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Article

Synthesis and Antimicrobial Evaluation of Some New Fused Quinolones Heterocyclic Compounds

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Abstract: The compound 3-formyl-4-hydroxy-2-oxo-1-phenyl-1, 2-dihydro quinoline **2** was synthesized efficiently *via* Reimer-Tieman reaction. Reaction of compound **2** was reacted with hydrazine hydrate, phenyl hydrazine, malononitrile, acetyl acetone yielded a series of heterocyclic derivatives fused or isolated with the quinolinone nucleus. Also, 2-amino-3-cyano pyranoquinolinone derivative 17 was reacted and subjected to react with either formic acid or acetic anhydride/phosphoric acid mixture giving the newly prepared dihydropyranoquinolinone derivative 19. All the structure of the synthesized compounds was elucidated via both the elemental and spectral data. Also, the antimicrobial activities and fungal strain studies were occurred and some of them showed potent activities in comparison with standard antibiotics.

Keywords: 3-formyl quinolinone, Reimer-Tieman reaction pyrano quinoline, antimicrobial

1. Introduction

Throughout the last decades, synthesis of new quinolinone heterocyclic compounds had been a subject of considerable interest due to its wide applicability. These heterocyclic compounds occur very widely in bioactive naturally plants and most of them have interesting biologically and pharmaceutical interests. Also, the importance of multicomponent reactions aimed to synthesize hybrid fused quinolinone heterocyclic compounds had been recognized, and great efforts have been focused on the modelling and development of one-pot procedures for this strategy[1, 2, 3].

A series of compounds originated from 8-hydroxyquinoline and styrylquinoline derivatives were recently prepared as potential inhibitors for HIV-1 integrase.[4, 5] These compounds showed a significant

resemblance to some novel antifungal agents, namely homoallylamines, and therefore have potential antifungal activity.[6-9] Furthemore, in others publications reported the aforementioned compounds possess interesting herbicidal and antineoplastic activities[10-16].

Also, Oxazole and pyrazole moieties represented substantial class of heterocycles due to its highly obvious biological and pharmacological activities as reported in many of literature. Several methods have been reported for the synthesis of oxazole and pyrazole derivatives including 1,3-cycloaddition reaction.[17-19] pyrazole based compounds have antianxiety, antipyretic, analgesic,[20] treating Alzheimer's diseases.[21]

Herein, we designed new condensed heterocyclic quinolinone derivatives depending on the synergistic effect of formyl group with the hydroxyl moiety. Furthermore, these new compounds were screened for their potential biological behavior.

2. Materials and Methods

2.1. Chemistry

2.1.1. General

All melting points are reported in degree Celsius (°C) (uncorrected) and were measured on a Gallenkamp apparatus. The IR spectra were measured using the KBr disks technique on a Mattson 5000 and Thermo Scientific Nicolet iS10 FTIR Spectrometers at Mansoura University. The 1H-NMR spectra were measured on a Burker advance III 400 MHz (Beni Suef University) and JEOL ECA II 500 MHz (Mansoura University) using tetramethylsilane (TMS) as an internal reference and using (DMSO-d_6), chloroform ($CDCl_3$) as a solvent. The signals' multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, m = multiplet. Exchangeable protons were detected through D_2O test. EI-Mass spectra were carried out on direct probe controller inlet part to single quadropole mass analyzer in thermo scientific GCMS model ISQ LT using thermo X-Calibur software at the regional center for mycology and biotechnology (RCMB), Al-Azhar university, Nasr city, Cairo. The mass spectroscopy system was used to confirm the purity of compounds as well as explore the characteristic fragmentation and the expected molecular weight. Elemental analysis (C, H and N) were (C, H and N) were executed at Cairo University. The biological screenings were performed at Beni Suef University and the stock cultures of the tested organisms were obtained from the microbiological lab, Faculty of Postgraduate Studies for Advanced Sciences.

2.1.2. Synthesis

3-Formyl-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline (2)

The compound was prepared according to the published procedure[22] (TLC, m.p., and spectral data) were completely compatible with published data.

4-Hydroxy-1-phenyl-3-((2-phenylhydrazono)methyl)quinolin-2(1*H*)-one (3b)

A mixture of compound **2** (8 mmol, 2.12 g) was refluxed with phenyl hydrazine (0.8 mL) in EtOH (20 mL) for 4 hrs. the yellow crystals which was formed, collected by filtration and recrystallized from EtOH/DMF to afford **3b** as yellow crystals; (0.28 g, 68% yield); m.p. > 300 °C; IR (KBr, *v*/cm^{-1}): 3428 (OH), 3254 (NH), 1626 (CO), 1601(C=C), 1572 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.52- 6.48 (m, 2H, ArH), 7.65- 7.23 (m, 10H, ArH), 7.94-7.92(d, 1H, ArH, *J* = 7.6 Hz), 8.1- 8.08 (d, 1H, ArH, *J* = 8 Hz), 8.42 (s, 1H, C-CH=N), 10.67 (s, 1H, NH, exchangeable with D_2O), 13.7 (s, 1H, OH, exchangeable with D_2O); Anal. calcd for $C_{22}H_{17}N_3O_2$ (355.40): C, 74.35; H, 4.82; N, 11.82%. Found: C, 74.28; H, 4.89; N, 11.85%.

5-Phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (4)

A solution of compound **2** (2 mmol, 0.53 g) refluxed with hydrazine hydrate 80% (0.4 mL) in EtOH (10 mL) for 1 h. the precipitate which was formed filtered off, washed with water, dried and recrystallized from EtOH/DMF to afford compound **4** as yellow crystals; (0.28 g, 68% yield); m.p. > 300 °C; IR (KBr, *v*/cm^{-1}): 3245 (NH), 1653 (CO), 1607 (C=C), 1534 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.41- 6.39 (d, 1H, ArH, *J* = 8.4 Hz), 7.54- 7.17 (m, 4H, ArH), 7.62- 7.58 (m, 3H, ArH), 8.08- 8.06 (d, 1H, ArH, *J* = 8 Hz), 8.36 (s, 1H, -N=CH-C); EI-MS *m/z* (%): 262.03 [M$^+$+1] (33.71), 261.09 [M$^+$] (100), 247.85 (10.43), 178.18 (15.52); Anal. calcd for $C_{16}H_{11}N_3O$ (261.28): C, 73.55; H, 4.24; N, 16.08%. Found: C, 73.73; H, 4.32; N, 16.20%.

2,5-Dioxo-6-phenyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (5)

An equimolar amounts of compound **2** (2 mmol, 0.53 g) and malononitrile (2 mmol, 0.13 g) were refluxed in ethanol (10 mL) in the presence of piperidine (0.5 mL) for 4 hrs. the yellow solid which was formed after cooling , filtered off and recrystallized from EtOH/DMF to give compound **5** as yellow crystals; (0.21 g, 67% yield); m.p. = 208- 210 °C; IR (KBr, *v*/cm^{-1}): 2208 (CN), 1710 (CO), 1645 (CO), 1603 (C=C), 1582 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.53- 6.51 (d, 1H, ArH, *J* = 8.8 Hz), 6.85 (s, 1H, C-CH=C), 7.37- 7.33 (m, 3H, ArH), 7.67- 7.48 (m, 3H, ArH), 8.14- 8.12 (d, 1H, ArH, *J* = 8 Hz); EI-MS *m/z* (%): 315.06 [M$^+$+1] (15.62), 314.04 [M$^+$] (89.99), 313.08 [M$^+$-1] (100), 313.08 (47.81), 311.13 (68.91), 306.05 (10.74), 237.10 (16.30); Anal. calcd for $C_{19}H_{10}N_2O_3$ (314.30): C, 72.61; H, 3.21; N, 8.91%. Found: C, 72.78; H, 3.29; N, 8.85%.

3-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)methylene)pentane-2,4-dione (6)

A mixture of compound **2** (4 mmol, 1.06 g) and acetyl acetone (4 mmol, 0.41 mL) was heated in ethanol (10 mL) in the presence triethyl amine (5 drops) for 1 h. The yellow solid was precipitated after cooling was collected and recrystallized from EtOH/DMF to give compound **6** (1.15g, 83 % yield); yellow crystals; m.p. = 258- 260 °C; IR (KBr, *v*/cm^{-1}): 3398 (OH), 1716 (CO), 1691(CO), 1620 (C=C), 1562 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.07 (s, 6H, 2CH$_3$), 6.34- 6,32 (d, 1H, ArH, *J* = 8 Hz), 7.24-

7.08 (m, 5H, ArH), 7.57- 7.47 (m, 3H, ArH), 8.055- 8.04 (d, 1H, ArH, *J* = 7.2 Hz); Anal. calcd for $C_{21}H_{17}NO_4$ (347.37): C, 72.61; H, 4.93; N, 4.03%. Found: C, 72.72; H, 4.89; N, 4.09%.

3-((3,5-dimethyl-4*H*-pyrazol-4-ylidene)methyl)-4-hydroxy-1-phenylquinolin-2(1*H*)-one (7)

A mixture of compound **6** (1 mmol, 0.35 g) and hydrazine hydrate 80% (1 mL) in EtOH (10 mL) were refluxed for 2 hrs. The reaction mixture was poured into crushed ice and neutralized with diluted HCl. The resulting pale yellow solid was filtered off, repeatedly washed with water , dried well and recrystallized from ethanol to give **7** as yellow crystals; (0.22 g, 64 % yield); m.p. > 300 °C; IR (KBr, *v*/cm^{-1}): 3204 (OH), 1653 (CO), 1599 (C=C), 1561 (Ar); EI-MS *m/z* (%): 344.05 [M^++1] (14.70), 343.03 [M^+] (32.29), 341.98 [M^+-1] (20.43), 340.06 (56.52), 339.02 (47.33), 262.95 (100), 260.92 (41.36), 166.94 (49.02), 76.83 (39.71); Anal. calcd for $C_{21}H_{17}N_3O_2$ (343.39): C, 73.45; H, 4.99; N, 12.24%. Found: C, 73.55; H, 4.95; N, 12.11%.

3-Amino-4-hydroxy-1-phenylquinolin-2(1*H*)-one hydrochloride (8)

The compound was prepared according to the published procedure[23] (TLC, m.p., and spectral data) were completely compatible with the published data.

2-Mercapto-5-phenyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (9)

A mixture of compound **8** (3.6 mmol, 1.04 g), KOH (8 mmol, 0.24 g in 2 mL H_2O) and CS_2 (36.4 mmol, 2.2 mL) in ethanol (15 mL) was refluxed for 4 hrs. The mixture was cooled, poured into ice cold water (100 mL) and neutralized with diluted HCl. The formed product was filtered, washed with water, dried and recrystallized from ethanol to give compound **9** as colorless crystals; (0.8 g, 76% yield); m.p. > 300 °C; IR (KBr, *v*/cm^{-1}): 1676 (C=O), 1635 (C=C), 1591 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.65- 6.63 (d, 1H, ArH, *J* = 8.4 Hz), 7.43- 7.39 (m, 3H, ArH), 7.52- 7.48 (m, 1H, ArH), 7.69- 7.59 (m, 3H, ArH), 7.97- 7.95 (d, 1H, ArH, *J* = 8 Hz); EI-MS *m/z* (%): 295 [M^++1] (21.50), 293.99 [M^+] (100), 292.94 [M^+-1] (63.56), 196.06 (5.68); Anal. calcd for $C_{16}H_{10}N_2O_2S$ (294.33): C, 65.29; H, 3.42; N, 9.52%. Found: C, 65.38; H, 3.46; N, 9.47%.

5-Phenyl-3,5-dihydrooxazolo[4,5-*c*]quinoline-2,4-dione (10)

To a mixture of compound **9** (1 mmol, 0.29 g) in sodium hydroxide solution (10%, 15 mL), a sdolution of H_2O_2 (30%, 5 mL) was added drop wisely with stirring at room temperature. The stirring continued for 1 h then neutralized with diluted HCl. The solid was collected, washed with water and recrystallized from ethanol to afford **10** as colorless crystals; (0.28 g, 68% yield); m.p. = 290-292 °C; IR (KBr, *v*/cm^{-1}): 3456 (OH), 1801 (lactonic C=O), 1675 (amidic C=O), 1635 (C=C), 1592 (Ar); EI-MS *m/z* (%): 279.21 [M^++1] (7.54), 278 [M^+] (100), 276.93 [M^+-1] (51.71), 251.95 (21.56), 248.97 (23.60), 195.93

(29.10), 167.13 (24.29); Anal. calcd for $C_{16}H_{10}N_2O_3$ (278.27): C, 69.06; H, 3.62; N, 10.07%. Found: C, 69.17; H, 3.56; N, 10.11%.

2-(Methylthio)-5-phenyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (11)

To a suspension of compound **9** (1 mmol, 0.29 g) in aqueous ethanol (10 mL) and KOH (1.1 mmol, 0.05 g), methyl iodide (1.5 mmol, 0.93 mL) was dropwise added with stirring at room temperature for 1 h. the mixture was neutralized with diluted HCl. The solid which had been formed was collected, washed with water and recrystallized from ethanol to afford **11** as a colorless needles; (0.25 g, 82 % yield); m.p. = 230-232 °C; IR (KBr, *v*/cm^{-1}): 1692 (CO), 1589 (C=C), 1558 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.51 (s, 3H, -S-CH_3), 6.64- 6.62 (d, 1H, ArH, *J* = 8.4 Hz), 7.4- 7.36 (m, 3H, ArH), 7.5- 7.46 (m, 1H, ArH), 7.68- 7.58 (m, 3H, ArH), 8- 7.98 (d, 1H, ArH, *J* = 7.6 Hz); Anal. calcd for $C_{17}H_{12}N_2O_2S$ (308.36): C, 66.22; H, 3.92; N, 9.08%. Found: C, 66.17; H, 3.86; N, 9.11%.

Reaction of compound 1 with formaldehyde and / or benzaldehyde

"Synthesis of Diquinolinylm methane derivatives 12a,b general procedure"

A mixture of compound **1** (3 mmol, 0.711 g), formaldehyde (%37, 1.5 mmol, 0.12 mL) or benzaldehyde (1.5 mmol, 0.15 mL) in EtOH (20 mL) and a catalytic amount of morpholine (1 mL) was refluxed with stirring for 1 h. the precipitate which was formed after cooling was collected by filtration and recrystallized from ethanol to give:

Di (4-hydroxy-3-oxo-1-phenyl-1*H*-quinolin-3-ylm) methane (12a)

As yellow crystals; yield (0.47 g, 65%); m.p. > 300 °C; IR (KBr, *v*/cm^{-1}): 3432 (OH), 1632 (CO), 1606 (C=C), 1551 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.97 (s, 2H, -CH2-) , 6.5-7.2 (m, 8H, Ar-H), 7.3-8.02 (m, 10H, Ar-H), 12.4 (s, 2H, 2OH); EI-MS *m/z* (%): 487 [M^++1] (33.2), 486 [M^+] (100), 391.07 (2.49); Anal.calcd for $C_{31}H_{22}N_2O_4$ (486.53): C, 76.53; H, 4.56; N, 5.76%. Found: C, 76.45; H, 4.64; N, 5.78%.

Phenyl di (4-hydroxy-3-oxo-1-phenyl-1*H*-quinolin-3-ylm) methane (12b)

As a yellow crystals; Yield (55%,0.46 g); m.p. = 248- 250 °C; IR (KBr) *v* max/cm^{-1} = 3441 (OH), 1657 (2CO), 1601 (C=C); ^{1}H NMR (DMSO-d_6) δ = 6.36-6.37 (d, 2H, Ar-H, *J* = 8.5 Hz), 6.76 (s, 1H, -CH-), 7.04-7.60 (m, 21H, Ar-H), 7.67- 7.99(d, 2H, Ar-H, *J* = 7.0 Hz); Anal. calcd for $C_{37}H_{26}N_2O_4$ (562.63): C, 78.99; H, 4.66; N, 4.98%. Found: C, 79.12; H, 4.75; N, 4.95%.

3-(((4-Aminophenyl)imino)methyl)-4-hydroxy-1-phenylquinolin-2(1*H*)-one) (15)

A mixture of compound **1** (0.01 mol, 2.37 g), triethyl orthoformate (0.01 mol, 1.68 mL) and *p*-phenylene diamine (0.01 mol, 1.08 g) was heated in ethylene glycol (15 mL) with stirring at 110 °C for 1 h. then after, the temperature was gradually increased to 200 °C till ethanol stopped to distilled from the

reaction mixture. After complete evaporation of the alcohol, the mixture was treated with ethanol (15 ml). The mixture was left overnight at room temperature till complete precipitation of the product. The precipitate was collected and recrystallized from ethanol to afford **15** as brown crystals; (2.56 g, 72% yield); m.p. = 294-296 °C; IR (KBr, *v*/cm^{-1}): 3487 (OH), 3330 and 3245 (NH_2), 1641 (CO), 1601 (C=C); EI-MS *m/z* (%): 357.08 [M^++1] (25.10), 356.08 [M^+] (100), 355.06 [M^+-1] (23.47), 340.07 (18.51), 339.06 (5.27); Anal. calcd for $C_{22}H_{17}N_3O_2$ (355.40): C, 74.35; H, 4.82; N, 11.82%. Found: C, 74.44; H, 4.88; N, 11.89%.

2-Amino-5-oxo-4,6-diphenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (17)

The compound was prepared according to the published procedure[24] (TLC, m.p., and spectral data) were completely compatible with published data.

4,6-Diphenyl-4,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5(3*H*)-dione (19)

A mixture of compound **17** (13 mmol, 0.5 g) and formic acid 88% (12 mL) was refluxed and the reaction was monitored *via* TLC. After completion the reaction, the mixture was cooled, the precipitate was filtered off, washed with diethyl ether and recrystallized from ethanol to yield compound **19** as brown needles; (0.33 g, 70% yield) m.p = 238-240 °C; IR (KBr, *v*/cm^{-1}): 1787 (lactonic CO), 1646 (amidic CO), 1599 (C=C), 1571 (Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 3-2.97 (d, 1H, -C-$\underline{CH_2}$-CH, *J* = 16 Hz), 3.65- 3.53 (m, 1H, CH_2-$\underline{CH}$-Ar), 4.55- 4.54 (d, 1H, C-$\underline{CH_2}$-CH, *J* = 6.5 Hz), 6.62- 6.60 (d, 1H, ArH, *J* = 8 Hz), 7.43- 7.22 (m, 8H, ArH), 7.64- 7.5 (m, 4H, ArH), 7.98- 7.96 (d, 1H, ArH, *J* = 10 Hz); EI-MS *m/z* (%): 368.07 [M^++1] (30.36), 367.06 [M^+] (100), 339.08 (45.58), 338.09 (52.02), 324.05 (4.59); Anal. calcd for $C_{24}H_{17}NO_3$ (367.12): C, 78.46; H, 4.66; N, 3.81%. Found: C, 78.58; H, 4.71; N, 3.86%.

N.B

The same product **19** was prepared by refluxing compound **17** (2 mmol, 0.78 g) with acetic anhydride (7mL) and phosphoric acid (7 mL) for 12 hrs. The product was completely identical (TLC, m.p. and spectral data) with the above authentic sample.

2.2. Biological Evaluation

2.2.1. Antimicrobial activity

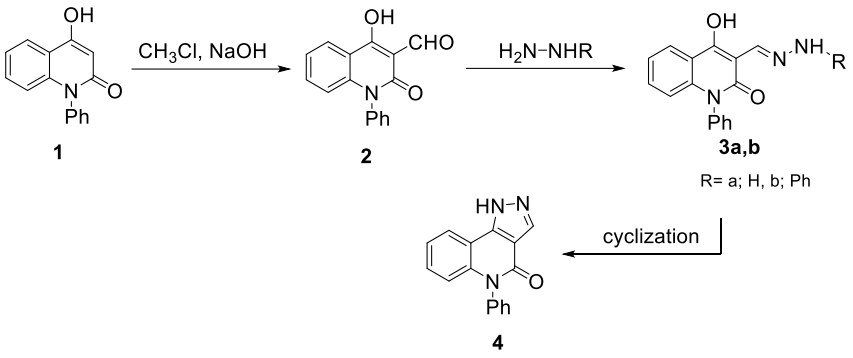
The antimicrobial activity of the synthesized compound was estimated by standardized disk agar diffusion method. The compounds were dissolved in DMSO, which has no inhibition activity, to obtain a concentration of 100 μg mL^{-1}. The test was performed on medium potato dextrose agars (PDAs) containing an infusion of 200 g of potatoes, 6 g of dextrose, and 15 g of agar.[25] The plates were incubated at 28 °C for fungi and at 37 °C for bacteria. Diameters of the inhibition zone (mm) were measured after 18-24 hours.

3. Results and Discussion

3.1. Chemistry

In this study, our versatile precursor 3-formyl-4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline **2** has been prepared *via* Reimer-Tieman reaction according to the published procedure,[22] by treatment of one equivalent of 4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline **1** with forty equivalent $CHCl_3$ in the presence of NaOH solution.

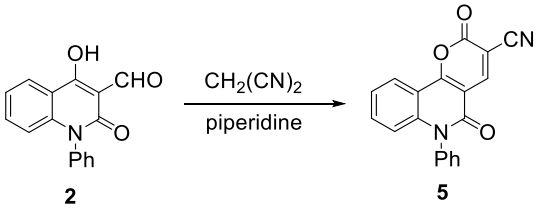
Refluxing of compound **2** with hydrazine hydrate and phenyl hydrazine yielded *via* nucleophilic condensation reaction, the corresponding hydrazones **3a,b**. the hydrazine **3a** was directly cyclized without separation giving pyrazolo quinolone derivative **4** as shown in **Scheme 1**.



Scheme 1

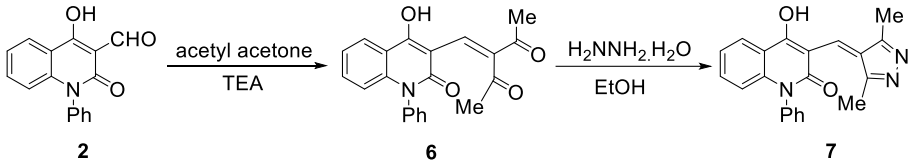
Quinolinone and pyranone are two substantial classes of natural products possessing nitrogen/oxygen bioactive heterocyclic compounds.[26,27] In this study we planned to construct hybrid compounds containing both structures which have been synthesized in a good yield using knoevenagel condensation followed by intramolecular cyclization and finally autoxidation forming 2,5-dioxo pyranoquinoline-3-nitrile derivative **5 (Scheme 2)**.

The structure of **5** was established via inspection of its analytical and spectral data. The infrared spectrum showed two lactam and lactone groups at ν = 1645 and 1710 cm^{-1}, respectively. In addition to nitrile stretching band at ν = 2208 cm^{-1}. ^{1}H-NMR spectrum of **5** showed a singlet one proton at δ = 6.85 ppm for pyran-H, two doublets signals of H-9 at δ = 6.51 ppm with $J_{coupling}$ = 8.8 Hz and δ = 8.13 ppm with $J_{coupling}$ = 8.8 Hz and the remainder aromatic protons showed as multiplet at δ = 7.32-7.66 ppm.



Scheme 2

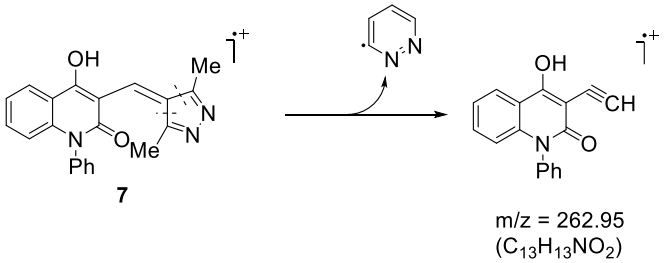
Pyrazole and pyrazolyl quinoline compounds have attracted continued interest through the last years and consider the core structure in different pharmaceutics.[28,29] Thus, our strategy aimed to synthesize these compounds, condensation of compound **2** with acetyl acetone yielded the corresponding acetyl acetone derivative **6** which subsequently was reacted with hydrazine hydrate to form pyrazolyldene quinolinone derivative **7** as shown in **Scheme 3**.



2 **6** **7**

Scheme 3

The structure of compound **6** was established *via* inspection of its analytical and spectral data. The infrared spectrum showed three ketonic and lactam stretching at ν = 1716, 1691, and 1620 cm^{-1}. Whereas, ^{1}H-NMR spectrum showed a singlet at δ = 2.07 ppm attributable to two methyl groups, in addition to the **10** aromatic protons appeared as multiplet at δ = 6.32- 8.06 ppm. Also, the structure elucidation of compound **7** showed clearly in its infrared spectrum the disappearance of two carbonyl stretching and only the lactam group appeared at ν = 1653 cm^{-1}. The mass spectrum of **7** showed the molecular ion peak at *m/z* = 343.06 corresponding to its molecular weight [$C_{21}H_{17}N_3O_2$]. The base peak showed at *m/z* = 262.95 from extrusion of pyrdazine ring *via* hemolytic fission of carbon/carbon pyrazole moiety as shown in the following pathway **(Scheme 4)**.



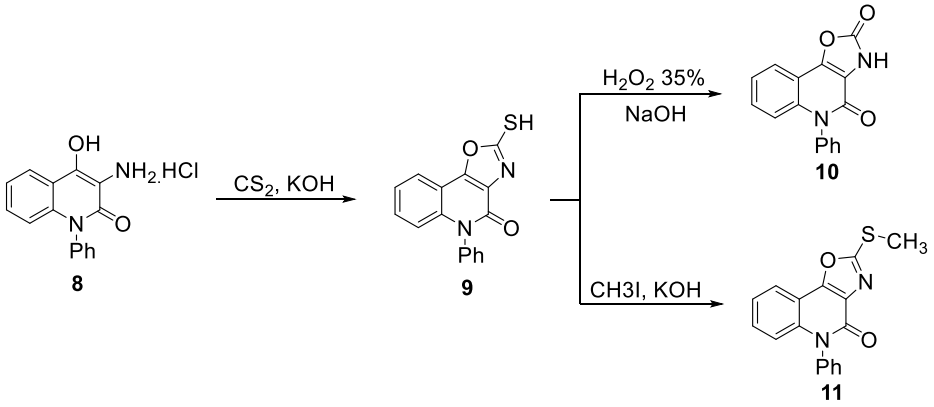
7

Scheme 4

Also, in this study we had planned to synthesize a different oxazolo quinolone compounds starting from highly functionalized hydrochloric salt of 3-amino-4-hydroxy-1-phenyquinolin-2(1*H*)-one **(8)** which was synthesized by the known procedures.[23] Refluxing compound **8** with carbon disulfide in the presence of potassium hydroxide solution yielded in quantitative yield the compound, 2-mercapto-5-phenyloxazolo[4,5-*c*]quinolin-4(5*H*)-one **(9)**. Oxidation of the latter compound **9** by using mixture of H_2O_2 and NaOH yielded oxazolo quinolin-2,4-dione derivative **10**.

Lassigne test of the product **10** showed clearly lack the sulfur element. As well as, the elemental analysis and spectral data confirm its structure. Moreover, the thiol group of compound **9** was easily

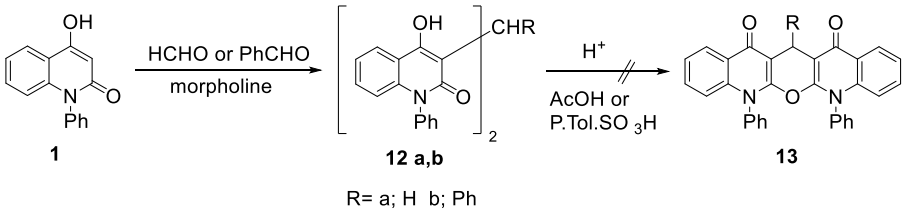
alkylated at treatment it with methyl iodide in the presence of KOH solution, to yield the corresponding methylthio oxazolo quinolin-4-one derivative **11 (Scheme 5)**.



Scheme 5

^{1}H-NMR spectrum of compound **11** showed in addition the multiplet aromatic protons, a singlet three protons of methylthio group δ = 2.51 ppm.

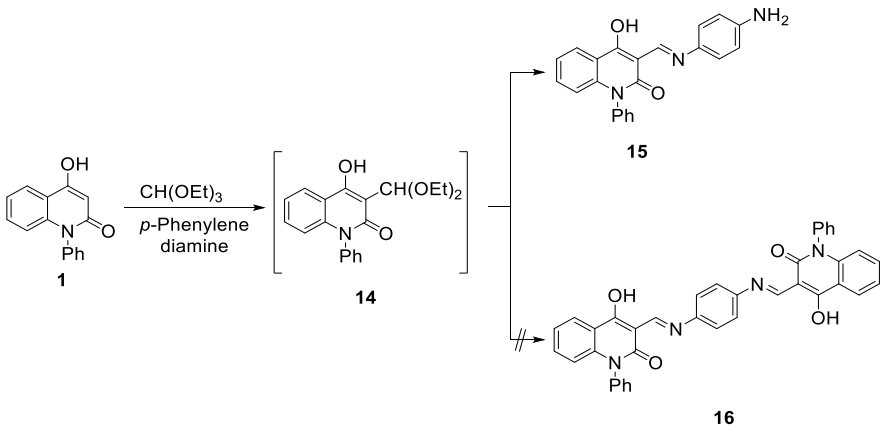
Moreover, our versatile compound **1** was treated with formaldehyde as well as benzaldehyde by the ratio (2:1) as a model of aliphatic and aromatic aldehyde in basic medium giving *via* nucleophilic addition followed by dehydration yielded the diquinolinylm methane **12a,b**, Unsuccessful attempts to achieve the desired interesting diquinolinum pyran derivative **13** by using different acidic conditions as shown in **Scheme 6**.



Scheme 6

The ^{1}H-NMR spectrum of the latter products **12a, b** showed clearly lack the H-3 quinoline moiety and instead an aliphatic CH_2 or CH at δ = 3.97 and 6.76 ppm, respectively. Also, the mass spectrum of **12a** gave its molecular ion at *m/z* = 486 which in accordance with its molecular weight.

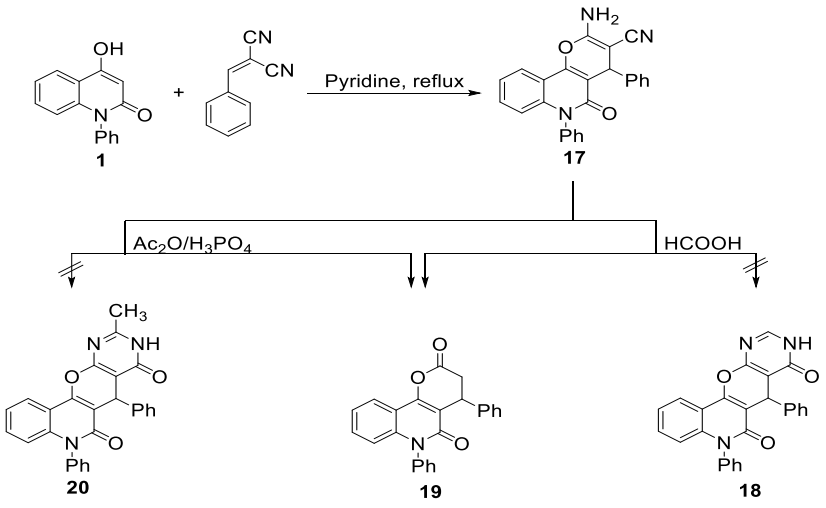
Also, condensation of compound **1** with triethyl orthoformate and *p*-Phenylenediamine as an example of aromatic amine gave compound **14** which directly reacted in one pot reaction with the aromatic amine giving only phenylimino methyl quinoline derivative **15**, the bis phenylimino methyl quinoline compound **16** couldn't be separated **(Scheme 7)**.



Scheme 7

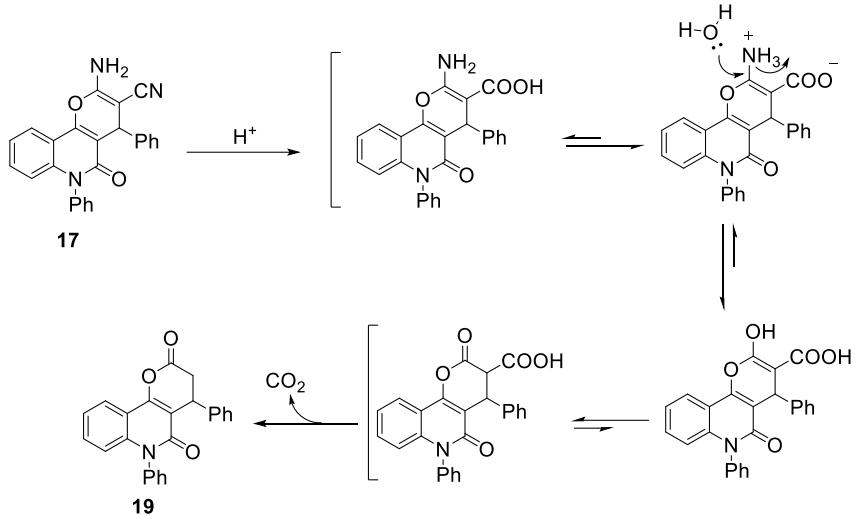
The structure of compound **15** was established through the correct elemental analysis, in addition the spectral data which showed in the infrared spectrum the hydroxyl and amino groups stretching at ν = 3487, 3330 and 3245 cm^{-1} in addition the lactam carbonyl stretching at ν = 1641 cm^{-1}. Also, the mass spectrum gave its molecular ion at *m/z* = 356.08 as base peak which in agreement with the molecular weight.

Also, in our strategy and as an attempt to synthesize the interesting pyrimidine heterocyclic ring condensed with the pyranoquinoline skeleton, the compound **17** which was prepared according to the published procedure,[24] reacted with formic acid in the presence of acetic anhydride to construct the desired compound **18**, the latter compound **18** couldn't be prepared and instead, the compound dioxo pyranoquinoline **19** was separated. The same compound **19** was also prepared instead the quinolinopyrano pyrimidine analogue **20** at treatment of **17** with acetic anhydride in the presence of phosphoric acid **(Scheme 8)**.



Scheme 8

The suggested mechanism of the formation of compound **19** is that under vigorous conditions, the nitrile group has been hydrolyzed to the corresponding carboxylic acid which underwent decarboxylation and hydrolysis of enamine functionality to give the observed product **19** as outlined in **scheme 9**.



Scheme 9

The elemental analysis and spectral data of compound **19** were in accordance with the suggested structure. The infrared spectrum showed the lactam and lactone group at v = 1646 and 1787 cm^{-1}, respectively. Whereas, ^{1}H-NMR spectrum showed three signals at δ 2.98, 3.59 and 4.55 ppm attributable to the three aliphatic protons. The mass spectrum showed the molecular ion at *m/z* = 367.06, whereas the base peak showed at *m/z* = 339.08 due to the extrusion of CO_2 moiety. All the spectral data as well as the thin layer chromatography (TLC) of the samples from the two different reactions were completely compatible.

3.2. Biological evaluation and structure activity relationships (SARs)

2.2. Antimicrobial activity

The synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* (gram +ve) and *Proteus vulgaris* (gram -ve) and against *Candida albicans* to evaluate their antifungal activities. The activity was estimated by the disc diffusion method[30] and the common antibiotic Doxycycline and Fluconazole was used as reference drugs. The activity index (%) was calculated from the following equation:

$$\text{Activity index} = \frac{\text{diameter of the inhibition zone of the tested compound}}{\text{diameter of the inhibition zone of the reference drug}} \times 100$$

From **table 1**, compound **3b** show higher antibacterial activities than the standard antibiotics Doxycycline against *Staphylococcus aureus* as gram-positive bacteria and *Proteus vulgaris* as gram-negative bacteria, while compound **7** and **12b** appeared an excellent antifungal agent. More over compound **12b** showed higher activity than the standard antibiotic Doxycycline against *Proteus vulgaris* and

Staphylococcus aureus because of the role of phenyl group. Our postulate was suggested by comparison with the activity of compound **12a**. The activity of oxazolo quinolinone **9** was equal against *Proteus vulgaris* while showed higher activity against *Staphylococcus aureus* compared to that of the standard antibiotic. The unique antimicrobial activity of that compound related to the SH group.

Table 1. Evaluation of Antimicrobial activity

Compound	*Staph aureus*		*Proteus vulgaris*		*Candida albicans*	
	D[a] (mm)	**AI[b] (%)**	**D[a] (mm)**	**AI[b] (%)**	**D[a] (mm)**	**AI[b] (%)**
3b	15.2	101.6	10.5	105.0	6.8	42.7
4	14.3	95.3	8.4	84	10.9	68.3
5	9.0	60.3	NA[c]	NA[c]	NA[c]	NA[c]
6	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
7	11.4	76.3	8.9	88.5	16.6	103.6
9	15.4	102.8	10.0	100.0	13.2	82.7
10	6.9	46.0	6.0	60.0	10.5	65.6
11	10.6	70.6	6.6	66.3	7.64	47.8
12a	NA[c]	NA[c]	NA[c]	NA[c]	8.5	53.4
12b	16.3	108.7	10.3	103.0	16.0	100.0
15	10.4	69.4	7.7	76.8	8.8	55.3
19	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
Control (DMSO)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
Doxycycline	15.0	100.0	10.0	100.0	NA[c]	NA[c]
Fluconazole	NA[c]	NA[c]	NA[c]	NA[c]	16.0	100.0

D[a]: Diameter of inhibition zone, AI[b]: Activity Index, NA[c]: No Activity

4. Conclusions

In the present work, some novel pyrazolo quinolinone and oxazolo quinolinone were successfully synthesized starting from precursors **1** and **8**. The antimicrobial activities of the prepared compounds assessed for their activities towards bacterial and fungal strains in vitro. The new products **3b**, **7**, **9**, **12b** revealed promising antimicrobial activity. Further works including molecular docking studies is currently underway.

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