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SYNTHESIS OF SOME NOVEL 3-(5-(ARYLAZO)-2-HYDROXYBENZYLIDENEAMINO)-2-PHENYLQUINAZOLIN-4(3*H*)-ONE DERIVATIVES AND THEIR BIOLOGICAL SCREENING

Naqui J. Siddiqui*[1], Mohammad Idrees[1], Swati Dhamange[2]

[1*]Department of Chemistry, Government Institute of Science, Nagpur, Maharashtra, India.
[2]Department of Chemistry, Government Science College, Gadchiroli Maharashtra, India.

ABSTRACT

Few novel 3-(5-(arylazo)-2-hydroxybenzylideneamino)-2-phenylquinazolin-4(3*H*)-ones (3a-e) were synthesized by condensation of 2-phenyl-3-amino quinazolinones-4-(3*H*)-one (1) with 5-arylazo salicylaldehydes (2a-e). The structures of these novel compounds have been established on the basis of chemical transformation reactions, element analysis, and interpretation of spectral data produced from IR, ^{1}H NMR, Mass spectra. The biological activities of the synthesized compounds was done *in-vitro* against four different bacteria strains that is *E. coli, S. aureus, B. thurengienesis* and *E. aerogenes* using disc diffusion method. The zone of inhibition was calculated in mm and compared against the standard drug Chloramphenicol. The results revealed that the synthesized compounds can be used as better antibacterial agents.

KEYWORDS

Schiff's base, Quinazolinone, Hydrazine hydrate and Azosalicyladehyde.

Author for Correspondence:

Naqui Jahan Siddiqui,

Department of Chemistry,

Government Institute of Science,

Nagpur, Maharashtra, India.

Email: naquiphd.2010@gmailcom

INTRODUCTON

Derivatives of Quinazolin-4(3*H*)-ones are heterocycles containing quinoline nucleus and known since decades as a potential class of pharmacologically active compounds. Schiff's bases of quinazolinone-4-(3*H*) one has also found to possess interesting biological activities, this have enthused substantial research work which has led to the synthesis and biological screening of several derivatives bearing this moiety. The most common synthetic method to get quinazolin-4-one is based on reaction of anthranilic acid and chloro acetyl chloride. Several methods have been reported in the

literature for the synthesis of quinazolinone and aryl-substituted quinazolinone compounds[1-10]. Metal complex Schiff bases have also been used in oxidation reaction[11]. Substitution at the 2 and 3 positions of the quinazoline nucleus plays a pivotal role in different activities such as anticancer[12], anti-inflammatory[13], antidiuretic[14] and anticonvulsant[15] activities. 2, 3-Dihydroquinazolin-4 (1*H*)- ones in particular, have good biological activities and are also key intermediates for the synthesis of quinazolin-4(3*H*)-ones[16-17]. In view of the inspection and importance of the research work on these heterocycles it was projected to synthesize few novel Schiff's bases of quinazolinone-4-(3*H*)-one and explore them as potential antimicrobial compounds.

MATERIAL AND METHODS

The reactions were monitored by E. Merck TLC aluminum sheet silica gel_{60} F_{254} and visualizing the spot in UV cabinet or Iodine chamber. The melting points were recorded in open capillary in paraffin bath and are uncorrected. Chemicals used for the synthesis were of AR grade, Merck and SD Fine. ^{1}H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using TMS as an internal reference and DMSO-d_6 as solvent. Chemical shifts are given in ppm. IR spectra were recorded on a Shimadzu IR spectrophotometer (KBr, v max in cm^{-1}). Waters Micromass Q-TOF micro, mass spectrophotometer was used to record the mass spectra. Thermo scientific (Flash-2000) was utilized for elemental (CHN) analysis and the results obtained are in good conformity with the calculated values.

Experimental

Starting materials required for the synthesis of the title compounds such as 3-amino-2-phenyl quinazoline-4-(3*H*)-one (1) was done by the literature method. Substituted anilines such as, 4-ethoxyaniline (a), p-choro-aniline (b), p-bromo aniline (c), p-toluidine (d) and 2-ethoxyaniline (e) were diazotized using sodium nitrite in HCl to get 2a-e[18].

3-amino-2-phenyl quinazoline-4-(3*H*)-one (1)

MF, $C_{14}H_{11}ON_3$, Colour, White crystal Yield, 72% MP, 177°C, Recrystallizing solvent, Ethanol

5-[(4-ethoxyphenyl) diazenyl]-2-hydroxybenzaldehyde (2a)

MF, $C_{15}H_{14}O_3N_2$ Colour, Yellow shiny crystals MP, 125-127°C, Yield, 65.30% , Recrystallizing solvent, CH_3COOH.

5-[(4-chlorophenyl) diazenyl]-2-hydroxybenzaldehyde (2b)

MF, $C_{13}H_9ClO_2N_2$ Colour, Yellow shiny crystals MP, 108-109°C,Yield, 67.54% Recrystallizing solvent, CH_3COOH.

5-[(4-bromophenyl) diazenyl]-2-hydroxybenzaldehyde (2c)

MF, $C_{13}H_9BrO_2N_2$ Colour, Yellow shiny crystals, MP, 112-113°C,Yield, 69.25% Recrystallizing solvent, CH_3COOH.

2-hydroxy-5-[(4-methylphenyl) diazenyl] benzaldehyde (2d)

MF, $C_{14}H_{12}O_2N_2$ Colour, Yellow shiny crystals, MP, 152-154°C,Yield, 68.25% Recrystallizing solvent, CH_3COOH; IR, 3185(-OH), 3030(ArH), 2918(-CH_3), 1575(-C=C-), 2742(-CHO), 1619(-N=N-) cm^{-1}; ^{1}H NMR, 11.41(s, 1H, -CHO), 2.40(s, 3H, -CH_3), 10.37(s, 1H, -OH), 7.18-8.18(m, 7H, ArH) ppm; MS, 241[M+1]+; Calculated: C, 70.00 H, 5.00 N, 11.76 Found: C, 68.909 H, 4.927 N, 10.823.

5-[(2-ethoxyphenyl) diazenyl]-2-hydroxybenzaldehyde (2e)

MF, $C_{15}H_{12}O_3N_2$, Colour, Yellow shiny crystals, Yield, 49%, MP, 120-122°C, Recrystallizing solvent, CH_3COOH.

General procedure for the synthesis of Schiff's bases of quinazolin-4-ones (3a-e)

Equimolar mixture of 3-amino-2-phenyl quinazoline-4-(3*H*)-one (0.002M) and substituted azosalicyldehydes (0.002M, 2a-e) with 2-3 drops of glacial acetic acid were refluxed in ethanol (20mL) for 2-3h. The reaction mixture was cooled at room temperature and the crystals formed were filtered, washed with water and recrystallized from suitable solvent (Scheme No.1).

5[(4-ethoxy phenyl diazenyl)]-2-hydroxybenzylidine-amino-2-phenylquinazoline-4-(3*H*)-one (3a)

MF, $C_{29}H_{23}O_3N_5$; Colour, Yellow; MP, 235-237°C; Yield, 70.0%; Recrystallizing solvent, Ethyl acetate; IR, 3632, 3132(-OH), 3040(ArH), 2883, 2923(CH_3, CH_2), 1604(C=N), 1045(C-N), 1502, 1475(C=C) cm^{-1}; ^1H NMR, 10.97(-OH), 8.28(CH=N), 9.35(s, 1H, ArH) 7.01-8.28, (m,15H, ArH), 4.10-4.15(q, 2H, OCH_2), 1.39-1.42(t, 3H, CH_3) ppm; MS, 490$[M+H]^+$, 512$[(M+Na)^+]$; Calculated: C,71.16 H, 4.70 N, 14.31 Found: C, 70.99 H, 4.72 N, 14.36.

5[(4-chloro phenyl diazenyl)]-2-hydroxybenzylidine amino-2-phenylquinazoline-4-(3*H*) - one (3b)

MF, $C_{27}H_{18}ClO_2N_5$; Colour, Orange; MP,172-174°C; Yield,69.0% ; Recrystallizing solvent, 1,4-dioxane; IR, 3641(-OH), 3033(ArH), 2881, 2921(CH_3, CH_2), 1734(C=N), 1521, 1469(C=C), 1040(C-N) cm^{-1}; ^1H NMR, 10.99(-OH), 9.52(CH=N), 7.31-8.24(m,16H, ArH) ppm; MS, 481$[M+H]^+$; Calculated: C, 67.57 H, 3.78 N, 14.59 Found: C, 68.01 H, 3.89 N,14.63.

5[(4-bromo phenyl diazenyl)]-2-hydroxybenzylidine amino-2-phenylquinazoline-4-(3*H*)- one (3c)

MF, $C_{27}H_{18}BrO_2N_5$; Colour, Orange; MP,180-182°C; Yield,71.0%; Recrystallizing solvent, 1,4-dioxane; IR, 3637(-OH), 3031(ArH), 2873, 2925(CH_3, CH_2), 1744(C=N), 1544, 1464(C=C), 1044(C-N) cm^{-1}; ^1H NMR, 10.85(-OH), 9.72(CH=N), 7.24-8.11(m,16H, ArH) ppm; MS, 526$[M+2]^+$; Calculated: C, 61.84 H, 3.46 N, 13.36 Found: C, 62.04 H, 3.39 N,13.18.

5[(4-methyl phenyl diazenyl)]-2-hydroxybenzylidine amino-2-phenylquinazoline-4-(3*H*)-one (3d)

MF,$C_{28}H_{21}O_2N_5$; Colour, Orange; MP,192-194°C; Yield,68.0%; Recrystallizing solvent, 1, 4-dioxane; IR, 3592(-OH), 3029(ArH), 2864, 2918(CH_3, CH_2), 1742(C=N), 1551, 1423(C=C), 1051(C-N) cm^{-1}; ^1H NMR, 10.85(-OH), 9.72(CH=N), 7.24-8.11(m,16H, ArH), 1.01-1.24(t, 3H, CH_3) ppm; MS, 460$[M+H]^+$; Calculated: C, 73.19 H, 4.61 N, 15.24 Found: C, 72.99 H, 4.63 N, 15.38.

5[(2-ethoxy phenyl diazenyl)]-2-hydroxybenzylidine amino-2-phenylquinazoline 4-(3*H*) -one (3e)

MF, $C_{29}H_{23}0_3N_5$; Colour, Yellow; MP, 244-246°C; Yield, 77.0%; Recrystallizing solvent, Ethyl acetate; IR, 3631(-OH), 3041(ArH), 2881, 2926(CH_3, CH_2), 1734(C=N), 1044(C-N), 1514, 1463(C=C) cm^{-1}; ^1H NMR, 10.96(-OH), 9.38(CH=N), 7.15-8.29(m,16H, ArH), 4.12-4.19(q, 2H, OCH_2), 1.45-1.48(t, 3H, CH_3) ppm; MS, 491$[M+1]^+$; Calculated: C, 71.15 H, 4.74 N, 14.31 Found: C, 71.04 H, 4.79 N, 14.46.

Antimicrobial activity

The novel synthesized heterocyclic compounds were screened for their *in-vitro* antimicrobial activity using paper disc diffusion method against two Gram positive bacterial strains, *B. thurengienesis* and *S. aureus* and two Gram negative strains, *E. coli* and *E. aerugenes* using Chloramphenicol as the standard drug.

General Procedure: Determination of Zone of Inhibition by paper disc diffusion method

Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant concentration of 31-500µg/mL. Whatmann No.1 sterile filter paper discs (6mm) were impregnated with solution and allowed to dry at room temperature. *In-vitro* antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd, Mumbai. Petri plates were prepared by pouring 10mL of agar for bacteria containing microbial culture was allowed to solidify. The discs were then applied and the plates were incubated at 37°C for 24h (bacteria) and the inhibition zone was measured in mm. The zone of inhibition at concentration of 500µg/mL is given in the Table No.1.

RESULTS AND DISCUSSION

The synthesis of the novel compounds (3a-e) is described in reaction Scheme No.1. The identities of the newly synthesized compounds have been established on the basis of their elemental analysis and spectral data[19] such as IR, ^1H NMR and Mass spectral studies.

The compounds bearing bromo, chloro, hydroxyl, ethoxy and methyl groups in different position of

benzene ring of 5-arylazo salicylaldehydes (2a-e) and its treatment with 3-amino-2-phenyl quinazoline-4(3*H*)-one (1) resulted in synthesis of new Schiff's bases of quinazolinone-4-(3*H*)-one (3a-e) derivatives is shown in Scheme No.1. Chemical reaction of 3a with alcoholic $FeCl_3$ gave violet colouration indicating the presence of –OH group. Disappearance of $–NH_2$ and –CHO stretching bands in the IR spectra of 3a, and appearance of band around 1604 cm^{-1} is due to C=N stretch, while other absorption bands including aromatic and aliphatic stretch was observed at the expected region, which indicated formation of the title compound by the condensation of $–NH_2$ and –CHO group of the reactant. Similarly, the ^1H NMR spectrum showed a singlet at δ 8.28 ppm assigned due to azomethine proton (CH=N), a quartet in the range of δ 4.10 to 4.15 ppm for two protons of $–CH_2$ and a triplet in between δ 1.39-1.42 ppm for three protons of $–CH_3$, of $-OCH_2CH_3$ group respectively, while a multiplet in the range of δ 7.01 to 8.28 ppm due to fifteen aromatic protons, confirms the formation of 3a. It's structure was further confirmed by mass spectrum with a molecular ion peak at *m/z* 490 $[M+H]^+$, 512 $(M+Na)^+$, and estimation of % of C, H and N in elemental analysis was found to be satisfactory with the calculated values of these elements present in 3a, as it was projected, which determines the molecular formula and this is in agreement with $C_{29}H_{23}O_3N_5$ (Scheme No.1).

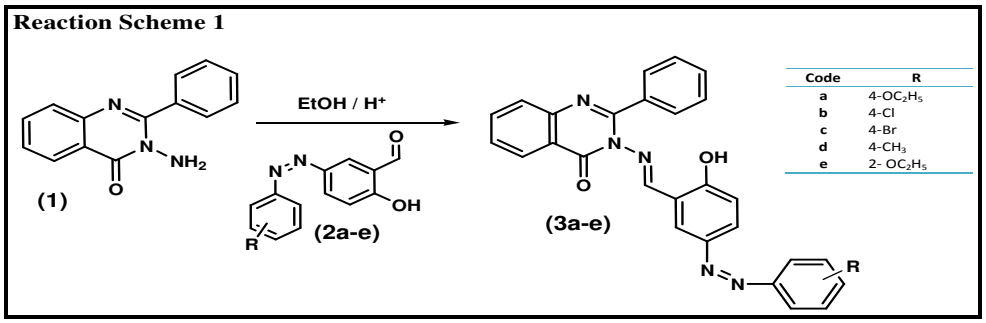
Similarly, physical, chemical and elemental analysis have been done for rest of the compounds and the data achieved revealed satisfactory results for these compounds and are specified in the experimental part.

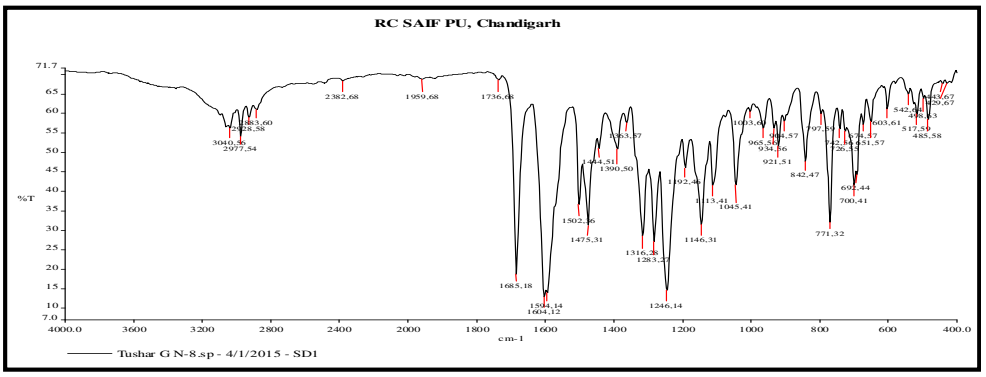
Antimicrobial activity

Synthesized title compounds (3a-e) were screened for antimicrobial activity. Table No.1, shows the inhibition zone calculated in mm at different concentrations from 31-500 µg/mL as compared with the standard. Data obtained revealed that the test compounds were poorly active at the lower concentration from 31-250 µg/mL but showed better activity at 500µg/mL. Chloro and bromo substituted quinazoline-4(3*H*)-ones i.e. 3b and 3c were found to show even better activity than the standard chosen while 3a, 3d and 3e showed good activity against all of the four selected bacterial strains.

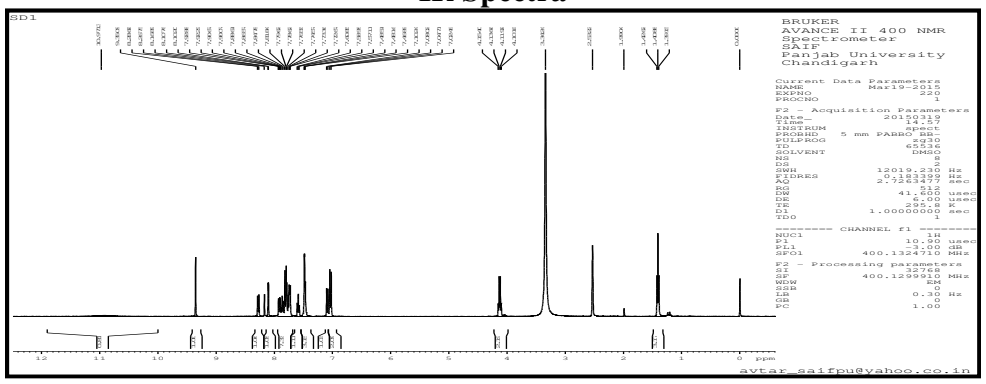
Table No.1: Antibacterial Activities of Synthesized compounds (3a-e) against Chloramphenicol

Compd. No	Code of the compound	Zone of inhibition in mm				Chloramphenicol
		Antibacterial activity at Conc. of 500 µg/mL				
		Gm +ve		Gm –ve		
		S. aureus	***B. Thurengienesis***	***E . coli***	***E . aerogenes***	
1	3a	19	19	17	15	21
2	3b	30	29	31	27	30
3	3c	28	27	30	28	28
4	3d	18	17	15	15	25
5	3e	16	14	14	12	20

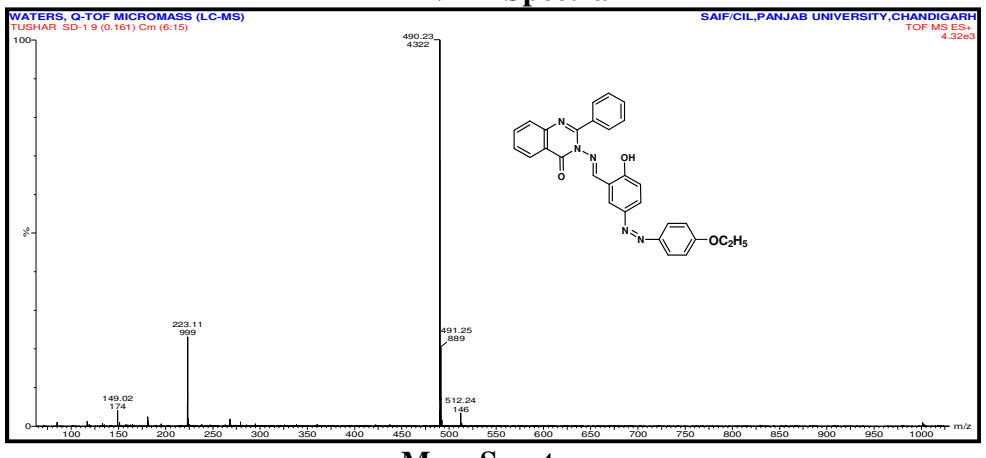




IR Spectra



^{1}H NMR Spectra



Mass Spectra

Figure No.1: IR, ^{1}HNMR and Mass Spectra of representative compound: 3a

CONCLUSION

Synthesis of some new Schiff's bases of quinazolin-4-ones (3a-e) obtained from aryl azosalicyldehydes (2a-e) and 2-phenyl-3-amino quinazolinones-4-(3*H*)-one (1) has been synthesized easily in a good yield. Synthesized compounds were found to have better biological activity than even the standard drug and hence can be used as better antibacterial agents. The structural identities of the newly synthesized compounds have been established by elemental and spectral analysis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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