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Synthesis, characterization, X-ray structures, and biological activity of some metal complexes of the Schiff base 2,2′-(((azanediylbis (propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol

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β-Carotene–linoleic acid assay

ABSTRACT

A pentadentate Schiff base, 2,2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**), has been synthesized via the reaction of salicylaldehyde with N^1-(3-aminopropyl)propane-1,3-diamine [$HN(C_3H_6NH_2)_2$] in absolute ethanol. Refluxing a mixture of **1** with the hydrated acetate salts of nickel(II), zinc(II), iron(II), and copper(II) affords each of the expected M(II)–Schiff base complexes. These complexes have been characterized by means of FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry as well as UV–Vis spectrophotometry and elemental analysis. In addition, the molecular structures of the copper(II) and nickel(II) complexes were determined by means of X-ray crystallography. Antioxidant and antibacterial activities of **1** and its complexes were evaluated in vitro. Highest DPPH radical-scavenging activity was observed for Fe(II)-**1** with an IC_{50} of 0.39 mg mL^{-1}, followed by **1** (IC_{50} = 3.38 ± 0.01 mg mL^{-1}). Use of the β-carotene–linoleic acid bleaching assay revealed that **1** has the highest antioxidant activity and has significant inhibition of lipid peroxidation with I% of 94.21 ± 0.003%, followed by Fe(II)-**1** and Ni(II)-**1** with I% of 34.29 ± 2.08% and 30.77 ± 1.91%, respectively. Antibacterial activity of **1** and its transition-metal complexes was investigated by use of disk diffusion assay; Zn(II)-**1** and Ni(II)-**1** exert a high inhibition of the growth of all bacterial strains with inhibition diameters ranging from 8 to 14 mm.

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1. Introduction

Schiff bases comprise an important class of organic compounds with a variety of uses; they have been extensively employed as ligands in the formation of transition-metal complexes [1]. In addition, Schiff bases exhibit a wide range of antibacterial, antifungal, and anti-inflammatory activity [2]. They have played an important role in the development of coordination chemistry, as manifested by a large number of publications, ranging from purely synthetic work to physicochemically [3] and biochemically relevant studies of metal complexes which have a wide range of applications [4–8]. Schiff bases containing heterocyclic moieties have interesting properties due to their diverse anticancer, antiviral, fungicidal, bactericidal, and anti-HIV activity [9]. Thus, the development of new chemotherapeutic Schiff bases is now attracting the attention of medicinal chemists [10].

Several research groups have been involved in the synthesis and biological screening of Schiff bases [2,9–12]. Zhou et al. [2] prepared a number of Schiff bases derived from 2-aminothiazoles and substituted benzaldehyde, and the in vitro antitumor activity of the resulting products toward three human tumor cell lines was evaluated. On the other hand, Ronad and co-workers [11] synthesized a series of Schiff bases from 7-amino-4-methylcoumarin and benzaldehydes; the anti-inflammatory and analgesic activities of some of the prepared compounds were comparable to or greater than a reference drug. A number of Schiff bases has been obtained

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by Bertinaria and colleagues [12] via the condensation of aromatic and heteroaromatic aldehydes with coumarin acetohydrazides under conventional and microwave conditions; the products displayed moderate to potent activity against different strains of bacteria. In a similar fashion, the synthesis and antiglycation activity of bis-Schiff bases of isatins have been described by Khan et al. [10], who observed a remarkable effect on antiglycation activity due to the presence of electron-withdrawing groups on isatin. Patel and Parmar [9] synthesized novel and optically active Schiff bases by treating substituted benzaldehyde with different amines; these workers discovered that the presence of nitro, methoxy, and halogen substituents on the phenyl ring increases the activity of the prepared compounds against bacteria. Quite recently [13], the synthesis and characterization of a number of new Schiff bases derived from metronidazole have been undertaken and their antigiardial and antimicrobial activity was evaluated. In addition, six Schiff bases, prepared by reaction of N^1-(3-aminopropyl)propane-1, 3-diamine with different derivatives of benzaldehyde, were evaluated in vitro for their antimicrobial activity against a number of pathogenic Gram-positive and Gram-negative bacteria as well as *Candida* by the twofold serial dilution method; some of these Schiff bases displayed significant anticandida activity with an MIC of 24 μg mL^{-1} and were judged to be promising and potential antifungal agents [14].

Schiff base–metal complexes have interesting biological properties; these species exhibit diverse biological activity as anticancer agents [15], bactericides [16], antiviral agents [17], and fungicides [18], and they display other biological properties [19]. Metal complexes of Schiff bases, synthesized from substituted salicylaldehyde and various amines, have been investigated extensively because of their wide applicability [20–23]; these Schiff bases normally coordinate to metal ions via the azomethine nitrogen [24]. Preparation, characterization, and biological activity of a number of Schiff base–metal complexes have been reported [25–30]. Furthermore, there has been considerable recent interest in transition-metal complexes formed by oxadiazole, triazole, and related ligands which are common components of some biologically important molecules [31]. In view of the broad interest in Schiff base–metal complexes, and owing to the substantial biological importance of these species, we describe herein the synthesis, characterization, and X-ray structures of some metal complexes of the pentadentate ligand 2,2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**), which can be prepared from salicylaldehyde and N^1-(3-aminopropyl)propane-1,3-diamine. Antioxidant and antibacterial activities of the Schiff base and of its metal complexes have been evaluated.

2. Experimental

2.1. Materials, methods, and instrumentation

Each of the following chemicals was purchased and used without further purification: N^1-(3-aminopropyl)propane-1,3-diamine [$HN(C_3H_6NH_2)_2$] and salicylaldehyde from Acros Organics; 2,2′-diphenyl-1-picrylhydrazyl (DPPH), β-carotene, linoleic acid, butylated hydroxy toluene (BHT), and TWEEN 40 from Sigma–Aldrich. Each of the following salts, used as received, was obtained from Fluka: nickel(II) acetate tetrahydrate, zinc(II) acetate dihydrate, iron(II) acetate tetrahydrate, and copper(II) acetate dihydrate. Using glass plates pre-coated with silica gel (E. Merck Kiesegel 60 F254, 0.25-mm layer thickness), we monitored the progress of reactions by means of thin-layer chromatography (TLC). Melting points (uncorrected) were measured in open capillary tubes with a Stuart Scientific melting point apparatus. Infrared spectra (IR) were obtained, as KBr disks, on a Nicolet-MAGNA-IR-560 spectrophotometer; characteristic peaks are reported in wavenumbers (cm^{-1}). We acquired ^1H and ^{13}C NMR spectra with the aid of a Bruker DPX 300-MHz spectrometer with DMSO-d_6 as solvent and TMS as the internal standard; chemical shifts are expressed in ppm. High-resolution mass spectra (HRMS) were obtained with an electrospray ion-trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7 Tesla) instrument. Samples were dissolved in acetonitrile, diluted in a spray solution (methanol-water 1:1 v/v containing 0.1% formic acid), and infused by use of a syringe pump at a flow rate of 2 mL min^{-1}. External mass calibration was conducted with monoprotonated arginine clusters in the mass range m/z 175–871. Elemental analyses (C, H, and N) were carried out with EuroVector EA3000 instrumentation, and the observed results agreed with the calculated percentages to within ±0.4%. Compounds were checked for purity with the aid of thin-layer chromatography; glass plates, precoated with silica gel (60GF254, Fluka) were employed.

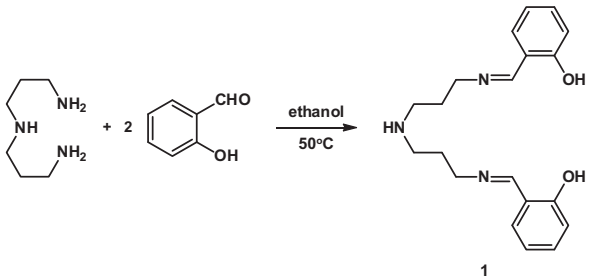
2.2. Synthesis of Schiff base **1**

We prepared the desired Schiff base, 2,2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**), as a yellow oil in 95% yield, according to a procedure [32] involving the reaction of N^1-(3-aminopropyl)propane-1,3-diamine (30 mL, 0.208 mol) with salicylaldehyde (50.7 g, 0.416 mol) in absolute ethanol (250 mL) as depicted in Scheme 1. We confirmed the structure of **1** by means of ^1H NMR, ^{13}C NMR, IR, and HRMS data, all identical with those found in the literature [32].

2.3. General procedure for preparation of Schiff base–metal complexes

Schiff base–metal complexes were synthesized according to the following modified general procedure outlined by Raman and coworkers [33]. A mixture of the Schiff base (0.0020 mol) and the metal salt (0.0010 mol)-[$Ni(OAc)_2{\cdot}4H_2O$], [$Cu(OAc)_2{\cdot}2H_2O$], [$Fe(OAc)_2{\cdot}4H_2O$], or [$Zn(OAc)_2{\cdot}2H_2O$]-in 25 mL of ethanol–distilled water (with the ligand–metal ratio kept at 2:1) containing a few drops of KOH (0.1%) was refluxed for 1–2 h. Cooling the mixture afforded the colored solid product, which was collected by filtration, washed several times with hot ethanol and distilled water, and dried in air. Using the same general procedure, we prepared the following complexes:

(a) Copper(II) complex. M.p.: 107–110 °C. UV–Vis (EtOH) λ_{max} (nm), ε_{max} [$M^{-1}\,cm^{-1}$]: λ_{max} (600), ε_{max} [641]. *Anal.* Calc. for $C_{20}H_{23}N_3O_2Cu$: C, 59.91; H, 5.78; N, 10.48. Found: C, 59.72; H, 5.73; N, 10.35%. HRMS (ESI) m/z: calcd. for $C_{20}H_{24}N_3O_2Cu$ $[M+H]^+$401.12645, found 401.11590. Single crystals, suitable for X-ray crystallography, were obtained by recrystallization from a 1:1 ethanol–water mixture.



1

Scheme 1. Pathway for preparation of the Schiff base, 2,2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**), from N^1-(3-aminopropyl)propane-1,3-diamine and salicylaldehyde.

(b) Nickel(II) complex. M.p.: 270–271 °C. UV–Vis (EtOH) λ_{max} (nm), ε_{max} [M^{-1} cm^{-1}]: λ_{max} (600), ε_{max} [23.3]. *Anal.* Calc. for $C_{20}H_{23}N_3O_2Ni$: C, 60.64; H, 5.85; N, 10.61. Found: C, 60.41; H, 5.92; N, 10.78%. HRMS (ESI) *m/z*: calcd. for $C_{20}H_{24}N_3O_2Ni$ $[M+H]^+$ 396.12220, found 396.12165. Single crystals, suitable for X-ray crystallography, were obtained by recrystallization from a 1:1 ethanol–water mixture.

(c) Zinc(II) complex. M.p.: 149–151 °C. UV–Vis (EtOH) λ_{max} (nm), ε_{max} [M^{-1} cm^{-1}]: λ_{max} (500), ε_{max} [1.41]; the zinc complex does not absorb at 600 nm. *Anal.* Calc. for $C_{20}H_{23}N_3O_2Zn{\cdot}H_2O$: C, 57.08; H, 5.99; N, 9.99. Found: C, 56.98; H, 6.03; N, 10.17%. HRMS (ESI) *m/z*: calcd. for $C_{20}H_{24}N_3O_2Zn$ $[M+H]^+$ 402.11600, found 402.11545. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.84 (m, 5H), 2.93–3.39 (m, 4H), 4.46 (m, 4H, CH=NCH_2), 6.47 (t, J = 7.1 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 7.02 (dd, J = 1.6, 1.6 Hz, 2H), 7.14 (t, J = 6.9 Hz, 2H), 8.04 (s, 2H, CH=N). ^{13}C NMR (DMSO-d_6): 29.8 (–CH_2–), 49.5 (NH–CH_2), 59.2 (=N–CH_2), 113.2, 119.1, 123.2, 133.4, 134.9, 168.3 (C_{arom}), 171.4 (HC=N). Recrystallization attempts yielded heavily twinned crystals; a crystal structure determination remains a future endeavor.

(d) Iron(II) complex. M.p.: 112–115 °C. UV–Vis (EtOH) λ_{max} (nm), ε_{max} [M^{-1} cm^{-1}]: λ_{max} (500), ε_{max} [2145]; λ_{max} (600), ε_{max} [719]. *Anal.* Calc. for $C_{20}H_{23}N_3O_2Fe$: C, 61.08; H, 5.89; N, 10.69. Found: C, 60.96; H, 5.97; N, 10.52%. HRMS (ESI) *m/z*: calcd. for $C_{20}H_{23}N_3O_2Fe$ $[M]^+$ 393.11397, found 393.11342. Efforts to grow a single crystal were unsuccessful.

2.4. Crystallographic measurements

Single-crystal X-ray diffraction data were collected with the aid of an Oxford Diffraction Xcalibur (Mo) X-ray source (λ = 0.71073 Å) at 273 ± 2 K. Collection and reduction of data, as well as cell refinement, were performed with the CrysAlisPro software package [34]. Empirical absorption corrections were applied with spherical harmonics implemented in the SCALE3 ABSPACK algorithm. We found that the nickel(II) and copper(II) complexes crystallize in the monoclinic space group $P2_1/c$. Crystal structures of these nickel(II) and copper(II) complexes can be described as asymmetric units with a metal coordinated to the ligand ($C_{20}H_{23}N_3O_2$); these structures were obtained with *R* values of 0.0354 and 0.0445, respectively. Crystal structures were solved with the aid of the Olex2 program [35] and refined with full matrix least-squares cycles by means of the F^2 SHELXL-97 program [36]. Hydrogens were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. All crystallographic plots were obtained with the aid of the Olex program. Selected crystal data and parameters for the nickel(II) and copper(II) complexes are given in Table 1.

Table 1
Crystallographic data and structure refinement details for Ni(II)-**1** and Cu(II)-**1** complexes.

	Ni(II)-**1**	Cu(II)-**1**
Empirical formula	$C_{20}H_{23}N_3O_2Ni$	$C_{20}H_{23}N_3O_2Cu$
Formula weight	366.77	400.97
Crystal color and morphology	Green plates	Dark green blocks
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Crystal size (mm)	0.75 × 0.49 × 0.02	0.60 × 0.37 × 0.22
a (Å)	12.0058(4)	10.6912(6)
b (Å)	14.0488(6)	16.5434(15)
c (Å)	11.3176(4)	10.7214(9)
β (°)	101.477(4)	98.680(6)
V (Å^3)	1870.7(2)	1874.6(3)
Z	2	1
ρ (mg m^{-3})	1.302	1.150
μ (mm^{-1})	0.57	0.10
F (000)	776	127
θ range (°)	3.43–25.00	3.12–25.00
Data collected (*hkl*)	±14, −16 to 15, ±13	−12 to 5, −10 to 19, −10 to 11
Reflections collected/unique	6779/3298	5138/2898
R_{int}	0.0322	0.0163
Data/restraints/parameters	3298/0/239	2898/0/239
Goodness-of-fit (GOF) on F^2	1.028	1.056
Final R_1, wR_2 [$I > 2(I)$]	0.0354, 0.0740	0.0594, 0.1114
R_1, wR_2 (all data)	0.0526, 0.0824	0.0445, 0.1023

2.5. Antioxidant activity

2.5.1. DPPH radical-scavenging activity

We measured the ability of the investigated compounds to donate a hydrogen atom or an electron on the basis of the bleaching of the purple-colored methanol solution of 2,2′-diphenyl-1-picrylhydrazyl (DPPH); this spectrophotometric assay uses the stable DPPH radical as a reagent [37]. An amount of 50 μL of various concentrations of the samples was added to 5 mL of a 0.004% solution of DPPH in methanol. After an incubation period of 30 min at room temperature, the absorbance was read against a blank at 517 nm with the aid of a Techcomp 8500 UV–Vis spectrophotometer. Inhibition of DPPH free radical in percent (*I*%) was calculated from the equation, $I\% = [(A_{blank} - A_{sample})100]/A_{blank}$, where A_{blank} is the absorbance of the control reaction (containing all reagents except the tested compound) and A_{sample} is the absorbance of the tested compound. We calculated the sample concentration providing 50% inhibition (IC_{50}) from a plot of *I*% versus concentration. Assays were carried out in triplicate.

2.5.2. β-Carotene–linoleic acid assay

Antioxidant activity of all compounds was evaluated by means of the β-carotene–linoleic acid model system [38]. A solution was prepared by dissolution of 4 mg of β-carotene in 2 mL of chloroform. One milliliter of this solution was placed into a 100-mL round-bottom flask. After the chloroform was removed at 40 °C under vacuum, 25 μL of linoleic acid, 200 mg of TWEEN 40, and 100 mL of distilled water were added to the flask with vigorous shaking. Aliquots (2.5 mL) of this emulsion were transferred into different test tubes containing 350 μL of 2 mg mL^{-1} of each tested compound. Absorbance at 490 nm was read at different times with a spectrophotometer. Inhibition of lipid peroxidation was calculated from the equation, $I\% = (A_{sample}/A_{BHT})100$, where A_{sample} is the absorbance of the compound and A_{BHT} is the absorbance of a sample with BHT (the latter serving as a standard).

2.6. Antibacterial activity

We used the following bacterial strains in the bioassays: (a) Gram-negative—*Acinetobacter baumanii* ATCC 19606 and *Citrobacter freundii* ATCC 8090; Gram-positive—*Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 10876, and *Enterococcus faecalis* ATCC 49452. Microorganisms were cultured overnight at 37 °C in a nutrient agar. Suspensions of the bacterial strains with an optical density of McFarland 0.5 were made in isotonic sodium chloride solution. Petri dishes of sterile Mueller–Hinton agar were seeded with the appropriate bacterial suspension. Sterile, 6-mm-diameter filter-paper disks were impregnated with the tested compound. Two other sterile blank disks, one impregnated with water and one with DMSO, were used as negative controls. After incubation for 24 h at 37 °C, all plates were observed for zones of growth inhibition, and the diameter of these zones was measured in millimeters. Additionally, and for comparative purposes, standard gentamicin (10 mg/disk) was included in the test as a positive control. For data analysis, the clear zone of inhibition around each disk was measured (in mm) and compared to a known sensitivity drug.

2.7. Statistical analysis

All determinations were conducted in triplicate and results were calculated as mean ± standard deviation (SD). Statistical analysis was performed with the aid of Student's *t* test for significance; differences were considered significant at $p \leqslant 0.05$.

3. Results and discussion

3.1. Chemistry

As depicted in Scheme 1, condensation of salicylaldehyde and N^1-(3-aminopropyl)propane-1,3-diamine in a 2 :1 M ratio, according to a published procedure [33], afforded the Schiff base, 2, 2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**). Full characterization of **1** was based on FT-IR, NMR, and mass spectrometry as well as elemental analysis. A strong absorption band at 1650 cm^{-1} attributable to azomethine (C═N) groups and a broad band at 3432 cm^{-1} due to phenolic (OH) groups were seen in the IR spectrum for **1**. Moreover, the ^1H NMR spectrum of **1** showed the azomethine protons (HC═N) as singlets at 8.36 ppm along with a complex set of multiplets in the range from 6.80 to 7.30 ppm that arise from aryl and phenolic protons.

Copper(II), zinc(II), nickel(II), and iron(II) complexes, with the general formula ML, were prepared by reaction of **1**, dissolved in ethanol, with an appropriate metal salt in a 2:1 ligand-to-metal ratio. These metal complexes were obtained as pure solids and were air stable. These newly synthesized complexes were characterized with the aid of elemental analysis and by IR, NMR (for the zinc(II) complex), and high-resolution mass spectral data; DEPT experiments were employed to differentiate secondary and quaternary carbons from primary and tertiary ones. Thus, the mass spectra display the correct molecular ion peaks, and the HRMS results are in good agreement with the calculated values. In addition, IR spectra for the synthesized complexes showed absorption bands that correspond to the different functional groups present. Taken together, these data, presented in detail in the experimental section, are consistent with the suggested structures.

3.2. Spectroscopic studies

To study the mode of binding of Schiff base to metal in the complexes, the IR spectrum of the free ligand was compared with the spectra of the various metal complexes. A comparison of the IR spectrum of the ligand with those of its metal(II) complexes revealed significant changes, as shown in Table 2. A wide absorption band of medium intensity in the range of 3316–3580 cm^{-1} observed in the IR spectrum for the Schiff base is due to the intramolecular linkage (OH···NH), whereas the sharp, intense band at 1650 cm^{-1} is attributed to the azomethine group (C═N). In the IR spectra for the metal complexes, the azomethine band is shifted to lower frequencies (1625–1640 cm^{-1}) [39], which indicates that the nitrogen atom of the azomethine group is coordinated to the metal ion. In addition, the new bands at 440–550 cm^{-1} and at 580–640 cm^{-1} confirm the nature of the metal–ligand bonding; these bands are assigned to M(II)–N and M(II)–O vibrations, respectively.

Electronic spectra of metal-free ligand and its copper complex (in ethanol) are dominated by intraligand transitions associated with functional groups of the ligand. Strong absorption bands around 222, 244, 268, and 365 nm for the copper(II) complex and 222, 244, 272, and 365 nm for the nickel(II) complex correspond to π–π^* and n–π^* transitions. On the other hand, the appearance of a weak, broad peak in the 525–730 nm region, in the visible spectrum of the nickel(II) complex, is due to the *d*–*d* electronic transition of the metal orbitals.

Table 2
Infrared absorption bands of ligand (**1**) and its copper(II), iron(II), nickel(II), and zinc(II) complexes.

Species	Absorption band, ν (cm^{-1})					
	ν(C═N)	ν(O–H)	ν(C═C)	ν(C–H)	ν(M–O)	ν(M–N)
1	1650	3432	1548	2941	–	–
Cu(II)-**1**	1640	–	1550	2925	580	525
Fe(II)-**1**	1625	–	1550	2925	600	440
Ni(II)-**1**	1625	–	1500	2925	600	475
Zn(II)-**1**	1640	3400	1550	2950	600	550

3.3. X-ray structure analysis

3.3.1. Crystal structures of nickel(II) and copper(II) complexes

Perspective views of the nickel(II) and copper(II) complexes are shown in Fig. 1. Selected geometric parameters are listed in Table 3 and selected distances and angles are given in Table 4. These two complexes crystallize in $P2_1/c$. For all of the newly prepared complexes, the ligand (**1**) acts as a pentadentate species, coordinating

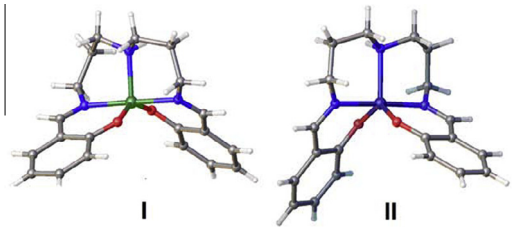
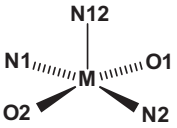


Fig. 1. Asymmetric units for nickel(II)- and copper(II)–Schiff base complexes: (**I**) Ni(II)-**1** and (**II**) Cu(II)-**1**.

Table 3
Selected bond lengths (Å) and bond angles (°) for copper(II) and nickel(II) complexes.

Cu(II)-**1**			
Bond lengths			
Cu(1)–N(1)	1.936(3)	N(2)–C(7)	1.279(8)
Cu(1)–O(2)	1.959(2)	N(2)–C(8)	1.442(8)
Cu(1)–N(2)	1.972(4)	C(14)–N(1)	1.267(5)
Cu(1)–O(1)	2.031(2)	N(12)–C(11)	1.462(7)
Cu(1)–N(12)	2.175(4)	N(12)–C(10)	1.483(7)
O(2)–C(20)	1.303(4)	N(1)–C(13)	1.477(5)
Bond angles			
N(1)–Cu(1)–O(2)	91.75(12)	N(1)–Cu(1)–N(12)	89.97(16)
N(1)–Cu(1)–N(2)	177.57(18)	O(2)–Cu(1)–N(12)	116.83(13)
O(2)–Cu(1)–N(2)	86.86(13)	N(2)–Cu(1)–N(12)	92.4(2)
N(1)–Cu(1)–O(1)	92.32(12)	O(1)–Cu(1)–N(12)	108.85(12)
O(2)–Cu(1)–O(1)	134.13(12)	C(11)–N(12)–C(10)	110.4(5)
N(2)–Cu(1)–O(1)	87.23(15)		
Ni(II)-**1**			
Bond lengths			
Ni(1)–O(2)	1.9611(19)	O(2)–C(20)	1.306(3)
Ni(1)–O(1)	1.9828(17)	O(1)–C(1)	1.314(3)
Ni(1)–N(1)	2.011(2)	N(1)–C(14)	1.280(3)
Ni(1)–N(2)	2.020(2)	N(1)–C(13)	1.473(3)
Ni(1)–N(12)	2.045(2)	N(12)–C(10)	1.476(3)
N(2)–C(7)	1.274(3)	N(12)–C(11)	1.479(3)
N(2)–C(8)	1.454(3)		
Bond angles			
O(2)–Ni(1)–O(1)	146.40(8)	O(2)–Ni(1)–N(12)	110.93(9)
O(2)–Ni(1)–N(1)	90.70(8)	O(1)–Ni(1)–N(12)	102.31(9)
O(1)–Ni(1)–N(1)	92.98(8)	N(1)–Ni(1)–N(12)	91.94(8)
O(2)–Ni(1)–N(2)	86.98(8)	N(2)–Ni(1)–N(12)	88.87(9)
O(1)–Ni(1)–N(2)	88.98(8)	C(10)–N(12)–C(11)	112.4(2)
N(1)–Ni(1)–N(2)	177.67(8)		

Table 4
Bond lengths (Å) and bond angles (°) for crystals of copper(II) and nickel(II) complexes.



M	Bond 1[a]	Bond 2[b]	N12M	Angle 1[c]	Angle 2[d]	Angle 3[e]
Cu	1.955	1.995	2.176(3)	89.49	89.59	102.02
Ni	2.016	1.972	2.045(2)	89.84	89.98	98.51

[a] Bond 1 = (N1M + N2M)/2.
[b] Bond 2 = (O1M + O2M)/2.
[c] Angle 1 = [(N1MO2) + (O1MN2)]/2.
[d] Angle 2 = [(N1MO1) + (O2MN2)]/2.
[e] Angle 3 = [(N1MN12) + (N2MN12) + (O1MN12) + (O2MN12)]/4.

through three nitrogen and two oxygen atoms, encircling the metal ion, and spanning itself in the equatorial plane. Distances and angles of the ligand are in agreement with the published structure of the ligand salt with chloride [40]. For both the nickel(II) and copper(II) complexes, the central metal ion attains a five-coordinate trigonal–bipyramidal geometry with a stereospecific N_3O_2 chromophoric center. For these two complexes, the equatorial positions are occupied by one (NH) aminic nitrogen atom and two hydroxy oxygen atoms (O1 and O2) lying in a square plane; the M–N and M–O bond lengths and the bond angles in the complexes are in agreement with the values reported in the literature [41,42]. According to Table 4, angles 1 and 2 for the nickel(II) and copper(II) complexes are close to 90°, which is consistent with a distorted trigonal–bipyramidal geometry. Dihedral angles between the N–N–N–M and N–N–O–O planes are 85.29° and 86.64°, respectively, for the nickel(II) and copper(II) complexes, respectively, which reveals the distortion from trigonal–bipyramidal geometry. In addition, the distorted geometry of the complexes can be determined by means of the index τ [43]. For an ideal trigonal bipyramid, τ is 0.67; in the case of the present nickel(II) and copper(III) complexes, τ = 0.52 and 0.72, respectively.

3.4. Biological activity

3.4.1. Antioxidant activity of the Schiff base and its metal complexes

Antioxidants can deactivate radicals by two major mechanisms: (a) hydrogen atom transfer (HAT) or (b) single electron transfer (SET). Usually, HAT-based methods are quite rapid (typically completed in seconds to minutes) and measure the classic ability of an antioxidant to quench free radicals by hydrogen atom donation. On the other hand, SET-based methods detect the ability of the potential antioxidant to transfer one electron to reduce a compound; these methods are usually slow and require a long time to reach completion [44]. Data obtained in this study clearly demonstrate that the prepared compounds are capable of scavenging a wide range of free radicals.

We employed the antioxidant properties of the ligand and its metal complexes using different in vitro methods to compare the results and to establish some structure–activity relationships for each method [45]. These studies were conducted with different concentrations of **1** and its metal complexes; BHT was used as a standard.

3.4.1.1. DPPH radical-scavenging activity. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable, violet-colored free radical often used to measure radical-scavenging activity; antioxidants react with DPPH, converting it to colorless 1,1-diphenyl-2-picrylhydrazine, and the degree of discoloration indicates the radical-scavenging ability of the antioxidant. Accordingly, we determined the reduction capacity of an antioxidant by measuring the decrease in absorbance of DPPH at 517 nm; data were obtained from a plot of the percentage scavenging ability of an antioxidant versus concentration [46,47]. Inhibitory effects of the Schiff base and its iron(II) and nickel(II) complexes on DPPH were concentration dependent, as displayed in Fig. 2. Results revealed that the Fe(II)-**1** complex exhibits good activity as a free-radical scavenger in comparison with **1** itself (Fig. 3). These results are in agreement with previous studies of metal complexes [48–51], in which the metal complex is more active than the ligand itself. Transition metal ions, such as nickel(II), copper(II), and zinc(II), may differ in their IC_{50} values and propensities for scavenging free radicals. In the present investigation, the iron(II) and copper(II) complexes were more potent in eliminating free radicals than the zinc(II) and nickel(II) species.

3.4.1.2. β-Carotene–linoleic acid method. For a subject system, free radicals, arising from the oxidation of linoleic acid, attack the highly unsaturated β-carotene, causing a decrease in the absorbance at 470 nm. Results presented in Fig. 4 show that **1**, Ni(II)-**1**, and Fe(II)-**1** inhibit the oxidation of β-carotene. After a reaction time of 24 h, it was found that **1** has the highest antioxidant activity with an *I*% of 69.72 ± 1.00%, followed by Fe(II)-**1** and then Ni(II)-**1** with *I*% values of 34.29 ± 2.08% and 30.77 ± 1.91%, respectively; on the other hand, Cu(II)-**1** exhibited no activity. Apparently, the presence of hydroxyl groups on the aromatic ring of **1** makes it a potent antioxidant that can be used as a potential drug for the prevention of diseases promoted by free radicals. In recent work, Liu [52] reported on the protective effects of hydroxyl-substituted Schiff bases against free radical-induced peroxidation of triolein in micelles, hemolysis of human red cells, and oxidation of DNA.

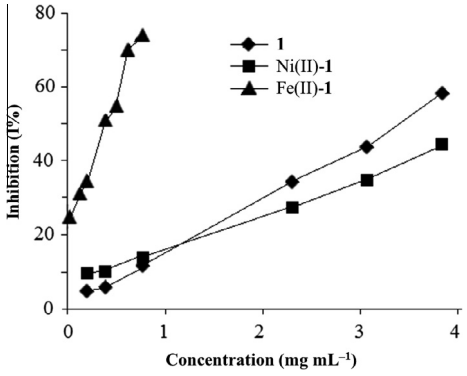


Fig. 2. DPPH radical-scavenging activity of ligand and complexes. Each value is expressed in terms of the mean and its standard deviation for a triplicate set of determinations.

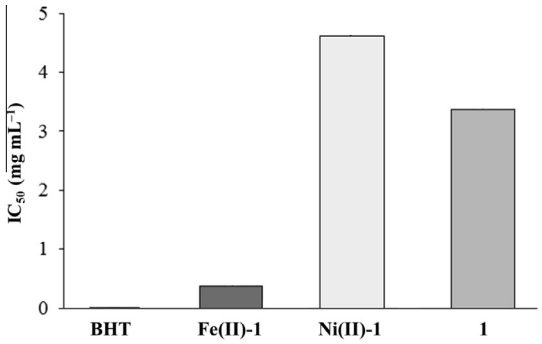


Fig. 3. IC_{50} inhibitory concentration of ligand and complexes for 50% of DPPH radical. Comparison was made against BHT: $p \leqslant 0.001$.

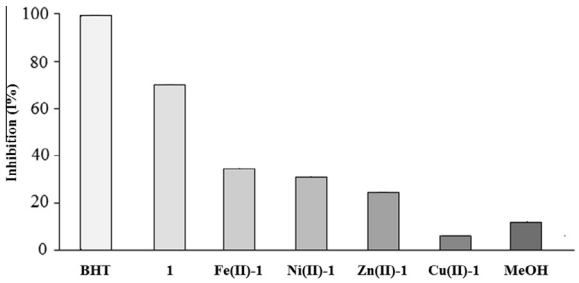


Fig. 4. Antioxidant activity of β-carotene bleaching in the presence of ligand and metal complexes, methanol, and BHT during 24 h. Each value is expressed as the mean of triplicate determinations.

Table 5
Diameters of inhibition zones of bacterial growth induced by **1** and its metal complexes, and by the antibiotic gentamicin.

	Diameter of inhibition zone (mm)[a]				
Bacterium	**1**	Zn(II)-**1**	Cu(II)-**1**	Ni(II)-**1**	gentamicin
A. baumanii ATCC 19606	–	9	–	9	11
C. freundii ATCC 8090	–	10	9.5	8.5	13
S. aureus ATCC 25923	14	12.5	12	10.5	33
B. cereus ATCC 10876	–	12.5	10	9.5	18
E. faecalis ATCC 49452	10	11.5	–	8	30

[a] The Fe(II)-**1** complex did not show any activity.

3.4.2. Antibacterial activity

Antibacterial activity of **1** and its metal complexes was determined by use of the agar-well diffusion method. We screened **1** and its complexes against five bacterial strains; results presented in Table 5 reveal that **1** and its complexes have some activity, but they were not as active as the standard drug (gentamicin). On the basis of criteria established by the Clinical Laboratory Standards Institute (CLSI) [53], all of the bacterial strains listed in Table 5 were resistant to **1** and its complexes with inhibition zone diameters ⩽14 mm. However, the results in Table 5 do reveal that **1** has a high inhibitory activity, that the Zn(II)-**1** and Ni(II)-**1** complexes are most active against both Gram-positive and Gram-negative bacteria, and that Fe(II)-**1** displays no inhibitory effect. In addition, the results demonstrate that **1** is most active against *S. aureus*, that Zn(II)-**1** is most active against *B. cereus* and *S. aureus*, and that Cu(II)-**1** is most active against *S. aureus*, whereas Ni(II)-**1** is least active against most strains. Furthermore, the antimicrobial activity profile of **1** and its metal complexes indicated that *S. aureus* is the most susceptible bacterium of all tested strains and that the activity is more pronounced on Gram-positive bacteria. This contrast in sensitivity between Gram-positive and Gram-negative bacteria might be related to differences in the morphological constitutions among these microorganisms. Gram-negative bacteria have an outer phospholipid membrane carrying the structural lipopolysaccharide components; this makes the cell wall impermeable to antimicrobial substances. Gram-positive bacteria, on the other hand, are more susceptible because they only have an outer peptidoglycan layer which is permeable [54,55].

4. Conclusions

We have synthesized the Schiff base, 2,2′-(((azanediylbis(propane-3,1-diyl))bis(azanylylidene))bis(methanylylidene))diphenol (**1**), by the reaction of salicylaldehyde with N^1-(3-aminopropyl)propane-1,3-diamine in absolute ethanol. Reaction of **1** with an appropriate metal salt of copper(II), iron(II), nickel(II), or zinc(II) affords metal complexes with the general formula ML. These metal complexes have been characterized with the aid of various spectroscopic methods, and the X-ray structures of the copper(II) and nickel(II) species were obtained. Both **1** and its ML complexes were (a) tested in vitro for their antioxidant activity by means of the DPPH and β-carotene–linoleic acid bleaching methods and (b) screened for their antibacterial activity against a number of Gram-positive and Gram-negative bacterial strains. Results revealed that Fe(II)-**1** exhibits the highest DPPH radical-scavenging activity with an IC_{50} of 0.39 mg mL^{-1}, whereas the β-carotene–linoleic acid bleaching assay revealed that the Schiff base–metal complexes have significant antioxidant activity.

Antibacterial activity of the Schiff base and its complexes was investigated by means of the disk diffusion assay; Zn(II)-**1** and Ni(II)-**1** exert high activity against the growth of all tested bacterial strains with inhibition diameters ranging 8 to 14 mm. In addition, inhibition zones of about 14 and 10 mm were exhibited by **1** against *S. aureus* ATCC 25923 and *E. faecalis* ATCC 49452, respectively, whereas Fe(II)-**1** did not show any inhibitory effect against tested strains.

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Appendix A. Supplementary material

CCDC 1000619 and CCDC 1000618 contain supplementary crystallographic data for the nickel(II) and copper(II) complexes, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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