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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIBACTERIAL STUDIES OF SCHIFF BASES DERIVED FROM SULPHA DRUGS

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ABSTRACT:
Schiff base ligands synthesized by the condensation of dapsone with salicylaldehyde, o-vanillin, 2,4-dihydroxyacetophenone and 2,4-dihydroxybenzophenone were characterized and investigated by physical and spectral techniques, namely, elemental analysis, melting point, ^{1}H NMR, IR, UV-Vis spectra, and mass spectrometry measurements. The Schiff bases were screened for antibacterial activity in vitro against Gram positive and Gram negative bacteria viz. *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* using standard agar cup plate or well diffusion method. The ligand L^1H and L^2H were found to be highly active against all bacterial strains whereas the ligand L^3H_2 and L^4H_2were highly active against *Escherichia coli*, *Staphylococcus aureus*and*Klebsiella pneumoniae* and moderately active against *Pseudomonas aeruginosa.*

KEYWORDS: Sulpha drug, Dapsone,Antibacterial activity, Salicylaldehyde, o-vanillin

INTRODUCTION:

In the 1930s, Sulpha drugs were developed as the first medicines effective against bacterial diseases. They appeared as the first "sensation medications" at a time when death from bacterial infections such as pneumonia and blood poisoning were common[i]. A group of synthetic organic compounds called sulfonamides are capable of constraining bacterial growth and activity[ii]. Sulfonamides are compounds that contain sulfur in a -SO_2NH_2 moiety directly attached to a benzene ring[iii]. Schiff base compounds which contain the azomethine (imine) group (–RC=N–) are usually prepared by the condensation of a primary amine with an active carbonyl compound[iv]. The sulfonamide derivatives have been widely used in clinical medicine as pharmacological agents with a wide variety of biological actions, Schiff bases are also known to be anticancer and antiviral agents[v]. Sulfonamides are well renowned for their antibacterial[vi-viii], antitumor[ix], diuretic[x], and antithyroid[xi] activities.

The presence of azomethine and sulfonamide functional group is responsible for antimicrobial activity, which can be transformed depending upon the type of substituent present on the aromatic rings. The condensation of sulfa drugs with aldehydes or ketones gives biologically

active Schiff bases. Keeping in view, the pronounced biological activity of the Schiff bases derived from sulfa drugs, it was thought worthwhile to synthesize, characterize and to study the antimicrobial activity of Schiff bases derived from salicylaldehyde, o-vanillin, 2,4-dihydroxyacetophenone and 2,4 dihydroxybenzophenonewithdapsone and sulphapyridine.

EXPERIMENTAL:

MATERIALS AND METHODS

All the solvents used were of analytical reagent grade purchased from SD Fine and Merck. Pure sample of dapsone was obtained from Shah Scientific Pvt. Ltd. Mumbai. Solvents were purified and dried before use by literature method[xii]. The ligand used in the present work is not commercially available; hence, it was synthesized in the laboratory.

Microanalyses of carbon, hydrogen and nitrogen of the ligands were carried out on a Perkin Elmer CHN 2400 elemental analyzer. ^{1}H-NMR spectra of the ligands were recorded in DMSO-d_6 solution on EM-360, 60 MHz NMR Spectrometer. The electronic spectra of the ligands were recorded on a Shimadzu UV/Vis spectrophotometer in the region 200-1000 nm. The Fourier-transform infrared (FTIR) spectra of ligands were recorded as KBr pellets using Shimadzu spectrometer (IRAffinity-1S). Mass spectra of synthesized compounds were carried out on Thermo scientific TSQ 8000 Gas Chromatograph- Mass Spectrometer.

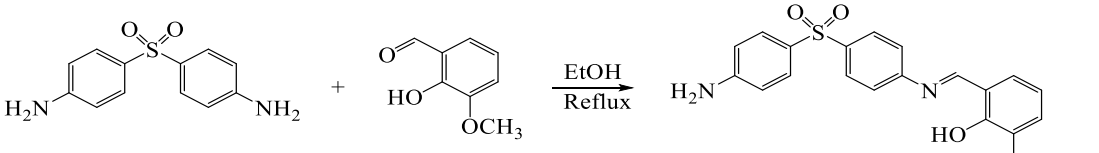
GENERAL PROCEDURE

FOR THE PREPARATION OF 2(((4-((4-AMINOPHENYL) SULPHONYL) PHENYL) IMINO) METHYL)) -6-METHOXY PHENOL (SCHEME-1)

Equimolar solutions of o- vanillin (1.58 g, 10 mmol) and dapsone (2.48g, 10 mmol) were mixed separately in ethanol (50 ml) and refluxed for 1 h. The solution was concentrated and cooled. Orange coloured precipitate was obtained which was filtered off and recrystallized from ethanol. The purity of the compounds were checked by thin layer chromatography (TLC).

2(((4-((4-aminophenyl) sulphonyl) phenyl) imino) methyl)) -6-methoxy phenol (L^{1}H):

M. P. 248^{0}C, IR 3232(OH Hydrogen bonded) cm^{-1}, 3454, 3361(NH_2) cm^{-1}, 1598(C=N) cm^{-1}, 1320 (SO_2 asym) cm^{-1}, 1130(SO_2 sym) cm^{-1},^{1}H NMR(DMSO-d_6, δ ppm, 60 MHz): 12.65 ppm (1H, S, -OH), 8.93 ppm (1H, S, azomethine, -HC=N), 5.90- 7.89 ppm (11H, M, ArH), 3.84 ppm (3H, S, -OCH_3); Anal. Data for $C_{20}H_{18}N_2O_4S$(382.10): Calcd C 62.81, H 4.74, N 7.33, S 8.38; Found C 62.66, H 4.79, N 7.26, S 8.32.



4,4'-sulfonyldianiline + 2-hydroxy-3-methoxy benzaldehyde → (*E*)-2-(((4-((4-aminophenyl)sulfonyl)phenyl)imino) methyl)-6-methoxyphenol

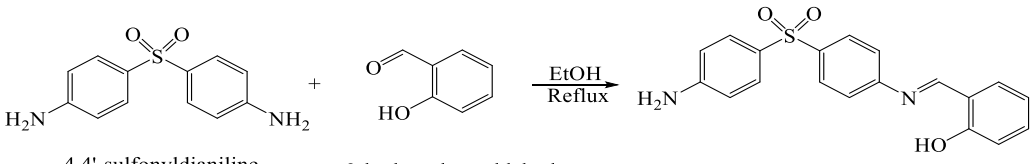
(Scheme-1)

FOR THE PREPARATION OF 2(((4-((4-AMINOPHENYL) IMINO) METHYL)) PHENOL(SCHEME-2)

Equimolar (0.01m) solutions of Salicylaldehyde (2ml) and dapsone (2.48g) were separately dissolved in ethanol and refluxed for two hours. The volume of reaction mixture was reduced to one third and cooled at 0^{o}C. The solid residue was filtered off and recrystallized by ethanol. The purity of the compound was checked by thin layer chromatography (TLC).

2(((4-((4-aminophenyl) imino) methyl)) phenol (L^{2}H):M. P. 240^{o}C, IR 3228(OH Hydrogen bonded) cm^{-1}, 3460, 3367(NH_2) cm^{-1}, 1614(C=N) cm^{-1}, 1300 (SO_2 asym) cm^{-1}, 1145 (SO_2 sym) cm^{-1},^{1}H NMR (DMSO-d_6, δ ppm, 60 MHz), 12.54 ppm (1H, S, -OH), 8.89 ppm (1H, S, azomethine, -HC=N), 5.87- 7.88 ppm (12H, M, ArH), 3.36 ppm (2H, S, -NH_2);Anal. Data for

$C_{19}H_{16}N_2O_3S$ (352.11): Calcd C 64.82, H 4.58, N 7.95, S 9.10; Found C 64.82, H 4.65, N 7.89, S 9.02.



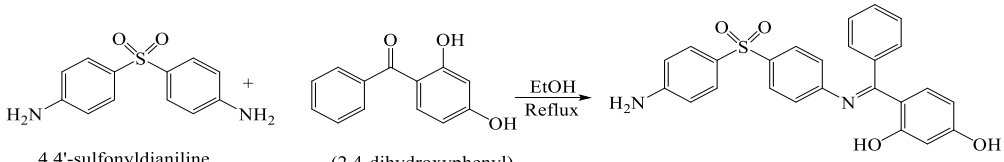
4,4'-sulfonyldianiline | 2-hydroxybenzaldehyde | (*E*)-2-(((4-((4-aminophenyl) sulfonyl)phenyl)imino)methyl)phenol

(Scheme-2)

FOR THE PREPARATION OF 4(((4-((4-AMINOPHENYL) PHENYL) IMINO)(PHENYL)(METHYL)) BENZENE-1,3 DIOL (SCHEME-3)

Equimolar (0.01m) solutions of (2,4-dihydroxyphenyl)(phenyl)methanone(2.14g) and dapsone (2.48g) were separately dissolved in ethanol and refluxed for one and half hour. The volume of reaction mixture was reduced to one third and cooled at 0^0C. The solid residue was filtered off and recrystallized by ethanol. The purity of the compound was checked by thin layer chromatography (TLC).

4(((4-((4-aminophenyl) phenyl) imino)(phenyl)(methyl)) benzene-1,3 diol (L^3H_2): M. P. 118^0C, IR 3340(OH Hydrogen bonded) cm^{-1}, 3456, 3394(NH_2) cm^{-1}, 1593(C=N) cm^{-1}, 1296 (SO_2 asym) cm^{-1}, 1107 (SO_2 sym) cm^{-1},^{1}H NMR (DMSO-d_6, δ ppm, 60 MHz), 12.44 ppm (1H, S, -OH), 6.40- 7.60 ppm (16H, M, ArH), 3.45 ppm (3H, S, -OCH_3), 2.49 ppm (2H, S, -NH_2));Anal. Data for $C_{25}H_{20}N_2O_4S$ (444.11): Calcd C 67.55, H 4.54, N 6.30, S 7.21; Found C 67.70, H 4.70, N 6.49, S 7.27.



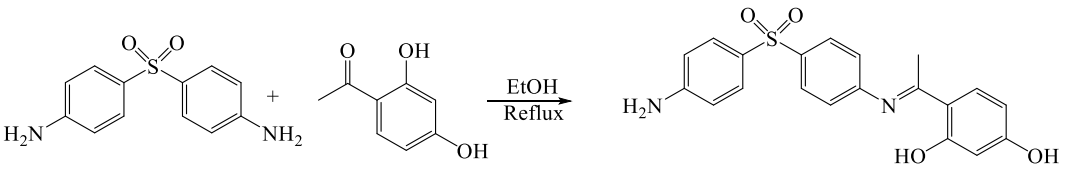
4,4'-sulfonyldianiline | (2,4-dihydroxyphenyl) (phenyl)methanone | (*E*)-4-(((4-((4-aminophenyl)sulfonyl) phenyl)imino)(phenyl)methyl)benzene-1,3-diol

(Scheme-3)

FOR THE PREPARATION OF 4-(1-((4-((4-AMINOPHENYL) SULPHONYL) PHENYL) IMINO) ETHYL) BENZENE-1,3 DIOL (SCHEME-4)

Equimolar (0.01m) solutions of 1-(2,4-dihydroxyphenyl)ethan-1-one(1.52 g) and dapsone (2.48g) were separately dissolved in ethanol and refluxed for one hour. The volume of reaction mixture was reduced to one third and cooled at 0^0C. The solid residue was filtered off and recrystallized by ethanol. The purity of the compound was checked by thin layer chromatography (TLC).

4-(1-((4-((4-aminophenyl) sulphonyl) phenyl) imino) ethyl) benzene-1,3 diol (L^4H_2): M. P. 86^0C, IR 3395(OH Hydrogen bonded) cm^{-1}, 3333, 3305(NH_2) cm^{-1}, 1626(C=N) cm^{-1}, 1372 (SO_2 asym) cm^{-1}, 1139 (SO_2 sym) cm^{-1},^{1}H NMR (DMSO-d_6, δ ppm, 60 MHz), 12.68 ppm (1H, S, -OH), 5.92- 7.94 ppm (11H, M, ArH), 3.39 ppm (2H, S, -NH_2), 2.54 ppm (3H, S, -CH_3));Anal. Data for $C_{20}H_{18}N_2O_4S$ (382.43): Calcd C 62.81, H 4.74, N 7.33, S 8.38; Found C 62.83, H 4.68, N 7.41, S 8.42.



4,4'-sulfonyldianiline

1-(2,4-dihydroxyphenyl)ethan-1-one

(*E*)-4-(1-((4-((4-aminophenyl)sulfonyl)phenyl)imino)ethyl)benzene-1,3-diol

(Scheme-4)

RESULTS AND DISCUSSION

The newly synthesized ligands are characterized by elemental analysis, IR, ^{1}H NMR, mass and repeated M. P. determination studies. The C, H and N analyses of the ligands satisfactorily coincide with their proposed molecular formula.In order to find out the binding modes (donor sites) towards the metal ion, the Infrared Spectra of the ligands were recorded. The absorption band of donor atom either disappeared or showed increase/ decrease in absorption frequencies due to formation of the complex.

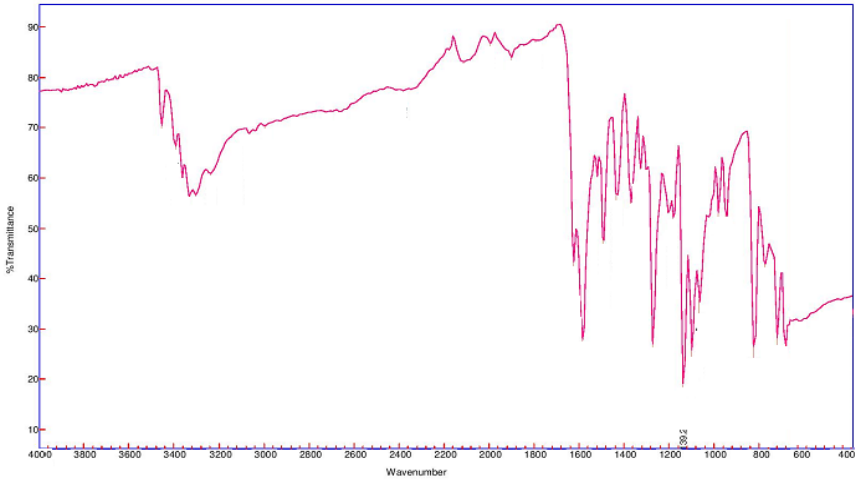


Figure 1: IR spectrum of the ligand L^4H_2

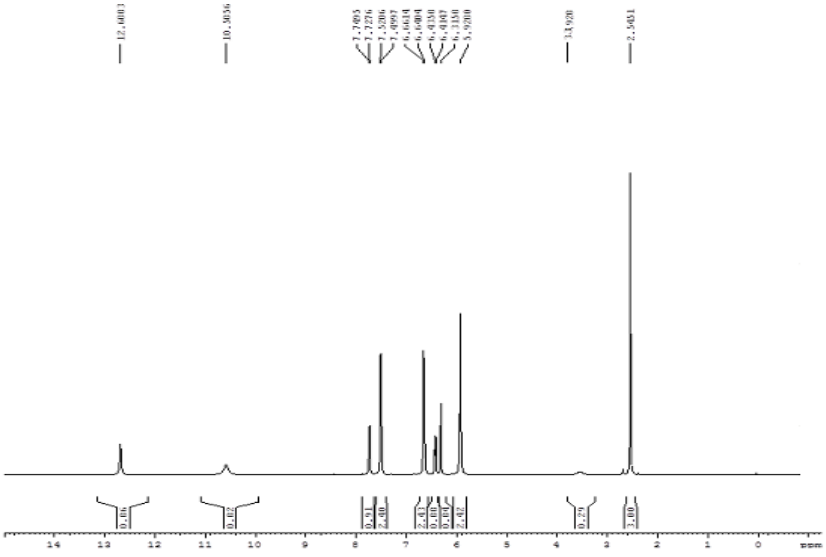


Figure2:^{1}H NMR spectrum of ligand L^4H_2

Mass spectra of the ligands

The FAB mass spectrum of ligand L^1H shows molecular ion peak $[M]^+$ at m/z 382.10; the other important peaks appearing at m/z 248, 227, 221, 157, 151 and 93 correspond to $[C_{12}H_{12}N_2O_2S]^+$, $[C_{14}H_{13}NO_2]^+$, $[C_{14}H_{13}NO]^+$, $[C_6H_7NO_2S]^+$, $[C_8H_9NO_2]^+$ and $[C_6H_7N]^+$ fragment ion. For the ligand L^2H, FAB mass spectrum shows molecular ion peak at m/z 352.09 while other important peaks at m/z 248, 197, 181, 157, 121 and 93 correspond to fragment ion $[C_{12}H_{12}N_2O_2S]^+$, $[C_{13}H_{13}NO]^+$, $[C_{13}H_{13}N]^+$, $[C_6H_7NO_2S]^+$, $[C_7H_7NO]^+$ and $[C_6H_7N]^+$ respectively. The FAB mass spectrum of ligand L^3H_2 shows molecular ion peak at m/z 444 while other daughter peaks at m/z 289, 273, 248, 200, 157 and 93 correspond to fragment ion $[C_{19}H_{15}NO_2]^+$, $[C_{19}H_{15}NO]^+$, $[C_{12}H_{12}N_2O_2S]^+$, $[C_{13}H_{12}O_2]^+$, $[C_6H_7NO_2S]^+$ and $[C_6H_7N]^+$ respectively. The FAB mass spectrum of the ligand L^4H_2 shows molecular ion peak at m/z 382 and other intense peaks at m/z 248, 227, 211, 157, 138, 122 and 93 correspond to ion $[C_{12}H_{12}N_2O_2S]^+$, $[C_{14}H_{13}NO_2]^+$, $[C_{14}H_{13}NO]^+$, $[C_6H_7NO_2S]^+$, $[C_8H_{10}O_2]^+$,$[C_8H_{10}O]^+$ and $[C_6H_7N]^+$ respectively.

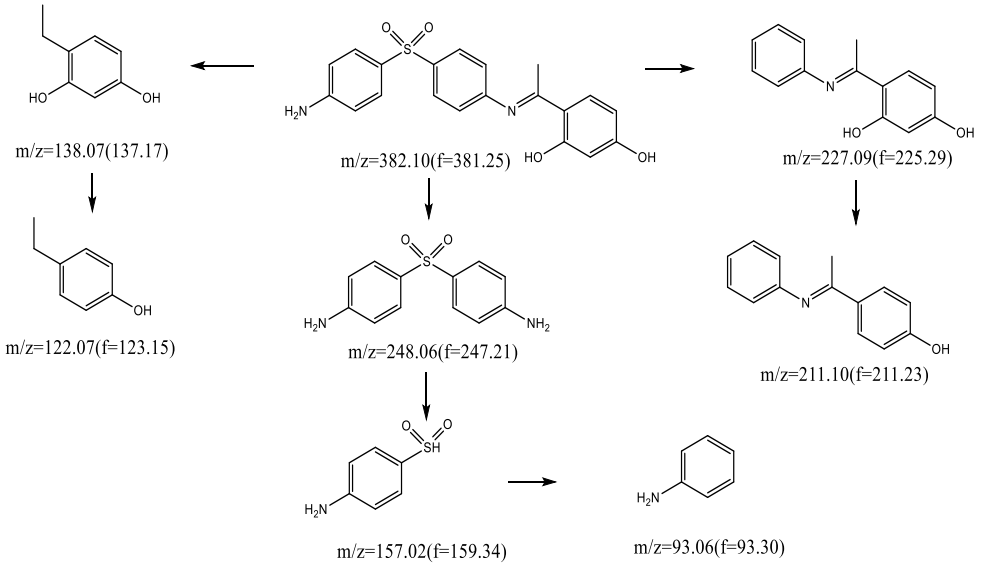


Figure3: Mass fragmentation pattern of ligand L^4H_2

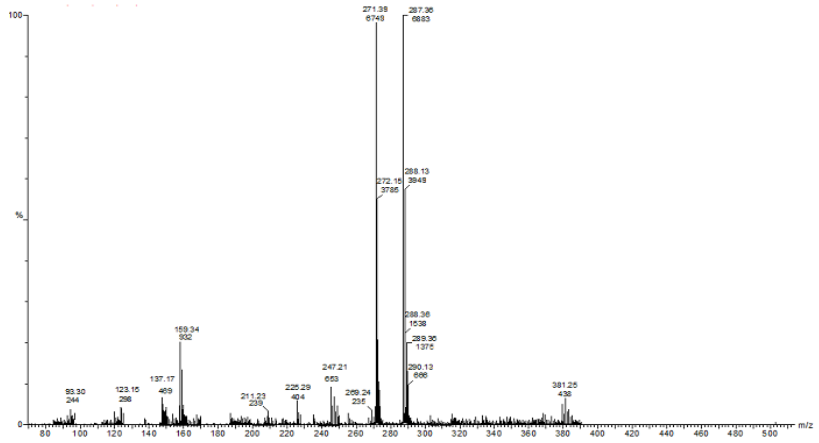


Figure 4: Mass spectrum of the ligand L^4H_2

ANTIMICROBIAL ACTIVITY:

In the present study, Schiff base ligands were screened for antibacterial activity in vitro against Gram positive and Gram negative bacteria viz. *Escherichia coli*, *Staphylococcus aureus*,

Pseudomonas aeruginosa and *Klebsiella pneumoniae*using standard agar cup plate or well diffusion method.

The ligand L^1H and L^2Hwere found to be highly active against all bacterial strains whereas the ligand L^3H_2 and L^4H_2were highly active against *Escherichia coli*, *Staphylococcus* and *Klebsiella pneumoniae* and moderately active against *Pseudomonas aeruginosa*.

Table: Antibacterial activity of ligands

S.N.	**Ligands**	***E. coli* (mm)**	***S. aureus* (mm)**	***P. aeroginosa* (mm)**	***K. pneumoniae* (mm)**
1.	L^1H	S_{23}	S_{25}	S_{21}	S_{32}
2.	L^2H	S_{22}	S_{23}	S_{20}	S_{25}
3.	L^3H_2	S_{21}	S_{22}	S_{18}	S_{29}
4.	L^4H_2	S_{20}	S_{18}	S_{22}	S_{26}

S- Sensitive (Bactericidal) R- Resistant (Bacteriostatic)

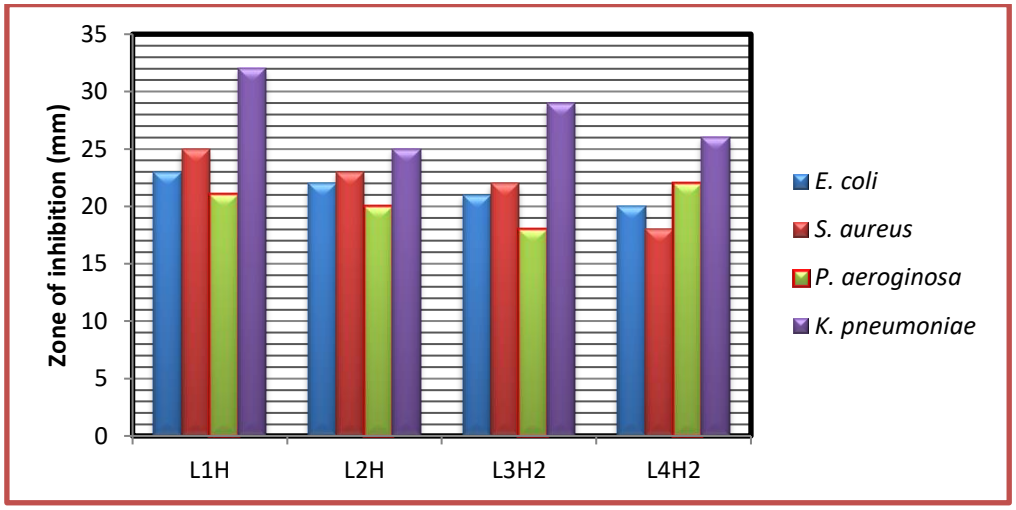


Figure 5: Antimicrobial activity of ligands

CONCLUSION:

In the present study, Schiff base ligands were synthesized and characterized by elemental analysis, melting point, ^{1}H NMR, IR, UV-Vis spectra, and mass spectrometry measurements. IR spectra of ligands show two prominent bands due to symmetric and asymmetric SO_2 stretching vibration. The mass spectra of ligands show molecular ion peaks in good agreement with the empirical formula suggested by elemental analysis. The antibacterial activity of all the compounds was tested against bacterial pathogens, *E. coli, S. aureus, P. aeruginosa* and *K. pneumoniae*. It has been found that the synthesized Schiff bases show significant antimicrobial activity.

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