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## "(E)- N'-(2,5-dimethoxybenzalidene) naphthalene-2-sulfonohydrazide" تحضير وتوصيف وتقييم النشاط البيولوجي للمركب

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**Synthesis, Characterization and Evaluation of Biological Activity of  
Sulfonylhydrazide-Schiff Base" (E)- N'-(2,5-dimethoxybenzalidene) Naphthalene-  
2-sulfonylhydrazide"**

تحضير وتوصيف وتقييم النشاط البيولوجي للمركب

"(E)- N'-(2,5-dimethoxybenzalidene) naphthalene-2-sulfonylhydrazide"

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**Abstract:** Condensation reaction of naphthalene -2-Sulfonylhydrazide, as starting material with 2,5-dimethoxy benzaldehyde was used to produce (E)-N'-(2,5-dimethoxybenzalidene) naphthalene-2-sulfonylhydrazide. The Schiff base product was isolated, purified and then spectrally characterized via UV-Vis, GC/MS, FT-IR, <sup>1</sup>H and <sup>13</sup>C NMR analysis, where strong evidences confirmed the formation of the desired product. Antimicrobial activity of Schiff base product was evaluated in vitro against several types of bacteria such as: Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae and MRSA by Minimum Inhibitory Concentration (MIC) test using tetracycline (TE) as a standard antibiotic. The tests showed a promising bacteriostatic effect of this compound against gram negative bacteria such as P. aeruginosa and K. pneumoniae, such character is valuable for biological applications.

**Keywords:** Sulfonylhydrazide Schiff Base, Biological Activity.

**المستخلص:** تم استخدام تفاعل تكثيف النفثالين -2-سلفونيل هيدرازيد، كمادة بدء مع 2,5-داي ميثوكسي بنزالدهيد لإنتاج (E)-N'-(2,5-ديميثوكسي بنزالدين) النفثالين-2-سلفونوهيدرازيد. تم عزل المنتج الأساسي وتنقيته ثم تمييزه طيفياً عن طريق تحليل UV-Vis و GC / MS و FT-IR و <sup>1</sup>H و <sup>13</sup>C NMR، حيث أكدت الأدلة القوية على تكوين المنتج المطلوب. تم تقييم النشاط المضاد للميكروبات للمركب الناتج في المختبر ضد عدة أنواع من البكتيريا مثل: Escherichia coli و Staphylococcus aureus و Pseudomonas aeruginosa و Klebsiella pneumoniae و MRSA عن طريق اختبار الحد الأدنى من التثبيط باستخدام اختبار التتراسيكلين (TE) كمضاد حيوي قياسي. أظهرت الاختبارات تأثيراً واعداً لهذا المركب ضد البكتيريا سالبة الجرام مثل P. aeruginosa و K. pneumoniae، وهذه الخاصية ذات قيمة للتطبيقات البيولوجية.

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## INTRODUCTION:

Schiff bases are regarded as the most important azomethine group organic compounds acted as an intermediate for many processes (Da Silva C.M. et al., 2011). Schiff bases are basically formed by condensation process of primary amines and aldehydes or ketones carbonyl groups (Yang Z. and Sun P., 2006; Al-Abdaly B.I. and Ahmed N.K., 2017; Hussain Z. et al., 2014; Warad I. et al., 2019). Aromatic Schiff bases are more stable than aliphatic one, this may be due to conjugation (Hussain Z. et al., 2014), such aromatic Schiff bases can be obtained from plant as naturally occurring like ancistrocladidine which used as antimalarial agent (Ay E., 2016). Many studies have shown the way in which sulfonyl hydrazide can be prepared by condensation reaction (Asegbeloyin J.N. et al., 2019), which start by any group has sulfonyl chloride and hydrazine or amines, such reaction is carried out in a suitable solvent like: THF, DMSO and alcohols (Yang F-L. and Tian S-K., 2017; Senkal B.F. et al., 2001; Backes G.L. et al., 2014; Safaei-Ghomi J., 2007). Sulfonyl hydrazide is a starting point for many chemical reactions, which is considered as a crucial compounds in many fields of life such as medicine, some examples about these reaction are 3-sulfonyl nitrile and 3-Aryl benzofuran-thioether (Li W. et al., 2017 ; Zhao X. et al., 2015). Sulfonamide was used as an inhibitor for HIV- Protase (Kumar S., 2010; Özdemir ÜÖ. et al., 2009; Tahriri M. et al., 2017; Alyar S. and Karacan N., 2009). Many Schiff bases are commonly known in medicine since they are used to design medicinal compounds (Balan K. et al., 2017). Schiff base compounds act as antibacterial such as, N-(salicylidene)-2-hydroxyaniline which is effective against Mycobacterium tuberculosis H37Rv (Da Silva CM. et al., 2011). Thus, Schiff base compounds are considered as a mediate means to prepare various bioactive compounds (Jarrahpour A. et al., 2004).

This research is aiming to synthesis and spectral characterization of a new sulfonyl-Schiff base product from naphthalene-2-sulfonylhydrazide and by using substituted aldehydes, evaluating it as an antibacterial agent.

## EXPERIMENTAL:

### Materials and Instrumentation:

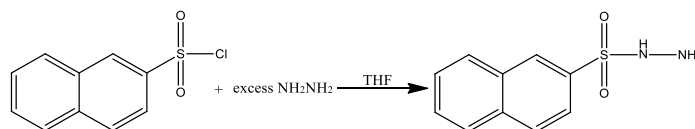
All reagents and solvents were used in synthesis and biological parts were purchased from Sigma Aldrich Chemical Company (USA), and used without further purification. Elemental analysis were applied on Elementar-vario EL analyzer. The melting point recorded for Schiff bases from Saturates Melting point apparatus SMP-3. FT-IR (Perkin-Elmer Spectrum) spectrometer was used to gain IR spectra. Shimadzu UV-VIS-NIR (UV-3101PC, TCC-260) scanning spectrophotometer was used to control the reaction by absorption measurements. <sup>1</sup>H and <sup>13</sup>C (JNM-ECZ600R/S1) Spectrometer were performed on 600MHz in Qatar University to acquire NMR-data, using CDCl<sub>3</sub> as solvent .

### Synthesis:

#### Synthesis of starting material naphthalene-2-sulfonylhydrazide (AZ):

The white solid product was formed by addition of excess amounts of hydrazine hydrate (NH<sub>2</sub>-NH<sub>2</sub>.H<sub>2</sub>O) to stoichiometric amount of naphthalene-2-sulfonylchloride (Warad I. et al., 2019; Da Silva C.M. et al., 2011), in a THF solvent as shown in Scheme 1. After 2-hours of stirring at room temperature,

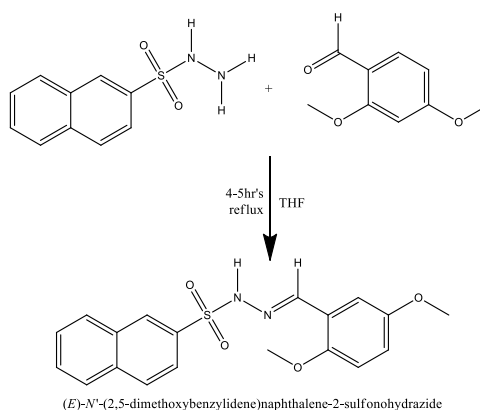
The THF was evaporated, then a precipitate was washed with distilled water for several time. Then it was left to be dried in a desiccator at room temperature.



Scheme 1: The chemical reaction that shows the formation of Naphthalene-2-sulfonylhydrazide.

#### Synthesis of sulfonylhydrazide Schiff base:

The Sulfonylhydrazide Schiff base was prepared as in Scheme 2. An equivalent amount of naphthalene-2-sulfonylhydrazide was added to 2, 5-dimethoxy benzaldehyde in a THF solvent. The solution was refluxed for 4-5-hours at 66°C, after that the solvent was evaporated. The precipitated product was washed with distilled water.



Scheme 2: Chemical reaction shows the formation of Sulfonylhydrazide Schiff base.

#### Anti-Bacterial Minimum Inhibitory Concentration (MIC) Method:

The Schiff base compound was tested for its MIC by micro-broth dilution method in sterile 96-wells micro-titer plate. A concentration of 2000 mg/l of Schiff base was prepared by dissolving appropriate amount of Schiff base product in 10% DMSO, and then it was two folded-serially diluted in nutrient broth directly in the wells with a final volume of 1000  $\mu$ l. The final concentration of Schiff base achieved after dilution were (1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.872, 3.9 and 1.95 mg/l). After that, a bacterial inoculum size of 10<sup>4</sup> CFU/ml was added to each well. Negative control wells containing either 100  $\mu$ l NB only, or 100  $\mu$ l DMSO with bacterial inoculum, or Schiff base and nutrient broth without bacteria were included as well. Each Schiff bases was run in duplicate. The microliter plate was then covered and incubated at 37°C for 24 hrs. MIC was determined by visual inspection.

#### RESULTS AND DISCUSSION:

The desired compound was prepared according to scheme 2, the compound was found to be soluble in THF, some alcohols and chlorinated solvents such as chloroform, and it was insoluble in water. The newly Schiff base yellow powder compound was verified by melting point (159°C), GC/MS spectroscopy, UV-Visible, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR.

**Spectral Analysis for Schiff base and the starting material:****GC-MS and Elemental Analysis:**

The elemental analysis of the starting material and Schiff base were matched with the proposed molecular formula, for starting material, ( $C_{10}H_{10}N_2O_2S$ ) the calculated data of elemental analysis were (C, 54.04; H, 4.53%, N 12.61%, O 14.40%, S 14.43%), and it was found to be matched with the experimental data as: (C, 54.11; H, 4.62%, N 12.4%, O 14.41%, S 14.37%). One other hand, for the Schiff base with a chemical formula of  $C_{19}H_{18}N_2O_4S$ , was calculated and it was found to be (C, 61.61; H, 4.90%, N 7.56%, O 17.28%, S 8.66%) and this also with a good correlation with the experimental analysis (C, 61.73; H, 5.02%, N 7.71%, O 17.71%, S 8.72%).

The GC/MS of starting material is agreeable with expected structure  $[M^+] = 221.2$  m/z and  $222.17$  m/z for  $[M+1]$ . The GC/MS data confirmed the desired structure for of the Schiff base especially the most possible fragments at 252, 241 m/z etc. The value for  $[M+1]$  was  $370.2$  m/z represented the proposed formula weight for the Schiff base product, while theoretical value was  $371.1$  m/z (as shown in Figure 1).

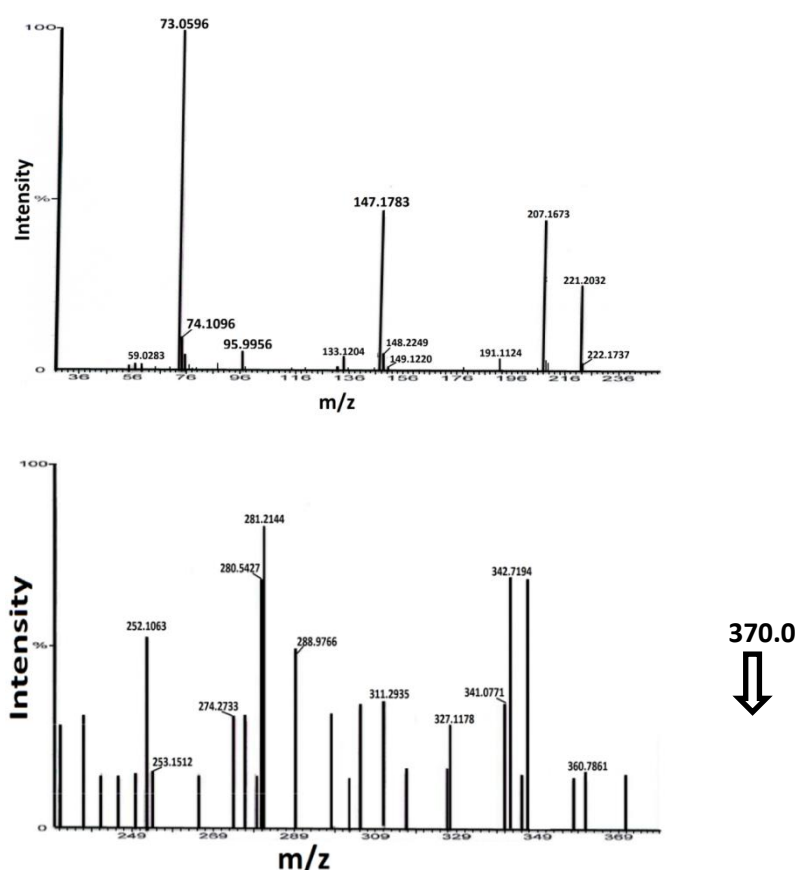


Figure 1: (A) GC/MS spectrum for starting material and (B) for the Schiff base GC/MS spectrum.

**Experimental and Theoretical DFT/IR Spectral Analysis:**

All reagents which were used to produce the Schiff base compound were analyzed using FT-IR in the range of  $3500\text{--}400$   $\text{cm}^{-1}$ . The FT-IR was used to monitor the condensation reaction; IR-spectra of all reactants and products were acquired and compared. There was a shifting and changes in IR- spectra as an evidence of formation of a new Schiff base compound; The carbonyl group of 2,5-Dimethoxy benzaldehyde  $\nu(C=O)$  peak was shown at  $1666$   $\text{cm}^{-1}$ , after the completion of the reaction it was shifted

to 1610 as an evidence of formation  $\nu$  (C=N). The (N-H) peak at 3152  $\text{cm}^{-1}$  was also shifted with  $\Delta\nu = 205 \text{ cm}^{-1}$ , this reflecting the formation of Schiff base compound, as illustrated in Figure 2.a

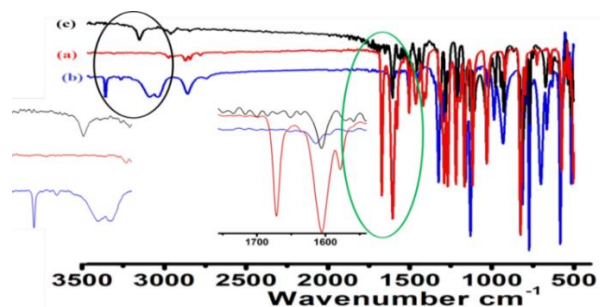


Figure 2.a: FTIR-spectra: a) 2,5-Dimethoxy benzaldehyde. b) The starting material. c) Schiff base product.

The DFT- theoretical vibrational spectrum was performed to check it functional groups, as shown in Figure 2.b

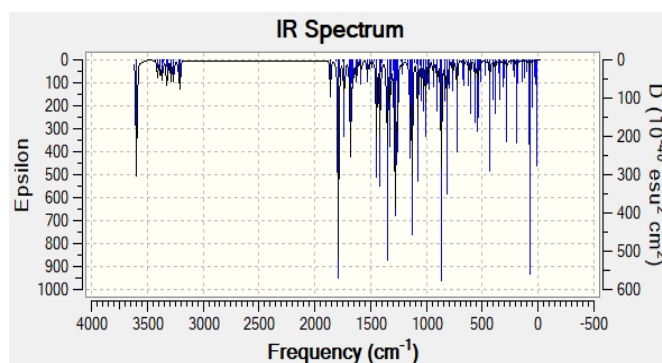


Figure 2.b: DFT-FTIR in gaseous phase for the Schiff base compound.

The experiment DFT/ FT-IR stretching vibrations of the functional groups are matched well, when comparing the DFT-B3LYP IR calculation in gaseous state with the experimental solid IR. The main vibrational stretching [ $\nu$  (N-H),  $\nu$  (C=N),  $\nu$  (C=C),  $\nu$  (C-H)] with its chemical shifts are illustrated in Table 1. There was a good correlation between experimental and theoretical IR data. A coefficient of determination ( $R^2$ ) was found to be 0.9992.

Table 1: Comparison between Experimental and DFT- FTIR values for main vibrational stretching for Schiff base compound

| Mode stretching | Exp.- FTIR<br>( $\text{cm}^{-1}$ ) | DFT-FTIR<br>( $\text{cm}^{-1}$ ) |
|-----------------|------------------------------------|----------------------------------|
| $\nu$ (N-H)     | 3152                               | 3164                             |
| $\nu$ (C=N)     | 1610                               | 1663                             |
| $\nu$ (=C-H)    | 3002                               | 2999                             |
| $\nu$ (-C-H)    | 2959                               | 2928                             |

#### NMR spectral analysis:

The  $^1\text{H-NMR}$  spectra of Schiff base product and starting material were recorded at room temperature in anhydrous  $\text{CDCl}_3$  solvent. To follow up the condensation reaction to form the desired product, the  $^1\text{H-}$

NMR of starting material was experimentally performed as shown in Figure 3 its spectrum showed eight signals a broad singlet (N-H, 3H,  $\delta = 3.1$  ppm), and seven signals in singlet (C-H,  $\delta = 7.5$  ppm), triplet of doublet (C-H,  $\delta = 7.55$  and 7.62 ppm) and doublet (C-H,  $\delta = 7.9, 8.1, 8.3$  and 8.6 ppm).

The  $^{13}\text{C}$ -NMR spectrum of starting material was shown in Figure 4, which revealed ten signals for all aromatic carbon cited to their expected chemical shift directly to the structure  $\delta = 124, 124.5, 127, 128.4, 128.7, 129.2, 131, 132, 134.4, 135.4$  ppm.

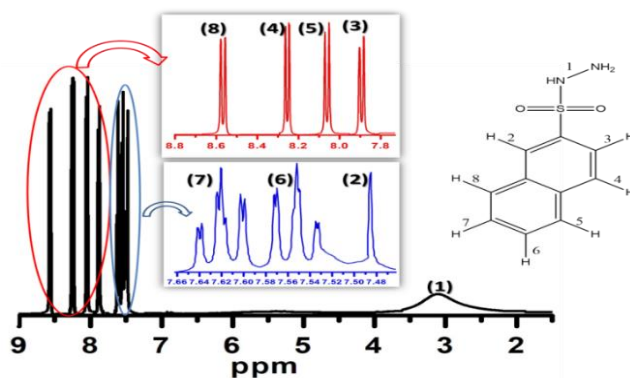


Figure 3:  $^1\text{H}$ -NMR spectrum of starting material in  $\text{CDCl}_3$  at room temperature.

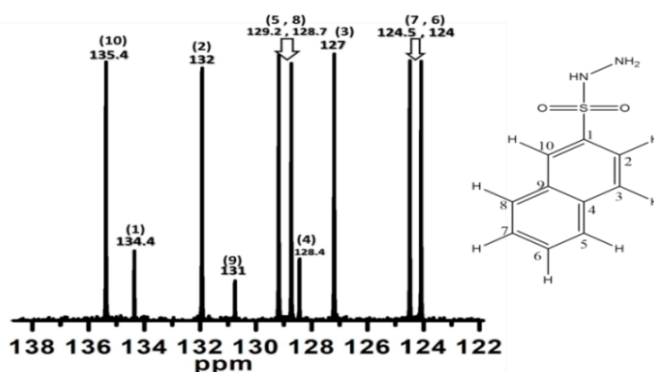


Figure 4:  $^{13}\text{C}$ -NMR spectrum represents the starting material in  $\text{CDCl}_3$  at room temperature.

The Figure 5.a showed Experiment  $^1\text{H}$ -NMR for Schiff base product and it has a detailed interpretation of compound. The presence of singlet ( $\text{CH}_3$ ,  $\delta = 3.6$  and 3.7 ppm), singlet (C-H,  $\delta = 6.2$  ppm) and doublet (C-H, 6.32 and 6.34 ppm) for benzene group, while naphthalene group has singlet (C-H,  $\delta = 7.8, 7.97$  ppm), doublet (C-H,  $\delta = 7.8, 7.9, 8.3$  and 8.8 ppm) and triplet (C-H,  $\delta = 7.5$  and 7.6 ppm), and azomethine group (C-H,  $\delta = 7.96$  ppm), N-H present at downfield region in 8.91 ppm. The theoretical  $^1\text{H}$ -NMR was illustrated in Figure 5.b, which was obtained from online website computation (Banfi D. and Patiny L., 2008), and this website can't detect the NH signal. Meanwhile, the comparison between theoretical and experimental  $^1\text{H}$ -NMR reflected a good correlation ( $R^2 = 0.9908$ ) between experimental with theoretical  $^1\text{H}$ -NMR data.

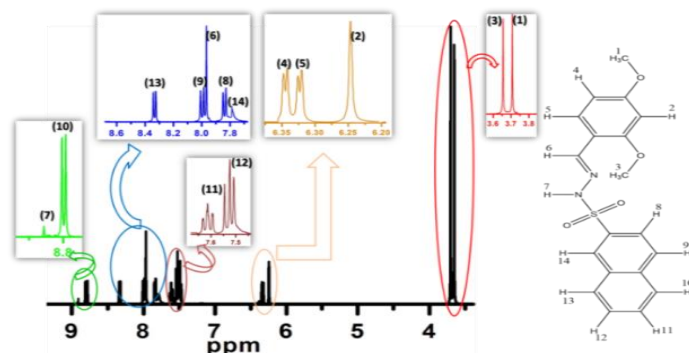


Figure 5.a: Experimental  $^1\text{H-NMR}$  spectrum represents the Schiff base compound in  $\text{CDCl}_3$ , at room temperature.

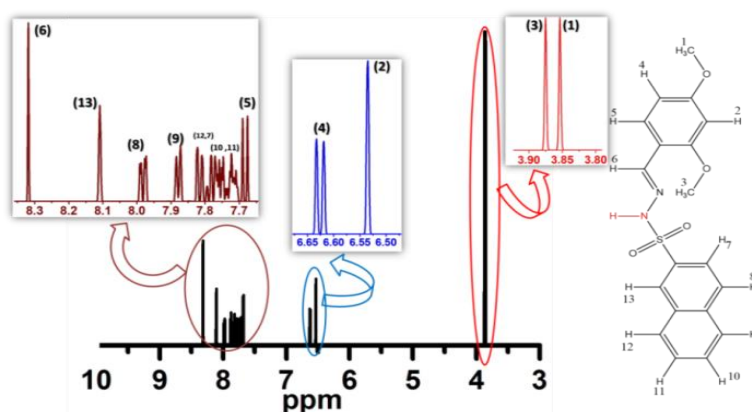


Figure 5.b. Theoretical  $^1\text{H-NMR}$  spectrum of Schiff base.

These values confirmed the supposed chemical structure of the Schiff base product. Such results also agreed with  $^{13}\text{C-NMR}$  spectra as shown in Figure 6 This spectrum showed 19-signals with different region one of them is azomethine carbon showed at ( $\delta=129$  ppm) while other signals were shown as deliberated by incremental methods.

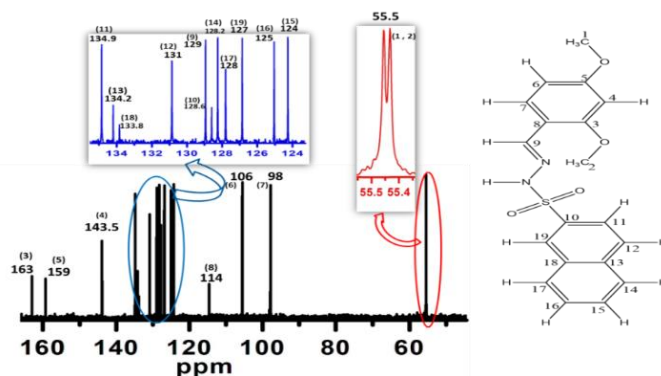


Figure 6:  $^{13}\text{C-NMR}$  spectrum represents the Schiff base in  $\text{CDCl}_3$  at room temperature.

#### UV-Visible analysis of Schiff base compound:

The electron transfer behavior in the desired Schiff base was performed in THF at room temperature. UV-Visible spectra of Schiff base and its starting material as an electron transfer were detected to monitor the condensation reaction. Figure 7 illustrates the absorption of Schiff base compound between (230-450 nm), Schiff base compound showed three strong peaks at ( $\lambda_{\text{max}}=236, 278$  and 317) nm which are



different from starting materials. Figure 7 is another tool to ensure the formation Schiff base compound, and that's through comparison between peaks of reaction components.

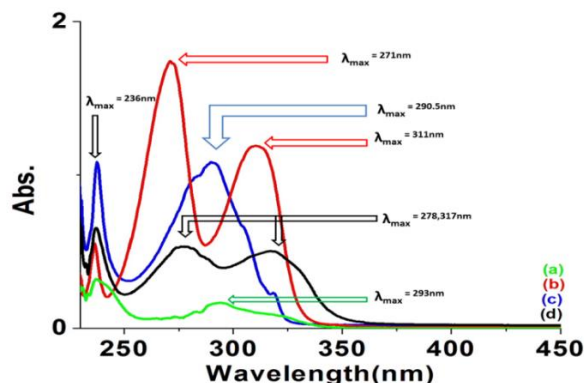


Figure 7: Experimental UV-visible spectra, a) Naphthalene sulfonyl chloride, b) 2,4-Dimethoxy benzaldehyde, c) Starting Material, d) Schiff base compound.

#### Summary of spectral data:

Yield 91%; m.p.= 159°C; yellow solid; formula  $C_{19}H_{18}N_2O_4S$ , FT-IR: 3152  $cm^{-1}$   $\nu$  (N-H), 1610  $cm^{-1}$   $\nu$  (C=N), 2959  $cm^{-1}$   $\nu$  (C-H), 3002  $cm^{-1}$   $\nu$  (=C-H), 1284  $cm^{-1}$   $\nu$  (C-O), 1315  $cm^{-1}$   $\nu$  (S=O);  $^1H$ -NMR (600 MHz,  $CDCl_3$ ,  $J=7.5$  Hz, ppm): 8.91 (s, 1H, N-H) 7.96 (s, 1H, N=C-H) azomethine group, the benzyl group consist 3.6 (s, 3H, =C-OCH<sub>3</sub>), 3.71 (s, 3H, N=CH-C=C-OCH<sub>3</sub>) 6.2 (s, 1H, CH<sub>3</sub>O-C-CH-OCH<sub>3</sub>) and 6.32 (d, 1H, N=CH-C-CH-CH-OCH<sub>3</sub>), 6.35 (d, 2H, CH=CH-COCH<sub>3</sub>) and naphthalene group has 7.8 (s, 1H, CH=C-CH=C-SO<sub>2</sub>), 7.84 (s, 1H, C-CH=CH-C-SO<sub>2</sub>), 8.01 (s, 1H, C-CH=CH-C-SO<sub>2</sub>), 8.3 and 8.8 (d, 2H, CH-CH=C-CH) and 7.5, 7.6 (t, 2H, CH-CH=CH-CH);  $^{13}C$ -NMR (600MHz,  $CDCl_3$ , ppm): 129 azomethine, 55.5, 98, 106, 114, 124, 125, 127, 128, 128.2, 128.6, 131, 133.8, 134.2, 134.9, 143.5, 159, 163,  $[M^+]=372$  m/z; UV-Visible (THF): 238, 278 and 317 nm.

#### Antibacterial Activity of Schiff Bases Compounds:

Schiff bases compounds as well as their metal complexes have a wide application in medical microbiology field. Those compounds may come to be an excellent alternate to antibiotics (21). Therefore, the current study was conducted to explore the antibacterial potential of the synthesized Schiff bases.

The antibacterial activity of the Schiff bases compounds were assessed by determining the MIC concentration for each Schiff base compound against MRSA, *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae* bacterial strains.

The obtained MIC results revealed that the Schiff base compound had a promising bacteriostatic effect against gram negative bacteria (*P. aeruginosa* and *K. pneumoniae*) as the MIC values (7.8125  $\mu g/ml$  and 15.625  $\mu g/ml$ , respectively). Meanwhile, the starting material had moderate bacteriostatic effect against all bacterial isolates under investigation with MIC values range (500  $\mu g/ml$  – 100  $\mu g/ml$ ). MRSA growth was inhibited by the starting material with MIC values 125  $\mu g/ml$  - 500  $\mu g/ml$  (Table 2).

Table 2. The MIC for Schiff base, starting material and tetracycline antibiotic

| Compounds              | Schiff base | Starting material | Tetracycline |
|------------------------|-------------|-------------------|--------------|
| MRSA                   | 0           | 500               | 250          |
| S. aureus              | 0           | 1000              | 500          |
| Escherichia Coli       | 15.625      | 1000              | 500          |
| Pseudomonas aeruginosa | 7.8125      | 500               | 500          |
| Klebsiella pneumonia   | 250         | 1000              | 500          |

## CONCLUSION:

A novel Schiff base compound containing sulfonylhydrazide functional group was synthesized in very good yield via condensation of naphthalene-2-sulfonylhydrazide with aldehydes. The structures of desired ligands were identified using FT-IR and NMR spectroscopy, and then the products were confirmed by UV-Vis spectrophotometry, Elemental analysis and GC/MS. Furthermore, DFT studies were carried out for the Schiff base compound. Excellent correlation ratios were detected when theoretical IR and NMR were compared to their experimental relatives. The promising bacteriostatic effect of this compound was against gram negative bacteria such as *P. aeruginosa* and *K. pneumoniae*, such character are valuable for biological applications.

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