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Synthesis of New Unsymmetrical Schiff Bases as Potential Antimicrobial Agents

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Abstract

New unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) were synthesized by using a two-stage method. The starting Schiff bases were prepared by the reaction of 2-aminophenol (or 2-amino-4-methylphenol or 2-amino-4-chlorophenol) with 1-nitro-2-naphthaldehyde. In these compounds, the nitro groups were reduced to amino groups using selective reducing agent and then 2-hydroxybenzaldehyde were added. Thus, three new unsymmetric Schiff base ligands were obtained. The antimicrobial activity of the synthesized unsymmetric Schiff bases were evaluated against some pathogenic strains (*Shigella dysenteria type 7, Listeria monocytogenes 4b, Escherichia coli, Salmonella typhi H, Staphylococcus epidermis, Brucella abortus, Micrococcus luteus, Bacillus cereus sp., Pseudomonas putida sp.)* and yeast (*Candida albicans*).

Keywords: Unsymmetrical Schiff base, Reducing Agent $Na_2S_2O_4$, Antimicrobial activity

Potansiyel Antimikrobiyal Ajanlar Olarak Yeni Asimetrik Schiff Bazlarının Sentezi

Öz

Yeni asimetrik Schiff bazları (**L_{3a}-L_{3c}**) iki aşamalı bir yöntem kullanılarak sentezlendi. 2-aminofenol (veya 2-amino-4-metilfenol veya 2-amino-4-klorofenol) ile 1-nitro-2-naftaldehitin reaksiyonundan başlangıç Schiff bazları hazırlandı. Seçici indirgeyici ajan kullanılarak bileşiklerdeki nitro grupları amino gruplarına indirgendi ve 2-hidroksibenzaldehit eklendi. Böylece, üç yeni asimetrik Schiff baz ligandı elde edildi. Sentezlenen asimetrik Schiff bazlarının antimikrobiyal aktiviteleri, bazı patojenik suşlar (*Shigella dysenteria type 7, Listeria monocytogenes 4b, Escherichia coli, Salmonella typhi H, Staphylococcus epidermis, Brucella abortus, Micrococcus luteus, Bacillus cereus sp., Pseudomonas putida sp.)* ve maya (*Candida albicans*) karşısında değerlendirildi.

Anahtar Kelimeler: Asimetrik Schiff bazı, İndirgeyici ajan $Na_2S_2O_4$, Antimikrobiyel aktivite

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Introduction

Schiff bases contain azomethine groups (-CH=N-) and are synthesized from condensation between amines and active carbonyl compounds. Schiff bases have a wide range of applications. They are used as dyes, liquid crystals, catalysts, polymer stabilisers [1, 2]. Schiff bases are usefull as intermediate in enzymatic reactions [3]. Some Schiff bases have been used as corrosion inhibitors for various metals and alloys [4,5]. Several Schiff base complexes have also been shown to inhibit tumor growth [6,7]. Schiff bases ligands and their complexes have many biochemical, clinical, pharmacological and biological properties [8-10]. They show a broad range activities including antimalarial, antibacterial, antiviral, antitumor, antifungal, antimicrobial, anti-inflammatory, antioxidant, anticancer, antidiabetic, antiproliferative, antipyretic properties, analgesic and anti-HIV properties [11-18].

Recently, unsymmetric Schiff bases have aroused interest among researchers due to their special structures such as organic photovoltaics, chelating ionophores [19]. Unsymmetrical Schiff base complexes, where the metal atom is in an unsymmetrical ligand environment play an important role in many biological systems [20]. These compounds may be used as catalysts for various organic transformations, as promising materials for optoelectronic applications [21-23]. They can potentially serve as photoactive materials [4]. Unsymmetric Schiff bases have recently been investigated as corrosion inhibitors for various metals and alloys in acid media [5,24]. But, there are few studies on (–CH=N-aryl-CH=N–) type unsymmetrical Schiff bases due to the fact that they cannot be synthesized directly. These type of unsymmetric diimines with respect to the unsymmetrical nature of the imine bond were first reported by our group proposing a new two step method [25]. Afterwards, that study was followed by potentiometric, tautomeric and antimicrobial studies of these type of unsymmetric Schiff bases [26-31].

The synthesis and characterization of (–CH=N-aryl-CH=N–) type three new ligands are reported in this paper. The biological activities of all unsymmetrical Schiff bases against some bacteria and yeast strains are also examined.

Material And Methods

Chemicals

All substances were supplied from Sigma-Aldrich and used without further

purification. Elemental analyzes were determined using a Leco CHNS-932 analyzer. Infrared spectra were recorded on a Mattson-5000 FT-IR instrument. ^{1}H-NMR spectra were carried out on a Bruker Avance 500 MHz instrument. Mass spectra were acquired with an Agilent Technologies 6410 Triple Quad instrument.

General Procedure for Synthesis of Unsymmetrical Schiff Bases (L_{3a}-L_{3c})

The starting Schiff bases (**L_{1a}**) (or **L_{1b}** or **L_{1c}**) were prepared by adding 50 mmol of 2-aminophenol (or 2-amino-4-chlorophenol or 2-amino-4-methylphenol) to a stirred solution of 1-nitro-2-naphthaldehyde (50 mmol) in ethanol (100 mL) and heating for 1 hour at 60 °C as we described previously [31]. The unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) were synthesized by using a two-stage method, as shown in Fig. 1. In the first step, 2 mmol of the starting Schiff base (**L_{1a}**) (or **L_{1b}** or **L_{1c}**) were dissolved in 100 mL ethanol-water solution (1 : 1) at 70 °C. The nitro group of these starting Schiff bases was reduced to an amino group (**L_{2a}-L_{2c}**) with solid sodium dithionite as reducing agent. For this purpose, 5 mmol of solid sodium dithionite was slowly added to the solution in small portions over the course of 1 hour, then the mixture was stirred for a further 1 hour at 45 °C. Thus, the amino derivative of these Schiff bases was obtained in solution. In the second step, 2 mmol of 2-hydroxybenzaldehyde in 25 mL ethanol was added to this solution for obtaining the unsymmetric Schiff bases (**L_{3a}-L_{3c}**) and was heated to reflux for 2 hours at 55 °C. The mixture was evaporated at room temperature in about 1 day. The orange product was treated with warm water and filtered. The crude product was recrystallized from ethanol.

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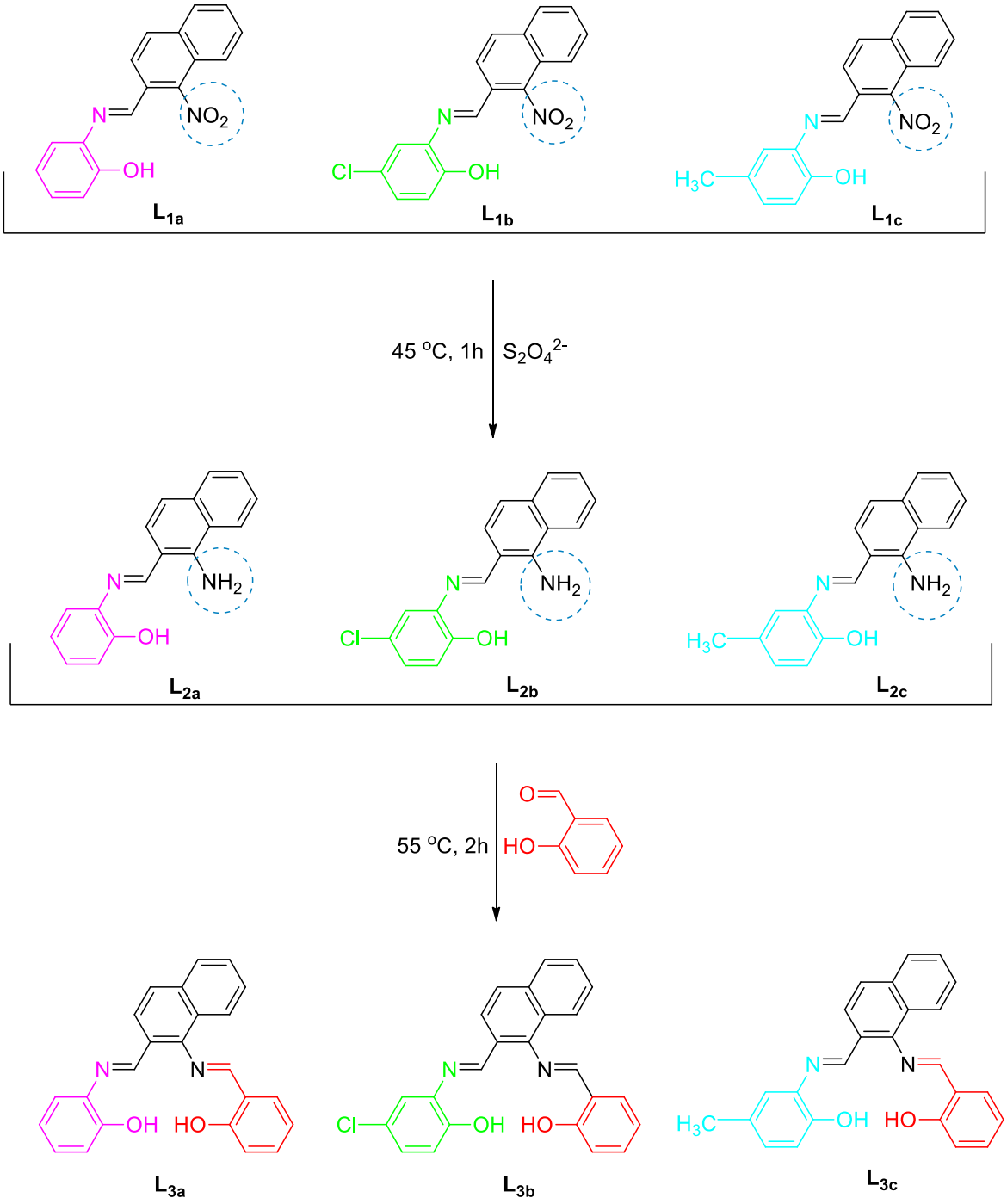

Figure 1. *Synthesis of unsymmetrical Schiff bases (**L**$_{3a}$-**L**$_{3c}$)*

(**L**$_{3a}$): It was obtained as a orange solid. Yield: 57%, m.p: 178 °C; IR (KBr, ν cm^{-1}): 3333 (OH), 3056 (CH)$_{arom.}$, 1610, 1600 (C=N), 1528-1456 (C=C)$_{ring}$; ^{1}H-NMR (500 MHz, DMSO-d$_6$, δ ppm): 9.88 (s, 1H, OH), 9.72 (s, 1H, CH=N), 9.57 (s, 1H, CH=N), 6.10-8.20 (m, arom.-H); MS m/z: 367.2 [M+H]$^+$. Anal. calcd. for $C_{24}H_{18}N_2O_2$: C, 78.69, H, 4.92, N, 7.65; found: C, 77.46, H, 4.74, N, 7.26.

(**L_{3b}**): It was obtained as a orange solid. Yield: 63%, m.p: 190 °C; IR (KBr, ν cm^{-1}): 3386 (OH), 3044 $(CH)_{arom.}$, 1604, 1588 (C=N), 1545-1460 $(C=C)_{ring}$; ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 9.96 (s, 1H, OH), 9.53 (s, 1H, CH=N), 8.85 (s, 1H, CH=N), 6.35-8.45 (m, arom.-H); MS m/z: 401.9 $[M+H]^+$. Anal. calcd. for $C_{24}H_{17}N_2O_2Cl$: C, 71.91, H, 4.24, N, 6.99; found: C, 73.85, H, 3.41, N, 6.02.

(L_{3c}): It was obtained as a orange solid. Yield: 61%, m.p: 200 °C; IR (KBr, ν cm^{-1}): 3330 (OH), 3054 $(CH)_{arom.}$, 1611, 1600 (C=N), 1545-1460 $(C=C)_{ring}$; ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 13.55 (s, 1H, OH), 10.16 (s, 1H, OH), 9.89 (s, 1H, CH=N), 9.65 (s, 1H, CH=N), 6.81-8.49 (m, arom.-H), 2.50 (s, CH_3); MS m/z: 381.2 $[M+H]^+$. Anal. calcd. for $C_{25}H_{20}N_2O_2$: C, 78.95, H, 5.26, N, 7.37; found: C, 77.88, H, 5.09, N, 6.88.

Investigation of Antimicrobial Activity

The unsymmetrical Schiff bases were studied for their antimicrobial with antifungal efficacy using well-diffusion method against *Shigella dysenteria type 7* (NCTC-9363), *Listeria monocytogenes 4b* (ATCC 19115), *Escherichia coli* (ATCC 1230), *Salmonella typhi H* (NCTC 901.8394), *Staphylococcus epidermis* (ATCC 12228), *Brucella abortus* (RSKK-03026), *Micrococcus luteus* (ATCC 93419), *Bacillus cereus sp.*, *Pseudomonas putida sp.* and *Candida albicans* (Y-1200-NIH). In this process, dimethyl sulfoxide (DMSO) was used as solvent control. It was determined that dimethyl sulfoxide did not show antimicrobial activity against studied strains. All unsymmetrical ligands were stored dry at room temperature and solved (3.5 μg/mL) in dimethyl sulfoxide. 1% (volume/volume) of a 24 hour culture of broth including 106 CFU/mL was poured into Petri dishes. Molten nutrient agar was used as culturing the test bacteria and it was stored at ca. 45 ^oC. The agar was poured into sterile petri dishes and was left for solidification. Later, holes of 6 mm diameter were pierced with sterile cork borer and the test solutions were added into each of the bores. Finally, the plates were incubated at 37^oC for 24 h. Average value determined for all the holes were used to compute the zone of inhibition growth. Pathogenic bacterial cultures and yeast were tested for resistance to five antibiotics (produced by Oxoid Ltd., Basingstoke, UK): kanamycin (it is bactericidal against gram negative bacteria and gram-positive bacteria and are indicated for the treatment of infections that are susceptible to microorganisms sensitive gram (-) and

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gram (+) are indicated), sulphamethoxazol (antibacterial agent affecting the synthesis of folic acid in sensitive bacteria), ampicillin (bactericidal that inhibit the growth of gram (-) bacteria), amoxicillin (it is a penicillin effective against gram (+) and gram (-) bacteria and is a broad spectrum antibiotic), nystatin (it binds with the sterols in the cell membrane of fungus and changes the membrane permeability).

Results And Discussion

Characterization of Unsymmetrical Schiff bases (L_{3a}-L_{3c})

Herein, (–CH=N-aryl-CH=N–) type unsymmetrical diimines (**L_{3a}-L_{3c}**) are prepared and spectroscopic data for all ligands are reported. (**L_{3a}**), (**L_{3b}**) and (**L_{3c}**) are tetradentate ligands with two imine nitrogens and two phenolic oxygens (Fig. 2). These tetradentate N_2O_2 type ligands (except for **L_{3a}**) are also unsymmetrical with respect to the substituents on the terminal phenolic residues. They are stable at room temperature, insoluble in water, slightly soluble in polar organic solvents.

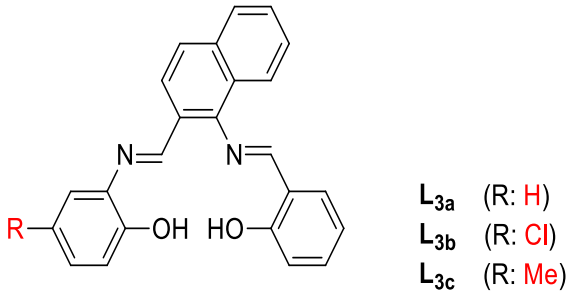

Figure 2. *Structures of unsymmetrical Schiff bases (**L_{3a}-L_{3c}**)*

The elemental analysis and mass spectroscopy results of unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) are presented in Table 1. The elemental analyses compatible with the chemical formulas of the compounds. The values of the molecular ion peaks and the fragmentation products are also consistent with the proposed structures of unsymmetric diimines. The molecular ion peaks are observed at the predicted values of m/z: 367.2 $[M+H]^+$ (**L_{3a}**), 401.9 $[M+H]^+$ (**L_{3b}**) and 381.2 $[M+H]^+$ (**L_{3c}**). The same fragmentation pathways appear for the highest intensity peaks in (**L_{3a}**) and (**L_{3b}**). Thus, peaks at m/z : 243.3 and m/z : 282.5 for (**L_{3a}**) and (**L_{3b}**), respectively, are attributed to the loss of the $[M-(C_7H_6NO-4H)]^+$, $[M-(C_7H_6NO-2H)]^+$ fragments. The highest intensity peak for (**L_{3c}**) at m/z : 228.1 is also attributed to the loss of the $[M-(C_8H_9NO_2-H)]^+$ fragment.

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Table 1. *Elemental analyses and mass spectral data for unsymmetrical Schiff bases*

Compound	**Formula** **Colour**	**Elemental analysis (calc.) %**			**Mass spectrum**		
		C	H	N	m/z	%	Peak
L_{3a}	$C_{24}H_{18}N_2O_2$	77.46	4.74	7.26	367.2	1.7	$[M+H]^+$
	Orange	(78.69)	(4.92)	(7.65)			
L_{3b}	$C_{24}H_{17}N_2O_2Cl$	73.85	3.41	6.02	401.9	5.2	$[M+H]^+$
	Orange	(71.91)	(4.24)	(6.99)			
L_{3c}	$C_{25}H_{20}N_2O_2$	77.88	5.09	6.88	381.2	15.4	$[M+H]^+$
	Orange	(78.95)	(5.26)	(7.37)			

The IR spectra for unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) are presented in Table 2 and are shown in Figure 3. Because of the two asymmetric imine groups, all ligands show two strong bands in the region 1588-1611 cm^{-1}, attributable to νC=N. The bands assigned to νC=C are observed in the ranges 1456-1545 cm^{-1}. The νOH and $\nu CH_{(arom.)}$ are observed in the 3330-3386 cm^{-1} and 3044-3056 cm^{-1} regions, respectively

Table 2. *The IR vibrational wavenumbers (cm^{-1}) and ^{1}H-NMR chemical shift (ppm) of the unsymmetrical Schiff bases*

Compound	**IR**				**^{1}H-NMR**			
	ν(OH)	$\nu(CH)_{arom.}$	ν(C=N)	$\nu(C=C)_{ring}$	OH	CH=N	Arom.-H	CH_3
L_{3a}	3333	3056	1610, 1600	1528-1456	n.o. 9.88(s) 1H	9.72(s) 1H 9.57(s) 1H	6.10-8.20 (m)	-
L_{3b}	3386	3044	1604, 1588	1545-1460	n.o. 9.96(s) 1H	9.53(s) 1H 8.85(s) 1H	6.35-8.45 (m)	-
L_{3c}	3330	3054	1611, 1600	1545-1460	13.55(s) 1H 10.16(s) 1H	9.89(s) 1H 9.65(s) 1H	6.81-8.49 (m)	2.50(s)

The ^{1}H-NMR spectra for unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) are presented in Table 2 and are shown in Figure 4. The ^{1}H-NMR spectra of all ligands show two signals in the ranges 8.85-9.65 ppm and 9.53-9.89 ppm. These singlets are observed due to the different chemical environments of the unsymmetric imine groups. The phenolic protons of all ligands are observed in the range 9.88-13.55 ppm. The aromatic protons are appeared in the range 6.10-8.49 ppm. Additionally, the peak attributable to CH_3 in L_{Me}-H is revealed at 2.50 ppm.

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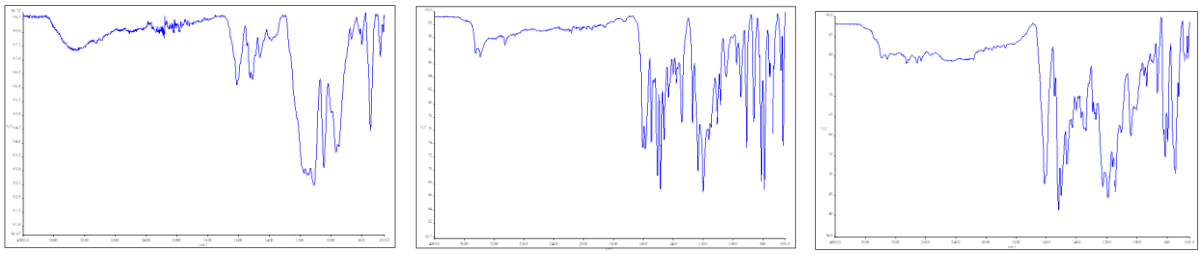
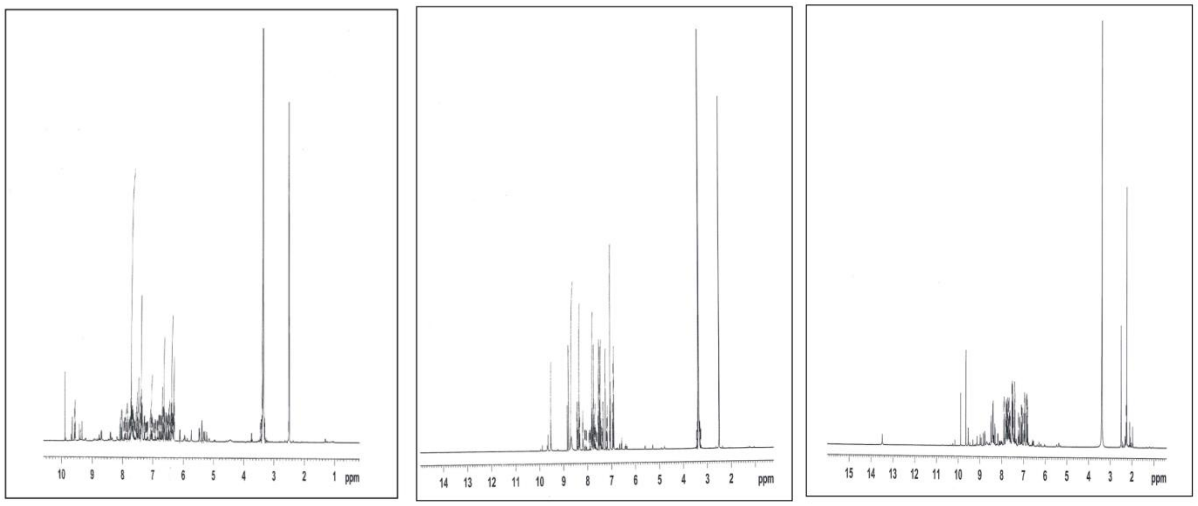


(a) **(b)** **(c)**

Figure 3. *IR spectra of* ***L$_{3a}$*** *(a),* ***L$_{3b}$*** *(b),* ***L$_{3c}$*** *(c).*



(a) **(b)** **(c)**

Figure 4. *^{1}H-NMR spectra of* ***L$_{3a}$*** *(a),* ***L$_{3b}$*** *(b),* ***L$_{3c}$*** *(c).*

Biological Evaluation

The antimicrobial activities for unsymmetrical Schiff bases (**L$_{3a}$-L$_{3c}$**) are presented in Table 3. The unsymmetrical Schiff bases were screened *in vitro* for antimicrobial activity against pathogenic strains gram positive *Listeria monocytogenes 4b, Staphylococcus epidermis, Micrococcus luteus, Bacillus cereus sp.*, gram negative *Shigella dysenteria type 7, Escherichia coli, Salmonella typhi H, Brucella abortus, Pseudomonas putida sp.* and antifungal activity against *Candida albicans*. All ligands and antibiotics are exhibited varying degree of inhibitory effects on the growth of different tested strains. It can be said that the functional substituents (H, Cl and CH_3) on the benzene ring selectively increase or decrease inhibition of the unsymmetric ligands [33]. (**L$_{3a}$**) and (**L$_{3b}$**)

show the highest antibacterial activity against *B.cereus sp.* The bacteria plays an important role as the causative agent of two types of food poisoning: diarrhea and emesis. It is one of the most virulent and destructive ocular pathogens among infections of the eye [34,35]. (**L_{3c}**) exhibits the highest activity against *M.luteus sp.* and shows a significant activity against *B.cereus sp. Micrococcus luteus* is associated with various infections, including recurrent bacteraemia, septic shock, septic arthritis, endocarditis, meningitis, and cavitating pneumonia. It can be an opportunistic pathogen, particularly in hosts with compromised immune systems, such as HIV patients [36]. (**L_{3a}**) and (**L_{3b}**) are inactive against *L.monocytogenes 4b* and *Sh.dys. typ 7*, respectively. Furthermore, all ligands (**L_{3a}-L_{3c}**) show more antifungal activity against *C. albicans* than commercial antifungal (positive control NYS100). It is an opportunistic human fungal pathogen that causes candidiasis especially for immunocompromised patients and for some immunologically weak individuals [37]. Finally, the unsymmetrical ligands are found to be good antibacterial and antifungal activity against the selected microorganisms. According to the results, these unsymmetric Schiff bases (**L_{3a}-L_{3c}**) can be suggested as biologically active compounds.

Additionally, the antibacterial activity of **L_{3a}**, **L_{3b}** and **L_{3c}** was also compared with five commercial antibiotics. **L_{3b}** and **L_{3c}** show higher antibacterial activity than SXT25 antibiotic, which is showed the highest activity for *P.putida sp.* The bacterium is known as opportunistic human pathogen capable of causing nosocomial infections [38].

Table 3. *Antimicrobial activities of unsymmetric diimines(diameter of zone of inhibition (mm))*

Microorganisms	**Compound**			**Positive Control**				
	L_{3a}	L_{3b}	L_{3c}	K30	SXT25	AMP10	AMC30	NYS100
S.aureus	19	14	14	25	24	30	30	-
L.monocytogenes 4b	-	15	18	15	11	16	22	-
E.coli	15	15	15	25	18	10	14	-
S.typhi H	12	11	13	20	17	11	19	-
Br. abortus	15	17	17	-	-	-	-	-
P.putida sp.	15	21	21	14	18	8	15	-
S.epidermis sp.	15	23	19					
Sh.dys. typ 7	12	-	15					
M.luteus sp.	12	20	23					
B.cereus sp.	23	30	20					
Candida albicans (Fungus)	28	22	30	-	-	-	-	20
DMF (control)	-	-	-	-	-	-	-	-

Standart reagents: K30 Kanamycin 30 µg, SXT25 Sulfamethoxazol 25 µg, AMP10 Ampicillin 10 µg, AMC30 Amoxycillin 30 µg, NYS100 Nystatin 100 µg.

Conclusions

New unsymmetrical Schiff bases (**L_{3a}-L_{3c}**) were prepared by a two step process. In this study we particulary chose to prepare these type ligands. Their significance is due to the unsymmetrical behavior with respect to the 'direction' of the imine bond. (i.e. -CH=N-aryl-CH=N). The structures of these compunds were confirmed by spectroscopic techniques. Furthermore, the antimicrobial study were reported herein. The results of the study show that these newly synthesized compounds (**L_{3a}-L_{3c}**) have broad spectrum antibacterial and antifungal activities. As a result, it can be said that the synthesized unsymmetrical Schiff bases may find practical applications in biological systems.

Acknowledgements

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