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Synthesis, Characterization and Biological Evaluation of New Series of Schiff Bases Derived from Hexamethylenediamine as Potential Antibacterial and Antifungal Agents

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ABSTRACT

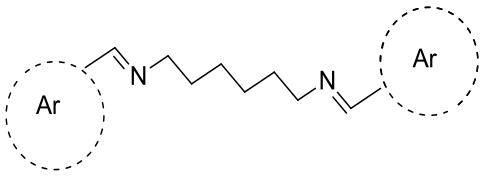
*We report herein synthesis, characterization and antimicrobial activity of four Shiff bases derived from hexamethylenediamine. Substitution of a nitro group on each aromatic ring in ortho, meta or para positions of N,N'-bis(phenylmethyl)hexane-1,6-diimineallowed to have a homogeneous series of positional isomers. These four symmetric diimine Schiff bases were characterized by conventional spectrometry methods (NMR, IR, MS), then tested against Gram-positive and Gram-negative bacterial strains. Among them, compounds **1b**, **1c**, **1d** were found to be active against bacterial strain Staphylococcus aureus CIP with MIC value of 375µg/ ml, 187.5µg /ml and 375µg /ml respectively. Candida Albicans fungal strain showed resistance to all synthesized Schiff base compounds, butin the other hand, Candida glabrata has been sensitive to all compounds with MIC of 1500µg/ ml and one more time except **1a**.*

Keywords: Schiff base, hexamethylenediamine, spectrometry, antimicrobial activity.

1. Introduction

Bacterial infections remain the most harmful to human health [1-2]. So, there is an urgent need for the development of new chemical entities more efficient than those currently available on the market and at the same time solving the problem of multi-drug resistance[3-4].Schiff bases, condensation products of primary amines with carbonyl compounds are considered as a very important class of organic compounds first reported by Hugo Schiff in 1864[5-6]. The common structural feature of these compounds is the azomethine group. Imine groups present in many natural compounds has been shown to be critical to their biological activities[7-8].Our systematic research on Schiff bases in general and diimines in particular allowed us to synthesize many compounds among which the series of compounds which is the subject of this study. From *N,N'*-bis (phenylmethylene)hexane-1,6-diamine, substitution of a nitro group on each aromatic ring and its systematic displacement in the positions *ortho*, *meta* and *para* led to have a homogeneous series of position isomers.Versatility of Schiff base ligands and important industrial applications of their complexes explain the numerous investigations carried out on these compounds. As part of our investigations on Schiff bases, we are interested in their biological activities. Indeed, Schiff bases have showed remarkable antiviral [9], antimicrobial [10], antifungal [11], antitumors [12], anticancer [13-14] and antibacterial activities [15-17].

The present paper deals with the synthesis, characterization and antimicrobial studies of all of the synthesized compounds shown in Figure**1**.



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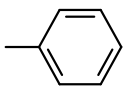
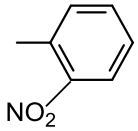
1a	
1b	

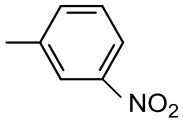
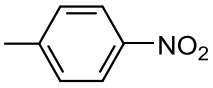
1c	
1d	

Figure **1**: structures of Schiff bases synthesized

2. Chemistry

Synthesis of title compounds was accomplished as outlined in figure **2**

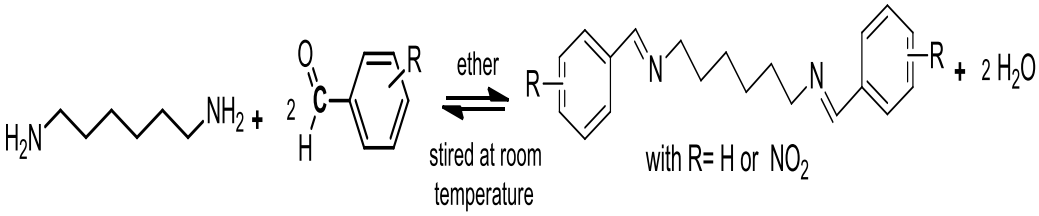


Figure 2. Way of general synthesis of compounds **1a-d**

3. Experimental protocols

All of the chemicals used in the syntheses were purchased from Sigma-Aldrich and were used as such. Thin layer chromatography was used to monitor the progress of the reactions. Melting points were determined in capillary tube using an MPD Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus and are uncorrected. IR spectra in the range 4000-400 cm^{-1} were obtained on a Bruker-Vector FTIR spectrophotometer, with samples investigated as thin film from CDCl3 solution. ^{1}H NMR spectra were recorded on a Bruker-Avance-300 spectrometer, operating at 300 MHz. Mass spectra were recorded on a TOF LCT Premier (WATERS) Spectrometer coupled to an HPLC Alliance 2695 chain.

3. Synthesis and characterization of the compounds

3.1. Synthesis and characterization of *N,N'*-bis(phenylmethylene)hexane-1,6-diamine

Benzaldehyde (0.4mmol) and hexane-1,6-diamine (0.2mmol) were dissolved in ether (30 ml). At room temperature, the mixture was stirred for three days to give a white milky precipitate. The precipitate obtained was filtered and recrystallized in ethanol Rf: 0.57 in hexane/acetone (50;50), yield: 61%, mp: 198,6°C; IR (Thin film from CDCl3 solution, cm^{-1})2936 ; 2856 ; 1638; ^{1}H NMR (300 MHz, CDCl3): 8.19(s, 2H), 7.32-7.65(m, 10H), 1.35-3.51(m, 12H); ^{13}C NMR (75 MHz, CDCl3): 160.86, 136.31, 134.46, 130.47, 128.55, 128.03, 61.87, 30.83, 27.15; ESI-HR-MS: peak at *m/z* 293.2095$[M + H]^{+}$ corresponding to $C_{20}H_{24}N_2$.

3.2. Synthesis and characterization of *N,N'*-bis(2-nitrophenylmethylene)hexane-1,6-diamine

2-nitrobenzaldehyde (0.4mmol) and hexane-1,6-diamine (0.2mmol) were dissolved in ether (30ml). At room temperature, the mixture was stirred for six days to give a light brown precipitate. The precipitate obtained was filtered and recrystallized in methanol Rf: 0.82 in hexane/acetone/acetate diethyl (20; 50; 30),yield: 98.19%, mp:65.6°C; IR (Thin film from CDCl3 solution, cm^{1}) 2926 ; 2860 ; 1633; 1522;^{1}H NMR (300 MHz, MeOD):8.56(s, 2H),7.75-8.10(m, 8H),1.38-3.61(m, 12H); ^{13}C NMR (75 MHz, MeOD): 154.10,146.29,127.94 , 127.15 , 128.81, 130.87 ,131.49,59.05, 28.01,24.46; ESI-HR-MS: peak at *m/z* 383.1726 $[M + H]^{+}$ corresponding to $C_{20}H_{22}N_4O_4$.

3.3. Synthesis and characterization of *N,N'*-bis(3-nitrophenylmethylene)hexane-1,6-diamine
3-nitrobenzaldehyde (0.4mmol) and hexane-1,6-diamine (0.2mmol) were dissolved in ether (30 ml). At room temperature, the mixture was stirred for four days to give a pale yelow precipitate. The precipitate obtained was filtered and recrystallized in methanol Rf: 0.88 in hexane/acetone (50;50),yield: 98 %, mp 82.6°C; IR (Thin film from CDCl3 solution, cm^{-1}): 2944, 2859, 1648,1522 ;^{1}H NMR (300 MHz, CDCl3): 8.50 (s, 2H),7.51-8.33(m, 8H),1.41-3.61(m, 12H); ^{13}C NMR (75 MHz, CDCl3): 158.67,148.46,138.38,134.05,129.06, 124.74, 122.52, 61.48, 30.63, 27.10;ESI-HR-MS: peak at *m/z* 383.1731$[M + H]^+$ corresponding to $C_{20}H_{22}N_4O_4$.

3.4. Synthesis and characterization of *N,N'*-bis(4-nitrophenylmethylene)hexane-1,6-diamine
4-nitrobenzaldehyde (0.8mmol) and hexane-1,6-diamine (0.4mmol) were dissolved in ether (30 ml). At room temperature, the mixture was stirred for three days to give a white precipitate. The precipitate obtained was filtered and recrystallized in methanolRf: 0.81 in hexane/acetone (50;50), yield: 86,26 %, mp 132,6°C;IR (Thin film from CDCl3 solution, cm^{-1}): 2853 ; 2819 ; 1643 ;1535; 850;^{1}H NMR (300 MHz, MeOD): 8.50 (s, 2H),7.98-8.30(m, 8H),1.39-3.64(m, 12H); ^{13}C NMR (75 MHz, MeOD): 155.92,146.44,139.27,126.14, 129.06, 121.33,59.33, 28.12,24.65;ESI-HR-MS: peak at *m/z* 383.1741 $[M + H]^+$ corresponding to $C_{20}H_{22}N_4O_4$.

4.Biological activity

4.1.Antibacterial testing
The bacterial cultures: *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* (CIP) 4.83, *Pseudomonas aeruginosa (*CIP) 103467, *E. coli* (CIP) 54127AFand*Staphylococcus aureus* sensitive to penicillinwere obtained from Pasteur Institute Collection (CIP) of Abidjan (Cote D'Ivoire) and also provided by the National Laboratory of Public Health of Abidjan (Cote D'Ivoire). The bacterial cultures were incubated at 37°C for 18 hours by inoculation into nutrient agar. Schiff bases were stored dry at room temperature and dissolved 1500µg/mL then 250µg/ml in dimethylsulfoxide (DMSO). Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media (15 cm^3) kept at 45^{o}C was poured in the Petridishes and allowed to solidify. Poured Petri plates (9 cm) were incubated with 50µL of normal saline solution of above culture media (10^5-10^6 bacteria per ml). Discs injected with prepared Schiff bases (50µl) were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37^{o}C for 18 hours. At the end of period the inhibition zones formed on media were measured with a zone reader in millimeters.

4.2. Antifungal testing
Pathogenic strains of *Candida albicans* and *Candida glabata*were obtained from National Laboratory of Public Health of Cote D'Ivoire and the Microbiology Laboratory of Swiss Scientific Research Center in Cote D'Ivoire. Schiff bases were stored dry at room temperature and dissolved 1500µg/ml in dimethylsulfoxide (DMSO). Antifungal activities of each compound were evaluated by the agar disc-diffusion method. Sabarod's agar media (15 cm^3) kept at 45^{o}C was poured in the Petri-dishes and allowed to solidify. Sterile, filter paper discs of 10mm diameter were impregnated with prepared Schiff bases (50µl) and were placed on to the media, seeded with fungus. The plates were then incubated at 37^{o}C for 1-3 days. At the end of period the inhibition zones formed on media were measured with a zone reader in millimeters.

5. Results and Discussion
Four symmetric Schiff bases have been synthesized from the condensation reaction of 1,6-diaminohexane with benzaldehyde, and *ortho, meta* or *para* NO_2-substituted benzaldehyde.The results of the antibacterial screening of compounds**1b**, **1c,** and**1d** at a concentration of 1500 µg/ml against *Staphylococcus aureus* (CIP) 4.83 and *Staphylococcus aureus* sensitive to penicillinhave been found. The inhibition zones were measured in mm and results are shown in Table **1**.The inhibition zones diameters were between 10 and 16 mm. The results indicated that, this compounds showed significant activity against *Staphylococcus aureus*(CIP) 4.83 than *Staphylococcus aureus* sensitive *to penicillin*, while they were found to be inactive against *Escherichia coli*(CIP) 54127AF, *Pseudomonas aeruginosa* (CIP) 103467,*Staphylococcus aureus* ATTC 25923.Antibacterial activity of these

compounds showed ascending order. When we increased concentration, area of inhibited growth also increased. We noted that compound **1a** without nitro group was inactive on all the strains. On the strain *Staphylococcus aureus*(CIP), the compound **1c**was the most active with a MIC of 187.5µg/ml, and the compounds **1b** and **1d**the least active with a MIC of 375µg/ml, whereas on the strain *Staphylococcus aureus* sensible, only compound**1c** has activity with a MIC value greater than 1500µg/ml.

TABLE 1: Measurement of inhibition diameters and value of minimum inhibition concentration (MIC) for antibacterial activity

	Measurement of inhibition diameters (mm)										Value of MIC (µg/ml)	
Strains tested	*Pseu a* CIP		*Sta a* CIP		*Sta a sens*		*E. coli* CIP		*Sta a* ATTC		*Sta a* CIP	*Sta* a sens
	Concentrations (µg/ml) C1=1500 : C2=250 : C3=25											
Compounds	C1	C2	C1	C2	C1	C2	C1	C2	C1	C2	MIC (µg /ml)	MIC (µg /ml)
1a	0	0	0	0	0	0	0	0	0	0	-	-
1b	0	0	13	10	0	0	0	0	0	0	375	-
1c	0	0	16	10	11	0	0	0	0	0	187.5	>1500
1d	0	0	16	10	0	0	0	0	0	0	375	-
Witnesses	C3	C3	C3	C3	C3	C3	C3	C3	C3	C3		
Gen	23	10	29	23	32	23	12	0	19	10	0.78	12.5
Tetra	0	0	36	29	27	19	29	17	24	15	0.0976	12.5

Values are averages of three repetitions; ***Gen****: Gentamicin;* ***Tetra****: Tetracycline;****Sta a sens****: Staphylococcus aureus sensitive to penicillin;****Sta a****:Staphylococcus aureus ;****Pseu a*** *:Pseudomonas aeruginosa ;****E. coli :****Escherichia coli*

All synthesized compounds show no antifungal activity even at 1500µg/ml against *C. albicans*, as shown in Table **2**.However, on *C.glabrata*, all compounds showed activities with inhibition diameters between 10 and 11 mm. Compound **1a** has a minimum inhibition concentration greater than 1500µg/ml, **on the other hand** for compounds **1b**, **1c**, **1d**the MIC value was1500µg/ml .

TABLE2: Measurement of inhibition diameters and value of minimum inhibition concentration (MIC) for antifungal activity

	Mean diameters of the inhibition zones (mm)		Value of MIC (µg/ml)	Value of MIC (µg/ml)
Strains tested	*C.albicans*	*C.glabrata*	*C.albicans*	*C.glabrata*
Compounds	Concentrations C1=1500 µg/ml		MIC (µg /ml)	MIC (µg /ml)
1a	0	10	-	>1500
1b	0	10	-	1500
1c	0	10	-	1500
1d	0	11	-	1500
Témoins	C3=25 µg/ml			
Ampho B	0	0	-	-
Nyst	11	0	50	-

Ampho B: *Amphotherine B;* ***Nyst****: Nystatin*

6. Conclusion

Schiff bases compounds **1a-d** were synthesized and characterized by spectral techniques. For antibacterial activities, compound **1a** without nitro groups was inactive on all the strains tested. On the other hand compounds **1b**, **1c**, **1d** with nitro groups have shown activities on the bacterial strains *Staphylococcus aureus* (CIP) 4.83 and *Staphylococcus aureus* sensitive to penicillin. However, it is noted that *meta* position of the nitro group was the most active with a minimum inhibition concentration of 187.5µg/ml. Concerning antifungal activities, no compound has positive result at the concentration tested with *C. albicans*. But, on *C. glabrata*, one more time, only nitro-substituted compounds (**1b**, **1c**, **1d**) showed activity with minimal inhibition concentrations of 1500µg/ml. The presence of the nitro group on the various benzene rings seems to be decisive for the manifestation of an important activity of these compounds.

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