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SYNTHESIS OF SOME NOVEL HETEROCYCLIC COMPOUNDS CONTAINING QUINOLONE MOIETY

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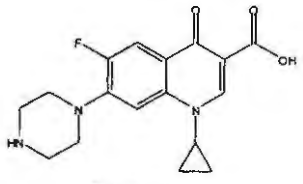
ABSTRACT

Syntheses of some new heterocyclic compounds incorporating quinolone moieties were achieved via reaction of 3-bromo-4-hydroxy-7-methoxyquinolin-2(1H)-one **(2)** with binucleophilic reagents. The reaction of 7-methoxyquinoline-2,4-dione **(1)** with Reimer-Tiemann reagent and / or $NaNO_2$ /HCl were also investigated. Constitutions of the new synthesized compounds were confirmed on the basis of both elemental analysis and spectral data.

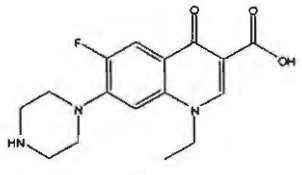
Keywords: Quinolone , Piperazine , Oxazol

INTRODUCTION

Quinolone systems are well known substances with great therapeutic importance, particularly in the treatment of viral [***Lins et la., (2010)***], HIV [***Ahmed et la., (2010)***], bacterial e.g Ciprofloxacin and Norfloracin **Fig.(1)** [***Yamamoto et la., (2007), Falgas et la., (2007)***], cancer [***Chen et la., (2002), Chen et la., (2004)***], malarial [***Winter et la., (2008)***], microbial [***Hooper et la., (2004)***], leishmanial [***Palit et al., (2008)***], diseases. They are, also, known as photo-proliferative [***Arya et la., (2007)***]. These compounds offer the potential ability to function as synthetic nucleoside analogue precursors.



Ciprofloxacin



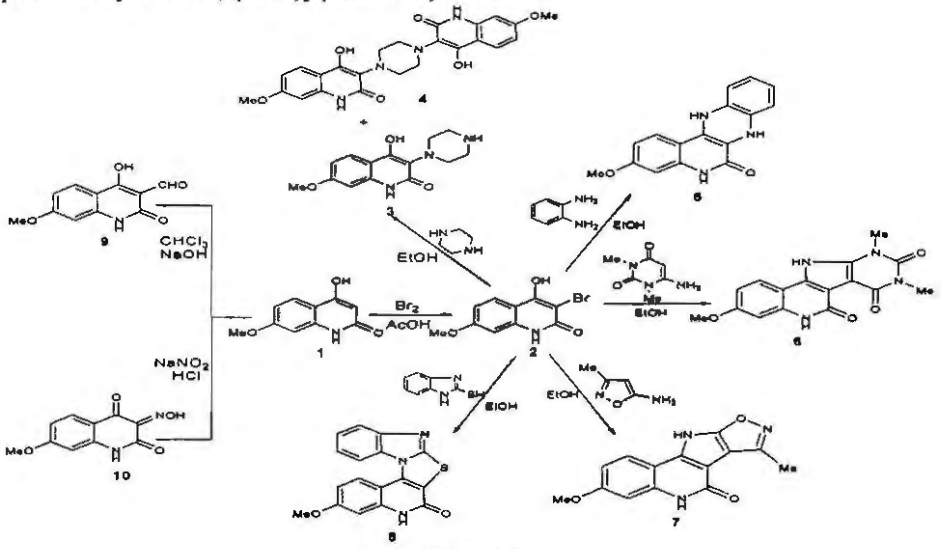
Norfloxacin

Fig.(1)

In view of the above biological importance and in continuation of our studies on the chemistry of 3-acetylquinolones [***Zoorob et al., (1986), Zoorob et al., (1985)***], we, herein, present this work as a part of our program directed towards developing new approaches for the synthesis of a variety of annulated heterocyclic compounds incorporating quinolone moieties, e.g, **5-8**.

RESULT AND DISCUSSION

We found that 3-bromo-4-hydroxyquinolin-2(1H)-one derivatives **2** are an excellent building block for the synthesis of the target compounds. Thus, condensation of 3-bromo-4-hydroxy-7-methoxyquinolin-2(1H)-one (**2**) [which was obtained by bromination of **1**, c.f. Experimental] with the dibasic secondary amine like piperazine gave the new quinolones **3** and **4** with mono- and bis-tertiary amine moities, respectively (Scheme 1). The structure of **4** was compatible with its ^{1}H-NMR spectrum which displayed multiple signals at 2.50 ppm corresponding to eight protons of piprazine moiety. Also, heating of **2** with the primary aromatic amine *o*-phenylenediamine afforded compound **5**. While, heating of compound **2**, with the cyclic enamines 6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione and 3-methylisoxazol-5-amine afforded compounds **6** and **7** respectively. Moreover, heating of **2** with 1H-benzo[d]imidazole-2-thiol yielded 12-methoxybenzo[1,2:2,3]thiazolo[5,4-c]quinolin-2(1H)-one **8**. IR spectra of **5-8** showed disappearance of an (OH) band. Finally, Reimer-Tiemann reaction upon **1** yielded 4-hydroxy-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**9**). The formyl derivative **9** was prepared according to the literature procedures [Abass et al., (2005), Tomita et al., (1951), Brown et al., (1954)]. Nitrosation of **1** with nitrous acid yielded 3-(hydroxyimino)-7-methoxyquinoline-2,4(1H,3H)-dione (**10**). Compound **10** was prepared according to the literature procedure [Cai et al., (1996)] (Scheme 1).



Scheme 1

EXPERIMENTAL

Common reagent grade chemicals were either commercially available or prepared by standard literature procedures. All reactions were monitored by thin-layer chromatography (TLC) and preparative thin layer chromatography (PTLC) carried out on 0.2-0.4 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection. All melting points were determined on capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on Nicolet NEXUS 470 FT-IR spectrophotometer in potassium bromide (KBr). Vibrational transition frequencies are reported in wave number (cm^{-1}). ^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer (300 and 75 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard. The solvent for NMR spectra were $CDCl_3$, and DMSO-d_6. High resolution mass spectra (HRMS) were recorded using both a Bruker HCT ultra and a high resolution (Bruker Daltonics microTOF) instruments from methanol or dichloromethane solutions using the positive Electrospray Ionization Mode (ESI). The Mass spectra (MS) were measured on (Kratos, 70 eV) MS equipment and/or a Varian MAT 311 a spectrometer. Elemental analyses were performed on a Hosli CH-Analyzer and are within ±0.3% of the theoretical values.

Synthesis of 3-Bromo-4-hydroxy-7-methoxyquinolin-2(1H)-one (2)

Stirring of **1** (0.5 g, 2.62 mmol) in glacial acetic acid (8 ml) for 15 min. formed a suspension solution. Then, addition of bromine (0.2 ml, 3.80 mmol), drop by drop, with stirring formed a clear solution which was stirred for further 15 min., then poured onto ice-cold water, to give a precipitate which was filtered off, dried and crystallized from benzene to afford 3-bromo-4-hydroxy-7-methoxyquinolin-2(1H)-one **2**, yield (0.59 g, 83.1%), m.p 198°C (Benzene); R_f = 0.59 [ethyl acetate: pet. ether(40:60)] (1:1); IR(KBr): γ/cm^{-1}= 3405 (HO), 3223 (NH), 2629 (CH, str.), 1637(CONH); MS(EI, 70 eV) m/z(%) = 271 (M^++1, 53.40), 269 (M^+-1, 41.40), 268 (M^+-2, 39.80), 191 (36.8), 150 (100, base peak), 148 (22.4); Anal. Calcd. for $C_{10}H_8BrNO_3$: C, 44.47; H, 2.99; N, 5.19 Found: C, 44.38; H, 2.87; N, 5.12.

General procedure for the synthesis of compounds 3 and 4

Refluxing of **2** (0.50 g, 1.85 mmol) with piprazine (0.16 g, 1.85 mmol) in (15 ml) of ethanol for 6 hours, then leaving the reaction mixture to cool at room temperature, deposited a solid product, which was collected by filtration and recrystallization from methanol to give 4-hydroxy-7-methoxy-3-(piperazin-1-yl)quinolin-2(1H)-one (**3**). The filtrate of the reaction was poured onto ice-cold water, the formed precipitate was filtered off, dried and crystallized from DMF/H_2O to afford bis compound 3,3'-(piperazine-1,4-diyl)bis(4-hydroxy-7-methoxyquinolin-2(1H)-one) (**4**).

4-Hydroxy-7-methoxy-3-(piperazin-1-yl)quinolin-2(1H)-one (3)

Yield 35.30%, m.p 180°C (MeOH); R_f = 0.91 [ethyl acetate: pet. ether(40:60)](2.5:4); IR(KBr): γ/cm^{-1}= 3444(OH), 2925(NH), 2852(CH, str.), 1616(CONH); ^{1}H-NMR (DMSO-d6): δ: 2.55 (s, 1H, NH, D_2O exchangeable), 3.19 (t, 8H, piprazine), 3.78(s, 3H, OCH_3), 6.54-6.75 (m, 3H, aromatic-CH), 7.94(s, 1H, CONH, D_2O exchangeable), 12.33(s, 1H, OH); HRMS(MicroTof): m/z for $C_{14}H_{17}N_3O_3$ calcd: 275.30, found: 276.100 (M^++1, base peak); MS(EI, 70 ev) m/z(%) = 276(M^++1,

100, base peak), 159(10.00), 83(90.00), 81(60.00). Anal. calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26 Found: C, 61.11; H, 6.27; N, 15.25.

3,3'-(Piperazine-1,4-diyl)bis(4-hydroxy-7-methoxyquinolin-2(1H)-one) (4)

Yield 15.00%, m.p > 315°C (DMF/H_2O); R_f = 0.37 [ethyl acetate: pet. ether(40:60)](1:2); IR(KBr): γ/cm^{-1}= 3442(OH), 3223 (NH), 2821(CH, str.), 1623(CONH); ^{1}H-NMR ($CDCl_3$-H): δ: 2.50(d, 8H, Piprazine), 3.80(s, 6H, 2 OCH_3), 6.90(m, 6H, aromatic-CH), 7.87(s, 2H, 2 CONH, D_2O exchangeable), 12.33(s, 2H, OH); MS(EI, 70 ev) m/z(%) = 466(M^++2, 5.01), 465(M^++1, 10.31), 464(M^+,0.04), 463(M^+-1, 2.26), 433(M^+-OMe, 4.23), 191(100.00, base peak), 190(21.77). Anal. calcd. for $C_{24}H_{24}N_4O_6$: C, 62.06; H, 5.21; N, 12.06 Found: C, 62.10; H, 5.23; N, 12.09.

General procedures for synthesis of polycyclic compounds 5-8

A mixture of **2** (0.50 g, 1.85 mmol) and appropriate bifunctional nucleophilic reagent (2.22 mmol), namely; *o*-phenylenediamine, 6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione, 3-methylisoxazol-5-amine, and 1H-benzo[d]imidazole-2-thiol in DMF (20-25 ml) was heated for 4-8 h at 120^{0}C. The reaction mixture was left overnight at room temperature whereby the crystalline precipitate was filtered off, dried then recrystallized from the proper solvent to give compounds **5-8**, respectively.

3-Methoxyquinolino[4,3-b]quinoxalin-6[5H, 7H, 12H]-one (5)

Yield 40.0%, m.p 163-4°C (EtOH); R_f = 0.35 [ethyl acetate: pet. ether(40:60)](2.5:4); IR(KBr): γ/cm^{-1}= 3223(NH), 2850(CH, str.), 1625(CONH); ^{1}H-NMR (DMSO-d6): δ: 3.35(s, 2H, 2NH, D_2O exchangeable), 3.79(s, 3H, OCH_3), 6.82-7.75(m, 7H, aromatic-CH), 9.68(s, 1H, CONH, D_2O exchangeable); MS(EI, 70 ev) m/z(%) = 281(M^++2, 2.16), 280(M^++1, 2.54), 279(M^+, 8.45), 149(76.26), 57(100, base peak), 56(24.40), 55(46.36), 54(6.62). Anal. calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05 Found: C, 68.78; H, 4.72; N, 15.09.

2,4-Dimethyl-9-methoxypyrimido[4',5':2,3]pyrrolo[4,5-c]quinolin-3, 5,6(7H) trione(6)

Yield 15.00%, m.p > 315°C (EtOH); R_f = 0.37 [ethyl acetate: pet. ether(40:60)](1:2); IR(KBr): γ/cm^{-1}= 3223 (NH), 2629 (CH, str.), 1640 (CONH); ^{1}H-NMR (DMSO-d6): δ: 3.29(s, 6H, 2NCH_3), 3.79(s, 3H, OCH_3), 5.21(s, 1H, NH, D_2O exchangeable), 6.82-7.75(m, 3H, aromatic-CH), 8.01(s, 1H, CONH, D_2O exchangeable); MS(EI, 70 ev) m/z(%) = 327 (M^++1, 1.57), 326 (M^+, 3.62), 325 (M^+-1, 1.50), 324 (M^+-2, 2.46), 175 (6.56), 174 (4.10), 173 (2.35), 155 (100.00, base peak), 154 (5.37), 153 (2.39). Anal. calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17 Found: C, 58.92; H, 4.37; N, 17.19.

4-Methyl-8-methoxyisoxazolo[5', 4': 2,3]pyrrolo[4,5-c]quinolin-5(1H)-one (7)

Yield 49.41%, m.p 275-8°C (DMF/H_2O); R_f = 0.40 [ethyl acetate: pet. ether(40:60)] (3:4); IR(KBr): γ/cm^{-1}= 3223 (NH), 2629 (CH, str.), 1625 (CONH); ^{1}H-NMR (DMSO-d6): δ: 2.50(s, 3H, CH_3), 3.88(s, 3H, OCH_3), 5.10(s, 1H, NH, D_2O exchangeable), 6.87-7.45(m, 3H, aromatic-CH), 8.008(s, 1H, CONH, D_2O exchangeable); MS(EI, 70 ev) m/z(%) = 270 (M^++1, 1.86), 269 (M^+, 3.68), 268 (M^+-1, 2.89), 208 (100, base peak), 150 (39.15), 149 (13.23), 148 (5.30), 122 (34.88), 121

(5.91). Anal. calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61 Found: C, 62.48; H, 4.16; N, 15.58.

12-Methoxybenzo[d]imidazo[1', 2': 2,3] thiazolo[5,4-c]quinolin-2(1H)-one (8)

Yield 9 %, m.p >315°C (DMF/H_2O); R_f = 0.23 [ethyl acetate: pet. ether (40:60)](3:4); IR(KBr): γ/cm^{-1}= 3223 (NH), 2629 (CH, str.), 1621 (CONH); ^{1}H-NMR (DMSO-d6): δ: 3.80(s, 3H, OCH_3), 6.87-7.95(m, 7H, aromatic-CH), 8.006(s, 1H, CONH, D_2O exchangeable); MS(EI, 70 ev) m/z(%) = 321(M^+, 2.41) 320(M^+-1, 2.05), 308 ((M^+-CH_3)+2, 22.92), 307 [(M^+-CH_3)+1, base peak], 306 (M^+-CH_3, 14.54), 290 (M^+-OCH_3, 1.44), 170 (2.01), 151 (4.40), 150 (34.23). Anal. calcd. for $C_{17}H_{11}N_3O_2S$: C, 63.5zo4; H, 3.45; N, 13.08 Found: C, 63.51; H, 3.49; N, 13.11.

4-Hydroxy-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (9)

Compound 1 (0.5 g, 2.62 mmol) was refluxed with Chloroform (14 g, 100.84 mmol) and NaOH 15% (8.5 ml) for 3h. The reaction mixture was, next, left overnight at room temperature, whereby the deposited yellow precipitate was filtered off, dried then recrystallized from DMF/H_2O to afford **9**, yield 92.5%, m.p >315°C (dec.) (DMF/H_2O); R_f = 0.23 [ethyl acetate: pet. ether(40:60)](1:2); IR(KBr): γ/cm^{-1}= 3569(OH), 3237(NH), 2966(CH, str.), 1633(CO), 1610(CONH), 1513(C=C); HR MS(MicroTof; m/z for $C_{11}H_9NO_4$ calcd:219.19 found: 218.0459(M^+-1). Anal. calcd. For $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39 Found: C, 60.31; H, 4.17; N, 6.36.

3-(Hydroxyimino)-7-methoxyquinoline-2,4(1H,3H)-dione (10)

A solution of $NaNO_2$ (0.24 g, 3.48 mmol) in 10 ml (0.2 N) NaOH was added to a cold solution of 1 (0.5 g, 2.62 mmol) in 10 ml (0.2 N) NaOH. After stirring at 0-5°C the reaction mixture was acidified with HCl (2N, 4.87 ml) then stirred for 1 h to give a yellow precipitate. The precipitate was washed with water, filtered off, dried and crystallized from ethanol to afford **10**, yield 22.81%, m.p 164-5°C (EtOH); R_f = 0.37 [ethyl acetate: pet. ether(40:60)](1:2); IR(KBr): γ/cm^{-1}= 3328 (OH), 3225 (NH), 2629 (CH, str.), 1648 (CO), 1608 (CONH); MS(EI, 70 ev) m/z(%) = 203 (M^+-OH, 13.0), 202 (M^+-(OH+H), 30.40), 149 (39.10), 55 (100.0, base peak). Anal. calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72 Found: C, 54.59; H, 3.63; N, 12.69.

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الملخص العربى

فى هذا البحث تم تخليق مركبات جديدة غير متجانسة الحلقة والمحتوية على نواة الكينولون عن طريق تفاعل ٣-برومو-٤-هيدروكسى-٧-ميثوكسىكينولن-٢(H1)-ون مع كواشف ثنائية النيوكليوفيل ومن جانب اخر كما تم دراسة تأثير كاشف ريمر- تيمن وأيضا تكوين مشتق النيروز من مركب ٧-ميثوكسى كينوولين-٤,٢-دايون تم أثبات التراكيب البنائية للمركبات الجديدة من خلال التحاليل الدقيقة ومن نتائج الاطياف.