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Synthesis, Characterization and Biological Activity Evaluation of Schiff Bases Derived from 1,8-Diaminonaphtalène

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Abstract

The compounds have been synthesized and characterized by routine MS, IR and NMR spectrometry methods. The compounds are all active on bacterial strains with the exception of *Salmonella typhimirium*, with a MIC value of 7.5 mg/mL. They show a percentage of anti-radical activity of 75.476 ± 5.070 for the compound DAN-S and of 68.142 ± 6.539 for the compound DAN-OV. The compounds are sensitive to the two champions used. DAN-S compound is then the most active.

Keywords

Schiff Base, Spectrometry, Antioxidant, Antimicrobial Activity, Inhibition, 1,8-Diaminonaphthalene

1. Introduction

In the last years, Schiff base ligands and complexes [1] have been studied extensively and have received considerable attention because of their variety of applications in physical, biochemical, analytical and industrial fields. Schiff base compounds played an important role in the development of coordination chemistry [2] [3], and were currently attracting the attention of medicinal chemistry [4]. Indeed, many studies have been reported regarding the biological activities

of Schiff bases, including their anticancer, antibacterial, antifungal, antimalaria, antiproliferative, antiinflammatory, antiviral, antipyretic and herbicidal activities [5] [6] [7] [8] [9]. Thus Sharma *et al.* [10] investigated the compounds *N*,*N*′-bis(phenylmethylene)cyclohexane-1,2-diamine, *N*,*N*′-bis(meta-nitrophenylmethylene)cyclohexane-1,2-diamine and *N*,*N*′-bis(para-nitro phenylmethylene)cyclohexane-1,2-diamine. They showed that these three compounds are inactive on Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus ATCC 25923 and Staphylococcus epidermidis. Similarly, for these authors [10], these three Schiff bases also turn out to have no antifungal activity on *Candida albicans* and *Candida glabrata* strains even at 500 µM corresponding to the maximum concentration at which they carried out the tests. Kangah and collaborators made the study of **Synthesis,** Characterization and Biological Evaluation of New Series of Schiff Bases Derived from Hexamethylenediamine as Potential Antibacterial and Antifungal Agents [11], and the study of Synthesis, Characterization and Antimicrobial Evaluation of Symmetric *α*-Diimine Schiff Bases Derived from Cis and Trans Racemic Mixture of Cyclohexanediamine [12].

It is well known now that oxidative stress is the main cause of several diseases such as cancer, cataract, amyotrophic lateral sclerosis, acute pulmonary distress syndrome, pulmonary edema and accelerated aging [13], or is the factor that increases the occurrence of multifactorial diseases such as Alzheimer's disease, rheumatism, cardiovascular disease and diabetes [14]. This alarming situation of the devastating effects of oxidative stress requires the scientific community to intensively search for new highly effective antioxidant molecules. Versatile Schiff bases, in addition to their wide range well known biological activities, can be a source of new molecules that possess excellent antioxidant properties. Like several authors [15] [16], our systematic structural and biological activities research on this kind of compound led us to synthesize many Schiff bases derived from 1,8-diaminonaphtalène.

2. Material and Methods

2.1. Material

Salicylaldehyde, Ortho-Vanilline, and benzene-1,8-diaminonaphtalene were procured from Aldrich and used without further purification. All organic solvents were purchased from Merck and dried before use. Melting points were determined in capillary tube using an MPD Mitamura.

Riken Kogyo (Japan) electrothermal melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker-Avance-300 spectrometer, operating at 300 MHz. The mass spectra were recorded on a TOF LCT Premier (WATERS) Spectrometer coupled to an HPLC Alliance 2695 chain.

2.2. Methods

2.2.1. Synthesis of *N*,*N*′-Bis(Phénol) Naphthalène-1,8-Diamine (DAN-S)

Salicylaldehyde (1.35 mL) and 1,8-diaminonaphthalene (1 g) were dissolved in

ether (20 mL). The mixture was stirred at room temperature for two days to give a brown precipitate. The precipitate obtained was filtered and rinsed in ether (yield: 43.95%, mp: 198.6˚C).

2.2.2. Synthesis of *N,N'*-Bis (3-Méthoxysalicylidène) Naphthalène-1,8-Diamine (DAN-OV)

Ortho-Vanilline (2.88 g) and 1,8-diaminonaphthalene (1.5 g) were dissolved in ether (60 mL). The mixture was heated at reflux for 07 hours to give a maroon precipitate. The precipitate obtained was filtered and rinsed in ether (yield: 56.25%, mp: 172.6˚C).

2.2.3. Biological Activity

1) Antibacterial Assays

The bacterial cultures: *Staphylococcus aureus* (CIP) 4.83, *Escherichia coli* ATCC 25922, and *Salmonella typhimirium* SO66, sensitive to penicillin were obtained from Pasteur Institute Collection (CIP) and also provided by the National Laboratory of Public Health of Côte 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 were dissolved in dimethylsulfoxide (DMSO) at concentrations of 1500 µg/mL followed by dilution to 250 µg/mL. Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media (15 cm^3) kept at 45˚C was poured in the Petri dishes and allowed to solidify. Poured Petri plates (9 cm) were incubated with 50 µL of normal saline solution of the above culture media (105 - 106 bacteria per ml). Discs injected with prepared Schiff bases (50 µL) were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37˚C for 18 hours. At the end of period, the inhibition zones formed on media were measured with a zone reader.

2) Antifungal Assays

Pathogenic strains of *Candida albicans* and *Candida glabrata* were obtained from National Laboratory of Public Health and the Microbiology Laboratory of Swiss Centre of Scentific Research of Côte d'Ivoire. Schiff bases were stored dry at room temperature and dissolved at 60 mg/mL in dimethylsulfoxide (DMSO). Antifungal activities of each compound were evaluated by the agar disc diffusion method. Sabouraud agar media (15 cm^3) kept at 45˚C was poured in the Petri-dishes and allowed to solidify. Sterile, filter paper discs of 10 mm diameter were impregnated with prepared Schiff bases (50 µL) and were placed onto the media, seeded with fungus. The plates were then incubated at 37˚C for 1 - 3 days. At the end of period, the inhibition zones formed on media were measured with a zone reader in millimeters.

2.2.4. Protocols of Antioxidant Activity Tests

1) *Test with DiPhenyl-1-PicrylHydrazyl (DPPH)

2,2-diphenyl-1-picrylhydrazyl was one of the first free radicals used to study structure-antioxidant activity relationship of phenolic compounds [17] [18] [19].

2) **Principle

Reduction of the free radical DPPH by an antioxidant can be followed by UV-Visible spectrometry, by measuring the decrease in absorbance at 517 nm caused by the antioxidants [20]. In the presence of free radical traps, purple-colored DPPH is reduced to yellow 2,2-diphenyl-1-picrylhydrazine [21].

3) **Dosage

DPPH radical traping activity was measured according to the protocol described by Lopes-Lutz *et al.* [22] and Athamena *et al.* [23]. 100 µL of each methanolic solution of the pure compound at different concentrations (3.125 - 100 mg/mL) were added to 2.5 mL of the methanolic solution of DPPH (0.025 g/L). In parallel, a negative control is prepared by mixing 100 µL of methanol with 2.5 ml of the methanolic solution of DPPH. Absorbance reading was made against a blank prepared for each concentration at 517 nm after 30 minutes of incubation in the dark and at room temperature. The positive control was represented by a solution of a standard antioxidant ascorbic acid, whose absorbance was measured under the same conditions as the samples and for each concentration [24].

The results were expressed in inhibition percentages (I%) of free radical using the following formula:

$$I\% = [(\text{Abs of con neg} - \text{Abs sample})/\text{Abs of con neg}] \times 100$$

I%: Percentage of DPPH inhibition.

Abs Sample: Absorbance of the sample.

Abs of con neg: Absorbance of negative control.

3. Results and Discussion

3.1. Mass Spectra (MS) and IR

The mass spectra and the infrared spectra of the synthesized compounds are given in Table 1.

3.2. MS Study

The mass spectra (HR-ESI-MS) of the title compounds show peaks corresponding to the molecular ions at m/z 367.02 $[M + H]^+$, and corresponds to $C_{24}H_{18}N_2O_2$ for compounds **DAN-S**. For compound **DAN-OV** the peak at m/z 427.12 $[M + H]^+$, corresponds to the molecular formula $C_{26}H_{22}N_2O_4$.

3.3. IR Study

The IR spectra show characteristic bands at 1600.28 cm^{-1} for compound **DAN-S**,

Table 1. Mass spectrum and selected infrared data.

Compound	molar mass (g/mol)	Mass spectrum $[M + H]^+$ (g/mol)	infrared spectrum: (Cm^{-1})	
			(νC=N)	(νC-H)
DAN-S	366	367.02	1600.28	2834.70 - 2955.23
DAN-OV	426	427.12	1598	3321.09

1598 cm^{-1} for compound **DAN-OV**. These bands correspond to the elongation vibration of the two azométhine vibrators C=N present in each molecule structure. Thus, the fact of obtaining only one vibration band νC=N for the two C=N bonds attests that the molecules studied are symmetric. The absence of N-H vibrator bands around 3500 cm^{-1} in the spectra confirms the absence of an amine group in the synthesized products. The multi-bands located between 2834.70 cm^{-1} and 3321.09 cm^{-1} indicated in Table 1, correspond to νC-H elongation of vibrations.

3.4. ^{1}H NMR Spectroscopy

^{1}H NMR spectral data in deturated CDCL3 solution of the synthesized compounds are given in Table 2.

The resonance of protons has been assigned on the basis of their integration and multiplicity patterns [25]. The ^{1}H NMR spectra exhibit signals at 7.95 ppm, 8.13 ppm, for compounds **DAN-S** and **DAN-OV**, respectively, attributed to the iminic CH=N-protons**.** The multi-signals within the 7.95 - 6.58 ppm range are assigned to the aromatic protons of both rings**.** The ^{1}H-NMR spectral data of the Schiff bases synthesized are in accord with the proposed structures.

3.5. Antibacterial Activity

The results of antibacterial screening of compounds DAN-S, DAN-OV, at a concentration of 60 mg/mL and 15 mg/mL against *Staphylococcus aureus*, *Salmonella typhimirium* and *Escherichia coli* are shown in Table 3. The inhibition zones diameters were between 10 and 18 mm. The results indicate that, these compounds show significant activity against *Staphylococcus aureus* and *Escherichia coli*.

3.6. Antifungal Activity

All the compounds including amphotericin B show antifungal activity against C. albicans and *C. tropicalis* as shown in Table 4. The inhibition zones diameters were between 10 mm and 14 mm. Compounds DAN-S seem to be more active than DAN-OV on C. glabrata.

3.7. Anti-Radical Activity by DPPH Method

The determination of antioxidant activity of the title compound was carried out

Table 2. ^{1}H NMR data[a-c] of compounds with general formula.

Compound	Molecular formula	N=CH (s)	C_6H_4 (5) (m)
DAN-S	$C_{24}H_{18}N_2O_2$	7.953	7.504 - 6.461
DAN-OV	$C_{26}H_{22}N_2O_4$	8.13	7.75 - 6.514

[a]Multiplicity is given as s = singlet, m = multi-signals. [b]Chemical shits in ppm; [c]Integration: number of protons in brackets.

according to one chemical technique: Trapping of free radical DPPH test. The results are recorded in Table 5.

The analysis of the table shows that; our compounds have antioxidant activity with the technique used. Compared to vitamin C, this activity is modest. The addition of the methoxy group in the meta position on the phenyl group (DAN-OV) disadvantages the antioxidant activity as shown in the histogram Figure 1 below in the localized concentration range between 100 and 3.12 mg/mL.

Table 3. Mean diameters (mm) of the inhibition zones and Value of Minimum Inhibitory Concentration (MIC) values for antibacterial activity.

Mean diameters of the inhibition zones (mm)							**Value of MIC (mg/mL)**		
Strains tested	*E. coli*		*Sal. typhi.*		*Sta. aureus*				
	Concentrations (mg/mL) C1 = 60, C2 = 15						*E. coli*	*Sal. typhi.*	*Sta. aureus*
Compounds	C1	C2	C1	C2	C1	C2			
DAN-S	18	19	-	-	12	15	7.5	-	7.5
DAN-OV	11	13	-	-	13	10	7.5	-	7.5
	Witnesses								
Gen.	30	29	30	29	32	29	0.007	0.007	0.007

Values are averages of three repetitions; *Gen*: *Gentamicin*, *E. Coli*: *Escherichia coli*, *Sal. Typhi*: *Salmonella typhimirium*, *Sta. Aureus*: *Staphylococcus aureus*.

Table 4. Measurement of inhibition diameters and value of minimum inhibition concentration (MIC) for antifungal activity.

Mean diameters of the inhibition zones (mm)					**Value of MIC (mg/mL)**	
Strains tested	*Candida albicans*		*Candida tropicalis*			
	Concentrations (mg/mL) C1 = 60, C2 = 15				*Candida albicans*	*Candida tropicalis*
Compounds	C1	C2	C1	C2		
DAN-S	12	15	11	14	7.5	7.5
DAN-OV	10	13	10	0	7.5	60
	Witnesses					
Amph. B	30	29	30	29	0.007	0.007

Values are averages of three repetitions, Amph. B: Amphotericin B.

Table 5. Inhibition percentage values by DPPH method.

Compounds	Means of inhibition % + standard deviation
DAN-OV	68,142 ± 6539
DAN-S	75,476 ± 5070
Vitamin C	88,802 ± 6820

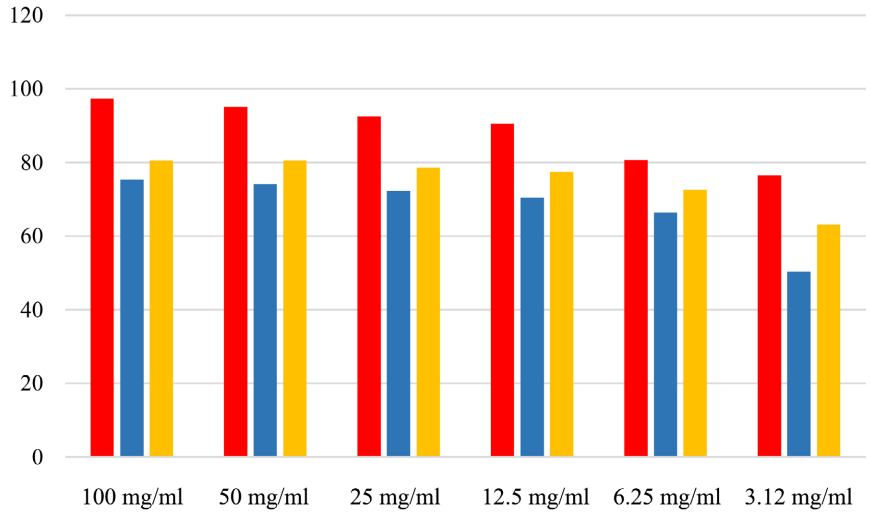

Figure 1. Antioxidant activity of the compounds obtained by the DPPH method at the concentration varying from 100 to 3.12 mg/mL.

4. Conclusions

In this work, the biological study shows that our compounds exhibit antibacterial activity against Escherichia coli and Staphylococcus aureus strains with an MIC of 7.5 mg/mL, but are all inactive against *Salmonella typhimirium*. In terms of antifungal activity, the compounds are also active on the two strains of *Candida albicans* and Candida tropicalis.

With a percentage of 75.476 ± 5.070, the DAN-S compound has the highest radical activity. In view of these results, the compound DAN-S would be the best pharmacophore.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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