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Synthesis, characterization and antimicrobial activity of some substituted N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides

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Abstract

Reaction of 8-hydroxy quinoline with ethyl chloroacetate to form 1-(quinolin-8-yloxy) butan-2-one (1). Compound 1 react with hydrazine hydrate in ethanol yield 2-(quinolin-8-yloxy) acetohydrazide (2). The condensation of (2) with various aldehydes yield the corresponding substituted N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides (3a-j). The compounds obtained were identified by spectral data and have been screened for antimicrobial activity.

Key words: Quinoline, schiff's base, antimicrobial activity.

Introduction

Compounds containing azomethine group (-CH=N-) is known as schiff bases. Day by day Schiff bases are more frequently applied for the betterment of human welfare. The importance of the Schiff base is due its versatile nature. Literature survey shows that many Schiff bases exhibit biological activities such as antifungal (Aliasghar et al. 2007) antibacterial (Sarı et al. 2003), antitumor (Saidul et al. 2002), anti-inflammatory (Iana et al. 2004), and Anticonvulsant (Verma et al. 2004).

Quinolines are a major class of alkaloids and play an important role in the fields of natural products and medicinal chemistry. Several methods for synthesizing quinoline have been known since the late 1800s (Skraup 1880) Quinolines and their derivatives are also important constituents of pharmacologically active synthetic compounds such as anti-inflammatory (Mohd and Rajesh 1998), antimicrobial agents (Abduallaa et al. 1992) cytotoxic activity (Kuo et al. 1993), antidotal and antibacterial (Awada et al. 1988).

This initiated the synthesis of compounds containing both the quinoline coupling schiff base systems in the same matrix to serve as a new scaffold for the synthesis of antimicrobial agents. The present work deals with the reaction of 2-(quinolin-8-yloxy) acetohydrazide (2) with different aromatic aldehydes to form schiff's bases (3a-j). Finally, the structures of all the various synthesized compounds were assigned on the basis of IR and ^{1}H NMR spectral data and these compounds were screened for their antimicrobial activity.

Experimental

Melting points were determined with open capillary and are uncorrected. I.R spectra were recorded on a Shimadza FTIR model 8010 spectrophotometer, ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker supercon FT-NMR instrument using TMS as internal standard.

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General procedure for Synthesis of 1-(quinolin-8-yloxy) butan-2-one (1)

An equimolar mixture of 8- hydroxy quinoline (0.01 mol, 1.43gm), ethyl chloroacetate (0.01mol, 138gm) and anhydrous potassium carbonate (0.02mol, 3.76gm) in dry acetone (60 ml) was refluxed on a water bath for 24 hr. The inorganic solid was filtered and the excess solvent was removed on a rota vapour, dried and recrystalized from ethanol. The compound was separated as reddish brown crystals.

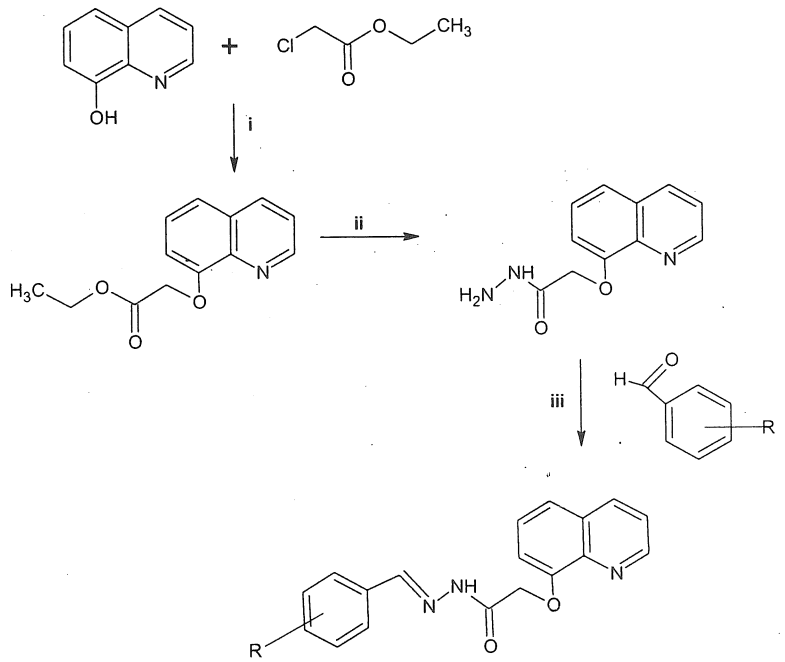
General procedure for Synthesis of 2-(quinolin-8-yloxy) acetohydrazide (2)

To a suspension of (1) (0.01 mol) in absolute ethanol (50 ml), hydrazine hydrate (99%, 0.015 mol) was added and the reaction mixture was refluxed for 15hrs. The solution was concentrated and allowed to cool overnight. The resulting solid obtained was filtered, washed with cold ethanol, dried and recrystalized from ethanol. The compound was separated as brown crystals.

General procedure for the Synthesis of N'- arylidene -2-(quinolin- 8 -yloxy) aceto hydrazide (3a- j)

Equimolar quqntity of the hydrazide compound (2, 0.01mol) and various aromatic aldehydes (3a-j, 0.01mol) in ethanol (50 ml) were heated on a water bath for 4-8 hrs. The resulting Schiffs bases (3a-j) were cooled and poured into crushed ice. The precipitate thus obtained was filtered washed with cold water and purified by recrystallized from ethanol. The physicochemical and spectral data of the compounds (3a-j) is described in Tables 1 and 2.

Scheme

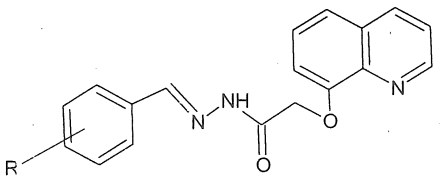


Where R: H, 4-Cl, 4-Br, 4-NO_2, 4-OH, 4-CH_3, 4-OCH_3, 4-N $(CH_3)_2$, 3-OH, 4-OCH_3, 3, 4-$(OCH_3)_2$

Scheme: Synthesis, characterization and antimicrobial activity of some substituted N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides

Reagents and conditions: **i.** dry acetone, K_2CO_3 reflux 24 h; **ii.** NH_2NH_2, abs. EtOH, reflux 15 h; **iii.** aryl Aldehydes, abs. EtOH, reflux 5-6 h.

Table 1. Physicochemical Characterization of N'-arylidene-2-(quinolin-8-yloxy) acetohydrazides 3a-j.



3a-j

Sl. No.	*R*	Physical state	Mol. formula	% yield	m.p.°C
3a	H	white crystals	$C_{18}H_{15}N_3O_2$	68	120-23
3b	4-Cl	yellow crystals	$C_{18}H_{14}N_3O_2Cl$	84	138-40
3c	4-Br	brown crystals	$C_{18}H_{14}N_3O_2Br$	70	123-26
3d	4-NO_2	cream crystals	$C_{18}H_{14}N_4O_4$	72	92-94
3e	4-OH	orange crystals	$C_{18}H_{15}N_3O_3$	76	105-07
3f	4-Me	colorless crystals	$C_{19}H_{17}N_3O_2$	75	143-46
3g	4-OMe	Cream crystals	$C_{19}H_{17}N_3O_2$	75	83-85
3h	4-$N(CH_3)_2$	yellow crystals	$C_{20}H_{20}N_4O_2$	86	140-42
3i	3-OH, 4-OMe	colorless crystals	$C_{19}H_{17}N_3O_4$	76	125-27
3j	3,4-$(OMe)_2$	white crystals	$C_{20}H_{19}N_3O_4$	62	172-75

Table 2. Spectral Characterization of N'-arylidene-2-(quinolin -8-yloxy) acetohydrazides 3a-j.

Sl. No.	*R*	IR (KBr) cm^{-1}	^1H NMR (DMSO D_6, 400 MHz) δ ppm
IIIa	H	3431 (NH), 3112, 3109, 2978, 2812,1640 (C=O), 1580 (N=CH), 1569, 1501, 1474, 1380, 1250, 1155, 1070, 925, 817, 771.	11.50 (s, 1H, CONH), 9.90 (s, 1H, N=CH), 8.76- 6.54 (m, 11H, Ar), 5.01 (s, 2H, O-CH_2- O).
IIIb	4-Cl	3351 (NH), 3098, 3011, 2977, 2812, 1645 (C=O), 1580 (N=CH), 1560, 1509, 1478, 1382, 1258, 1160, 1066, 927, 820, 776.	11.70 (s, 1H, CONH), 9.90 (s, 1H, N=CH), 8.72-6.60 (m, 10H, Ar), 5.02 (s, 2H, -OCH_2).
IIIc	4-Br	3350(NH), 3100, 3042, 2968, 2811, 1640 (C=O), 1582 (N=CH), 1558, 1511, 1480, 1370, 1250, 1150, 1066, 927, 817, 771.	11.70 (s, 1H, CONH), 9.90 (s, 1H, N=CH), 8.72-6.60 (m, 10H, Ar), 5.02 (s, 2H, -OCH_2).
IIId	4-NO_2	3348 (NH), 3120, 3020, 2960, 2858, . 1648(C=O), 1582 (N=CH), 1380, 1350, 1560, 1518, 1478, 1386, 1355, 1250, 1148, 1060, 930, 811, 778.	11.50 (s, 1H, CONH), 9.90 (s, 1H, N=CH), 8.76- 6.54 (m, 11H, Ar), 5.01 (s, 2H, O-CH_2- O).
IIIe	4-OH	3345 (NH), 3110, 3018, 2967, 2822, 1640 (C=O), 1580 (N=CH), 1562, 1505, 1480, 1378, 1255, 1158, 1066, 930, 820, 775.	11.28 (s, 1H, CONH), 9.90 (s, 1H, N=CH), 8.76- 6.70 (m, 10H, Ar), 5.02 (s, 2H, OCH_2), 3.42 (b, s, 1H, OH).
IIIf	4-Me	3348 (NH), 3121, 3015, 2958, 2815, 1638 (C=O), 1586 (N=CH), 1552, 1510, 1476, 1377, 1250, 1150, 1068, 932, 815, 772.	11.18 (s, 1H, CONH), 9.92 (s, 1H, N=CH), 8. 88-6.60 (m, 10H, Ar), 5.01 (s, 2H, OCH_2), 2.51 (s, 3H, CH_3)
IIIg	4-OMe	3340(NH), 3110, 3025, 2971, 2860, 1645(C=O), 1580 (N=CH), 1378, 1361, 1558, 1515, 1480, 1379, 1350, 1256, 1158, 1058, 927, 810, 778.	11.30 (s, 1H, CONH), 9.88 (s, 1H, N=CH), 8.66- 6.54 (m, 10H, Ar), 5.02 (s, 2H, OCH_2), 3.78 (b, s, 1H, OH).
IIIh	4-$N(CH_3)_2$	3348(NH), 3121, 3028, 2978, 2859, 1646(C=O), 1578 (N=CH), 1375, 1362, 1554, 1520, 1476, 1381, 1348, 1266, 1152, 1051, 930, 812, 774.	11. 20(s, 1H, CONH), 9.50 (s, 1H, N=CH), 8. 86 -6.70 (m, 10 H, Ar), 5.01 (s, 2H, OCH_2), 2.21 (s, 6H, -N($CH_3)_2$)
IIIi	3-OH, 4-OMe	3448 (NH), 3120, 3129, 2980, 2845,1645 (C=O), 1578 (N=CH), 1558, 1511, 1484, 1378, 1255, 1156, 1068, 925, 817, 771.	11. 30(s, 1H, NH), 9.8 0 (s, 1H, N=CH), 8. 78 -6.66 (m, 9 H, Ar), 5. 02 (s, 2H, OCH_2), 4. 50 (b, s, 1H, -3-OH of phenyl), 3.56 (s, 3H, 4-OCH_3 of phenyl).
IIIj	3,4-$(OMe)_2$	3440(NH), 3125, 3026, 2981, 2862, 1648(C=O), 1581 (N=CH), 1561, 1362, 1565, 1520, 1478, 1380, 1360, 1266, 1161, 1061, 930, 815, 771.	11.10(s, 1H, NH), 9.77 (s, 1H, N=CH), 8.88 (m, 9 H, Ar), 5.01 (s, 2H, OCH_2), 3.32 (s, 6H, -$(OCH_3)_2$)

In Vitro Evaluation of Antibacterial Activity of Compounds 3a-j

Broth microdilution method (Goto et al. 1981) using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of synthesized compounds *3a-j* against Gram-positive (*S. aureus and B. Subtilis*) and Gram-negative (*S. typhi and E. coli*) bacteria. The antibacterial activity of the test compounds was compared with ampicillin. Twofold serial dilutions of the test compounds and reference drugs were prepared in Muller-Hinton agar. Test compounds, standard drug ampicillin (6.4 mg) were dissolved in dimethylsulfoxide (DMSO, 1 ml) and the solution was diluted with distilled water (9 ml). Further progressive serial dilutions with melted Muller-Hinton agar were performed to obtain the required concentrations from 5-100 μg/ml. The petri dishes were inoculated with 1-5 x 10^4 colonies forming units (cfu/ml) and incubated at 37 °C for 18 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the tested compound that yields no visible growth on the plate. To ensure that

the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments. The results of the study are described in Table 3.

In Vitro Evaluation of Antifungal Studies of Compounds 3a-j

Antifungal activities of all the synthesized compounds were preliminarily screened for the in vitro growth inhibitory activity against *A. Niger* and *C. Albicans* by using the disc diffusion method [40]. The fungi were cultured in potato dextrose agar medium. Potato dextrose agar medium (prepared from potato 150 g; dextrose 5 g and agar 2 g in 200 ml of distilled water) was poured in the sterilized Petri plates and allowed to solidify. The plates were inoculated with a spore suspension of *A. Niger* and *C. Albicans* (106 spores/ml of medium). The compounds to be tested were dissolved in acetone to a final concentration (weight/volume) of 0.5%,1% and 2%and soaked in filter paper discs (Whatmann no. 4, 5 mm diameter). These discs were placed on the already seeded plates and incubated at 28 ± 2 °C for four days. To avoid the activity of the solvent that is used in the test solutions, a solvent only treated plate was maintained, which showed a 1 mm diameter zone of inhibition. Finally, after four days, the minimum inhibition zone was measured the results are tabulated in table **3** Clotrimazole was used as standard.

Table 3. *In vitro* Anti-bacterial and Anti-fungal activity data of N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides 3a-j.

Minimum inhibitory concentrations (MICs) µg/ml							
Sl. No.	***R***	***S. aureus***	***B.Subtilis***	***E. Coli***	***S.typhi***	***C.Albicans***	***A.niger***
3a	H	75	55	75	75	100	100
3b	4-Cl	25	30	50	50	25	50
3c	4-Br	25	25	50	50	25	50
3d	4-NO_2	50	50	50	75	100	100
3e	4-OH	75	100	100	100	50	50
3f	4-Me	100	100	100	100	75	100
3g	4-OMe	25	25	50	50	50	50
3h	4-$N(CH_3)_2$	75	75	75	100	50	50
3i	3-OH, 4-OMe	50	100	50	100	100	100
3j	3,4-$(OMe)_2$	50	50	50	50	100	100
	Ampicillin	>12.5	>12.5	>12.5	>12.5	-----	-----
	Clotrimazole	----	----	----	-----	>25	>25

Results and Discussions

From the results it is evident that most of the compounds are very weakly active and few are moderately active against staphylococcus aureus and bacillus subtilis but compounds 3b & 3c possess good activity against fungi candida albicans and compound 3e and 3g showed moderate activity.

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