J* = 8.85 Hz, *J* = 2.28 Hz, ArH), 7.71 (dd, 1H, *J* = 8.08 Hz, *J* = 2.28 Hz, ArH), 8.05 (d, 1H, *J* = 9.00 Hz, ArH), 8,42 (d, 1H, *J* = 1.98 Hz, ArH); ^{13}CNMR (75 MHz, $CDC1_3$): δ 13.56, 42.24, 17.68, 52.37, 52.68, 60.94, 63.21, 124.22, 124.28, 125.32, 128.38, 128.73, 129.19, 130.15, 130.82, 131.25, 133.86, 134.95(-CCl), 137.86, 145.43, 146.50, 148.00, 148.10, 152.61, 155.75, 167.88; ESI-MS: *m/z* 549 (M^++H). HRMS calculated for$C_{30}H_{27}Cl_2N_3O_3$(M^++H) calculated 549.1756 found 549.1750.

Ethyl 6-chloro-2-((4-(4-fluorobenzoyl) piperazin-l-yl) methyl)-4-phenylquinoline-3-carbox- ylate (6e)

m.p. 216-218°C; IR (KBr): *V*max 2984, 2920, 2811, 1721, 1629, 1605, 1564, 1510, 1481, 1458, 1431, 1400, 1340, 1315, 1279, 1261, 1219, 1157, 1127, 1069, 999, 955, 882, 836, 747, 701, 664, 647, 612, 577 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.79 Hz, CH_3), 2.32-2.72 (m, 4H, 2- CH_2), 3.20-3.82 (m, 4H, 2-CH_2), 3.91-4.11 (m, 4H, -$COCH_2$ $ArCH_2$), 7.07 (t, 2H, *J* = 8.30 Hz, ArH), 7.30-7.46 (m, 4H, ArH), 7.47-7.63 (m, 4H, ArH), 7.68 (dd, 1H, *J* = 9.06 Hz, *J* = 2.26 Hz, ArH), 8.05 (d, 1H, *J* = 9.06 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 13.54, 52.59, 52.69, 60.93, 63.38, 115.41, 115.59, 125.32, 127.00, 127.45, 128.36, 128.69, 129.23, 129.28, 129.34, 130.82, 131.18, 131.59, 133.00, 135.00, 145.44, 146.40, 156.03, 162.35(-CF), 164.32, 167.87, 169.36; ESI-MS: *m/z* 532 (M^++H); HRMS (ESI) calculated for $C_{30}H_{28}ClFN_3O_3$ (M^++H) calculated 532,1797 found 532.1776.

III. General procedure for the synthesis of (E)-3-(4-bromophenyl)-l-(6-chloro-2-methyl-4-phenylquinolin-3-yl) prop-2-en-l-one (11a-e)

To a well stirred solution of acetylquinoline(**9)** (5 g, 16.94 mmol) and *p*-bromo-benzaldehyde (3.41 g, 18.64 mmol) in ethanol (50 mL) and water (10 mL) was added slowly 40% KOH solution over 2 min at room temperature, stirring was continued for 12 h. After completion of reaction, water (40 mL) was added to the reaction mixture and extracted with ethyl acetate (3x60 mL) and the collected organic layers were dried over Na_2SO_4 and evaporated under reduced pressure, to obtain crude residue which was purified by column chromatography using EtOAc/hexane (2:8) as an eluent to give yellow colored solid **11a** (6.87 g, 88 %). m.p. 214-216 ^{o}C; IR (KBr): *V*max 3609, 3542, 3395, 3059, 2957, 2922, 2852, 2310, 1906, 1709, 1671, 1646, 1622, 1601, 1582, 1562, 1482, 1441, 1385, 1362,1312, 1278, 1220, 1197, 1179, 1157, 1125, 1073, 1046, cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H, $ArCH_3$), 6.47 (d, 1H, *J* = 16.24 Hz, =CH), 6.97 (d, 1H, *J* = 16.24 Hz, =CH), 7.11 (d, 2H, *J* = 8.30 Hz, ArH), 7.16-7.24 (m, 2H, ArH), 7.26-7.41 (m, 6H, ArH), 7.49 (d, 1H, *J* = 2.26 Hz, ArH), 7.60 (dd, 1H, *J* = 8.87 Hz, 2.26 Hz, ArH), 7.97 (d, 1H, *J* = 8.87 Hz, ArH); ^{13}CNMR (75 MHz, $CDC1_3$): δ 23.91, 125.04, 125.41, 126.01, 127.87, 128.63, 128.97, 129.62, 129.87, 130.51, 131.12, 132.21, 132.53, 132.79, 133.16, 134.45, 144.65, 145.08, 146.12, 155.27, 196.84; ESI-MS: *m/z* 462 (M^++H).

This procedure was followed for the preparation of all chalcones of quinolines 11**b-e.**

(E)-3-(benzo[d][l,3]dioxol-5-yl)-l-(6-chloro-2-methyl-4-phenylquinolin-3-yl)prop-2-en-1-one (11b)

m.p. 199-201 ^{o}C; IR (KBr): *V*max 3062, 3012, 2900, 2782, 1664, 1640, 1620, 1598, 1580, 1501, 1485, 1446, 1389, 1359, 1340, 1309, 1255, 1214, 1158, 1125, 1102, 1079, 1036, 976, 929, 880, 862, 834, 807, 752, 704 cm^{-1}; ^{1}HNMR (300 MHz, $CDC1_3$): δ 2.69 (s, 3H, $ArCH_3$), 5.99 (s, 2H, -OCH_2O), 7.42 (d, 1H, *J* = 16.17 Hz, =CH), 6.75 (d, 1H, *J* = 8.08 Hz, ArH), 6.78-6.85 (m, 2H, ArH), 7.00 (d, 1H, *J* = 16.17 Hz, =CH), 7.27-7.31 (m, 2H, ArH), 7.38-7.45 (m, 3H, ArH), 7.58 (d, 1H, *J* = 2.28 Hz, ArH), 7.68 (dd, 1H, *J* = 9.00 Hz, 2.28 Hz, ArH), 8.06 (d, 1H, *J* = 9.00 Hz, ArH); ^{13}CNMR (125 MHz, $CDC1_3$): δ 23.87, 101.69, 106.44, 108.57, 125.03, 125.36, 125.63, 126.09, 128.27, 128.52,

128.81, 129.79, 130.43, 130.93, 132.37, 133.42, 134.48, 144.47, 145.98, 146.81, 148.38, 150.34, 155.34, 196.92; ESI-MS: *m/s* 428 (M^++H).

(E)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(4-(trifluoromethyl) phenyl) prop-2-en-1-one (11c)
m.p. 181-183^{o}C; IR(KBr): *V*max 3063, 3019, 2926, 2853, 1650, 1608, 1565, 1480, 1443, 1414, 1387, 1323, 1280, 1218, 1201, 1166, 1126, 1067, 1046, 1015, 981, 919, 860, 832, 756, 706 cm^{-1}; ^{1}H-NMR (300 MHz, $CDC1_3$): δ 2.70 (s, 3H, $ArCH_3$), 6.60 (d, 1H, *J* = 16.24 Hz, = CH), 7.12 (d, 1H, *J* = 16.24 Hz, =CH), 7.20-7.83 (m, 10H, ArH), 7.70 (dd, 1H, *J* = 8.87 Hz, 1.7 Hz, ArH), 8.08 (d, 1H, *J* = 8.87 Hz, ArH); ^{13}CNMR (125 MHz, $CDC1_3$): δ 18.87, 101.69, 106.44, 118.57, 125.03, 125.36, 125.63, 126.09, 128.27, 128.52, 128.81, 129.72, 130.43, 130.93, 131.37, 133.42, 134.48, 144.47, 145.28, 146.81, 148.38, 150.34, 157.34, 187.0,: ESI-MS: *m/z* 452 (M^++H).

(E)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(naphthalen-l-yI)prop-2-en-l-one (11d) m.p. 186-188 ^{o}C; IR (KBr): *V*max 3058, 3014, 2956, 2924, 2853, 1698, 1644, 1598, 1566, 1510, 1479, 1442, 1388, 1346, 1310, 1277, 1240, 1217, 1202, 1157, 1125, 1079, 1049, 1029, 1003, 973, 704, 665, 624, 589 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.77 (s, 3H, ArH_3), 6.86 (d, 1H, *J* = 16.05 Hz, = CH), 7.33-7.57 (m, 9H, ArH), 7.64 (d, 1H, *J* = 2.07 Hz, ArH), 7.70 (dd, 1H, *J* = 8.87 Hz, 2.26 Hz, ArH), 7.74-7.92 (m, 3H, ArH), 7.98 (d, 1H, *J* = 16.05 Hz, = CH), 8.10 (d, 1H, *J* = 8.87 Hz, ArH); ^{13}CNMR (75 MHz, $CDC1_3$): δ 23.96, 122.87, 124.85, 125.08, 125.32, 125.51, 126.32, 127.07, 128.67, 128.81, 128.97, 129.98, 130.06, 130.50, 131.11, 131.25, 132.51, 133.55, 134.47, 143.37, 144.66, 146.09, 155.36, 1196.96; ESI-MS: *m/z* 434 (M^++H).

(*E*)-l-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(4-(dimethylainino) phenyl) prop-2-en-l-one (11e)
m.p. 207-208 ^{o}C; IR (KBr): *V*max 2922, 2853, 1631, 1586, 1523, 1480, 1436, 1367, 1334, 1311, 1269, 1225, 1180, 1165, 1123, 1079, 1046, 1030, 1016, 977, 945, 879, 833, 814, 756, 703, 665, 599 cm^{-1}; ^{1}HNMR (300 MHz, $CDC1_3$): δ 2.70 (s, 3H, $ArCH_3$), 3.02 (s, 6H, 2-CH_3), 6.45 (d, 1H, *J* = 16.13 Hz, =CH), 6.59 (d, 2H, *J* = 8.80 Hz, ArH), 7.00 (d, 1H, *J* = 16.13 Hz, =CH), 7.19-7.33 (m, 4H, ArH), 7.35-7.44 (m, 3H, ArH), 7.56 (d, 1H, *J* = 2.20 Hz, ArH), 7.66 (dd, 1H, *J* = 8.80 Hz, 2.20 Hz, ArH), 8.06 (d, 1H, *J* = 8.80 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 23.32, 39.53, 111.52, 120.94, 121.65, 124.25, 125.96, 128.20, 128.51, 129.50, 130.19, 130.68, 130.81, 130.94, 133.70, 134.35, 143.29, 145.24, 148.84, 152.15, 155.08, 195.62; ESI-MS: *m/z* 427 (M^++H).

IV. General procedure for the synthesis of (E)-3-([1,1'-biphenyI]-4-yl)-l-(6-chloro-2-methyl-4-phenylquinolin-3-yI)prop-2-en-1-one (13a-e)
To a stirred solution of compound **11a** (0.2 g, 0.4 mmol) and phenyl boronic acid (0.052g, 0.4 mmol) in toluene: EtOH (10 ml) were added $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol), K_2CO_3 (0.11 g, 0.8 mmol) and reaction mixture was heated at 90 ^{o}C for 10 h. Reaction mixture was worked up with water and extracted with ethyl acetate (3 x 20 ml). Combined ethyl acetate layer was dried over sodium sulphate, concentrated under reduced pressure to give solid product which was purified by silica gel chromatography to obtain compound **13a** (0.163 g, 89%). m.p. 222-224 ^{o}C; IR (KBr): *V*max 3059, 3029, 2924, 2852, 1699, 1643, 1620, 1596, 1557, 1516, 1482, 1445, 1409, 1388, 1338, 1312, 1278, 1219, 1185, 1158, 1124, 1079, 1046, 1005, 980, 946, 832, 761, 701, 667, 645 cm^{-1}; ^{1}H-NMR (300 MHz, $CDC1_3$): δ 2.71 (s, 3H, $ArCH_3$), 6.63 (d, 1H, *J* = 16.61 Hz, = CH), 7.14 (d, 1H, *J* = 16.61 Hz, = CH), 7.28-7.50 (m, 10H, ArH), 7.52-7.63 (m, 5H, ArH), 7.69 (dd, 1H, *J* = 9.06 Hz, 2.26 Hz, ArH), 8.07 (d, 1H, *J* = 9.06 Hz, ArH); ^{13}C-NMR (125 MHz, $CDC1_3$): δ 23.91, 125.06, 126.11, 126.97, 127.34, 127.54, 128.02, 128.58, 128.90, 129.86, 130.50, 131.00, 132.43, 132.80, 133.34, 134.48, 139.78, 143.82, 144.58, 146.08, 146.45, 155.32, 197.08; ESI-MS: *m/z* 460 (M^++H); HRMS calculated for $C_{31}H_{23}NOCl$ (M^++H) calculated 460.1462 found 460.1465.

(*E*)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(4'-chloro-[1,1-biphenyl]-4-yl)prop-2-en-1-one (13b)
m.p. 232-234 ^{o}C; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H, $ArCH_3$), 6.63 (d, 1H, *J* = 16.43 Hz, =CH), 7.13 (d, 1H, *J* = 16.43 Hz, =CH), 7.28-7.65 (m, 14H, ArH), 7.69 (dd, 1H, *J* = 9.25 Hz, 2.45 Hz, ArH), 8.07 (d, 1H, *J* = 9,25 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 23.93, 125.04, 126.06, 127.36, 127.52, 128.17, 128.22, 128.58, 128.88, 128.95, 129.07, 129.86, 130.51, 131.01, 132.43, 133.11, 133.27, 134.18, 134.46, 138.20, 142.44, 144.56, 146.10, 155.29, 197.04; ESI-MS: *m/z* 494 (M^++H); HRMS calculated for $C_{31}H_{22}NOC1_2$ (M^++H) calculated 494.1073 found 494.1068.

(*E*)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(3'-fluoro-[1,1'-biphenyl]-4-yl)prop-2-en-1-one (13c)
m.p. 212-214 ^{o}C; IR (KBr): *V*max 3062, 3030, 2958, 2924, 2852, 1644, 1589, 1558, 1517, 1480, 1442, 1388, 1338, 1313, 1292, 1259, 1220, 1205, 1186, 1158, 1124, 1079, 1046, 1010 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H, $ArCH_3$), 6.63 (d, 1H, *J* = 16.61 Hz, = CH), 7.02-7.08 (m, 1H, ArH), 7.13 (d, 1H, *J* = 16.61 Hz, = CH), 7.27-7.49

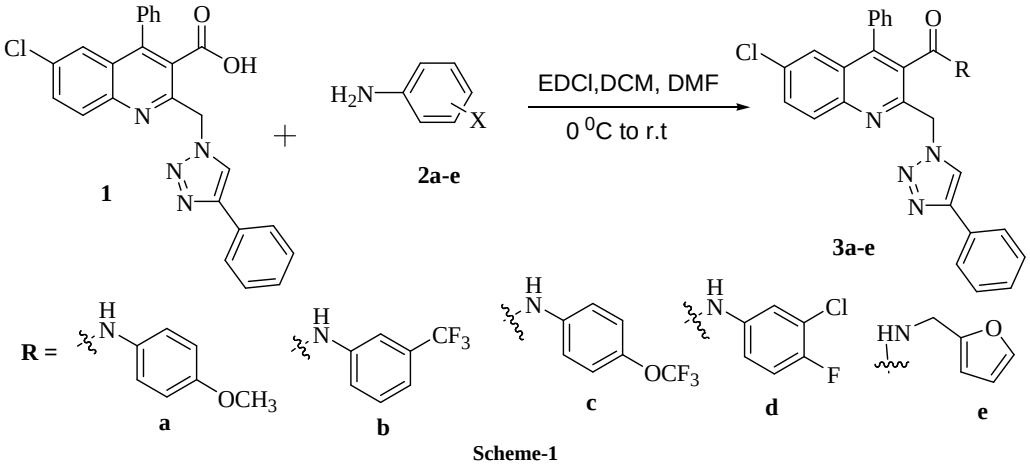
(m, 11*H*, ArH), 7.55 (d, 2H, *J* = 8.30 Hz, ArH), 7.60 (d, 1H, *J* = 2.26 Hz, ArH), 7.70 (dd, 1H, *J* = 9.06 Hz, 3.02 Hz, ArH), 8.07 (d, 1H, *J* = 9.06 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 2396, 114.68, 114.97, 122.59, 122.62, 125.06, 126.07, 127.53, 127.63, 128.60, 128.91, 128.94, 129.87, 130.36, 130.47, 130.54, 131.03, 132.45, 133.26, 133.37, 134.47, 144.57, 146.07, 146.13, 155.31, 161.51, 197.09; ESI-MS: *m/z* 478 (M-+H); HRMS calculated for $C_{31}H_{22}NOClF$ (M^++H) calculated 478.1368 found 478.1366.

(E)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(4'-hydroxy-[1,1'-biphenyl]-4-yl)prop-2-en-l-one (13d)
m.p. 202-204 ^{o}C; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.72 (s, 3H, $ArCH_3$), 6.62 (d, 1H, *J* = 16.61 Hz, =CH), 6.91 (d, 2H, *J* = 9.06 Hz, ArH), 7.12 (d, 1H, *J* = 16.61 Hz, =CH), 7.28-7.56 (m, 11H, ArH), 7.60 (d, 1H, *J*= 2.26 Hz, ArH), 7.69 (dd, 1H, *J* = 9.06 Hz, 2.26 Hz, ArH), 8.09 (d, 1H, *J* = 9.06 Hz, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 23.53, 115.97, 125.16, 126.25, 126.85, 126.93, 128.28, 128.62, 128.99, 129.80, 129.96, 130.22, 131.27, 131.92, 131.98, 132.67, 133.50, 134.30, 143.63, 145.08, 145.61, 147.00, 155.40, 156.45, 196.99; ESI-MS: *m/z* 476 (M^++H); HRMS calculated for $C_{31}H_{23}NO_2Cl$ (M^++H) calculated 476.1411 found 476.1421.

(*E*)-1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)prop-2-en-1-one (13e)
m.p. 225-227 ^{o}C; IR (KBr): *V*max 3060, 3028, 3009, 2956, 2928, 2837, 1641, 1596, 1556, 1525, 1497, 1480, 1442, 1388, 1296, 1275, 1248, 1225, 1181, 1158, 1124, 1080, 1042, 999, 980, 705, 668, 644 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H, $ArCH_3$), 3.85 (s, 3H, $ArOCH_3$), 6.62 (d, 1H, *J* = 16.05 Hz, =CH), 6.97 (d, 2H, *J* = 8.68 Hz, ArH), 7.12 (d, 1H, *J* = 16.05 Hz, =CH), 7.28-7.47 (m, 7H, ArH), 7.48-7.56 (m, 4H, ArH), 7.59 (d, 1H, *J* = 2.26 Hz, ArH), 7.69 (dd, 1H, *J* = 9.06 Hz, 2.26 Hz, ArH), 8.07 (d, 1H, *J* = 9.06 Hz, ArH); ^{13}CNMR (125 MHz, $CDCl_3$): δ 23.93, 55.33, 114.34, 125.06, 126.12, 126.97, 127.02, 128.05, 128.56, 128.85, 128.93, 129.85, 130.51, 130.95, 132.14, 132.18, 132.40, 133.37, 134.49, 143.45, 144.54, 146.09, 146.65, 155.33, 159.73, 197.12;ESI-MS:*m/z*490(M^++H).HRMS calculated for $C_{32}H_{24}O_2ClN$(M^++H) calculated 490.1471 found 490.1491.

RESULTS AND DISCUSSION

To a solution of quinoline-3-carboxylic acid**1** in dry CH_2C1_2 was added EDCl at 0^{o}C under nitrogen atmosphere and stirred for 20 min. To this well stirred solution *p*-methoxy aniline **2** was added slowly over 5 min at the same temperature and reaction mixture was allowed to stir for 8 h. After completion of reaction, reaction mixture was diluted with CH_2Cl_2 and washed with water, dried over sodium sulphate and solvent was evaporated under reduced pressure resulted crude product 75-78%,which was purified by silica gel column chromatography to get triazole coupled quinoline-3-carboxamide[14]**3a**. Physical properties of **3(a-e)** are tabulated in Table-1

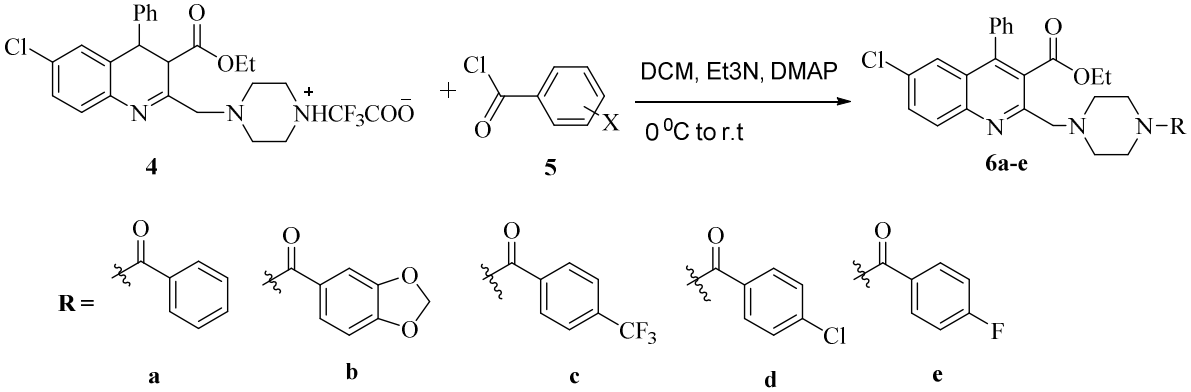


Scheme-1

Table-1 Physical data of synthesized derivatives (3a-e)

S.No	compound	Time (hours)	Yield (%)	Color	M.p°c
1	3a	8	78	White solid	220-223
2	3b	6	75	White solid	231-233
3	3c	6	76	White solid	212-214
4	3d	7-8	78	White solid	229-231
5	3e	6-7	75	White solid	213-214

To a mixture of Boc-deprotected product **4** and Et_3N in dry CH_2Cl_2 at 0^oC under nitrogen atmosphere was added catalytic amount of DMAP and stirred for 30 min. To this reaction mixture benzoyl chloride **5** was added drop wise over 10 min. The resulting reaction mixture was further stirred for 6hrs at room temperature[15], diluted with CH_2Cl_2 and water. Organic layer was separated and aqueous phase was extracted with CH_2Cl_2.The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, by eluting with 30% ethyl acetate/petroleum ether to afford to **6a** (95-98%), Physical properties of **6(a-e)** are tabulated in Table-2.

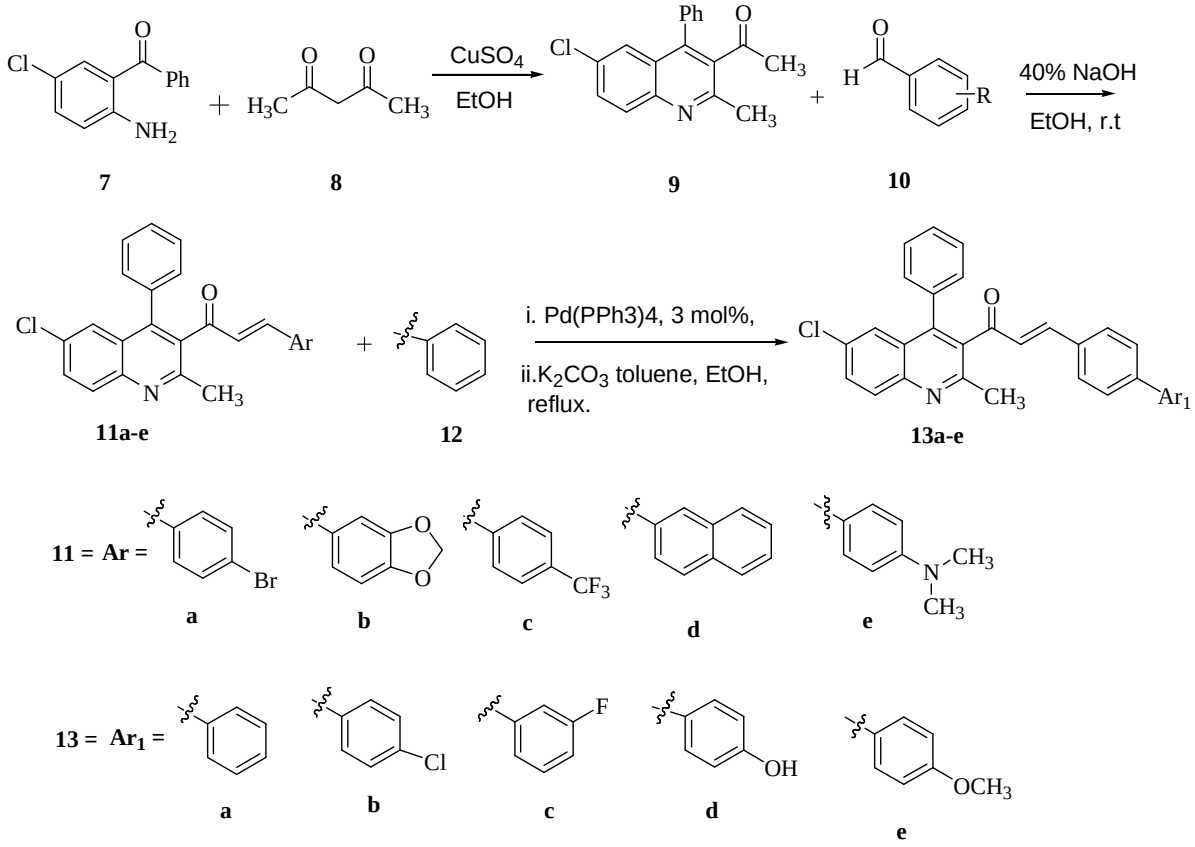


Scheme-2

Table-2 physical data of synthesized derivatives (6a-e)

S.No	compound	Time (hours)	Yield (%)	Colour	M.p°c
1	6a	6	98	Colorless solid	239-241
2	6b	6	95	Colorless solid	219-221
3	6c	5	96	Colorless solid	230-232
4	6d	6	98	Colorless solid	239-241
5	6e	6	95	Colorless solid	216-218

To a well stirred solution of acetylquinoline **9** and *p*-bromo-benzaldehyde **10** in ethanol and water was added slowly 40% KOH solution over 2 min at room temperature, stirring was continued for 12 h. After completion of reaction, water was added to the reaction mixture and extracted with ethyl acetate and the taken organic layers were dried over Na_2SO_4 and evaporated under reduced pressure, to obtain crude residue,it was purified by column chromatography using Ethyl acetate/hexane (2:8) as an eluent to give yellow colored solid 11(85-88%).To a stirred solution of compound[16]**11** and phenyl boronic acid **12** in toluene:EtOH were added $Pd(PPh_3)_4$, K_2CO_3 and reaction mixture was heated at 90^oC for 10 h. Reaction mixture was worked up with water and extracted with ethyl acetate .Combined ethyl acetate layer was dried over sodium sulphate, concentrated under reduced pressure to give solid product it was purified by silica gel chromatography to obtain compound **13** (85-89%). Physical properties of **11(a-e)** and **13(a-e)** are tabulated in Table-3.



Scheme-3

Table-3 physical data of synthesized derivatives (11a-e and 13a-e)

S.No	compound	Time (hours)	Yield (%)	Colour	M.p°c
1	11a	12	88	yellow color solid	214-216
2	11b	12	85	yellow color solid	199-201
3	11c	11	86	yellow color solid	181-2183
4	11d	12	88	yellow color solid	186-188
5	11e	12	85	yellow color solid	207-208
6	13a	10	89	yellow color solid	222-224
7	13b	10	88	yellow color solid	232-234
8	13c	9	85	yellow color solid	212-214
9	13d	10	88	yellow color solid	202-204
10	13e	9	85	Yellow color solid	225-227

Antibacterial Activity:

It is well known that Quinoline derivatives possess antibacterial activity[17-20]. Furthermore, halogen substituent was introduced into the basic structure anticipating an improvement of biological activity because their incorporation was proved to be influencing the biological activity in various heterocycles as well as coumarins[21]. Electron withdrawing groups like halogens will increase bactericidal potential as they alter the nature of the compound in such a way as to promote binding to the target(s)[22]. According to Rajendra Prasad et al in designing the compounds bearing electron withdrawing substituents (with high degree of binding linearity) results in high molecular weights to exhibit an improved antibacterial activity [23]. Similarly, the significant inhibition shown by substituted Quinoline was attributed to substituents like hydroxymethyl / hydroxy / methoxy / ethyl ester groups[24]. Tejaskumar Shah and Vikas Desai also reported that the presence of methoxy-, chloro-, and fluoro groups enhanced the antibacterial activity in isoxazoline derivatives [25].

The antibacterial screening data showed that most of the compound 3a-e, 6a-e, 11a-e and 13a-e showed moderate to excellent activities against the used microorganisms (**Table-4**) compared to the reference drug as *Chloramphenicol*.

These results suggested that the introduction of halogen substituent increased the hydrophobicity of the synthesized compounds and lead to the increase of the antibacterial activity [26]. In the present study, it is observed that good activity was shown by the prepared derivatives against the studied Gram positive bacteria and very poor activity against Gram negative bacteria. The good and poor antibacterial activities of the prepared derivatives against Gram positive and Gram negative bacteria can be explained based on their cell outer layers [27]. Gram positive bacteria have an ineffective and permeable outer barrier made of peptidoglycan layer, which is responsible for permeability of drug constituents. However, Gram negative bacteria have an impermeable outer membrane to drug constituents, as cell wall contains multilayered peptidoglycan and phospholipidic [28]. Among the compounds screened, 3b, 6a, 11c and 13c showed high activity. The observed antibacterial activity profile suggested that the presence of halogen functional group – bromine had enhanced the activity.

Table-4: Antibacterial activity

Compound	*Zone of inhibition (mm)**					
	Escherichia coli (MTCC 40) (Gram-negative) (Conc. µg/ml)			*Staphylococcus aureus (MTCC 96 (Gram-positive) (Conc. µg/ml)*		
	200	*100*	*50*	*200*	*100*	*50*
3a	10	13	14	24	15	25
3b	24	27	21	14	15	15
3c	10	15	12	8	11	12
3d	8	6	18	11	6	18
3e	9	-	-	25	-	-
6a	25	22	32	15	22	32
6b	15	12	12	23	14	12
6c	23	22	21	19	22	21
6d	20	20	32	17	20	30
6e	13	12	12	20	12	12
11a	20	20	21	16	20	20
11b	11	-	-	22	-	-
11c	22	11	17	13	11	17
11d	15	15	20	15	10	11
11e	14	11	11	26	29	19
13a	12	6	8	3	6	9
13b	3	6	9	22	6	9
13c	22	18	19	15	18	20
13d	11	12	12	-	12	12
13e	15	11	14	24	25	20
Chloramphenicol	31	30	21	33	30	23

CONCLUSION

We have accomplished an efficient, convenient, and inexpensive and diversity oriented method for the synthesis of various polysubstituted quinolines through the condensation of o-amino aryl carbonyls with ketones containing an active methylene group by using catalytic amount of $CuSO_4.5H_2O$ at room temperature. Further by applying this protocol we have synthesized the new derivatives of quinoline-2-yl-l, 2, 3-triazoles carrying amides at 3rd position of quinoline ring. Again we prepared different piperazine amides of quinolines at 2nd position with the important pharmacophoric group's methoxy, trifluoromethyl and fluoro group also we have been synthesized phenylsulfonylpiperazine quinolines with different groups on phenyl ring. Further we used acetylquinoline to prepare chalcones and biphenyl chalcones.

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