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Research Article

SYNTHESIS AND EVALUATION OF SCHIFF'S BASE OF 4-QUINAZOLINONE ANALOGUES AS ANTIMICROBIAL AGENTS

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ABSTRACT

Some new biological active 6-bromo-3-({5[3, 4-substituted) diazenyl]-2-hydroxybenzylidene} amino-2-benzylquinazoline-4(3H)-one were synthesized by reaction of synthesized quinazoline derivative with substituted azo salicylaldehyde. The structure of the synthesized compounds has been established on the basis of IR, ^{1}HNMR, Mass spectra and elemental analysis. The compounds have been evaluated for their in-vitro antimicrobial activity against different human pathogens using disc diffusion assay.

Keywords: Schiff's base, Quinazolinone, Antimicrobial activity.

INTRODUCTION

The evolution of resistance to antimicrobial agents that are used to control pathogens in medicine and agriculture is a well documented problem[1-2]. There is pressing need to develop new agents and therapeutic strategies for the treatment of pathogenic infectious diseases.

Schiff's base are the compounds containing azomethine group (-HC=N) formed by condensation of primary amine and carbonyl compounds are known as imine. Schiff's base derivatives are the subject of renowed interest because they have been found to be useful intermediates for the synthesis of various heterocyclic compounds and have a wide variety of application in many fields. Schiff's bases have been posses antimicrobial activity[3-4], anti-malarial[5], anticancer[6], antioxidant[7], antituberculosis[8] and anticonvulsant[9]. Quinazoline derivatives also exhibit broad range of biological activities such as fungicidal[10], antibacterial[11], anti-inflammatory[12], antihelmintic[3], cytotoxic[14] and anticancer agents [15]. The present study is designed in order to synthesize a new series of Schiff's bases with quinazoline moiety as potential antimicrobial agents.

MATERIAL AND METHODS

All the melting points were determined routinely in open capillaries and are uncorrected the purity of the compounds was routinely checked by thin layer chromatography (TLC)using silicagel G. ^{1}HNMR were recorded on Bruker DRX 300 (300 MHz) spectrometer using TMS as an internal standard. IR spectra were recorded in KBr on Shimadzu FTIR spectrophotometer. Mass spectra on Jeol-Sx 102 instrument and elemental analysis were performed on Calo Erba 1108 analyzer.

Synthesis of 2-hydroxy-5-[phenyldiazenyl]benzaldehyde (Ia-g)

Aniline (3.72) was dissolved in aqueous hydrochloric acid (28 mL,6N) and mechanically stirred at 0-5°C. A cold solution of sodium nitrite (5gm / 10mL water) was added drop wise to the constantly stirred reaction mixture. The diazotized solution was immediately added in small portion to salicylaldehyde (5 ml dissolved in 40 Ml, 6 N NaOH), with constant stirring at 0-5°C. The stirring was continued for 4h. The solid obtained was filtered under suction washed with cold water and recrystallised from ethanol.

IR (KBr): 3181(Ar-OH), 1664 (C=O), 1599 (N=N), 1025 cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 7.00-8.16 (m, Ar-H), 10.02 (1H,s, CHO), 11.26 (1H, s, OH); MS m/z: 227 (M^+).

Synthesis of 3-amino-2-benzyl-6-bromoquinazoline-4(3H)-0ne (III)

A mixture of 2-benzyl-6-bromo-3,1-benzoxazin-4-one (II) (0.01mol) and hydrazine hydrate 35mL was refluxed in ethanol (10mL) for 4h. The reaction mixture was cooled to room temperature. The crystals formed were filtered, washed with water and dried. The product thus formed were recrystallised from ethyl acetate.

IR (KBr): 3300 and 3150 (-NH_2),1675 (C=O), 1610 (C=N) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 4.8 (s, 2H, NH_2), 7.1-8.1(m,4H, Ar-H); MS m/z: 317 (M^+).

Synthesis of 6-bromo-3-({5[3,4 substituted)diazenyl]-2-hydroxybenzylidene}amino-2-benzylquinazoline-4(3H)-one(IVa-IVg)

Equimoler mixture of (Ia-g) and (III) was refluxed for 10h in DMF. The reaction mixture was cooled in ice-bath and a drop of sulfuric acid was added. The product separated as light brown solid on addition of requisite amount of water, which was repeatedly washed with water followed by ethanol.

6-bromo-3-{2 hydroxy-5-[(-phenyldiazenyl] phenyl} methyliden amino-2-benzylquinazoline-4(3H)-one (IVa)

IR (KBr): 3223 (-OH str.), 3061 (Ar-CH str.), 1666 (C=O str.), 1604 (CH=N str.), 1523 (N=N str), 690 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 5.69 (s,1H,OH), 6.8-7.8 (m, Ar-CH), 9.35 (s, CH=N); MS m/z 525 (M^+).

6-bromo-3-({5[4-nitro)diazenyl]-2-hydroxybenzylidene}amino-2-benzylquinazoline-4(3H)-one (IVb)

IR (KBr): 3217 (-OH str.), 3082 (Ar-CH str.), 1625 (C=O str.), 1600 (CH=N str.), 1545 (N=O str.), 1517 (N=N str.), 665 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 5.61 (s,1H,OH), 6.9-7.9 (m, Ar-CH), 9.21 (s, CH=N); MS m/z 570 (M^+).

6-bromo-3-({5[3-nitro)diazenyl]-2-hydroxybenzylidene}amino-2-benzylquinazoline-4(3H)-one (IVc)

IR (KBr): 3235 (-OH str.), 3065 (Ar-CH str.), 1629 (C=O str.), 1610 (CH=N str.), 1560 (N=O str.), 1535 (N=N str.), 670 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 5.68 (s,1H,OH), 6.9-7.9 (m, Ar-CH), 9.4 (s, CH=N); MS m/z 570 (M^+).

6-bromo-3-({5[4-methoxy)diazenyl]-2-hydroxybenzylidene}amino-2-benzylquinazoline-4(3H)-one (IVd)

IR (KBr): 3260 (-OH str.), 3034 (Ar-CH str.), 1635 (C=O str.), 1610 (CH=N str.), 1515 (N=N str.), 625 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 3.2 (-OCH_3), 5.75 (s,1H,OH), 7.1-7.8 (m, Ar-CH), 9.6 (s, CH=N); MS m/z 555 (M^+).

6-bromo-3-({5[3-methoxy)diazenyl]-2-hydroxybenzylidene}amino-2-benzylquinazoline-4(3H)-one (IVe)

IR (KBr): 3255 (-OH str.), 3021 (Ar-CH str.), 1629 (C=O str.), 1621 (CH=N str.), 1525 (N=N str.), 610 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6,

δ ppm): 3.4 (-OCH_3), 6.1 (s,1H,OH), 7.1-7.8 (m, Ar-CH), 9.8 (s, CH=N); MS m/z 555 (M^+).

6-bromo-3-({5[4-chloro)diazenyl]-2-hydroxybenzylidene} amino-2-benzylquinazoline-4(3H)-one (IVf)

IR (KBr): 3298 (-OH str.), 3060 (Ar-CH str.), 1640 (C=O str.), 1600 (CH=N str.), 1534 (N=N str.), 610 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 5.9 (s,1H,OH), 7.1-7.8 (m, Ar-CH), 9.7 (s, CH=N); MS m/z 559 (M^+).

6-bromo-3-({5[3-chloro)diazenyl]-2-hydroxybenzylidene} amino -2-benzylquinazoline-4(3H)-one (IVg)

IR (KBr): 3310 (-OH str.), 3050 (Ar-CH str.), 1635 (C=O str.), 1600 (CH=N str.), 1510 (N=N str.), 610 (C-Br str.) cm^{-1}; ^{1}HNMR (DMSO-d_6, δ ppm): 5.8 (s,1H,OH), 6.9-7.8 (m, Ar-CH), 9.7 (s, CH=N); MS m/z 559 (M^+).

Table 1: Some characteristics of the compounds.

Comp.	R	M.P. (°C.)	Yield	Mol.Formula	Mol.wt.
Ia	H	141	78	$C_{13}H_{10}N_2O_2$	226.23
III	-	145	67	$C_{14}H_{10}BrN_3O$	316.15
IVa	H	209	63	$C_{27}H_{18}BrN_5O_2$	524.36
IVb	4-NO_2	162	76	$C_{27}H_{17}BrN_6O_4$	569.36
IVc	3-NO_2	165	60	$C_{27}H_{17}BrN_6O_4$	569.36
IVd	4-OCH_3	130	68	$C_{28}H_{20}BrN_5O_3$	554.39
IVe	3-OCH_3	124	65	$C_{28}H_{20}BrN_5O_3$	554.39
IVf	4-Cl	151	73	$C_{27}H_{17}BrClN_5O_2$	558.81
IVg	3-Cl	140	69	$C_{27}H_{17}BrClN_5O_2$	558.81

Antimicrobial screening

The newly synthesized compounds were evaluated for their antimicrobial activity against bacterial strains such as *S. aureus* and *E. coli* and fungi such as *A. niger, A.fumigatus, P. italicum* and *F. graminearum* by disc diffusion method at a concentration of 500 µg/mL. All the bacterial culture were grown in nutrient agar and fungi were grown in potato dextrose agar. Ampicillin and Fluconazole used as standard for comparison of antibacterial and antifungal activities respectively. DMF used as a solvent. The zone of inhibition measured (in mm) after 24h of incubation at 37^{0}C. The results are reported in table 2.

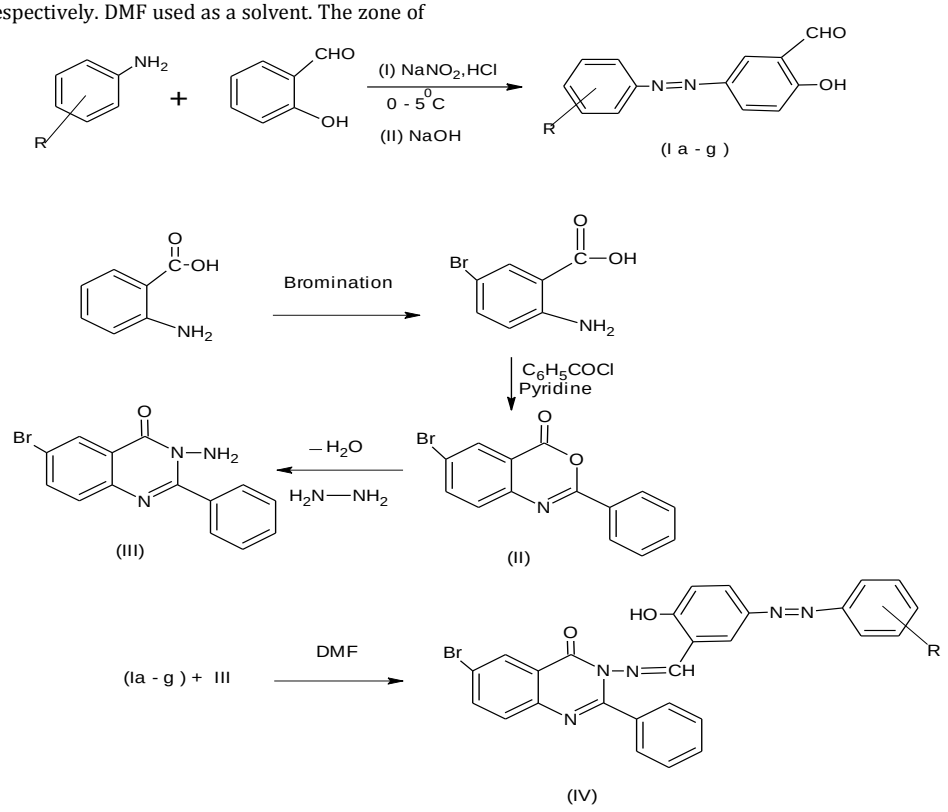
Table 2: In-vitro antimicrobial activity (IVa-g).

Comp.	Antibacterial		Antifungal		
	S. aureus	E. coli	A. niger	A. fumigatus	P. italicum
IVa	06	70	05	04	05
IVb	08	09	08	10	11
IVc	10	11	10	11	15
IVd	12	14	07	08	08
IVe	15	17	07	08	09
IVf	12	13	13	14	11
IVg	13	15	12	10	09
Ampicilline	18	21	-	-	-
Flucanazole	-	-	24	24	22
Control	-	--	-	-	-

RESULTS AND DISCUSSION

In-vitro Antimicrobial activity of the target compounds was performed by disc diffusion techniques using *S. aureus, E. coli* as the human bacterial pathogens and *A. niger, A. fumigatus, P.italicum* and *F. graminearum* as the fungal strains. All the compounds are active against tested pathogens. *E. coli* are more inhibited as compaired to *S. aureus.* The most potent compounds are IVd, IVe, IVf and IIIg. Compounds IVe & IVg show significant activity against *E. coli* and compound IVe show good activity against *S. aureus*. In fungal strains IVf show good activity against *A. niger.* IVf & IVc show significant activity against *A. fumigatus* and *P. italicum* respectively. On the basis of our experiments and results we conclude that:

- Activity of the schiff's bases enhances on substitution.
- Compounds substituted with 3-OCH_3 and 4-Cl group show higher activity against *E.Coli.*
- Schiff's base derivatives with NO_2 group at 3rd position and –Cl group at 4 th position were found to increase the antifungal activity.



R= H, 4-NO_2, 3-NO_2, 4-OCH_3, 3-OCH_3, 4-Cl, 3-Cl
Figure 1: Synthetic route of Compounds

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