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Synthesis, Characterization and Biological Activity of (N^1E, N^2Z)-N^1, N^2-Bis ((1-Phenyl-3-Aryl-1*H*-Pyrazol-4-Yl) Methylene) Benzene-1, 2-Diamines

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ABSTRACT

Seven novel Pyrazole ring containing Schiff's bases (N^1E, N^2Z)-N^1,N^2-bis((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene) benzene-1,2-diamines (6a-g) have been synthesized from 1-phenyl-3-aryl-1H-pyrazole-4-carbaldehyde (4a-g), and benzene-1, 2-diamine (5) by Microwave Irradiation method. The newly synthesized compounds were characterized by using IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral data and Elemental analysis. These compounds were evaluated for their antibacterial activity against Gram positive viz. Staphylococcus aureus and Bacillus subtilis and Gram negative viz. Escherichia coli, Klebsiella pnemoniae strains using a micro dilution method. Synthesized compounds showed activity against a panel of microorganisms.

Keywords: (*E*)-1-phenyl-2-(1-phenylethylidene)hydrazine,1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehyde, Schiff's base, Antibacterial activity.

INTRODUCTION

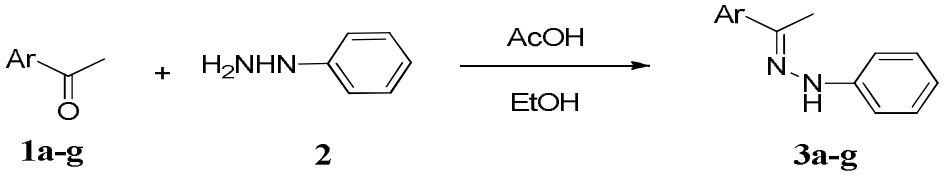
Schiff's Bases exhibit extensive biological and pharmacological activities because of the presence of azomethine carbon. Schiff bases have recently assumed greater importance as biologically active and were used as antibacterials[1], antivirals[2], antifungals[3, 4], antitumors[5, 6], insecticides[7], antihelmintics[8] and antiemetics[9]. Several Schiff's bases possess cytotoxic[10], anti-inflammatory[11], antipyretic[12], analgesics[13], diuretic [14], and antispasmodic[15, 16] activities. The Pyrazoles[17-19] and Schiff bases[20,21] were found to possess wide therapeutic activities and are also important pharmacophores. Therefore we planned the synthesis of Pyrazole containing Schiff bases. From the survey of literature it is observed that very few reports are available on pyrazole containing Schiff's bases. In view of the above it is worthwhile to synthesise pyrazole containing Schiff's bases. The present paper reports the synthesis, characterization and biological activity of pyrazole containing Schiff's bases.

MATERIALS AND METHODS

Melting points (m.p.) were determined using Boetieus micro heating apparatus and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Perkin- Elmer FT-IR spectrum BX. ^{1}H NMR spectra were recorded

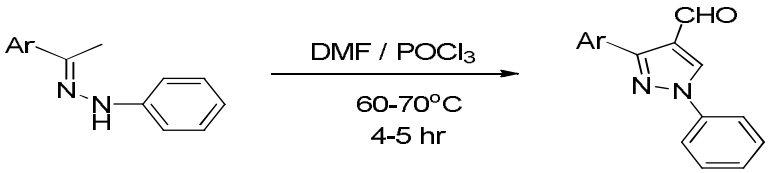
on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). Elemental analysis were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Quatro Lc micromas (Waters Manchester.UK). (70 eV) mass spectrometer. For microwave irradiation a L.G. (M-2349E, 2450 MHz) domestic microwave oven was used. We performed disc diffusion method to identify the antibacterial activity on **Gram positive bacteria** *viz. Staphylococcus aureus* and *Bacillus subtilis and* **Gram negative bacteria** *viz. Escherichia coli, Klebsiella pnemoniae.*

Scheme: Step-1: Synthesis of (*E*)-1-phenyl-2-(1-phenylethylidene) hydrazine: To a solution of Phenyl hydrazine (0.05mol) and substituted acetophenones (0.05mol) in Ethanol (20ml) in the presence of 1mL Glacial Acetic acid and the whole mixture was refluxed in water bath for 4 hr. The reaction progress was checked by TLC. After completion of the reaction, the reaction mixture was poured into ice cold water and the resulting solid was filtered, dried and recrystallized from methanol to obtain compound **3** yield 90%, The mass spectrum of the compound **(3b)** showed molecular ion peak at *m/z* = 241[M+H]$^+$.



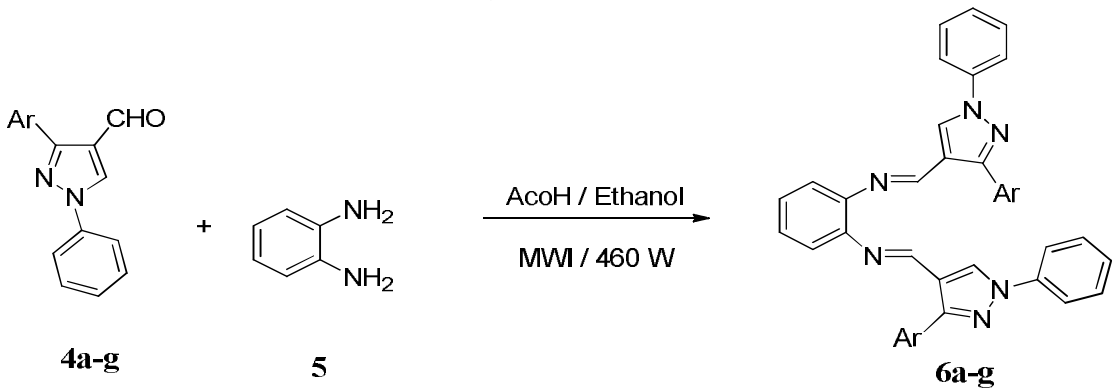
1a-g **2** **3a-g**

Step-2: Synthesis of 1-phenyl-3-aryl-1H-pyrazole-4-carbaldehyde: To the ice-cold solution of DMF (0.1 mol) and (*E*)-1-phenyl-2-(1-phenylethylidene) hydrazine (0.01 mol) phosphorous oxychloride (0.02 mol), was added drop wise with stirring under ice-cold conditions. After the addition, the reaction mixture was refluxed at 60-70^{o}C for 4-5 hrs. Solution was cooled and poured into crushed ice and neutralized with $NaHCO_3$ solution. The solid obtained was filtered under suction and recrystallised from methanol. The mass spectrum of the compound **(4b)** showed molecular ion peak at *m/z* = 279[M+H]$^+$.



3a-g **4a-g**

Step-3: Synthesis of (N^1E, N^2Z)-N^1, N^2-bis ((1-phenyl-3-aryl-1H-pyrazol-4-yl) methylene) benzene-1,2-diamines:



4a-g **5** **6a-g**

To a mixture of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehyde **(4a-g)** (0.01mol), benzene-1,2-diamine **(5)** (0.005mol), in the presence of Glacial Acetic acid in ethanol were irradiated under microwave at 460 watt for 6-8 min. The reaction progress was checked by TLC. After completion of the reaction the reaction mixture was poured into ice cold water and the resulting solid was filtered, dried and recrystallized from ethanol to obtain the compounds **(6a-g).** Details of the melting points and yields of the compounds were presented in the table 1.

Table 1: Physical data for Schiff's bases (6a-g)

Compounds	Ar	M.P(^{o}C)	Reaction Time MWI (min)	Yield (%)
6a	Phenyl	132	8	79
6b	4-Methoxy Phenyl	159	6	88
6c	4-Chloro Phenyl	175	6	80
6d	4-Floro Phenyl	192	7	75
6e	4-Bromo Phenyl	241	8	78
6f	2,4-Dichloro Phenyl	294	6	84
6g	2,6-Dichloro Phenyl	286	7	82

RESULTS AND DISCUSSION

(N^1-*E*, N^2*Z*)-N^1,*N*^{2}-Bis- ((1-phenyl-3-(4 - methoxy phenyl)- 1*H* – pyrazol – 4 -yl) methylene) benzene-1,2-diamine (6b): IR (KBr): The IR (KBr) spectrum of compound (6b) showed significant peak at 1602.85 cm^{-1} (for C=N) and a peak at 1506.41 cm^{-1} (for C=C); The ^{1}H-NMR ($CDCl_3$) of compound (6b) represented two singlets at δ 3.66 and 3.85 for two -OCH_3 group protons. One siglet peak is observed at 8.18 for two Pyrazole ring protons and another singlet appeared at 8.80 for two Imine protons, all the aromatic protons appear as multiplets by matching the number of protons of the compound (6b). On the basis of ^{13}C NMR ($CDCl_3$) spectra the following signals were assigned to the compound (6b). δ 55.299, 55.393 indicates the presence of two –OCH_3 groups, Two signals at δ 159.665, 159.948 indicates the presence of two Imine carbons of Schiff's base moiety and two peaks observed at δ 159.893, 160.379 for Two quaternary aromatic carbons having methoxy groups of compound (6b). Mass: The mass spectrum of the compound (6b) showed molecular ion peak at *m/z* = 629[M+H] $^{+}$; Elemental Analysis: Found: C, 76.43; H, 5.14; N, 13.38. Based on the above spectral data and Elemental analysis the compound (6b) is confirmed as(N^1*E*,N^2*Z*)-N^1, *N*^{2}-Bis-((1phenyl-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)benzene-1,2-diamine.

Spectral data and structure elucidation of (N^1*E*, N^2*Z*)-*N*^{1}, *N*^{2}-bis((1-phenyl, 3-aryl-1*H*-pyrazol-4-yl) methylene)benzene-1,2-diamines

1. (N^1*E*,N^2*Z*)-*N*^{1},*N*^{2}-bis((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)benzene-1,2-diamine (6a): IR (KBr): 1602.63 cm^{-1} (for C=N), 1506.19 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$): 6.73-6.75 (d, 8.0Hz, Ar-H, 2H); 6.84-7.00(m, 4H, Ar-H); 7.16-7.20 (m, Ar-H, 3H); 7.30-7.34 (m, Ar-H, 3H); 7.43-7.45 (m, 4H, Ar-H); 7.59 -7.78 (m, Ar-H, 6H); 7.86-7.88 (d, 8.8Hz, Ar-H, 2H); 8.19 (s, 2H, Py- H); 8.82 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 110.618, 110.665, 112.436, 112.315, 114.658, 114.233, 118.477, 118.502, 119.421, 119.629, 122.316, 122.742, 122.846, 123.516, 124.468, 124.693, 124.814, 126.563, 127.541, 127.790,

128.548, 129.149, 129.253, 129.473, 129.566, 129.695, 129.783, 130.254, 134.668, 139.473, 143.741, 145.895, 147.692, 150.385, 150.561, 151.494, 159.574, 160.560; MS: *m/z* = 569[M+H]$^+$; Elemental Analysis: Calculated for $C_{38}H_{28}N_6$: C, 80.26; H, 4.96; N, 14.78. Found: C, 80.29; H, 4.97; N, 14.80.

2. (*N*^{1}*E*,*N*^{2}*Z*)-N^1, *N*^{2}-Bis ((1phenyl-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine (6b): IR (KBr): 1602.85 cm^{-1} (for C=N), 1506.41 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$: 3.66 (s, -OCH_3, 3H); 3.85 (s, -OCH_3, 3H), 6.77-6.79 (d, 8.8Hz, Ar-H, 2H); 6.87-6.89 (d, 8.0Hz, Ar-H, 2H); 6.99-7.01 (d, 8.0Hz, 2H, Ar-H); 7.18-7.20 (m, Ar-H, 3H); 7.31-7.34 (m, 2H, Ar-H); 7.45-7.47(m, 3H, Ar- H); 7.60-7.62 (d, 8.4Hz, 2H, Ar-H); 7.70-7.72 (d, 8.0Hz, 2H, Ar-H); 7.77-7.79 (d, 8.4Hz, Ar-H, 2H); 7.86-7.88 (d, 8.8Hz, Ar-H, 2H); 8.18 (s, 2H, Py-H); 8.80 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 55.299, 55.393, 110.661, 112.528, 114.116, 114.301, 114.555, 116.107, 118.718, 119.149, 119.220, 119.920, 122.662, 122.715, 123.112, 124.734, 124.797, 124.915, 126.395, 127.053, 127.094, 128.846, 129.102, 129.204, 129.276, 129.545, 129.655, 130.159, 134.932, 139.460, 143.101, 145.923, 147.096, 150.582, 150.653, 151.397, 159.665, 159.948, 159.893, 160.379; MS: *m/z* = 629[M+H]$^+$; Elemental Analysis: Calculated for $C_{40}H_{32}N_6O_2$: C, 76.41; H, 5.13; N, 13.37. Found: C, 76.43; H, 5.14; N, 13.38.

3. (*N*^{1}*E*,*N*^{2}*Z*)-*N*^{1}, N^2–Bis ((1 phenyl -3-(4-chlorophenyl)--1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine(6c):IR (KBr): 1602.35 cm^{-1} (for C=N), 1506.22 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$): 77-6.79 (d, 8.8Hz, Ar-H, 2H); 6.87-6.89 (d, 7.4Hz, Ar-H, 2H); 6.99-7.34 (m, Ar-H, 6H); 7.45-7.47 (m, Ar-H, 4H); 7.60-7.72 (m, 4H, Ar-H); 7.77-7.79 (d, 8.8Hz, Ar-H, 2H); 7.86-7.88 (d, 7.4Hz, Ar-H, 2H); 8.17 (s, 2H, Py-H); 8.81 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 110.661, 110.683, 114.029, 114.235, 115.447, 115.642, 117.489, 117.650, 119.243, 119.511, 122.252, 122.455, 123.832, 124.434, 124.497, 124.617, 126.494, 127.556, 127.654, 128.147, 129.392, 129.539, 129.374, 129.390, 129.542, 131.248, 135.036, 136.347, 139.457, 143.392, 143.644, 146.223, 147.394, 150.602, 150.678, 151.230, 160.443, 160.477; MS: *m/z* = 637[M+H]$^+$; Elemental Analysis: Calculated for $C_{38}H_{26}Cl_2N_6$: C, 71.59; H, 4.11; Cl, 11.12; N, 13.18. Found: C, 71.61; H, 4.12; Cl, 11.13; N, 13.19.

4. (*N*^{1}*E*,*N*^{2}*Z*)-*N*^{1}, *N*^{2}-Bis ((1-phenyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine(6d): IR (KBr):1601.93 cm^{-1} (for C=N), 1505.86 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$): 6.76-6.88 (m, Ar-H, 4H); 6.99-7.01(d, 8.0Hz, 2H, Ar- H); 7.16-7.18 (m, Ar-H, 2H); 7.24-7.25 (m, Ar-H, 2H); 7.45-7.48 (m, Ar-H, 4H); 7.60-7.62 (d, 8.0Hz, 2H, Ar- H); 7.70-7.79 (m, Ar-H, 4H); 7.86-7.88 (m, Ar-H, 2H); 8.23 (s, 2H, Py-H); 8.86 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 110.661, 110.473, 114.120, 114.158, 116.592, 116.397, 118.373, 118.029, 119.382, 119.826, 122.649, 122.735, 123.312, 123.452, 124.468, 124.814, 126.390, 126.130, 127.114, 128.857, 129.122, 129.504, 129.776, 129.912, 129.950, 130.160, 134.936, 139.461, 143.120, 145.826, 147.196, 150.642, 150.660, 151.384, 159.389, 159.651, 162.041, 162.076; MS: *m/z* = 605[M+H]$^+$; Elemental Analysis: Calculated for $C_{38}H_{26}F_2N_6$: C, 75.48; H, 4.33; F, 6.28; N, 13.90. Found: C, 75.50; H, 4.34; F, 6.29; N, 13.91.

5. (*N*^{1}*E*,*N*^{2}*Z*)-*N*^{1}, *N*^{2}-Bis ((1-phenyl-3-(4-bromophenyl)-1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine(6e):IR (KBr): 1602.74 cm^{-1} (for C=N), 1506.27 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$): 6.78-6.78 (d, 8.0Hz, Ar-H, 2H); 6.87-7.35 (m, Ar-H, 8H); 7.45-7.47 (m, Ar- H, 4H); 7.60-7.74 (m, Ar-H, 6H); 7.82-7.84 (d, 8.0Hz, Ar-H, 2H); 8.17(s, 2H, Py-H); 8.79 (s, 2H, Imine-H);^{13}C-NM R ($CDCl_3$) : 110.661, 110.670, 114.124, 114.128, 114.578, 114.582, 118.912, 118.918, 119.222, 119.226, 122.634, 122.647, 123.115, 123.126, 124.487, 124.495, 126.355, 126.359, 127.694, 127.842, 129.102, 129.204, 129.276, 129.285, 130.658, 130.664, 134.932, 134.960, 136.644, 137.521, 143.101, 143.923, 147.096, 150.582, 150.653, 151.397, 159.665, 159.948; MS: *m/z* = 725[M+H]$^+$; Elemental Analysis: Calculated for $C_{38}H_{26}Br_2N_6$: C, 62.83; H, 3.61; Br, 22.00; N, 11.57. Found: C, 62.84 H, 3.62; Br, 22.02; N, 11.58.

6. (*N*^{1}*E*,*N*^{2}*Z*)-*N*^{1},*N*^{2}-Bis ((1-phenyl-3-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine (6f): IR (KBr): 1603.18 cm^{-1} (for C=N), 1507.51 cm^{-1} (for C=C); ^{1}H-NMR ($CDCl_3$): 6.77-6.79 (d, 8.0Hz, Ar-H, 2H); 6.87-6.89 (d, 8.8Hz, Ar-H, 2H); 6.99-7.02 (m, 2H, Ar-H); 7.31-7.35 (m, Ar-H, 6H);

7.60-7.79 (d, 8.0Hz, Ar-H, 6H); 7.86-7.88 (d, 8.8Hz, Ar-H, 2H); 8.15 (s, 2H, Py-H); 8.76 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 110.563, 112.625, 114.180, 114.498, 114.775, 116.770, 118.516, 119.352, 119.564, 120.625, 122.692, 122.791, 123.414, 124.635, 124.757, 125.813, 126.596, 127.433, 127.596, 128.646, 129.214, 129.350, 129.485, 129.662, 129.754, 130.459, 134.635, 136.243, 136.249, 140.150, 143.516, 145.627,147.594,150.587, 150.651, 151.395, 159.580, 160.212; MS: *m/z* = 705$[M+H]^+$; Elemental Analysis: Calculated for $C_{38}H_{24}Cl_4N_6$: C, 64.61; H, 3.42; Cl, 20.07; N, 11.90. Found: C, 64.62; H, 3.43; Cl, 20.08; N, 11.91.

7. (N^1E,N^2Z)-N^1,N^2-Bis ((1-phenyl-3-(2,6-dichlorophenyl)-1*H*-pyrazol-4-yl) methylene) benzene-1,2-diamine (6g): IR (KBr): 1602.99 cm^{-1} (for C=N), 1506.72 cm^{-1} (for C=C): ^{1}H-NMR ($CDCl_3$): 6.80-6.82 (m, Ar-H, 3H); 6.84-6.84 (m, Ar-H, 3H); 6.99-7.01 (d, 8.0Hz, Ar-H, 2H); 7.15-7.17 (d, 8.0Hz, Ar-H, 2H); 7.22-7.79 (m, 8H, Ar-H); 7.86-7.88 (m, Ar-H, 2H); 8.13 (s, 2H, Py-H); 8.70 (s, 2H, Imine-H); ^{13}C-NMR ($CDCl_3$): 110.661, 112.643, 114.189, 114.390, 114.875, 116.769, 118.818, 119.650, 119.762, 120.925, 122.792, 122.995, 123.512, 124.832, 124.799, 125.911, 126.392, 127.532, 127.794, 128.840, 129.116, 129.350, 129.474, 129.765, 129.859, 130.559, 134.932, 137.622, 137.724, 140.650, 140.714, 145.823, 147.696, 150.682, 150.753, 151.497, 159.754, 159.993; MS: *m/z* = 705$[M+H]^+$; Elemental Analysis: Calculated for $C_{38}H_{24}Cl_4N_6$: C, 64.61; H, 3.42; Cl, 20.07; N, 11.90. Found: C, 64.62; H, 3.43; Cl, 20.08; N, 11.91.

APPLICATIONS

Biological activity of (N^1E, N^2Z)-N^1, N^2-bis ((1-phenyl, 3-aryl-1*H*-pyrazol-4-yl)methylene) benzene-1,2-diamines: The newly synthesized compounds (6a-g) were screened for their antibacterial activity against Gram negative bacteria *viz. Escherichia coli* and *Klebsiella pnemoniae*, and Gram-positive bacteria *viz. Staphylococcus aureus* and *Bacillus subtilis* at concentration 50 mg/ml using disc diffusion method. The test organism was a two hour culture of *Escherichia coli, Klebsiella pnemoniae, Staphylococcus aureus* and *Bacillus subtilis* incubated and grown in peptone-water medium (temp-37^{o}C). DMF was used as solvent control which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37^{o}C for 24 h. The growth inhibition zones around the discs were observed that the examined compound inhibits the growth of microorganism. Each assay in this experiment was repeated three times. All the compounds were found to show strong activity against Gram-positive and Gram negative bacteria *viz. Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pnemomiae*. Gentamycin is used as standard. These results are given in table 2.

Table 2: Antibacterial studies of the synthesized compounds (6a-g)

Compounds	Antibacterial activity zone of inhibition(mm)			
	S. aureus	***E.coli***	***Bacillus subtilis***	***Klebsiella***
Gentamycine	20	18	15	17
6a	08	07	06	-
6b	09	-	-	-
6c	07	06	07	-
6d	09	08	08	-
6e	11	10	10	07
6f	10	10	08	-
6g	09	09	08	-

Graphical representations are shown in fig.1

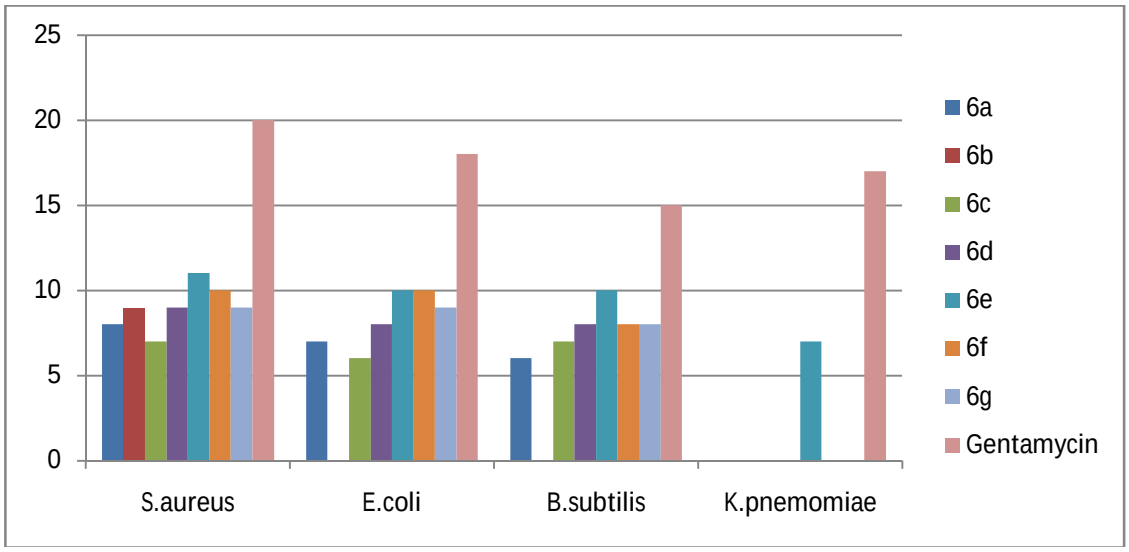


Fig 1. Graphical representation of Antibacterial activity of (N^1E, N^2Z)-N^1, N^2-bis ((1-phenyl,3-aryl-1*H*-pyrazol-4-yl)methylene) benzene-1,2-diamines.

The compound (N^1E,N^2Z)-N^1, N^2-Bis((1-phenyl-3-(4-bromophenyl)-1*H*-pyrazol-4-yl)methylene)benzene-1,2-diamine **(6e)**showed better activity among all the compounds against Gram-positive bacteria and Gram negative bacteria. Compounds (N^1E,N^2Z)-N^1,N^2-Bis((1-phenyl-3-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl) methylene)benzene-1,2-diamine **(6f)** and (N^1E,N^2Z)-N^1,N^2-Bis((1-phenyl-3-(2,6-dichlorophenyl)-1*H*-pyrazol-4-yl)methylene)benzene-1,2-diamine **(6g)** were found to show moderate activity against Gram-positive bacteria *viz. Staphylococcus aureus* and *Bacillus subtilis.* The same compounds were found to show moderate activity against Gram negative bacteria *viz. Escherichia coli* and *Klebsiella pnemoniae.*

CONCLUSIONS

In this chapter the title compounds (N^1E, N^2Z)-N^1, N^2-bis ((1-phenyl,3-aryl-1*H*-pyrazol-4-yl)methylene) benzene-1,2-diamines are synthesized by microwave irradiation method. Microwave irradiation method is an easy, high yielding, convenient and green method. The process proved to be a simple, environmentally friendly technique with high rate of acceleration was achieved in performing the reaction. All the compounds (6a-g) were in solid state, yellowish in color. The structures were established by, IR, ^{1}H-NMR & ^{13}C NMR, Mass spectrometry and Elemental analysis.

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