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Computational study and antimicrobial activity of few Dapsone Schiff base derivatives

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ABSTRACT

Condensation of 4,4-diaminodiphenyl sulfone (Dapsone) with aliphatic and aromatic aldehydes yielded a few Schiff base derivatives in good yields. The optimized structural parameters (bond lengths and bond angles) of three azomethine compounds have been obtained by using the GAUSSIAN 09 program package. Conformer of compound **1** has the highest energy, which has less stability than compounds **2** and **3** at the same model. The synthesized compounds were screened for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and fungicidal activity against *Aspergillus niger* and *Candida albicans*. All compounds exhibited potent antibacterial and antifungal activity with the reference standard ciprofloxacin and Amphotericin B, respectively.

1. Introduction

The condensation products of primary amines with carbonyl compounds were first reported by Schiff in 1864 and the products are often referred to as Schiff bases [1-3]. Schiff bases have wide applications in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities [4] with the increasing incidence of deep mycosis, there has been increasing emphasis on the screening of new and more effective antimicrobial drugs with low toxicity [5]. Dapsone (4,4-diaminodiphenylsulphon) has been proved to be a powerful antibacterial agent [6]. Dapsone is the most widely used drugs in the treatment of leprosy and it inhibits foliate synthesis of M-Leprae [7].

Schiff bases are associated with antibacterial, antifungal and antitubercular activities have diverse biological activities [8-12]. The present work includes modification of dapsone drug by synthesis, characterization and antimicrobial study of dapsone Schiff base derivatives.

2. Experimental

2.1. Instrumentation

The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs. ^{1}H and ^{13}C NMR spectra were measured on a Bruker at 400 MHz, with TMS as internal reference at Konstanz University, Germany. Microanalysis for carbon, hydrogen and nitrogen were carried out by a Perkin-Elmer 240B Elemental Analyzer. Melting points were measured by a Philip Harris melting point apparatus and uncorrected.

2.2. Synthesis

2.2.1. Synthesis of 4-{[4-(ethylideneamino)phenyl]sulfonyl} aniline **(1)**

10 mmol (0.44 g) of acetaldehyde in 25 mL ethanol was added to 10 mmol (2.48 g) of hot ethanolic solution of 4,4-diaminodiphenylsulphon, two drops of conc. H_2SO_4 was added and resulting solution was refluxed for 4h and then lift overnight in refrigerator, the solid product obtained was filtered and washed with acetone and the final product was recrystallized by using chloroform:ethanol (8:2, *v*:*v*) to yield yellow-brown crystals of compound **1** (Figure 1).

4-{[4-(Ethylideneamino)phenyl]sulfonyl}aniline (**1**): Color: Yellow-brown. Yield: 80%. M.p.: 247-249 °C.

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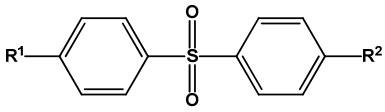


R^1: N=CHCH$_3$, R^2: NH_2 (1)
R^1: N=CHCH$_3$, R^2: N=CHCH$_3$ (2)
R^1: N=CH(C_6H_4)OH, R^2: NH_2 (3)

Figure 1. Preparative structures for compounds 1-3.

FT-IR (KBr, ν, cm^{-1}): 3450 (NH), 2967 (CH), 3020 (CH), 1600-1550 (C=C, C=N), 1370 (SO, SO_2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.51 (d, 3H, CH_3), 6.70-6.88 (m, 4H, Ar-H), 7.48-7.51 (m, 4H, Ar-H), 9.21 (s, 1H, -CH=N), 10.20 (s, 2H, NH_2). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 30.3 (1C, CH_3), 114.5-129.7 (12C, Ar-C), 161.5 (1C, CH=N). Anal. calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; Found: C, 61.45; H, 5.22; N, 10.51%.

2.2.2. Synthesis of N,N-(sulfonyldibenzene-4,1-diyl) diethanimine (2)

This compound was prepared by the same method given for compound **1** by using 4,4-diaminodiphenylsulphone 10 mmol (2.48 g) and 20 mmol (0.88 g) of acetaldehyde in hot ethanol to give compound **2** (Figure 1).

N,N-(sulfonyldibenzene-4,1-diyl)diethanimine (**2**): Color: Brown. Yield: 76%. M.p.: 218-221 °C. FT-IR (KBr, ν, cm^{-1}): 3455 (NH), 2760 (CH), 3015 (CH), 1600-1560 (C=C, C=N), 1375 (SO, SO_2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.13 (d, 6H, CH_3), 6.60-7.17 (m, 8H, Ar-H), 9.17 (s, 2H, CH=N). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 31.6 (2C, CH_3), 113.8-129.0 (12C, Ar-C), 162.8 (1C, CH=N). Anal. calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; Found: C, 64.23; H, 5.52; N, 9.51%.

2.2.3. Synthesis of 2-(((4-((4-aminophenyl)sulfonyl)phenyl) imino)methyl)phenol (3)

This compound was prepared by the same method given for compound **1** by using 4,4-diaminodiphenylsulphon 10 mmol (2.48 g) and 10 mmol (1.22 g) of 2-hydroxy benzaldehyde in hot ethanol to give compound **3** (Figure 1).

2-(((4-((4-aminophenyl)sulfonyl)phenyl)imino)methyl) phenol (**3**): Color: Orange. Yield: 78%. M.p.: 231-233 °C. FT-IR (KBr, ν, cm^{-1}): 3610 (OH), 3450 (NH), 2755 (CH), 3022 (CH), 1605-1560 (C=C, C=N), 1370 (SO, SO_2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.40 (s, 1H, OH), 6.70-7.51 (m, 12H, Ar-H), 9.18 (s, 1H, CH=N), 10.27 (s, 2H, NH_2). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 112-152 (18C, Ar-C), 161.2 (1C, CH=N). Anal. calcd. for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95; Found: C, 64.98; H, 4.82; N, 8.25%.

2.3. Computational study

To simulate the geometric structures of synthesized compounds, we employed theoretical calculations. All the calculations were performed by using the GAUSSIAN 09 program package [13]. The DFT method and B3LYP level was used to optimize all the structures reported. A basis set was 6-311G for all atoms [14,15].

2.4. Antimicrobial activity

The synthesized compounds were screened *in vitro* for their antibacterial activity against bacteria: *Staphylococcus aureus, Escherichia coli*, and *Bacillus subtilis* using the disc-agar diffusion technique [16]. Muller Hinton agar was used as culture media for antibacterial activity. The antifungal activities were tested against fungus: *Aspergillus niger* and *Candida albicans* by diffusion method using. Recommended concentration 50 µg/mL and 100 µg/mL of the test samples in DMSO solvent was introduced in the respective method. Antibiotic drug ciprofloxacine are used as control for bacteria and Amphotericin B for fungi, respectively. Petri plates containing 20 mL of Mueller Hinton Agar were used for all the bacteria tested. Candida albicans and *Aspergillus niger* strains were cultivated in Sabouraud's dextrose agar. Sterile Whatman no. 1 filter paper disks (6 mm in diameter) impregnated with the solution in DMSO of the test were placed on the Petri plates. A paper disk impregnated with dimethylsulfoxide (DMSO) was used as negative control. The plates were incubated for 24 h in the case of bacteria and 72 h for fungi at 35 °C. The inhibition zone diameters were measured in millimeters.

3. Results and discussion

3.1. Synthesis

The present work describes the synthesis of some Schiff bases by reaction of 4,4-diaminodiphenyl sulfone with acetaldehyde in 1:1 and 1:2 ratio and with salicyldehyde 1:1 ratio to produce the corresponding Schiff base derivatives **1**, **2** and **3** in good yields, respectively. IR spectra for all compounds displayed common features in certain regions and characteristic bands in the fingerprint and other regions. The IR spectra confirm the presence of the azomethine group (-CH=N) stretching with a sharp region around 1600 cm^{-1}. ^{1}H NMR spectra of all compounds show signal due to azomethine protons (CH=N) at 9.17-9.21 ppm, ^{1}H NMR spectra of compounds **1** and **2** shows a singlet at the range 1.14-2.51 ppm due to CH_3 group which disappear in compound **3**. The ^{13}C NMR spectrum of all compounds was measured in DMSO-d_6. ^{13}C NMR spectra gave further support to the formation of these compounds. The spectra revealed the presence of –CH=N group around 160 ppm.

3.2. Computational study

The structures of studied compounds are shown in Figure 1. Selected of properties calculated theoretically in this study are given in Table 1. Optimized geometries of compounds representative are given in Figure 2. B3LYP has long been recognized as a good tool due to the fact that it is computationally less demanding for inclusion of electron correlation and could provide accurate geometries [17], meanwhile, a previous study [18].

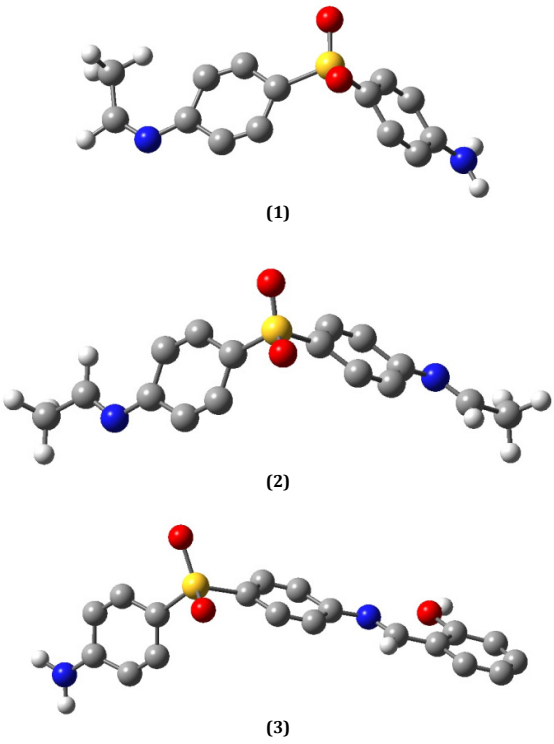
All the structures reported are confirmed to be local minima from frequency analysis. The general geometries of molecule all compounds are very similar. The values of bond lengths, bond angles, torsion angle and total energy were calculated for the three studied compounds, as well as highest occupied molecular orbital energy (HOMO) and lowest unoccupied molecular orbital energy (LUMO) energies and the difference between then (ΔE). Conformer of compound **1** has the highest energy, which has less stability than compounds **2** and **3** at the same model.

Table 1. Selected bond angles and torsion angles for studied compounds.

Molecule no	1	2	3
Bond length (Å)			
N=C	1.291	1.295	1.308
S=O	1.473	1.394	1.676
S-C	1.811	1.676	1.926
C-N	1.382	1.382	1.387
C-H	1.097	1.116	1.104
Angles bond (°)			
C-S-C	103.791	99.394	106.791
N=C-H	114.640	122.984	119.617
Dihedral angles (°)			
C-S-C-C	73.87	79.419	63.752
C-N=C-H	-179.96	0.093	-0.167

Table 2. Values of total energy, binding energy and HOMO-LUMO energy gap for studied compounds.

Compound no	Total energy (eV)	Binding energy (eV)	HOMO Energy (eV)	LUMO Energy (eV)	ΔE difference LUMO-HOMO
1	- 32500.6167	-121.2255639	-8.274	-7.244	1.029
2	- 34601.9774	-129.2554962	-8.832	-7.128	1.703
3	- 39690.1301	-136.9567332	-8.194	-7.311	0.882



(1) **(2)** **(3)**

Figure 2. Representation of molecules **1**,**2** and **3** obtained from gas geometry optimization.

In the present study, the HOMO-LUMO gap of the molecules are 1.029, 1.703 and 0.882 eV for compounds **1**-**3**, respectively as shown in Table 2 which clearly indicates that the molecules **1** and **2** are stable, but compound **1** is less stable than **2** and **3**. In general, the all molecules gave similar HOMO and LUMO orbitals.

From bond lengths notes are great similarities between the three compounds except minor changes in the lengths of bonds S=O, C=N, C-N for compound **3** as a little longer than the lengths of the bonds of compounds **1** and **2** because of electron donating by terminal phenyl group in compound **3**. The angles is observed that the C-S-C which is located in the middle of the molecule, in compound **2** is 99.394 ° and this list confirms that the compound **2** is the most curvature of the middle because it contains two identical terminals. Measurements and angles Quartet noted that all particles not planar structures (lengths angles less than 180 °).

The total energy, binding energy and HOMO-LOMO energy gap computed by using same method and basis set for the studied compounds **1**, **2** and **3** summarized in Table 2. The HOMO-LOMO energy gap reveals that the energy gap reflects the chemical activity of the molecule [19]. From values of the HOMO-LUMO energy gap observe the compounds **2** have higher stability compare with **1** and **3**, this due to symmetric of molecules. While compound **3** which has less stability from **1** and **2** due to they do not possess a symmetrical installation in a space.

Forms of HOMO and LUMO (Figure 3), the electrons donor in compounds **1** and **3** are in atoms of nitrogen, sulfur and oxygen in addition to some π orbitals of benzene molecules. The electron receptors are π electrons of benzene molecules [20]. Electrons donors and receptors in compound **2** are almost π orbitals of benzene molecules only.

Table 3. Microbial activities of the Schiff-base derivatives of dapsone drug.

	Diameter of inhibition zone in mm for different microbial species									
	S. Aures		*E. Coli*		*B. Cerus*		*C. Albicans*		*A. Niger*	
Concentration (µg/mL)	50	100	50	100	50	100	50	100	50	100
Compound										
Dapson	13	18	18	22	12	12	15	17	18	20
1	15	24	12	18	13	14	12	15	20	20
2	21	23	15	18	12	13	12	15	20	21
3	15	19	15	20	12	12	10	18	15	18
Ciproflaxacine	30		28		-		-		-	
Amphotericin B	-		-		-		-		25	

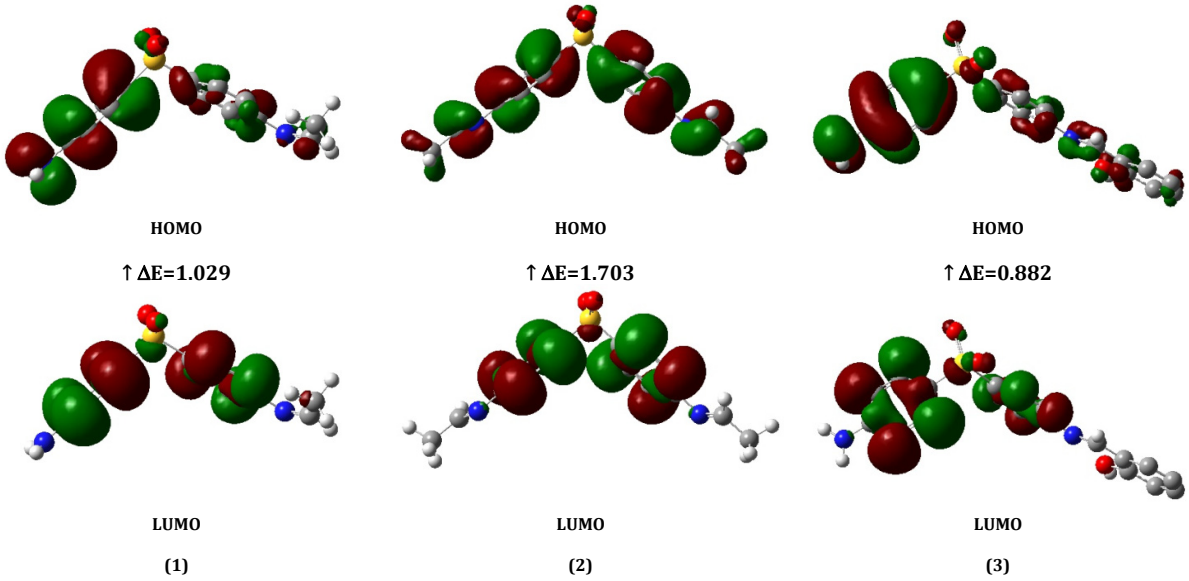


Figure 3. Representation of the HOMO and LOMO orbitals of molecules **1**,**2** and **3**.

3.3. Antimicrobial activity

The studied compounds have been screened for their *in vitro* antibacterial and antifungal activities, using the disc-agar diffusion technique [16,21] by measuring the inhibition zone in mm. Antibiotic drug ciprofloxacine, was used as control. The antibacterial activity of the synthesized compounds were tested against two Gram positive bacteria (*Bacillus cerus* and *Staphycoccus aureus*) and one Gram negative bacteria (*Escherichia Coli*) at a concentration of 50 µg/mL and 100 µg/mL using DMSO as a solvent, which not effected the growth of microbes. Muller Hinton agar was used as culture media for antibacterial activity. The results of the antimicrobial activity are shown in Table 3.

It is observed that the activity of compounds increases with an increase in the concentration of the solutions. All the synthesized compounds show activity against all the bacterial species. However, the compounds had the highest effect against *E. coli* and *S. Aureus* but moderate effect against *B. cerus*. It is worth noting that all compounds have highest activity against *S. aureus* than dapsone drug at 50 and 100 µg/mL.

The results on antifungal activity of the Schiff bases show high-moderate activity towards all the fungal species such as *Candida albicans* and *Aspergillus niger*. However, both all compounds show higher activity in *Aspergillus niger* and moderate in *Candida albicans*, Table 3.

4. Conclusion

In conclusion a series of some Schiff bases of dapsone compounds were prepared by convent method. Computational study shows that compound **1** has less stability than other compounds at the same model. The antimicrobial activity was evaluated against three bacterial strains and two fungal species. All derivatives exhibited antibacterial and antifungal activities.

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