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تخليق وتقييم إمكانات مضادات الليباز والالتحام الجزيئي للمركب الجديد N '- (2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide

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Synthesis and Evaluation of Anti-Lipase Potential and Molecular Docking of N'-(2-Hydroxy-5-Nitrobenzylidene) Naphthalene-2-Sulfonohydrazide

تخليق وتقييم إمكانات مضادات الليبازوالالتحام الجزيئي للمركب الجديد N '- (2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide

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Abstract: N'-(2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide (SB) was prepared by condensation reaction, of naphthalene-2-sulfonylchloride with 2-Hydroxy-5-nitrobenzaldehyde. The Schiff base product (SB) was isolated, purified and then spectrally characterized via UV-Vis, FT-IR, 1H and 13C NMR analysis, where strong evidences confirmed the formation of the desired product. Pancreatic porcine lipase inhibition of the Schiff base product was evaluated and compared with the reference "Orlistat". The product was an active as a lipase enzyme inhibitor with IC50 42.65±0.97 mcg/ml. The molecular docking of the compound with porcine pancreatic lipase was investigating, the results of theoretical docking explained the experimental one since several hydrogen bonds between the Schiff base compound and amino acids in lipase were detected. Antimicrobial activity of SB product was also evaluated in vitro against several types of bacteria such as: Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia and MRSA by Minimum Inhibitory Concentration (MIC) test using tetracycline (TE) as a standard antibiotic. Results showed a bacteriostatic effect of this compound against bacteria such as MRSA, P. aeruginosa and K. pneumoniae.

Keywords: Sulfonyl hydrazide Schiff Base, Spectral Characterization, Antimicrobial Activity, Pancreatic Lipase Inhibition, Auto docking.

المستخلص: تم تحضير (SB) N '- (2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide وهو مركب جديد عن طريق تفاعل التكثيف ، من النفثالين-2-سلفونيل كلوريد مع 2-هيدروكسي-5-نيتروبنزالديهايد. تم عزل المنتج الأساسي (SB) وتنقيته ثم توصيفه طيفيًا عن طريق تحليل UV-Vis و FT-IR و C NMR 131H ، حيث أكدت الأدلة القوية تكوين المركب المطلوب. تم تقييم قدرة المركب الناتج على تثبيط إنزيم الليباز ومقارنته بالمرجع "أورليستات". كان المنتج نشطًا كمثبط لإنزيم الليباز مع IC50 42.65 ± 0.97 ميكروغرام / مل. تم التحقيق في الالتحام الجزيئي للمركب مع انزيم الليباز ، وقد أوضحت ذلك نتائج الالتحام النظري، حيث تم اكتشاف العديد من الروابط الهيدروجينية بين المركب والأحماض الأمينية في الليباز. تم أيضًا تقييم النشاط المضاد للميكروبات للمركب الناتج (SB) في المختبر ضد عدة أنواع من البكتيريا مثل: Escherichia coli و Staphylococcus aureus و Pseudomonas aeruginosa و Klebsiella pneumonia و MRSA عن طريق اختبار الحد الأدنى من التثبيط باستخدام اختبار

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التتراسيكلين (TE) كمضاد حيوي معياري. أظهرت النتائج وجود تأثير مضاد للجراثيم لهذا المركب ضد البكتيريا مثل MRSA و P. Aeruginosa و K. pneumoniae.

الكلمات المفتاحية: قاعدة شيف هيدرازيد السلفونيل ، التوصيف الطيفي ، مضادات الميكروبات، تثبيط ليباز البنكرياس ، الالتحام التلقائي.

INTRODUCTION:

Schiff bases are basically formed by condensation process of primary amines and aldehydes or ketones carbonyl groups (Ashraf et al., 2011; Bhat and Murali, 2014; Kandile et al., 2017; Imran et al., 2014). Sulfonyl hydrazide Schiff bases start by any group has sulfonyl chloride and hydrazine or amine, such reaction is carried out in suitable solvents like: THF, DMSO and alcohols (Hussain et al., 2014; Warad et al., 2019; Ay 2016; Matar et al., 2015).

Schiff bases compounds have many applications in our daily life for example, they are being used in dyes and pigments industry, corrosion inhibitor and catalysis (Campbell and Nguyen, 2001). Many Schiff bases are commonly known in medicine since it is used to design medicinal compounds (Shokohi-pour et al., 2016). They have wide range of biological activities which include antibacterial, anti-inflammatory, anticancer and antiviral (Santerre et al., 1958; Patai 1970; Abu-El-Halawa et al., 2007; Hadda et al., 2013). Schiff base compounds act as antibacterial such as, N-(salicylidene)-2-hydroxyaniline which is an effective agent against Mycobacterium tuberculosis H37Rv (Da Silva et al., 2011). Thus, Schiff base compounds are considered as a mediate means to prepare various bioactive compounds (Vigato and Tamburini, 2004).

The importance of sulfonyl hydrazide as an essential issue whether at level of bio-reactions or synthesis reaction come from the involvement of C-S bond in its structure (Singh et al., 2013). It is represented in drugs such as methane sulfonyl hydrazide which shows antibacterial effect (Ozdemir et al., 2015). Sulfonyl hydrazide behaves also as DNA binder agent and has antitumor actions against several tumor types (Silva et al., 2006). Sulfonyl hydrazine's derivatives also behave as cancer chemotherapeutic agents such as: 1, 2- bis (methylsulfonyl) -1-2 (methylamino) carbonyl-hydrazine, which exhibits broad anti-cancer activities (Zhao et al., 2015). Cloretazine was detected to inhibit-enzymes which contain thiols functional group (Rice et al., 2005). Derivatives of Sulfonylhydrazide have potent analgesic applications (Chohan et al., 2006). Sulfonylhydrazide Schiff bases also have resemblance to other material prepared like azomethine (C=N) and sulfonamide (O2-S-N). Schiff base compounds have capacity to bind with DNA as clearly appeared in many studies (Aouad et al., 2019). DNA plays a crucial role in the process of treating diver pathologies, such as cancer. DNA- intercalators, was the leading cause in drugs discovery (Hadda et al., 2013). The compounds bind with double stranded DNA through groove, covalent binding and intercalation such these sites are fit for the docking of several intercalators by autodock (Gilad and Senderowitz, 2013). The crucial function played by pancreatic lipase inhibition is to drain needles fat deposit. The mechanism in which these compounds worked is based on fat digestion, these inhibitors are covalently bind in the active site of pancreatic lipase and this binding results in a stable compound, there are several compounds show activity of pancreatic lipase such as saponins and flavonoids (Palayyan and Subramanian, 2017). This research aimed to synthesis and spectral characterization of a new compound

of Sulfonylhydrazide Schiff base N'- (2-Hydroxy-5 -nitrobenzylidene) naphthalene – 2 -sulfonohydrazide (SB), from naphthalene – 2 -sulfonylhydrazide by using substituted aldehydes, evaluating it as an antibacterial agent, testing the porcine pancreatic lipase inhibition activity besides studying its possible interaction with pancreatic lipase by using suitable auto docking software.

EXPERIMENTAL:

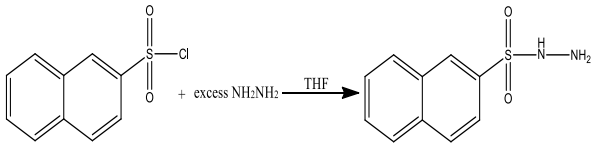
Materials and Instrumentation:

All reagents and solvents were used in synthesis and biological parts were purchased from Sigma -Aldrich Chemical Company Schnelldorf, (Germany), such as Orlistat, dimethyl sulfoxide, p-nitrophenyl butyrate and tris-HCl buffer and from Sigma (USA) we purchased porcine pancreatic lipase type (II) (100- 500 units/mg protein) used without further purification. 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. 1H and 13C (JNM-ECZ600R/S1) Spectrometer were performed on 600 MHz in Qatar University to acquire NMR-data, using CDCl3 as solvent. AUTO-DOCK version 4.5 was used for docking study .

SYNTHESIS:

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

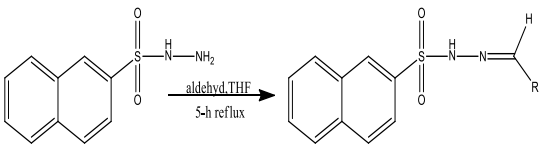
The white solid product was formed by addition of excess amounts of hydrazine hydrate (NH2-NH2.H2O) to stoichiometric amount of naphthalene-2-sulfonylchloride [5:1], in a THF solvent as shown in Scheme.1. After 2-hours of stirring at room temperature, two layers were formed, the organic layer was kept in order to evaporate the THF, then a residue was separated and washed with distilled water for several times. Then it was left to be dried in a desiccator at room temperature.



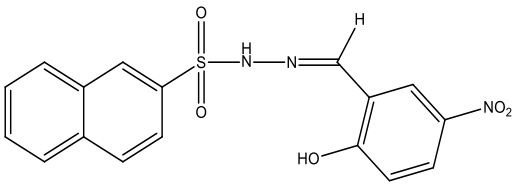
Scheme (1): The chemical reaction of Naphthalene-2-sulfonylhydrazide

General procedure of Sulfonylhydrazide Schiff bases:

The Sulfonylhydrazide Schiff base was prepared as in Scheme 2. The equivalent amount of naphthalene-2-sulfonylhydrazide was added to aldehyde compound. The solution refluxed for 5-hours at 70-80°C using THF as a solvent. After evaporating THF, a residue of N'-(2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide Scheme 3 was separated and washed with distilled water for several times. Then it was left to be dried in a desiccator at room temperature.



Scheme (2): represents the general chemical reaction of Sulfonylhydrazide Schiff base.



N'-(2-hydroxy-5-nitrobenzylidene)naphthalene-2-sulfonohydrazide

Scheme (3): Chemical structure of N'-(2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide

Pancreatic Lipase Inhibition:

The porcine pancreatic lipase inhibitory assay was adapted from (Bustanji et al., 2010; Zheng et al., 2010) with some modifications. Stock solutions of (1000 µg/ml) of tested products "SB and Orlistat" in 10% DMSO were prepared. Five different solutions were diluted from the stock solution with the following concentrations (50, 100, 200, 300, 400 µg/ml). 1mg/ml of a stock solution of pancreatic lipase enzyme in tris-HCl buffer was also prepared immediately before using it. Stock solution of p-nitrophenyl butyrate (PNPB) was prepared by dissolving 20.9 mg in 2 ml of acetonitrile. For each working test tube, 0.1ml of porcine pancreatic lipase (1 mg/ml) was added to a test-tube containing 0.2 ml from each diluted test-tubes containing (50, 100, 200, 300, 400 µg/ml) tested products. The resulting mixture was then made up to 1ml by adding tris-HCl solution and incubated at 37°C for 15 minutes. After the incubation period, 0.1ml of PNPB solution was then added to each test-tube. The mixture was again incubated for 30 min at 37°C. Pancreatic lipase activity was determined by measuring the hydrolysis of p-nitrophenolate to p-nitrophenol at 405 nm using UV-visible spectrophotometer. The same procedure was carried out for all the diluted solutions of the tested compound and for Orlistat (a positive control) using the same concentrations as mentioned above. The established tests were performed in triplicates.

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 µg/ml of Schiff base was prepared by dissolving appropriate amount of it in 10% DMSO, then it was two folded-serially diluted in nutrient broth directly in the wells with a final volume of 1000 µl. 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 µg\ml). After that, a bacterial inoculum size of 104 CFU/ml was added to each well. Negative control wells containing 100 µl DMSO with bacterial inoculum, or Schiff bases and nutrient broth without bacteria were included as well. The Schiff base was run in triplicate. The microtiter plate was then covered and incubated at 37°C for 24 hrs. MIC was determined by visual inspection. Then the contents of the wells with no turbidity after MIC evaluation were cultured on nutrient agar free of an antibacterial component using sterile cotton swabs and incubated at 37°C for 18 hrs. The lowest concentration which showed no bacterial growth was considered as MIC.

RESULTS AND DISCUSSION:

The Schiff base 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), FTIR, 1H-NMR, 13C-NMR and UV-Visible.

Summary of Spectral Analysis:

Naphthalene-2-sulfonylhydrazide (starting martial, NS); Yield 88%; m. p. = 123°C, the white product soluble in THF, alcohol solvents like methanol, ethanol and chlorinated solvents such as chloroform; molecular formula C10H10N2O2S. FT-IR: 3357 cm-1 ν(NH), 3070 cm-1 ν(=C-H), 1620 cm-1 ν(C=C), 1333 cm-1 ν(S=O); 1H-NMR (600 MHz, J=7.5 Hz, CDCl3, ppm): 3.1 broad (s, 3H, NH), 7.5 (s, 1H, C-CH=C-SO2), 7.55 and 7.62 (td ,2H, CH=CH-CH=C),7.9 (d, 1H, CH=CH-C-SO2), 8.1(d, 1H, CH=CH-CH=C), 8.3 and 8.6 (d, 1H, CH=C-CH=CH); 13C-NMR (600 MHz,CDCl3, ppm):124, 124.5, 127, 128.7, 129.2, 132, 135.4, 128.4, 131 and 134.4; [M+] = 221.2 m/z. UV-Visible (THF): 238 and 291 nm.

N'-(2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide (SB); Yield 85%; yellow solid; m. p.= 210°C; molecular formula C17H13N3O5S; FT-IR: 3192 cm-1 ν(N-H), 1634 cm-1 ν(C=N), 2997 cm-1 ν(=C-H), 1577 cm-1 ν(C=C), and 1341 cm-1 (N=O), 1321 cm-1 ν(S=O), 1163 cm-1 ν(C-O); 1H-NMR (600MHz, CDCl3, J=7.5 Hz, ppm): 8.5 (s, 1H, N=C-H) azomethine group,11.5 (s, 1H, NH), the benzyl group has 9.9 (s, 1H, CH=CH-OH), 7.04 (d, 1H, HO-CH=CH-CH), 7.1 (d, 1H, CH-CH-C-NO2), 7.97 (s, 1H,N-N=CH-C=CH-C-NO2) and naphthalene has 7.9 (s, 1H,C=CH-C-SO2), 8.064 (d, 1H, C=CH=CH=C-SO2), 8.093(d,1H,C= CH=CH=C), 8.095 (d, 1H, CH=CH=C-SO2), 8.36 (d, 1H, CH=CH=C)7.57 and 7.66 (t, 2H, CH=CH=CH=CH); 13C-NMR (600MHz, CDCl3, ppm): 128.3, 126.2, 126. 6, 128.2, 126.7, 139.9, 116.6, 119, 122.7, 132.4, 146.1, 127.7, 123.5, 135.4, 160.5, 133.6; [M+] = 374.9 m/z; UV-Visible (THF): 238, 278 nm.

Thermal Analysis of N'-(2-Hydroxy-5-nitrobenzylidene) naphthalene-2-sulfonohydrazide:

The thermal behavior of the Schiff base product was analyzed by TG/DTG in range of (0-800°C) temperature in open air atmosphere with 10°C min-1 as heat rate, Figure 1, describes the composition and the decomposition of the components and it is important to show the purity of compound.

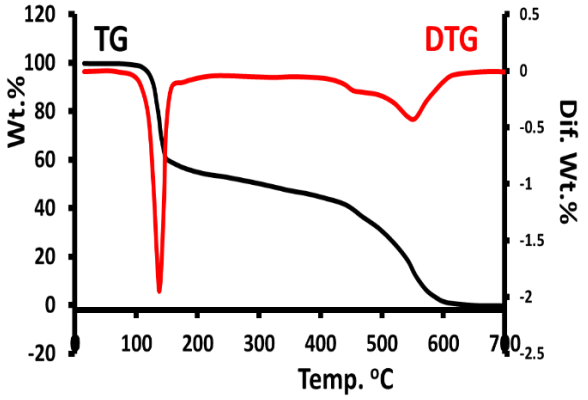


Figure (1): TG/DTG thermal curve of SB

The Figure (1) showed Schiff base decomposed in two steps, the first decomposition step started from 110°C and ended at 200°C, and the second step which carbon decomposition at 440-620°C, above 620°C the compound was completely decomposed.

Antibacterial Activity of Schiff Base Compound:

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 (Chahmana et al., 2019). Therefore, part of the current study was conducted to explore the antibacterial potential of the synthesized Schiff base product, one of the starting materials "naphthalene - 2 - sulfonylhydrazide" and tetracycline was used as standard. The antibacterial activity of the tested compounds was assessed by determining the MIC concentration for the compound against MRSA, S. aureus, E. coli, P. aeruginosa, and K. penumonia bacterial strains. SB was administered to all mentioned bacterial except for E. coli. On the other hand, NB and TE were applied for all types of tested bacteria. NB shows inferior effect as bacteriostatic compared to tetracycline, but it shows similar effect against Pseudomonas aeruginosa. While, administering the SB against Klebsiella pneumonia shows the greatest effect. The MIC was 125µg/ml when SB was used while it was 500µg/ml in Tetracycline. To lesser extent, SB has good outcome against MRSA at concentration of 125 µg/ml compared to 250 µg/ml using tetracycline. In the other hand, it hasn't any bacteriostatic effect against Pseudomonas aeruginosa and S. aureus.

Table (1): The MIC for SB, NB and TE antibiotic.

Types of Bacteria	Compounds		
	SB	NB	TE
MRSA	125	500	250
S. aureus	1000	1000	500
Escherichia Coli	0	1000	500
Pseudomonas aeruginosa	500	500	500
Klebsiella pneumonia	125	1000	500

Lipase enzyme inhibition activity for Schiff base compounds:

The inhibition of lipase activity can be used for determination of the potential suitability of food products or food compounds to serve as anti-obesity agents (De la Garza et al., 2011) On the other hand, this activity can indirectly influence the inhibition of inflammatory process, since obesity is associated with chronic inflammation and is a major risk factor for many diseases such as diabetes, chronic kidney disease, and cardiovascular diseases (Toita et al., 2016). The lipolytic mechanism of lipases and their role in the pathogenesis of inflammation and obesity is still poorly understood. Orlistat is one of the well-known anti-obesity agents inducing inhibition of lipase activity by interaction with the catalytic sites of the enzyme. The compound SB showed anti-lipase activities at various concentrations in Figure (2). In general, the activity of lipase decreased by increasing the concentration of Orlistat and the SB compound. The IC50 values for the drug and SB compound were calculated and the degree of lipase inhibition was plotted as shown in Figure (2). The IC50 values represent the concentration of the inhibitors at which 50% of the enzyme is inhibited and it is generally used to express the inhibitory effect of the lipase

enzyme. Particularly, at given doses 50 µg/ml, 100 µg/ml, 200 µg/ml and 300 µg/ml the lipases inhibition percentage was very close ranging from %66.76 to %68.7 and this lower than the reference compound which is Orlistat. At the same doses of Orlistat, the inhibition of lipase activity was ranging from 91.05 to 97.4. Interestingly was found at higher dosage 400 µg/ml the lipase inhibition activity was similar in both SB and Orlistat %97.75. The tested compound SB was distinguished as anti-lipase activate. Orlistat is known as pancreatic lipase inhibitor which is perfectly used as anti-obesity drug, Orlistat and compound of SB the IC50 values were calculated as (12.3±0.35) and (42.65±0.97) µg /mL, respectively as shown in **Figure(2)**.

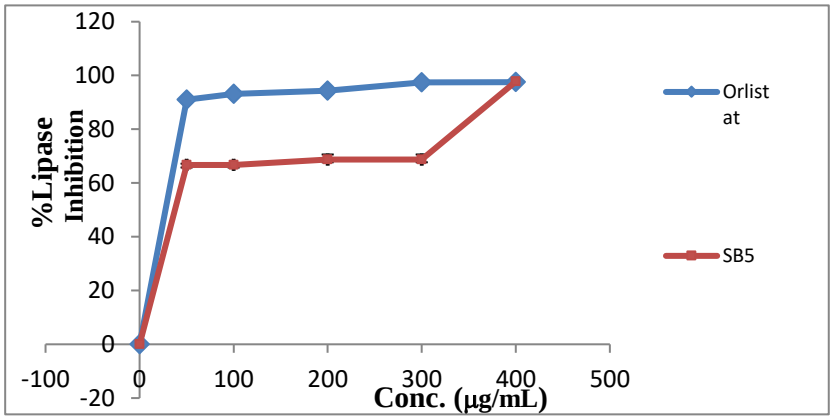


Figure (2): IC_{50} (µg/mL) values for SB compound comparing with Orlistat (IC_{50}= 12.3µg/mL) as reference.

Auto Docking:

The molecular docking results could be analyzed based on the tabulated score and the interaction between the docking molecular sites of lipase functional groups, since the desired compound containing N, O and S heteroatoms with lone pair of electrons, therefore, several hydrogen bonds expected to be formed. Docking of such compounds with porcine pancreatic lipase was performed to figure out the binding mode between the tested compound SB and lipase since such compound reflected a lipase inhibition experimentally .

The docking result was illustrated in Figure (3) where it is reflected the desired SB as a strong binder. Three strong hydrogen bonds exist between lipase and SB, The amino acid

residues TYR 370 and LYS 42 form two H-bonds within 2.137 and 1.911°A, respectively and the remaining residue GLU 371 served as H-bond donors (within 1.717°A). The H-bond distance between GLU 371 and SB was the shortest among the three hydrogen bond distances, as seen in Figure (3c and d).

The docking results consistent with the experimental porcine pancreatic lipase result of the same Schiff base. Therefore, such material is considered to be promising lipase inhibitors drug.

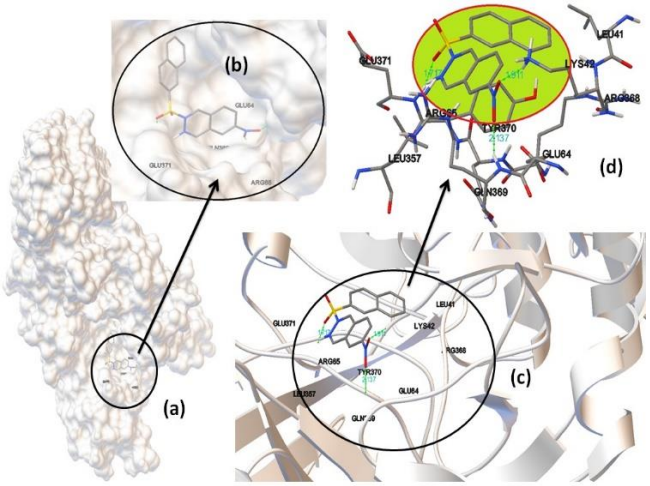


Figure (3) Detailed view of the docked poses of SB derivatives and the corresponding interacting amino acids within the binding site of pancreatic lipase enzyme.

CONCLUSION:

A novel Schiff base compound containing Sulfonylhydrazide functional group was synthesized in very good yield via condensation of naphthalene-2- sulfonylhydrazide with 2-hydroxy-5- nitrobenzaldehyde. The structure of desired ligand and the product was identified using FT-IR and NMR spectroscopy, and then the products were confirmed also by UV-Vis spectrophotometry.

The promising bacteriostatic effect of this compound was against bacteria such as MRSA, and K. pneumoniae, also it was active as a lipase enzyme inhibitor such characters are valuable for biological applications. The molecular docking was studied for the compound SB with porcine pancreatic lipase, the results of theoretical docking explained the experimental one since several hydrogen bonds between the SB and amino acids in lipase were detected .

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