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Synthesis and Microbial Activity of 5-Heterocyclo-8-hydroxyquinolines

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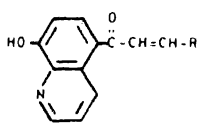
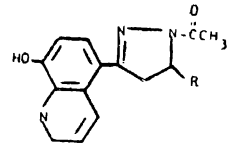
A new series of 5-substituted-cinnamoyl-8-hydroxyquinoline (1a–e) were prepared via the reaction of 5-acetyl-8-hydroxyquinoline with the selected aldehydes. 5 Pyrazolino-, isooxazolino-, and/or pyrmidine-thiono-8-hydroxyquinoline (2–4 respectively) were obtained from the reaction of 1a–e with hydrazines, hydroxylamine and thiourea. Michael addition of active methylene compounds, e.g. malononitrile, cyanoethyl acetate, to the chalcones (1a–e) in presence of ammonium acetate gave the corresponding nicotinonitrile derivatives (6 and 7) while the reaction of 1 with ethyl acetoacetate gave the cyclohexenone derivative (8) containing 8-hydroxyquinoline moiety.

NEW members of pyrazolines[1], isoxazolines[2,3], pyrimidinethiones[3], nicotinonitriles[4] and cyclohexenones[5] have been prepared for their wide application in different fields, but these containing 8-hydroxyquinoline moiety have not been reported yet. In this work 5-heterocyclo-substituted-8-hydroxyquinolines (**2a-e**–**8a-e**) were prepared to evaluate the effect of substitution on the microbial activity of the 8-hydroxyquinoline nucleus.



1a ; R=C_6H_5
b ; R=*p*-$OCH_3C_6H_4$
c ; R=*p*-ClC_6H_4
d ; R=α-furyl
e ; R=*n*-C_3H_7



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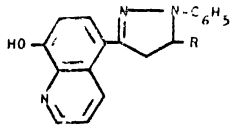
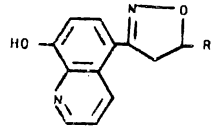
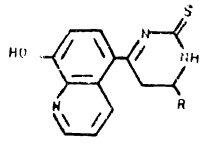


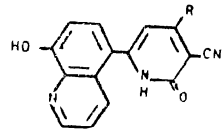
3a–e



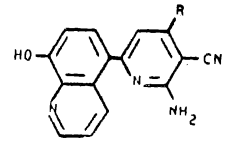
4a–e



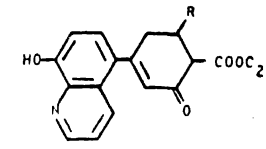
5a–e



6a–e



7a–e



8a–e

Experimental

All melting points are uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 599B spectrophotometer and nmr spectra ($CDCl_3$) on a Varian EM 390 (90 MHz) spectrometer.

5-Substituted-cinnamoyl-8-hydroxyquinolines (**1a–e**): To a solution of 5-acetyl-8-hydroxyquinoline (5 g, 0.03 mol) and the selected aldehydes (0.03 mol) in ethanol (50 ml) was added 10% alcoholic NaOH (5 ml) and the reaction mixture was stirred at room temperature for 5–10 h. The reaction mixture was allowed to stand in a refrigerator overnight. It was then acidified with dilute HCl, poured onto crushed ice and neutralised with excess sodium acetate. The resulting solid was washed with water, then with ice-cold methanol (5 ml) and recrystallised from the appropriate solvent (Table 1). These chalcones gave green colour when their alcoholic solutions were treated with $FeCl_3$ solution.

5-[1-Acetyl-5-substituted-Δ²-pyrazolin-3-yl]-8-hydroxyquinoline (**2a–e**): A mixture of the chalcones (**2a–e** ; 1 g, 0.004 mol) and 98% hydrazine hydrate (1 ml) in glacial acetic acid (30 ml) was refluxed for 7 h. The reaction mixture was cooled and the resulting solid was washed with alcohol and recrystallised from the appropriate solvent (Table 1).

5-[1-Phenyl-5-substituted-Δ²-pyrazolin-3-yl]-8-hydroxyquinolines (**3a–e**): A solution of the chalcones (**1a–e** ; 1 g, 0.004 mol) in absolute ethanol

TABLE 1—PHYSICAL DATA OF COMPOUNDS*

Compd. no.	Yield %	M.p.** °C	Mol. formula
1a	68	102–04[a]	$C_{18}H_{13}O_3N$
b	80	185–86[b]	$C_{19}H_{15}O_3N$
c	84	160–61[b]	$C_{18}H_{12}O_3NCl$
d	62	269–70[a]	$C_{15}H_{15}O_2N$
e	85	153–54[a]	$C_{16}H_{11}O_3N$
2a	67	258–59[a]	$C_{20}H_{17}O_2N_3$
b	66	203–05[a]	$C_{21}H_{19}O_3N_3$
c	68	205–07[a]	$C_{20}H_{16}O_2N_3Cl$
d	52	320d[a]	$C_{17}H_{19}O_2N_3$
e	65	125–27[a]	$C_{18}H_{15}O_3N_3$
3a	60	218–19[a]	$C_{24}H_{19}ON_3$
b	62	151–53[a]	$C_{25}H_{21}O_2N_3$
c	70	80–81[a]	$C_{24}H_{18}ON_3Cl$
d	51	282–84[c]	$C_{21}H_{21}ON_3$
e	53	188–90[a]	$C_{22}H_{17}O_2N_3$
4a	67	240–41[a]	$C_{18}H_{14}O_2N_2$
b	62	235–36[a]	$C_{19}H_{16}O_3N_2$
c	67	149–50[a]	$C_{18}H_{13}O_2N_2Cl$
d	52	102–04[a]	$C_{15}H_{16}O_2N_2$
e	53	139–40[a]	$C_{16}H_{12}O_3N_2$
5a	60	196–98[a]	$C_{19}H_{15}ON_3S$
b	58	206–08	$C_{20}H_{17}O_2N_3S$
c	62	202–04	$C_{19}H_{14}ON_3SCl$
d	55	138–40	$C_{16}H_{17}ON_3S$
e	57	178–80	$C_{17}H_{13}O_2N_3S$
6a	47	288–89[a]	$C_{21}H_{15}O_2N_3$
b	36	246–48	$C_{22}H_{15}O_3N_3$
c	36	218–19	$C_{21}H_{12}O_2N_3Cl$
d	34	323–25	$C_{18}H_{15}O_2N_3$
e	35	116–18	$C_{19}H_{11}O_3N_3$
7a	47	332d	$C_{21}H_{14}ON_4$
b	59	253d	$C_{22}H_{16}O_2N_4$
c	48	285d	$C_{21}H_{13}ON_4Cl$
d	34	308–10	$C_{18}H_{16}ON_4$
e	40	312	$C_{19}H_{12}O_2N_4$
8a	76	218–20[a]	$C_{24}H_{21}O_4N$
b	83	318–20[a]	$C_{25}H_{23}O_5N$
c	74	308–10	$C_{24}H_{20}O_4NCl$
d	59	125–27	$C_{21}H_{23}O_4N$
e	60	335d	$C_{22}H_{19}O_5N$

*All compounds gave C, H and N analyses results within the range ; compounds having S and Cl also showed satisfactory results.

**Solvent for crystallisation : [a]EtOH, [b]AcOH, [c]MeOH.

(30 ml), phenylhydrazine (1 ml) and piperidine (2 drops) was refluxed for 5 h. The resulting solid was washed with ethanol and recrystallised from the appropriate solvent (Table 1).

5-[5-Substituted-Δ^2-isoxazolin-3-yl]-8-hydroxyquinoline (**4a–e**) : A mixture of the chalcones (**1a–e** ; 1 g, 0.004 mol), hydroxylamine hydrochloride (0.4 g, 0.006 mol) and NaOH (0.2 g, 0.002 mol) in absolute ethanol (30 ml) was refluxed for 6 h. The reaction mixture was then concentrated, neutralised with dilute HCl, and the resulting solid was washed with ethanol and recrystallised from the appropriate solvent (Table 1).

5-[6-Substituted-7(H)-2-thio-1,2,5,6-tetrahydropyrimidine-4-yl]-8-hydroxyquinolines (**5a–e**) : A mixture of the chalcones (**1a–e** ; 1 g, 0.004 mol), thiourea (0.3 g, 0.004 mol) and potassium hydroxide (0.4 g, 0.004 mol) in absolute ethanol (30 ml) was refluxed for 12 h. The reaction mixture was concentrated, neutralised with dilute HCl, and the resulting solid was washed with water and recrystallised from alcohol (Table 1).

Michael addition on chalcones :

5-[1,5-Dihydro-2-oxo-4-substituted-nicotinonitrile-6-yl]-8-hydroxyquinolines (**6a–e**) : A mixture of the chalcones (**1a–e** ; 0.002 mol), ethyl cyanoacetate (0.002 mol), ammonium acetate (0.002 mol) and n-butanol (5 ml) was refluxed for 10 h. The reaction mixtures were cooled and the resulting solid was washed with water and crystallised from ethanol (Table 1).

5-[2-Amino-4-substituted-nicotinonitrile-6-yl]-8-hydroxyquinoline (**7a–e**) : A mixture of the chalcones (**1a–e** ; 0.002 mol), malononitrile (0.001 mol), ammonium acetate (0.002 mol) and n-butanol (5 ml) was refluxed for 8 h. The reaction mixture was cooled and the resulting solid was air-dried and recrystallised from ethanol (Table 1).

5-[7-Carboxyethyl-2-oxo-6-substituted-3-cyclohexen-4-yl]-8-hydroxyquinolines (**8a–e**) : A mixture of Na (0.1 g) in absolute ethanol (10 ml) and ethyl acetoacetate (0.2 ml, 0.002 mol) was stirred for 1 h. To the resulting mixture, the chalcones were added and refluxed for 5 h. It was than cooled and poured into dilute HCl and the resulting solid was recrystallised from ethanol (Table 1).

Antimicrobial activity :

Biological activity of the selected compounds were tested. Compounds **1–8** were dissolved in ethylene glycol (10 mg/100 ml) and the biological activity was tested by diffusion plate method[6]. The antifungal activity was determined against *Penicillum notatum*, *Aspergillus flavus* and *Stachybotrys atra* and the antibacterial activity against *Bacillus subtilis*, *Micrococcus luties* and *Serratia Sp.*

Bacterial suspension was prepared by adding sterile distilled water (10 ml) to 10-day old culture of the test bacteria grown on a nutrient agar[7]. Aliquot (1 ml) of the bacterial suspension was added to it followed by the test compound, incubated at 37° and then the inhibition zone was measured after 24 h. The experiments were repeated thrice.

Spore suspension was prepared by adding sterile distilled water (10 ml) to 10-day old culture of the test fungus grown on nutrient agar[8]. Aliquot of the spore suspension was added followed by the test compound, incubated at 37° and the inhibition zone was then measured after 3 days. The experiments were carried out in triplicate.

Results and Discussion

The reaction of 5-acetyl-8-hydroxyquinoline with the selected aldehydes in the presence of alcoholic sodium hydroxide gave new series of 5-substituted-cinnamoyl-8-hydroxyquinoline (**1a–e**). These compounds were identified by elemental analysis as well as by ir and nmr spectral data. Ir spectra showed bands at 1 680–1 660 (COCH=CH), 1 600 (C=C)

and 3 345 cm^{-1} (OH). Nmr spectra showed the disappearance of $COCH_3$ signal at δ 2.4 and the appearance of a multiplet at δ 6.8 – 8 (8-H).

Interaction of **1a – e** with hydrazines, hydroxylamine and thiourea under the experimental conditions gave the corresponding 5-[azolopyrimidinethiono]-8-hydroxyquinoline (**2a – e**, **3a – e**, **4a – e** and **5a – e**, respectively). Ir spectra showed bands at 1 600 (C=N), 1 720 – 1 700 (CO) and 3 350 cm^{-1} (OH) for *N*-acetylpyrazoline derivatives (**2a – e**); at 1 280 cm^{-1} (C – N) with the lack of NH_2 band for *N*-phenylpyrazoline derivative (**3a – e**); at 1 190 – 1 050 cm^{-1} (isoxazoline ring) for compounds (**4a – e**); and at 1 170 (C=S), 1 495 (C – N – S) and 3 350 cm^{-1} (OH) for the pyrimidine thione derivatives (**5a – e**).

Michael addition of the active methylene compounds ethyl cyanoacetate, malononitrile and ethyl acetoacetate to chalcones (**1a – e**) under the experimental conditions gave the corresponding nicotinonitrile and cyclohexenone derivatives (**6a – e**, **7a – e** and **8a – e**, respectively).

The ir spectra revealed characterestic bands at 1 600 (C=N), 1 750 (CO), 2 200 (C≡N), 3 100 (NH) and 3 300 cm^{-1} (OH) for **6a – e**; at 1 600 (C=N), 3 230 – 3 130 (NH_2), 2 180 (C≡N) and 3 400 cm^{-1} (OH) for **7a – e**; and at 1 720 (COOEt), 1 620 cm^{-1} (CO-conjugated) and 1 590 cm^{-1} (C=N) for **8a – e**. The nmr ($CDCl_3$) of **6a** showed signals at δ 2.7 (1H, s, CH), 9 3 (1H, s, NH) and 6.7 – 8 (11H, m, ArH).

5-Acetyl-8-hydroxyquinoline is quite potent against the organisms under test. The chalcone derived from 5-acetyl-8-hydroxyquinoline and its cyclised pyrimidinethione (**5b**) were effective only towards *S. atra*. This potency is much less in other cyclised pyrazole, isoxazole, nicotinonitriles and cyclohexenone derivatives.

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