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Synthesis and study of antimicrobial agents of newly 6-nitro-4-hydroxy-2-quinolone derivatives

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ABSTRACT

*Present work describes the synthesis of 6-nitro-4-hydroxy-2-quinolone derivatives by Nitration of 4-hydroxyquinolines **Ia,b** give 4-hydroxy-6-nitroquinolines **IIa,b.** Alkaline hydrolysis of **IIa,b** give 5-nitrosalisylic acid **V**. Compounds **IIa,b** reacted by the condensation with substituted aryl aldehyde e.g anisaldehyde and bezaldehyde in ethanol and with thiourea, semicarbazide and urea, to give **VIa-d** and **VIIa-c** respectively. The structure of all these newly synthesized compounds are established by elemental analysis, IR, ^{1}H-NMR spectral data. These compounds were evaluated for microbial screening against Gram positive & Gram negative bacteria and fungi strains such as Aspergillus nigar and Aspergillus flavus. Most of these compounds showed moderate to good activity against all the species of bacteria and fungi.*

Key words: 6-nitro-4-hydroxy-2-quinolone, , aldehydes, urea and its derivatives, antimicrobial activity.

INTRODUCTION

A simple routes to obtain a series of acryloyl and ethylidene derivatives of 6-nitro-4-hydroxy-2-quinolone structures are of great interest because of the involvement of these 4-hydroxy-2-quinolone derivatives in various biological fields[1-4] They are used in medicinal and drugs field with wide range such as antithyroid and antituberculosis activities [5] ,anti-inflammatory [6] ,PET radioligands for the glycine- binding site of NMDA receptors [7], molluscicidal and larvicidal activities[8], antimicrobial agents [9] , anti angiogenics [10],aldose reductase inhibitor [11],multiple sclerosis therapies[12], anti HIV [13],antitumor[14], antidepressant[15],antioxdants [16] tyrosine kinase inhibiting agents [17] anticonvulsants[18] and antiseptic agents [19]. They are also useful intermediates in the manufacture of azo dyes [20-22] .

Over the past two decades, 4-hydroxy-2-quinolone derivatives have attracted much attention due to their considerable biological and pharmacological activities so these assets prompted us to prepare some new substituted quinolinone derivatives with potential biological activity. In light of these observations we have synthesized some new acryloyl and ethylidene from reaction of 6-nitro-4-hydroxy-2-quinolones with substituted aryl aldehyde ,urea and its derivatives in good yield . Most the synthesized compounds **VIa-d** and **VIIa-c** were screened for their antimicrobial evaluation against *Escherichia coli*, *Bacillus cereus*, *Aspergillus niger*, *Aspergillus flavus*. Most of the compounds showed from moderate to good activity.

MATERIALS AND METHODS

Melting points were uncorrected and determined in an open capillary tube **.** Yields corresponded to pure products. IR spectra were recorded on a Perkin Elmer SP-880 spectrophotometer and ^{1}H-NMR spectra on a Varian 270 MHz spectrometer, using DMSO-*d6* as a solvent and tetramethylsilane (TMS) as an internal standard (chemical shifts in δ ppm). Microanalysis were carried out at the Microanalytical Unit at Cairo and El-Mansoura Universities

General procedure for preparation of 3-acetyl-4-hydroxy-6-nitro-(2H)-quinolinone IIa,b:
To a solution of 3- acetyl-4-hydroxy-2(1H)-quinolinones **Ia,b** (0.01 mole) in Conc. H_2SO_4 (30ml) added powdered KNO_3(3.2 g) during one hour at temperature below - 5°C with continuous stirring then added Conc. HNO_3dil (1:4) (5 ml) during 2 h at the same temperature. The brown liquid formed was poured onto crushed ice and the solid product was filtered and crystallized from EtOH to give yellow crystals of the target products **IIa,b**.

3-Acetyl-4-hydroxy-1-methyl-6-nitro-(2H)-quinolinone (IIa)
Yield (75%); yellow crystals; mp. 332-334°C;IR(KBr, cm^{-1}):3425 (OH),3083(CHarom),1689,1628(C=O) ,1530 (NO_2). Anal. calcd. for $C_{12}H_{10}N_2O_5$ (262.06) C,54.97;H,3.84; N ,10.68 .Found : C,54.89;H,3.64;N,10.72 %.

3-Acetyl-1-ethyl- 4-hydroxy-6-nitro-(2H)-quinolinone (IIb)
Yield(65%); yellow crystals; m.p.206-208°C;IR(KBr,cm^{-1}) 3424(OH), 3093(CHarom),1697, 1626 (C=O), 1533(NO_2). Anal.calcd. for $C_{13}H_{12}N_2O_5$(276.07) C,56.52;H,4.38; N,10.14.Found: C,56.67;H,4.51;N,10.22%.

Preparation of 2-hydroxy-5-nitrobenzoic acid V
To a solution of 4-hydroxyquinolinones **IIa,b**(0.001 mole) with refluxed with aqueous 20% KOH solution (20ml) for 20 h, cool, pour into ice water and acidify using dil. HCl, then filtered the product to give 5- nitrosalicylic acid .m.p. 229-230°C and lit .m.p.233-235°C[23] .

Preparation of substituted 3-acryloyl-6-nitro-4-hydroxy 2(1H) quinolone (VIa-d).
A mixture of 3-acetyl derivatives **II a,b** (0.01 mole), appropriate aromatic aldehydes (0.01 mole) and two drops of piperidine was heated on water bath for 1 hr.The product was triturated with ethanol, filtered off and crystallized from the proper solvent to give target products.

Spectroscopic data of compounds
(*E*)-1-Methyl-4-hydroxy-3-(phenyl)acryloyl-6-nitroquinolin -2(1*H*)-one(VIa)
Yield(53%); yellow crystals; m.p.261-263°C; IR(KBr,cm^{-1}:3448(OH) , 3090(CHarom),1640, 1612 (C=O), 1521(NO_2). ^{1}H NMR(DMSO-*d6*) : δ ppm3.43 (s,3H,CH_3), 7.01-7.49 (2H,olefinicH),7.40-8.81 (m, 7H,ArH),12.20(s,1H,OH). Anal.calcd. for $C_{19}H_{14}N_2O_5$ (350.32) C,65.14;H ,4.03;N,8.00 .Found : 65.37; H,4.11;N,8.03%.

(*E*)- 4-hydroxy- 1-methyl -3-(3-(4-methoxyphenyl) acryloyl-6-nitroquinolin-2(1*H*)-one(VIb)
Yield(35%);yellow crystals;m.p.265-267°C; IR(KBr, cm^{-1}) : 3448(OH) ,3101(CHarom), 1648,1613(C=O), 1531(NO_2). Anal.calcd. for $C_{20}H_{16}N_2O_6$ (380.43) C,63.14;H,4.23;N, 7.39.Found : 63.26; H,4.18;N,7.15%.

(*E*)- 1-ethyl-4-hydroxy- 3-(phenyl)acryloyl-6-nitroquinolin-2(1*H*)-one(VIc)
Yield(63%);yellow crystals;m.p.242-244°C; IR(KBr, cm^{-1}): 3424(OH) ,3091(CHarom), 1700,1609(C=O),1521(NO_2). Anal.calcd. for $C_{20}H_{16}N_2O_5$ (364.35) C,65.93;H,4.43;N,7.69.Found : 65.74; H,4.23;N,7.79%.

(*E*)-1-Ethyl-4-hydroxy-3-(3-(4-methoxyphenyl)acryloyl)-6-nitroquinolin-2(1*H*)-one(VId)
Yield(45%);brown crystals;m.p.211-213°C; IR(KBr, cm^{-1}): 3446 (OH) ,3089(CH arom) , 1668,1615 (C=O),1525(NO_2).

^{1}H NMR(DMSO-*d6*) : δ ppm 3.88(s,3H,OCH_3), 7.55-7.60(q,2H,olefinic H) , 4.29(q,2H, N-CH_2) ,1.32(t,3H,CH_3) ,7.63-8.82 (m,7H,ArH) ,12.20 (s,1H,OH),Anal.calcd. for $C_{21}H_{18}N_2O_6$ (394.38) C,63.96;H,4.60;N,7.10.Found : 63.70; H,4.83; N,7.32 %.

Preparation of urea ,thiourea , and semicarbazide derivatives of 3-acetyl-1-methyl or 1- ethyl- 6-nitro-4-hydroxy2(1H) quinolone(VIIa-c)
A mixture of 3-acetyl derivatives **II a,b** (0.01 mole) in ethanol (10ml) with urea and its derivatives (0.01mole) was refluxed for 1 hr and left to cool. The solid formed was filtered and crystallized from the proper solvent to give target products .

(*E*)-1-(1-(4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene) thiourea(VIIa)
Yield(40%);yellowish brown crystals;m.p.186-188°C; IR(KBr, cm^{-1}) :3676,3650(NH_2),3423(OH) ,3092(CHarom), 1670,1607 (C=O), 1525(NO_2) . Anal.calcd. for $C_{13}H_{12}N_4O_4S$ (320.32) C,48.74;H,3.77;N,17.49.Found : 48.65; H,3.65;N,17.58%.

(*E*)-1-(1-(4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinolin-yl)ethylidene)semicarbazide (VIIb)
Yield(56%); yellowish brown crystals;m.p.198-200°C; IR(KBr,cm^{-1}): 3676,3652(NH_2), 3423(OH) ,3088(CHarom), 1669,1616 (C=O), 1520(NO_2). Anal.calcd. for $C_{13}H_{13}N_5O_5$ (319.22) C,48.90;H,4.10;N,21.94.Found : 48.89; H,4.36;N,21.73%.

(*E*)-1-(1-(1-ethyl-4-hydroxy-6-nitro-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene) urea(VIIc)
Yield(60%);yellowish brown crystals; m.p.175-177°C; IR(KBr, cm^{-1}) 3676,3650(NH_2), 3447(OH), 3093(CH arom), 1680, 1610 (C=O), 1522(NO_2). ^{1}H-NMR : 2.09(s,3H,CH_3), 4.28 (q,2H,N-CH_2),1,30(t,3H,CH_3),7.78-8.60(m,,3H,Ar H) ,12.03 (s,1H,OH), 8.60(s,2H,NH_2).. Anal.calcd. for $C_{14}H_{14}N_4O_5$ (318.23) C,52.83;H, 4.43;N,17.60. Found :52.88; H,4.67;N,17.72%.

Antimicrobial Activity
Most of synthesized nitroquinolinone derivatives **VIa-d**& **VIIa-c** were screened for their antibacterial and antifungal activity tested in vitro against Gram positive bacterium *Bacillus cereus*, Gram negative bacterium *Escherichia coli* and two fungi *Aspergillus nigar* and *Aspergillus flavus.*

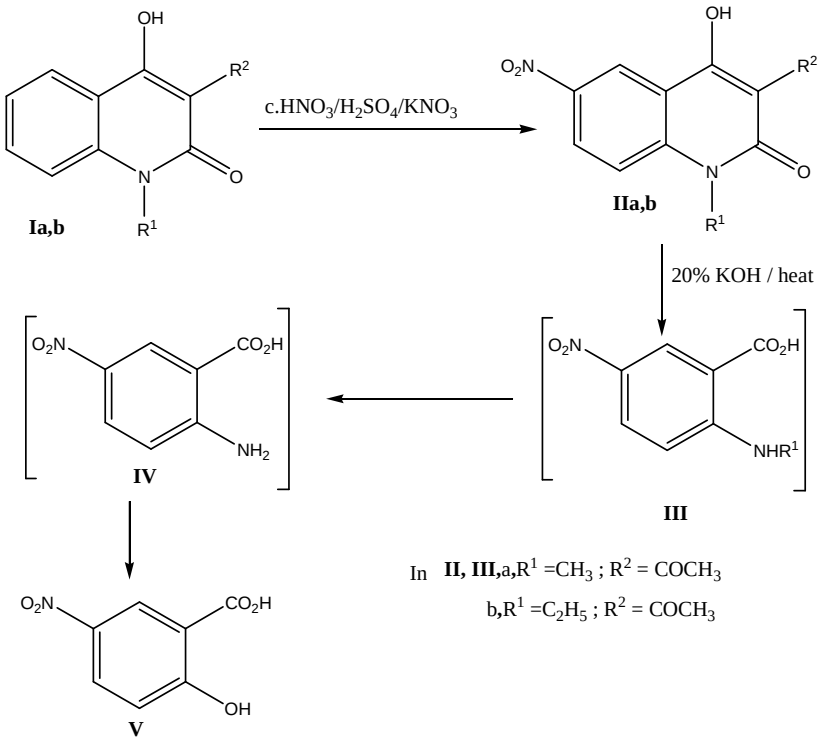
Nutrient agar medium has been utilized for growing test organisms. The diameters zones have been used as a parameter to express the anti- microbial activity where most of the compounds were tested at a unique conc.of 200 – 300 µL . These synthesized compounds were biologically evaluated and results are reported in **Table 1**.

Table 1 Antimicrobial study of newly 6-nitro-4-hydroxy-2-quinolone derivatives

Comp. No.	Bacteria		Fungi	
	Escherichia coli	*Bacillus cereus*	*Aspergillus flavus*	*Aspergillus nigar*
IIa	+	+++	+	+
IIb	+	+++	+++	+
VId	+	+	+	+
VIIa	+	-	+	-
VIIb	-	+++	+	+
VIIc	-	-	++	+

Highly active: +++; large clearing zone/ Moderately active; ++ ; medium clearing zone
Slightly active: + ; small clearing zone/ Inactive : - ; no clearing zone.

Scheme 1:



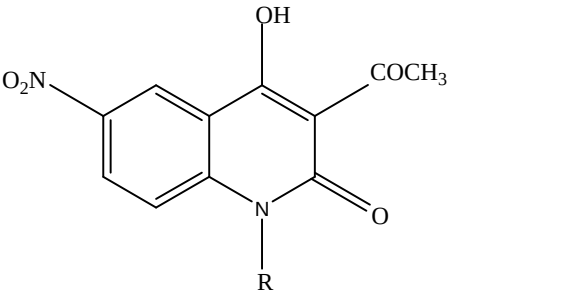
RESULTS AND DISCUSSION

It has been found that , 6-nitro-4-hydroxy-2(1H)-quinolones **IIa,b** were prepared through nitration of 4-hydroxy-2(1H)-quinolones **Ia,b** using a mixture of concentrated nitric acid and concentrated sulphuric acid in the presence of

potassium nitrate at -5^{0}C. Hydrolysis of **IIa,b** with 20% aqueous potassium hydroxide gave 5-nitrosalicylic acid **V** [23] . Formation of 5-nitrosalicylic acid **V** in this reaction was taken as evidence that nitration of 4-hydroxy-2(1H)-quinolones **Ia,b** occurred at position 6 (**Scheme 1**).

In this work, we have studied the reactivity of 6-nitro-4-hydroxy-2(1H)-quinolones **II** towards different reagents . Thus, **II** reacted readily with aromatic aldehydes in presence of ethanol and catalytic amounts of piperidine for which four products **VI a-d** seemed possible. Structures **II** were readily ruled out by analytical data of the reaction products. Thus, structures **VI** were established for the reaction products based on IR spectrum of compound **VIa** showed the presence of absorption bands at 3448cm^{-1} for of group OH ,at 1640 and 1612 cm^{-1} for CO groups, one absorption band at 1521 for NO_2 group. ^{1}H-NMR spectra which revealed the presence of CH_3 at δ = 3.43 ppm, the disappearance of signal of aromatic proton in position 6 at δ 7.32 ppm due to addition of NO_2 group, aromatic protons at δ = 7.40-8.81ppm and OH group at δ = 12.20 ppm Also, IR spectrum of compound **VId** showed the presence of absorption bands at 3446cm^{-1} for of group OH ,at 1668 and 1615 cm^{-1} for CO groups and one absorption band at 1525 for NO_2 group . ^{1}H-NMR spectra which revealed the presence of OCH_3 at δ = 3.88 ppm ,aromatic protons at δ = 7.63-8.82ppm and OH group at δ = 12.20 ppm (**scheme2**)

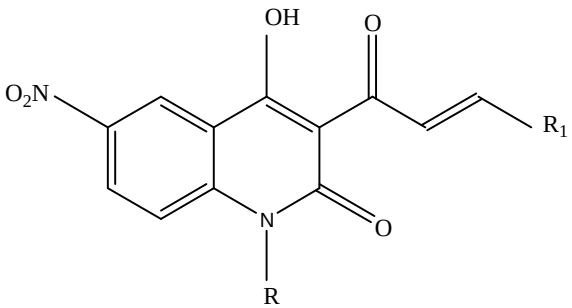
Scheme2



IIa,b

R=CH_3,C_2H_5

R_1=C_6H_5,$C_6H_4OCH_3$(p) R_1CHO



VIa-d

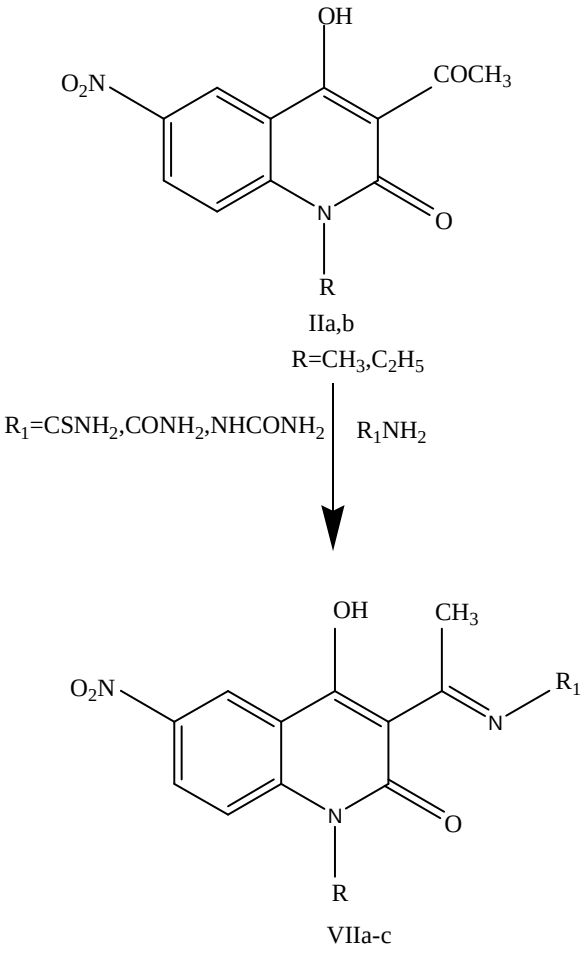
a R=CH_3, R_1=C_6H_5

b R=CH_3, R_1=$C_6H_4OCH_3$(p)

c R=C_2H_5, R_1=C_6H_5

d R=C_2H_5, R_1=$C_6H_4OCH_3$(p)

Scheme3



a R=CH_3, R_1=$CSNH_2$

b R=CH_3, R_1=$NHCONH_2$

c R=C_2H_5, R_1=$CONH_2$

Also, 6-nitro-4-hydroxy derivatives **VII** was prepared by the condensation reaction of 6-nitro-4-hydroxy2(1H)-quinolone **IIa,b** with urea and its derivatives .The IR spectrum of compound **VIIb** showed the presence of absorption bands at 3676,3652 for NH_2 group ,3423cm^{-1} for OH group , ,at 1669and 1616 cm^{-1} for CO groups, one absorption band at 1520 for NO_2 group. IR spectrum of compound **VIIc** showed the presence of absorption bands at 3676,3650 for NH_2, 3447cm^{-1} for OH group , at 1680 and 1610cm^{-1} for CO groups, one absorption band at 1522 for NO_2 group. ^{1}H-NMR spectra which revealed the presence of CH_3 at δ = 2.09 ppm ,aromatic protons at δ = 7.78-8.60 ppm,NH_2 group at δ=8.60 and OH group at δ = 12.03ppm. Also, the disappearance of absorption band of aromatic proton in position 6 at δ 7.33 due to addition of NO_2group (**Scheme 3**).

CONCLUSION

In summary, we have described a simple method for the synthesis of substituted 6-nitro-4-hydroxy-2-quinolone .The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity. The presence of nitro group in position 6 and presence of hydroxyl at position 4 as active in both antibacterial and antifungal screening.

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