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# POTENTIALLY ACTIVE HETEROCYCLES DERIVED FROM 6,8-DICHLORO-3-AMINO-2-METHYLQUINAZOLIN-4(3*H*)-ONE :SYNTHESIS AND ANTIBACTERIAL ACTIVITY

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**Abstract:** 6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)-one have been prepared from anthranilic acid by chlorination using molecular chlorine. This quinazolin-4 (3*H*)-one, on condensing with substituted haloaldehydes in presence of traces of acetic acid yielded schiff bases, which on reacting with chloroacetylchloride yielded 2-azetidinones and with thioglycolic and gave 4-thiazolidinones in good yield. All the synthesised schiff bases, 2-azetidinones and 4-thiazolidinones were screened for their antibacterial activity against *E. coli, S. aureus*, *X. citri* and *E. carotovora*. Some of the compounds show better activity than standard antibiotic *Tetracycline*.
**Keywords**:3,5-dichloroanthranilic acid, schiff bases, 2-azetidinones, 4-thiazolidinones, antibacteiral activity.

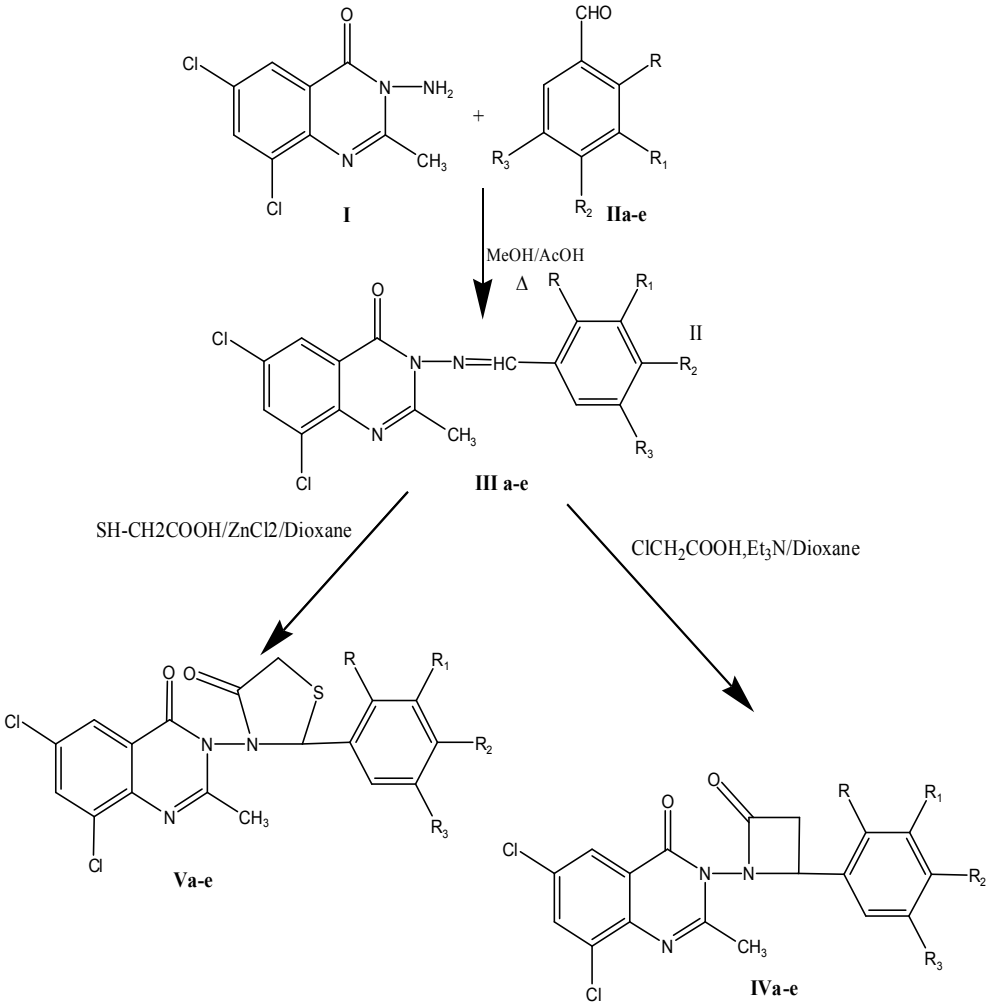
## Introduction

Compounds bearing the quinazoline moiety are endowed with various types of biological activities. Quinazoline derivatives have been reported as antitubercular[1], antiinflammatory[2], antihypertensive[3], narcotic antagonist[4], antileishmanial[5], bronchodilatory[6], analgesic[7], anticonvulsant[8], antitumor[9], antifungal[10] activities and as aldose reductase inhibitor[11]. 2-azetidinones are found to possess antifungal, antibacterial[12], herbicidal[13] and antitubercular[14] activities. While 4-thiazolidinones are well known for their anticonvulsant[15], antioxidant[16], antiinflammotary[17], and antibacterial[18] activities. Further literature survey revels that no one has studied the synthesis of schiff bases, azetidinones and thiazolidinones having 6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)-one moiety and halogeno aryl moiety.

In light of these observations we have synthesized some new schiff bases from 6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)-one by treating them with halogenated arylaldehydes in good yield. The newly synthesized schiff bases **(IIIa-e)** were then subjected to react with chloroacetyl chloride and thioglycolic acid to get corresponding 2-azetidinones **(IVa-e)** and 4-thiazolidinones **(Va-e)** respectively **(Scheme)**. These heterocycles then screened for their antibacterial activity against *E.coli, S. aureus*, *X. citri* and *E. carotovora* using *Tetracyclin* as standard antibiotic. Interestingly some of the compounds exhibit better activity.

## Experimental

All the melting points are taken in open capillaries and are uncorrected. The IR spectra in KBr were recorded on a Perkin- Elmer 157 Spectrometer ($\nu_{max}$ in $cm^{-1}$) and $^1H$ NMR (DMSO-d6) spectra on a Bruker WM 400FTMHz spectrometer (chemical shifts in $\delta$ ppm). Mass spectra were recorded on a JMSD-300 instrument fitted with JMS2000 data system at 70ev. The homogeneity and purity of the compounds were ascertained by TLC on silica gel G- plates and the spots were visualised by using in iodine vapours.




**SCHEME**

**1. Synthesis Schiff Bases :( IIIa-e)**

An equimolar mixture of 6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)- one (0.001m) and 3-bromo, 4-hydroxy, 5-methoxybenzaldehyde (0.001m) in methyl alcohol (15mL) containing acetic acid (0.5mL) was refluxed for 3h. Excess of solvent was distilled off and residue was kept in cold. The solid was filtered and recrystallised from acetic acid.

**2. Synthesis of 2-Azetidinones: (IVa-e)**

A solution of 3-(3-bromo, 4-hydroxy, 5-methoxybenzalmino)-6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)-one (0.001m) in dry dioxane (50mL) was added to a well stirred mixture of chloroacetylchloride (0.001m) and triethylamine (0.003m) at 0°C. The reaction mixture was stirred for 6h. Excess of dioxane was distilled off. The resultant solution was poured into ice cold water, seperated solid was filtered, washed with cold water and recrystallised from ethyl alcohol.

**3. Synthesis of 4-Thiazolidinones: (Va-e)**

A solution of 3-(3-bromo, 4-hydroxy, 5-methoxybenzalmino)-6,8-dichloro-3-amino-2-methylquinazolin-4 (3*H*)-one (0.001m) in DMF (30mL) containing a pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.001m) was refluxed for 8h. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered,washed with cold water and recrystallised form DMF-water (60:40 v/v).

**In vitro Antimicrobial Screening [19]**

Most of the new target synthesized compounds were tested for their antibacterial activity *in vitro* against *Escherichia coli, Staphylococcus aureus, Xanthomonas citri and Erwinia carotovora* employing the nutrient agar disc diffusion method at 50-100 µg/mL concentration using Tetracyline as standard drug.The screening results present in table 1.

**Table-1:Physical, analytical and antibacterial activity of compounds (Va-e, VIa-e and VIIa-e)**

| S.N. | R | $R_1$ | $R_2$ | $R_3$ | M.P. in °C | Molecular Formula | Halogen analysis (%) | | Zone of inhibition in (mm) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | Calcd. | *E. coli* | *S. aureus* | *X. citri* | *E. carotovora* |
| **IIIa** | H | Br | OH | $OCH_3$ | 272 | $C_{17}H_{12}N_3O_3Cl_2Br$ | 33.40 | (33.04) | 20 | 17 | 15 | 18 |
| **IIIb** | H | I | OH | $OCH_3$ | 254 | $C_{17}H_{12}N_3O_3Cl_2I$ | 39.42 | (39.28) | 27 | 21 | 24 | 22 |
| **IIIc** | OH | Br | H | Br | 227 | $C_{16}H_9N_3O_2Cl_2Br_2$ | 46.13 | (45.65) | 20 | 19 | 16 | 18 |
| **IIId** | OH | I | H | I | 237 | $C_{16}H_9N_3O_2Cl_2I_2$ | 54.42 | (54.16) | 26 | 25 | 24 | 22 |
| **IIIe** | OH | Cl | H | Cl | 242 | $C_{16}H_9N_3O_2Cl_4$ | 33.98 | (33.81) | 13 | 12 | 15 | 12 |
| **IVa** | H | Br | OH | $OCH_3$ | 192 | $C_{19}H_{13}N_3O_4Cl_3Br$ | 35.31 | (34.95) | 21 | 16 | 17 | 15 |
| **IVb** | H | I | OH | $OCH_3$ | 232 | $C_{19}H_{13}N_3O_4Cl_3I$ | 40.64 | (40.22) | 28 | 24 | 25 | 24 |
| **IVc** | OH | Br | H | Br | 210 | $C_{18}H_{10}N_3O_3Cl_3Br_2$ | 45.22 | (45.75) | 14 | 18 | 11 | 17 |
| **IVd** | OH | I | H | I | 221 | $C_{18}H_{10}N_3O_3Cl_3I_2$ | 53.65 | (53.28) | 25 | 23 | 23 | 21 |
| **IVe** | OH | Cl | H | Cl | 230 | $C_{18}H_{10}N_3O_3Cl_5$ | 36.14 | (35.96) | 19 | 16 | 12 | 18 |
| **Va** | H | Br | OH | $OCH_3$ | 245 | $C_{19}H_{14}N_3SO_4Cl_2Br$ | 28.10 | (28.43) | 15 | 19 | 13 | 13 |
| **Vb** | H | I | OH | $OCH_3$ | 273 | $C_{19}H_{14}N_3SO_4Cl_2I$ | 34.42 | (34.25) | 27 | 24 | 25 | 22 |
| **Vc** | OH | Br | H | Br | 300 | $C_{18}H_{11}N_3SO_4Cl_2Br_2$ | 39.52 | (39.82) | 15 | 18 | 10 | 14 |
| **Vd** | OH | I | H | I | 268 | $C_{18}H_{11}N_3SO_3Cl_2I_2$ | 48.65 | (48.21) | 14 | 20 | 24 | 25 |
| **Ve** | OH | Cl | H | Cl | 217 | $C_{18}H_{11}N_3SO_3Cl_4$ | 28.58 | (28.71) | 10 | 13 | 09 | 15 |
| *Tetracyline* | | | | | | | | | 25 | 22 | 24 | 23 |

## Result and Discussion

In summary, we have synthesized a novel class of five Schiff Bases, five 2-azetidinones and five 4-thiazolidinones as potential antibacterial agents. All synthesized compounds have shown mild to good activity against the pathogenic bacteria. Compound no**. IIIb,IVb,Vb** with iodine at 2nd,hydroxy at 3rd and methoxy at 4th position where as in compound no.**IIId,IVd ,Vd** with hydroxyl at 2nd and iodine at 3rd and 5th position have shown to be more potent than Tetracyline.

**Spectral data of selected Compounds:**

**IIIa: IR (cm-1)** 3259**,** 1670, 1595, 1500.**1H NMR** (DMSO-$d_6$) δ: 2.54(s, 3H, CH3),3.95(s,3H, OCH3),7.48-8.20(m,4H,Ar-H),8.75(s,1H,=CH),8.90(s,1H,OH)

**IIIc: IR (cm-1)** 3310**,** 1665, 1589, 1505.**1H NMR** (DMSO-$d_6$) δ: 2.68(s, 3H, CH3), 7.04-8.40(m, 4H, Ar-H), 8.78(s,1H,=CH),10.55(s,1H,OH).

**IIId: IR (cm-1)** 3270**,** 1668, 1598, 1500.**1H NMR** (DMSO-$d_6$) δ: 2.64(s, 3H, CH3),7.08-8.35(m,4H,Ar-H),8.85(s,1H,=CH),10.60(s,1H,OH).

**IVa: IR (cm-1)** 3380**,** 1770, 1685,1614,1595, 1390.**1H NMR** (DMSO-$d_6$) δ: 2.55(s, 3H, CH3),2.73 (s,1H,N-CH-C),3.98(s,3H, OCH3),4.44(s,1H,CH-Cl),7.25-8.16(m,4H,Ar-H),8.84(s,1H,OH).

**IVc: IR (cm-1)** 3315**,** 1775, 1688,1614,1595, 1395.**1H NMR** (DMSO-$d_6$) δ: 2.60(s, 3H, CH3),2.75 (s,1H,N-CH-C), 4.45(s,1H,CH-Cl),7.20-8.30(m,4H,Ar-H),10.60(s,1H,OH).

**IVd: IR (cm-1)** 3305**,** 1770, 1689,1610,1585, 1400.**1H NMR** (DMSO-$d_6$) δ: 2.62(s, 3H, CH3),2.75 (s,1H,N-CH-C), 4.42(s,1H,CH-Cl),7.22-8.38(m,4H,Ar-H),10.55(s,1H,OH).

**Va: IR (cm-1)** 3275**,**1780, 1688,1620,1578,1540,1465.**1H NMR** (DMSO-$d_6$) δ: 2.62(s, 3H, CH3),3.15 (s,1H,CH), 3.92(s,1H,OCH3),4.90(s,1H, CH2S),7.35-8.45(m,4H,Ar-H),8.95(s,1H,OH).

**Vc: IR (cm-1)** 3295**,**1778, 1685,1625,1575,1540,1460.**1H NMR** (DMSO-$d_6$) δ: 2.60(s, 3H, CH3),3.25 (s,1H,CH), 4.95(s,1H,CH2S),7.25-8.35(m,4H,Ar-H),10.67(s,1H,OH).

**Vd: IR (cm-1)** 3290**,**1783, 1680,1630,1575,1545,1477.**1H NMR** (DMSO-$d_6$) δ: 2.65(s, 3H, CH3),3.22 (s,1H,CH), 4.87(s,1H, $CH_2S$),7.4-8.5(m,4H,Ar-H),10.60(s,1H,OH).

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