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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL SCHIFF BASES AND HYDRAZONES DERIVED FROM 8-HYDROXY QUINOLINE MOIETY

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Abstract: 8-Hydroxyquinoline reacts with ethyl chloroacetate in the presence of anhydrous K2CO3 to yield ethyl (quinolin-8-yloxy) acetate **(1).** The ethyl ester reacts with hydrazine hydrate and forms 2- (quinolin-8-yloxy) acetohydrazide **(2),** which on condensation with various aldehydes gives *N*'-benzilidine-2-(quinolin-8-yloxy)} acetohydrazides **(3a-j).** The hydrazide upon reaction with various substituted acetophenones yields N'-(1-phenylethylidine)-2-(quinolin-8-yloxy)} acetohydrazides **(4a-j).** The newly synthesized compounds were assigned on the basis IR, MASS and ^{1}H NMR spectral data. All the compounds have been screened for their antibacterial and antifungal activity by the cup-plate method. Some of the compounds showed good activity against all the organisms.
Key words: Quinoline, Schiff bases, Hydrazones, Antibacterial, and Antifungal activity**.**

Introduction

Quinoline and their derivatives are receiving increasing importance due to their wide range of biological and pharmacological activities Quinoline ring structure is obtained by *ortho*-condensation of benzene ring with pyridine. It is also called l-azanapthalene or benzo[b] pyridine. It was first isolated by Runge in 1834, from coal tar bases and subsequently Gerhardt in 1842 obtained it from the alkaline pyrolysis of cinchonine, an alkaloid related to quinoline. The numbering in quinoline commences from the nitrogen atom which is assigned position-1[1]. A number of biological activities have been associated with quinoline-containing compounds such as anti-inflammatory[1], antiallergic[2], antimalarial[3], antibacterial[4], antiproliferative[5], anticancer[6] and antiparasitic[7] activities. In the present study, a novel series of schiff bases and hydrazones derived from 8-OH Quinoline moiety was reported here. The structures of the newly synthesized compounds were elucidated on the basis of IR, MASS and ^{1}H NMR spectral data. All the compounds have been screened for their in-vitro biological activity. The reaction sequence for the synthesis of the title compounds is outlined in **Scheme - 01.**

Experimental

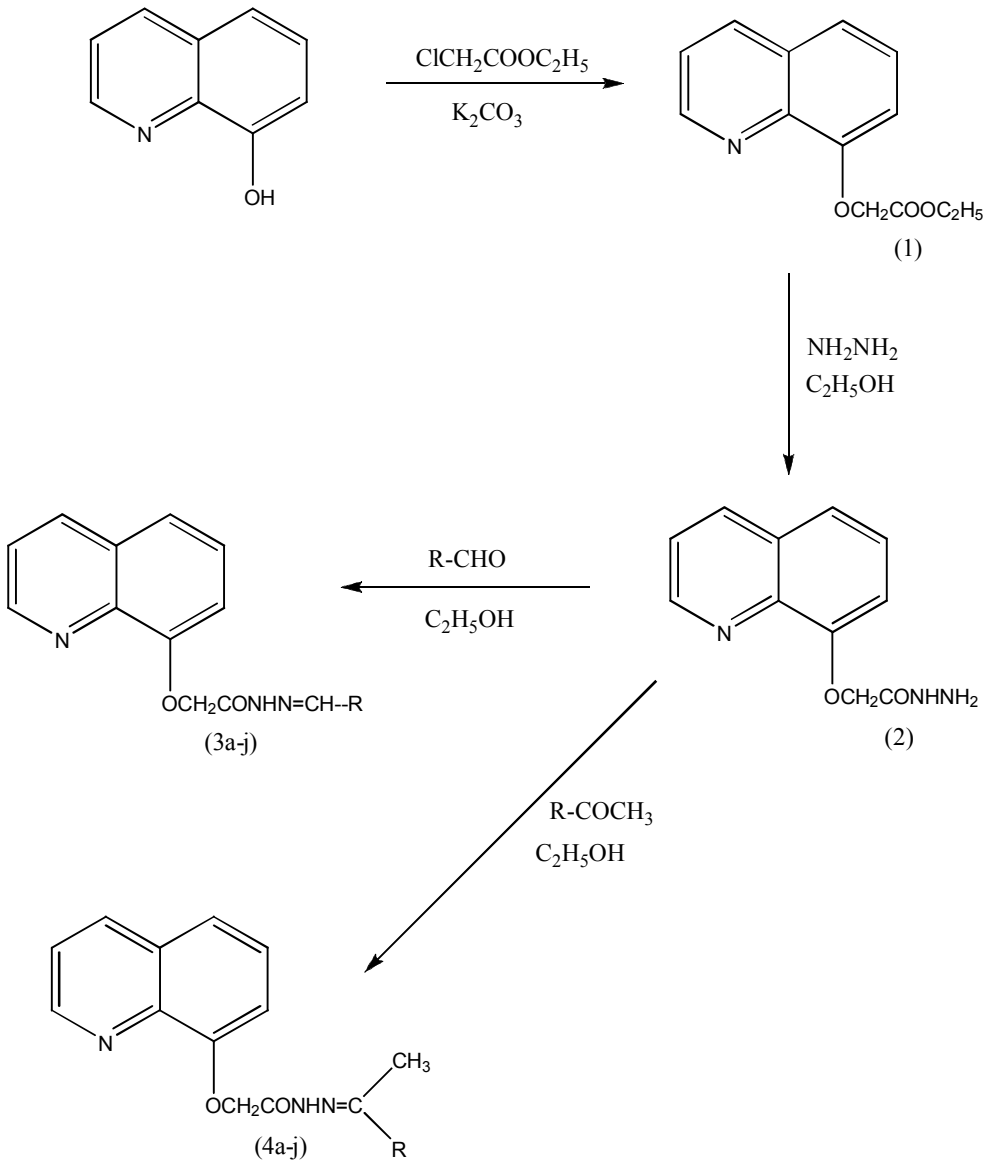
Melting points were determined by open capillary method and are uncorrected. Silica gel G plates were used for TLC and spots were located by UV or in iodine chamber. The IR spectrum (in KBr pellets) is recorded by using SHIMADZU PERKIN ELMER 8201 PC IR SPECTROMETER and frequencies are expressed in cm^{-1}. The PMR spectra were recorded on BRUKER AVANCE II 400 NMR SPECTROMETER in $CDCl_3$ and DMSO with TMS as an internal standard and values are expressed in δ ppm. The FAB mass spectra were recorded on JEOL SX-102/DA-6000 Mass spectrometer operating at 70ev. Elemental analyses were performed for C, N and were within ± 0.4% of theoretical values.

Synthesis of 8-quinolinoxyacetic acid hydrazide[8]

A mixture of ester (0.01 mol) in absolute ethanol (50 ml) and hydrazine hydrate (99%, 0.015 mol) was added and the reaction mixture was refluxed for about 15 hours. The solution was concentrated and allowed to cool over night. The resulting solid obtained was filtered, washed with cold ethanol and recrystallized from ethanol. The compound was separated as shining colourless needle shaped crystals. Yield 75%, mp 107^0C.

IR (KBr):3120 (NH), 1640 (C=O), 1610 (Ar-H). **NMR (DMSO-d_6)**: 4.87(s, 1H, OCH_2), 7.1-8.3 (m, 8H, 6Ar-H, & 2 NH_2), 9.1 (s, 1H, C-NH), **MASS:** m/z 217 (M^+)

Scheme-01



Synthesis of *N*'-benzilidine-2-(quinolin-8-yloxy)} acetohydrazides (3a-j).

To solution of hydrazide (0.01mol) in absolute alcohol(30ml), substituted aldehydes (0.01mol) and a few drops of glacial acetic acid were added and the mixture is refluxed for about 8 hours .The reaction mixture is cooled and poured into 100ml of ice cold water and the precipitated compound is filtered and recrystallized from alcohol.

3b: IR (KBr cms^{-1}): 3066 (C –H), 1699 (C=O), 1614 (C=N), 1587 (C=C), 1119 (C-O-C), 749 (C-Cl). **^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm):** 4.42 (2H, s, -OCH_2) , 7.11-9.12 (11H, m, Ar-H), 9.71 (IH, s, -CONH). **MASS(m/z):** 340 (M+ 1).

3c: IR (KBr cms^{-1}): 2930 (C-H), 1698 (C=O), 1623 (C=N), 1570 (C=C), 1107 (C-O-C) .**^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm):** 2.11 (3H, s, -OCH_3), 4.68 (2H, s, -OCH_2), 7.23-8.82 (11H, m, Ar-H), 9.36 (IH, s, -CONH). **MASS(m/z):** 335 (M+)

3d: IR (KBr cms^{-1}): 3148 (C-H), 2916 (C-H), 1681 (C=O), 1606 (C=N), 1557 (C=C), 831 (C-O-C). **^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm):** 2.39 (3H, s, -CH_3), 4.98 (2H, s, -OCH_2), 7.19-9.0 (11H, m, Ar-H). 12.16 (1H, s, -CONH). **MASS (m/z):** 320 (M+ 1).

Similarly other derivatives **(3a-j)** were synthesized and their physical data is given in table-1.

Synthesis of N'-(1-phenylethylidine)-2-(quinolin-8-yloxy)} acetohydrazides (4a-j)

To a solution of hydrazide (0.01mol) in absolute alcohol (30ml), substituted acetophenones (0.01mol) and a few drops of glacial acetic acid were added and refluxed for about 24-32 hours. The reaction mixture is allowed to

cool and the separated compound is collected and recrystallized from alcohol.

4a: IR (KBr cms^{-1}): 3055 (C-H), 1685 (C=O), 1602 (C=N), 1565 (C=C), 1080 (C-O-C). **^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm):** 3.14 (3H, s, -CH_3), 4.84 (2H, s, -OCH_2) 7.46-7.53 (11H, m, Ar-H), 8.97(1H,s,-CONH),**MASS(m/z):** 320 (M+ 1).
4b: IR (KBr cms^{-1}): 3125 (C-H), 1682 (C=O), 1553 (C=C), 1159 (C-O-C).
^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm): 2.31 (3H, s, CH_3), 2.59 (2H, s, OCH_2), 7.37-8.95 (10H, m, Ar-H), 9.31 (1H, s, CONH),**MASS(m/z):** 355 (M+ 2).
4i: IR (KBr cms^{-1}): 2924 (C-H), 1665 (C=O), 1597 (C=C), 1114 (C-O-C).
^{1}H NMR ($CDCl_3$/ DMSO-d_6, ppm): 3.54 (3H, s, -CH_3), 4.54 (2H, s, -OCH_2), 7.05-7.88 (10H, m, Ar-H), 9.36 (1H, s,-CONH), 10.54 (1H, s, -OH). **MASS(m/z):** 336 (M+ 1)

Similarly other derivatives **(4a-j)** were synthesized and their physical data is given in table-2

Antimicrobial activity

All the newly synthesized compounds **(3a-j & 4a-j)** were screened for their *in-vitro* antimicrobial activity by employing cup-plate method[9]. The antimicrobial activity was carried out against *P.aeruginosa, E.coli* (gram negative), *B.subtilis, S.aureus* (gram-positive) and for antifungal activity against *A.niger, C.albicans* by measuring the zone of inhibition in mm. The activities were performed at a conc. of 50 µg/ml. Streptomycin and Griseofulvin were used as standard drugs for comparision of antibacterial and antifungal activities respectively. DMF was used as solvent control. The antimicrobial activity data is reported in table-3 & 4.

Results and discussions

The purity of the compounds synthesized compounds was checked by performing TLC and by determining the melting points. All the final synthesized compounds were purified by recrystallization using appropriate solvents. All the compounds were elucidated on the basis of IR, ^{1}H NMR and Mass spectral data. The compounds were screened for their antibacterial and antifungal activity by cup-plate method against various Gram positive, Gram negative bacteria and fungal stains. among the synthesized compounds, compounds **3c, 3h, 3j, 4c, 4j** have shown maximum activity against all the four bacteria and in the antifungal activity the compounds **3i, 4c,4i** have shown maximum activity against both the fungi. But all the synthesized compounds were less active when compared to the standard drugs.

TABLE -1: Physical data of compounds 3a-j

Comp	R-CHO	Physical State	Molecular Formula	Molecular Weight	M.P (^{0}C)	% Yield
3a	C_6H_5	Green crystals	$C_{18}H_{15}N_3O_2$	305	105-107	55
3b	p-Cl	Green crystals	$C_{18}H_{14}ClN_3O_2$	339	132-134	60
3c	p-OCH_3	Light Brown Crystals	$C_{19}H_{17}N_3O_3$	335	118-120	65
3d	p-CH_3	Yellow Brown Crystals	$C_{19}H_{17}N_3O_2$	319	148-150	52
3e	p-$(CH_3)_2N$	Dark Brown Crystals	$C_{20}H_{20}N_4O_2$	348	166-168	60
3f	o-Cl	Brown Crystals	$C_{18}H_{14}ClN_3O_2$	339	108-110	58
3g	m-Br	Black Crystals	$C_{18}H_{14}BrN_3O_2$	383	153-155	66
3h	p-OH	Dark Brown Crystals	$C_{18}H_{15}N_3O_3$	321	125-127	64
3i	m-OH	Brown Crystals	$C_{18}H_{15}N_3O_3$	321	103-105	62
3j	p-Br	Yellow Crystals	$C_{18}H_{14}BrN_3O_2$	383	161-163	58

TABLE -2: Physical data of compounds 4a-j

Comp	R-C0CH_3	Physical State	Molecular Formula	Molecular Weight	M.P (^{0}C)	% Yield
4a	C_6H_5	Dark yellow crystals	$C_{19}H_{17}N_3O_2$	319	113-115	72
4b	p-Cl	white crystals	$C_{19}H_{16}ClN_3O_2$	353	143-145	68
4c	p-OCH_3	Light Brown Crystals	$C_{20}H_{19}N_3O_3$	349	128-130	76
4d	p-CH_3	Yellow Crystals	$C_{20}H_{19}N_3O_2$	333	108-110	66
4e	m-NO_2	Brown Crystals	$C_{19}H_{16}N_4O_4$	364	151-153	73
4f	p-NO_2	Red Crystals	$C_{19}H_{16}N_4O_4$	364	165-167	78
4g	p-NH_2	Creamy white Crystals	$C_{19}H_{18}N_4O_2$	334	132-134	69
4h	p-Br	Violet Crystals	$C_{19}H_{16}BrN_3O_2$	397	119-121	65
4i	p-OH	White Crystals	$C_{19}H_{17}N_3O_3$	335	171-173	80
4j	O-OH	Yellow Crystals	$C_{19}H_{17}N_3O_3$	335	121-123	80

Table-3: Antimicrobial and Antifungal Data of Compounds 3a-j

Comp	Diameter of zone of inhibition. (mm)					
	P.aeruginosa	***S.aureus***	***E.coli***	***B.subtilis***	***C.albicans***	***A. niger***
3a	10	10	11	09	09	11
3b	11	11	10	09	08	10
3c	12	10	10	10	10	10
3d	10	09	12	10	11	09
3e	09	08	12	11	10	11
3f	09	07	13	10	10	10
3g	08	10	12	12	09	10
3h	09	10	11	12	10	09
3i	09	11	10	10	11	11
3j	10	10	10	12	10	10
DMF	-	-	-	-	-	-
Streptomycin	17	18	19	18	-	-
Griseofulvin	-	-	-	-	20	21

Table-4: Antimicrobial and Antifungal Data of Compounds 4a-j

Comp	Diameter of zone of inhibition. (mm)					
	P.aeruginosa	***S.aureus***	***E.coli***	***B.subtilis***	***C.albicans***	***A. niger***
4a	12	11	08	10	11	10
4b	11	10	12	11	10	11
4c	10	12	11	12	10	12
4d	09	12	10	13	09	10
4e	11	08	11	10	08	09
4f	08	09	12	10	07	08
4g	07	10	09	12	07	09
4h	11	10	10	12	10	10
4i	10	11	10	13	11	11
4j	12	11	10	12	11	10
DMF	-	-	-	-	-	-
Streptomycin	17	18	19	18	-	-
Griseofulvin	-	-	-	-	20	21

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