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Research Article

# SYNTHESIS OF CERTAIN THIAZOLYL-PYRAZOLINE DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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## ABSTRACT

A series of pyrazole derivatives containing thiazole moiety (4a-4g) are synthesized by the cyclisation of thiocarbamoyl pyrazoles with 2-bromoacetophenone. The thiocarbamoyl pyrazoles are obtained by the simple and efficient condensation of indolyl chalcones with thiosemicarbazide. The synthesized compounds 4a-4g are screened for their antibacterial and antifungal activities. The compound 4f exhibited both antibacterial and antifungal activity against all the microbial organisms used. The structures of all the compounds are assigned on the basis of elemental analysis, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data.

**Keywords:** Pyrazoline, thiosemicarbazide, Thiocarbamoyl pyrazoline, Antibacterial activity, Anti fungal activity

## INTRODUCTION

The synthesis of various heterocyclic compounds having more than one heteroatom with structural and functional novelty has been increased in the recent years. The wide variety of these heterocycles have been explored for developing pharmaceutically important molecules like chalcones and their derivatives like pyrazoles and thiazoles. Pyrazole derivatives have gained great interest due to their pharmacological activities such as antidepressant<sup>1</sup>, antioxidant<sup>2</sup>, antiinflammatory<sup>3</sup>, anticancer<sup>4</sup>, antiviral<sup>5</sup>, antibacterial<sup>6</sup>, antifungal properties and etc. They have been found to possess a variety of industrial applications. A wide spectrum of pharmacological activities are associated with pyrazole derivatives when present along with indole nucleus<sup>7,8</sup>. Pyrazole derivatives with a phenyl group at the 5-position possess good film forming properties and also exhibit excellent characteristics of blue photo luminescence and electroluminescence<sup>9</sup>. Also pyrazole derivatives containing thiazole ring have attracted the researchers due to their varied biological activities<sup>10-14</sup>. Hence, it was thought interesting to explore the study of such molecules. Earlier we have reported the pyrazole derivatives of nicotinic acid hydrazides<sup>15</sup>. In the present study, we have synthesized some thiazolo pyrazoles and assigned their structures on the basis of elemental analyses, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopic methods. The synthesized compounds are screened for antimicrobial activities.

## MATERIALS AND METHODS

Melting points of the all the compounds were determined on a capillary melting point apparatus and were uncorrected. All chemicals and reagents used in the present study were purchased from Alfa Aesar and MERCK. The <sup>1</sup>H NMR spectra were recorded on BRUKER AVANCE III 400 MHz multi nuclei solution NMR spectrometer at ambient temperature with TMS as internal standard. Infrared spectra were recorded in KBr on a Shimadzu 8201 (4000-400cm<sup>-1</sup>) FTIR spectrophotometer. Elemental analyses were performed for C, H, N and S and were found to be within ± 0.5% of the theoretical values. Analytical TLC was performed on pre coated silica gel plates. The reactions were monitored and the purity of the products were checked using TLC.

### General procedure for the synthesis of derivatives of (E)-3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one: (2a – 2g)

A mixture of indole-3-carboxaldehyde **1** (0.01 mol) and various substituted acetophenones (0.01mol) was refluxed in the presence of methanolic NaOH for 6 to 25 hrs. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The solid obtained was filtered and recrystallised from ethanol to obtain pure chalcones. The purity of the product was checked on TLC using the mixture of toluene and ethyl acetate as mobile phase.

### (E)-3-(1H-indol-3-yl)1-phenylprop-2-en-1-one: (2a)

Prepared by the above method from **1**(0.01mol) and simple acetophenone (0.01mol).

Dark Brown crystalline solid. M.P.: 182 ± 2°C.

IR(KBr, cm<sup>-1</sup>): 3145(NH), 2924(Ar-C-H), 1639(C=O), 1595(-CH=CH);

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ(ppm)): 7.22-8.13(m,10H,Ar), 7.66(d, 1H, J = 15Hz, H<sub>α</sub>), 8.06(d,1H, J=15Hz,H<sub>β</sub>), 11.82(s,1H,NH)

**(E)-1-(4-chlorophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one: (2b)**

Yellow crystalline solid. M.P: 184± 2°C.

IR(KBr, cm<sup>-1</sup>): 3217(NH), 2924(Ar-C-H), 1631, (C=O), 1581 (-CH=CH), 738;

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ (ppm)): 7.24-8.10(m, 9H, Ar), 7.52(d,1H, J=15Hz, H<sub>α</sub>), 8.03(d, 1H,J=15Hz, H<sub>β</sub>), 11.77(s,1H,NH)

**5-(1H-indol-3-yl)-3-phenyl-4,5-dihydropyrazole-1-carbothioamide: (3a-3g)**

A mixture of appropriate indolyl chalcone (0.01mol) (3a-3g), thiosemicarbazide (0.015mol) and NaOH (0.02mol) in dry ethanol was refluxed for 16 hrs. The progress of the reaction was monitored by TLC. The excess of solvent was removed under reduced pressure and the reaction mixture was poured into ice cold water. The product obtained was filtered, washed with water and recrystallised with ethanol.

**3-chlorophenyl-5-(1H-indol-3-yl)-4,5-dihydropyrazole-1-carbothioamide:(3a)**

<sup>1</sup>H NMR: 3.27(dd,1H, H<sub>A</sub>, J<sub>AB</sub>=18.0Hz, J<sub>AX</sub>=3.5Hz), 3.80(dd,1H, H<sub>B</sub>, J<sub>AB</sub>=18.0Hz, J<sub>BX</sub>=11.5Hz), 6.19 (dd,1H, H<sub>X</sub>, J<sub>AX</sub>=3.5Hz, J<sub>BX</sub>=11.5Hz), 6.83-7.96 (m,9H,Ar-H),7.97 (d,2H,NH<sub>2</sub>), 10.96(d,1H,NH);

<sup>13</sup>C NMR: 176.12(C=S), 154.13(C=N), 136.5, 135.0, 130.1, 128.8, 128.7, 124.3, 123.9, 120.9, 118.7, 115.4, 111.8 (Ar-C), 57.2 (CH), 40.8 (CH<sub>2</sub>)

**3-hydroxyphenyl-5-(1H-indol-3-yl)-4,5-dihydropyrazole-1-carbothioamide:(3f)**

<sup>1</sup>H NMR: 3.37(dd,1H, H<sub>A</sub>, J<sub>AB</sub>=18.0Hz, J<sub>AX</sub>=3.5Hz), 3.82 (dd,1H, H<sub>B</sub>, J<sub>AB</sub>=18.0Hz, J<sub>BX</sub>=11.5Hz), 6.15 (dd,1H, H<sub>X</sub>, J<sub>AX</sub>=3.5Hz, J<sub>BX</sub>=11.5Hz), 6.83-8.05 (m,9H,Ar-H), 8.07 (d,2H, NH<sub>2</sub>), 10.03(s,1H,NH), 10.28(s,1H,OH);

<sup>13</sup>C NMR: 187.03 (C=S), 161.54(C=N), 159.8, 137.7, 137.5, 132.5, 130.6, 129.9, 125.2, 123.9, 122.6, 121.0, 120.3, 118.6 (Ar-C), 57.2(CH), 40.9(CH<sub>2</sub>)

**1-(4-phenylthiazol-2-yl)-5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro pyrazole: (4a-4g)**

The derivatives of 1-(4-phenylthiazol-2-yl)-5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro pyrazole were obtained by refluxing the compounds 3a-3g with 2-bromo-acetophenone in Ethanol for 6-7 hrs. The reaction mixture was poured into crushed ice. The solid obtained was filtered and recrystallised from ethanol to obtain pure compounds. The purity of the product was checked on TLC using the mixture of hexane and ethyl acetate as mobile phase. (Scheme-1)

**1-(4-phenylthiazol-2-yl)-5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro pyrazole (4a):**

IR (KBr, cm<sup>-1</sup>): 3124(NH), 2962(Ar-C-H), 1569(C=N), 1097(C-N);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.58(dd,1H, Ha), 3.92 (dd,1H, Hb), 6.09 (dd,1H, Hx), 6.82 -8.19(m, 16H, Ar), 10.82 (s,1H, NH).

**3-(4- chlorophenyl)-5-(1H-indol-3-yl)-1-(4-phenylthiazol-2-yl)-4,5-dihydro-Pyrazole (4b):**

IR (KBr, cm<sup>-1</sup>): 3234(NH), 2920(Ar-C-H), 1587(C=N), 1085(C-N);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.52(dd,1H, Ha), 4.01(dd,1H, Hb ), 6.00(dd,1H, Hx) (J<sub>AB</sub>=16.8Hz, J<sub>AX</sub>=5.2Hz, J<sub>BX</sub>=11.2Hz), 6.92 – 7.96(m,15H, Ar), 10.58 (s,1H, NH);

<sup>13</sup>C NMR, δ (ppm): 163.99, 151.6(C=N), 150.5, 136.5, 134.5, 134.3, 130.2, 128.9, 128.4, 127.9, 127.4, 125.5, 124.7, 121.1, 118.8, 118.4, 114.3, 111.9, 104.0 (Ar-C), 58.03(CH), 41.16(CH<sub>2</sub>)

**3-(4 bromophenyl)-5-(1H-indol-3-yl)-1-(4-phenylthiazol-2-yl)-4,5-dihydropyrazole (4c):**

IR (KBr, cm<sup>-1</sup>): 3217 (NH), 2966(Ar-C-H), 1598(C=N),1107 (C-N);

<sup>1</sup>H NMR: (500MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.55 (dd,1H, Ha), 3.86(dd,1H, Hb), 6.03(dd,1H, Hx), ( J<sub>AB</sub>=14.2Hz, J<sub>AX</sub>=5.6Hz, J<sub>BX</sub>=11.6Hz), 6.78 – 8.11 (m,15H, Ar), 10.232 (s,1H, NH)

<sup>13</sup>C NMR: δ (ppm): 151.6(C=N), 137.90 – 103.4 (Ar-C), 58.38 (CH), 41.35(CH<sub>2</sub>)

**5-(1H-indol-3-yl)-3-(4 nitrophenyl)-1-(4-phenylthiazol-2-yl)-4,5-dihydropyrazole (4d):**

IR (KBr, cm<sup>-1</sup>): 3217 (NH), 2924 (Ar-C-H), 1568 (C=N), 1094 (C-N);

<sup>1</sup>H NMR (500MHz, DMSO-d<sub>6</sub>, δ (ppm)): ): 3.65 (dd,1H, Ha), 4.48(dd,1H, Hb), 6.42(dd,1H, Hx), (J<sub>AB</sub>=17.2 Hz, J<sub>AX</sub>=5.2 Hz, J<sub>BX</sub>=12.06 Hz), 7.80 – 8.20 (m,15H, Ar), 11.09 (s,1H, NH);

**5-(1H-indol-3-yl)-3-(4-methoxyphenyl)-1-(4-phenylthiazol-2-yl)-4,5-dihydropyrazole(4e):**

IR (KBr, cm<sup>-1</sup>): 3342(NH), 2920(Ar-C-H), 1560(C=N), 1080(C-N);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.54(dd,1H, Ha), 3.86(dd,1H, Hb ), 5.97(dd,1H, Hx) ( J<sub>AB</sub>=17.2 Hz, J<sub>AX</sub>=6.0 Hz, J<sub>BX</sub>=12.0 Hz), 6.76 – 8.09(m,15H, Ar), 9.25 (s,1H, NH),3.86(s,3H,OCH<sub>3</sub>);

**3-(4 hydroxyphenyl)- 5-(1H-indol-3-yl)- 1-(4-phenylthiazol-2-yl)-4,5-dihydropyrazole (4f):**

IR (KBr, cm<sup>-1</sup>): 3427(OH), 2922(Ar-C-H), 1570(C=N), 1120(C-N);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.43 (dd,1H, Ha), 3.78 (dd,1H, Hb ), 5.92 (dd,1H, Hx) ( J<sub>AB</sub>=16.8 Hz, J<sub>AX</sub>=5.2 Hz, J<sub>BX</sub>=11.2 Hz), 6.72 – 8.01(m,15H, Ar), 10.03 (s,1H, OH), 11.04(s,1H,NH);

**5-(1H-indol-3-yl)-3-(4 methylphenyl)- 1-(4-phenylthiazol-2-yl)-4, 5-dihydropyrazole(4g):**

IR (KBr, cm<sup>-1</sup>): 3147(NH), 2978(Ar-C-H), 1594(C=N), 1114(C-N);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ (ppm)): 3.50 (dd,1H, Ha), 4.01 (dd,1H, Hb ), 5.97 (dd,1H, Hx) ( J<sub>AB</sub>=17.2 Hz, J<sub>AX</sub>=5.2 Hz, J<sub>BX</sub>=11.6 Hz), 6.90 – 8.00(m,15H, Ar), 11.07(s, 1H,NH), 3.22(s,3H,CH<sub>3</sub>);

Table 1: Physico-chemical characterization of the synthesized compounds

Compound	R	M.P. °C ±2	M.W.	Yield	M.F.	Elemental Analysis Calculated(found) %
4a	H	225	420	72	C <sub>26</sub> N <sub>4</sub> H <sub>20</sub> S	C74.29(75.35);H4.76(4.84); N13.33(13.25); S7.62(7.10)
4b	Cl	184	455	75	C <sub>26</sub> N <sub>4</sub> H <sub>19</sub> SCl	C68.57(68.85);H4.18(4.19); N12.31(12.60); S7.03(6.91)
4c	Br	204	499	65	C <sub>26</sub> N <sub>4</sub> H <sub>19</sub> SBr	C62.53(62.05); H3.81(3.11); N11.22(10.95); S6.41(6.32)
4d	NO <sub>2</sub>	170	465	48	C <sub>26</sub> N <sub>5</sub> H <sub>19</sub> SO <sub>2</sub>	C67.10(66.65);H4.09(3.62);N15.05(14.87);S6. 88(6.35)
4e	OCH <sub>3</sub>	180	450	52	C <sub>27</sub> N <sub>4</sub> H <sub>22</sub> SO	C72.00(71.63);H4.89(4.65);N12.44(12.01);S7. 11(6.75)
4f	OH	135	436	42	C <sub>26</sub> N <sub>4</sub> H <sub>20</sub> SO	C71.56(70.82);H4.59(4.13);N12.84(12.52);S7. 34(7.03)
4g	CH <sub>3</sub>	168	434	58	C <sub>27</sub> N <sub>4</sub> H <sub>22</sub> S	C74.65(74.32);H5.07(5.01);N12.90(12.85);S7. 37(7.13)

**In-vitro Antibacterial Assay:**

The Antibacterial activity for all the synthesized compounds were studied against the gram negative bacteria *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi* & *Escherichia coli*. All the microorganisms were maintained at 4°C on nutrient agar slants.

This study was performed by Agar well diffusion method<sup>16</sup>. The test microorganisms were seeded into Mueller Hinton agar by spread plate 10µl (10<sup>6</sup>). For agar well diffusion method, the well (0.7 cm) was loaded with 50µl of the test compound on the seeded agar plate. The plates were incubated overnight at 37°C. Microbial growth was determined by measuring the diameter of zone of inhibition. The result was obtained by measuring the zone diameter.

**In-vitro Antifungal screening:**

The synthesized compounds were evaluated for their in-vitro antifungal activity against *Candida albicans* using the same cup plate method with Potato Dextrose Agar (PDA) medium. The PDA medium were purchased from high media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5mg) was dissolved in 5 mL of dimethyl sulfoxide (1000µg/ml). Zone of inhibition produced by each compound was measured in mm and results are presented in Table-2

**Minimum inhibitory Concentration (MIC) of compound 4f:**

The minimum inhibitory concentration (MIC) was performed by the serial dilution technique using 96-well microplates<sup>17</sup>. The 12 wells of each row were filled with 0.5 ml sterilized Mueller Hinton broth. Sequentially, wells 3–12 received an additional 100µl of a mixture of culture medium and Compound-4f. The active compound-4f dissolved in Dimethyl Sulfoxide (DMSO) against *K. pneumoniae*, *P. aeruginosa*, *S. typhi* & *E. coli* serially diluted to create a concentration sequence from 50 to 1000µg/ml. Well 1 served as growth control and well 2 as solvent control. The deep-wells were incubated for 24h at 37°C. The resulting turbidity was observed, and after 24h MIC was determined to be that where

growth was no longer visible by assessment of turbidity by optical density readings at 600nm with a micro plate reader.

**RESULTS AND DISCUSSION**

The synthesis of the new compounds, i.e., the derivatives of 1-(4-phenylthiazol-2-yl)-5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro pyrazole (4a-4g) was carried out as shown in the Scheme-1. The Claisen-Schmidt reaction of various substituted aromatic ketones and indole-3-carboxaldehyde generates different substituted chalcones 2a-2g. These chalcones reacted with thiosemicarbazide in the presence of sodium hydroxide and ethanol to give thiocarbamoyl pyrazolines(3a-3g) which when refluxed with 2-bromoacetophenone in ethanol gave the corresponding 1-(4-phenylthiazol-2-yl)-5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro pyrazole(4a-4g). The spectral data and analytical data of all the compounds were in full agreement with the proposed structures.

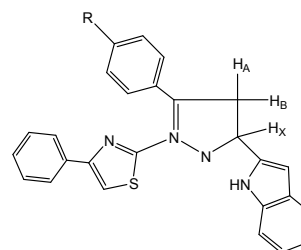
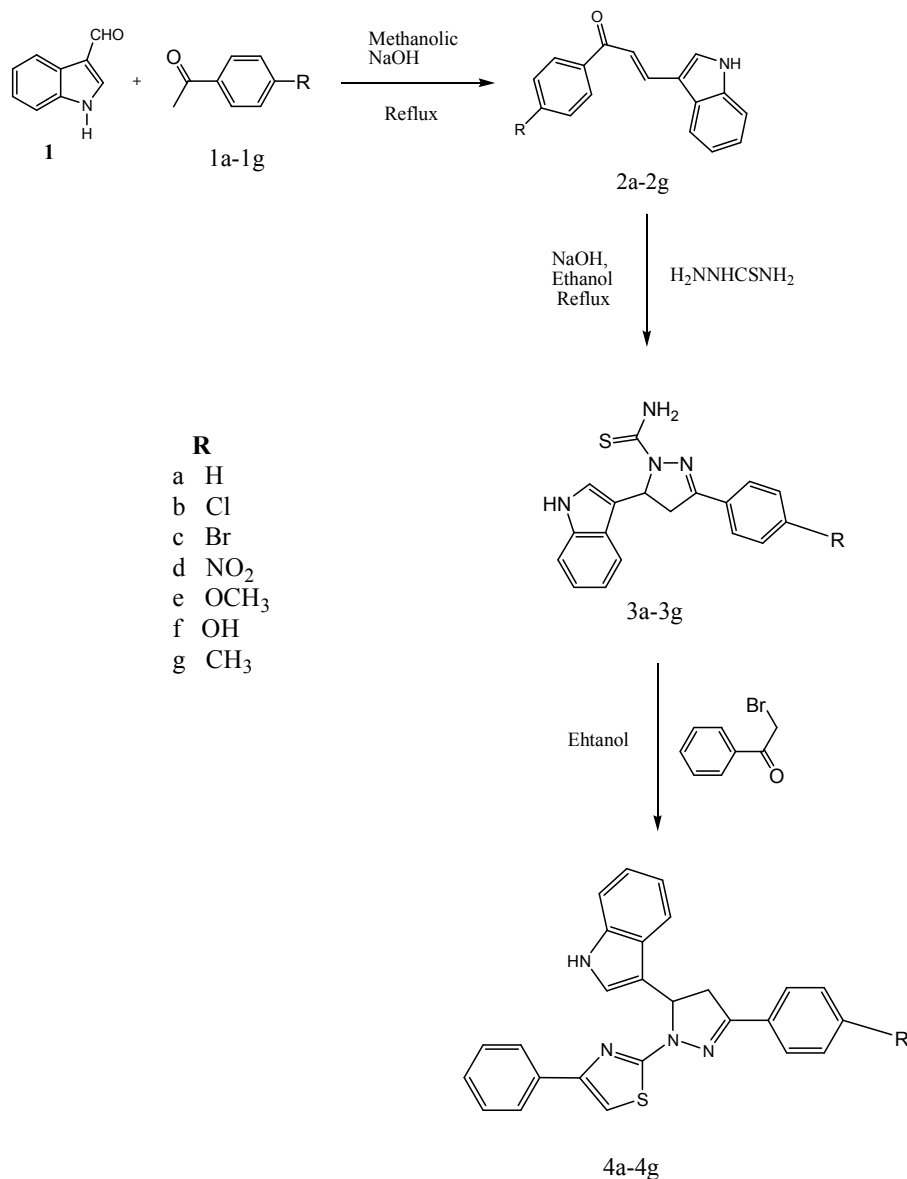


Figure-1

The IR spectrum of compounds 4a-4g revealed characteristic bands<sup>18</sup> at 1560 – 1594 cm<sup>-1</sup> (C=N), 1080 – 1114 cm<sup>-1</sup> (C-N) and 3120 – 3234 cm<sup>-1</sup> (N-H). In the <sup>1</sup>H NMR spectra of these compounds, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the pyrazoline ring gave an ABX spin system<sup>19</sup> (Figure-1). The CH<sub>2</sub> protons of the pyrazoline ring resonated as a pair of doublet of doublets at δ 3.50 – 3.65 ppm (Ha) and δ 3.85 – 4.01 ppm (Hb). The CH (Hx) proton appeared as a doublet of doublets at δ 5.97 - 6.42 ppm due to vicinal coupling with the two magnetically non-

equivalent protons of the C-4 carbon of pyrazoline ring. The J values were calculated for these signals and found to be  $J_{AB}=17.2$  Hz,  $J_{AX}=5.2$  Hz,  $J_{BX}=12.06$  Hz. The -NH proton of indole ring appeared as a singlet above  $\delta$  9.00 ppm. The other protons of aromatic ring and phenyl substituents were observed at the expected regions. The 5-H proton of thiazole

was observed as a singlet between 8.30 – 8.60 ppm. The  $^{13}\text{C}$  NMR spectra of all the compounds were recorded in DMSO and spectral signals are in good agreement with the given structure. The C-4 and C-5 carbons of pyrazole ring resonated at  $\delta$  41.35 ppm and 58.10 ppm respectively.



Scheme-1: Synthesis of thiazolo pyrazole derivative

Table 2: Antibacterial and Anticandidal activity of synthesized compounds:

Clinical isolates	Zone of inhibition by series of compound in diameter						
	4a	4b	4c	4d	4e	4f	4g
<i>Escherichia coli</i>	-	-	-	8mm	8mm	16mm	-
<i>Salmonella typhi</i>	-	-	-		-	10mm	9mm
<i>Klebsiella Pneumoniae</i>	-	-	-	8mm	7mm	12mm	-
<i>Psuedomonas aeruginosa</i>	-	10mm	-	-	-	9mm	-
<i>Candida Albicans</i>	-	-	-	-	-	14mm	-

(-) No zone of inhibition

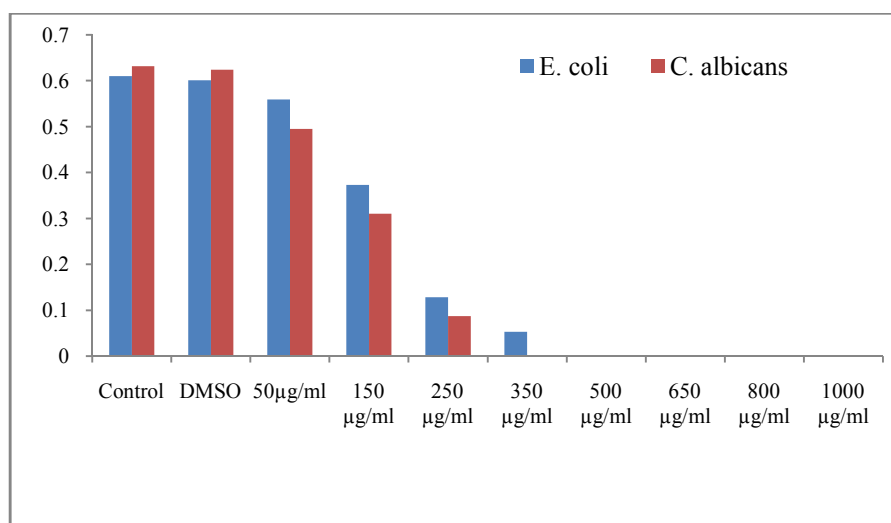


Figure 2: MIC determination of compound 4f

### Antibacterial activity

The results of in-vitro antimicrobial activities of the compounds (4a-4g) against various microbes are summarized in Table-2. The compound 4f exhibited good antibacterial activity against all the bacteria, *E.Coli*, *K.pneumoniae*, *P.aeruginosa* and *S.typhi*.

The compounds 4d and 4e were found to be moderately active against *E. Coli* and *K.pneumoniae* while 4b and 4g exhibited activity against *P.aeruginosa* and *S.typhi* respectively. The compounds 4a & 4C did not show any activity against all the four bacteria used. The graph shows the MIC of the compound 4f (Fig2) which is 250µg/ml. The antibacterial results of present study indicated that presence of hydroxyl group in the phenyl ring increased the antibacterial activity of the compounds.

### Antifungal activity

The antifungal screening data of the compounds revealed a good response of compound 4f to the tested fungi, *Candida albicans*. None of the other synthesized compounds was found to be active against *C. albicans*.

## CONCLUSION

A series of 4-phenylthiazole derivatives of 2-pyrazolines were synthesized, characterized by analytical and spectral study and their in-vitro anti bacterial and anti fungal activities have been determined. Among the synthesized compounds, the compound 4f with the hydroxyl group in the 3-phenyl ring was active against all the microorganism used. The MIC value of compound 4f was found to be 250 µg ml<sup>-1</sup> against *E. coli* and *C. albicans*. The behavior of the pyrazoline 4f towards the clinical isolates led to the conclusion that the antimicrobial activity of such compounds is effective with the introduction of a specific substituent.

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