

# *In vitro* Antimicrobial Investigations of Newly Synthesized Transitional Bivalent Metal Complexes Derived from 8-Hydroxyquinoline

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## ABSTRACT

**Introduction:** Novel Cu(II), Co(II) and Ni(II) complexes of 8-hydroxyquinolineazo analogues are synthesized from 5-((3-nitrophenyl)diazenyl) quinolin-8-ol (**4a**) and 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol (**4b**). **Methods:** The structural environment and elemental composition of the synthesized metal complexes are confirmed by FT/IR, <sup>1</sup>H NMR and CHNS/O elemental analyzer. The  $\lambda_{\max}$  and molecular mass are determined with the help of UV-visible and LC-MS spectrometer. **Results:** The magnetic susceptibility study suggested that the synthesized complexes are proposed with tetrahedral geometry. Among the six complexes, the bis bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] copper (**4aLig<sub>2</sub>Cu**) and bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] copper (**4bLig<sub>2</sub>Cu**) showed significant antimicrobial activity. **Conclusion:** It was found that the metal complexes showed enhanced antimicrobial activity in comparison to their corresponding ligands.

**Key words:** Spectroscopic, Magnetic susceptibility, Antimicrobial, 8-Hydroxy quiniline, Antibiogram.

## INTRODUCTION

Antimicrobial resistance is a global problem which challenges our ability to combat common infectious diseases. This occurs naturally over time through genetic changes or may result due to the vitality of the germs those are not killed with their ceaseless growth. According to the opinion of World Health leaders, antibiotic resistant microorganisms are the nightmare bacteria that cause a notable disaster to a huge population in the world. According to the current outcome, 2 million people are suffering from serious infections and 23,000 people are dying due to these superbugs in the United States every year. Also the report of antibiotic resistance threats in the United States 2013 reveals that *Candida* causes serious illness among hospital patients is show-

ing an unambiguous increase in multidrug resistance.<sup>1</sup> According to the global report on surveillance of World Health Organisation in 2014, the antibiotic resistance due to *Escherichia coli* in urinary tract infections and the resistance offered by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* etc. in case of pneumonia is highest in the south-east, east central and south Atlantic states (antimicrobial resistance: global report on surveillance, WHO 2014). To forestall the deadly infections due to the antibiotic resistant superbugs, the WHO recommended instructions are preventing infections and preventing the spread of resistance, tracking resistant bacteria, improving the use of today's antibiotics and promoting the development of new antibiotics and develop-

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ing new diagnostic tests for resistant bacteria. Though many investigations are going on to combat the multidrug resistant microorganisms since past few years, still a lot many inventions are required for development of newer and potent molecules for enhancement of the Antibiotic treatment options. 8-Hydroxyquinoline (8-HQ) the quinoline derivative can obtain from plants as well as synthetically in the laboratory. 8-HQ possesses potent coordinating ability and good metal recognition properties.<sup>2</sup> In addition to these they have good chelating ability toward a great number of metal cations.<sup>3</sup> Among seven isomeric mono hydroxyquinolines, only 8-HQ is capable of forming complexes with divalent metal ions through chelation.<sup>4</sup> The heterocyclic nitrogen compounds bearing 8-HQ nucleus have potential biological activities as well as good complexing agents.<sup>5,6</sup> 8-hydroxyquinoline and its derivatives are well known bidentate ligands. It has been used as a fungicide in agriculture and a preservative in the textile, wood, and paper industries.<sup>7</sup> 8-hydroxyquinoline derivatives have versatile therapeutic activities such as antiseptic,<sup>8</sup> antiviral,<sup>9</sup> antimicrobial,<sup>10</sup> antitumor,<sup>11</sup> anti-inflammatory,<sup>12</sup> anti-asthmatic and analgesic,<sup>13</sup> antioxidant,<sup>5</sup> anti-neurodegenerative & anti-diabetic<sup>14</sup> and anti-HIV. The organic compounds coordinated with metals cause drastic change in the biological property of the ligand.<sup>15</sup> The transition metal complexes have shown significant biological actions including antibacterial, antifungal and anticancer activities.<sup>5</sup> Metal ions can induce toxicity but metal imbalance can cause many diseases. In this regards, 8-HQ which is a potent chelator may restore metal balance and can be useful for the treatment of metal-related diseases. Moreover the azo compounds are known to be involved in numbers of biological functions, such as inhibition of nucleic acids, protein synthesis, nitrogen fixation and carcinogenesis.<sup>16</sup> Azo derivatives and their metal complexes are also very important pigments for synthetic leather and vinyl polymers.<sup>17</sup> They are the potent pharmaceuticals agents which having versatile therapeutic activities like antiseptic,<sup>18</sup> antimicrobial<sup>19-22</sup> antidiabetic,<sup>23</sup> antineoplastic,<sup>24</sup> antitumor<sup>25</sup> activities, DNA, RNA, and protein synthesis, nitrogen fixation, and carcinogenesis.<sup>26</sup> The azo compounds based on 8-hydroxyquinoline play a central role as chelating agents for large number of metal ions, as they can form a stable six-member ring after complexation with the metal ion. The intra-molecular and intermolecular association through hydrogen bonding could be assumed to exist in 5-(substituted phenylazo)-8-hydroxyquinoline derivatives.<sup>27</sup> In the continuation of our earlier reported work,<sup>5</sup> the present investigation is mainly focused on the synthesis of a wide range of

metal complexes by co-ordination of transitional metal chlorides with 8-hydroxyquinolineazo analogues and to investigate their biological properties.

## EXPERIMENTAL SECTION

### Chemicals and Analysis

All the chemicals used in the present studies were of synthetic grade and sourced from Merck specialties Ltd. (Mumbai, India) and used without purification. The Elemental analysis of the novel synthesized molecules for C, H, N and S were performed using *Perkin Elmer* model 2400 CHNS/O analyzer. Further the prepared products were analyzed by FT/IR (*JASCO* FT/IR 4100 Spectrophotometer) using KBr pellets. *Shimadzu*-Mass spectrophotometer with column  $C_6$  (150 mm  $\times$  4.6 mm), 5 $\mu$ m particle size was used to determine the molecular mass. The <sup>1</sup>H NMR spectra were recorded on a *Bruker* <sup>1</sup>H NMR 400 MHz using DMSO-*d*<sub>6</sub> as a solvent with tetramethylsilane as an internal standard and the chemical shifts were reported on  $\delta$  ppm. The UV-Vis spectroscopy (*Jasco* V-630 Spectrophotometer) is used to study  $\lambda_{max}$  of the synthesized molecules. The melting points were determined by open capillary method (*Elico*) and are uncorrected. Faraday balance technique was employed to measure the magnetic susceptibility of the metal complexes. The *in vitro* antimicrobial activities against different bacterial and fungal pathogens were performed by agar well diffusion method, sourced from CSIR IMTECH, India, Chandigarh.

### Synthesis of 5-((3-nitrophenyl) diazenyl) quinolin-8-ol (4a) and 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol (4b)

The synthesis of the compounds 5-((3-nitrophenyl) diazenyl) quinolin-8-ol (**4a**) and 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol (**4b**) azo analogues was carried out as earlier reported.<sup>5</sup>

### Synthesis of metal complexes of azoquinoline analogues (4a Lig<sub>2</sub>M and 4b Lig<sub>2</sub>M)<sup>17,21</sup>

A mixture of 25mL was prepared with appropriate transitional metal ions Cu(II), Co(II) and Ni(II) of 10 mmol in ethanol and water 1:1. The above mixture was added to the solution of respective azo compounds **4a** and **4b** (0.40 g, 10 mM) in ethanol and water in equal ratio to obtain 50 mL. The resulting solution was refluxed for 30 min at a controlled temperature not more than 78°C. The obtained precipitates were filtered and washed with equal proportion of ethanol-water and finally re-crystallized from diethyl ether. The progress of reaction was

monitored by TLC with solvent system of ethyl acetate and cyclohexane at 1:5.

**5-((3-nitrophenyl) diazenyl) quinolin-8-ol (4a):** Gray colour; Yield 90 %;  $R_f$ : 0.7, mp ( $^{\circ}\text{C}$ ): 278-280; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 463; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 3432 (O-H str.), 1608 (C=C str.), 1586, (C=N str. Quinolinylyl), 1506 (-N=N-), 1338 ( $\text{NO}_2$  str.);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 9.67 (s, 1H, 8-OH), 8.10-8.66 (4H, Aryl-H), 9.11 (d, Quinolinylyl H-2), 7.78 (d, Quinolinylyl H-3), 8.33 (d, Quinolinylyl H-4), 7.87 (d, Quinolinylyl H-6), 7.32 (d, Quinolinylyl H-7); LC-MS (% area); 93;  $m/z$ : 295.17 (M+1); Analysis for  $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}_3$ : Calcd % C, 61.22; H, 3.43; N, 19.04; Found %: C, 61.25; H, 3.41; N, 19.07.

**5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol (4b):** Dark red colour; Yield 97 %;  $R_f$ : 0.8, mp ( $^{\circ}\text{C}$ ): 260-263; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 404; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 3290 (O-H str), 2922 ( $\text{CH}_2$  str  $\text{CH}_3$ ), 1578 (C=N str. Quinolinylyl), 1503 (-N=N-), 621 (C-Br), 885 (1, 2, 4 trisubst. Ar-H);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 9.21 (s, 1H, 9.21), 2.51 (s, 3H,  $\text{CH}_3$ ), 7.61- 7.83 (3H, Aryl-H), 8.91(d, Quinolinylyl H-2), 7.55 (d, Quinolinylyl H-3), 8.11 (d, Quinolinylyl H-4), 7.91 (d, Quinolinylyl H-6), 7.34 (d, Quinolinylyl H-7); LC-MS (% area); 99.84;  $m/z$ : 342.18 (M+1); Analysis for  $\text{C}_{16}\text{H}_{12}\text{BrN}_3\text{O}$ : Calcd % C, 56.16; H, 3.53; N, 12.38; Found %: C, 56.14; H, 3.55; N, 12.40.

**Bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] copper (4a Lig<sub>2</sub>Cu):** Coffee red colour; Yield 83 %;  $R_f$ : 0.8, mp ( $^{\circ}\text{C}$ ): 293-295; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 440; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 1639 (C=N str. Quinolinylyl), 1580 (C=C str.), 1504 (-N=N-), 1338 ( $\text{NO}_2$  str.), 546 (M-O), 488 (M-N);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 8.69 (s, 1H, 3-nitro phenyldiazenyl H-2), 8.41(d, 1H, 3-nitro phenyldiazenyl H-4), 7.88 (m, 1H, 3-nitro phenyldiazenyl H-5), 8.38 (d, 1H, 3-nitro phenyldiazenyl H-6), 9.31(d, 1H, Quinolinylyl H-2), 8.13(m, 1H, Quinolinylyl H-3), 9.10 (d, 1H, Quinolinylyl H-4), 7.79(d, 1H, Quinolinylyl H-6), 7.22 (d, 1H, Quinolinylyl H-7); LC-MS (% area); 91.73;  $m/z$ : 651.01(649.06) (M+1); Analysis for:  $\text{C}_{30}\text{H}_{18}\text{CuN}_8\text{O}_{62+}$ : Calcd % C, 55.43; H, 2.79; Cu, 9.78; N, 17.24; Found %: C, 55.45; H, 2.81; Cu, 9.81; N, 17.21.

**Bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] cobalt (4a Lig<sub>2</sub>Co):** Black colour; Yield 87 %;  $R_f$ : 0.5, mp ( $^{\circ}\text{C}$ ): 291-293; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 457; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 1638 (C=N str. Quinolinylyl), 1584 (C=C str.), , 1506 (-N=N-), 1332 ( $\text{NO}_2$  str.), 545 (M-O), 438 (M-N);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 8.71 (s, 1H, 3-nitro phenyldiazenyl H-2), 8.41(d, 1H, 3-nitro phenyldiazenyl H-4), 7.89 (m, 1H, 3-nitro phenyldiazenyl H-5), 8.38 (d, 1H, 3-nitro phenyldiazenyl H-6), 9.29(d, 1H, Quinolinylyl H-2), 8.11(m, 1H, Quinolinylyl H-3), 9.12 (d, 1H, Quinolinylyl H-4), 7.78 (d, 1H, Quinolinylyl H-6),

7.19 (d, 1H, Quinolinylyl H-7); LC-MS (% area); 89;  $m/z$ : 644.13 (645.07) (M-1); Analysis for:  $\text{C}_{30}\text{H}_{18}\text{CoN}_8\text{O}_{62+}$ : Calcd % C, 55.83; H, 2.81; Co, 9.13; N, 17.36; Found %: C, 55.84; H, 2.79; Co, 9.11; N, 17.33.

**Bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] nickel (4a Lig<sub>2</sub>Ni):** Coffee red colour; Yield 91 %;  $R_f$ : 0.8, mp ( $^{\circ}\text{C}$ ): 292-295; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 462; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 1648 (C=N str. Quinolinylyl), 1581 (C=C str.), 1504 (-N=N-), 1337 ( $\text{NO}_2$  str.), 505 (M-O), 440 (M-N);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 8.73 (s, 1H, 3-nitro phenyldiazenyl H-2), 8.43(d, 1H, 3-nitro phenyldiazenyl H-4), 7.89 (m, 1H, 3-nitro phenyldiazenyl H-5), 8.36 (d, 1H, 3-nitro phenyldiazenyl H-6), 9.33(d, 1H, Quinolinylyl H-2), 8.13(m, 1H, Quinolinylyl H-3), 9.13 (d, 1H, Quinolinylyl H-4), 7.77(d, 1H, Quinolinylyl H-6), 7.23 (d, 1H, Quinolinylyl H-7); LC-MS (% area); 86.19;  $m/z$ : 645.29 (644.07) (M+1); Analysis for:  $\text{C}_{30}\text{H}_{18}\text{N}_8\text{NiO}_{62+}$ : Calcd % C, 55.85; H, 2.81; N, 17.37; Ni, 9.10; Found %: C, 55.87; H, 2.83; Ni, 9.11; N, 17.38.0

**Bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] copper (4b Lig<sub>2</sub>Cu):** Brick red colour; Yield 85 %;  $R_f$ : 0.6, mp ( $^{\circ}\text{C}$ ): 284-286; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 415; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 2920 ( $\text{CH}_2$  str.  $\text{CH}_3$ ), 1567(C=N str. Quinolinylyl), 1501 (-N=N-), 701 (C-Br), 884 (1, 2, 4 trisubst. Ar), 527 (M-O), 451 (M-N);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 2.33 (s, 3H,  $\text{CH}_3$ ), 7.76 (s, 1H, 4-bromo-3-methyldiazenyl, H-2), 7.64 (d, 1H, 4-bromo-3-methyldiazenyl, H-5), 7.65 (d, 1H, 4-bromo-3-methyldiazenyl, H-6), 9.25 (d, Quinolinylyl H-2), 8.29 (m, Quinolinylyl H-3), 8.90 (d, Quinolinylyl H-4), 8.00 (d, Quinolinylyl H-6), 7.26 (d, Quinolinylyl H-7); LC-MS (% area); 87.34;  $m/z$ : 744.96(744.94) (M+2); Analysis for  $\text{C}_{32}\text{H}_{22}\text{Br}_2\text{CuN}_6\text{O}_{22+}$ : Calcd % C, 51.53; H, 2.97; Br, 21.42; Cu, 8.52; N, 11.27; Found %: C, 51.48; H, 2.94; Br, 21.44; Cu, 8.55; N, 11.32.

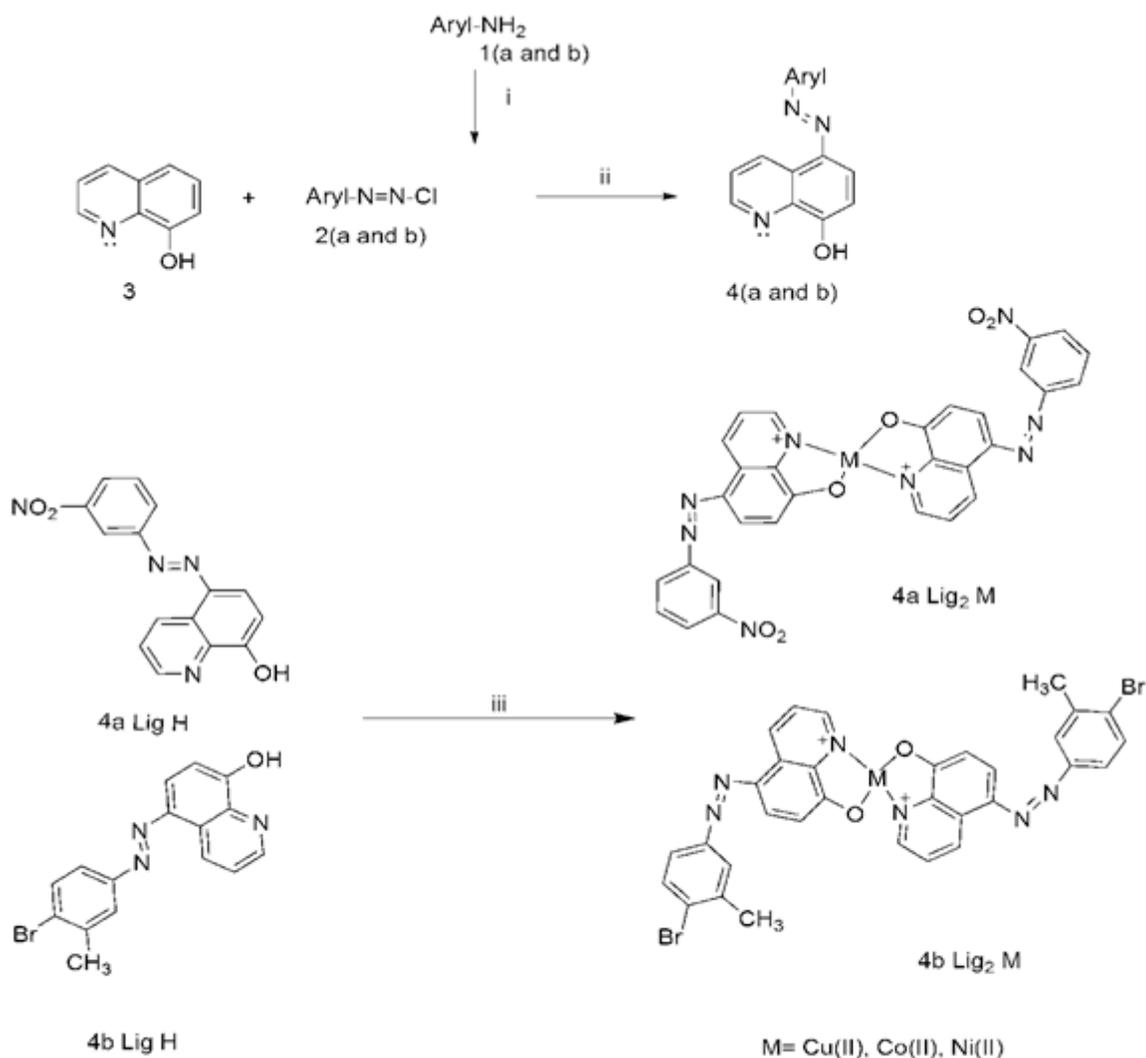
**Bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] cobalt (4b Lig<sub>2</sub>Co):** Brick red colour; Yield 81 %;  $R_f$ : 0.5, mp ( $^{\circ}\text{C}$ ): 278-281; UV-vis ( $\lambda_{\text{max}}$ , nm, DMSO): 473; IR (KBr,  $\gamma$ ,  $\text{cm}^{-1}$ ): 2922 ( $\text{CH}_2$  str.  $\text{CH}_3$ ), 1573 (C=N str. Quinolinylyl), 1499 (-N=N-), 711 (C-Br), 885 (1, 2, 4 trisubst. Ar), 510 (M-O), 431 (M-N);  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$  ppm, 300 MHz): 2.35 (s, 3H,  $\text{CH}_3$ ), 7.79 (s, 1H, 4-bromo-3-methyldiazenyl, H-2), 7.67 (d, 1H, 4-bromo-3-methyldiazenyl, H-5), 7.68 (d, 1H, 4-bromo-3-methyldiazenyl, H-6), 9.19 (d, Quinolinylyl H-2), 8.12 (m, Quinolinylyl H-3), 9.03 (d, Quinolinylyl H-4), 7.89 (d, Quinolinylyl H-6), 7.19 (d, Quinolinylyl H-7); LC-MS (% area); 99.34;  $m/z$ : 739.3 (740.95) (M-1); Analysis for  $\text{C}_{32}\text{H}_{22}\text{Br}_2\text{CoN}_6\text{O}_{22+}$ : Calcd % C, 51.85; H, 2.99; Br, 21.56; Co, 7.95; N, 11.34; Found %: C, 51.87; H, 2.97; Br, 21.53; Co, 7.94; N, 11.32.

*Bis 8, 8'* [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] nickel (**4b Lig<sub>2</sub>Ni**): Brick red colour; Yield 91 %;  $R_f$ : 0.7, mp (°C): 282-284; UV-vis ( $\lambda_{max}$ , nm, DMSO): 405; IR (KBr,  $\gamma$ ,  $cm^{-1}$ ): 2921 (CH<sub>2</sub> str. CH<sub>3</sub>), 1566 (C=N str. Quinoliny), 1463 (-N=N-), 702 (C-Br), 884 (1, 2, 4 trisubst. Ar), 566 (M-O), 471 (M-N); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>,  $\delta$  ppm, 300 MHz): 2.31 (s, 3H, CH<sub>3</sub>), 7.73 (s, 1H, 4-bromo-3-methyldiazenyl, H-2), 7.71 (d, 1H, 4-bromo-3-methyldiazenyl, H-5), 7.64 (d, 1H, 4-bromo-3-methyldiazenyl, H-6), 9.21(d, Quinoliny H-2), 8.57 (m, Quinoliny H-3), 8.98 (d, Quinoliny H-4), 7.85 (d, Quinoliny H-6), 7.19 (d, Quinoliny H-7); LC-MS (% area); 99.12; *m/z*; 739.3 (739.95) (M<sup>+</sup>); Analysis for C<sub>32</sub>H<sub>22</sub>Br<sub>2</sub>N<sub>6</sub>NiO<sub>22</sub><sup>+</sup>: Calcd % C, 51.86; H, 2.99; Br, 21.56; N, 11.34; Ni, 7.92; O, 4.32; Found %: C, 51.82; H, 2.97; Br, 21.58; Ni, 7.91; N, 11.31.

## SCHEME-1

### Antimicrobial Evaluation

The above newly synthesized metal complexes of 8-hydroxyquinolineazo analogues were investigated over different freshly sub cultured microbial strains viz. *Escherichia coli* (MTCC 614), *Klebsiella pneumonia* (MTCC 109) and *Candida albicans* (MTCC 3017) were procured from the Institute of Microbial Technology and Gene bank (IMTECH), Chandigarh, India. *Staphylococcus aureus* and *Cryptococcus neoformans* were obtained from University Department of Pharmaceutical Sciences, Utkal University. Ampicillin and fluconazole were used as reference antibiotics for bacterial and fungal strains respectively. Employing McFarland turbidity standard No. 0.5, the antimicrobial diffusion



assay was performed using a cell suspension of about  $1.5 \times 10^6$  CFU mL<sup>-1</sup>. The antimicrobial activity of the novel metal complexes of 8-hydroxyquinoline azo analogues were performed by agar well diffusion method using sterile molten nutrient agar and Sabouraud dextrose agar medium respectively for antibacterial and antifungal investigation.<sup>28</sup> The diameter of zone of inhibition was measured using the Hi-Antibiotic Zone Scale (*Hi-Media*). Each test compound was screened six times against individual strains.

### Minimum inhibitory concentration (MIC)

A stock solution of synthesized compounds at a concentration level of 1mgmL<sup>-1</sup> and reference antibiotics was prepared using DMF. Further, five different concentrations of (500-31.25 µgmL<sup>-1</sup>) were prepared by serial dilution fold dilution method. Further the different concentrations prepared from respective compounds were loaded into the wells and incubated at 37°C for 18-24 h. After incubation MIC was determined.<sup>29</sup>

### Statistical analysis

The observed data on zone of inhibitions were subjected to one way- analysis of variance. Through Dunnett Post Hoc test ([https://www.statstodo.com/SSizAOV\\_Pgm.php](https://www.statstodo.com/SSizAOV_Pgm.php)) Mean zone of inhibition for each compound on each strain was compared with the reference antibiotic. The test of significance was done at 5% level of type one error. The research hypothesis was 'the zone of inhibition for test compound was higher than the reference antibiotic against the hypothesis of no difference (null hypotheses) which states that there is no significant difference between the zone of inhibition of the test compound and reference antibiotics.

### Sample size determination

A minimum sample size of five was calculated taking probability of type 1 error ( $\alpha$ ) = 0.05, Power (1- $\beta$ ) = 0.8, Number of groups 13 within group SD=2. However a sample size of six has been taken in the study for each compound against each strain.

## RESULTS AND DISCUSSION

### Chemistry

The synthesis of compounds 5-((3-nitrophenyl) diazenyl) quinolin-8-ol (**4a**) and 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol (**4b**) were earlier reported<sup>5</sup>. These both ligands are prepared by the coupling of mixture of diazotised substituted primary aromatic amine with 8-hydroxy quinoline in mild condition. Further, the transitional metal complexes analogues were

synthesized by the addition of respective metal chlorides to alcoholic solution of the ligands. The mixture was refluxed and finally the obtained complexes were re-crystallized from diethyl ether (**Scheme-1**).

The elemental analysis of all the compounds shows good agreement with their calculated values.

The FT/IR spectra gave valuable information regarding the location of different functional groups attached to the metals. The spectrum of the ligands **4a** and **4b** showed vibration band at range of 3432 and 3290 cm<sup>-1</sup> which attributed to  $\nu$  OH str. group of 8-HQ. The bands appeared at 1506 and 1503 cm<sup>-1</sup> in the ligands corresponds to  $\nu$  -N=N- str. All the complexes showed the vibration bands at a range of 1506-1463 cm<sup>-1</sup> which corresponds to  $\nu$  -N=N- str. A new set of frequency bands observed at the region of 566-500 cm<sup>-1</sup> and 488-431 cm<sup>-1</sup> corresponding to  $\nu$  M-O and  $\nu$  M-N in all the complexes respectively. The FT/IR absorption band of hydroxyl group of 8-HQ at 3432-3290 cm<sup>-1</sup> in respective ligands **4a** and **4b** has been found to be diminished in all their respective complexes which indicates that the 8-hydroxyquinoline azo analogue (**4a** and **4b**) has been reacted with metal chloride and subsequently deprotonation and co-ordinate the metal with 1,8 position of quinoline. However there is no significant changes in the vibration bands of  $\nu$  -N=N- (azo group) is found to be observed in the ligands and their respective com-

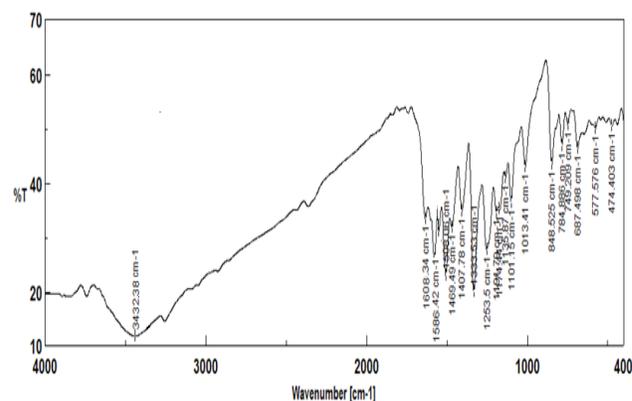


Figure 1: FT/IR spectra of 5-((3-nitrophenyl) diazenyl) quinolin-8-ol (**4a**).

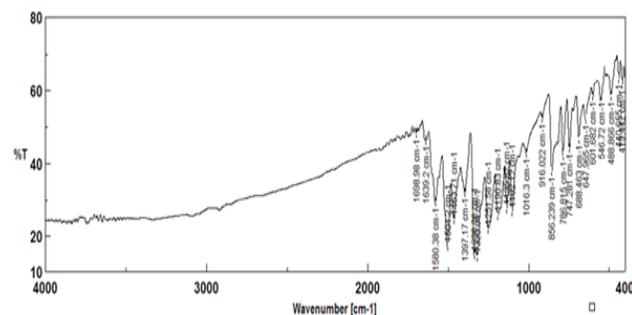


Figure 2: FT/IR spectra of bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] copper (**4a Lig<sub>2</sub>Cu**).

The  $\lambda_{\max}$  of the synthesized compounds was measured on UV-Visible spectrophotometer. The absorption spectra of the compounds (**4a**, **4b**, **4a Lig<sub>2</sub> M** and **4b Lig<sub>2</sub> M**) were measured at a concentration of  $10^{-5}$  to  $10^{-6}$  M, in the region 200–600 nm using DMSO as a solvent. The UV-Visible spectra of the ligand **4a** showed the  $\lambda_{\max}$  at 463 nm whereas its transitional metal complexes with **Cu(II)** and **Co(II)** showed at 440 and 457 nm respectively. However there is no significant change in the  $\lambda_{\max}$  of the ligand **4a** and its metal complex (**4aLig<sub>2</sub>Ni**) is found to be observed. The ligand **4b** showed the  $\lambda_{\max}$  at 404 nm whereas its complexes with **Cu(II)** and **Co(II)** showed bathochromic shift at 415 and 473 nm respectively. There is no considerable difference in  $\lambda_{\max}$  found to be observed in compound **4b** and its metal complex **4bLig<sub>2</sub>Ni**. The observed  $\lambda_{\max}$  by the synthesized ligand **4b** and its complexes suggested that insertion of **Cu(II)** and **Co(II)** to ligand **4b** may be responsible for showing bathochromic shift. Interestingly it is found to be observed that when the metals are attached with 3-nitrophenyl conjugated 8-HQ azo

plexes may be due to non involvement of azo moiety with metal ions. The FT/IR spectra of ligand **4a**, **4a Lig<sub>2</sub>Cu** and **4b Lig<sub>2</sub>Cu** is depicted in Figure 1, Figure 2 and Figure 3 respectively.

All the synthesized compounds showed five quinoline aromatic protons with a range of  $\delta$  7.19- 9.33 ppm in their <sup>1</sup>H NMR spectral data. The <sup>1</sup>H NMR spectra of synthesized the ligands **4a** and **4b** showed a broad singlet peak at  $\delta$  9.67 and 9.21 ppm, corresponding to hydroxyl group of 8-hydroxyquinoline whereas, the quinoline protons with a range of  $\delta$  7.33- 9.11 ppm. In all the complexes, the broad singlet peak due to hydroxyl group of 8-HQ is found to be abolished which indicates deprotonation and co-ordination of metal and oxygen of the ligands. In all the complexes of ligand **4a**, the 3-nitrophenyldiazenyl H-2 proton showed at a range of  $\delta$  8.73-8.69 ppm. Similarly, in all the complexes of ligand **4b**, the methyl proton showed the singlet at  $\delta$  2.31-2.35 ppm. The <sup>1</sup>H MNR spectra of the complexes **4aLig<sub>2</sub>Cu** and **4bLig<sub>2</sub>Ni** is illustrated in Figure 4 and Figure 5.

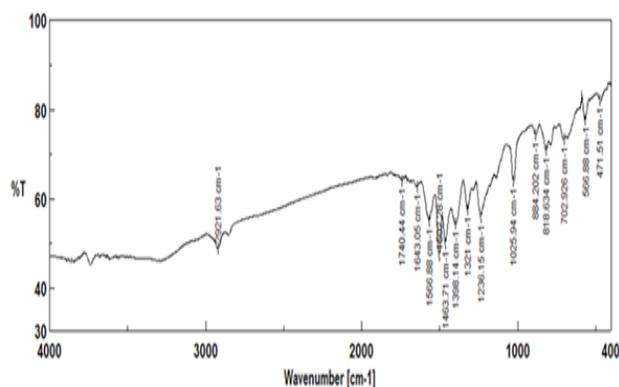


Figure 3: FT/IR spectra of bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] nickel (**4b Lig<sub>2</sub>Ni**).

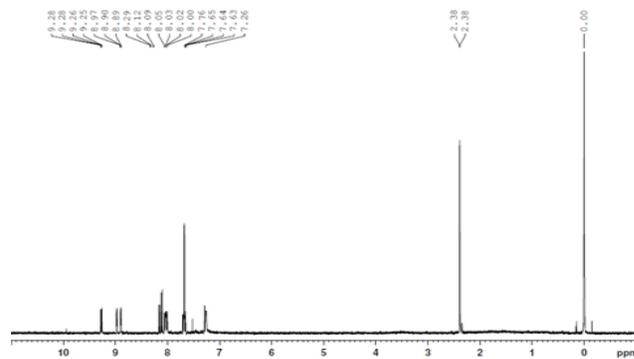
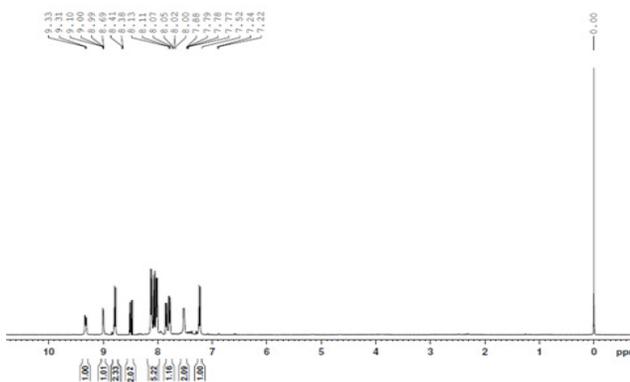


Figure 5: <sup>1</sup>H NMR spectra of bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] nickel (**4b Lig<sub>2</sub>Ni**).



analogue (**4a**), the  $\lambda_{\text{max}}$  showed by the complexes found to be less than the lignd **4a** at the same time the metals when attached with 4-bromo-3-methyl conjugated 8-HQ azo analogue (**4b**) they showed a good bathochromic shift than their ligand **4b**. Somehow this may be due to the nature of different functionalities present in the synthesized complexes. The overlay in UV-Visible spectra of the ligands and their respective metal complexes is illustrated in Figure 6.

### Magnetic susceptibility and LC-MS study

The magnetic susceptibility of **Co(II)** complexes at room temperature lies at a range 5.07 and 4.93 BM for **4a Lig<sub>2</sub>Co** and **4b Lig<sub>2</sub>Co** respectively suggests the tetrahedral geometry. The **Ni(II)** complexes for **4a Lig<sub>2</sub>Ni** and **4b Lig<sub>2</sub>Ni** showed magnetic moment at 2.97 and 3.09 BM whereas **Cu(II)** complexes at 1.99 and 1.83 BM respectively which is nearer to the reported value suggesting for the tetrahedral geometry.<sup>17,30</sup> The compounds **4a** and **4b** act as bidentate ligand by chelating to transitional metal ions to establish the proposed structure (**Scheme-1**).

The predicted molecular weight of the synthesized ligands and their complexes was confirmed by LC-MS. The compound bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] nickel (**4b Lig<sub>2</sub>Ni**) having molecular ion peak 739.3 (M<sup>+</sup>) strongly reveals the predicted molecular formula C<sub>32</sub>H<sub>22</sub>Br<sub>2</sub>N<sub>6</sub>NiO<sub>22</sub><sup>+</sup> (Figure 7).

### Antimicrobial screening

The antimicrobial activity of the synthesized compounds is investigated against *E. coli*, *K. pneumonia*, *S. aureus*, *C. albicans* and *C. neoformans*. The mean  $\pm$  S.D. of zone of inhibition for each microbial strain has been compared by one way-analysis of variance and the resulting *p* value (Table 1). Most of the complexes showed better zone of inhibition than their ligands. However the complexes **4a Lig<sub>2</sub>Cu** and **4b Lig<sub>2</sub>Cu** showed excellent significant antimicrobial activity in comparison

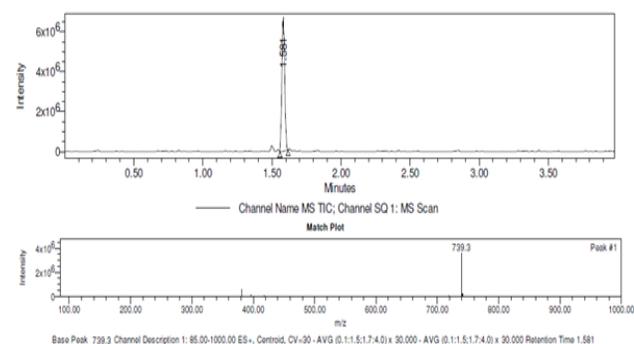


Figure 7: LCMS of bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] nickel (**4b Lig<sub>2</sub>Ni**).

to standard drugs. All the complexes showed potentially significant antimicrobial activity against *S. aureus* except **4b Lig<sub>2</sub> Ni**. However the gram positive bacterial strain *S. aureus* is found to be resistant towards the ligands **4a** and **4b**. The enhancement of antimicrobial activity of the ligands may be due to chelation of transitional metals with them. Complexation reduces the polarity of metal ion by coordinating with ligands and increases the lipophilicity of the metals.<sup>31</sup> Thus it facilitates the novel synthesized complex to penetrate the lipid cell membrane of microorganisms and inhibit their growth. No compounds showed any effective antimicrobial activity against *C. albicans*. However it is found to be observed that when the ligands are complexed with the respective metals showed pronounced antimicrobial activity even more than that of the reference antibiotics used. In our earlier reported research it is found to be observed that the (3-nitro phenyl and 4-bromo-3-methyl) 8-hydroxy quinoline azoanalogues showed no antimicrobial activity against *S. aureus* but when the same ligands coor-

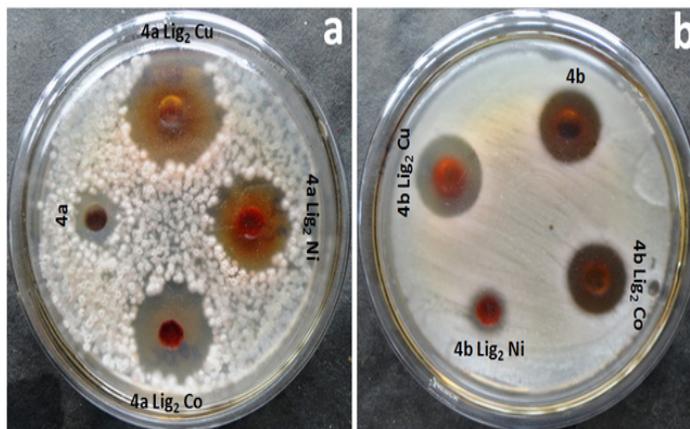
Compounds	<i>E. coli</i>	<i>K. pneumonia</i>	<i>S. aureus</i>	<i>C. albicans</i>	<i>C. neoformans</i>
<b>4a</b>	9.83 $\pm$ 1.84	-	-	14.17 $\pm$ 1.6	8.83 $\pm$ 1.17
<b>4b</b>	11.5 $\pm$ 1.23	21.67 $\pm$ 2.07*	-	12.33 $\pm$ 2.66	13.17 $\pm$ 2.23
<b>4a Lig<sub>2</sub> Cu</b>	16.5 $\pm$ 1.87*	19.5 $\pm$ 1.64*	17.17 $\pm$ 2.04*	21.5 $\pm$ 2.07*	21.33 $\pm$ 2.34
<b>4a Lig<sub>2</sub> Co</b>	16.83 $\pm$ 2.4*	16.67 $\pm$ 2.73	17.17 $\pm$ 3.6*	8.83 $\pm$ 1.33	17.5 $\pm$ 2.17
<b>4a Lig<sub>2</sub> Ni</b>	9.33 $\pm$ 2.25	8.83 $\pm$ 1.17	16.5 $\pm$ 3.21*	12.5 $\pm$ 1.23	13.67 $\pm$ 3.01
<b>4b Lig<sub>2</sub> Cu</b>	14.83 $\pm$ 2.56	18.17 $\pm$ 2.79*	19.5 $\pm$ 2.17*	21.5 $\pm$ 2.35*	27.5 $\pm$ 2.17*
<b>4b Lig<sub>2</sub> Co</b>	15.33 $\pm$ 4.76	17.17 $\pm$ 2.99	17.83 $\pm$ 1.6*	12.83 $\pm$ 2.23	15.83 $\pm$ 2.56
<b>4b Lig<sub>2</sub> Ni</b>	14.67 $\pm$ 3.45	16.5 $\pm$ 1.76	14.83 $\pm$ 3.13	8.67 $\pm$ 1.37	8.67 $\pm$ 1.37
RA	12.67 $\pm$ 1.51	15.33 $\pm$ 1.97	13 $\pm$ 1.67	19.33 $\pm$ 4.68	24.17 $\pm$ 1.94

Table 1: Antimicrobial activity (Zone of inhibition in mm) of novel synthesized transitional metal complexes derived from 8-HQ analogues against different microbial strains (mean $\pm$ S.D.)

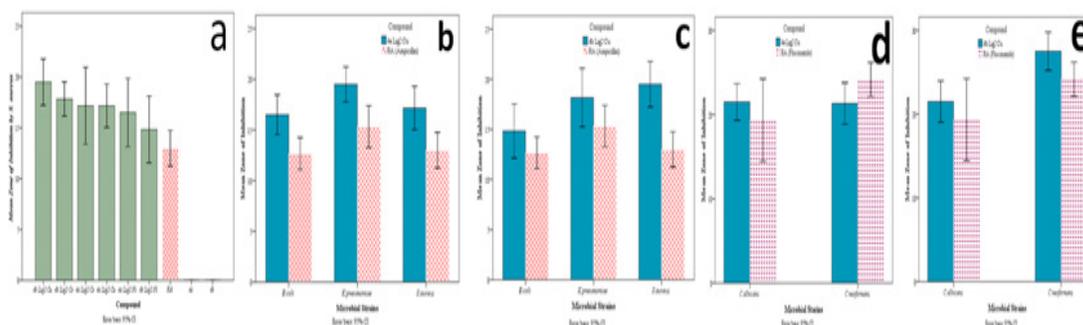
Results expressed in Mean $\pm$ S.D. (n = 6). The data were analyzed by One Way ANOVA followed by Dunnett's Post Hoc test, (statistical significance at \*p<0.05 in comparison to RA (Reference Antibiotic): Ampicillin (antibacterial); fluconazole (antifungal); - No zone of inhibition, *E. coli*-*Escherichia coli*; *K. pneumonia*-*Klebsiella pneumoniae*; *S. aureus*-*Staphylococcus aureus*; *C. albicans* - *Candida albicans*; *C. neoformans* - *Cryptococcus neoformans*.

minated with transitional metals showed tremendous significant antimicrobial activity. The antibiogram of the ligands **4a**, **4b** and their complexes are presented in Figure 8. The statistical interpretation of the complexes **4a Lig<sub>2</sub> Cu** and **4b Lig<sub>2</sub> Cu** against all the strains and the antimicrobial activity of all the compounds against *S. aureus* is explained with the help of error bars in Figure 9.

Minimum inhibitory concentrations  
 The inhibitory property of the novel synthesized 8-hydroxyquinolineazo analogues and their metal complexes was determined in terms of MIC ( $\mu\text{g mL}^{-1}$ ). The synthesized complexes **4aLig<sub>2</sub>Cu**, **4aLig<sub>2</sub>Co**, **4bLig<sub>2</sub>Cu** and **4bLig<sub>2</sub>Co** exhibited potential antimicrobial activity by inhibiting the growth of different microbial strains at MIC level  $31.25\mu\text{g mL}^{-1}$ . (Table 2).



**Figure 8: Antibiogram pattern of the transitional metal complexes of the ligands 4a and 4b against *C. neoformans* and *C. albicans* respectively.**



**Figure 9: Statistically interpreted antimicrobial activity of [all the synthesized compounds against *S. aureus* (a), **2aLig<sub>2</sub>Cu** and **2bLig<sub>2</sub>Cu** against different bacterial strains (b and c) respectively and **2aLig<sub>2</sub>Cu** and **2bLig<sub>2</sub>Cu** against different fungal strains (d and e) respectively] with the help of error bars.**

<b>Table 2: Minimum inhibitory concentration MIC (<math>\mu\text{g/ml}</math>) of novel synthesized transitional metal complexes derived from 8-HQ analogues against different microbial strains</b>					
<b>Compounds</b>	<b><i>E. coli</i></b>	<b><i>K. pneumonia</i></b>	<b><i>S. aureus</i></b>	<b><i>C. albicans</i></b>	<b><i>C. neoformans</i></b>
4a	>500	-	-	125	500
4b	125	31.25	-	125	125
4a Lig <sub>2</sub> Cu	31.25	31.25	31.25	31.25	31.25
4a Lig <sub>2</sub> Co	31.25	31.25	31.25	500	31.25
4a Lig <sub>2</sub> Ni	500	>500	31.25	125	125
4b Lig <sub>2</sub> Cu	31.25	31.25	31.25	31.25	31.25
4b Lig <sub>2</sub> Co	31.25	31.25	31.25	125	31.25
4b Lig <sub>2</sub> Ni	62.5	31.25	62.5	>500	>500

- No zone of inhibition, *E. coli*- *Escherichia coli*, *K. pneumonia*- *Klebsiella pneumonia*, *S. aureus* -*Staphylococcus aureus*; *C. albicans* - *Candida albicans*, *C. neoformans* - *Cryptococcus neoformans*.

## CONCLUSION

This research work comprises of the synthesis of a series of six complexes with their two respective ligands (**4a**) 5-((3-nitrophenyl) diazenyl) quinolin-8-ol and (**4b**) 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol. The synthesized complexes bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] copper (**4aLig<sub>2</sub>Cu**) and bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] copper (**4b Lig<sub>2</sub>Cu**) showed significant antimicrobial activity against most of the microbial strains. The observed antimicrobial effect reveals a strong structure activity relationship between the ligands and their respective complexes. It is found that introduction of transition metal **Cu(II)** to the above synthesized ligands may be responsible for exhibiting excellent antimicrobial activity against different microbial strains than the parent noncomplex ligands. Though other metal complexes also showed potential antimicrobial activities but particularly the **Cu(II)** attached ligands showed significant antimicrobial activities in comparison to the standard.

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## CONFLICT OF INTEREST

The authors have no conflict of interest.

## ABBREVIATION USED

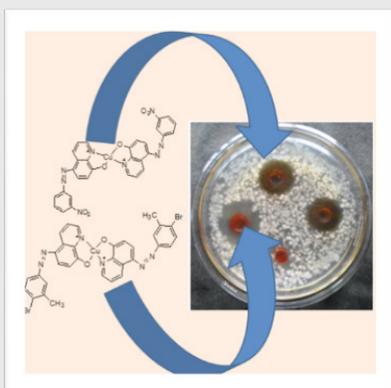
WHO: World Health Organization; 8-HQ: 8-Hydroxy quinoline; FT/IR: Fourier transform infrared spectroscopy; UV-Vis: Ultra violet visible spectroscopy; NMR: Nuclear magnetic resonance spectroscopy; LC-MS: Liquid chromatography and mass spectrometry; TLC: Thin layer chromatography; Lig: Ligand; BM: Bohr magneton; MIC: Minimum inhibitory concentration; MTCC: Microbial type culture collection; IMTECH: Institute of microbial technology; CFU: Colony forming unit; DMSO: Dimethyl sulphoxide; RA: Reference antibiotic.

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## PICTORIAL ABSTRACT



## SUMMARY

- A new series of metal complexes were synthesized from the ligands 5-((3-nitrophenyl) diazenyl) quinolin-8-ol and 5-((4-bromo-3-methylphenyl) diazenyl) quinolin-8-ol.
- The novel synthesized metal complexes are characterized to confirm their structural environment.
- The *in vitro* antimicrobial activity of the synthesized complexes was investigated against different microbial strain and results were statistically interpreted.
- It is found to be observed that the synthesized complex bis 8, 8' [5-((3-nitrophenyl) diazenyl) quinolinium] copper (**4aLig<sub>2</sub>Cu**) and bis 8, 8' [5-((4-bromo-3-methylphenyl) diazenyl) quinolinium] copper (**4bLig<sub>2</sub>Cu**) showed significant antimicrobial activity in comparison to standard (ampicillin/fluconazole).

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