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Synthesis, antimicrobial activity and modelling studies of some new metal complexes of Schiff base derived from sulphonamide drug in vitro

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ABSTRACT

Palladium(II) and cobalt(II) complexes of Schiff base derived from 4-aminobenzene sulfonamide (Sulfonamide drug) were prepared by convenient method. Reaction of sulfonamide with 2-hydroxy-1-naphthaldehyde gave the Schiff base compound **1** in good yield. Treatment of compound **1** with $CoCl_2.6H_2O$ and $PdCl_2$yielded new metal complexes **2** and **3**, respectively. The synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Bacillus cereus*, *Salmonella spp.* and *Staphylococcus aureus*. Additionally, the compounds were tested for antifungal activity against *Aspergillus niger* and *Candida albicans*. Some compounds exhibited good antibacterial and antifungal activity. Molecular modeling studies were performed and showed hydrogen binding and hydrophobic interactions.

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1. Introduction

It has been reported that the biologically active compounds show greater activity when administered as metal complexes than as free compound. The efficacy of the sulpha drugs can be enhanced upon co-ordination with a suitable metal ion [1]. Schiff bases are used as pigments and dyes, catalysts, intermediates inorganic synthesis and as polymer stabilizers. A number of Schiff's base molecules show biological activities including antibacterial, antifungal, antidiabetic, antitumor, antiproliferative, anticancer, anti-corrosion and anti-inflammatory activities [2-5]. Sulphonamides were the first drugs found to act selectively and could be used systematically as preventive and the therapeutic agents against various diseases [6].

Sulfur ligands are widespread among co-ordination components of biological transition metal complexes which possess many applications such as diuretic, antiglaucoma or antiepileptic drugs among others [7-9]. The use of metal complexes as chemotherapeutic drugs has become a vibrant and growing area of research in recent time.

Some of the metal based drugs already in market are *cis*-platin (anticancer drug), silverderma (silver complex of sulfadiazine for skin burn treatment), flammazine (zinc complex of sulfadiazine for animal burn) [10]. Saha *et al.* have reported the metal complexes of palladium(II) and platinum(II) of 3,5-dimethyl-2'-pyrimidyl)pyrazole as potent anticancer agents [11]. The aim of the present work was to synthesize some new metal complexes of Schiff base derived from sulfonamide drug and study of their biological activity as antimicrobial agents.

2. Experimental

2.1. Instrumentation

Melting points are uncorrected and were measured on a Philip Harris melting point apparatus and uncorrected. The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs. NMR spectra were recorded on 400 MHz spectrometers (Bruker, Germany) with TMS as an internal standard and on the δ scale in ppm. Mass spectra (EI, 70 eV) were recorded on MAT 8200 spectrometers (Finnegan MAT, USA).

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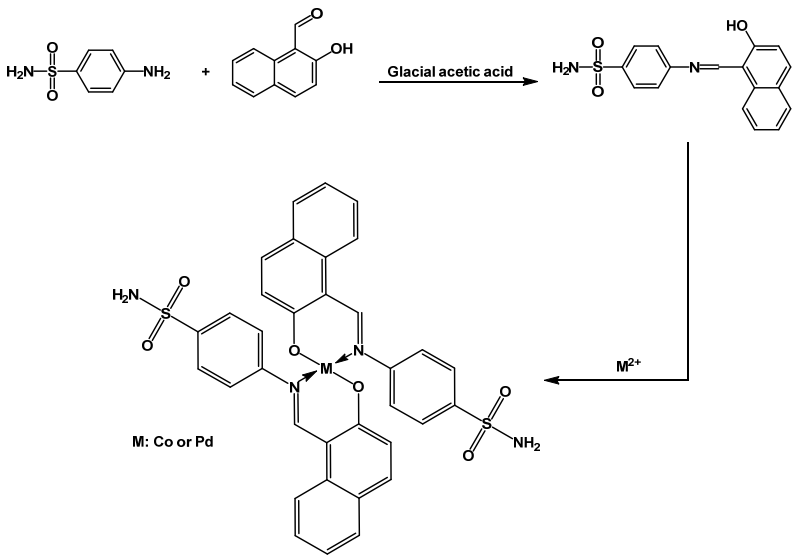


Scheme 1

2.2. Synthesis

2.2.1. Synthesis of Schiff-base, 4-{[(2-hydroxynaphthalen-1-yl)methylidene]amino}benzenesulfonamide (1)

To a solution of sulfonamide(1.37, 2.00 mmol) in EtOH (20 mL) was added ethanolic solution of 2-hydroxy-1-naphthaldehyde (0.76 g, 2.00 mmol) followed by addition of catalytic amount of glacial acetic acid drop wise and the mixture was heated under reflux for 3 h. The reaction mixture was then cooled in an ice bath and the crude product thus obtained was collected by filtration, further purified by recrystallization from ethanol gave compound **1** (Scheme 1). Color: Yellow. Yield: 78%. M.p.: 276-278 °C. FT-IR (KBr, ν, cm^{-1}): 3420-3335 (OH, NH), 3082-3063 (CH-aromatic), 1622 (C=C), 1602 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 15.46 (s, 1H, OH), 9.70 (s, 1H, CH=N), 8.52-7.01 (m, 10H, Ar-H), 7.43 (s, 2H, NH_2). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 171.5 (C, C-OH), 156.9 (C-CH=N), 147.2 (C, Ar-C), 141.9 (C, Ar-C), 138.1 (C, Ar-C), 133.5 (C, Ar-C), 129.5 (C, Ar-C), 128.7 (C, Ar-C), 127.6 (C, Ar-C), 127.2 (C, Ar-C), 124.2 (C, Ar-C), 122.6 (C, Ar-C), 121.2 (C, Ar-C), 121.0 (C, Ar-C), 109.3 (C, Ar-C). MS (EI, *m/z* (%)): 326 (M^+, 100).

2.2.2. Synthesis of cobalt complex (2)

Schiff base ligand **1** (5 mmol) was dissolved in 20 mL of ethanol solution, then 2.5 mmol of the $CoCl_2.6H_2O$ was added. A stirrer was inserted and the reaction mixture was heated to about 75-80 °C for 2 h. The precipitate that was formed filtered and washed severally with ethanol and dried in an oven at about 70 °C to yield cobalt complex **2** (Scheme 1). Color: Pale-green. Yield: 73%. M.p.: 195-196 °C. FT-IR (KBr,ν, cm^{-1}): 3395-3325 (NH), 3065, 3024 (CH-aromatic), 1627 (C=C), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.68 (s, 2H, 2CH=N), 8.53-7.11 (m, 20H, Ar-H), 7.45 (s, 4H, $2NH_2$). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 170.8 (2C, C-O), 159.50 (2C, CH=N), 147.2-109.3 (C-Ar). MS (EI, *m/z* (%)): 709 (M^+, 100).

2.2.3. Synthesis of palladium complex (3)

Palladium(II) complex was prepared in the same manner using $PdCl_2$ in place of $CoCl_2.6H_2O$ to yield palladium complex **3** (Scheme 1). Color: Yellow-brown. Yield: 77%. M.p.: 174-176 °C. FT-IR (KBr, ν, cm^{-1}): 3380-3317 (NH), 3057, 3023 (CH-aromatic), 1619 (C=C), 1605 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.52 (s, 2H, 2CH=N), 8.44-7.08 (m, 20H, Ar-H), 7.47 (s, 4H, $2NH_2$). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 167.6 (2C, C-O), 152.3 (2C, CH=N), 144.6-112.9 (C-Ar). MS (EI, *m/z* (%)): 758 (M^+, 100).

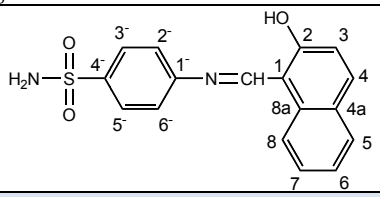
2.3. Antimicrobial activity

The synthesized compounds were screened *in vitro* for their antibacterial activity against: *Escherichia coli*, *Salmonella spp*., *Staphylococcus aureus*, *Bacillus cereus.* Additionally, the compounds were tested for antifungal activity against *Aspergillus niger* and *Candida albicans* using the paper disc-agar diffusion technique on Muller Hinton agar as a culture media for antibacterial activity [12]. The test compounds were dissolved in DMSO solvent and recommended concentrations (50, 100 and 200 µg/mL) were used in the disc-agar diffusion technique. Antibiotic drug ciprofloxacin and nystatin were used as control for bacteria and fungi, respectively. Petri plates containing 20 mL of Mueller Hinton Agar were used for all the bacteria tested. *Aspergillus niger* and *Candida albicans* strains were cultivated in Sabouraud dextrose agar. Sterile Whatman no. 1 filter paper disks (6 mm in diameter) impregnated with the solution in DMSO of the test was placed on the Petri plates. A paper disk impregnated with dimethylsulfoxide was used as negative control. The plates were incubated for 24 h at 37 °C in the case of bacteria and 72 h that 27 °C for fungi. The inhibition zone diameters were measured in millimeters. The bacteria and fungi were supplied from department of Microbiology, College of Veterinary Medicine, University of Basrah.

2.4. Molecular modeling analysis

The molecular docking was performed using SYBYL-X 1.1 and the docking results were shown by PyMOL [13]. Our molecular docking analysis of the new analogues based on the modelling study which was performed to understand the binding mode of these analogues with the aspartate aminotransferase (ATT) of *E. coli* [14] binding pocket (PDB code: 1ahg, [15]).

Table 1. HSQC data for Schiff-base of sulphanamide (L).



^{1}H (ppm)	^{13}C (ppm)	Assignment
9.70	156.9	C, H (CH=N)
8.50	121.0	C, H (5)
7.95	138.0	C, H (4)
7.93	128.0	C, H (3', 5')
7.81	121.5	C, H (2', 6')
7.80	130.0	C, H (7)
7.55	129.0	C, H (8)
7.38	125.0	C, H (6)
7.00	122.0	C, H (3)

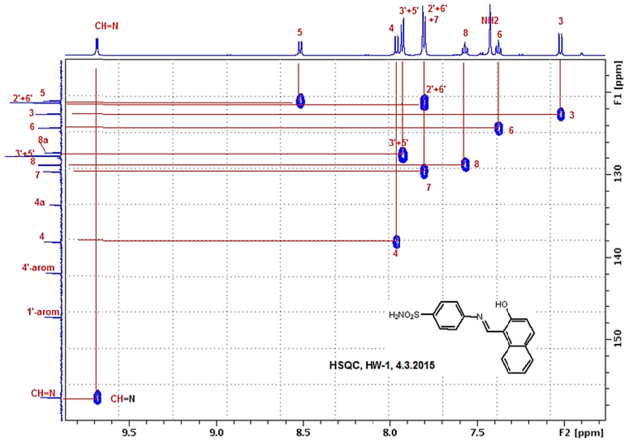


Figure 1. HSQC-NMR of Schiff base derived from sulfonamide.

3. Results and discussion

3.1. Chemistry

Treatment of 4-aminobenzenesulfonamide with 2-hydroxy-1-naphthaldehyde in ethanol and catalytic amount of glacial acetic acid under reflux afforded the desired imine derivative **1** in 78% yield, Scheme 1. The ligand **1** reacted with metal(II) ions; Co and Pd in 2:1 ratio forming complexes in good yields, Scheme 1. The structures of the synthesized compounds were assigned by the IR and ^{1}H, ^{13}C and 2D NMR and mass spectra.

The IR spectra displayed common features in certain regions and characteristic bands in the finger print and other regions. The spectra for all compounds were characterized by the presence of broad strong bands in the rang 3420-3317 cm^{-1} attributed to ν(O-H) and ν(N-H) for ligand **1** and NH symmetrical and unsymmetrical for compound **2** and **3**. The IR spectra confirm the presence of the azomethine group (-C=N) stretching with a sharp region around 1608-1605 cm^{-1}. In addition, the bands at the region 1627-1619 cm^{-1} were assigned to the C=C aromatic group.

In the ^{1}H NMR spectra of synthesized compounds **1**-**3**, the hydroxy proton were resonated as singlet at the regions δ 15.46 for compound **1**, which this signal disappear in complex compounds **2** and **3**. In the ^{1}H NMR spectra of compounds **1**-**3**, the singlets at δ 9.70, 9.68 and 9.52 ppm were assigned for the imino protons (CH=N). The multiplets at the regions δ 8.53-7.01 ppm were attributed to the aromatic protons.

In the ^{13}C NMR spectra of compounds **1**-**3**, the resonances at δ 171.5, 170.8 and 167.6 ppm, respectively, were assigned for the aromatic carbon atom (C-O). The spectra revealed the presence of CH=N group around δ 156.9, 159.5 and 152.3 ppm. The ^{1}H, ^{13}C HSQC NMR spectrum of Schiff base **1** showed a cross peak at δ_H/δ_C = 9.70/156.9 ppm due to azomethine group (N=CH). Thus, the correlation of protons and carbon in aromatic rings such as δ_H/δ_C = 8.52/121.0, 7.95/138.0 ppm and other positions can be assigned to the protons and carbon atoms of the aromatic ring, Table 1, Figure 1.

The gradient selected ^{1}H, ^{13}C HMBC-NMR spectrum of compound **1** revealed two $^{1,3}J_{C,H}$. Thus, the imino proton (CH=N) at δ 9.70 ppm showed two $^{1,3}J_{C,H}$ correlations: first one with C-1 of the naphthyl ring at δ 160.3 ppm, the second correlation with the aromatic carbon atom C-6' at δ 109.3 ppm and the last one with the aromatic carbon atom C-1' at δ 147.2 ppm. Other correlations between protons and carbon atoms can be assigned in Figure 2.

3.2. Antibacterial and antifungal activity

The synthesized compounds were screened for their *in vitro* antibacterial and antifungal activities, using the paper disc-agar diffusion technique by measuring the inhibition zone in mm [11]. The antibiotics, ciprofloxacin and nystatin were used as a control against bacteria and fungi, respectively. The antibacterial activity of the synthesized compounds were tested against two Gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and two Gram negative bacteria

Table 2. Antibacterial activity of some Schiff base and metal complex compounds.

Compound	Diameter of inhibition zone in mm for different microbial species											
	E. coli			*B. cereus*			*Salmonella spp.*			*S. aureus*		
	50 µg/mL	100 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL
1	-	18	22	-	20	22	-	-	9	-	-	18
2	-	-	-	-	-	18	-	-	-	-	-	15
3	-	-	7	-	-	-	7	9	10	7	12	15
Ciprofloxin	10			12			24			10		

Table 3. Antifungal activity of some Schiff base and metal complex compounds.

Compound	Diameter of inhibition zone in mm for different microbial species					
	A. niger			*C. albicans*		
	50 µg/mL	100 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL
1				-	20	22
2	-	-	-	-	-	18
3	-	-	7	-	-	-
Nystatin	15			12		

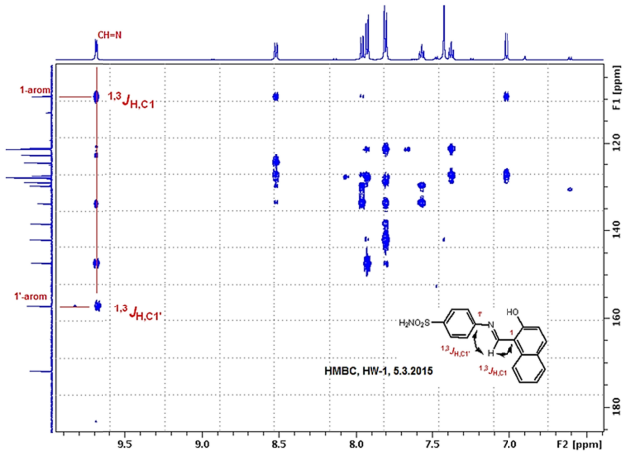


Figure 2. HMBC-NMR of Schiff base derived from sulfonamide.

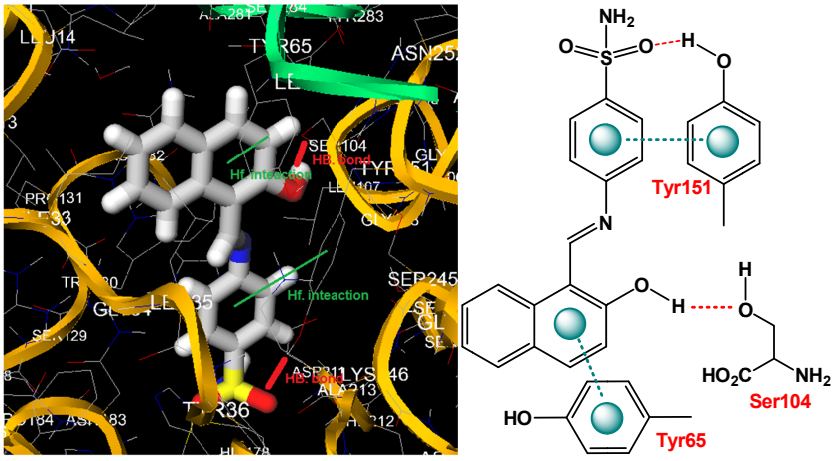


Figure 3. Docked conformation of compound **1** showing two hydrogen bonds: Tyr151 with one oxygen atom of SO_2 group, Ser104 OH group with hydrogen atom of the phenolresidue. It also exhibits hydrophobic interactions between phenyl ring of Tyr151 and aromatic ring of the phenylsulfonamide moiety as well as phenyl group of Tyr65 with phenol aromatic ring of AAT of *E. coli* enzyme residues.

(*Escherichia coli* and *Salmonella spp.*) at a concentration of 50, 100 and 200 µg/mL using DMSO as a solvent, which not effected the growth of microbes. Mueller Hinton agar was used as culture media for antibacterial activity. The results of the antimicrobial activity are shown in Tables 2 and 3.

All these compounds exhibited moderate to good activity against all the bacterial species. However, Schiff base **1** had the highest activity against *E. Coli* and *B. Cereus*, but compound **2** inactive against *E. Coli* and *Salmonella spp.,* inaddition to compound **3** which showed a moderate activity against *E. coli*, *S. cereus* and *Salmonella spp.* but inactive against *B. cereus*. It is worth noting that all compounds have activity against both Gram positive and negative bacteria. On the other hand, the antifungal activity of the synthesized compounds showed

moderate activity towards all the fungal species such as *Aspergillus niger* and *Candida spp*., except compounds **1** and **2** which exhibit no activity against *Aspergillus niger*.

3.3. Molecular modeling analysis

Compound **1** has been selected for the docking modeling study, since its binding energy score -8.3, with indicating a selectivity of phenyl azomethin and phenol groups in their binding to the enzyme pocket Figure 3. As shown in Figure 3, the aromatic ring of compound **1** was fitted into an aromatic rich sub-pocket surrounded by the aromatic side chains of Tyr151 and Tyr65, in addition to two hydrogen bondings. The synthesized molecule was located in the middle of the binding pocket, anchoring the oxygen atom of the SO_2 group in a favourable position for hydrogen bonding with the OH group of Tyr151, in addition to a hydrogen bonding between the oxygen atom of phenolic group and hydroxyl group for Ser104 of the aspartate amino transferase (AAT) enzyme. Overall, the combination of hydrophobic interaction andπ-stacking appears to govern the binding of compound **1** with AAT of *E. coli* [16].

4. Conclusion

In conclusion, some new cobalt(II) and palladium(II) complexes containing sulphanamide were prepared by convent method. The antimicrobial activity was evaluated against four bacterial strains and two fungal species. The synthesized compounds exhibited good antibacterial and antifungal activities. Molecular modeling studies were performed, showing the hydrogen bindings and hydrophobic interactions.

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