Organic Chemistry
Current Research
ISSN: 2161-0401

El-Gamal, Organic Chem Curr Res 2016, 5:2
DOI: 10.4172/2161-0401.1000168

Research Article Open Access

Synthesis and Antimicrobial Evaluation of Polyfunctionally Heterocyclic Compounds Bearing Quinoline Moiety

Kamal M El-Gamal*

Organic Chemistry Department, Al-Azher University, Naser City, Cairo, 11884, Egypt

Abstract

2-Aminoquinoline-3-carbonitrile 2 was reacted with ethylcyanoacetate to give 3. The latter was used to synthesize different heterocyclic derivatives comprising pyridine, coumarin, pyrimidine, thiophene, and thiazole rings. The synthetic methods depended on regioselective attack and/or cyclization by the cyanoacetamido moiety as a key compound on various chemical reagents. The competition of the reaction pathways including dipolar cyclization, dinucleophilic-bielectrophilic attack, and β-attack that leads to the diversity of the synthesized products. All these newly synthesized compounds were characterized by elemental analysis and spectral data, and screened for their antimicrobial activity.

Keywords: 2-aminoquinoline-3-carbonitrile; Pyridine; Coumarin; Pyrimidine; Thiophene; Thiazole; Antimicrobial activity

Introduction

Quinoline nucleus is often used for the design of many synthetic compounds with diverse pharmacological properties [1]. Quinoline and its derivatives are receiving important due to their wide range of biological activities as antitumor [2], antibacterial [3], anticonvulsant [4], analgesic [5], antiallergic [6], antiamoebic [7]. In addition it also exhibit good antimalarial [8], antihistaminic [9], antitubercular [10], and antineurodegerative activity [11]. In our work, the ring anillation of quinoline to amino that was converted into cyanoactamide moiety and the latter was used to synthesize different heterocyclic derivatives comprising thiophene, thiazole, pyridine, pyrimidine, and coumarin rings that exhibit some interesting pharmacological activities [12]. Further, the mechanistic and synthetic pathways depended on cyclization by the cyanoactamide moiety as the key precursor on various chemical reagents. The simplicity of the synthetic procedures mainly involved reactions under mild conditions, and convenience of yield production. The newly synthesized compounds were evaluated for their antimicrobial activity.

Experimental

General

Melting points were measured in capillary tube on a Graffin melting point apparatus and are uncorrected. The IR spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer using KBr discs (λ max in cm^{-1}). ^{1}H NMR spectra were performed on Gemini 300BB (300 MHz), and 300 MHz for ^{13}C NMR) spectrometer, using TMS as internal standard and DMSO-d6 as solvent; the chemical shifts are reported in ppm (δ) and coupling constant (J) values are given in Hertz (Hz). Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). All of the new compounds were analyzed for C, H and N and agreed with the proposed structures within ± 0.4% of the theoretical values by the automated CHN analyzer. Mass spectra were recorded on Hewlett Packard 5988 spectrometer at the RCMB. The purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F 254 precoated sheets. All analyses were performed at the Micro-analytical Unit of Cairo University, Cairo, Egypt.

Chemistry

2-Aminoquinoline-3-carbonitrile (2): To the well stirred solution of 2-chloroquinoline-3-carbonitrile [13-16] (1) (1.88 g, 0.002 mmol) and tetrabutylammonium bromide (0.202 g, 0.0005 mmol), chlorobenzene (15 mL) and sodium azide (0.39 g, 0.006 mol) in water (5 mL) were added and the reaction mixture was stirred under reflux for 1.5 hrs., at completion of time powdered sodium borohydride (0.302 g, 0.008 mmol) was added to the reaction mixture portion wise cautiously over a period of 30 mint. The same reaction mixture was then refluxed for 2-3 hrs. On completion (TLC) the aqueous phase was separated and extracted with chlorobenzene, and combined organic layer was washed with water and drying using anhydrous sodium sulphate. The solvent was recovered under vacuum, the content was treated with n-hexane and the solid thus formed was filtered, washed with cold methanol, dried and crystalized from methanol: chloroform (7:3 V/V). Our procedure differs from the reported [17-19] one but it modifies the other one [20] to get the compound 2 according to the preferred procedure [21].

Yield 75%, M.p. 228-230°C. IR (KBr, ν, cm^{-1}): 3350, 3296, 2972, 2865, 2215. ^{1}H NMR (300 MHz, [D6] DMSO): δ = 6.54(s, 2H, NH_2), 7.19-7.23 (t, 1H, C6-H quinoline), 7.42-7.46 (t, 1H, C7-H quinoline), 7.59-6.62 (d, 1H, C5-H quinoline), 7.76-7.80 (d, 1H, C8-H quinoline), 8.36 (s, 1H, C4-H quinoline). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 84.6 (C-3), 117.7 (CN), 119.4, 122.3, 125.1, 127.2, 132.7 (Ar-C), 153.9 (C-8), 156.8 (C-4), 164.1 (C-2). MS (m/z): 169.18 (23, M+). Analytically calculated for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found. C, 71.10; H, 4.44; N, 24.91.

2-Cyano-N-(3-cyanoquinolin-2-yl) acetamide (3): To a solution of 2-aminoquinoline-3-carbonitrile (2) (1.69 g, 0.01 mmol) in dimethylformamide (30 mL), ethyl cyanoacetate (1.13 g, 0.01 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solid product formed upon pouring onto ice/water mixture was collected by filtration and crystallized from 1, 4-dioxane.

***Corresponding author:** Kamal M El-Gamal, Organic Chemistry Department, Al-Azher University, Naser City, Cairo, 11884, Egypt, Tel: +20235333442; E-mail: drkamalelgaml72@gmail.com

Received: August 20, 2016; **Accepted:** September 16, 2016; **Published:** September 25, 2016

Citation: El-Gamal KM (2016) Synthesis and Antimicrobial Evaluation of Polyfunctionally Heterocyclic Compounds Bearing Quinoline Moiety. Organic Chem Curr Res 5: 168. doi: 10.4172/2161-0401.1000168

Yield 71%, M.p. 129-130°C. IR (KBr, ν, cm^{-1}): 3332, 3020, 2837, 2265, 2195 (2CN), 1655. ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.28 (s, 2H, CH_2), 6.83 (s, 1H, NH), 7.19-7.23 (t, 1H, C6-H quinoline), 7.55-7.58 (t, 1H, C7-H quinoline), 7.62-7.65 (d, 1H, C5-H quinoline), 7.73-7.77 (d, 1H, C8-H quinoline), 8.27 (s, 1H, C4-H quinoline). MS (m/z): 236.23 (12.15, M+). Analytically calculated for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72. Found. C, 65.89; H, 3.57; N, 23.66.

Synthesis of 3-cyanoquinolin-2-yl functionalized 2-pyridone derivatives (4a-d): To a solution of 3 (2.36 g, 0.01 mmol) in 1,4-dioxane (25 mL) and dimethylformamide (5 mL) containing triethylamine (1.00 mL), either malononitrile (0.66 g, 0.01 mmol) or ethyl cyanoacetate (1.13 g, 0.01 mmol), acetyl acetone (1.00 g, 0.01 mmol) or ethyl acetoacetate (1.33 g, 0.01 mmol) was added. The reaction mixture, in each case, was heated under reflux for 5 h, then cooled and neutralized by pouring onto ice/water mixture containing few drops of hydrochloric acid. The solid products formed, in each case, was filtered off and crystallized from 1, 4-dioxane/dimethylformamide mixture (3:2).

2-(4,6-Diamino-3-cyano-2-oxopyridin-1(2H)-yl) quinoline-3-carbonitrile (4a): Yield 77%, M.p. 198-199°C. IR (KBr, ν, cm^{-1}): 3335, 3270 ($2NH_2$), 3075, 2832, 2242, 2198(2CN), 1625. ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ=2.95, 2.99 (2s, 4H-$2NH_2$, D_2O exchangeable), 7.69 (s, 1H, C5-H pyridine), 7.22-7.26 (t, 1H, C6-H quinoline), 7.52-7.55 (t, 1H, C7-H quinoline), 7.60-7.63 (d, 1H, C5-H quinoline), 7.78-7.83 (d, 1H, C8-H quinoline), 8.45 (s, 1H, C4-H quinoline). MS (m/z): 302.29 (9.18, M+). Analytically calculated for $C_{16}H_{10}N_6O$: C, 63.57; H, 3.33; N, 27.80. Found. C, 63.31; H, 3.56; N, 27.90.

2-(4-Amino-3-cyano-6-hydroxy-2-oxopyridin-1(2H)-yl) quinoline-3-carbonitrile (4b): Yield 63%, M.p. 235-237°C. IR (KBr, ν, cm^{-1}): 3479 (OH), 3337 (NH_2), 3099, 2840, 2229, 2195(2CN), 1658. ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ=4.24 (s, 2H-NH_2 D_2O exchangeable), 6.45 (s, 1H, C5-H pyridine), 7.29-7.32 (t, 1H, C6-H quinoline), 7.57-7.60 (t, 1H, C7-H quinoline), 7.64-7.66 (d, 1H, C5H quinoline), 7.80-7.84 (d, 1H, C8-H quinoline), 8.66 (s, 1H, C4-H quinoline), 11.73(s, 1H, OH, D_2O exchangeable). MS (m/z): 303.27 (16.5, M+). Analytically calculated for $C_{16}H_9N_5O_2$: C, 63.37; H, 2.99; N, 23.09. Found. C, 63.65; H, 3.04; N, 22.87.

2-(3-Cyano-4, 6-dimethyl-2-oxopyridin-1(2H)-yl) quinoline-3-carbonitrile (4c): Yield 70%, M.p. 158-160°C. IR (KBr, ν, cm^{-1}): 3102, 2842, 2242, 2198(2CN), 1625. ^{1}H NMR (300 MHz, [D6] DMSO): δ = 2.21, 2.34 (2s, 6H, 2CH3), 6.55 (s, 1H, C5-H pyridine), 7.17-7.20 (t, 1H, C6-H quinoline), 7.41-7.44 (t, 1H, C7- H quinoline), 7.69-7.72 (d, 1H, C5-H quinoline), 7.80-7.82 (d, 1H, C8-H quinoline), 8.33 (s, 1H, C4-H quinoline). MS (m/z): 300.31 (4.11, M+). Analytically calculated for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found. C, 71.95; H, 4.24; N, 18.77.

2-(3-Cyano-6-hydroxy-4-methyl-2-oxopyridin-1(2H)-yl) quinoline-3-carbonitrile (4d): Yield 60%, M.p. 213-214°C. IR (KBr, ν, cm^{-1}): 3482 (OH), 3104, 2822, 2212, 2188(2CN), 1633. ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ = 2.43 (s, 3H, CH3), 6.83 (s, 1H, C5-H pyridine), 7.29-7.32 (t, 1H, C6-H quinoline), 7.50-7.53(t, 1H, C7-H quinoline), 7.64-7.67 (d, 1H, C5-H quinoline), 7.76-7.81 (d, 1H, C8-H quinoline), 8.39 (s, 1H, C4-H quinoline), 12.02(s, 1H, OH D_2O exchangeable). MS (m/z): 302.29 (7.09, M+). Analytically calculated for $C_{17}H_{10}N_4O_2$: C, 67.55; H, 3.33; N, 18.53. Found. C, 67.48; H, 3.22; N, 18.19.

Synthesis of the amide derivatives 5 and 6: To a solution of 3 (2.36 g, 0.01 mmol) in 1,4-dioxane (25 mL) containing piperidine (1.00 mL) salicylaldehyde (1.22 g, 0.01 mmol) or benzaldehyde (1.06 g, 0.01 mmol) was added. The reaction mixture in each case was heated under reflux for 5 h. The solid products formed upon pouring onto ice-water mixture containing few drops of hydrochloric acid was collected by filtration and crystallized from 1,4-dioxane.

N-(3-cyanoquinolin-2-yl)-2-oxo-2H-chromene-3-il-carboxamide (5): Yield 64%, M.p. 256-257°C. IR (KBr, ν, cm^{-1}): 3355, 3101 2855, 2215, (CN), 1722 1660(2C=O). ^{1}H NMR (300 MHz, [D6] DMSO-D_2O): δ = 6.97 (s, 1H, C4-H coumarin), 7.02-7.80 (m, 8H), 8.12 (s, 1H, C4-H quinoline), 8.90 (s, 1H, NH D_2O exchangeable). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 44, 95.1, 114.1, 116.8, 118.7, 121.8, 122.5, 124, 125.1, 125.4, 127, 127.2, 128.1, 131.9, 138.5, 147.3, 150.4, 159.3 (O-C=O), 163, 167. MS (m/z): 300.31 (10.6, M+). Analytically calculated for $C_{20}H_{11}N_3O_3$: C, 70.38; H, 3.25; N, 12.31. Found. C, 70.14; H, 3.07; N, 12.22.

2-Cyano-N-(3-cyanoquinolin-2-yl)-3-phenylacrylamide (6): Yield 86%, M.p. 122-123°C. IR (KBr, ν, cm^{-1}): 3339(NH), 3078 2849, 2255, 2203 (2CN), 1640(C=O). ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ= 6.45 (s, 1H, NH D_2O exchangeable), 7.00-8.11 (m, 9H), 8.25 (s, 1H, C4-H quinoline), 8.57 (s, 1H, benzylidene CH). MS (m/z): 324.34 (17.1, M+). Analytically calculated for $C_{20}H_{12}N_4O$: C, 70.06; H, 3.73; N, 17.27. Found. C, 70.17; H, 3.99; N, 17.36.

4-Amino-2-hydroxybenzo[b] [1,8] naphthyridine-3-carbonitrile (7): A solution of 3 (2.36 g, 0.01 mmol) in 1, 4-dioxane (20 mL) containing triethylamine (2 mL) was heated under reflux for 5 h. The solid product formed upon pouring onto ice/water was collected by filtration, and crystallized from 1, 4-dioxane.

Yield 63%, M.p. 110-111°C. IR (KBr, ν, cm^{-1}): 3444 (OH, enol form), 3337, 3215 (NH_2, NH), 3104, 2838, 2199 (CN), 1622(C=O, keto form). ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ = 3.71 (s, 2H-NH_2 D_2O exchangeable), 5.13 (s, 1H, OH, D_2O exchangeable), 7.29- 8.66 (m, 5H, quinoline). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 85.2, 116.9, 120.1, 126.8, 128.2, 129.9, 130.1, 136.5, 147.1, 159, 160.2, 166.1(C-OH). MS (m/z): 236.23 (3.9, M+). Analytically calculated for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72. Found. C, 66.25; H, 3.27; N, 23.80.

Synthesis of 3-cyanoquinolin-2-yl functionalized pyridone derivatives (8a, b): To a solution of 6 (3.24 g, 0.01 mmol) in 1,4-dioxane (25 mL) and dimethylformamide (5 mL) containing triethylamine (1.00 mL), either malononitrile (0.66 g, 0.01 mmol) or ethyl cyanoacetate (1.13 g, 0.01 mmol) was added. The reaction mixture, in each case, was heated under reflux for 5 hours then cooled and neutralized by pouring onto ice/water mixture containing few drops of hydrochloric acid. The solid products formed, in each case, was filtered off and crystallized from ethanol 95%.

Ethyl 2-amino-5-cyano-1-(3-cyanoquinolin-2-yl)-1,6-dihydro -6-oxo-4-phenyl-pyridine-3-carboxylate (8a): Yield 82%, M.p. 268-269°C. IR (KBr, ν, cm^{-1}): 3320 (NH_2), 3063, 2851, 2216, 2192 (2CN), 1687, 1635 (2C=O). ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ = 1.16 (t, J = 8.00 Hz, 3H, CH3), 3.81 (s, 2H, NH_2 D_2O exchangeable), 4.28 (q, J = 8.00 Hz, 2H, CH_2), 7.20-7.22 (t, 1H, C6-Hquinoline), 7.45-7.48(t, 1H, C7-H quinoline), 7.60-7.62 (d, 1H, C5-H quinoline), 7.79-7.82 (d, 1H, C8-H quinoline), 8.50 (s, 1H, C4-H quinoline). MS (m/z): 435.43 (14.15, M+). Analytically calculated for $C_{25}H_{17}N_5O_3$: C, 68.96; H, 3.94; N, 16.08. Found. C, 68.80; H, 4.01; N, 16.12.

6-Amino-1-(3-cyanoquinolin-2-yl)-2-oxo-4-phenyl-1, 2-dihydropyridine-3, 5-dicarbonitrile (8b): Yield 70%, M.p. 273-274°C. IR (KBr) cm^{-1}: 3311 (NH_2), 3092, 2251, 2222, 2203 (3CN), 1631 (C=O). ^{1}H NMR (300 MHz, [D6] DMSO- D_2O): δ = 3.97 (s, 2H, NH_2 D_2O exchangeable), 7.29-7.31 (t, 1H, C6-H quinoline), 7.41-7.44 (t, 1H, C7-H quinoline), 7.65-7.68 (d, 1H, C5-H quinoline), 7.77-7.80 (d, 1H, C8-H quinoline), 8.62 (s, 1H, C4-H quinoline). MS (m/z): 338.38 (3.7, M+). Analytically calculated for $C_{23}H_{12}N_6O$: C, 71.13; H, 3.11; N, 21.64. Found. C, 71.50; H, 3.05; N, 21.59.

Synthesis of pyrazole carboxamide derivatives (9a, b): To a solution of compound 6 (3.24 g, 0.01 mmol) in 1, 4-dioxane (25 mL) and dimethylformamide (10mL), either hydrazine hydrate 90% (0.50 g, 0.01 mmol), or phenyl hydrazine (1.08 g, 0.01 mmol) was added. The reaction mixture, in each case, was heated under reflux for 3 h. The solid products formed, in each case, upon pouring onto ice/water mixture containing few drops of hydrochloric acid were collected by filtration, and crystallized from 1, 4-dioxane/dimethylformamide mixture (3:2).

3-Amino-N-(3-cyanoquinolin-2-yl)-5-phenyl-1H-pyrazole-4-carboxamide (9a): Yield 70%, M.p. 197-199°C. IR (KBr, ν, cm^{-1}): 3421, 3267 (NH_2, 2NH), 3086, 2836, 2206 (CN), 1627 (C=O). ^1H NMR (300 MHz, [D6] DMSO- D_2O): δ = 3.93 (s, 2H-NH_2 D_2O exchangeable), 6.89 (s, 1H, NH D_2O exchangeable), 7.23-8.52 (m, 10H, quinoline and phenyl), 8.72 (s, 1H, NH exchangeable with D_2O). MS (m/z): 354.36 (22.20, M+). Analytically calculated for $C_{20}H_{14}N_6O$: C, 67.79; H, 3.98; N, 23.72. Found. C, 67.71; H, 3.92; N, 23.81.

3-Amino-N-(3-cyanoquinolin-2-yl)-1, 5-diphenyl-1H-pyrazole-4-carboxamide (9b): Yield 82%, M.p. 137-138°C. IR (KBr, ν, cm^{-1}): 3419, 3250 (NH_2, NH), 3099, 2843, 2214 (CN), 1623 (C=O). ^1H NMR (300 MHz, [D6] DMSO- D_2O): δ = 3.96 (s, 2H-NH_2, D_2O exchangeable), 7.39 (s, 1H, NH, D_2O exchangeable), 7.11- 8.46 (m, 15H, quinoline and 2 phenyl). MS (m/z): 430.46 (15.60, M+). Analytically calculated for $C_{26}H_{18}N_6O$: C, 72.55; H, 4.21; N, 19.52. Found. C, 72.63; H, 4.39; N, 19.80.

2-Cyano-N-(3-cyanoquinolin-2-yl)-2-(2-phenylhydrazono) acetamide (10): To a cold solution (0-5°C) of 3 (2.36 g, 0.01 mmol), in absolute ethanol (20 mL) containing sodium hydroxide (1.00 g) an equimolar amount of cold solution diazotized aniline was gradually added while stirring. The solid product formed upon cooling in an ice-bath was filtered, washed with water and crystallized from 1, 4-dioxane.

Yield 60%, M.p. 147-148°C. IR (KBr, ν, cm^{-1}): 3359, 3221 (2NH), 3121, 2871, 2253, 2205 (2CN), 1685 (C=O). ^1H NMR (300 MHz, [D6] DMSO): δ = 7.34- 8.59 (m, 10H, quinoline and phenyl), 9.18 (s, 1H, NH), 11.02 (s, 1H, NH) MS (m/z): 340.34 (40.11, M+). Analytically calculated for $C_{19}H_{12}N_6O$: C, 67.05; H, 3.55; N, 24.69. Found. C, 67.11; H, 3.40; N, 24.81.

2-(4-Amino-6-oxo-3-phenyl-2-thioxo-2, 3-dihydropyrimidin-1(6H)-yl) quinoline-3-carbonitrile (11): Equimolar amounts of 3 (2.36 g, 0.01 mmol) and phenyl isothiocyanate (1.35 g, 0.01 mmol) in 1,4-dioxane (20 mL) containing triethylamine (1.0 mL) were heated under reflux for 7. After cooling, the reaction mixture was acidified by hydrochloric acid (few drops) and the crude product was precipitated, collected by filtration and crystallized from 1, 4-dioxane.

Yield 80%, M.p. 256-257°C. IR (KBr, ν, cm^{-1}): 3437, 3232 (NH_2), 3072, 2827, 2205 (CN), 1618(C=O). ^1H NMR (300 MHz, [D6] DMSO-D_2O): δ = 3.97 (s, 2H, NH_2, exchangeable with D_2O), 6.99 (s, 1H, C5-H pyrimidine), 7.01- 8.53 (m, 10H, quinoline and phenyl). ^{13}C NMR (DMSO-d6) δ: 44.4, 72.9, 95.3, 117.1, 120, 124, 124.9, 125.2, 126.4 (2C), 127.2, 129.2 (2C), 132.1, 134.5, 147.8, 166.2, 166.6 (C-NH_2), 167, 177.3. MS (m/z): 371.42 (9.10, M+). Analytically calculated for $C_{20}H_{13}N_5O$ S: C, 64.68; H, 3.53; N, 18.86. Found. C, 64.66; H, 3.59; N, 18.90.

Synthesis of 3-cyanoquinolin-2-yl- functionalized thiophene derivative (12) and thiazole derivative (13): Equimolar amounts of 3 (2.36 g, 0.01 mmol) and phenyl isothiocyanate (1.35 g, 0.01 mmol) in dimethylformamide (20 mL) and potassium hydroxide were stirred overnight, then added ethylchloroacetate (1.22 g, 0.01 mmol) or chloroacetone (0.92 g, 0.01 mmol) while stirring were continued for 20 h. The products formed upon pouring onto ice/water mixture containing few drops of hydrochloric acid were collected by filtration and crystallized from ethanol 95% to afford compound 12 and 13 respectively.

Ethyl 3-amino-4-((3-cyanoquinolin-2-yl) carbamoyl)-5-(phenylamino) thiophene-2-carboxylate (12): Yield 80%, M.p. 124-125°C. IR (KBr, ν, cm^{-1}): 3338, 3219 (2NH, NH_2), 3058, 2834, 2209 (CN), 1702, 1632(2C=O). ^1H NMR (300 MHz, [D6] DMSO- D_2O): δ = 1.24 (t, J = 9.00 Hz, 3H, CH3), 4.09 (q, J = 9.00 Hz, 2H, CH_2), 4.33 (s, 2H, NH_2, exchangeable with D_2O), 6.97 (s, 1H, NH, exchangeable with D_2O), 7.17- 8.60 (m, 10H, quinoline and phenyl), 9.90 (s, 1H, NH, exchangeable with D_2O), MS (m/z): 457.50 (13.12.10, M+). Analytically calculated for $C_{24}H_{19}N_5O_3S$: C, 63.01; H, 4.19; N, 15.31. Found. C, 63.22; H, 4.12; N, 15.30.

2-Cyano-N-(3-cyanoquinolin-2-yl)-2-(4-methyl-3-phenyl-3H-thiazol-2-ylidene) acetamide (13): Yield 80%, M.p. 124-125°C. IR (KBr, ν, cm^{-1}): 3377 (NH), 3061, 2840, 2202, 2160 (2CN), 1641(C = O). ^1H NMR (300 MHz, [D6] DMSO): δ = 1.39 (s, 3H, CH3), 6.83 (s, 1H, C5 –H thiazole), 7.29- 8.53 (m, 10H, quinoline and phenyl), 9.70 (s, 1H, NH). MS (m/z): 409.46 (6.50, M+). Analytically calculated for $C_{23}H_{15}N_5OS$: C, 67.47; H, 3.69; N, 17.10. Found. C, 67.55; H, 3.73; N, 17.00.

Synthesis of 3-cyanoquinolin-2-yl- functionalized 3-phenylazo-2-pyridone derivatives (14a, b): To a solution of 10 (3.40 g, 0.01 mmol) in absolute ethanol (25 mL) and dimethylformamide (5 mL) containing triethylamine (1.00 mL), either of ethyl cyanoacetate (1.13 g, 0.01 mmol) or malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 7 h, then cooled and neutralized by pouring onto ice/water mixture containing few drops of hydrochloric acid. The solid products formed, in each case, was filtered off and crystallized from ethanol/dimethylformamide mixture.

Ethyl 2, 4-diamino-1-(3-cyanoquinolin-2-yl)-6-oxo-5-(phenyldiazenyl)-1, 6-dihydropyridine-3-carboxylate (14a): Yield 65%, M.p. 161-162°C. IR (KBr, ν, cm^{-1}): 3359, 3230 (2NH_2), 3070, 2852, 2208 (CN), 1722, 1625 (2C = O). ^1H NMR (300 MHz, [D6] DMSO- D_2O): δ = 1.21 (t, J = 9.30 Hz, 3H, CH3), 3.16, 3.23 (2s, 2H each, 2NH_2 D_2O exchangeable), 4.10 (q, J = 9.30 Hz, 2H, CH_2), 7.23- 8.66 (m, 10H, quinoline and phenyl), MS (m/z): 453.45 (7.3, M+). Analytically calculated for $C_{24}H_{19}N_7O_3$: C, 63.57; H, 4.22; N, 21.62. Found. C, 63.45; H, 4.28; N, 21.94.

2-(2, 4-Diamino-3-cyano-6-oxo-5-(phenyldiazenyl)-1, 6-dihydropyridine)-3-cyanoquinoline (14b): Yield 65%, M.p. 208-209°C. IR (KBr) cm^{-1}: 3358, 3240 (2NH_2), 3087, 2834, 2251, 2204(2CN), 1671(C = O). ^1H NMR (300 MHz, [D6] DMSO- D_2O): δ = 3.19, 3.45 (2s, 2H each, 2NH_2, D_2O exchangeable), 7.20- 8.46 (m, 10H, quinoline and phenyl), MS (m/z): 406.46 (8.5, M+). Analytically calculated for $C_{22}H_{14}N_8O$: C, 65.02; H, 3.47; N, 27.57. Found. C, 65.11; H, 3.56; N, 27.36.

Antimicrobial Activity

All newly synthesized compounds were test for their *in vitro* growth inhibitory activity against a standard strain of two gram positive bacteria viz., *Bacillus subtilis, Staphylococci aureus* and two gram negative bacteria viz., *Escherichia coli*, *Pseudomonas aeruginosa*, in addition to fungi (*Candida albicans*). Antibacterial activity was done by the disk diffusion method. Were the bacteria and fungi sub cultured in BHI medium and incubated for 18h at 37°C, and then the bacterial cells were suspended according to the McFarland protocol in saline solution to produce a suspended of about 10-5CFU ml 1:10 µ of this suspension was mixed with 10 ml of sterile antibiotic agar at 40°C and poured onto an agar plate. Five paper disks (6.0 mm diameter) were fixed onto nutrient agar plate. The solutions of different compounds under test at a concentration of 500 in 5% DMSO were poured in the cup/well of bacteria seeded agar plates. These plates were incubated at 37°C for 24 hours for E. coli and fungi for 4 days at 27°C, whereas plates of other three bacteria were incubated at 27°C for 24 hr. The standard antibiotics used were *streptomycin* (all at 500 µg/ml) and standard antifungal used were fluconazole at 500 µg/ml, the control solution (only 5% DMSO) did not reveal any inhibition. The zone of inhibition produced by each compound was measured in mm.µg/ml. The results of antimicrobials studies are given in Table 1. The discussion and comparison of antibacterial activity were given with respect to *streptomycin* antibiotic and antifungal screening was compared with fluconazole.

Results and Discussion

The synthetic method adopted to obtain the newly synthesized compound 2 that was prepared by nucleophilic substitution depending on modification of the reported [20] procedure. Where we are going to development of efficient protocols for the preparation of biologically active heterocyclic derivatives along with the versatility of the organic synthon [21]. We herein report the synthesis of 2-aminoquinoline-3-carbonitrile (2) and the strategy depend on an efficient one-pot via in situ generation of tetrazoloquinoline, on contrast to other procedure involving separation then thermal decomposition of formed tetrazole [28] in addition, to other procedure involving harsh conditions [22-26]. We elected to examine the conversion of 1 into 2 with the goals of optimizing reaction conditions under liquid-liquid phase-transfer conditions using chlorobenzene and water as solvent and tetrabutylammonium bromide as catalyst (Figure 1), depending on activated aromatic systems such chloro [27] and a few heteroaromatic systems [27] that can undergo nucleophilic substitution by azide ions. Chloro functionality in 2-position of quinoline-3-carbonitrile [13-16] was found to be labile towards nucleophilic substitution reactions [20,21], so by addition of sodium azide to this chloro functionality in 2-position it forms heterocyclic azide that spontaneously cyclized to give the fused tetrazole form. It well be reported that tetrazole are lipophilic, metabolically stable compounds [28]. In our literature tetrazole can be synthesized directly by a [3+2] dipolar cycloaddition between organoazide and C=N of quinoline ring this reaction occurs through a concerted and regioselective [29,30] [3+2] cycloaddition. It's well-known that phase transfer catalyst technique shows the novelty of using sodium borohydride [31] as an efficient reducing agent for tetrazoles, to afford pure product in high yields and offers the advantages of permitting a one-pot conversion of 1 into 2 with very simple operative conditions. Thus, in a modified procedure, synthetic strategies based on phase transfer catalyst were adopted and evaluated for the cleavage of tetrazoloquinoline intermediate A (Figure 2) keeping sodium borohydride as a reducing agent [31]. In liquid-liquid phase-transfer conditions, tetrabutylammonium bromide was used as catalyst and chlorobenzene together with water (3:1) was preferred as solvent. Chlorobenzene was used as a solvent to elevate the reaction temperature 20°C higher than bromobenzene [28]. The higher temperature of the reaction mixture facilitates thermal decomposition of tetrazole intermediate that enhanced by using water and it showed unimolecular N_2 elimination [32] to produce intermediate B (Figure 3) and this elimination was affected by no tetrazole ring substituent are placed 33. Association of liquid-liquid phase-transfer catalyst with azidolysis by using chlorobenzene and water as solvents proved to be cleaner, rate enhancing and yield improving as compared to direct conversion of chloro to amino functionality under harsh conditions [31-35]. In contrast azidolysis followed by reduction facilitate the indirect amination. Thus azide and tetrazole formation followed by reduction can be viewed a best pathway as latent amino functionalities. The generality of this reaction has been shown by the formation of tetrazole intermediate A (Figure 3) in good yields according to the reported [28] procedure but in this letrature we aimed to formation of tetrazole in situ that exposed to higher temperature condition where it targeted the use of chlorobenzene due to its higher temperature than other solvent as bromobenzene and in this stage the elevated temperature cause decomposition of formed tetrazole then comes the role of water in the reaction where it cause azidolysis of intermediate B (Figure 3) and this accompanied by N_2 elmination then comes the role of catalyst where

Compound No	Concentration (mg/l)	Microorganism (Inhibition zone)				
		Basillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
2	500	12	12	11	14	15
3	500	11	13	14	12	6
4a	500	12	10	10	12	12
4b	500	11	12	12	13	14
4c	500	7	13	12	11	12
4d	500	9	14	14	8	12
5	500	13	6	16	10	11
6	500	7	14	13	12	12
7	500	12	11	08	15	9
8a	500	14	13	17	16	14
8b	500	16	14	15	12	16
9a	500	9	15	13	14	13
9b	500	8	9	14	11	10
10	500	12	12	12	8	8
11	500	15	13	16	6	15
12	500	10	8	12	12	8
13	500	9	11	14	13	6
14a	500	16	17	15	14	16
14b	500	15	16	15.5	15	17
Streptomycin	500	25.0	25.7	25.0	25.80	-
Fluconazole	500	-	-	-	-	20.5

Table 1: Antimicrobial activity of synthesized 3-cyanoquinolin-2-yl-functionalized derivatives.

Citation: El-Gamal KM (2016) Synthesis and Antimicrobial Evaluation of Polyfunctionally Heterocyclic Compounds Bearing Quinoline Moiety. Organic Chem Curr Res 5: 168. doi: 10.4172/2161-0401.1000168

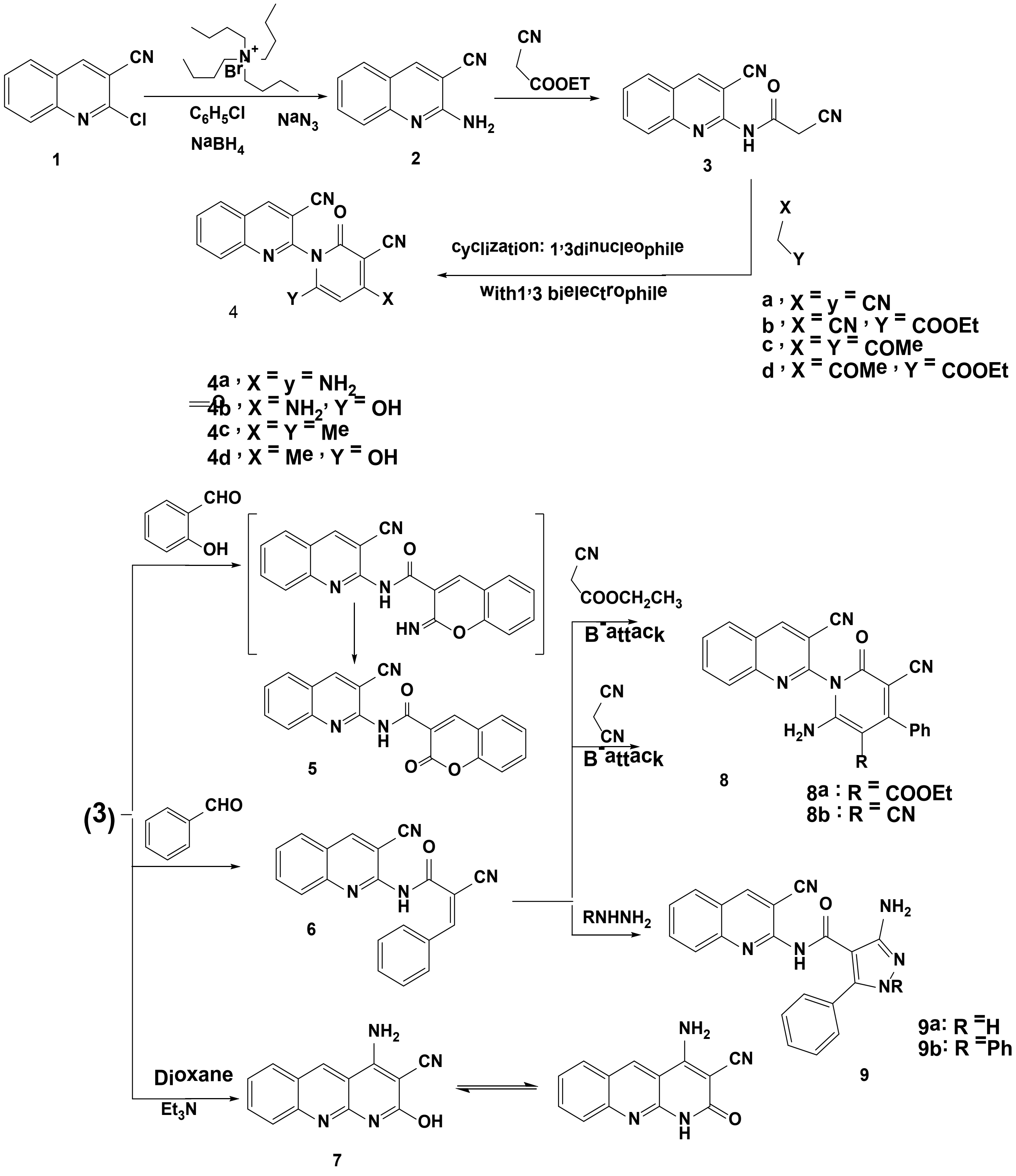

Figure 1: General synthetic route to new derivatives 4-9.

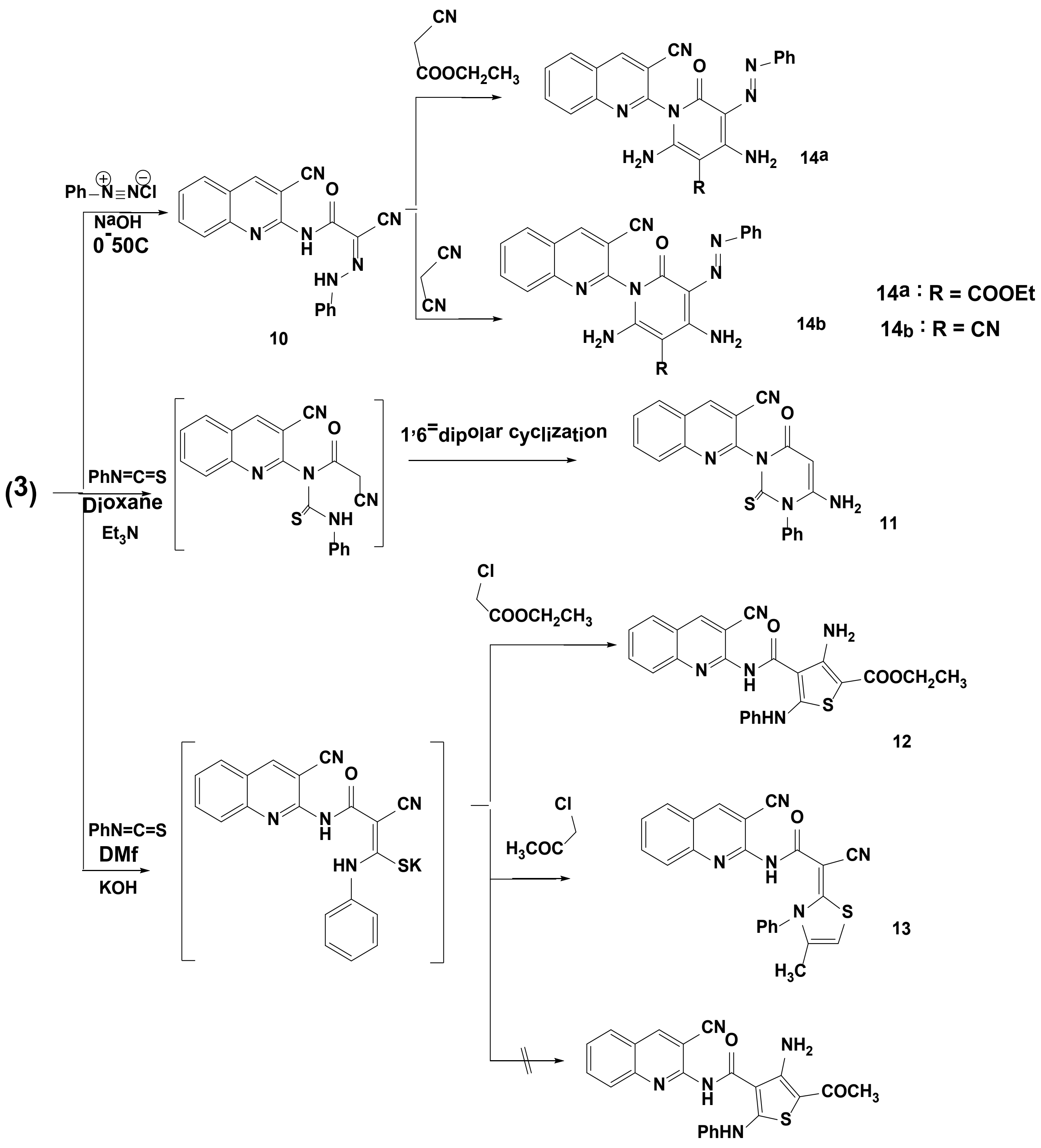

Figure 2: General synthetic route to new derivatives 10-14.

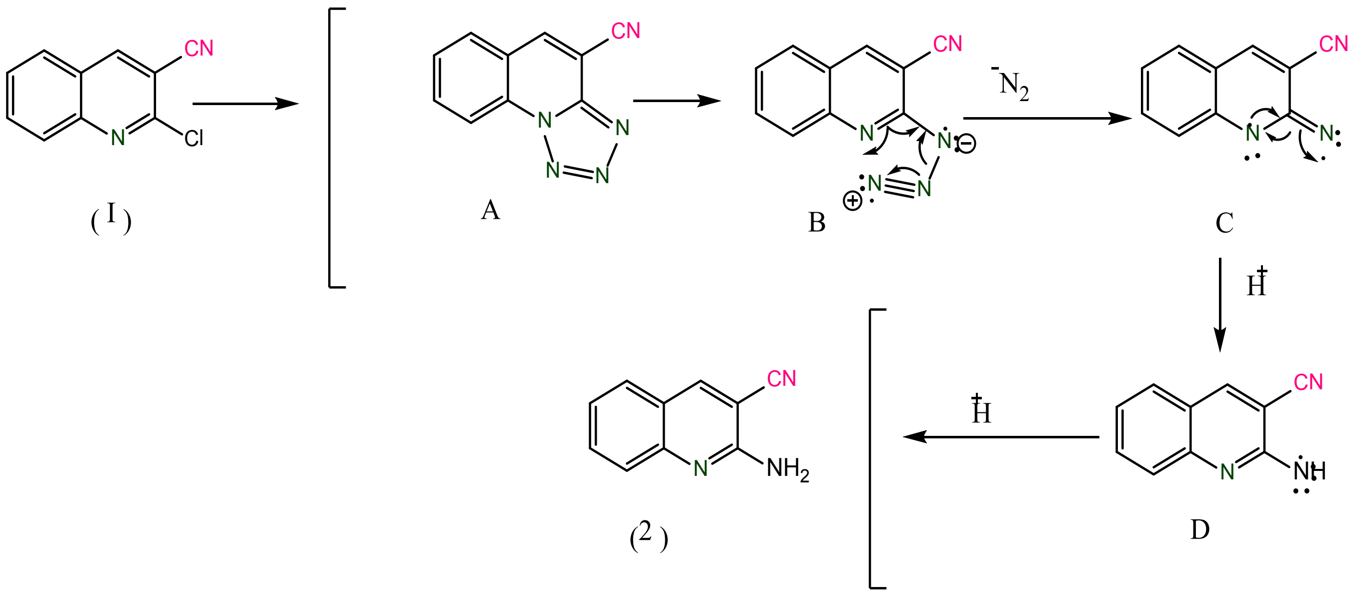

Figure 3: Proposed mechanism and possible intermediates.

we use quaternary ammonium halide that dissolved in the aqueous phase and it undergoes anion exchange with the anion of the reactant. The ion-pair formed can cross the liquid-liquid interface due to its lipophilic nature and diffuses from the interface into the organic phase, this step being the phase-transfer that lead to formation of intermediate C (Figure 3). and the catalyst subsequently, returns to the aqueous phase and the cycle continues. At this important stage, role of sodium borohydride was come as reducing agent to form the intermediate D (Figure 3) then reduction was continued, and on complete the reaction time to afford the corresponding 2-aminoquinoline-3-carbonitrile (2). Where its IR-spectra of 2 showed the appearance of NH_2 Stretching band at 3350 cm^{-1}, which when react with ethylcyano acetate give the key precursor 3 in which IR revealed the presence of C=O at 1655 cm^{-1}. Moreover, the ^1H NMR spectrum exhibited singlet at δ 4.28 for the acetamido CH_2 and a singlet at δ 6.83 ppm for the amidic NH. By subjecting the compound 3 to reaction with active methylene reagents the respective 2-pyridone derivatives 4a-d were obtained. The appearance of the pyridine C5-H protons at δ 6.83- 6.45 ppm and appearance of exchangeable proton that disappear with D_2O or CH_3 as in compound 4 c, d will prove the proposed structures. When compound 3 react with salicylaldehyde and benzaldehyde it give compounds 5 and 6 respectively, the structure of the resulting compound 5 was confirmed by appearance of two C=O one belong the amidic at 1660 cm^{-1} and one at high frequency C=O stretching at 1722 cm^{-1} cited for the coumarin oxo (not present in imino intermediate), proved by ^{13}C NMR at δ 159.3 in addition to, ^1H NMR of C4-H of coumarin at δ 6.97(absent in the start), this also beside the compound 6 in which IR containing two stretching band at 2255 cm^{-1}, 2203 cm^{-1} (2CN) that prove the structure of compound 6 in addition to, its ^1H NMR spectra of 6 showed the presence of one singlet at δ 8.57 ppm due to the presence of benzylidene CH. when compound 3 react with dioxane in presence of triethyl amine it afford compound 7, and the structure of the produced compound were confirmed from its IR and ^1H NMR where the presence of OH, and NH_2 confirm the structure of compound 7. On the other hand, treatment of the benzylidene derivative 6 with methylene carbonitrile reagents afforded the respective pyridone derivatives 8 a, b The reaction takes place via β -attack on the benzylidene moiety in 6 followed by 1,6-intramolecular dipolar cyclization with concomitant aromatization. The ^1H NMR spectra of 8a and 8b showed the presence of one singlet for each at δ 3.81 and δ 3.97 ppm, respectively, due to the presence of the NH_2 group. When compound 6 reacted with either hydrazine hydrate or phenyl hydrazine, the corresponding pyrazole systems 9a, b were obtained as the major products. The reaction involves β-attack on the C=C moiety in 6 with subsequent 1, 5-intramolecular dipolar cyclization and concomitant aromatization. Microanalysis and spectral data of 9a, b were fully consistent with the proposed structures. Where the ^1H NMR spectra of 9a and 9b showed the presence of one singlet for each at β 3.93 and δ 3.96 ppm, respectively, due to the presence of the NH_2 group. On the other hand, compound 3 reacted with benzenediazonium chloride to give the phenylhydrazo derivative 10, the ^1H NMR spectrum of compound 10 revealed two singlets at δ 9.18 and 11.02 ppm (exchangeable with D_2O) due to (2 NH) groups. The latter compound 10 reacted with either malononitrile or ethyl cyanoacetate to give the 3-phenylazo-pyridone derivatives 14a and 14b, respectively. The proposed structures were based on analytical and spectral data. The IR of compound 14a and 14b showed disappereance of NH stretching band and its ^1H NMR spectra of 14a and 14b showed the presence of two singlets for each at δ 3.16, 3.23 ppm, and 3.19, 3.45 ppm respectively, due to the presence of (2 NH_2) groups and this data will prove the cyclization and formation of pyridine ring. The studying of the reaction of compound 3 with phenyl isothiocyanate in 1, 4-dioxane containing triethylamine involved a nucleophilic attack by the amidic NH function in 3 on the C=S terminal of the isocyanate reagent to produce the acyclic intermediate. The latter then underwent 1,6-dipolar cyclization to afford compound 11 as the major product, the structure of this compound was proven by the presence of two singlets at δ 6.99 and 3.97 ppm due to pyrimidine C3-H and NH_2, respectively. On the other hand, we studying the reactivity of active methylene reagents towards phenyl isothiocyanate in basic dimethylformamide followed by heterocyclization with α-halocarbonyl compounds. These reactions lead to the formation of either thiophene (compound 12) or thiazole (compound 13) systems depending on reaction conditions and the nature of the α-halocarbonyl reagent in which the reaction takes place through the intermediate of the potassium sulphide salt. The disappearance of CH_2 singlet observed in the precursor 3, and the appearance of D_2O exchangeable NH_2 singlet at δ 4.33 ppm for compounds 12 and appearance of one singlet at δ 1.39 ppm for compounds 13 as well as the appearance of singlet at 6.83 ppm assigned to a thiazole C_5-H proton in compound 13 (not present in the structure containing thiophen and amino substituent), all this are considered sufficient to confirm the structures of 12 and 13.

Conclusion

We have synthesized polyfunctionalized heterocyclic systems based on 2-cyano-N-(3-cyanoquinolin-2-yl) acetamide (3) using convenient method. The antimicrobial activity of all synthesized compounds showed moderate of antimicrobial activity, From the screening data it was found some derivative (8a, b), 11 and 14 a, b that containing pyridine ring have encouraging antifungal activity, which need to be further investigation to get better antifungal and antibacterial agents in the future. Microbiological testing of the newel synthesized compounds was performing in the Regional Center for Mycology and Biotechnology, Department of Microbiology, Faculty of Science, Al-Azher University, Cairo, Egypt.

Acknowledgments

The authors would like to express their sincere thanks to all members in the Regional Center for Mycology and Biotechnology, Department of Microbiology, Faculty of Science, Al-Azher University, Cairo, Egypt, for performing the antimicrobial testing.

References

1. Michael JP (1997) Quinoline, quinazoline and acridone alkaloids. Nat Prod Rep 14: 605-618.
2. Kouznetsov VV, Puentes CO, Bohorques ARR, Zacchino SA, Sortino M, et al. (2006) A Straight-forward Synthetic Approach to Antitumoral Pyridinyl Substituted 7H-Indino [2,1-C] Quinoline Derivatives via Three-Component Imino Diels-Alder Reaction. Lett Org Chem 3: 300-304.
3. Kamal MG (2015) Synthesis and Antimicrobial Evaluation of New Polyfunctionally Substituted Heterocyclic Compounds Derived from 2-cyano-N-(3-cyanoquinolin-2-yl) acetamide. J Org Chem 5: 1-9.
4. Guan LP, Jin QH, Tian GR, Chai KY, Quan ZS (2007) Synthesis of some quinoline-2(1H)-one and 1, 2, 4 - triazolo [4,3-a] quinoline derivatives as potent anticonvulsants. J Pharm Pharm Sci 10: 254-262.
5. Kumar S, Singhal V, Roshan R, Sharma A, Rembhotkar GW (2007) Piperine inhibits TNF-α induced adhesion of neutrophils to endothelial monolayer through suppression of NF-κB and IκB kinase activation. Eur J Pharmacol 575: 177-186.
6. Pingle MS, Vartale SP, Bhosale VN, Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2-methylthio-4H-pyrimido [2,1-b] [1,3] benzothiazole and its reactions with selected nucleophiles. ARKIVOC 190-198.
7. Wright CW, Addae-Kyereme J, Breen AG, Brown JE, Cox MF (2001) Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents. J Med Chem 44: 3187-3194.
8. Chakravarti SS, Sen PK, Choudhari S, Das M (1985) Ind J Chem 248: 737.
9. Freek LA, Martin JL, Willson R. J Am Chem Soc 946, 68, 1285.
10. Lee CH, Lee H (2011) Relaxant effect of quinoline derivatives on histamine-induced contraction of the isolated guinea pig trachea. J Korean Soc Appl Biol Chem 54: 118-123.
11. Ukrainets IV, Liu YAA, Tkach AA, AV Turov (2009) 4-Hydroxy-2-quinolones 166*. Synthesis, isomerism, and antitubercular activity of 3-arylaminomethylene-quinoline-2,4-(1H,3H)-diones. Chem Heterocycl Compd 45: 802-808.
12. Chowdhury AZM, Shibata Y (2001) Synthesis of New Fused Pyrimidines by Isocyanate and Isothiocyanate. Chem Pharm Bull 49: 391.
13. Wright TL (1985) US Pat 4: 540-786.
14. Neelima BB, Amiya PB (1986) J Het Chem 23: 925-930.
15. Kangani CO, Kelly DE, Day BW (2006) One-pot synthesis of aldehydes or ketones from carboxylic acids via in situ generation of Weinreb amides using the Deoxo-Fluor reagent. Tetrahedron Lett 47: 6289-6292.
16. Monir AS, Ismail MM, Barakat SES, Abdul- Rahman AAA, Bayomi AH (2004) Synthesis and antimicrobial activity of some new 1H-pyrazolo [3,4-b] Qinoline derivatives. Bull Pharm Sci Assiut 27: 237-245.
17. Reddy KS, Iyengar DS, Bhalerao UT (1983) Chem Let 1745.
18. Keith JM (2006) One-Step conversion of pyridine N-oxides to tetrazolo [1,5-a] pyridines. J Org Chem 71: 9540-9543.
19. Huisgen RA (1968) Cycloadditions - definition, classification, and characterization. Chem Int Ed 7: 321.
20. Ramadan AM, Afaf MAH, Saeed MR, Mohamed AI, Kamal US (2009) Fused Quinoline Heterocycles IX: First Example of a 3,4-Diamino-1H-pyrazolo[4,3-c] quinoline and a 3-Azido-1H-1,2,4,5,6,6a-hexaazabenzo [a] indacene. J Chem Sci 64: 973-979.
21. Kamal MEG (2015) Synthesis and Antimicrobial Evaluation of New Polyfunctionally Substituted Heterocyclic Compounds Derived from 2-cyano-N-(3-cyanoquinolin-2-yl) acetamide. Amer J Org Chem 5: 1-9.
22. Bekhit AA, El-Sayed OA, Tak AA, Hassan YA, Muhammed KSM (2004) Synthesis, characterization and cytotoxicity evaluation of some new platinum (II) complexes of tetrazolo [1, 5-a] quinolones. Europ J Med Chem 39: 499-505.
23. Hartwig JFS (1997) 116.
24. Hartwig JF (1998) Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: Scope and mechanism. Angew Chem Int Ed Engl 37: 2046.
25. Frost CG, Mendoncua PJ (1998) Chem Soc Perkin Trans 1: 2615.
26. Belfield AJ, Brown GR, Foubister AJ (1999) Tetrahedron 55: 11399-11428.
27. Jaime FS, Liu Y, Muchowski J, Putman D (1998) Allyl amines as ammonia equivalents in the preparation of anilines and heteroarylamines. Tetrahedron Lett 39: 1313.
28. Miller DR, Svenson DC, Gillan EG (2004) Synthesis and Structure of 2,5,8-Triazido-s-Heptazine: An Energetic and Luminescent Precursor to Nitrogen-Rich Carbon Nitrides. J Am Chem Soc 26: 5372-5373.
29. Butler RN (1996) Comprehensive Heterocyclic Chemistry II. Pergamon, Oxford, pp: 621-678.
30. Huisgen RJ (1968) Org Chem 33: 2291-2297.
31. Carpenter WR (1962) The Formation of Tetrazoles by the Condensation of Organic Azides with Nitriles. J Org Chem 27: 2085-2088.
32. Kato H, Ohmori K, Suzuki K (2001) Convenient procedure for one-pot conversion of azides to N-monomethylamines. Synlett 1003-1005.
33. Vitaly GK, Cheblakov PB, Niria BG (2011) Tautomerism and Thermal Decomposition of Tetrazole: High-Level ab Initio Study. J Phys Chem 115: 1743-1753.
34. Nicholas P, Michael RZ (2012) J Phys Chem A 116: 1519-1526.
35. Smith L, Wong WC, Kiselyov AS, Burdzovic WS, Mao Y, et al. (2006) Bioorganic and Medicinal Chemistry.

Citation: El-Gamal KM (2016) Synthesis and Antimicrobial Evaluation of Polyfunctionally Heterocyclic Compounds Bearing Quinoline Moiety. Organic Chem Curr Res 5: 168. doi: 10.4172/2161-0401.1000168