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# Synthesis and Spectral Studies of 4,4′-(Hydrazine-1,2-diylidenedimethylylidene)-*bis*-(2-methoxyphenol) and Its Transition Metal Complexes with Promising Biological Activities

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The study describes the synthesis, characterization and biological activity of a novel Schiff base ligand and its transition metal complexes. The Schiff base ligand was obtained by a condensation reaction between 4-hydroxy-3-methoxybenzaldehyde (*p*-vanillin) and hydrazine hydrate using ethanol as solvent. A new series of Ni(II) and Fe(III) complexes were also derived by reaction of prepared Schiff base ligand with $NiCl_2$ and $FeCl_3$. Both the ligand and its metal complexes were characterized by solubility, melting point and elemental analysis. These compounds were further identified by analytical techniques, FTIR, NMR and mass spectrometry. The ligand and its transition metal complexes were also subjected to *in vitro* biological activities *i.e.* antimicrobial, antiangiogenic and DNA photo cleavage. For antimicrobial activity compounds were tested against two strains of bacteria and two strains of fungi. Different concentrations of prepared compounds were treated with fertilized chicken eggs and plasmid DNA to find out antiangiogenic and DNA photocleavage activity, respectively.

**Keywords: *p*-Vanillin, Schiff base, Hydrazine hydrate, Antimicrobial activity, Anti-angiogenic activity, DNA-photocleavage activity.**

## INTRODUCTION

Schiff bases has been characterized by presence of C=N linkage and usually are prepared by condensation reaction between carbonyl compound and primary amine. These condensation reactions are very effective due to good electrophilic property of the carbonyl toward amine group [1]. Hence Schiff bases has been found to established a unique position in the field of clinical and pharmaceuticals because of a wide range of activities. The biological activity includes antibacterial, antifungal, anti-inflammatory, antiproliferative, antiangiogenic, DNA-photocleavage, herbicides, nematicides. *etc*. [2]. Generally, Schiff bases have been widely used as ligands due to their high stability upon complexation with transition metals and their excellent solubility in common solvents [3]. Complexation actually results in movement of electrons from ligand to vacant *d*-orbitals of the metal atom or sometime from low oxidation state metals to ligands thus establish strong bonding through syngerstism [4]. That is why biological activity of many Schiff bases has been found to be increased upon complexation with metals especially with transition metals due to availability of vacant *d*-orbitals [5,6]. A wide range of Schiff base ligands and their transition metal complexes has been prepared in last many years but still there is a need to synthesize new Schiff bases with unique activities. Actually due to regular use of antibiotics, microbes have acquired resistance towards many available antimicrobials. As a result, researchers have been forced to increase the variety of drugs. So there is a need to incorporate Schiff base ligands and their transition metal complexes into variable and effective mode of medication. The researches have proved that the spectrum of drugs can be increased by complexation of Schiff base ligands with transition metals [7,8]. Various types of carbonyl compounds and amines have been used to prepare different Schiff base ligands. The study of previous decades showed the high activity and efficiency of vanillin compounds towards diseases like tumor, bacterial and fungal growth regulators [9-11].

This inspires to prepare a new novel Schiff base ligand and metal complexes so that the choice of biological drugs can be increase to reduce the effect of disease. 4-Hydroxy-3-

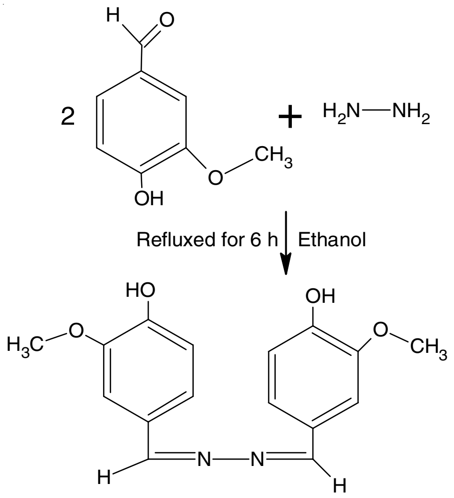
methoxybenzaldehyde (*p*-vanillin) is a natural compound with phenolic, aldehyde and ether group obtained from vanilla bean. It exists in the form of position isomer and also induces mutations which result in enhancement of chromosomal aberrations in living system [12,13]. The condensation product of vanillin and an amine exhibit excellent biological activity and very good complexation ability with transition metal atoms [14-16]. Hence, a new Schiff base ligand has been prepared by condensation reaction between 4-hydroxy-3-methoxybenzaldehyde (*p*-vanillin) and hydrazine hydrate. The Schiff base ligand has been reacted with $NiCl_2$ and $FeCl_3$ to synthesize its transition metal complexes which shows very good complexation ability [17-19].

The structures of Schiff base ligands and its transition metal complexes were assigned on the basis of solubility, melting point, elemental analysis, FTIR, NMR and mass spectrometry. The compounds were also screened for various biological activities. Antimicrobial activity was assayed by using disc diffusion method against four different species of bacteria and fungi. The compounds were also screened for antiangiogenic and DNA-photocleavage activities, where antiangiogenic was done by using fertilized chicken eggs while DNA-photocleavage activity was observed by agarose gel electrophoresis method.

## EXPERIMENTAL

All the chemicals used in synthesis were of A.R. grade and used as received without any further purification. All the chemical reactions for preparation of Schiff base were performed on magnetic stirrer equipped with a hot plate and all reactions to synthesize metal complexes were performed on water bath with water condenser using ethanol as solvent. The ligand was purified with methanol before preparation of metal complexes. The melting point of raw material was determined using open capillary method. Micro spectra for determining C, H and N were performed using Perkin-Elmer 2400 CHN elemental analyzer. $^1H$ NMR spectra were recorded on BRUKER AVANCE II spectrophotometer at frequencies of 400 MHz using DMSO as solvent and TMS as internal reference standard. The $^1H$ NMR chemical shifts were expressed in ppm. IR spectra were recorded on Perkin Elmer FT-IR Spectrometer in 4000-400 $cm^{-1}$ range using KBr pellet. Mass spectra were obtained on WATERS, Q-TOF MICROMASS (ESI-MS) mass spectrometer. Biological activities *viz.* antimicrobial, antiangiogenic and DNA-photocleavage activity were done by using disc diffusion assay, CAM assay and agarose gel electrophoresis method, respectively.

**Synthesis of Schiff base ligand:** 4-Hydroxy-3-methoxybenzaldehyde (2 mol) was added to 20 mL of ethanol in 100 mL round bottom flask. The content was dissolved at room temperature with hand shaking. To this solution, 1 mol of hydrazine hydrate was added. The content was refluxed on a water bath with a water condenser for 6 h. A dark yellow solid was obtained. The product was filtered and dried in a vacuum desicator over silica (**Scheme-I**). The product was purified several times by using methanol. The prepared Schiff base was soluble in DMSO and DMF. Dark yellow crystals, yield: 70%, m.p.: 256 ºC, IR (KBr, $\nu_{max}$, $cm^{-1}$): 1650 (s), (C=N); 1235 (s), (C=O); 3408 (br, OH). $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ ppm: 6.8-7.7 (m, 3H, -Ph); 8.5 (s, 1H, CH=N) 8.2 (s, 1H, O-H); 3.8 (Br, 3H, O-$CH_3$). MS (relative intensity): *m/z* value $[M]^+$ calcd. (found): 300.5 (300). Anal. calcd. (found) % for $C_{16}N_2H_{16}O_4$, C, 64.00 (64.20), H, 5.33 (5.30), N, 9.33 (9.40), O, 21.30 (21.10).

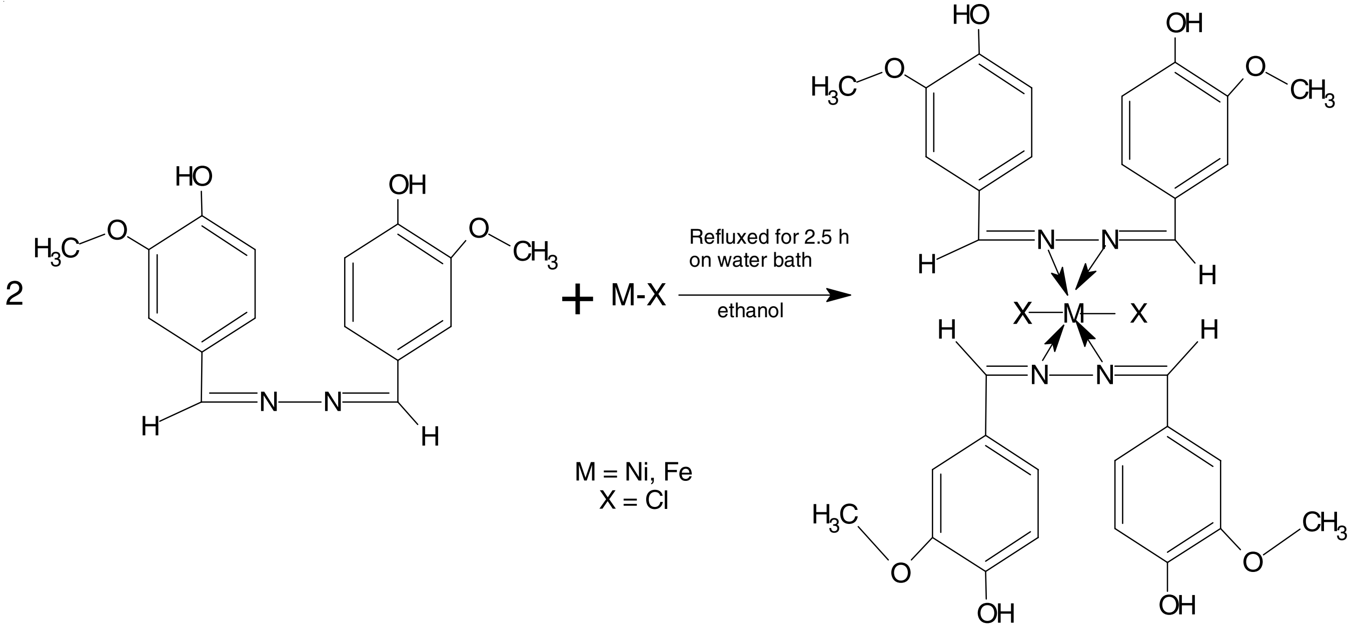


**Scheme-I:** Preparation of ligand

**Synthesis of nickel (II) complex:** Schiff base ligand (2 mol) was introduced in 250 mL round bottom flask which contains 20 mL of hot ethanol. The content was mixed thoroughly. To this mixture 1 mol $NiCl_2$ was added and the resulting solution was refluxed on water bath for 2.5 h using a water condenser. The precipitate was filtered off, washed with methanol several times and dried over silica in a vacuum desicator (**Scheme-II**). The synthesized metal complex was soluble in DMSO and DMF. Yield: 88%, IR (KBr, $\nu_{max}$, $cm^{-1}$): 1614 (s), (C=N); 1250 (s), (C=O); 3465 (br, OH); 444 (s, M-N). $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ ppm: 7.4-8.0 (m, 3H, -Ph); 8.4 (s, 1H, CH=N); 8.1 (s, 1H, O-H); 3.6 (Br, 3H, $OCH_3$). MS (relative intensity): *m/z* value $[M]^+$ calcd. (found): 729.6 (730). Anal. calcd. (found) % for $C_{32}N_4H_{32}O_8NiCl_2$: C, 52.63 (52.60); H, 4.39 (4.40); N, 7.68 (7.66); O, 17.54 (17.53); Ni, 8.04 (8.07).

**Synthesis of iron(III) complex:** Schiff base ligand (2 mol) was introduced in 250 mL round bottom flask which contains 20 mL of hot ethanol. The content was mixed thoroughly. To this mixture 1 mol $FeCl_3$ was added and the resulting solution was refluxed on water bath for 2.5 h using a water condenser. The precipitate was filtered off, washed with methanol several times and dried over silica in a vacuum desicator (**Scheme-II**). The synthesized metal complex was soluble in DMSO and DMF. Yield: 53%, IR (KBr, $\nu_{max}$, $cm^{-1}$): 1573 (s, C=N); 1599 (s, C=O); 3420 (br, OH); 455 (s, M-N). $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ ppm: 7.2-7.9 (m, 3H, -Ph); 8.7 (s, 1H, CH=N); 8.0 (s, 1H, OH); 3.4 (Br, 3H, $OCH_3$). MS (relative intensity): *m/z* value $[M]^+$ calcd. (found): 727.3 (727). Anal. calcd. (found) % for $C_{32}N_4H_{32}O_8FeCl_3$: C, 52.83 (52.80); H, 4.40 (4.42); N, 7.71 (7.73); O, 17.61 (17.59); Fe, 7.68 (7.66).

**Biological studies:** As described [20,21], disc diffusion assay was applied for antimicrobial activity, CAM assay was adopted for antiangiogenic activity and agarose gel electrophoresis method by using supercoiled DNA pUC19 was applied for DNA photocleavage activity.



**Scheme-II:** Preparation of Ni and Fe complexes

## RESULTS AND DISCUSSION

Schiff base ligand was prepared by condensation reaction between 4-hydroxy-3-methoxybenzaldehyde (*p*-vanillin) and hydrazine hydrate. Synthesized Schiff base ligand was then allowed to react with $NiCl_2$ and $FeCl_3$ to prepare respective metal complexes. The synthesized Schiff base ligand and its transition metal complexes were intensely coloured. The solubility test for Schiff base and its metal complexes in different solvents, established their solubility in ethanol, DMSO and DMF. Both Schiff base and metal complexes were obtained in good yield. After that spectroscopic and elemental analysis was done to confirm the authenticity of the products. Hence, the structure of the compound established on the basis of combined use of IR, NMR spectroscopy and mass spectrometry.

**FTIR spectral analysis:** IR spectroscopy provides information regarding the nature of functional groups present in Schiff base ligand and metal complexes. A sharp peak at 1650 $cm^{-1}$ for ν(>C=N) linkage supported the condensation reaction between *p*-vanillin and hydrazine hydrate [22]. This value of imine linkage get shifted to 1614 and 1573 $cm^{-1}$, indicated that the nitrogen atom take part in coordination with Ni and Fe ion. In addition, broad band at 3465 and 3420 $cm^{-1}$ confirmed the existence of hydroxyl group *i.e.* ν(OH) in the spectra of metal complexes [23]. However the corresponding strong absorption of ν(OH) for ligand was found to exhibit at 3408 $cm^{-1}$. Presence of these absorption bands in ligand and metal complexes specify that the phenolic -OH did not participate in bond formation with metals. The far IR spectra of complexes have shown ν(OH) bands in the region 455-444 $cm^{-1}$ region. This occurrence indicates the coordination between metals and lone pair of electron on nitrogen atom of the ligand [24,25].

**NMR spectral analysis:** Structures of Schiff base ligand and its metal complexes were further confirmed on the basis of NMR spectra where ligand shows a singlet at δ 8.5 ppm corresponding to proton of azomethine group [26] and this singlet was appear at δ 8.4 and δ 8.7 ppm after complexation with metals. A multiplet between δ 6.8-7.7 ppm due to phenyl protons of benzene ring was observed in spectra of ligand, between δ 7.4-8.0 ppm for Ni(II) and between δ 7.2-7.9 ppm was found in the spectra of Fe(III) complex [27]. Similarly, a band at 8.2 confirmed the presence of -OH moiety on the aromatic ring. Presence of methoxy group was shown by a strong band at δ 3.8 ppm while this band occupied values at δ 3.6 and δ 3.4 ppm for methoxy groups of metal complexes [28].

**Mass spectral analysis:** The mass spectral analysis confirmed the molecular formula and proposed structure of Schiff base ligand and its metal complexes. The molecular ion peak attributed to parent ligand with molecular formula, $C_{16}H_{16}N_2O_4$ at 300 *m/z*, indicated the formation of a hydrazone Schiff base. In addition to the peak due to molecular ion, the mass spectra also exhibit peaks assigned to various fragments obtained after thermal cleavage of ligand. The peaks at 268 *m/z* for $C_{15}H_{12}N_2O_3$ and at 151 *m/z* for $C_8H_9NO_2$ give an idea about the stability of fragments (Fig. 1). The mass spectra of metal complexes have shown peak at *m/z* 729.6 and *m/z* 727.3 for nickel(II) and iron(II) complexes, respectively which also has confirmed the presence of metal atoms in ligand and hence prove that coordination indeed occur.

**Antimicrobial activity using disc diffusion assay:** The antimicrobial activity (Table-1) outlines the results obtained for the inhibition zones generated by the synthesized Schiff base and its transition metal complexes. The activity was resolute *in vitro* against two different strains of bacteria (*S. aureus* and *K. pneumoniae*) and two strains of fungi (*A. niger* and *Trichophyton rubrum*) in terms of zone of inhibition in mm. In the study, the zone of inhibition have been found between 12-20 mm for ligand while in case of transition metal complexes it ranged between 14-22 mm for Ni and 14-23 mm

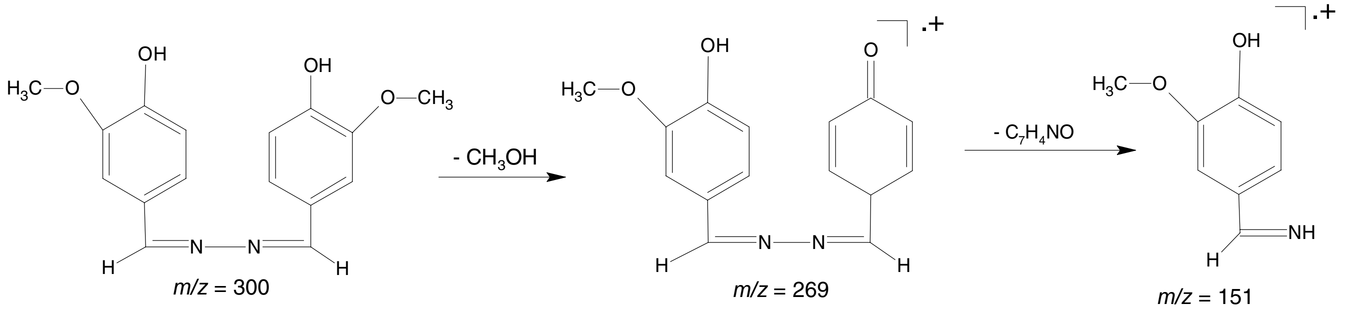


Fig. 1. Proposed mass fragmentation pattern of ligand

TABLE-1
ANTIMICROBIAL RESULT OF HYDRAZONE SCHIFF BASE LIGAND AND ITS NI AND FE COMPLEXES

| Hydrazone Schiff base | Zone of inhibition (mm) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bacterial strains | | | | | | | | Fungal strains | | | | | | | |
| | *S. aureus* | | | | *K. pneumoniae* | | | | *A. niger* | | | | *Trichophytonrubrum* | | | |
| Dosages (ppm) | 100 | 150 | 200 | 250 | 100 | 150 | 200 | 250 | 100 | 150 | 200 | 250 | 100 | 150 | 200 | 250 |
| Ligand | 12 ± 0.5 | 14 ± 0.7 | 15 ± 0.4 | 18 ± 0.6 | 13 ± 0.5 | 15 ± 0.7 | 16 ± 0.5 | 19 ± 0.7 | 13 ± 0.5 | 14 ± 0.7 | 17 ± 0.5 | 18 ± 0.5 | 12 ± 0.7 | 13 ± 0.5 | 16 ± 0.5 | 20 ± 0.6 |
| Ni complex | 14 ± 0.5 | 15 ± 0.7 | 17 ± 0.6 | 20 ± 0.4 | 16 ± 0.5 | 17 ± 0.5 | 20 ± 0.7 | 22 ± 0.6 | 14 ± 0.6 | 17 ± 0.4 | 19 ± 0.7 | 21 ± 0.7 | 15 ± 0.6 | 17 ± 0.5 | 19 ± 0.7 | 21 ± 0.4 |
| Fe complex | 16 ± 0.5 | 18 ± 0.7 | 18 ± 0.6 | 23 ± 0.4 | 15 ± 0.5 | 17 ± 0.5 | 20 ± 0.7 | 21 ± 0.6 | 14 ± 0.6 | 16 ± 0.4 | 19 ± 0.7 | 21 ± 0.7 | 17 ± 0.6 | 18 ± 0.5 | 19 ± 0.7 | 20 ± 0.4 |
| Standards solvent | 21 mm (Neomycin, 250 ppm); 2 mm | | | | 23 mm (Neomycin, 250 ppm); 3 mm | | | | 24 mm (Fluconazole, 250 ppm); 1 mm | | | | 9 mm (Fluconazole, 250 ppm); 2 mm | | | |

Data represented as the average mean of three values with ± 0.5 to ± 0.7 standard deviation.

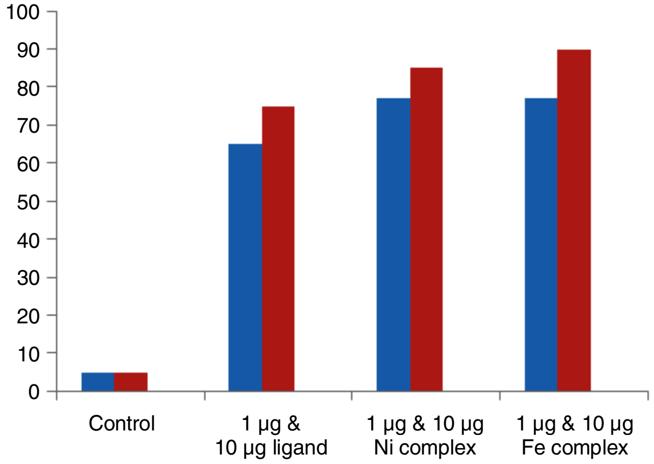


Fig. 2. Antiangeogenic activity of ligand and its Ni and Fe complexes

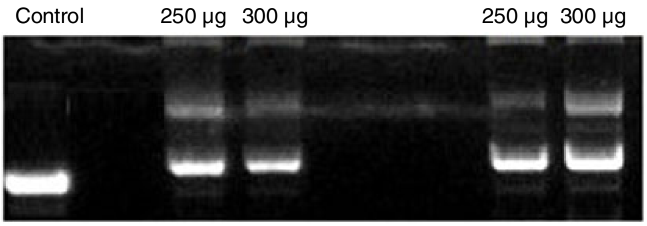


Fig. 3. DNA Photo-cleavage of transition metal complexes

for Fe ion for each treatment [29]. It can be deduced from the results that the Schiff base and its metal complexes exhibit moderate to high activity on growth of tested bacterial and fungal species when compared with common antibiotics *i.e.* neomycin and antifungal *i.e.* fluconazole. The antimicrobial results evidently show that the activity of metal complexes is higher than that of corresponding ligand. It means that complexation increases the antimicrobial activity, which can be explained on the basis of overtone and chelation theory.

**Antiangeogenic activity using chorioallantoic membrane (CAM) assay:** *Ex vivo* CAM assay was used to find the antiangeogenic activity of prepared Schiff base and its transition metal complexes. A scoring method was used to appraise the level of antiangiogenic activity of compounds by counting total number of blood vessels or undeveloped blood vessels over CAM in terms of branch points. The results (Fig. 2) clearly indicate that all the compounds were able to reduce the CAM microvessel formation. The percentage of inhibition was found to be 65, 77, 78 and 75, 85, 90 for 1 µg and 10 µg concentration of synthesized compounds. The significant differences were found on comparison with untreated control.

**DNA photo-cleavage assay using agarose gel electrophoresis method:** DNA cleavage activity of the synthesized Schiff base and their transition metal complexes was studied by agarose gel electrophoresis using supercoiled DNA from plasmid such as pUC19. The result obtained after analysis assures that proposed novel Schiff base ligand and their transition metal complexes have outstanding DNA cleaving and binding potential in comparison to ligand. It has been observed that (Fig. 3) metal complexes were able to convert super coiled plasmid DNA to open form, which was correlated with DNA cleaving activity of hydrazinecarboxamide based Schiff base using plasmid DNA [30,31]. Therefore, in near future novel DNA cleaving agent could play an important role in designing biological active drugs.

The result obtained after analysis assures that proposed novel Schiff bases and its transition metal complexes proved as excellent antimicrobial agents. The synthesized compounds are also acted as antiangeogenic and DNA photo-cleavage agents. Hence, the study is also helpful in synthesis of new biologically active compounds and in understanding their use as efficient drugs in the field of clinical and pharmaceuticals [31].

## Conclusion

A novel Schiff base and two new Schiff base complexes of Ni(II), Fe(III), have been synthesized. The Schiff base was synthesized by condensation reaction between 4-hydroxy-3-methoxybenzaldehyde (*p*-vanillin) and hydrazine hydrate in ethanol at 60 ºC. After that transition metal complexes of nickel and iron were prepared by reacting Schiff base with corresponding metal(II) chlorides. The Schiff base and its transition metal complexes were characterized by IR, $^1$H NMR and mass spectrometry. IR and NMR spectra indicate the formation of expected hydrazone Schiff base ligand and transition metal(II) complexes and mass spectra has confirmed it. The antimicrobial activity of Schiff base and its metal complexes have shown that they act as good antimicrobial agents against four different species of bacteria and fungi as well as a potent antiangiogenesis and DNA-photo cleavage agent.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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