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Synthesis of new 6-substituent 2-phenyl and 2-(furan-2-yl)-3-phenyl-quinoline-4-carboxylic acid derivatives

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ABSTRACT

A synthesis of substituted quinolines has been achieved by the Doebner reaction which is a three component coupling of arylaldehyde, *p*-amino-acetophenone and phenyl pyruvic acid. The products of 2,3-diary-6-acetyl-quinoline-4-carboxylic acids were obtained by Claisen Schmidt condensation reaction with aldehydes in the presence of sodium hydroxide in order to give the corresponding α,β-unsaturated carbonyls. The substituted α,β-unsaturated carbonyls were condensed with urea, thiourea, hydrazine, phenyl hydrazine, semicarbazide hydrochloride and ethanolamine to synthesized 2-pyrimidinone, 2-pyrimidinethion, pyrazoline-1-phenyl, pyrazoline, pyrazoline-1-carboxamide and 1,4-oxazepines derivatives, respectively, with good yields. The purity and identities of products were elucidated through thin layer chromatography (TLC), melting point and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and LC-Mass).

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1. Introduction

Quinoline also known as 1-azanapthaline, 1-benzazine or benzo[b]pyridine is a heterocyclic organic compounds, with formula C_9H_7N and it is a colorless liquid with strong odor. It was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge [1]. It can form salt with acids and displays reactions similar to those of pyridine and benzene. It shows both electrophilic and nucleophilic substitution reactions. It is nontoxic to humans on oral absorption and inhalation [2]. Quinoline is a pharmacologically valuable scaffold that is prevalent in a variety of biologically active synthetic and natural compounds [3], throughout the 20th century, the chemistry of quinolones has been the subject of intense study and different interesting bioactivity such as anticancer [4], antibacterial [5], antifungal [6], antitumor [7], anti-HIV-1 [8], antileishmanial [9] and antimalarial activity [10]. There are number of natural products of quinoline skeleton used as a medicine or employed as lead molecule for the development newer and potent molecules. For example, quinine was isolated as the active ingredient from the bark of Cinchona trees and has been used for the treatment of malaria [11]. The increased resistance of microbial to known quinolines is constantly demanding to generate novel quinolines to meet the requirements [12]. These quinolines have been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit. Further, these compounds are used as building blocks of various other compounds such as α,β-unsaturated carbonyls, pyrazolines, cyanopyridines, isoxazoles, sulphonamides, arylamides, thiopyrimidines and amino pyrimidines *etc.* [13]. These compounds are known to possess biological activities [14].

In the present work, our interest towered the development of novel heterocycles. The synthesis of 6-substituent-2,3-diaryl-4-quinoline carboxylic acid (**1**,**9**) were reported. The resulting compounds were then condensed with arylaldehydes to product analogies α,β-unsaturated carbonyls which were cyclized with urea derivatives, hydrazine derivatives and monoethanolamine to form pyrimidinone/thiones, pyrazoline, and oxazepines rings.

2. Experimental

2.1. Instrumentation

The ^{1}H and ^{13}C spectra were recorded on Ultrashield 500 plus instrument (Bruker, Germany) using $CDCl_3$ as solvent and operating at 500 MHz for protons. Chemical shifts (δ) are

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given from TMS (0.00 ppm) as an internal standard for ^{1}H NMR. Mass spectra analysis was carried out using a Bruker Daltonics Squire 4000 instrument. Melting points were determined on an automatic Electrothermal melting point apparatus and are uncorrected. The IR spectra were determined in potassium bromide pellets on an Agilent Cary 630 FT-IR system.

2.2. General method for synthesis 2, 3-diaryl-quinoline-4-carboxylic acid derivatives (1, 9)

In round bottom flask equipped with a reflux condenser were placed 0.236 mol of the required aromatic aldehyde, 0.25 mol of freshly distilled phenyl pyruvic acid and 200 mL of absolute ethanol. The mixture was heated on a boiling water-bath and a solution of 0.248 mol of *p*-amino-acetophenone in a 100 mL of absolute ethanol was added slowly with frequent shaking within 1 hour. The mixture was refluxed on a water-bath for 3 hours and left to stand overnight, filtered, washed with little ether and recrystallized from ethanol to yield compounds **1** and **9** (Scheme 1).

6-Acetyl-2,3-diphenylquinoline-4-carboxylic acid (**1**): Color: Off white crystals. Yield: 2.91 g, 93%. M.p.: 210-212 °C. FT-IR (KBr, ν, cm^{-1}): 3247 (O-H), 3090 (Ar-H), 1679 (C=O) (keto), 1668 (C=O) (acid), 1600 (C=C), 1362 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 2.65 (s, 3H, CH_3), 7.16-7.45 (m, 6H, Ar-H), 7.67 (t, 2H, Ar-H), 7.98 (d, 2H, H-Ar), 8.22 (d, 1H, CH quinoline), 8.41 (d, 1H, CH quinoline), 9.45 (s , 1H, CH quinoline), 12.82 (s , 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 26.45 (CH_3), 127.70 (Ar-C), 128.22 (Ar-C), 128.53 (Ar-C), 128.78 (Ar-C), 129.02 (Ar-C), 129.37 (Ar-C), 129.58 (*C*H-CH-CN), 133.46 (Ar-C-*C*), 135.78 (*C*-COOH), 166.50 (COOH), 189.12 (C=O). MS (EI, *m/z* (%)): 367.43 (M^+, 2.3), 248.11 (M^+-C_8H_3O, 40.5), 205.00 (M^+-$C_9H_4O_3$, 6.1), 124.05 (M^+-$C_{15}H_9O_3$, 100).

6-Acetyl-2-(furan-2-yl)-3-phenylquinoline-4-carboxylic acid (**9**): Color: Beige crystals. Yield: 2.40 g, 82%. M.p.: 143-145 °C. FT-IR (KBr, ν, cm^{-1}): 3243 (OH), 3144 (Ar-H), 1675 (C=O) (keto), 1667 (C=O) (acid), 1599 (C=C), 1362 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 2.65 (s, 3H, CH_3), 6.32 (t, 1H, H-furyl), 7.30 (t, 1H, H-Ar), 7.35 (t, 2H, H-Ar), 7.70 (d, 2H, H-Ar), 7.75 (d, 1H, H-furyl), 7.95 (d, 1H, H-furyl), 8.22 (d, 1H, CH quinoline), 8.42 (d, 1H, CH quinoline), 9.66 (s, 1H, CH quinoline), 10.68 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 26.49 (1C. CH_3), 110.19 (1C, *C*H=CH-O), 127.31 (1C, Ar-C), 128.33 (2C, Ar-C), 129.43 (2C, Ar-C), 133.53 (1C, Ar-C-*C*), 142.91 (1C, *C*H-O-C), 148.52 (1C, C-N=C), 166.17 (1C, COOH), 196.07 (1C, C=O). MS (EI, *m/z* (%)): 357.34 (M^+, 17.8), 318.29 (M^+- C_2H_3O, 32.14), 293.06 (M^+- C_4H_3O, 7.9) 248.11(M^+-$C_6H_6O_2$, 100).

2.3. General method for synthesis α,β-unsaturated carbonyl derivatives (2 and 10)

A mixture of 0.01 mol of the required aromatic aldehyde 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 hours at room temperature and kept for overnight at room temperature. The mixture was poured into crushed ice and acidified with dilute hydrochloric acid. The α,β-unsaturated carbonyl derivatives were precipitated out as solid, filtered, dried and recrystallized from ethanol to yield compounds (**2** and **10**) (Scheme 1).

6-Cinnamoyl-2,3-diphenylquinoline-4-carboxylic acid (**2**): Color: Pale yellow crystals. Yield: 1.22 g, 86%. M.p.: 110-112 °C. FT-IR (KBr, ν, cm^{-1}): 3285 (OH), 3060 (C-H) (=CH_α), 3045 (C-H) (=CH_π), 1682 (C=O) (keto), 1657 (C=O) (acid), 1598 (C=C), 1356 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 7.22-7.74 (m, 12H, H-Ar, H_α-C=), 7.58-7.76 (m, 3H, H-Ar, H_β-C=), 7.93 (d, 2H, H-Ar), 8.13 (d, 1H, CH quinoline), 8.51 (d, 1H, CH quinoline), 9.72 (s, 1H, CH quinoline), 12.11 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 121.69 (1C, -C_α=), 127.81 (1C, CH-*C*H-CN), 127.66 (2C, Ar-C), 128.24 (1C, Ar-C), 128.48 (2C, Ar-C), 128.69 (1C, Ar-C), 129.00 (2C, Ar-C), 129.35 (2C, Ar-C), 129.53 (1C, *C*H-CH-CN), 133.46 (1C, Ar-C-*C*), 134.84 (1C, -C_β=), 135.90 (1C, *C*-COOH), 141.56 (1C, Ar), 189.14 (1C, C=O), 166.76 (1C, COOH). MS (EI, *m/z* (%)): 455.52 (M^+, 4.8), 437.18 (M^+-18, 100), 303.25 (M^+-$C_{12}H_{10}$, 7.5).

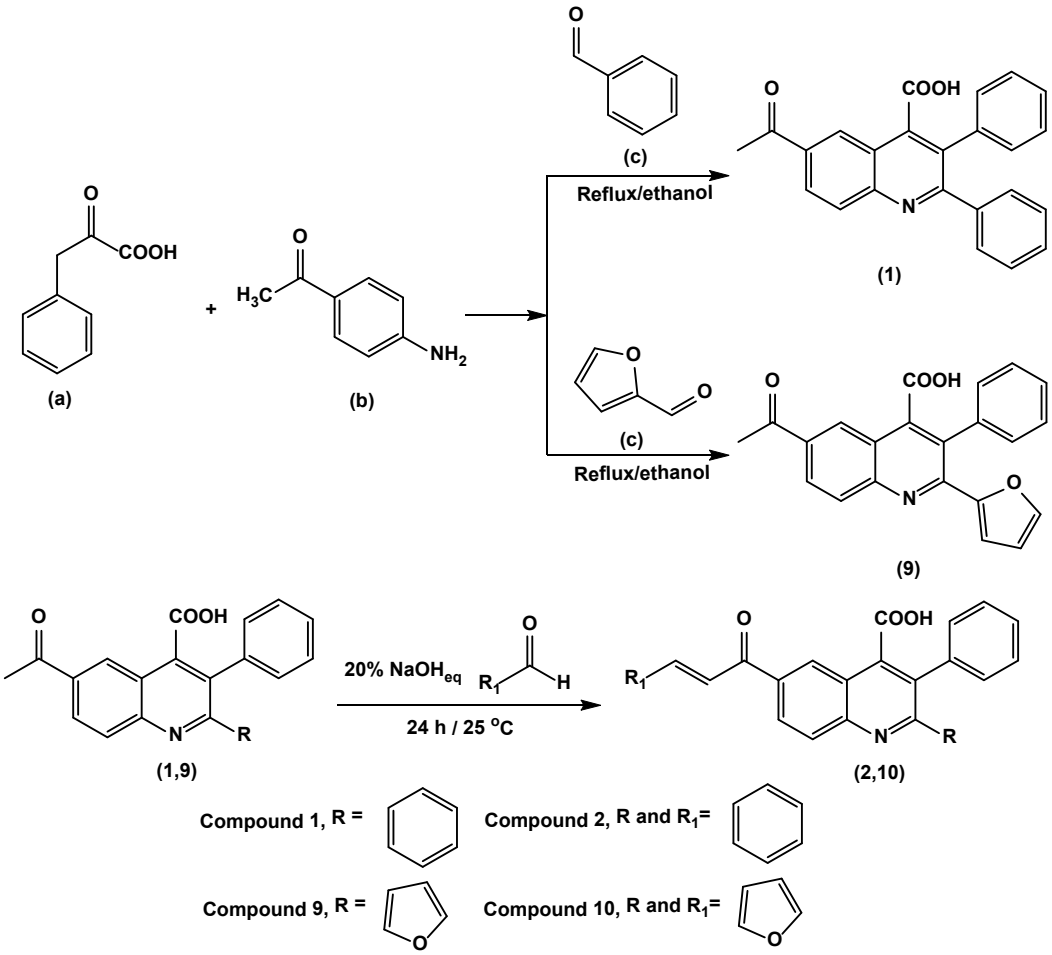
2-(Furan-2-yl)-6-(3-(furan-2-yl) acryloyl)-3-phenyl quinoline-4-carboxylic acid (**10**): Color: Beige crystals. Yield: 1.56 g, 78%. M.p.: 148-150 °C. FT-IR (KBr, ν, cm^{-1}): 3275 (OH), 3060 (C-H) (=CH_α), 3045 (C-H) (=CH_π), 1672 (C=O) (keto), 1660 (C=O) (acid), 1600 (C=C), 1365 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 6.16-6.32 (m, 2H, 2H-furyl), 7.23 (t, 1H, H-Ar), 7.36 (t, 2H, H-Ar), 7.70 (d, 2H, H-Ar), 7.73-7.78 (m, 2H, H-furyl, H_α-C=), 7.95 (d, 1H, H-furyl), 7.99-8.10 (m, 3H, 2H-furyl, H_β-C=), 8.12 (d, 1H, CH quinoline), 8.19 (d, 1H, CH quinoline), 9.66 (s, 1H, CH quinoline), 10.62 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 110.18 (1C, *C*H=CH-O), 119.99 (1C, -C_β=), 127.31 (1C, Ar-C), 128.62 (2C, Ar-C), 129.43 (2C, Ar-C), 131.25 (1C, -C_α=), 133.55 (1C, Ar-C-*C*), 140.76 (1C, *C*H-O-C), 142.90 (1C, *C*H-O-C), 148.54 (1C, *C*-N=C), 166.21 (1C, COOH), 196.08 (1C, C=O). MS (EI, *m/z* (%)): 435.44 (M^+, 1.1), 382.06(M^+-C_3H_2O, 100), 360.11 (M^+- C_6H_5, 58.1), 360.11 (M^+- $C_{11}H_8O_2$, 77.4),

2.4. General method for synthesis 2-pyrimidinone/thiones derivatives (3, 4, 11 and 12)

A mixture of 0.01 mol of α,β-unsaturated carbonyl (**2** or **10**), 0.01 mol of urea or thiourea dissolved in 50 mL of ethanol and 6 mL of aqueous sodium hydroxide (10%) was added. The reaction of mixture was heated under reflux for 3 h. TLC monitoring was extensively done. The product when cool was poured in ice-cold water. The solid mass which separated out was filtered washed with water and recrystallized from ethanol to yield compounds **3**, **4**, **11** and **12** (Scheme 2).

6-(2-Oxo-6-phenyl-1, 2-dihydropyrimidin-4-yl)-2,3-diphenyl quinoline-4-carboxylic acid (**3**): Color: Yellow crystals. Yield: 0.42 g, 70%. M.p.: 175-177 °C. FT-IR (KBr, ν, cm^{-1}): 3226 (OH), 3090 (CH), 3015 (NH), 1692 (C=O) (acid), 1672 (C=O) (amide), 1601 (C=C), 1376 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 5.73 (s, 1H, CH), 7.14-7.38 (m, 8H, H-Ar), 7.46 (d, 2H, H-Ar), 7.62-7.67 (m, 3H, H-Ar) 7.85 (d, 2H, H-Ar), 8.02 (d, 1H, CH quinoline ring), 8.85 (d, 1H, CH quinoline), 9.83 (s, 1H, CH quinoline), 10.02 (s, 1H, NH), 12.32 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 101.05 (1C, *C*H-CNH), 122.03 (1C, *C*-CCOOH), 127.46 (1C, Ar-C), 127.70 (2C, Ar-C), 127.80 (2C, Ar-C), 128.08 (1C, Ar-C), 128.41 (2C, Ar-C), 128.45 (2C, Ar-C), 128.70 (1C,Ar-C), 128.97 (2C, Ar-C), 129.04 (2C, Ar-C), 129.34 (1C, *C*H-CH-CN), 133.05 (1C, Ar-C-*C*), 133.36 (1C, *C*-COOH), 141.25 (1C, Ar), 157.12 (1C, C=O), 166.94 (1C, COOH). MS (EI, *m/z* (%)): 497.54, ([M^++2], 56.1), 496.16 ([M^++1], 5.4), 495.18 (M^+, 3.2), 248.11 (M^+- $C_{16}H_{12}N_2O$, 100).

2,3-Diphenyl-6-(6-phenyl-2-thioxo-1,2-dihydropyrimidin-4-yl)quinoline-4-carboxylic acid (**4**): Color: Yellow crystals. Yield: 0.41 g, 68%. M.p.: 165-167 °C. FT-IR (KBr, ν, cm^{-1}): 3209 (OH), 3210 (NH), 1692 (C=O) (acid), 1672 (C=O) (amide), 1600 (C=N), 1426 (C=C), 1210 (C=S), 1365 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 5.96 (s, 1H, CH), 7.13-7.34 (m, 8H, H-Ar), 7.39 (d, 2H, H-Ar), 7.61-7.68 (m, 3H, H-Ar), 7.84 (d, 2H, H-Ar), 8.02 (d, 1H, CH quinoline), 9.02 (d, 1H, CH quinoline), 9.24 (s, 1H, CH quinoline), 10.02 (s, 1H, NH), 12.43 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 101.05 (1C, *C*H-CNH), 121.91 (1C, C-CCOOH), 127.30 (1C, Ar-C), 127.67 (2C, Ar-C), 127.81 (2C, Ar-C), 128.13 (1C, Ar-C), 128.37 (2C, Ar-C), 128.48 (2C, Ar-C), 128.70 (1C,Ar-C), 128.88 (2C, Ar-C), 129.14 (2C, Ar-C), 129.34 (1C, *C*H-CH-CN), 130.93 (1C, Ar-C-*C*), 133.44 (1C, *C*-COOH), 141.80 (1C, Ar), 174.97 (C, C-NH), 166.76 (1C, COOH).



Scheme 1. Synthesis of 2,3-diaryl -quinoline-4-carboxylic acid and α,β-unsaturated carbonyl analogues.

MS (EI, *m/z* (%)): 513.60 ([M⁺+2], 4.2), 512.18 ([M⁺+1], 8.7), 511.27(M⁺, 10.8), 437. 17 (M⁺-CHN$_2$S).

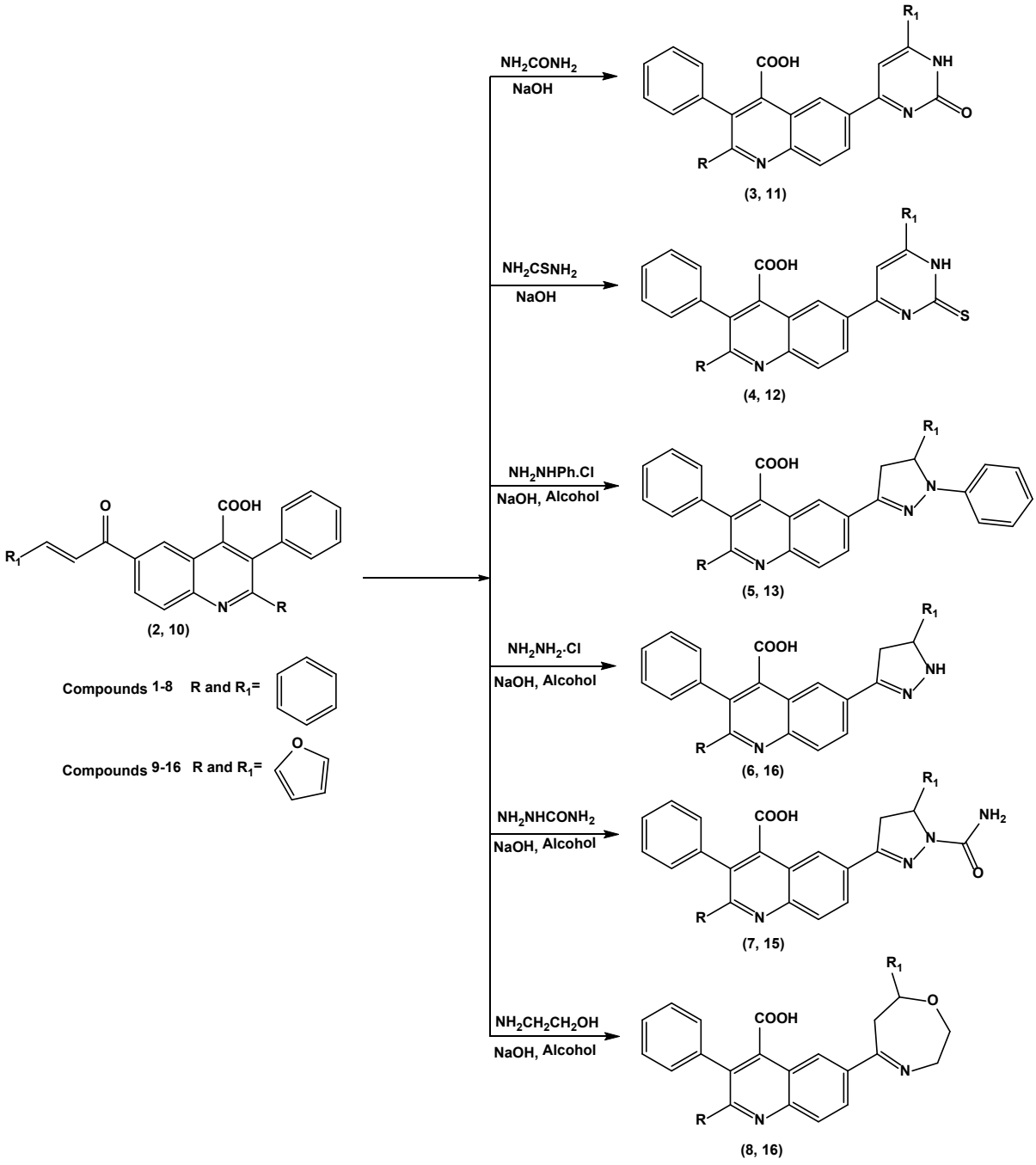
2-(Furan-2-yl)-6-(6-(furan-2-yl)-2-oxo-1, 2-dihydropyrimidin-4-yl)-3-phenylquinoline-4-carboxylic acid (**11**): Color: Brown crystals. Yield: 0.43 g, 72%. M.p.: 147-149 °C. FT-IR (KBr, ν, cm^{-1}): 3293 (OH), 3196 (NH), 3089 (CH), 1692 (C=O) (acid), 1673, 1672 (C=O) (amide), 1600 (C=C), 1376 (C-N). ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): 6.04 (s, 1H, CH), 6.17-6.33 (m, 2H, H-furyl),7.22- 7.36 (m, 3H, H-Ar), 7.68-7.80 (m, 5H, H-furyl , H-Ar), 7.96 (d, 1H, H-furyl), 8.10 (d, 1H, CH quinoline), 8.12 (d, 1H, CH quinoline), 9.67 (s, 1H, CH quinoline), 10.02 (s, 1H, NH), 11.01 (s, 1H, COOH). ^{13}C NMR (125 MHz, CDCl$_3$ δ, ppm): 110.18 (1C, *C*H=C-O), 110.84 (1C, *C*H=C-O), 112.44 (1C, *C*H-CNH), 128.32 (2C, Ar-C), 127.31 (1C, Ar-C), 128.62 (2C, Ar-C), 129.43 (2C, Ar-C), 133.55 (1C, Ar-C-*C*), 140.76 (1C, *C*H-O-C), 141.69 (1C, C-NH), 142.90 (1C, *C*H-O-C), 148.54 (1C, *C*-N=C), 156.28 (1C, C=O), 166.29 (1C, COOH). MS (EI, *m/z* (%)): 477.41 ([M⁺+2], 2.2), 476.13 ([M⁺+1], 1.3), 475.08(M⁺, 1.7), 382.09 (M⁺- C$_6$H$_7$O, 100).

2-(Furan-2-yl)-6-(6-(furan-2-yl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-3-phenylquinoline-4-carboxylic acid (**12**): Color: Brown crystals. Yield: 0.40 g, 67%. M.p.: 150-152 °C. FT-IR (KBr, ν, cm^{-1}): 3289 (OH), 3190 (NH), 1675 (C=O) (acid), 1600 (C=N), 1503 (C=N), 1226 (C=S), 1366 (C-N). ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): 6.04 (s, 1H, CH), 6.17-6.31 (m, 2H, H-furyl), 7.24- 7.36 (m, 3H, H-Ar), 7.69-7.78 (m, 5H, H-furyl , H-Ar), 7.95 (d, 1H, H-furyl), 8.10 (d, 1H, CH quinoline), 8.12 (d, 1H, CH quinoline), 9.67 (s, 1H, CH quinoline), 10.02 (s, 1H, NH), 10.89 (s, 1H, COOH). ^{13}C NMR (125 MHz, CDCl$_3$ δ, ppm): 110.19 (1C, *C*H=C-O), 110.84 (1C, *C*H=C-O), 112.43 (1C, *C*H-CNH), 127.31 (1C, Ar-C), 128.61 (2C, Ar-C), 129.43 (2C, Ar-C), 133.55 (1C, Ar-C-*C*), 140.76 (1C, *C*H-O-C), 141.73 (1C, C-NH), 142.90 (1C, *C*H-O-C), 148.55 (1C, *C*-N=C), 166.32 (1C, COOH). MS (EI, *m/z* (%)): 493.61, ([M⁺+2], 2.5), 492.17 ([M⁺+1], 4.9), 491.12 (M⁺, 5.1), 382.09 (M⁺- C$_6$H$_5$S, 100).

2.5. General method for synthesis pyrazoline/pyrazoline-1-phenyl/pyrazoline-1-carboxamide derivatives (5, 6, 7, 13, 14 and 15)

A mixture of 0.01 mol of α,β-unsaturated carbonyl (**2** or **10**), 0.01 mol of hydrazine hydrochloride, phenyl hydrazine hydrochloride or pyrazoline-1-carboxamide dissolved in 25 mL of ethanol and 1 mL of ethanolic sodium hydroxide (0.1 mol) was added. The reaction mixture was heated under reflux for 2 h. TLC monitoring was extensively done. The product when cool was poured in ice-cold water. The solid mass which separated out was filtered washed with water and recrystallized from ethanol to yield compounds **5**, **6**, **7**, **13**, **14** and **15** (Scheme 2).

6-(1,5-Diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-2,3-diphenyl quinoline-4-carboxylic acid (**5**): Color: Yellow crystals. Yield: 0.42 g, 70%. M.p.: 119-121 °C. FT-IR (KBr, ν, cm^{-1}): 2956 (CH$_2$), 1698 (C=O) (acid), 1601 (C=C), 1513 (C=N). ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): 3.71-3.75 (dd, 1H$_{(A)}$, CH$_2$, dd, 1H$_{(B)}$, CH$_2$), 4.99-5.02 (dd, 1H$_{(X)}$,-CH), 6.61-6.63 (m, 3H, H-Ar), 7.11-7.44 (m, 11H, H-Ar), 7.63-7.90 (m, 4H, H-Ar), 8.09 (d, 2H, H-Ar), 8.22 (d, 1H, CH quinoline), 8.43 (d, 1H, CH quinoline), 9.61 (s, 1H, CH quinoline), 12.32 (s, 1H, COOH).



Scheme 2. Synthesis of pyrimidinone/thiones, pyrazolines, and oxazepines substituent 2,3-diaryl-quinoline-4-carboxylic acids from α,β-unsaturated carbonyls.

^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 41.25 (1C, *C*H_2-CH), 63.31 (1C, C-N-N), 127.09 (2C, Ar-C), 127.69 (2C, Ar-C), 127.80 (2C, Ar-C), 128.08 (1C, Ar-C), 128.25 (2C, Ar-C), 128.55 (2C, Ar-C), 128.79 (1C,Ar-C), 128.95 (2C, Ar-C), 129.03 (2C, Ar-C), 129.38 (1C, *C*H-CH-CN), 133.05 (1C, Ar-C-*C*), 133.36 (1C, *C*-COOH), 141.12 (1C, Ar), 157.12 (1C, C=O), 166.38 (1C, COOH). MS (EI, *m/z* (%)): 547.17 ([M^++2], 1.4), 546.15 ([M^++1], 2.1), 545.15 (M^+, 5.7), 363.21 (M^+-$C_{12}H_{10}N_2$, 100).

2, 3-Diphenyl-6-(5-phenyl-4, 5-dihydro-1H-pyrazol-3-yl) quinoline-4-carboxylic acid (**6**): Color: Pale yellow crystals. Yield: 0.39 g, 65%. M.p.: 128-131 °C. FT-IR (KBr, ν, cm^{-1}): 3047 (NH), 2958 (C-H) (CH_2), 1679 (C=O) (acid), 1602 (C=C), 1520 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.70-3.74 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 4.93-4.95 (dd, $1H_{(X)}$,-CH), 7.19-7.33 (m, 5H, H-Ar), 7.50-7.69 (m, 6H, H-Ar), 7.93 (d, 2H, H-Ar), 8.02 (d, 2H, H-Ar), 8.31 (d, 1H, CH quinoline), 8.58 (d, 1H, CH quinoline), 9.88 (s, 1H, CH quinoline), 10.03 (s, 1H, NH), 12.46 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 41.27 (1C, *C*H_2-CH), 63.31 (1C, C-N-N), 127.59 (2C, Ar-C), 127.69 (1C, Ar-C), 127.90 (2C, Ar-C), 128.10 (1C, Ar-C), 128.53 (2C, Ar-C), 128.77 (1C, Ar-C), 128.92 (2C, Ar-C), 128.97 (2C, Ar-C), 129.37 (1C, *C*H-CH-CN), 133.05 (1C, Ar-C-*C*), 133.36 (1C, *C*-COOH), 141.69 (1C, Ar), 151.36 (1C, C=N), 166.17 (1C, COOH). MS (EI, *m/z* (%)): 471.18 ([M^++2], 64.7), 470.13 ([M^++1], 17.6), 469.15 ([M^+, 11.4), 274.24 (M^+-$C_{13}H_{12}N_2$, 100).

6-(1-Carbamoyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2,3 -diphenylquinoline-4-carboxylic acid (**7**): Color: Pale yellow crystals. Yield: 0.40 g, 67%. M.p.: 120-123 °C. FT-IR (KBr, ν, cm^{-1}): 3326 (OH), 3101 (NH), 2952 (C-H) (CH_2), 1706 (C=O) (acid), 1681 (C=O) (amide), 1600 (C=C), 1516 (C=N). ^{1}H NMR

(500 MHz, $CDCl_3$, δ, ppm): 3.70-7.74 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 4.93-4.98 (dd, $1H_{(X)}$, -CH), 6.01 (s, 2H, NH_2), 7.16-7.50 (m, 5H, H-Ar), 7.77-7.60 (m, 6H, H-Ar), 8.02-7.94 (m, 4H, H-Ar), 8.22 (d, 1H, CH quinoline), 8.47 (d, 1H, CH quinoline), 9.50 (s, 1H, CH quinoline), 12.30 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 41.27 (1C, CH_2-CH), 63.29 (1C, C-N-N), 127.40 (1C, Ar-C), 127.67 (2C, Ar-C), 127.82 (2C, Ar-C), 128.07 (1C, Ar-C), 128.46 (2C, Ar-C), 128.62 (1C,Ar-C), 128.85 (2C, Ar-C), 129.10 (2C, Ar-C), 129.52 (1C, *C*H-CH-CN), 133.71 (1C, *C*-COOH), 142.03 (1C, Ar), 150.16 (1C, C=N), 156.87 (1C, NH_2-C=O), 166.71 (1C, COOH). MS (EI, *m/z* (%)): 514.16 ([M^++2], 11.9), 513.16 ([M^++1], 13.9), 512.44 (M^+, 34.5), 274.24 (M^+-$C_{15}H_{14}N_2O$, 100).

2-(Furan-2-yl)-6-(5-(furan-2-yl)-1-phenyl-4, 5-dihydro-1H-pyrazol-3-yl)-3-phenylquinoline-4-carboxylic acid (**13**): Color: Pale yellow crystals. Yield: 0.39 g, 65%. M.p.: 145-150 °C. FT-IR (KBr, ν, cm^{-1}): 3276 (OH), 2805 (C-H) (CH_2), 1671 (C=O) (acid), 1598 (C=C), 1510 (C=N), 1269 (C-O). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.63-3.68 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 4.09-4.14 (dd, $1H_{(X)}$, -CH), 6.62 (d , 1H, H-furyl), 6.17-6.29 (m, 3H, H-furyl, H-Ar), 6.68 (d , 2H, H-Ar), 6.91-7.03 (m, 2H, H-futyl, H-Ar), 7.13-7.73 (m, 7H, H-furyl, H-Ar), 7.94 (d, 1H, H-furyl), 8.05 (d, 1H, CH quinoline), 8.11 (d, 1H, CH quinoline), 9.62 (s, 1H, CH quinoline), 12.16 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 39.98 (1C, *C*H_2-CH), 58.11 (1C, CH_2-*C*H), 110.46 (1C, *C*H=C-O), 112.70 (1C, *C*H=CH-O), 113.55 (2C, Ar-C), 113.95 (2C, Ar-C), 122.25 (1C, Ar -C), 127.31 (1C, Ar-C), 128.86 (2C, Ar-C), 129.24 (2C, Ar-C), 133.12 (1C, Ar-C-*C*), 142.08 (1C, *C*H-O-C), 142.21 (1C, *C*H-O-C), 143.21 (1C, Ar-C), 148.54 (1C, *C*-N=C), 154.04 (1C, C=N), 166.27 (1C, COOH). MS (EI, *m/z* (%)): 527.54 ([M^++2], 10.1), 526. 46 ([M^++1], 22.5), 525.18 (M^+, 11.3), 391.14 (M^+- $C_8H_7O_2$, 100).

2-(Furan-2-yl)-6-(5-(furan-2-yl)-4, 5-dihydro-1H-pyrazol-3-yl)-3-phenylquinoline-4-carboxylic acid (**14**): Color: Beige crystals. Yield: 0.41 g, 68%. M.p.: 167-169 °C. FT-IR (KBr, ν, cm^{-1}): 3358 (NH), 2926 (C-H) (CH_2), 1675 (C=O) (acid), 1599 (C=C), 1502 (C=N), 1215 (C-O). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.65-3.70 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2) 4.10-4.15 (dd, $1H_{(X)}$, -CH), 6.23-6.32 (m , 3H, H-furyl ring), 7.24-7.36 (m, 3H, H-Ar), 7.69-7.78 (m, 4H, H-furyl , H-Ar), 7.96 (d, 1H, H-furyl), 8.06 (d, 1H, CH quinoline), 8.77 (d, 1H, CH quinoline), 9.95 (s, 1H, CH quinoline), 10.11 (s, 1H, NH), 12.35 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 39.95 (1C, *C*H_2-CH). 51.01 (1C, CH_2-*C*H), 110.56 (1C, *C*H=C-O), 112.51 (1C, *C*H=CH-O), 127.32 (1C, Ar-C), 128.34 (2C, Ar-C), 129.77 (2C, Ar-C), 133.44 (1C, Ar-C-*C*), 141.93 (1C, *C*H-O-C), 144.45 (1C, Ar-C), 148.52 (1C, *C*-N=C), 155.74 (1C, C=N), 166.21 (1C, COOH). MS (EI, *m/z* (%)): 451.09 ([M^++ 2], 32.2), 450.02 ([M^++1], 12.9), 449.11 (M^+, 35.18) 437.14 (M^+-NH, 10.6).

6-(1-Carbamoyl-5-(furan-2-yl)-4, 5-dihydro-1H-pyrazol-3-yl)-2-(furan-2-yl)-3-phenylquinoline-4-carboxylic acid (**15**): Color: Beige crystals. Yield: 0.38 g, 64%. M.p.: 155-157 °C. FT-IR (KBr, ν, cm^{-1}): 3360 (NH), 2951 (C-H) (CH_2), 1703 (C=O) (acid), 1674 (C=O) (amide), 1603 (C=C), 1513 (C=N), 1216 (C-O). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.67-3.70 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 4.10-4.15 (dd, $1H_{(X)}$, CH), 6.66 (d, 1H, H-furyl), 6.69-6.72 (m, 3H, furyl, NH_2), 7.25-7.78 (m, 8H, H-furyl, H-Ar), 7.96 (d, 1H, H-furyl), 8.06 (s, 1H, CH quinoline), 8.10 (d, 1H, CH quinoline), 9.61 (s, 1H, quinoline), 12.46 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 39.89 (1C, *C*H_2-CH), 56.76 (1C, CH_2-*C*H), 110.85 (1C, *C*H=C-O), 112.51 (1C, *C*H=CH-O), 127.32(1C, Ar-C), 128.34 (2C, Ar-C), 129.77 (2C, Ar-C), 133.44 (1C, Ar-C-*C*), 141.93 (1C, *C*H-O-C), 144.45 (1C, Ar-C), 148.52 (1C, *C*-N=C), 155.74 (1C, C=N), 166.21 (1C, COOH). MS (EI, *m/z* (%)): 494.06 ([M^++2], 3.5), 493.11 ([M^++1], 2.8), 492.08 (M^+, 4.2), 434.08 (M^+-N_2H_2CO, 10.6).

2.6. General method for synthesis 1,4-oxazepines derivatives (8 and 16)

A mixture of 0.01 mol of α,β-unsaturated carbonyl (**2** or **10**), 0.01 mol of monoethanolamine dissolved in 25 mL of ethanol and 0.5 mL of ethanolic sodium hydroxide (0.1 mol) was added. The reaction mixture was heated under reflux for 4 h. TLC monitoring was extensively done. The product when cool was poured in ice-cold water. The solid mass which separated out was filtered washed with water and recrystallized from ethanol yield compound **8** and **16** (Scheme 2).

2,3-Diphenyl-6-(7-phenyl-2,3,6,7-tetrahydro-1,4-oxazepin-5-yl)quinoline-4-carboxylic acid (**8**): Color: Pale yellow crystals. Yield: 0.40 g, 67%. M.p.: 139-141 °C. FT-IR (KBr, ν, cm^{-1}): 3263 (OH), 2978 (C-H) (CH_2), 1682 (C=O) (acid), 1601 (C=C), 1505 (C=N), 1216 (C-O-C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.34-3.39 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 3.61 (t, 2H,-CH_2), 3.78 (t, 2H,-CH_2), 4.93 (dd, $1H_{(X)}$, CH), 7.17-7.48 (m, 5H, H-Ar), 7.78-7.61 (m, 6H, H-Ar), 7.97-8.01 (m, 4H, H-Ar), 8.22 (d, 1H, CH quinoline), 8.54 (d, 1H, CH quinoline), 9.95 (s, 1H, CH quinoline), 12.41 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 30.96 (1C, *C*H_2CHO), 63.34 (1C, CH_2-O), 127.71 (2C, Ar-C), 127.90 (2C, Ar-C), 128.23 (1C, Ar-C), 128.54 (2C, Ar-C), 128.80 (1C,Ar-C), 128.97 (2C, Ar-C), 129.04 (2C, Ar-C), 129.38 (1C, *C*H-CH-CN), 133.44 (1C, *C*-COOH), 141.21 (1C, Ar), 166.40 (1C, COOH). MS (EI, *m/z* (%)): 500.12 ([M^++2], 1.8), 499.11 ([M^++1], 5.4), 498.07 (M^+, 10.4), 453.12(M^+-C_2H_4O, 100).

2-(Furan-2-yl)-6-(7-(furan-2-yl)-2,3,6,7-tetrahydro-1, 4-oxazepin-5-yl)-3-phenylquinoline-4-carboxylic acid (**16**): Color: Brown crystals. Yield: 0.40 g, 67%. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3387 (OH), 2921 (C-H) (CH_2), 1692 (C=O) (acid), 1598 (C=C), 1509 (C=N), 1227 (C-O-C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.25-3.35 (dd, $1H_{(A)}$, CH_2, dd, $1H_{(B)}$, CH_2), 3.64 (t, 2H,-CH_2), 3.83 (t, 2H,-CH_2), 4.91-5.01 (dd, 1H, $1H_{(X)}$-CH), 6.67-6.79 (m, 2H, 2H-furyl), 7.31-7.69 (m, 8H, H-furyl, H-Ar),7.96 (d, 1H, H-furyl), 8.03 (d, 1H, CH quinoline), 8.08 (d, 1H, CH quinoline), 9.61 (s, 1H, CH quinoline), 12.35 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$ δ, ppm): 30.96 (1C, CH_2CHO), 45.44 (1C, CH_2-N), 58.71 (1C, CH_2-O), 110.86 (1C, *C*H=C-O), 112.43 (1C, *C*H=CH-O), 127.31 (1C, Ar-C), 128.36 (2C, Ar-C), 129.52 (2C, Ar-C), 134.11 (1C, Ar-C-*C*), 142.93 (1C, *C*H-O-C), 144.46 (1C, Ar-C), 146.59 (1C, *C*-N=C), 166.22 (1C, COOH). MS (EI, *m/z* (%)): 480.11 ([M^++2], 17.2), 479.10 ([M^++1], 8.5), 498.07 (M^+, 11.5), 437.14 (M^+- C_2H_4O, 100).

3. Results and discussion

The starting product structure of quinoline in this study has been synthesized by Doebner reaction which is a condensation reaction between phenyl pyruvic acid (a), primary aryl amines (b) and aldehydes (c) in absolute ethanol to form 2,3-diaryl-quinoline-4-carboxylic acid (**1** and **9**) (Scheme 1) [15]. The α,β-unsaturated carbonyls (**2** and **10**) were obtained in good yields by the Claisen-Schmidt condensation of the 6-acetyl-2,3-diaryl-quinoline-4-carboxylic acid derivatives and the substituted benzaldehydes in the base (NaOH) catalyzed and ethanol (Scheme 1) according to the literature [16].

The treatment of α,β-unsaturated carbonyls (**2** and **10**) with urea derivatives, hydrazine derivatives or monoethanolamine to yield pyrimidinone/thione [17], pyrazoline [18], and oxazepine [19] heterocyclic rings, respectively (Scheme 2) in reflux temperature was monitored by TLC techniques.

All chemical reagents are obtained from commercial suppliers and used without further purification [20]. The structure of the above-mentioned compounds was confirmed by IR, NMR and MS spectral data.

The formation of quinoline acid (**1** and **9**) was confirmed by the peak at ~3250 cm^{-1} in IR spectrum which is due to the OH stretching of carboxylic acid. A band at ~1670 cm^{-1} is due to C=O stretch of the acid group [21] and other band for C=O in acetyl group at ~1680 cm^{-1}.

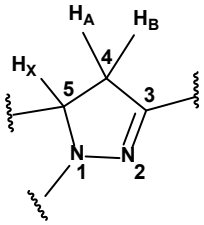


Figure 1. Carbon numbering of pyrazoline ring.

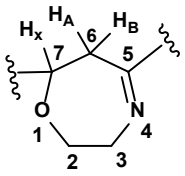


Figure 2. Carbon numbering of 1,4-oxazepine ring.

The ^{1}H NMR spectrum of compounds **1** and **9** showed doublet signals at δ 8.22/8.22 and 8.41/8.42 ppm and singlet at δ 9.45/9.66 ppm is due to quinoline-3H proton. The mass spectrum of compounds **1** and **9** showed a molecular ion peak at M^{+}, which is in agreement with the molecular formula.

The IR spectra of all α,β-unsaturated carbonyls (**2** and **10**) showed the characteristic peaks of particular carbonyl functional groups of enones in the region of ~1672-1682 cm^{-1}, and ~3060-3049 cm^{-1} stretching vibration for H-C bond of Cα=Cπ. The ^{1}H NMR spectra of α,β-unsaturated carbonyls showed characteristic of signals for α,β-protons at δ 7.22-8.10 ppm, this refers to the effect of resonance of the phenyl rings that bonded to β-carbon atom. The ^{13}C NMR spectra assignment of carbon atoms presented in α,β-unsaturated carbonyl derivatives showed the characteristic peak related to the α-C atom around δ ~131.25-134.84 ppm which was more deshielded than that of β-C atom approximately at δ ~119.99-121.69 ppm. Mass spectra of α,β-unsaturated carbonyls, showed the M^{+} consistent with their molecular formula of α,β-unsaturated carbonyls.

The structure of the pyrimidinones and pyrimidinthiones characteristic by IR spectra which showed the disappearance of two absorption bands and appearance of new absorption bands for NH, C=O and C=S groups around 3015-3210 cm^{-1}, ~1672 and ~1365 cm^{-1}, respectively. The ^{1}H NMR spectrums of compounds **3**, **4**, **11** and **12**, showed the singlet signal at δ 5.73-5.96 ppm due to the proton of CH-pyrimidinone and at δ 6.17 ppm for CH-pyrimidinthione. Also, singlet broad signal one proton of NH group appeared as δ 10.02 ppm. Further, ^{13}C NMR spectra exhibited confirmatory signals of the methyl carbon C5 around δ 101.05-112.12 ppm. Mass spectra exhibited molecular ion peak [M^{+}+2], appeared at different intensities, and confirmed the exact mass or molecular weights of the examined compounds **3**, **4**, **11** and **12**.

In the IR spectra of pyrazolines (**5**, **6**, **7**, **13**, **14** and **15**) appeared strong band at 1501-1520 cm^{-1} for C=N stretching vibration, beside the appearance of above bands, the most important evidence for the formation of 2-pyrazoline is the disappearance of carbonyl group band at 1672-1682 cm-^{1} special for the α,β-unsaturated carbonyl moiety. The ^{1}H NMR spectra of pyrazolines showed characteristic signals corresponding to the protons of C4 and C5 of 2-pyrazoline ring; they appearance of three doublet to doublet (dd) signals approximately at δ 3.63-5.05 ppm for each compound. The ABX type spin system pattern [22] of proton appeared as a doublet of doublets due to vicinal coupling with the two magnetically non-equivalent protons (H_A and H_B) of methylene at position 4 and methine proton (H_X) at position 5 in pyrazoline ring. The ^{13}C NMR spectra of pyrazolines, showed three signals approximately at δ 63.31-63.29, 39.95-41.27, 51.01-58.11 ppm belongs to C3, C4 and C5 for pyrazoline carbons (see Figure 1 for the carbon numbering). Mass spectra of pyrazolines showed the [M^{+}+2] confirmed with their molecular formula of pyrazoline derivatives.

The IR spectra of 1,4-oxazepines (**8** and **16**) showed typical peaks at ~1505-1509 cm^{-1} for C=N stretching vibration and at ~1216-1227 cm^{-1} for ethers. These peaks confirmed us that 1,4-oxazepines rings were formed. ^{1}H NMR spectra of compounds **8** and **16** showed similar effects on the chemical shifts of the pyrazoline protons signal of three doublet to doublet (dd) signals approximately at δ ~3.25-5.01 ppm for each compound due to the ABX spin pattern of two protons of methylene at position 6 and methine proton at position 7 in 1,4-oxazepine ring. The characteristic two triplet signals at δ ~3.61-3.63 and 3.73-3.83 ppm for each methylene protons in position 2 and 3 in 1,4-oxazepines ring. The ^{13}C NMR spectra of 1,4-oxazepines showed the signal for C2, C3 and C6 of the seven-membered ring appear in the range of δ 58.71, 45.44 and 30.96 ppm, respectively (see Figure 2 for the carbon numbering). Mass spectra of compounds **8** and **16** appear peak [M^{+}+2] and M^{+} these were consistent with product structures.

4. Conclusion

In this manuscript, we present the successful synthesis of some new heterocyclic compounds of 2,3-diaryl-quinoline-4-carboxylic acid as the core with good yields. The detail assignments of these compounds have been discussed by IR, ^{1}H NMR, ^{13}C NMR, and LC-MS spectra. Synthesis results of this work gave pyrimidinone/thione, pyrazoline, and oxazepine rings from α,β-unsaturated carbonyls could be useful for other chemists working on the field of heterocycles quinoline synthesis.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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