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Spectroscopic and bactericidal activity of 4-aminobenzamide derivatives

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Abstract

A series of 4-aminobenzamide derivatives of Schiff base compounds have been isolated from condensation of 1,2-dicarbonyl compounds such as benzil, o-phthaldehyde, 2,3-pentanedione, 2,3-butanedione and glyoxal with 4-aminobenzamide. The compounds were characterized by elemental analysis, electrochemical and various spectroscopic studies like IR, UV-Visible, ^{1}H and ^{13}C NMR spectroscopy. The prepared compounds were screened for antibacterial activity against Gram positive and Gram negative bacteria.

Keywords: Schiff base, 4-aminobenzamide derivatives, 1,2-dicarbonyl compounds, NMR, Antibacterial activity.

Introduction

Schiff bases are important class of compounds in medicinal and pharmaceutical field. It is considered as "privileged ligands" because they are easily prepared. Schiff bases form an important class of organic compounds with a wide variety of biological properties[1] including anticancer[2], antibacterial[3], antifungal, antioxidant[4] and herbicidal activities. Generally dicarbonyl compounds used in fermented food products, such as wine, brandy, vinegar and cheese. In addition, glyoxal, diacetyl and penta-2,3-dione were recognized in wine[5,6]. Fascinatingly, α-dicarbonyls have been observed in honey samples as an indicator of heating processes during manufacturing and storage[7].

Moreover, Glyoxal seems to be the major role in glucose autoxidation, a process which could also contribute to sugar protein modification in diabetes[8,9] and can be formed as a lipid peroxidation product. Similarly benzil employed as a photo initiator in polymer chemistry, building block of organic synthesis[10] and potent inhibitor of human carboxylesterases, enzymes involved in the hydrolysis of carboxylesters and many clinically used drugs[11]. *o*-Phthalaldehyde is a building block of heterocyclic compounds synthesis and a reagent in the analysis of amino acids. Moreover aminobenzamide derivatives can be used as agents for controlling animal parasite. It is also used to adjust curvature in polyamide curvature and DNA sequence selective recognition[12,13].

In the present work, we have synthesized number of new Schiff base compounds using different carbonyl compounds like Benzil, *o*-phthaldehyde, 2,3-pentanedione, 2,3- butanedione and glyoxal with 4-aminobenzamide. The structure of the Schiff base compounds were proposed from elemental analyses, some spectroscopic techniques and cyclic voltammetry studies. All the compounds were tested for antibacterial activity.

Materials and methods

Material and physical measurements: 4-aminobenzamide, 2,3-pentanedione, 2,3-butanedione, *o*-phthaldehyde, glyoxal and benzil were Purchased from Acros Organics, Loba chemie and S.D.Fine-Chem. Ltd respectively. n-Bu_4NClO_4 was acquired from Aldrich. The C, H and N were performed using a Carlo Erba 1106 elemental analyzer. The ^{1}H and ^{13}C NMR spectra obtained on a BRUKER 500 MHz spectrometer and DMSO-d_6 as solvent. The IR spectra were measured on KBr pellets with a FT-IR spectrophotometer (Jasco FT-IR-410) in the 4000-400 cm^{-1} range. The electronic spectra in the 200-800 nm range was recorded on UV/Vis Jasco 550 double beam, spectrophotometer. Electrochemical studies were measured using a CHI 1120A electrochemical analyzer in DMSO containing 0.1M n-Bu_4NClO_4 as the supporting electrolyte.

Synthesis of schiff base compounds from diketones: The BAB, PDAB and BDAD compounds were prepared by the reaction of ethanolic solution (20 ml) of benzil or 2,3-pentanedione or 2,3-butanedione (0.5 g, 2.37 mmole) was added to the two equivalent amount of 4-aminobenzamide (0.809 g, 5.94 mmole) in 20 ml of the same solvent. 2 drops of Conc. HCl were added to the reaction mixture and refluxed for 10-18 hours. The crystals were filtered and washed with cold ethanol, diethyl ether and dried in vacuum desiccator (Scheme-1).

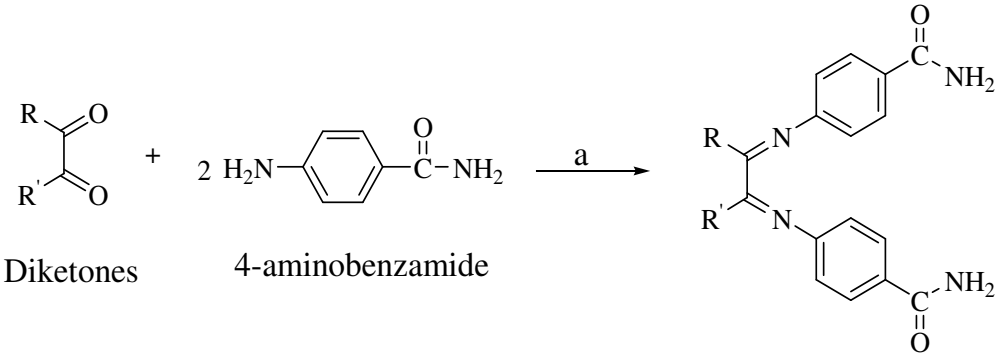
Synthesis of Schiff base compounds from dialdehyde: The compounds PAB and GAB were synthesized by literature method[14]. Ethanolic solution (20 ml) of *o*-phthaldehyde or glyoxal (0.5 g, 3.72 mmole) were added to a solution of 4-aminobenzamide (1.26 g, 9.31 mmole) in ethanol (20 ml). The reaction mixtures were heated at 70°C with stirring for 2 hours. The precipitate formed at the end of the period were filtered and washed with ethanol, diethyl ether and then dried in air.

The product was found to be TLC pure in 7:3 mixtures of hexane and ethyl acetate (Scheme-2).

Antibacterial studies: *Staphylococcus aureus* and *Escherichia coli* were used as a test organism for antimicrobial studies[15]. In an agar medium, the plate were incubated for 24 hours at 37°C. Activity was measured by inhibition of growth from the edge of the well. The diameter of the zone inhibition produced by the compounds was compared with standard drugs. The separate studies were carried out with solvent DMSO only and it showed no activity against any microbial strains.

Results and discussion

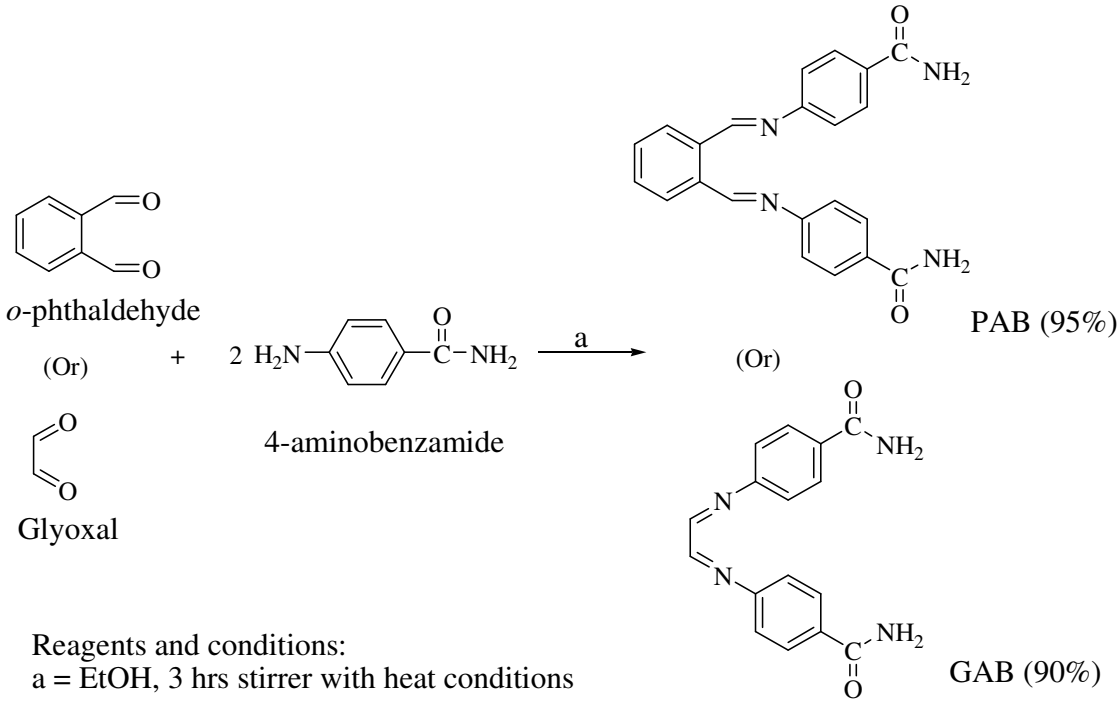
The novel BAB, PDAB, BDAB, PAB and GAB compounds were prepared by 1:2 condensation of dicarbonyl compounds (Benzil, 2,3-pentanedione, 2,3-butanedione, *o*-phthaldehyde and Glyoxal) with 4-aminobenzamide. The compounds have been characterized on the basis of elemental analyses, IR, UV, NMR spectral analyses and cyclic voltammetry studies. The infrared, electronic, ^{1}H and ^{13}C NMR spectra and cyclic voltammetry of Schiff base compounds are seen in Figure-(1-5) respectively. The purity was checked by TLC.



Reagents and conditions:
a = EtOH, Reflux 10-18 hrs

BAB : R = phenyl, R' = phenyl (80%)
PDAB : R = -CH_3, R' = -CH_2-CH_3 (85%)
BDAB : R = -CH_3, R' = -CH_3 (75%)

Scheme-1: Synthesis of Schiff base compounds BAB, PDAB and BDAB.



Reagents and conditions:
a = EtOH, 3 hrs stirrer with heat conditions

Scheme-2: Synthesis of Schiff base compounds PAB and GAB.

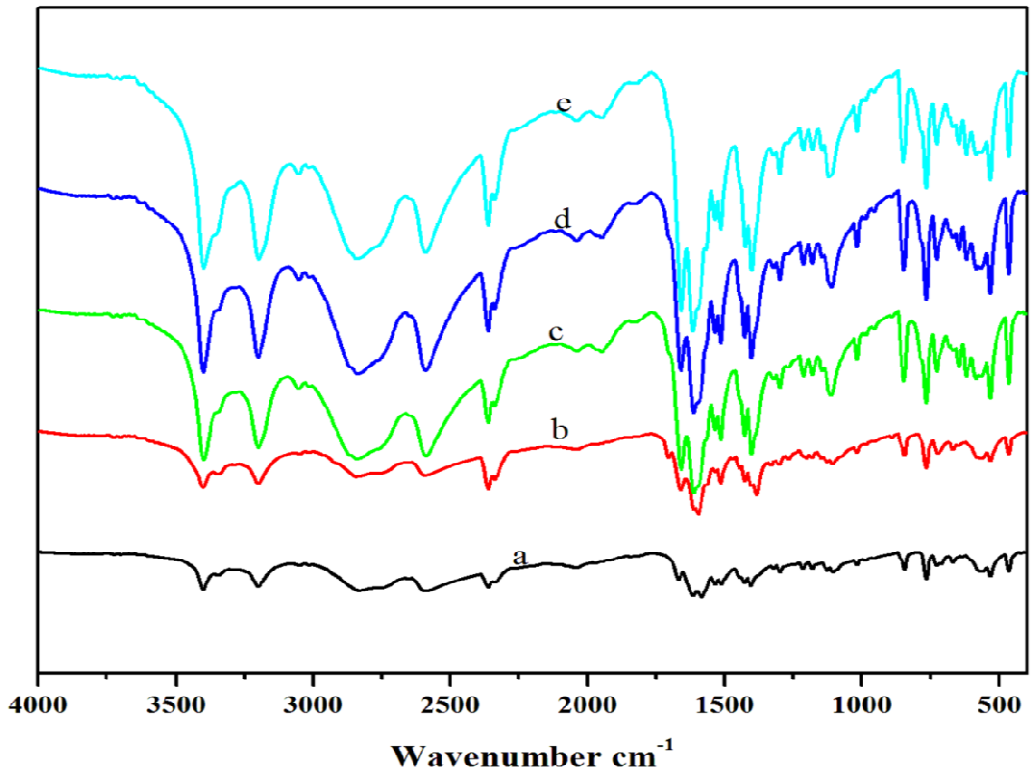


Figure-1: IR spectra of a) BAB, b) PAB, c) PDAB, d) BDAB, e) GAB.

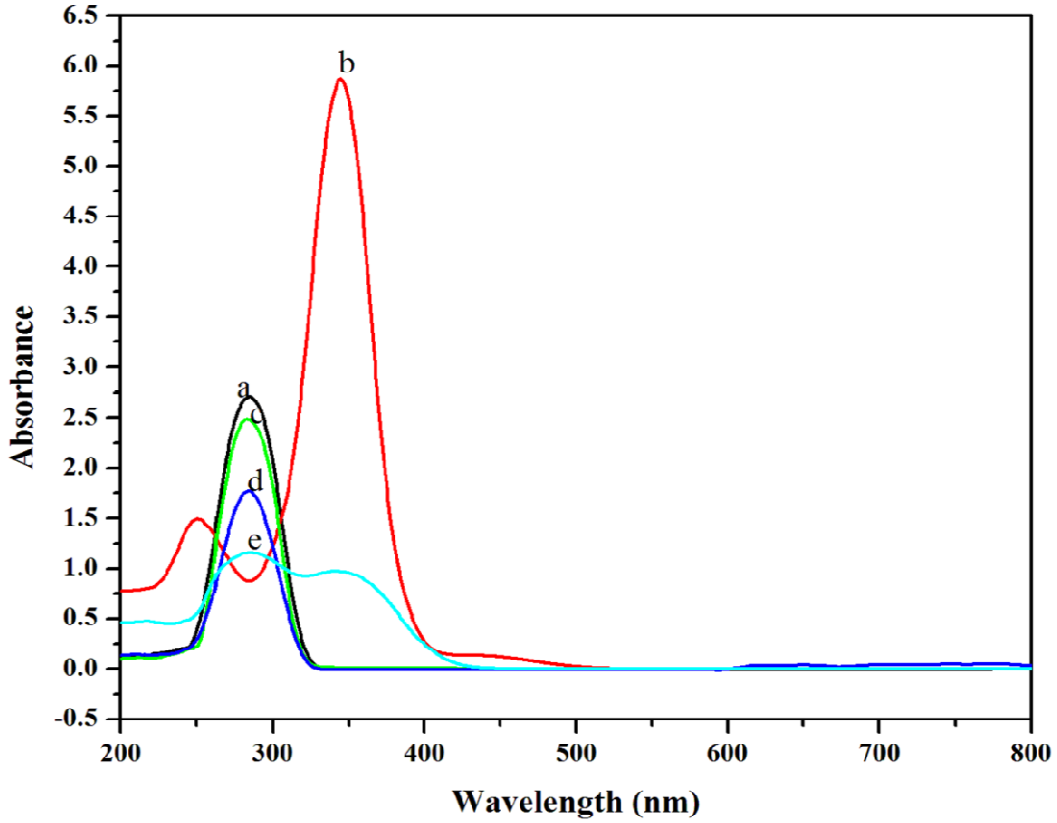


Figure-2: UV spectra of a) BAB, b) PAB, c) PDAB, d) BDAB, e) GAB.

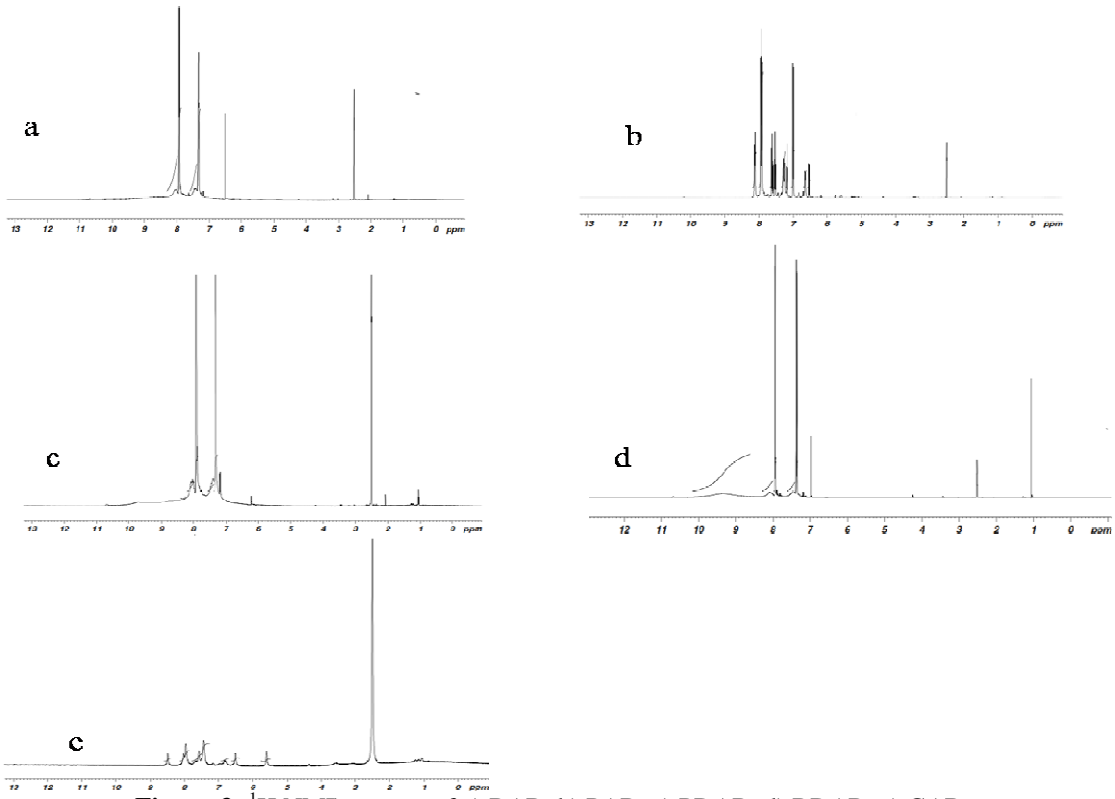


Figure-3: ^{1}H NMR spectra of a) BAB, b) PAB, c) PDAB, d) BDAB, e) GAB.

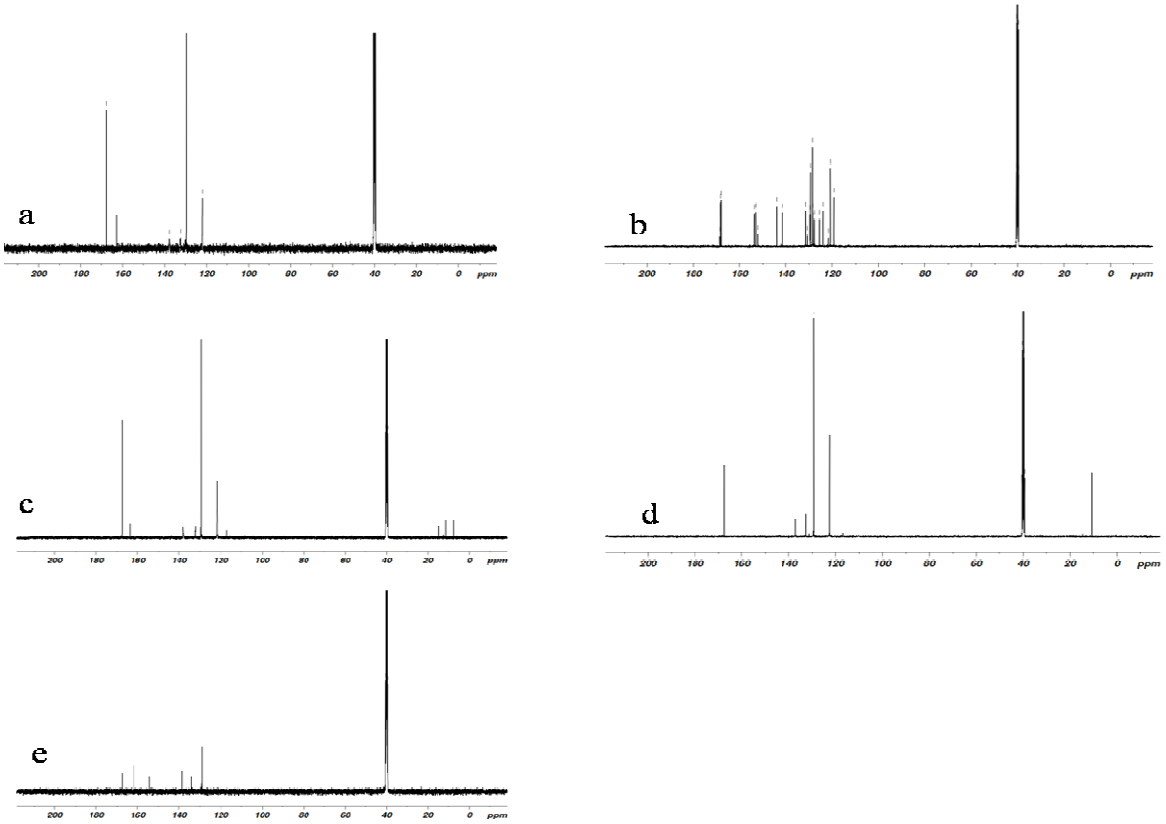


Figure-4: ^{13}C NMR spectra of a) BAB, b) PAB, c) PDAB, d) BDAB, e) GAB.

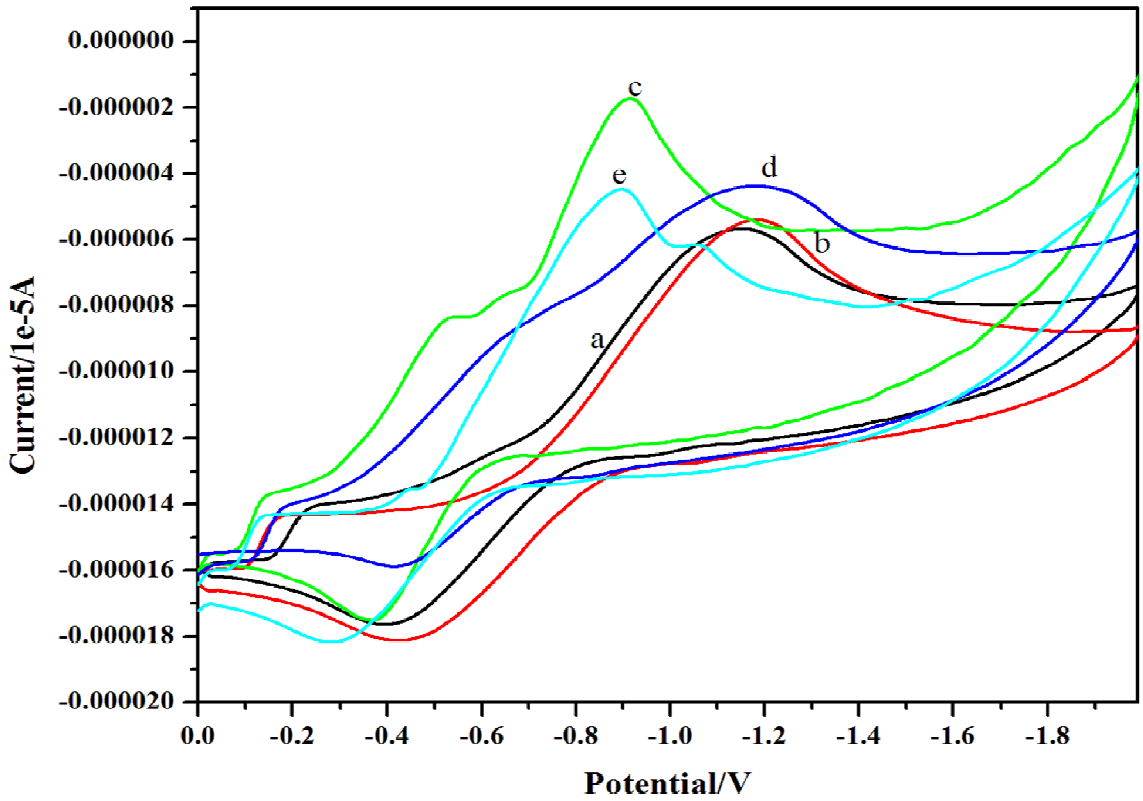


Figure-5: Cyclic voltammetry of a) BAB, b) PAB, c) PDAB, d) BDAB, e) GAB.

4,4'-(1,2-diphenylethane-1,2-diylidene)bis(azan-1-yl-1-ylidene)dibenzamide (BAB): Molecular formula: $C_{28}H_{22}N_4O_2$, M.W: 446.50, Color: White, Yield: 80 %, m.p: 230°C, Anal. Calc. for $C_{28}H_{22}N_4O_2$ (%): C, 75.53; H, 4.93; N, 12.55; O, 7.17. Found C, 75.32; H, 4.91; N, 12.54; O, 7.15. IR (KBr,), υ: 3401, 3200, 1667, 1584, 1511 cm^{-1}. UV (DMSO): $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ - 284 nm . ^{1}H NMR (δ): 6.54 (s, NH_2), 7 - 7.9 (m, Ar-H).^{13}C NMR (δ):163 (s, -C=N), 167 (s, -C=O), 121 -137 (m, Ar-C). Cyclic Voltammetry: E_{pc} -1.148 V. E_{pa} -0.393 V, $E_{1/2}$ -0.770 V, ΔE_p 755 mV.

4,4'-(pentane-2,3- diylidenebis (azan-1-yl-1-ylidene)) dibenzamide (PDAB): Molecular formula: $C_{19}H_{20}N_4O_2$, M.W: 336.39, Color: Pale Brown, Yield: 85 %, m.p: 215°C, Anal Calc. for $C_{19}H_{20}N_4O_2$ (%): C, 67.85; H, 5.95; N, 15.66; O, 9.52. Found C, 67.84; H, 5.91; N, 15.64; O, 9.51. IR (KBr), υ: 3395, 3199, 2818, 1656, 1612, 1534 cm^{-1}. UV (DMSO): $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ - 282 nm. ^{1}H NMR, δ (ppm): 1.0 (s, CH_3), 2.1 (s, CH_2) 6.2 (s, NH_2), 7 - 7.8 (m, Ar-H). ^{13}C NMR (δ): 8.0 (s, CH_3), 11 (s, CH_3CH_2), 14 (s, CH_2), 164 (s, -C=N), 167 (s, -C=O), 116 - 137 (m, Ar-C). Cyclic Voltammetry : E_{pc} -0.897 V, E_{pa} -0.281 V, $E_{1/2}$ -0.589 V, ΔE_p 616 mV.

4,4'- (butane-2, 3-diylidenebis (azan-1-yl-1-ylidene)) dibenzamide (BDAB): Molecular formula: $C_{18}H_{18}N_4O_2$, M.W: 322.36, Color: Pale Brown, Yield: 75 %; m.p: >250°C; Anal Calc. for $C_{18}H_{18}N_4O_2$ (%) : C, 67.08; H, 5.59; N, 17.39; O, 9.93. Found C, 67.07; H, 5.56; N, 17.38; O, 9.91. IR (KBr) υ: 3402, 3201, 2828, 1663, 1585, 1534 cm^{-1}. UV (DMSO): $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ - 284. ^{1}H NMR (δ): 1.1 (s, CH_3), 6.9 (s, NH_2), 7.3 - 7.9 (m, Ar-H). ^{13}C NMR (δ): 10.1 (s, CH_3), 167 (s, -C=N), 167 (s, -C=O), 122 - 137 (m, Ar-C). Cyclic Voltammetry : E_{pc} -0.936 V, E_{pa} -0.438 V, $E_{1/2}$ -0.687 V, ΔE_p 498 mV.

4,4'-(1E,1'E)-(1,2-phenylenebis(methan-1-yl-1-ylidene))bis (azan-1-yl-1-ylidene)dibenzamide (PAB): Molecular formula: $C_{22}H_{18}N_4O_2$, M.W: 370.40, Color: Pale Orange, Yield: 95 %, m.p: 263°C, Anal Calc. for $C_{22}H_{18}N_4O_2$(%): C, 71.35; H, 4.86; N, 15.13; O, 8.64. Found C, 71.34; H, 4.85; N, 15.11; O, 8.62. IR (KBr) υ: 3342, 3201, 1656, 1596, 1516 cm^{-1}. UV (DMSO): $\pi \rightarrow \pi^*$ - 251 nm and $n \rightarrow \pi^*$ - 343 nm. ^{1}H NMR (δ): 6.52 (s, NH_2), 6.6 - 7.9 (m, Ar-H), 8.1 (-CH=N). ^{13}C NMR (δ): 167 (s, -CH=N), 167.3 (s, -C=O), 119 -153 (m, Ar-C). Cyclic Voltammetry : E_{pc} -1.17 V, E_{pa} -0.421 V, $E_{1/2}$ -0.795 V, ΔE_p 749 mV.

4,4'- (ethane-1,2 -diylidenebis (azan-1-yl-1-ylidene)) dibenzamide (GAB): Molecular formula: $C_{16}H_{14}N_4O_2$, M.W: 294.31, Color: Pale Yellow, Yield: 90 %, m.p: 250°C, Anal Calc. for $C_{16}H_{14}N_4O_2$ (%): C, 71.35; H, 4.86; N, 15.13; O, 8.64. Found C, 71.34; H, 4.85; N, 15.11; O, 8.62. IR (KBr) υ: 3395, 3199, 2818, 1656, 1612, 1534 cm^{-1}. UV (DMSO): $\pi \rightarrow \pi^*$ - 284 nm and $n \rightarrow \pi^*$ - 343 nm. ^{1}H NMR (δ): 5.6 (s, NH_2), 8.1 (s, -CH=N) 6.5 - 8 (m, Ar-H); ^{13}C NMR (δ): 163(s, -CH=N), 169 (s, -C=O), 129 - 156 (m, Ar-C); Cyclic Voltammetry: E_{pc} -1.182 V, E_{pa} -0.410 V, $E_{1/2}$ -0.796 V, ΔE_p = 772 mV.

Antibacterial activity: The antibacterial activity of Schiff base compounds were assessed against Gram positive bacteria (*Staphylococcus aureus*), Gram negative bacteria (*Escherichia coli*) and the results are summarized in Figure-6 and 7.

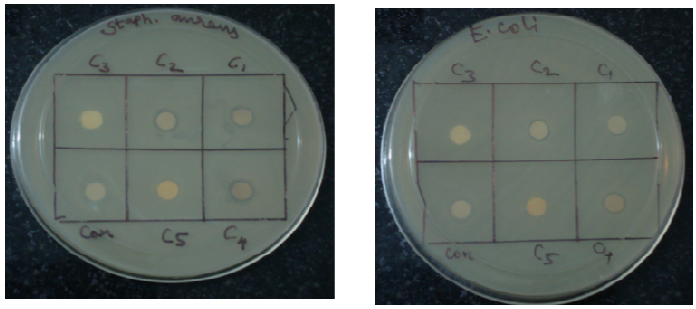


Figure-6: Antibacterial activity plate for Schiff base compounds.

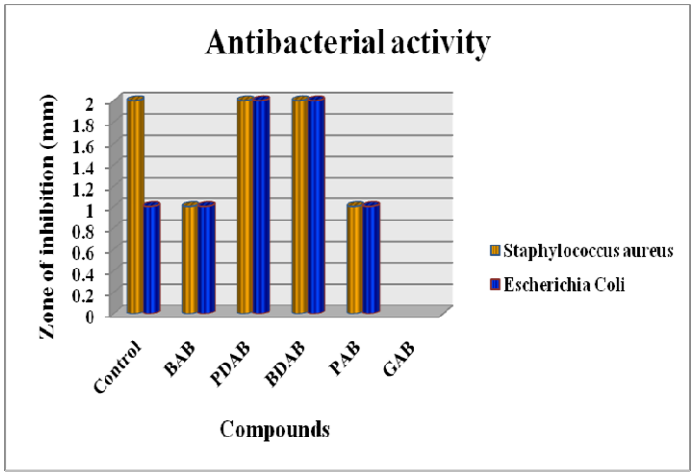


Figure-7: Antibacterial activity of Schiff base compounds.

Among the compounds screened all the Schiff base exhibit lower inhibition activity against *Staphylococcus aureus* and *Escherichia coli*. In *Staphylococcus aureus*, PDAB and BDAB compounds have some activity and other compounds do not show any activity. Similarly in *Escherichia coli*, PDAB and BDAB compounds showed lower activity and the other compounds do have nil activity. GAB doesn't show any activity in both strains.

Conclusion

The novel five Schiff base compounds were synthesized by condensation of various 1,2-dicarbonyl compounds like benzil, 2,3-pentanedione, 2,4-butanedione, *o*-phthaldehyde, glyoxal with 4-aminobenzamide. The formation of the compounds was ascribed by elemental analyses, IR, electronic, ^{1}H and ^{13}C NMR spectroscopy and cyclic voltammetric studies. The electrochemical study reveals that, all the Schiff base compounds have remarkable redox properties. The compounds showed lower biological activity against two (*Staphylococcus aureus* and *Escherichia coli*) pathogenic bacteria.

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