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Copper (II) and zinc (ii) metal-based salicyl-, furanyl-, thienyl- and pyrrolyl-derived ONNO, NNNO, ONNS & NNNS donor asymmetrically mixed schiff-bases with antibacterial and antifungal potentials

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Abstract

A new series of asymmetric salicyl-, furanyl-, thienyl- and pyrrolyl-derived ONNO, NNNO, ONNS & NNNS donor antibacterial and antifungal Schiff-bases and their copper(II) and zinc(II) metal complexes have been synthesized and characterized. IR spectra indicated the ligands to act as quartdentate towards divalent metal ions via two azomethine-N, deprotonated-O of salicyl, furanyl-O, thienyl-S and/or pyrrolyl-N. The magnetic moments and electronic spectral data suggest octahedral geometry for Cu(II) and Zn(II) complexes. NMR spectral data of the ligands and their diamagnetic zinc(II) complexes well-define their proposed structures/geometries. Elemental analyses data of the ligands and metal complexes agree with their proposed structures/geometries. The synthesized ligands, along with their metal complexes were screened for their antibacterial activity against *B. cereus, C. diphtheriae, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. typhi, S. dysenteriae and S. aureus* strains and for *in-vitro* antifungal activity against *T. schoenleinii, C. glabrata, P. boydii, C. albicans, A. niger, M. canis and T. mentagrophytes*. The results of these studies show the metal complexes to be more antibacterial/antifungal against one or more species as compared to the uncomplexed ligands. The brine shrimp bioassay was also carried out to study their *in-vitro* cytotoxic properties. Eight compounds, L_4, (**1**), (**7**), (**8**), (**11**), (**17**), (**19**) and (**23**) displayed potent cytotoxic activity with $LD_{50} = 1.445 \times 10^{-3}$, 1.021×10^{-3}, 7.478×10^{-4}, 8.566×10^{-4}, 1.028×10^{-3}, 9.943×10^{-4}, 8.730×10^{-4} and 1.124×10^{-3} M respectively, against *Artemia salina*.

Keywords: *Metal-Based, asymmetrically, schiff's-bases, antibacterial, antifungal*

Introduction

Schiff bases containing the group (–RC═N–) constitute [1–3] an important class of compounds which share a mechanism in enhancing different biological and pharmacological activities via coordination/chelation with metal ions [4–9]. They are capable of coordination with the metal ions through the azomethine linkage and other participating heteroatoms present in the molecule thus giving metal chelates which may serve as models [10] for metalloproteins. Our ongoing research has established [11–16] the fact that non-biologically active compounds become biologically active and less biologically active become more active upon coordination/chelation with metal ions. In order to expand this emerging area of metal-based drug chemistry we, now, wish to report a series of novel antibacterial and antifungal asymmetrically mixed ONNO, NNNO, ONNS & NNNS donor tetradentate Schiff bases (**L_1**)–(**L_{12}**) (Figure 1) and their copper(II) and zinc(II) metal complexes (**1**)–(**24**) (Figure 2). The synthesized Schiff-bases and their metal complexes were characterized by their IR, NMR, molar conductances, magnetic moments, electronic and elemental analyses data. All the Schiff-base ligands, along with their metal complexes were screened for their antibacterial activity against *Bacillus cereus, Corynebacterium diphtheriae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae and Staphylococcus aureus* bacterial strains and for *in-vitro* antifungal activity against *Trichophyton schoenleinii, Candid glabrata, Pseudallescheria boydii, Candida albicans, Aspergillus niger, Microsporum canis and Trichophyton mentagrophytes*. The Schiff-bases

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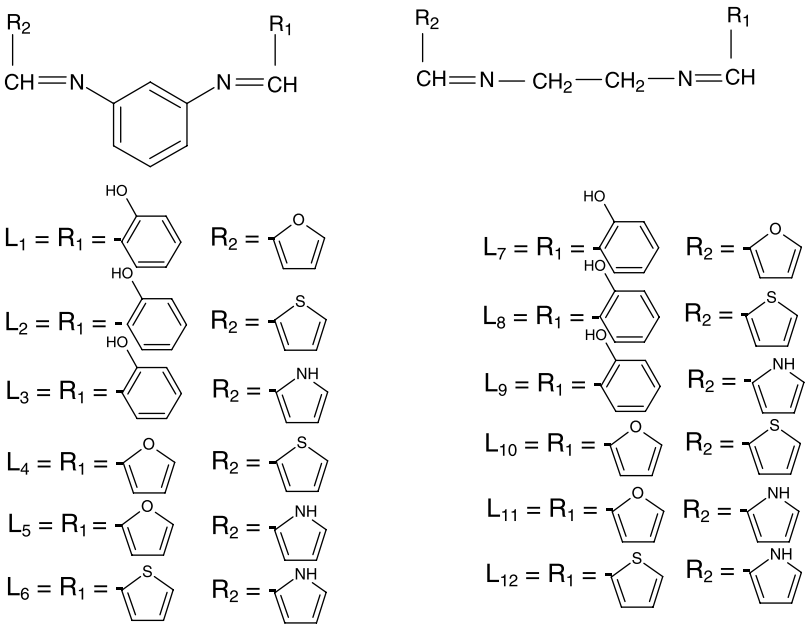
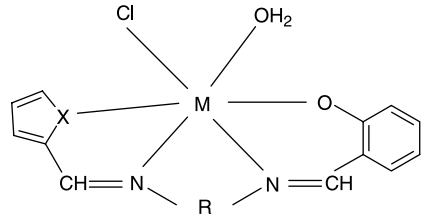
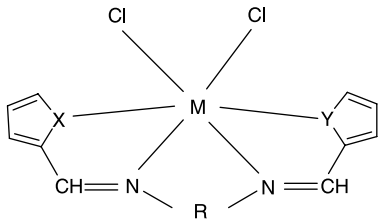


Figure 1. Proposed Structure of Schiff base Ligands.



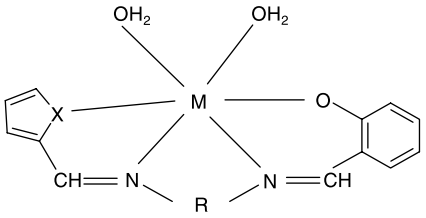
[A]

L_1 =R = Ph ; R_2 = X = O
L_2 = R = Ph ; R_2 = X = S
L_7 = R = -$(CH_2)_2$- ; R_2 = X = O
L_8 = R = -$(CH_2)_2$- ; R_2 = X = S



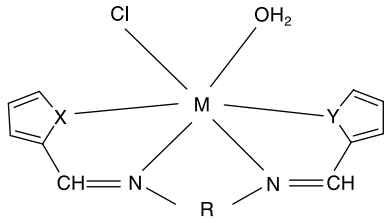
[B]

L_4 = R = Ph ; R_1 = X = O; R_2 = Y = S
L_{10} = R = -$(CH_2)_2$- ; R_1 = X = O; R_2 = Y = S



[C]

L_3 = R = Ph ; R_2 = X = N
L_9 = R = -$(CH_2)_2$- ; R_2 = X = N



[D]

L_5 = R = Ph ; R_1 = X = O; R_2 = Y = N
L_6 = R = Ph ; R_1 = X = S; R_2 = Y = N
L_{11} = R = -$(CH_2)_2$- ; R_1 = X = O; R_2 = Y = N
L_{12} = R = -$(CH_2)_2$- ; R_1 = X = S; R_2 = Y = N

Figure 2. Proposed Structure of the Metal (II) Complexes.

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showed varied antibacterial and antifungal activity against one or more strains respectively and their activity was enhanced on coordination/chelation. The reported compounds are not only good potentially candidates for use as antibacterials and antifungals but also provide a promising addition of a novel series of such metal-based drugs.

Experimental

Material and methods

Solvents used were of analytical grade. IR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer. NMR spectra were recorded on a Perkin-Elmer 283B spectrometer. UV-Visible spectra were obtained in DMF on a Hitachi U-2000 double-beam spectrophotometer. C, H and N analyses, Conductance and Magnetic measurements were carried out on solid compounds using the respective instruments. Melting points were recorded on a Gallenkamp apparatus and are not corrected. Metals were used as their hydrated chloride salts. The copper (II) and zinc (II) complexes were analyzed for their metal contents by EDTA titration [17]. Antibacterial and antifungal screening was done at HEJ Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Pakistan.

Preparation of ONNO derived asymmetric schiff-base (L_1)

To a magnetically stirred solution of 1,2-phenylene-diamine (2 mmol, 0.216 g) in methanol (30 mL) was added a solution of salicylaldehyde (2 mmol, 0.212 mL) in methanol (20 mL). The mixture was refluxed for 2 h. After completion of the reaction, monitored through TLC, it was cooled to room temperature to afford a yellow solid product which was filtered, washed with cold methanol, then with ether and dried. The product (2 mmol, 0.424 g) was dissolved in dioxane (25 mL) and added to a magnetically stirred solution of furfuraldehyde (0.1 mmol, 0.164 mL) in dioxane (15 mL). The mixture was refluxed for 2 h. After completion of the reaction, (TLC) it was cooled to room temperature and reduced to half its volume. It was then refrigerated to give a yellow crystalline product which was filtered and dried. The same method was applied for the preparation of all other ligands by condensation of 1,2-phenylenediamine and ethylenediamine respectively, with salicylaldehyde, furfuraldehyde, thiophene-2-carboxaldehyde and pyrrol-2-carboxaldehyde using the same conditions with their respective molar ratios. The order of addition of the respective aldehydes did not have any effect on the condensation process.

2-[(2-{[(2-furylmethylene]amino}phenyl)imino]methyl}-phenol (L_1). Yield 58%; m.p. 131°C; IR (KBr, cm^{-1}): 3264 (OH), 1615 (azomethine, HC═N), 1245 (C–O); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.1–7.3 (m, 4H, phenyl), 7.4–7.6 (m, 4H, phenol), 7.8–8.2 (m, 3H, furanyl), 8.74 (s, 1H, azomethine), 10.27 (s, 1H, OH); Anal. Calcd. for $C_{18}H_{14}N_2O_2$ (290.32): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.72; H, 4.41; N, 9.86%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.2–7.5 (m, 4H, phenyl), 7.6–7.8 (m, 4H, phenol), 7.9–8.4 (m, 3H, furanyl), 8.87 (s, 1H, azomethine).

2-[(2-{[(2-Thienylmethylene]amino}phenyl)imino]-methyl}phenol (L_2). Yield 54%; m.p. 140°C; IR (KBr, cm^{-1}): 3295 (OH), 1615 (azomethine, C═N), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.1–7.3 (m, 4H, phenyl), 7.4–7.6 (m, 4H, phenol), 7.8–8.3 (m, 3H, thienyl), 8.72 (s, 1H, azomethine), 10.27 (s, 1H, OH); Anal. Calcd. for $C_{18}H_{14}N_2OS$ (306.39): C, 70.56; H, 4.61; N, 9.14. Found: C, 70.86; H, 4.79; N, 9.34%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.2–7.4 (m, 4H, phenyl), 7.6–7.8 (m, 4H, phenol), 8.0–8.4 (m, 3H, thienyl), 8.98 (s, 1H, azomethine).

2-[(2-{[(1H-pyrrol-2-ylmethylene]amino}phenyl)-imino]methyl}phenol (L_3). Yield 56%; m.p. 183°C; IR (KBr, cm^{-1}): 3312 (NH), 3285 (OH), 1615 (azomethine, C═N); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.1–7.3 (m, 4H, phenyl), 7.4–7.6 (m, 4H, phenol), 7.8–8.3 (m, 3H, pyrrolyl), 8.72 (s, 1H, azomethine), 10.27 (s, 1H, OH), 12.20 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{15}N_3O$ (289.34): C, 74.72; H, 5.23; N, 14.52. Found: C, 74.62; H, 5.41; N, 14.86%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.3–7.5 (m, 4H, phenyl), 7.5–7.8 (m, 4H, phenol), 8.94 (s, 1H, azomethine), 8.3–8.5 (m, 3H, pyrrolyl).

2-[(2-{[(2-Furylmethylene]amino}phenyl)imino]-methyl}thienyl (L_4). Yield 51%; m.p. 134°C; IR (KBr, cm^{-1}): 1610 (azomethine, C═N), 1245 (C–O), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.1–7.3 (m, 4H, phenyl), 7.9–8.5 (m, 6H, thienyl, furanyl), 8.72 (s, 1H, azomethine); Anal. Calcd. for $C_{16}H_{12}N_2OS$ (280.35): C, 68.55; H, 4.31; N, 9.99. Found: C, 68.82; H, 4.45; N, 10.36%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.3–7.5 (m, 4H, phenyl), 8.2–8.6 (m, 6H, thienyl, furanyl), 8.98 (s, 1H, azomethine).

2-{[2-(2-Furylmethylene]amino}phenyl)imino]-methyl}pyrrol (L_5). Yield 53%; m.p. 142°C; IR (KBr, cm^{-1}): 3310 (NH), 1615 (azomethine, C═N), 1245 (C–O); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.1–7.3 (m, 4H, phenyl), 7.9–8.4 (m, 6H, furanyl, pyrrolyl), 8.72 (s, 1H, azomethine), 12.20 (s, 1H, NH); Anal.

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Calcd. for $C_{16}H_{13}N_3O$ (263.30): C, 72.99; H, 4.98; N, 15.96. Found: C, 73.32; H, 5.21; N, 16.24%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.2–7.4 (m, 4H, phenyl), 8.0–8.5 (m, 6H, furanyl, pyrrolyl), 8.97 (s, 1H, azomethine).

2-{[2-(2-Thienyllmethylene]amino}phenyl)imino]-methyl}pyrrol (L_6). Yield 51%; m.p. 148°C; IR (KBr, cm^{-1}): 3310 (NH), 1615 (azomethine, C=N), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.2–7.4 (m, 4H, phenyl), 7.9–8.4 (m, 6H, thienyl, pyrrolyl), 8.72 (s, 1H, azomethine), 12.20 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{13}N_3S$ (279.36): C, 68.79; H, 4.69; N, 15.04. Found: C, 68.98; H, 4.91; N, 15.23%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.3–7.5 (m, 4H, phenyl), 8.1–8.5 (m, 6H, thienyl, pyrrolyl), 8.98 (s, 1H, azomethine).

2-{[2-(2-Furyllmethylene]amino}ethyl)imino]methyl}-phenol (L_7). Yield 53%; m.p. 140°C; IR (KBr, cm^{-1}): 3310 (OH), 1610 (azomethine, C=N), 1245 (C–O); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.86 (m, 4H, NCH_2), 7.4–7.6 (m, 4H, phenol), 7.8–8.2 (m, 3H, furanyl), 8.74 (s, 1H, azomethine), 10.27 (s, 1H, OH) Anal. Calcd. for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.72; H, 5.41; N, 11.86%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 3.12 (m, 4H, NCH_2), 7.7–7.8 (m, 4H, phenol), 8.0–8.3 (m, 3H, furanyl), 8.98 (s, 1H, azomethine).

2-{[2-(2-Thienyllmethylene]amino}ethyl)imino]methyl}-phenol (L_8). Yield 51%; m.p. 124°C; IR (KBr, cm^{-1}): 3290 (OH), 1610 (azomethine, C=N), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.86 (m, 4H, NCH_2), 7.4–7.6 (m, 4H, phenol), 7.9–8.2 (m, 3H, thienyl), 8.74 (s, 1H, azomethine), 10.27 (s, 1H, OH) Anal. Calcd. for $C_{14}H_{14}N_2OS$ (258.34): C, 65.09; H, 5.46; N, 10.84. Found: C, 65.37; H, 5.22; N, 10.76%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 7.5–7.8 (m, 4H, phenol), 8.1–8.4 (m, 3H, thienyl), 9.14 (s, 1H, azomethine)

2-{[2-(2-Pyrollylmethylene]amino}ethyl)imino]methyl}-phenol (L_9). Yield 50%; m.p. 120°C; IR (KBr, cm^{-1}): 3315 (NH), 3290 (OH), 1610 (azomethine, C=N), 810 (C–N); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.85 (m, 4H, NCH_2), 7.4–7.6 (m, 4H, phenol), 7.8–8.1 (m, 3H, pyrrolyl), 8.74 (s, 1H, azomethine), 10.28 (s, 1H, OH), 12.20 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{15}N_3O$ (241.29): C, 69.69; H, 6.27; N, 17.41. Found: C, 69.56; H, 6.41; N, 17.86%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 3.10 (m, 4H, NCH_2), 8.0–8.34 (m, 4H, phenol), 8.5–8.7 (m, 3H, pyrrolyl), 8.99 (s, 1H, azomethine).

2-[(2-{[(2-Furylmethylene]amino}ethyl)imino]methyl}-thienyl (L_{10}). Yield 51%; m.p. 118°C; IR (KBr, cm^{-1}): 1610 (azomethine, C=N), 1245 (C–O), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.86 (m, 4H, NCH_2), 7.91–8.34 (m, 6H, furanyl, thienyl), 8.74 (s, 1H, azomethine); Anal. Calcd. for $C_{12}H_{12}N_2OS$ (232.31): C, 62.04; H, 5.21; N, 12.06. Found: C, 62.42; H, 5.41; N, 12.16%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 3.13 (m, 4H, NCH_2), 8.2–8.5 (m, 6H, furanyl, thienyl), 9.21 (s, 1H, azomethine).

2-{[2-(2-Furylmethylene]amino}ethyl)imino]methyl}-pyrrol (L_{11}). Yield 50%; m.p. 122°C; IR (KBr, cm^{-1}): 3310 (NH), 1615 (azomethine, C=N), 1245 (C–O); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.86 (m, 4H, NCH_2), 7.9–8.5 (m, 6H, furanyl, pyrrolyl), 8.74 (s, 1H, azomethine), 12.20 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{13}N_3O$ (215.25): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.75; H, 5.87; N, 18.73%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 3.16 (m, 4H, NCH_2), 8.16–8.57 (m, 6H, furanyl, pyrrolyl), 9.12 (s, 1H, azomethine).

2-{[2-(2-Thienyllmethylene]amino}ethyl)imino]methyl}-pyrrol (L_{12}). Yield 51%; m.p. 125°C; IR (KBr, cm^{-1}): 3310 (NH), 1615 (azomethine, C=N), 755 (C–S), 810 (C–N); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.86 (m, 4H, NCH_2), 7.9–8.3 (m, 6H, thienyl, pyrrolyl), 8.74 (s, 1H, azomethine), 12.20 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{13}N_3S$ (231.32): C, 62.31; H, 5.66; N, 18.16. Found: C, 62.54; H, 5.41; N, 18.36%. ^{1}H NMR of Zn(II) Complex (DMSO-d_6, δ, ppm): 3.14 (m, 4H, NCH_2), 8.12–8.36 (m, 6H, thienyl, pyrrolyl), 9.23 (s, 1H, azomethine).

Preparation of copper (II) complexe with L_1

For the preparation of copper (II) metal complexe, a solution of L_1 (10 mmol, 2.9 g) in methanol (50 mL) was added to a magnetically stirred solution of $CuCl_2.2H_2O$ (10 mmol, 1.7 g) in methanol (30 mL) at a required equimolar ratio of M:L (1:1). The mixture was refluxed for 3 h and then cooled to room temperature. On cooling a solid product was formed. The solid thus obtained was filtered, washed with methanol, then with ether and dried in air. Crystallization from hot methanol gave the desired metal complex. The same method was used for the preparation of all other complexes by using their respective hydrated copper (II) and zinc (II) salts as chlorides. The data for the complexes are shown in Table I.

Biological activity

*Antibacterial bioassay (*in-vitro*)*. All the synthesized ligands ($\mathbf{L_1}$)–($\mathbf{L_{12}}$) and their corresponding metal(II)

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Table I. Physical, Spectral and Analytical Data of the Metal (II) Complexes.

No.		M.P (°C)	B.M (μ_{eff})	IR (cm^{-1})	λmax (cm^{-1})	Calc. (Found) % C	H	N
1. $[Cu(L_1)(H_2O)Cl]$ $C_{18}H_{15}CuN_2O_3Cl$	[406.40]	210–212	1.3	1570 (C═N), 1215 (C–O), 425 (M–N), 525 (M–O), 315 (M–C1)	15210, 19645, 30255	53.20 (53.84)	3.69 (3.37)	6.90 (6.55)
2. $[Zn(L_1)(H_2O)Cl]$ $C_{18}H_{15}ZnN_2O_3Cl$	[405.89]	204–206	Dia	1570 (C═N), 1220 (C–O), 425 (M–N), 525 (M–O), 315 (M–Cl)	28555	53.22 (53.33)	3.70 (3.12)	6.90 (6.11)
3. $[Cu(L_2)(H_2O)Cl]$ $C_{18}H_{15}CuN_2O_2SCl$	[422.04]	218–220	1.5	1565 (C═N), 1215 (C–O), 425 (M–N), 525 (M–O), 395 (M–S), 315 (M–Cl)	15320, 19520, 30355	51.18 (51.87)	3.55 (3.48)	6.63 (6.36)
4. $[Zn(L_2)(H_2O)Cl]$ $C_{18}H_{15}ZnN_2O_2SCl$	[421.89]	208–210	Dia	1570 (C═N), 1220 (C–O), 430 (M–N), 530 (M–O), 385 (M–S), 315 (M–Cl)	29145	51.20 (51.61)	3.56 (3.78)	6.64 (6.69)
5. $[Cu(L_3)(H_2O)_2]$ $C_{18}H_{17}CuN_3O_3$	[386.54]	212–214	1.3	1572 (C═N), 1215 (C–O), 430 (M–N), 525 (M–O)	15325, 19530, 30415	55.88 (55.54)	4.40 (4.18)	10.87 (10.56)
6. $[Zn(L_3)(H_2O)_2]$ $C_{18}H_{17}ZnN_3O_3$	[386.39]	208–210	Dia	1565 (C═N), 1220 (C–O), 430(M–N), 515 (M–O)	28735	55.90 (55.78)	4.40 (4.52)	10.87 (10.74)
7. $[Cu(L_4)Cl_2]$ $C_{16}H_{12}CuN_2OSCl_2$	[414.54]	218–220	1.4	1570 (C═N), 425 (M–N), 395 (M–S), 315 (M–Cl), 525 (M–O)	15300, 19565, 30420	46.32 (46.68)	2.89 (2.77)	6.75 (6.37)
8. $[Zn(L_4)Cl_2]$ $C_{16}H_{12}ZnN_2OSCl_2$	[414.39]	210–212	Dia	1570 (C═N), 425 (M–N), 385 (M–S), 315(M–Cl), 525 (M–O)	28830	46.33 (46.94)	2.90 (2.55)	6.76 (6.37)
9. $[Cu(L_5)(H_2O)Cl]$ $C_{16}H_{14}CuN_3O_2Cl$	[379.34]	222–224	1.5	1570 (C═N), 425 (M–N), 315 (M–Cl), 525 (M–O)	15220, 19575, 30290	50.65 (50.57)	3.69 (3.48)	11.08 (11.24)
10. $[Zn(L_5)(H_2O)Cl]$ $C_{16}H_{14}ZnN_3O_2Cl$	[378.89]	214–216	Dia	1570 (C═N), 425 (M–N), 315 (M–Cl), 525 (M–O)	29110	50.67 (50.44)	3.70 (3.57)	11.09 (10.27)
11. $[Cu(L_6)(H_2O)Cl]$ $C_{16}H_{14}CuN_3SOCl$	[395.04]	218–220	1.5	1570 (C═N), 425 (M–N), 315 (M–Cl), 525 (M–O)	15225, 19570, 30295	48.60 (48.35)	3.54 (3.17)	10.63 (10.77)
12. $[Zn(L_6)(H_2O)Cl]$ $C_{16}H_{14}ZnN_3SOCl$	[394.89]	211–213	Dia	1570 (C═N), 425 (M–N), 315 (M–Cl), 525 (M–O)	28955	48.62 (48.87)	3.55 (3.26)	10.64 (10.91)
13. $[Cu(L_7)(H_2O)Cl]$ $C_{14}H_{15}CuN_2O_3Cl$	[358,09]	220–222	1.3	1570 (C═N), 425 (M–N), 525 (M–O), 1215 (C–O), 315 (M–Cl)	15250, 19540, 30325	46.92 (46.84)	4.19 (4.37)	7.82 (7.55)
14. $[Zn(L_7)(H_2O)Cl]$ $C_{14}H_{15}ZnN_2O_3Cl$	[357.89]	224–226	Dia	1570 (C═N), 425 (M–N), 525 (M–O), 1220 (C–O), 315 (M–Cl)	28555	46.94 (46.33)	4.19 (4.12)	7.82 (7.11)
15. $[Cu(L_8)(H_2O)Cl]$ $C_{14}H_{15}CuN_2O_2SCl$	[374.04]	218–220	1.5	1565 (C═N), 1215 (C–O), 425 (M–N), 525(M–O), 395 (M–S), 315 (M–Cl)	15315, 19590 30335	44.91 (44.87)	4.01 (4.48)	7.49 (7.36)
16. $[Zn(L_8)(H_2O)Cl]$ $C_{14}H_{15}ZnN_2O_2SCl$	[373.89]	212–214	Dia	1570 (C═N), 1220 (C–O), 430 (M–N), 525 (M–O), 385 (M–S), 315 (M–Cl)	29145	44.93 (44.61)	4.01 (4.78)	7.49 (7.69)
17. $[Cu(L_9)(H_2O)_2]$ $C_{14}H_{17}CuN_3O_3$	[338.54]	224–226	1.38	1572 (C═N), 1215 (C–O), 430 (M–N), 525 (M–O),	15285, 19605, 30395	49.62 (49.38)	5.02 (4.86)	12.41 (12.32)
18. $[Zn(L_9)(H_2O)_2]$ $C_{14}H_{17}ZnN_3O_3$	[338.39]	217–219	Dia	1565 (C═N), 1220 (C–O), 430 (M–N), 515 (M–O),	28735	49.65 (49.70)	5.02 (5.33)	12.41 (12.78)
19. $[Cu(L_{10})Cl_2]$ $C_{12}H_{12}CuN_2OSCl_2$	[366.54]	220–222	1.42	1570 (C═N), 425 (M–N), 395 (M–S), 315(M–Cl), 525 (M–O)	15295, 19610, 30315	39.29 (39.48)	3.27 (3.57)	7.64 (7.37)
20. $[Zn(L_{10})Cl_2]$ $C_{12}H_{12}ZnN_2OSCl_2$	[366.39]	217–219	Dia	1570 (C═N), 425 (M–N), 385 (M–S), 315(M–Cl), 525 (M–O)	29145	39.30 (39.54)	3.28 (3.55)	7.64 (7.37)
21. $[Cu(L_{11})(H_2O)Cl]$ $C_{12}H_{14}CuN_3O_2Cl$	[331.04]	222–224	1.50	1570 (C═N), 425 (M–N), 315 (M–Cl), 525 (M–O)	15255, 19595, 30420	43.50 (43.71)	4.23 (4.68)	12.69 (12.83)

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Table I – *continued*

No.		M.P (°C)	B.M (μ_{eff})	IR (cm^{-1})	λmax (cm^{-1})	Calc. (Found) % C	H	N
22.	$[Zn(L_{11})(H_2O)Cl]$ $C_{12}H_{14}ZnN_3O_2Cl$	[330.89]	210–212	Dia	1570 (C=N), 425 (M–N), 315 (M–Cl), 525 (M–O)	29110	43.52 (43.37)	4.23 (4.58)	12.69 (12.94)
23.	$[Cu(L_{12})(H_2O)Cl]$ $C_{12}H_{14}CuN_3SOCl$	[347.04]	228–230	1.52	1570 (C=N), 425 (M–N), 395 (M–S), 315 (M–Cl), 525 (M–O)	15245, 19587, 30255	41.49 (41.54)	4.03 (4.39)	12.10 (12.36)
24.	$[Zn(L_{12})(H_2O)Cl]$ $C_{12}H_{14}ZnN_3SOCl$	[346.89]	215–217	Dia	1570 (C=N), 425 (M–N), 385 (M–S), 315 (M–Cl), 525 (M–O)	28350	41.51 (41.76)	4.04 (4.28)	12.11 (12.46)

complexes (**1**)–(**24**) were screened *in-vitro* for their antibacterial activity against four Gram-negative (*E. coli*, *S. flexenari*, *P. aeruginosa and S. typhi)* and two Gram-positive (*B. subtilis* and *S. aureus*) bacterial strains using the agar well diffusion method [18]. Two to eight hours old bacterial inoculums containing approximately 10^4–10^6 colony forming units (CFU)/ml were used in these assays. The wells were dug in the media with the help of a sterile metallic borer with centers at least 24 mm. Recommended concentration (100 μL) of the test sample (1 mg/mL in DMF) was introduced in the respective wells. Other wells supplemented with DMF and reference antibacterial drug, imipenum served as negative and positive controls respectively. The plates were incubated immediately at 37°C for 20 h. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared [19] with the standard drug (Tables II & III). In order to clarify any participating role of DMF in the biological screening, separate studies were carried out with the solutions alone of DMF and they showed no activity against any bacterial strains.

*Antifungal activity (*in-vitro*)*. Antifungal activities of all compounds were studied against six fungal cultures, *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani* and *C. glaberata*. Sabouraud dextrose agar (Oxoid, Hampshire, England) was seeded with 10^5 (cfu) mL^{-1} fungal spore suspensions and transferred to petri plates. Discs soaked in 20 mL (10 μg/mL in DMF) of all compounds were placed at different positions on the agar surface. The plates were incubated at 32°C for seven days. The results were recorded as zones of inhibition (in mm) and compared with the standard drugs miconazole and amphotericin B.

Minimum inhibitory concentration (MIC). Compounds showing antibacterial activity over 80% were selected for minimum inhibitory concentration (MIC) studies (Table IV). The minimum inhibitory concentration was determined using the disc diffusion technique [20] by preparing discs containing 10, 25, 50 and 100 μg/mL of the compounds and applying the protocol.

Cytotoxicity (in-vitro). Brine shrimp (*Artemia salina* leach) eggs were hatched in a shallow rectangular plastic dish (22 × 32 cm), filled with artificial seawater, which was prepared [19] with commercial salt mixture and double distilled water. An unequal partition was made in the plastic dish with the help of a perforated device. Approximately 50 mg of eggs were sprinkled into the large compartment, which was

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Table II. Results of Antibacterial Bioassay Compounds (zone of inhibition in mm).

Bacteria	Compound (zone of inhibition in mm)																								
	L_1	**L_2**	**L_3**	**L_4**	**L_5**	**L_6**	**L_7**	**L_8**	**L_9**	**L_{10}**	**L_{11}**	**L_{12}**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**SD**
(a)	22	15	18	17	20	17	21	16	19	18	21	16	23	24	16	19	19	19	17	18	21	23	17	18	30
(b)	10	08	10	05	10	06	08	09	17	10	16	09	12	13	10	09	10	10	07	08	12	14	08	09	28
(c)	18	12	14	12	17	10	17	13	16	14	15	10	18	19	14	16	15	16	13	17	18	20	10	12	27
(d)	17	11	14	15	16	13	18	14	16	14	17	15	18	18	12	14	16	17	16	18	16	18	15	16	29
(e)	09	00	05	06	16	09	10	00	06	08	10	00	11	12	00	05	08	10	06	08	19	20	11	14	30
(f)	18	19	18	20	17	17	19	19	20	19	20	20	21	24	18	19	20	19	22	24	26	24	19	18	28
(g)	05	08	06	19	06	05	07	08	06	07	10	11	09	12	07	08	07	07	10	09	11	11	09	08	29
(h)	08	19	10	16	08	09	18	09	18	19	04	06	12	10	20	20	11	10	17	18	10	10	09	10	30
(j)	17	22	18	24	18	19	18	19	18	19	24	23	26	24	18	19	20	20	26	25	26	28	19	20	29
													13	14	15	16	17	18	19	20	21	22	23	24	
													21	22	16	17	20	22	18	19	23	25	17	19	
													10	12	15	16	18	19	12	15	18	19	09	10	
													19	18	15	17	16	17	16	18	17	18	12	13	
													17	18	15	17	18	20	15	19	17	18	17	18	
													12	14	08	05	08	10	08	09	12	12	07	08	
													19	19	22	24	22	23	17	19	22	22	21	23	
													07	08	10	11	08	10	08	09	12	14	13	14	
													10	11	10	10	20	21	20	21	05	07	07	08	
													18	19	20	23	18	19	21	22	24	26	24	25	

(*a*) = *B. cereus*, (*b*) = *C. diphtheriae*, (*c*) = *E. coli*, (*d*) = *K. Pneumoniae*, (*e*) = *P. mirabilis*, (*f*) = *P. aeruginosa*, (*g*) = *S. typhi*, (*h*) = *S. dysentriae*, (j) = *S. aureus* 10 < : weak; 10–16: moderate; >16: Significant. SD = Standard Drug Concentration used = 100 μg

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Table III. Results of Antifungal Bioassay (concentration used 200 μg/mL).

Organism	Compound (% inhibition)																													
	L_1	L_2	L_3	L_4	L_5	L_6	L_7	L_8	L_9	L_{10}	L_{11}	L_{12}	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	SD
(a)	30	00	35	35	00	30	00	00	42	00	37	00	40	45	00	28	38	40	40	42	00	05	35	37	00	00	00	30	45	A
(b)	00	17	00	00	00	00	00	30	00	00	00	30	00	00	25	27	00	00	00	00	00	00	00	00	00	00	38	40	00	B
(c)	15	00	00	00	00	00	00	00	00	25	00	28	20	25	00	10	00	00	00	00	00	32	00	00	00	00	00	32	00	C
(d)	00	00	00	00	25	00	00	24	00	00	00	00	00	00	00	00	00	00	00	00	30	35	00	00	00	00	29	32	00	D
(e)	00	15	00	00	00	00	30	00	00	00	00	00	00	00	20	25	00	00	00	00	00	00	00	00	38	40	00	00	00	E
(f)	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	F
(g)	00	00	00	00	00	00	00	30	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	G
																							18	19	20	21	22	23	24	
																							47	00	00	37	38	00	34	
																							00	00	00	00	00	35	38	
																							00	28	35	00	00	35	40	
																							00	00	00	00	00	00	00	
																							00	00	00	00	00	00	00	
																							00	00	00	00	00	00	00	
																							00	00	00	00	00	40	45	

(*a*) *T. schoenleinii*, (*b*) = *C. glabrata*, (*c*) = *P. boydii*, (*d*) = *C. albicans*, (*e*) = *A. niger*, (*f*) = *M. canis*, (*g*) = *T. mentagrophytes*

SD = Standard Drugs MIC μg/mL; A = Miconazole (70 μg/mL); B = Miconazole (110.8 μg/mL); C = Amphotericin B (20 μg/mL); D = Miconazole (98.4 μg/mL); E = Miconazole (73.25 μg/mL); F = Miconazole (110.8 μg/mL); G = Miconazole (85.10 μg/mL).

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Table IV. Results of Minimum Inhibitory Concentration (M) of Selected Compounds.

No.	L_4	L_{11}	1	2	7	8	9	10	16
B. cereus	–	–	–	1.783×10^{-7}	–	–	–	–	–
P. aeruginosa	–	–	–	1.232×10^{-7}	–	6.033×10^{-8}	6.289×10^{-7}	1.258×10^{-7}	1.339×10^{-7}
S. aureus	1.783×10^{-7}	4.646×10^{-7}	6.152×10^{-8}	1.232×10^{-7}	6.031×10^{-8}	6.033×10^{-8}	1.258×10^{-7}	2.516×10^{-8}	–
					18	21	22	23	24
					–	–	7.155×10^{-8}	–	–
					1.401×10^{-7}	–	–	–	6.842×10^{-8}
					–	1.430×10^{-7}	2.862×10^{-8}	1.368×10^{-7}	6.842×10^{-8}

darkened while the smaller compartment was opened to ordinary light. After two days nauplii were collected by a pipette from the lighted side. A sample of the test compound was prepared by dissolving 20 mg of each compound in 2 mL of DMF. From this stock solutions 500, 50 and 5 μg/mL were transferred to 9 vials (three for each dilutions were used for each test sample and LD_{50} is the mean of three values) and one vial was kept as control having 2 mL of DMF only. The solvent was allowed to evaporate overnight. After two days, when shrimp larvae were ready, 1 mL of seawater and 10 shrimps were added to each vial (30 shrimps/dilution) and the volume was adjusted with seawater to 5 mL per vial. After 24 h the numbers of survivors were counted. Data were analyzed by Finney computer program to determine the LD_{50} values [21]. The Results are shown in Table V.

Results and discussion

Chemistry

The Schiff-bases (**L_1**)–(**L_{12}**) were prepared by refluxing the appropriate amount of 1,2-phenylenediamine and ethylenediamine with the corresponding heteroaromatic (salicylaldehyde) and heterocyclic (furane-2-carboxaldehyde, thiophene-2-carboxaldehyde and pyrrol-2-carboxaldehyde) systems respectively in ethanol. In order to achieve asymmetrically desired product, the reaction was initially attempted in a single step by mixing and refluxing all the three starting materials i.e., phenylenediamine/ethylenediamine, salicylaldehyde and/or the corresponding heterocyclic (furane-2-carboxaldehyde, thiophene-2-carboxaldehyde and pyrrol-2-carboxaldehyde) systems together in 1:1 molar ratio. But, the product achieved was mixture of three compounds, symmetrically disalicylyl-derived (40%), difuranyl-derived (38%) and the desired asymmetrically salicyl- and furanyl-derived product in 20% yield. To avoid formation of undesired symmetrically substituted salicylyl- and furanyl-derived compounds, two step reactions were preferred. In the first step, phenylenediamine was refluxed with salicylaldehyde in equimolar ratio; the product was isolated and further treated with furane-2-carboxaldehde to achieve the desired Schiff-base (**L_1**). All other Schiff bases (**L_2**)–(**L_{12}**) were prepared according to the same method. The structures of the synthesized Schiff base ligands were established with the help of their IR, NMR and microanalytical data. All metal complexes (**1**)–(**24**) of these ligands were air and moisture stable and prepared by the stoichiometric reaction of the corresponding hydrated metal (II) chloride with the ligand, in a molar ratio M:L of 1:1. The Cu(II) complexes are intensely colored whereas the Zn(II) complexes were a pale yellow. All were amorphous solids which decomposed without melting, and were insoluble in common organic

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Table V. Brine Shrimp Bioassay Data of the Ligands (L_1)–(L_{12}) and their Metal (II) Complexes (1)–(24).

Compound	LD_{50} (M)
L^1	$>3.444\times10^{-3}$
L^2	$>3.264\times10^{-3}$
L^3	$>3.456\times10^{-3}$
L^4	1.445×10^{-3}
L^5	$>3.798\times10^{-3}$
L^6	$>3.580\times10^{-3}$
L^7	$>4.127\times10^{-3}$
L^8	$>3.871\times10^{-3}$
L^9	$>4.144\times10^{-3}$
L^{10}	$>4.304\times10^{-3}$
L^{11}	$>4.646\times10^{-3}$
L^{12}	$>4.323\times10^{-3}$
1	1.021×10^{-3}
2	$>2.464\times10^{-3}$
3	2.369×10^{-3}
4	$>2.370\times10^{-3}$
5	$>2.467\times10^{-3}$
6	$>1.304\times10^{-3}$
7	7.478×10^{-4}
8	8.566×10^{-4}
9	$>2.515\times10^{-3}$
10	$>2.516\times10^{-3}$
11	1.028×10^{-3}
12	$>2.419\times10^{-3}$
13	$>2.792\times10^{-3}$
14	$>2.794\times10^{-3}$
15	$>2.674\times10^{-3}$
16	$>2.674\times10^{-3}$
17	9.943×10^{-4}
18	$>2.802\times10^{-3}$
19	8.730×10^{-4}
20	$>2.729\times10^{-3}$
21	$>2.861\times10^{-3}$
22	$>2.862\times10^{-3}$
23	1.124×10^{-3}
24	$>2.737\times10^{-3}$

solvents and only soluble in DMF and DMSO. Molar conductance values of the soluble complexes in DMF (10^{-3} M solution at 25°C), indicated that all complexes of copper (II) and zinc(II) have initially lower values (14–18 $ohm^{-1}\ cm^{-2}\ mol^{-1}$) indicating that they are all non-electrolytic in nature [22]. The elemental analyses data agree well with the proposed formulae for the ligands and also confirmed the $[M(L)(H_2O)Cl]$, $[M(L)(H_2O)_2]$ and $[M(L)Cl_2]$ composition for both Cu(II), Zn(II) chelates. Efforts to grow good crystals of the ligands and their metal chelates for X-ray diffraction studies were unsuccessful due to their poor solubility in common organic solvents.

IR spectra. The important IR spectral bands of the ligands and its metal complexes are given in Table I. All ligands contain four potential donor sites: the salicyl-O and/or furanyl-O and/or thienyl-S and/or pyrrol-N and two azomethine-N. In the IR spectra of the ligands a sharp band observed at 1610–1615 cm^{-1} is assigned [23] to the ν(C=N) mode and medium sharp bands at 1245 due to stretching of salicyl and 1150, 810, 755 cm^{-1} due to the ν(C–O), ν(C–N) and ν(C–S) of furanyl, pyrrolyl and thienyl rings, respectively. Evidence of the nitrogen bonding of the azomethine (C=N) group to the central metal atom stems from the shift of the ν(C=N) frequency to lower frequency by 45–50 cm^{-1} in all of the complexes. This is further confirmed by the appearance of the new bands at 515–525, 425–430 and 385–395 cm^{-1} due to the ν(M–O), ν(M–N) and ν(M–S) [24].

The coordination through the salicyl ring oxygen is also revealed by shifting of the C–O band at 1245 cm^{-1} to much lower frequencies (1215–1220 cm^{-1}) in the complexes as compared to that of the ligands. A new band appearing at 315 cm^{-1} assigned [25] to the ν(M–Cl) mode in the metal complexes was however, indicative of the fact that chloride atoms are coordinated with the central metal atom.

NMR spectra. The ^{1}H NMR spectra of the free ligands and their diamagnetic Zn(II) chelates were done in DMSO-d_6. The ^{1}H NMR spectral data are reported along with the possible assignments in the experimental section. All the protons due to heteroaromatic and/or aromatic groups were found to be in their expected region [26]. The conclusions drawn from these studies lend further support to the mode of bonding discussed in their IR spectra. In the spectra of the diamagnetic Zn(II) complexes, these signals shifted downfield due to the increased conjugation and coordination to the metal atoms [27]. The number of protons calculated from the integration curves agreed with those obtained from the values of the expected CHN analyses. It was observed that DMSO did not have any coordinating effect neither on the spectra of the ligands nor on its metal complexes.

Electronic spectra. The electronic spectra of the Cu(II) complexes (Table I) showed two low-energy weak bands at 15,210–15,325 cm^{-1} and 19,520–19,645 cm^{-1} and a strong high-energy band at 30,255–30,420 cm^{-1}. The low-energy bands in this position typically are expected for an octahedral configuration and may be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions, respectively [28]. The strong high-energy band, in turn, is assigned to metal → ligand charge transfer. Also, the magnetic moment values (1.3–1.52 B.M) (Table1) for the copper(II) are indicative of anti-ferromagnetic spin-spin interaction through molecular association. Hence, the copper(II) complexes appear to be in the octahedral geometry with a dx^2-dy^2 ground state [29,30]. The electronic

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spectra of the Zn(II) complexes exhibited only a high-intensity band at 28,350–29,145 cm^{-1} and are assigned [31] to a ligand-metal charge transfer.

Biological activity

The antibacterial and antifungal activity results presented in Tables II, III & IV show clearly that all the newly synthesized compounds ($\mathbf{L_1}$)–($\mathbf{L_{12}}$) and their metal complexes (**1**)–(**24**) containing Cu(II) and Zn(II) possess good biological activity. New derivatives ($\mathbf{L_1}$)–($\mathbf{L_{12}}$) obtained by the condensation reaction were screened for their antibacterial activity against *B cereus, C diphtheriae, E coli, K pneumoniae, P mirabilis, P aeruginosa, S typhi, S dysenteriae and S aureus* and for antifungal activity against *T schoenleinii, C glabrata, P boydii, C albicans, A niger, M canis and T mentagrophytes*. All metal complexes exhibited a marked enhancement of activity on coordination with the metal ions. The compounds generally showed moderate antibacterial activity against two or four species and good activity against one or two species. However, they showed greater antifungal activity. It was evident from the data that this activity of the compounds was significantly increased upon coordination. This enhancement in the activity may be rationalized on the basis of their structures, mainly possession of an additional C=N bond with a heterocyclic or aromatic ring system. It has been suggested that the ligands with nitrogen and oxygen donor systems might inhibit enzymes, since enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by metal ions upon chelation. Chelation reduces the polarity [32,33] of the metal ion mainly because of the partial sharing of its positive charge with the donor groups and possibly the π-electron delocalization [34–38] within the whole chelate ring system formed during coordination. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favors its permeation through the lipoid layer of the membrane [39,40]. It has also been observed that some moieties containing groups such as azomethine or heteroaromatic systems present in the ligands exhibit extensive biological activities. These in turn, are responsible for increasing the hydrophobic character and liposolubility of the molecule in crossing the cell membrane of the microorganism and hence enhance the biological utilization ratio and activity of the drug.

Conclusion

The synthesized salicyl-, furanyl-, thienyl- and pyrrolyl-derived ONNO, NNNO, ONNS & NNNS donor asymmetrically mixed Schiff-bases showed potential antibacterial/antifungal properties. In comparison, the copper(II) and zinc(II) complexes of these compounds showed more activity against one or more bacterial/fungal strains thus introducing a novel class of ONNO, NNNO, ONNS & NNNS donor metal-based bactericidal and fungicidal agent.

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