An-Najah National University

Faculty of Graduate studies

Synthesis and Characterization of Sulfonylhydrazide-Schiff Bases, their Biological Activities and Molecular Docking

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This Thesis is submitted in Partial Fulfillment of the Requirements for the Degree of Master of Chemistry, Faculty of Graduate Studies, An-Najah National University, Nablus, Palestine.

2019

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Dedication

As I move from this chapter of my life, I would like to draw a note of warmest thanking for every one supported me throughout my years of education.

I owe a lot of thanks to my beloved parents who always are the shoulder I depend on thank you so much for the amazing job you did to help me.

I can’t stop thanking my dearest brothers, sisters and all my uncles for their wonderful presence in all rough time and for their believing in me. Great thanks for your efforts.

Bunches of thanks to my professors who inspire me that I can success beyond what I thought is possible.

Acknowledgments

All gratitude goes to almighty God who always leads me to successes. I would like to express my great thanks whoever helped me.

Deepest thanks and appreciation to my supervisor, Prof. Ismail Warad as well as to Prof. Mohammed Al-Nuri, for the golden role they played, and for their significant contribution in stimulating motivations, encouragements and guidance.

Furthermore, special thanks and much appreciations to Mr. Nafith Dweikat for his great effort to simplify and facilitate my works in lab and for his remarkable advices throughout my research.

Specially thanks are attributed to my parents, sisters (Rawa, Alia and Jana), brothers (Ahmad, Mohammad and Zaid) and my uncles especially Dr. Shaher Daraghmeh who supported me during my study.

Thanks are also due to my friends, particularly Mr. Mohammad Abu-Amer, who always has been my intimate friend, and thanks for Mr. Anas Al-Ali, who motivated me and provided me with adequate knowledge about Auto-Docking.

Finally, thanks to chemistry department at my University.

الإقرار

انا الموقع ادناه مقدم الرسالة التي تحمل العنوان:

Synthesis and Characterization of Sulfonylhydrazide-Schiff Bases, their Biological Activities and Molecular Docking

أقر بأن ما اشتملت عليه هذه الرسالة إنما هو نتاج جهدي الخاص، باستثناء ما تمت الاشارة اليه حيثما ورد، وأن هذه الرسالة ككل أو جزء منها لم يقدم من قبل لنيل أي درجة أو بحث علمي أو بحثي لدى أي مؤسسة تعليمية او بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree of qualification.

Student's name: **اسم الطالب:**

Signature: **التوقيع:**

Date: **التاريخ:**

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List of Abbreviations

Abbreviation	Naming
Az	Starting material(Napthalene-2-Sulfonylhydrazide)
SB	Schiff base
^{1}H and ^{13}C-NMR	Proton and Carbon Nuclear Magnetic Resonance
GC/Ms	Gas Chromatography/Mass spectrometry
EA	Elemental Analysis
TGA	Thermal gravity analysis
UV-Vis.	Ultra-Violet and Visible
FT-IR	Fourier-transform infrared
TLC	Thin layer chromatography
Mp	Melting point
°C	Degree Celsius
DFT	Density Functional Theory
MEP	Molecular Electrostatic Potential
FMO	Frontier Molecular Orbital
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
ν	Frequency
TE	Tetracycline
MIC	Minimum Inhibition Concentration
MBC	Minimum Bacteria Concentration
NUH	National University Hospital
IZD	Inhibition Zone Diameter
THF	Tetrahydrofuran
$CDCl_3$	Deuterated chloroform
DMSO	Dimethyl sulfoxide
R^2	Correlation coefficient

Synthesis and Characterization of Sulfonylhydrazide-Schiff Bases, their Biological Activities and Molecular Docking

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Abstract

The work in this thesis focused on condensation of naphthalene -2-Sulfonylhydrazide, as starting material with various aldehydes, in order to produce five novel Schiff base compounds. The desired Schiff bases were isolated, purified and then spectrally characterized *via* UV-Vis., GC/MS, FT-IR, EA, ^{1}H and ^{13}C NMR analysis. One of desired SB-products was subjected to TG/DTG thermal analysis.

The E/Z-structural isomers in one of desired SB's were optimized through B3LYP/DFT method. Several DFT computed processes like: MEP map, GRD, IR/B3LYP, FMO and HOMO-LUMO were performed.

In vitro antimicrobial activities of the desired SB's were evaluated against several types of bacteria such as: *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia* and *MRSA* by disk diffusion and (MIC, MBC) tests by using TE as a standard antibiotic. Pancreatic porcine lipase inhibition assay of the desired SB's making Orlistat as reference was evaluated.

Docking effect of the best lipase inhibitor SB with the same PDB-lipase was evaluated then matched the experimental result with the theoretical one.

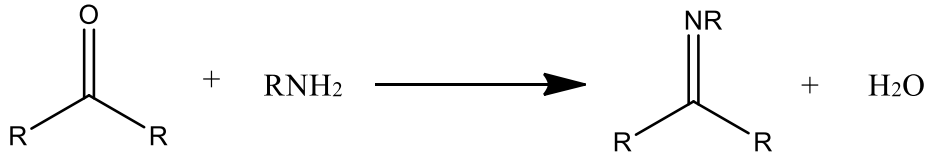
Chapter one

Introduction

1.1 Chemistry of Schiff base:

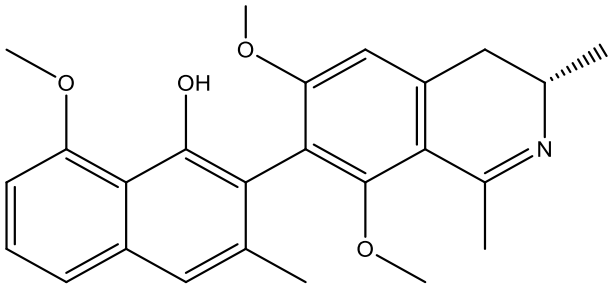
Schiff base is regarded as one of the most important azomethine group organic compounds acted as an intermediate for many processes (1).The existence of the lone pair of electron in SP^2-hybridized orbitals of nitrogen atom in the azomethine group, gives such compounds an interesting biological and chemical importance (2-5).

Schiff bases are basically formed by condensation process of primary amines and aldehydes or ketones carbonyl groups (6-9), as shown in **Scheme 1.1**



Scheme 1.1: General formation of Schiff base.

Aromatic Schiff bases are more stable than aliphatic one may be due to conjugation [8]. Such aromatic Schiff bases can be obtained from plant as naturally occurring like ancistrocladidine (**Scheme.1.2)** which used as antimalarial activity (10).

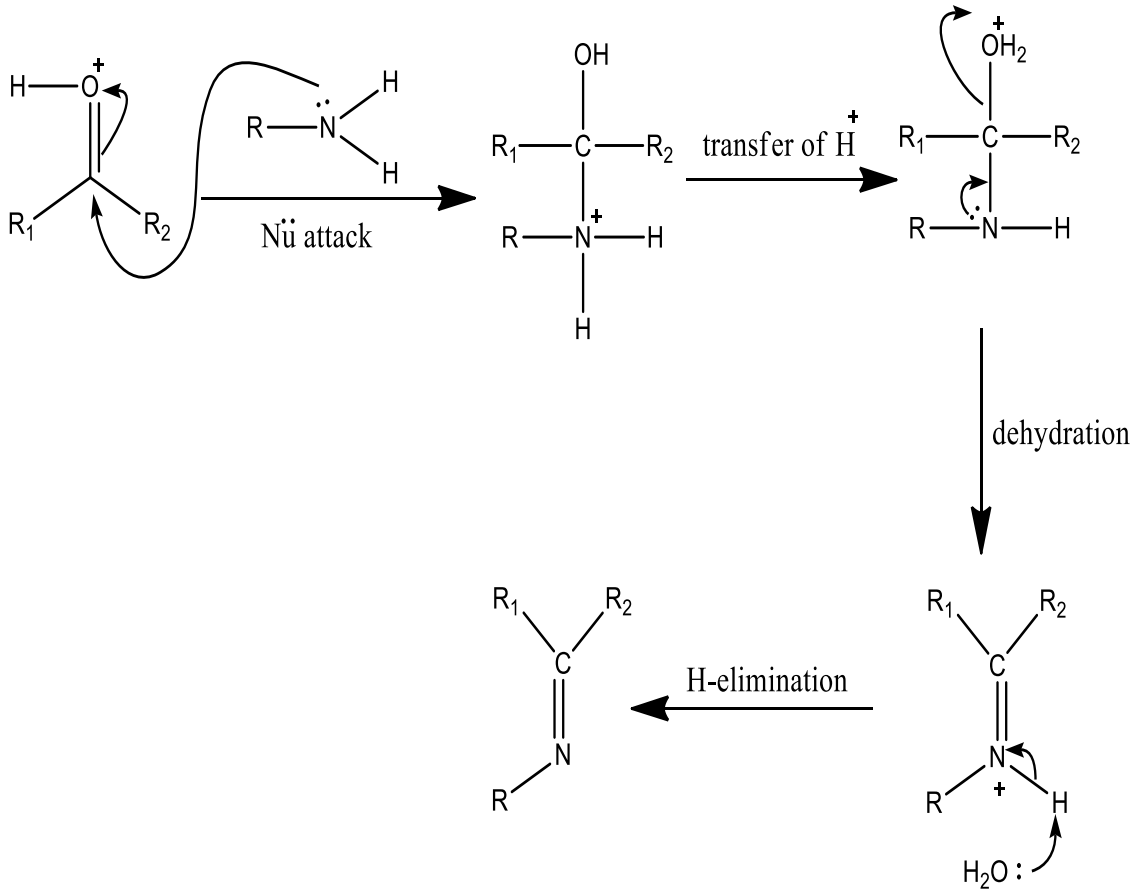


Scheme.1.2:-The structure of ancistrocladidine.

These SB compounds are considered to be medical compounds due to their biological activities in field of: antifungal, antimalarial, anticancer and DNA binding (11-13). In industrial applications they are used mostly as pigments and dyes (14). Moreover, Chemists design Schiff bases as polydentate ligands and their complexes served several areas in chemistry (15). Schiff bases are supposed to be notable ligands for metal ion coordination complexes due to their ease of synthesis, varieties in structural design, mode of ligations and huge applications (15-20). Such ligands were broadly used as poly-chelator compounds and have revealed high performance in the steric characteristics and electronic soft tuning of their metal complexes (20-23). Some of Schiff bases have been used as corrosion inhibitors for several metals (24).

1.2 The mechanism of Schiff base synthesis

The mechanism of SB synthesis is summarized through nucleophilic attack of the unshared pair of electron of nitrogen of amine on the e – deficient carbonyl group, then loss of water molecule to produce an imine (C=N).



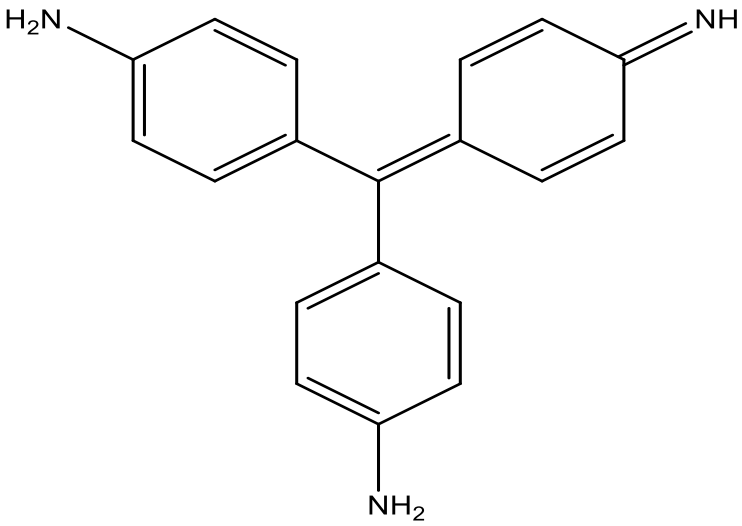
Scheme 1.3. The mechanism of Schiff base synthesis

In general, the classical Schiff base reaction is reversible one; it takes place in acidic or basic media through a reflux process. Amine is a nucleophile that attacks electrophile which is carbonyl carbon to give carbinolamine, then nitrogen atom is deprotonated by acid or base catalyzed, then lone pair of electrons back create a double bond between carbon and nitrogen and through loss of H_2O molecule, as shown in **Scheme 1.3** (25).

1.3 History of Schiff base

The Schiff base compound synthesized first after Hugo (Ugo) Schiff, in 1864 (Pisa, Italy). Her first study was on aniline with several compounds

such as acetaldehyde and benzaldehyde. Fuchsine Schiff compound as shown in **Scheme 1.4**, is used extensively in dyes industry (26; 27).



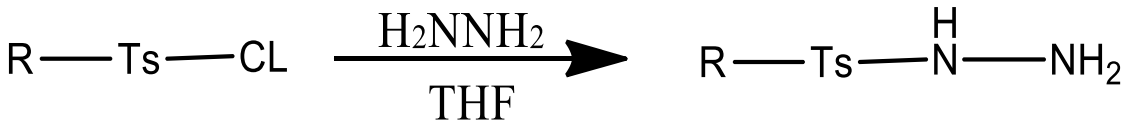
Scheme 1.4: Structure of Fuchsine Schiff base.

In 1990, water molecule was eliminated by dehydrating solvents such as trimethylorthoformate (28), then after that Chakraborti et al in 2014 developed this method (29), and it is concentrated on the type of electrophile (carbonyl group) and strong nucleophile (amine group), the substances act as either Lewis acid to make carbonyl group more active, and to catalyze the nucleophilic attack by amine then dehydrating step follow, the final step where water molecule was eliminated (30).

Recently, microwave irradiation was used instead of conventional method to synthesize organic compounds such as Schiff base products (31). It is an easy method where the compounds synthesized under free solvents condition which is considered as green chemistry. It reduces the reaction time and increases the percentage yield (31-33).

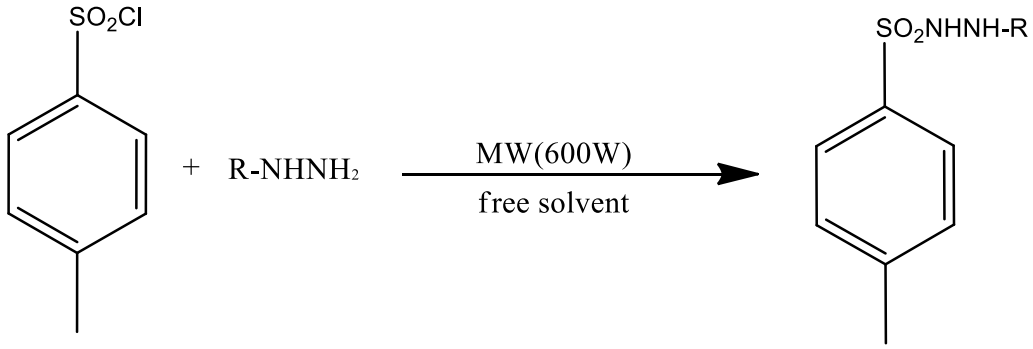
1.4 Sulfonyl Hydrazide:

Many studies have shown the way in which sulfonyl hydrazide can be prepared by condensation reaction, which start by any group has sulfonyl chloride and hydrazine or amines, such reaction is carried out in a suitable solvents like: THF, DMSO and alcohols (34-37), as shown in **Scheme 1.5.**



Scheme 1.5: Synthesis of sulfonyl hydrazide from hydrazine

Microwave irradiation is another method to prepare sulfonyl hydrazide, as shown in **Scheme 1.6**, which had first appearance in 1986, and it is regarded as friendly chemical environment because the reaction is done under free-solvent, and it reduce the time of reaction and high percentage yield (38).



Scheme 1.6 : Synthesis of sulfonyl hydrazide from hydrazine by microwave reactor.

Sulfonyl hydrazide is a starting point for many chemical reactions, which is considered as a crucial compounds in many fieldes of life such as

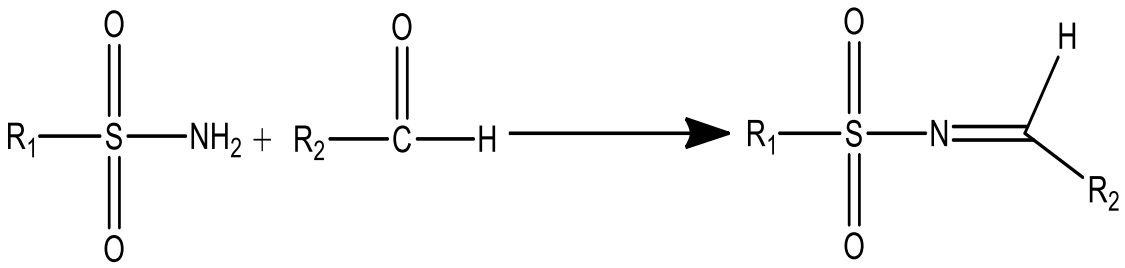
medicine, some examples about these reaction are 3-sulfonyl nitrile and 3-Aryl benzofuran-thioether (39; 40).

The importance of sulfonyl hydrazide as an essential issue whether at level of bioreaction or synthesis reaction come from the involvement of C-S bond in its structure (41). It is shown that its presence is important in the composition of chemical compounds, it is represented in drugs such as methane sulfonyl hydrazide which contains antibactrial effect (42). Sulfonyl hydrazide behaves as DNA binder agents and have antitumor actions against several tumor types (43). 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 (40; 42). Cloretazine was detected to inhibit-enzymes which contain thiols functional group (44). Derivatives of Sulfonyl hydrazone have potent analgesic applications (45). Furthuremore, sulfonyl hydrzide has been used in many aspects in industry which needs blowen agents for producing plastic (46).

1.5 Schiff base of sulfonyl hydrazide

Recently, many studies about Schiff bases involve sulfonyl group, as in sulfonamide (SO_2-NH_2) which is known as sulfa drug. It is used as an inhibitor for HIV- Protase (47-50). The condensation of sulfonyl hydrazide and carbonyl compound as an aldehyde produce another type of schiff base that is called sulfonyl hydrazide Schiff base (51).

Condensation of sulfonamide with aldehyde to furnish sulfonylhydrazide Schiff base, is elaborated in **Scheme 1.7**.



Scheme 1.7: General reaction of Sulfonylhydrazide Schiff base.

These types of reaction inspire create many applications which are based on biological activities, industrial drugs (52-56) Sulfonylhydrazide Schiff bases also have resemblance to other material prepared like azomethine (C=N) and sulfonamide (O_2-S-N) Sulfonyl hydrazides showed broad pharmacological applications such as antidiabetic, anti-inflammatory antitumor analgesic and anticancer activities (57-59).

1.6 Applications

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 (60). They have wide range in biological activity which includes antibacterial, anti-inflammatory, anticancer and antiviral (61-64).

1.6.1 Biological activities

The evolution in research has been fundamental matters which disclose various disciplines having a good chance to deal in numerous

common problematic issues which does exist by modernity. Medical science for example succeeded in eliminating fatal disease which threat lives, and prolong people's life. Actually, this is a great remark for a bright future for generations. The idea of synthetic drugs to figure out how to eradicate and to reduce disease is a significant accomplishment and is the result of team effort involving of chemists biologists and medical specialists. Among the most primary challenges encounter medical science are pathogen upgrades its capacity for combating disease, impair is ability to kill bacteria and , the appearance of new varieties of illness (57; 64; 65).

The study of biological activity of many structures is very important to improve medicine and cure diseases, there are about seven million compounds which synthesized and examined for biological properties (66-68). For example, 2-methyl-6-phenylethylpyridine (MPEP), which has electronic properties (π – electrons), which are used in various field especially in antidepressant and anxiolytic effect in animals [57].

The leading cause of the constant increase in the death rate is linked with contagious diseases is basically related to bacteria powerful immune capacity, as well as to the shortage of effectively tackling.

Having sophisticated antibacterial agents along with upgrading mechanisms of action is obviously a pressing medical need. Many studies have shown that Schiff base is antibacterial such as, N-(salicylidene)-2-hydroxyaniline is effective against *Mycobacterium tuberculosis H37Rv* (1).

Thus, Schiff base compounds are considered as a mediate means to prepare various bioactive compounds (69).

1.6.1.a-Antibacterial:

The main aim of synthesizing such antimicrobial compounds is to kill or inhibit the activity of pathogenic bacteria thus limit the complications on patients .Despite the fact of the existence of a gradual evolution in antibacterial therapies, several problems need to be solved for many available antibacterial drugs (70). This research focused on studding the anti-bacteria for some sulfonyl hydrazide Schiff bases for some bacteria strains such as:

a.1- *Escherichia coli*:

It is considered one of the most common species spreading in Middle East (71), it is a gram-negative, having a rod-shape, as shown in **Fig.1.1**, which appeared under microscope. It usually intrudes on human body, particularly in the gut of the body. Water, food and animals are the medium for transporting the intestinal infection, which cause diarrhea (72).

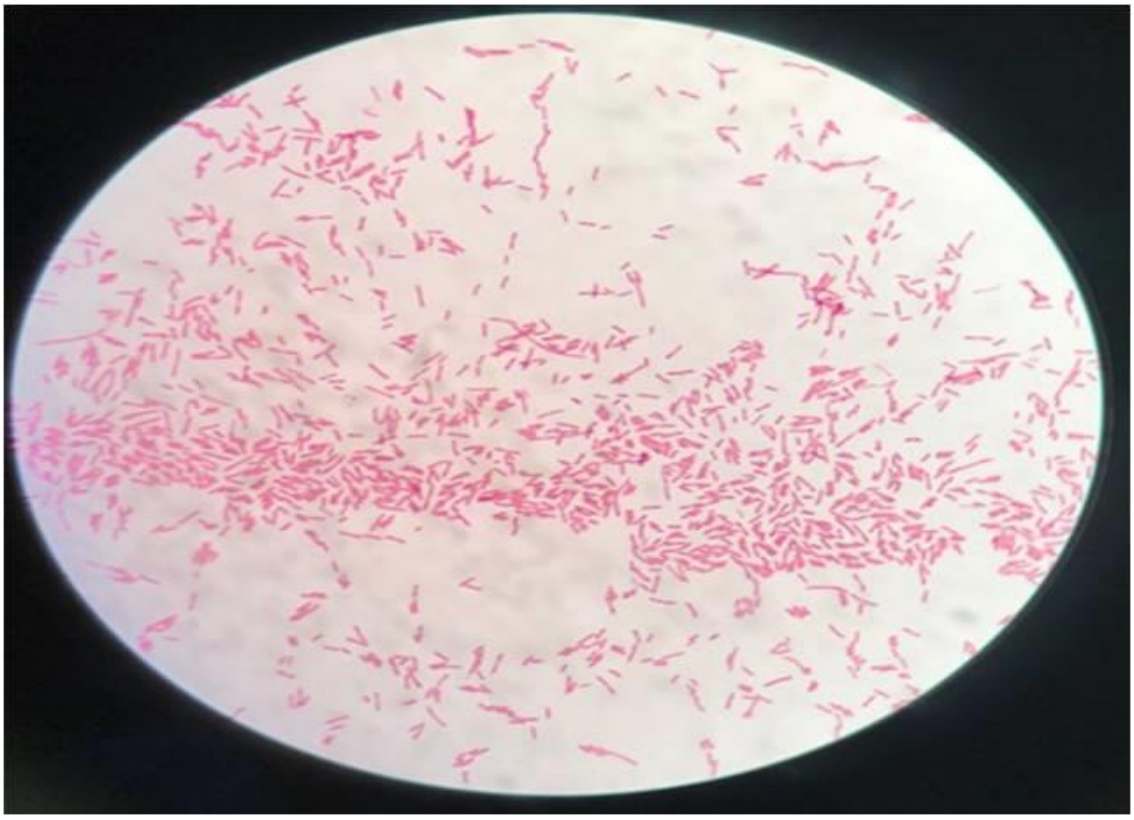


Fig.1.1: Escherichia coli bacteria

a.2- *Staphylococcus aureus*:

It is gram-positive bacteria, it has cocci-shape which is sorted in a cluster form, as shown in **Fig.1.3**, that showed under microscobe. It has serious effect in case it is transmitted to human, such as furuncles (73). Normally, it is existed in the surface of human skin and people who are exposed to such kind of bacteria strain (74).

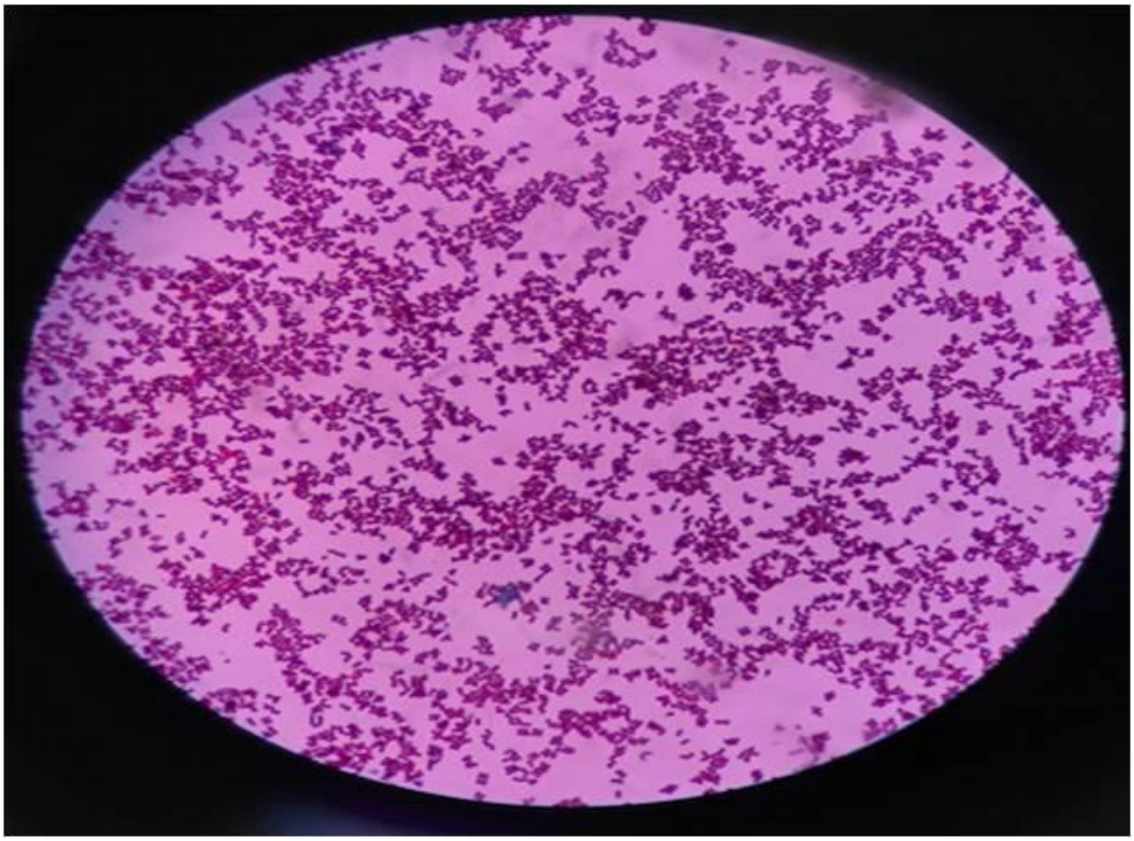


Fig.1.2:- Staphylococcus aureus bacteria

a.3- *Pseudomonas aeruginosa*:

It is an aerobic, gram-negative, that has rod-shape, as shown in **Fig.1.3**. Basically, it is found in wet environment such as water and soil. Although, it is hard to distinguish this kind among others, it has some symptoms in human such as, green nail and hot foot (75).

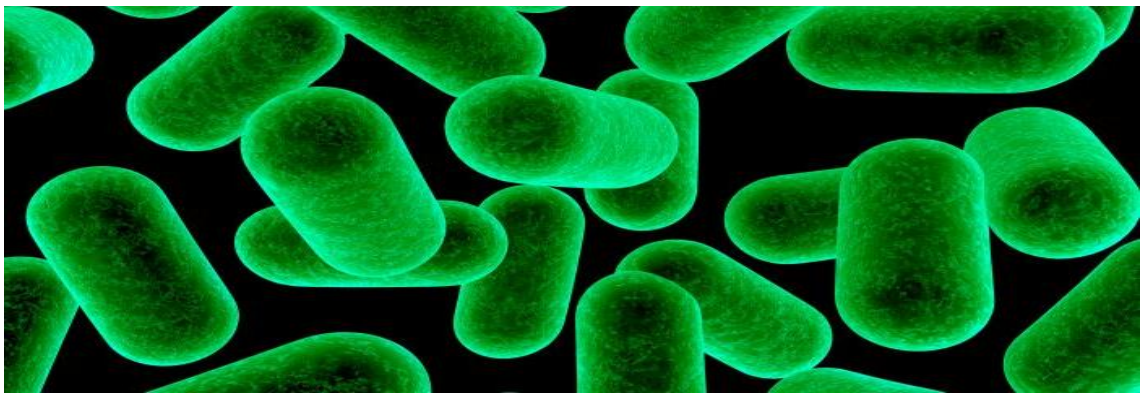


Fig.1.3: Pseudomonas aeruginosa bacteria

a.4- *Klebsiella pneumonia*:

It was discovered in 1882 by Carl Friedlande, when he isolated the lungs of those who died of this bacteria (76). It is described as gram-negative, non-spore-forming rod and aerobic bacteria, as shown in **Fig.1.5**, People in different ages are subjected to this bacteria especially infants and alcoholic (77).

Fig.1.4:- Klebsiella pneumonia bacteria

a.5- *Methicillin-resistant Staphylococcus aureus (MRSA)*:-

It is one of the most complex types of bacteria, since it is hard to cure, it is a gram-positive bacterium, as shown in **Fig.1.6**. People who are subjected to this kind are mainly workers in hospitals, the first appearance for this type of infection was in 1988, when a patient was admitted to the NUH. Some symptoms includes swelling, redness, high temperature (78) .

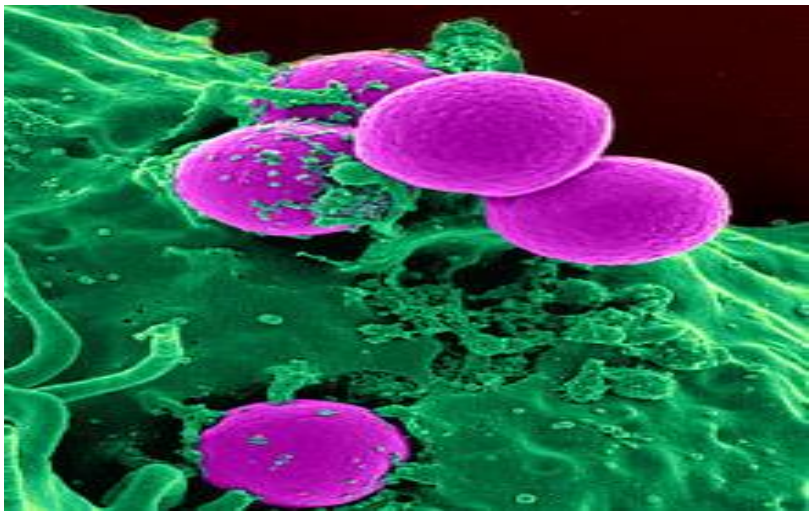


Fig.1.5:- MRSA bacteria

In this project, the synthesized Schiff base compounds were screening for the above-mentioned bacteria's strains by using disk diffusion methods, MIC and MBC.

1.6.1.b-Pancreatic Lipase Inhibition:

Many Schiff bases are commonly known in medicine since it is used to design medicinal compounds (79). 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 (80).

In this research, the Schiff bases compounds will used to test the porcine pancreatic lipase activity inhibitions.

1.6.2 Density Functional Theory (DFT):

In recent years, DFT studies become popular as theoretical Quantum chemical computational for many chemical reactions that's because it is easy to use and its provided many facilities such as (optimization of molecular structure, energies of chemical reactions,…) and this application agree with the experimental part (81; 82). In general Quantum chemical calculation has helped to understand many substances that's become new drugs (83).

The DFT-density functional theory methods have been used to determine several physical parameters of desired products which is very helpful in solving their molecular structures. Several physical measurements like FTIR, UV-vis, HOMO-LUMO, MPE, Mull and NPA, DOS, electronic transition and thermal parameters can be DFT-computed (84; 85),and these parameter are obtained from optimization of structure by using Gaussian software(86).

1.6.3 Auto-Docking:

Schiff base compounds have capacity to bind with DNA as clearly appeared in many studies (85). DNA plays a crucial role in the process of treating diver pathologies, such as cancer. DNA- intercalators, was the leading cause in drugs discovery (87). The compounds bind with double stranded DNA through three major aspects: groove, covalent binding and

intercalation as shown in **Fig. 1.7**, such these sites are fit for the docking of several intercalators by **AUTODOCK** (88).

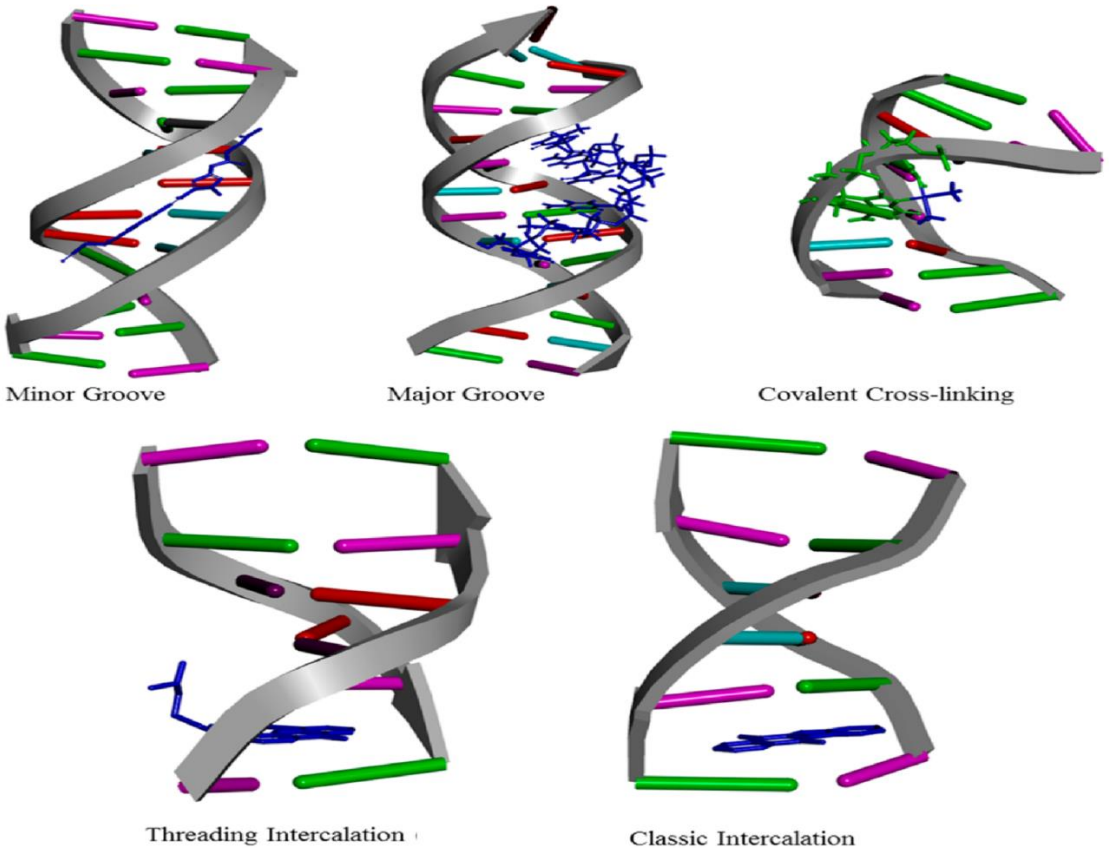


Fig. 1.6: Types of covalent binding between double stranded DNA with compound.

1.7 Objectives:

The major objectives of this study are the followings:

1. Synthesis and spectral characterization of a new family of sulfonyl-Schiff bases (SB) from naphthalene-2-sulfonylhydrazide and by using several substituted aldehydes.

2. Comparison between the experimental data and the optimized DFT-parameters like (optimization, MEP, FMO and GRD) of any solved structure from prepared compounds.

3. Evaluate the desired SB as antibacterial and enzyme inhibitor agents.

4. The thermal behavior of selected synthesized SB-ligands will be identified via TG/DTA analysis.

5. Performed docking analysis for (**SB_5**), the more active SB-compounds against Pancreatic porcine lipase.

1.8 Novelty:

The Novelty of this work appears in synthesis of Sulfonylhydrazide-Schiff bases by condensation of naphthalene-2-sulfonyl-hydrazide with different aldehydes. For the first time, the desired SB compounds expected to be highly antimicrobial and lipase inhibition activation. Matching between the experimental lipase inhibition and theoretical docking form to be very high in **SB_5**.

Chapter Two

Experimental Part

2.1 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.

TLC was performed to monitor the reactions when required. Elemental analysis were applied on Elementar-vario EL analyzer.

Thermal analysis was performed by TGA-1000, Deltachem Turkey Sanaf.

The melting point recorded for Schiff bases from Saturates Melting point apparatus SMP-3.

FT-IR(Perkin-Elemer Spectrum) spectrometer was used to gain IR spectra.

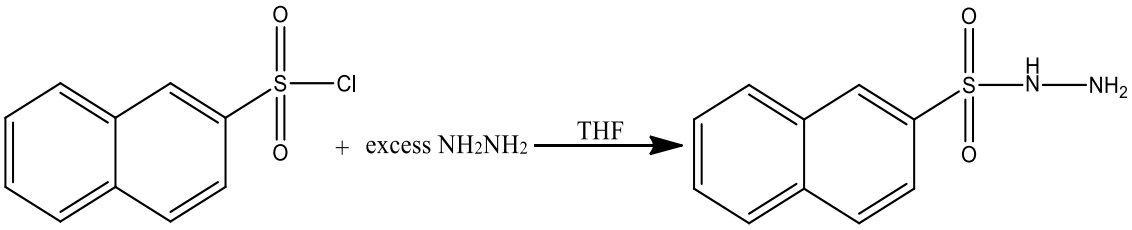
Shimadzu UV-VIS-NIR (UV-3101PC, TCC-260) scanning spectrophotometer was used to control the reaction by absorption measurements.

^{1}H and ^{13}C (JNM-ECZ600R/S1) Spectrometer were performed on 600MHz in Qatar University to acquire NMR-data, using $CDCl_3$ as solvent.

2.2 Synthesis

Synthesis of starting material (Naphthalene-2-sulfonylhydrazide):

The white solid product was formed by addition of excess amounts of hydrazine hydrate (NH_2-NH_2.H_2O) to stoichiometric amount of naphthalene-2-sulfonylchloride [5:1], in THF solvent as shown in **Scheme2.1**. After 2-hours of stir and at room temperature, two layers of excess hydrazine was separated, the organic layer remained in order to evaporate the THF, and then it washed and precipitated out with distilled water for several time.



Scheme 2.1:-The chemical reaction of Naphthalene-2-sulfonylhydrazide.

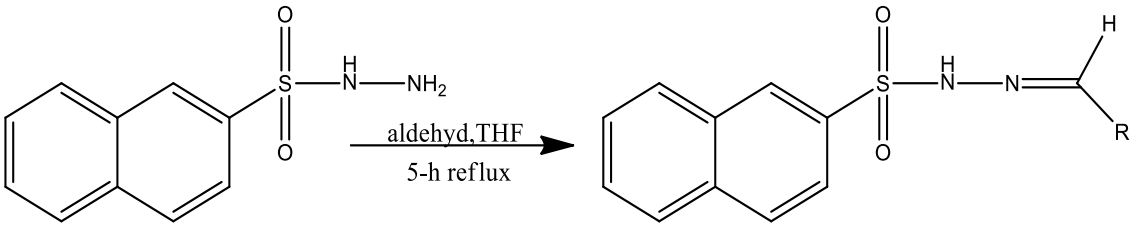
Compound (**Az**)

Naphthalene-2-sulfonylhydrazide; 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 $C_{10}H_{10}N_2O_2S$. FT-IR: 3357 cm^{-1} $\nu_{(NH)}$, 3070cm^{-1} $\nu_{(=C-H)}$, 1620 cm^{-1} $\nu_{(C=C)}$, 1333 cm^{-1} $\nu_{(S=O)}$;^{1}H-NMR(600MHz, J=7.5 Hz, $CDCl_3$, ppm): 3.1 broad(s, 3H, NH), 7.5 (s, 1H,C- CH=C-SO_2), 7.55 and 7.62(td ,2H, CH=CH-CH=C) ,7.9(d, 1H, CH=CH-C-SO_2), 8.1(d, 1H, CH=CH-CH=C), 8.3 and 8.6 (d, 1H, CH=C-

CH=CH); ^{13}C-NMR(600MHz,$CDCl_3$,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.

General procedure of Sulfonylhydrazide Schiff bases (SB_{1-5}):

The Sulfonylhydrazide Schiff base was prepared as in **Scheme2.2**. The equivalent amount of naphthalene-2-sulfonylhydrazide was added to aldehyde compound, were dissolved in THF solvent. The solution refluxed for 5-hours at 70-80℃. After evaporated solvent the product washed and precipitated with distilled water.



Sheme 2.2: General chemical reaction of Sulfonylhydrazide Schiff base.

Compound (**SB_1**)

N'-(2,4-dimethoxybenzalidene)naphthalene-2-sulfonohydrazide; Yield 91%; m.p= 159°C; yellow solid; formula $C_{19}H_{18}N_2O_4S$, FT-IR: 3152 cm^{-1} $\nu_{(N-H)}$, 1610cm^{-1} $\nu_{(C=N)}$, 2959cm^{-1} $\nu_{(C-H)}$, 3002cm^{-1} $\nu_{(=C-H)}$, 1284cm^{-1} $\nu_{(C-O)}$, 1315cm^{-1} $\nu_{(S=O)}$; ^{1}H-NMR(600MHz, $CDCl_3$, 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_3), 3.71(s, 3H,N=CH-C=C-OCH_3 6.2(s,1H,CH_3O-C-CH-OCH_3) and 6.32(d, 1H, N=CH-C-CH-CH-OCH_3), 6.35 (d, 2H, CH=CH-

COCH3) and naphthalene group has7.8 (s, 1H, CH=C-CH=C-SO_2), 7.84(s, 1H,C-CH=CH-C-SO_2), 8.01(s, 1H,C-CH=CH-C-SO_2), 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.

Compound (**SB_2**)

N'-((4-bromothiophen-2-yl) methylene) naphthalene-2-sulfonohydrazide. Yield 91%, white solid, m.p= 185°C; white solid; molecular formula $C_{15}H_{11}BrN_2O_2S_2$; FT-IR: 3154.5 cm^{-1} $\nu_{(N-H)}$, 1648 cm^{-1} $\nu_{(C=N)}$, 1557 cm^{-1} $\nu_{(C=C)}$, 1327.5 cm^{-1} $\nu_{(S=O)}$, 762 cm^{-1} $\nu_{(C-S)}$. ^{1}H-NMR(600MHz, $CDCl_3$, J=7.5 Hz, ppm): 9.8(s, 1H, NH),7.7 (s, 1H, N=C-H)azomethine group, thiophen group has 6.9 (s, 1H, BrC=CH-S), 7.1(s, 1H, Br-C=CH-C-S), in naphthalene ring 7.6 and 7.5(t, 2H, CH=CH-C), 8.1(s,1H, C=CH-C-SO_2), 7.9(d, 1H, C-CH=CH-C-SO_2) and 8..03(d, 2H, CH=C-CH=CH-C-SO_2), 8.3 and 8.8(CH-CH=C) ; ^{13}C-NMR(600MHz,$CDCl_3$,ppm): 110, 124, 125, 125.7, 127, 128.5, 129, 131, 132,133.4, 134.1, 135.3, 136.7, 138.3, 140.1(azomethine); [M^+]= 393.9 m/z; UV-Visible (THF): 238 and 308.5 nm.

Compound (**SB_3**)

N'-(furan-2-ylmethylene)naphthalene-2-sulfonohydrazide; Yield 93%; m.p= 144°C; light brown solid C;$_{15}H_{12}N_2O_3S$;FT- IR: 3253 cm^{-1} $\nu_{(N-H)}$,

1621 cm^{-1} $\nu_{(C=N)}$, 3087 cm^{-1} $\nu_{(=C-H)}$, 1359 cm^{-1} $\nu_{(S=O)}$, 1165 cm^{-1} $\nu_{(C-O)}$, 1594 cm^{-1} $\nu_{(C=C)}$; ^{1}H-NMR(600MHz, $CDCl_3$, J=7.5 Hz, ppm): 7.6 (s, 1H, N=C-H) azomethine group, 9.8 (s, 1H, NH), the furan group has 6.5 (d,1H, C-CH-C), 6.6 (d, 1H, O-CH=CH), 6.4 (t, 1H, N=CH-C=CH-CH) and naphthalene has 7.2 (s, 1H, C-CH=C-SO_2), 7.9 and 8.02(d, 2H, CH-CH=CH-CH-C), 8.4(d,1H, CH=C-CH=CH-C-SO_2), 8.7 (d, 1H, CH=C-CH=CH-C-SO_2), 7.4,7.6 (t, 2H, CH-CH=CH-CH-C); ^{13}C- NMR (600MHz, $CDCl_3$, ppm): 111.9, 115.9,124.3, 124.6, 126.9, 128.4, 129.1, 130.1, 131.1, 133.4, 134.3, 135.1, 137.8, 144.6(azomethine) and 148.2; [M^+]= 301.1m/z; UV-Visible (THF): 238 and 286 nm.

Compound (**SB_4**)

N'-((9-rthyl-9H-carbazol-1-yl)methylene)naphthalene-2-sulfonohydrazide; Yield 93%; orange solid; m.p=105°C; soluble in molecular formula $C_{25}H_{21}N_3O_2S$; FT-IR: 3183 $cm^{-1}_{(N-H)}$, 1602cm^{-1} $\nu_{(C=N)}$, 3064 cm^{-1} $\nu_{(=C-H)}$, 2966cm^{-1} $\nu_{(-C-H)}$, 1323cm^{-1} $\nu_{(S=O)}$; ^{1}H-NMR(600MHz, $CDCl_3$, J=7.5 Hz, ppm): 8.3 (s, 1H, N=C-H) azomethine group, 10.1(s, 1H, NH), the carbazol functional group has 3.7(t, 3H,CH_3-CH_2-N), 4.3(q, 3H,CH_3-CH_2-N), 7.44, 7.76 (t, 2H, C=CH=CH=CH), 7.57(t,1H, C=CH=CH=CH) 7.62and 7.91(d, 2H, N-C-C=CH=CH) 8.49(d,1H, N-C=CH=CH), 8.98(d, N=CH-C=CH=CH), and naphthalene contains 7.93(s, 1H, C=CH=C-SO_2), 8.2(d, 1H, C=CH=CH), 8.14(d, 1H, CH=CH=C-SO_2), 8.091 and 8.047(d, 2H, CH-CH=C), 7.27 and 7.61(t, 2H, CH=CH=CH=C); ^{13}C- NMR (600MHz, $CDCl_3$, ppm): 12.8, 24.3, 36.6, 63.4, 66.9, 107.5, 107.8, 118.5, 119.3,

119.6, 121.7, 121.9, 123, 123.2, 123.9, 124.2, 125.2, 125.9, 127.2, 127.9, 129.7, 133.2, 133.9, 140.2, 148.4; $[M^+]$=429.11 and $[M^{+2}]$=430.4 m/z; UV-Visible (THF): 238, 290 and 321 nm.

Compound (**SB_5**)

N'-(2-Hydroxy-5-nitrobenzylidene)naphthalene-2-sulfonohydrazide; Yield 85%; yellow solid; m.p=210°C; molecular formula $C_{17}H_{13}N_3O_5S$; FT-IR: 3192cm^{-1} $\nu_{(N-H)}$, 1634 cm^{-1} $\nu_{(C=N)}$, 2997 cm^{-1} $\nu_{(=C-H)}$, 1577 cm^{-1} $\nu_{(C=C)}$, and 1341 $cm^{-1}{}_{(N=O)}$,1321 cm^{-1} $\nu_{(S=O)}$,1163 cm^{-1} $\nu_{(C-O)}$; ^{1}H-NMR(600MHz, $CDCl_3$, 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-NO_2), 7.97 (s, 1H,N-N=CH-C=CH-C-NO_2) and naphthalene has 7.9(s, 1H,C=CH-C-SO_2), 8.064(d, 1H, C=CH=CH=C-SO_2), 8.093(d,1H,C= CH=CH=C), 8.095 (d, 1H, CH=CH=C-SO_2), 8.36 (d, 1H, CH=CH=C)7.57 and 7.66 (t, 2H, CH=CH=CH=CH); ^{13}C- NMR (600MHz, $CDCl_3$, 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.

2.4 Anti-Bacterial methods

a) Disk diffusion method:

The turbidity of the inoculum suspension was adjusted to the 0.5 McFarland standard and used within 15 min after adjustment. A sterile cotton swab was dipped into the adjusted suspension. The swab should be

rotated several times and pressed firmly on the inside wall of the tube to remove excess inoculum from the swab, then the dried surface of agar plate is inoculated by streaking the swab over the entire sterile agar surface. As a final step, the rim of the agar is swabbed. Later, the disc of Schiff bases was distributed onto the surface of the inoculated agar plate, each disc must be pressed down to ensure complete contact with the agar surface. The plates were inverted and placed in an incubator at 37°C. After 16 to 18 hrs. of incubation, each plate was examined. If the plate was satisfactorily streaked and the inoculum was correct, the resulting zones of inhibition will be uniformly circular, if individual colonies are apparent, the inoculum was too light and the test must be repeated. The diameters of the zones of complete inhibition were measured. Zones were measured to the nearest whole millimeter using a ruler which was held on the back of the inverted petri plate.

B) MIC and MBC methods:

All Schiff bases were tested for their Minimum Inhibitory Concentration (MIC) by micro-broth dilution method in sterile 96-wells micro-titer plate. The concentration which was used at the beginning is 2000 mg/ml of Schiff bases dissolved in 10% DMSO then they were two folded-serially diluted in nutrient broth directly in the wells with a final volume of 1000 µl. The final concentration of Schiff bases achieved after dilution were (1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.872, 3.9 and 1.95 µl). After that, a bacterial inoculum size of 10*4 CFU/ml was added to

each well. Negative control wells containing either 100 µl NB only, or 100 µl DMSO with bacterial inoculum, or Schiff bases and nutrient broth without bacteria were included as well. Each Schiff bases was run in duplicate. 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 MBC.

2.5 Pancreatic Lipase Inhibition procedure:

The porcine pancreatic lipase inhibitory assay was adapted from (89; 90) with some modifications. Prepared 1mg/ml (1000µg/ml) tested sample stock solution in 10% DMSO from which five different solutions were prepared with the following concentrations (50, 100, 200, 300, 400 µg/ml). While 1mg/ml stock solution of pancreatic lipase enzyme was prepared immediately before use was suspended in tris-HCl buffer. This procedure was carried out for all tested samples.

Stock solution of PNPB (p-nitrophenyl butyrate) 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) plant extract. 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 (p-nitrophenyl butyrate) 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.

Chapter Three

Results and Discussion

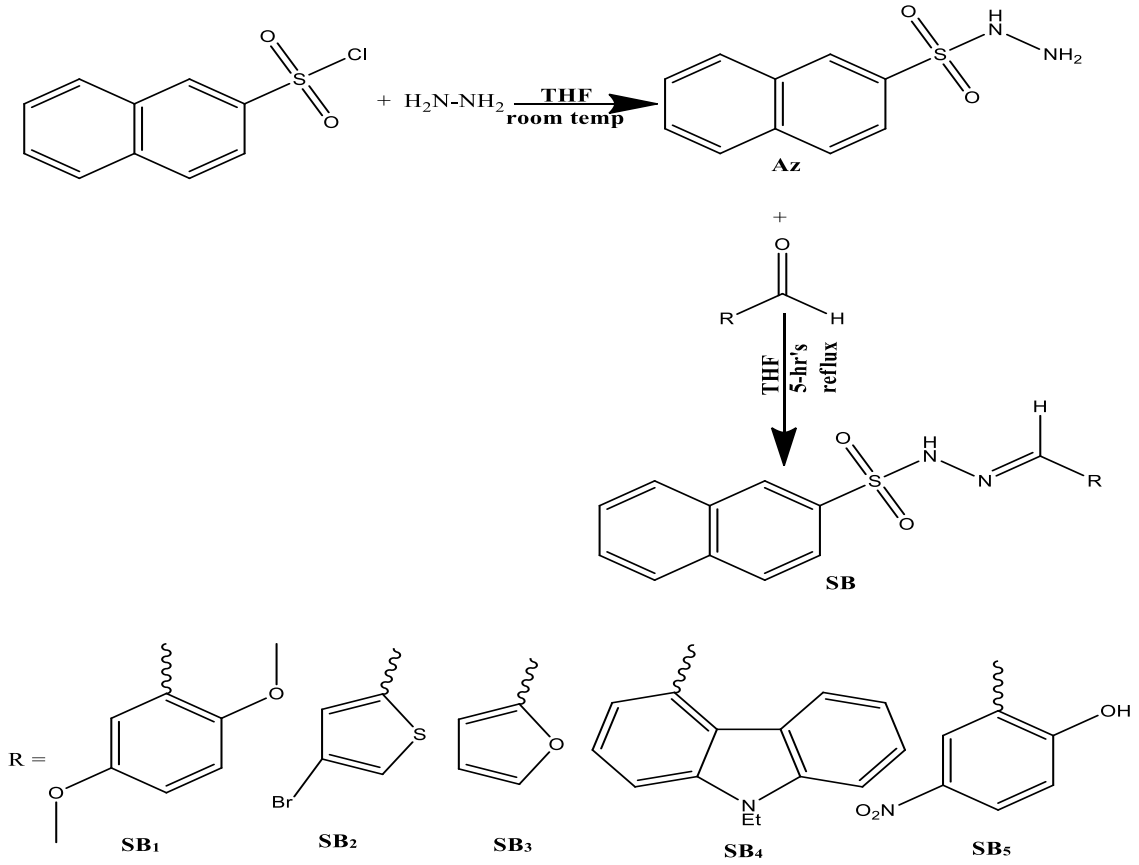
Part one

Chemistry part

(Spectral Analysis and DFT-Computational)

3.1 Synthesis of SB's:

The desired SB's were prepared according to **Scheme3.1**, all compounds (**SB_{1-5}**) found to be soluble in THF, alcohols like ethanol, methanol and chlorinated solvents such as chloroform. The newly Schiff base compounds verify by melting point, EA, UV-Visible, FTIR, ^{1}H-NMR, ^{13}C-NMR, GC/Ms spectroscopy. The purity of compounds is detected by TLC and TGA instrument.



3.1.1 Analysis spectra for SB_1 and Az:

3.1.1.a: Gas Chromatography-Mass spectrometry and elemental analysis:

The elemental analysis of **Az** and **SB_1** were matched with the proposed molecular formula.

For **Az**, $C_{10}H_{10}N_2O_2S$, calculated form (C, 54.04; H, 4.53%), and it is found to be experimentally as: (C, 54.11; H, 4.62%), for **SB_1**, $C_{19}H_{18}N_2O_4S$, was calculated and it is found (C, 61.61; H, 4.90%) and their experimental analysis found (C, 61.73; H, 5.02%).

The GC/MS of starting material is agreeable with expected structure $[M^+]$ = 221.2 m/z and 222.17m/z for $[M^{+1}]$ and the GC/MS data confirmed the desired structure for **SB_1**, the value is consistent with its proposed formula weight, m/z experimental value was for $[M^{+1}]$ = 370.2m/z, while theoretical value was 371.1m/z (as shown in **Fig. 3.1**).

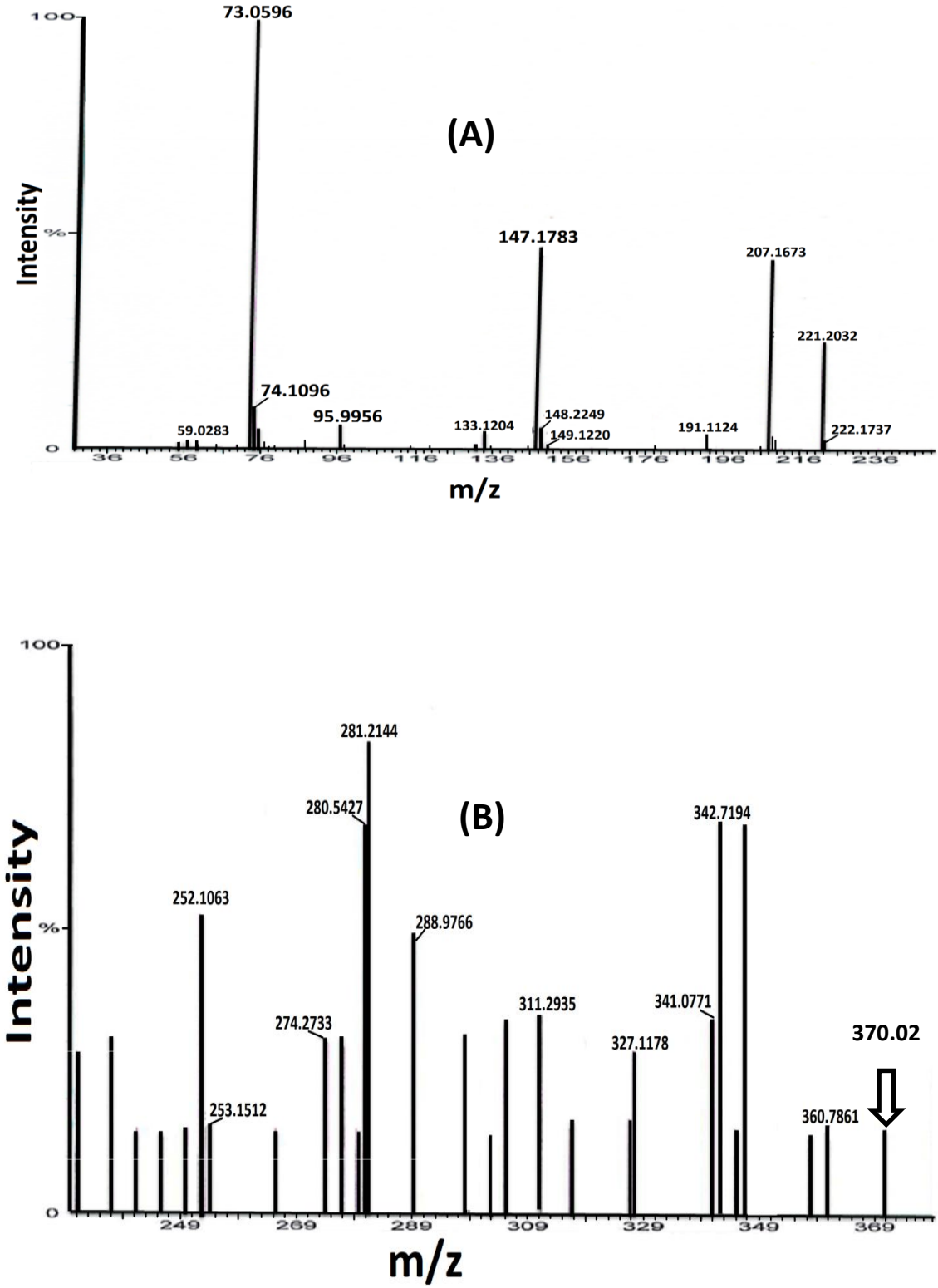


Fig. 3.1: (a) GC/MS spectrum for **Az** and (b) GC/MS spectrum of compound **SB$_1$**

3.1.1.b Experimental and Theoretical DFT/IR Spectral Analysis

All reagents which were used to produce **SB_1** optimized by FT-IR through 3500 – 400 cm^{-1} ranges. The FT-IR was used to monitor and adjust the condensation reaction, spectra components of reaction were compared, then their peaks were noted to be shifted, and this is a concrete evidence existence of new Schiff base compounds.

2,4-Dimethoxy benzaldehyde was used as carbonyl group to produce **SB_1**, its ν(C=O) peak shown at 1666 cm^{-1}, after Schiff base reaction the (C=N) in Schiff base product became 1610 cm^{-1} and the (N-H) peak was shifted to 3152 cm^{-1} with $\Delta\nu$ = 205 cm^{-1},this reflecting the formation of new **SB_1** compound, as illustrated in **Fig. 3.2**.a

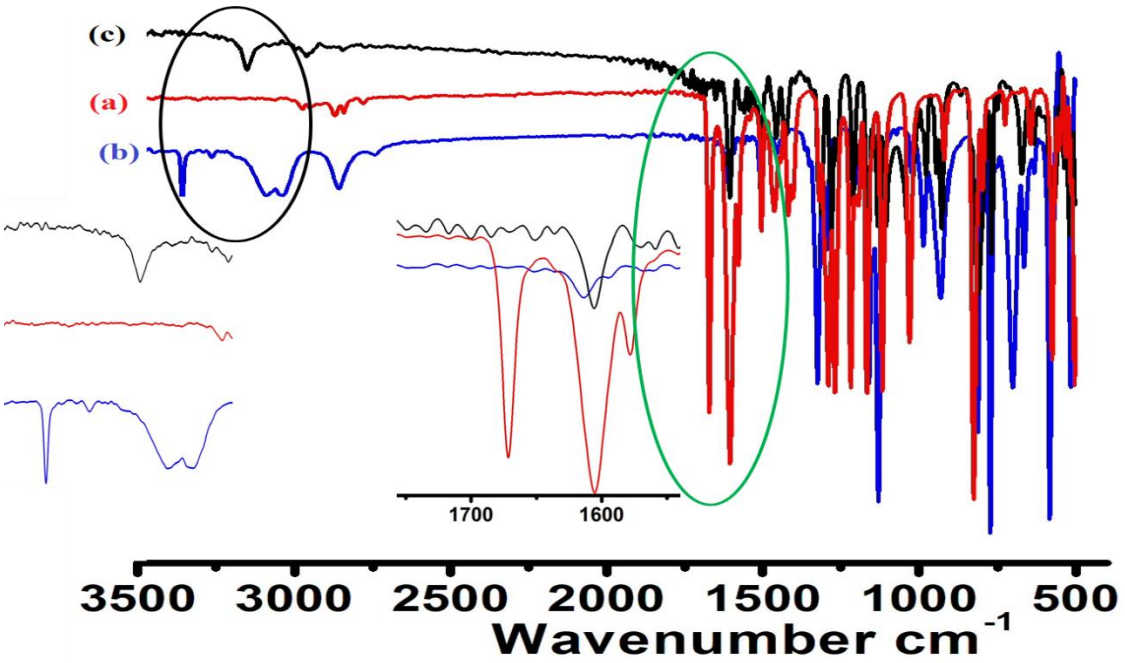


Fig. 3.2.a: FTIR-spectra: a) 2,4-Dimethoxy benzaldehyde. b) **Az**. c) Schiff base product **SB1**

The DFT- theoretical vibrational spectrum was performed to check it functional groups, as shown in **Fig. 3.2.b**

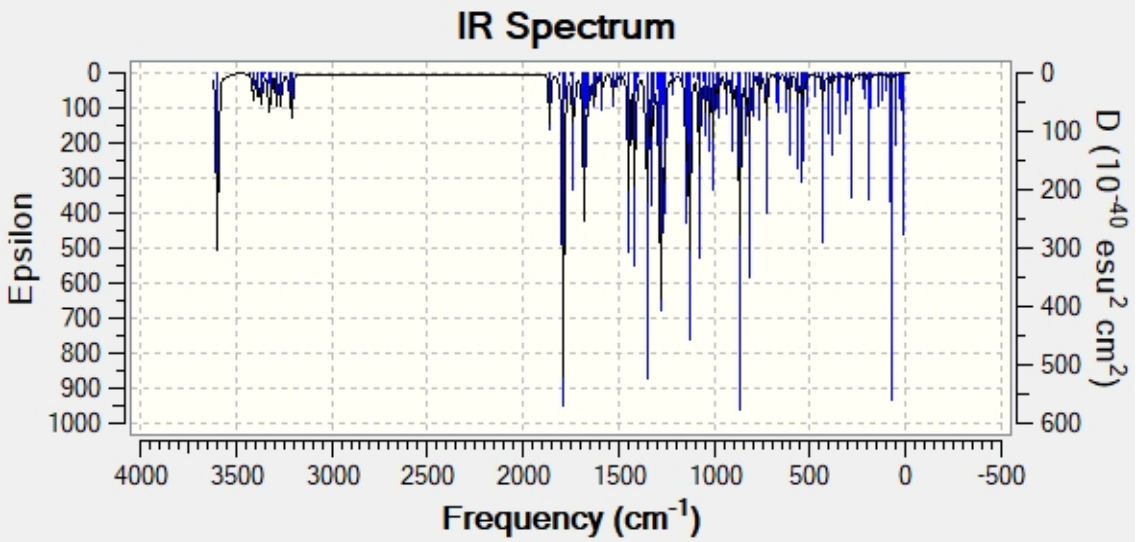


Fig. 3.2.b: DFT-FTIR in gaseous phase for **SB_1**.

The exp. 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 illustrate in **Table 3.1**. and **Fig. 3.2.c**.

Table 3.1: Comparison between Experimental and DFT- FTIR values for main vibrational stretching for **SB_1**.

Mode stretching	**Exp.- FTIR (cm^{-1})**	**DFT-FTIR (cm^{-1})**
$\nu_{(N-H)}$	3152	3164
$\nu_{(C=N)}$	1610	1663
$\nu_{(=C-H)}$	3002	2999
$\nu_{(-C-H)}$	2959	2928

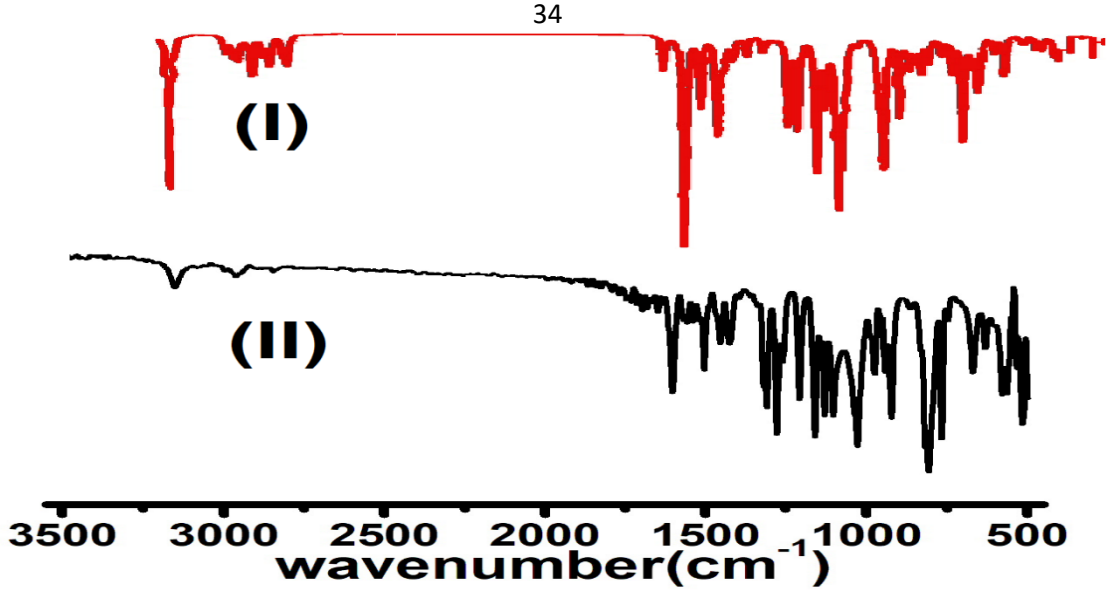


Fig. 3.2.c: **(|)** DFT-FTIR and **(||)** experimental FTIR for **SB_1.**

A significant R^2 value 0.9992 was determined, which is reflected an overall good matching between experimental and theoretical IR analysis, which were estimated by drawing Exp. vis DFT-FTIR as shown in **Fig. 3.2.d**.

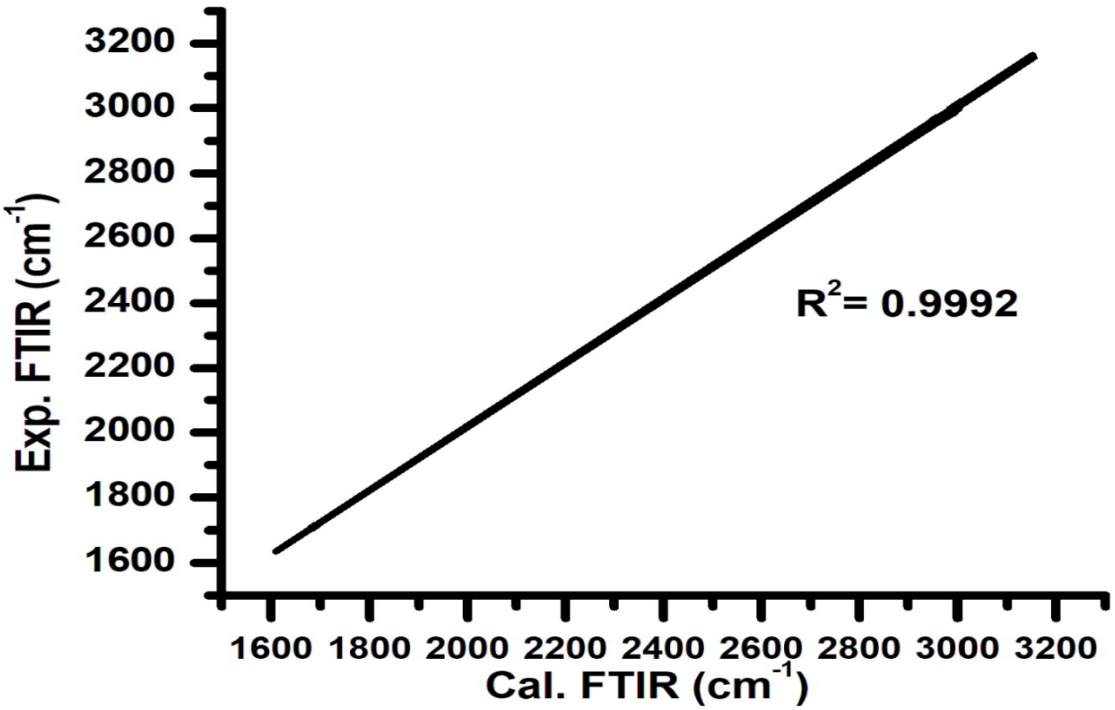


Fig. 3.2.d: Correlation diagram between DFT vis experimental FTIR for **SB_1**

3.1.1.c NMR spectral analysis

The ^{1}H-NMR spectra of **SB_1** and **Az** were recorded at room temperature in anhydrous $CDCl_3$ solvent.

To follow up the condensation reaction to form the desired SB's, the ^{1}H-NMR of starting material (**Az**) compound was experimentally performed as shown in **Fig. 3.3**, its spectrum showed eight signals a broad singlet (N-H, 3H, δ =3.1 ppm), and seven signals in singlet (C-H, δ = 7.5ppm), triplet of doublet (C-H, δ=7.55 and 7.62ppm) and doublet (C-H, δ = 7.9, 8.1, 8.3 and 8.6ppm).

The ^{13}C-NMR spectrum of starting material was shown in **Fig. 3.4** which revealed ten signals for all aromatic carbon cited to their expected chemical shift directly to the structure δ= 124, 124.5, 127, 128.4, 128.7, 129.2, 131, 132, 134.4, 135.4 ppm.

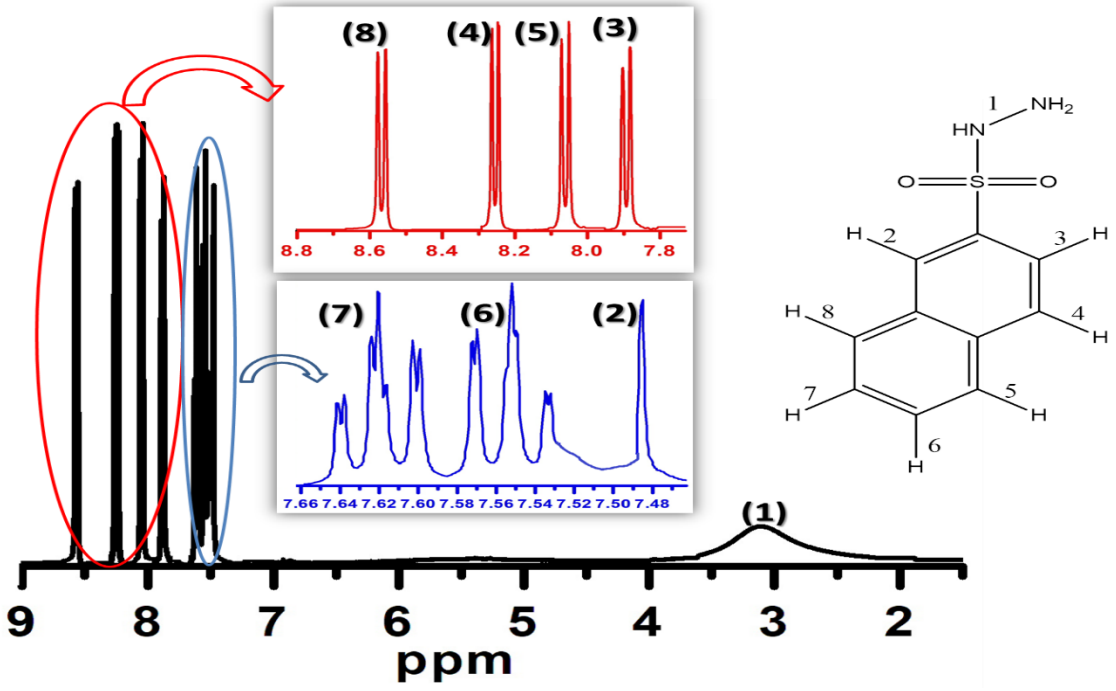


Fig. 3.3: ^{1}H-NMR spectrum of **Az** in $CDCl_3$ at room temperature.

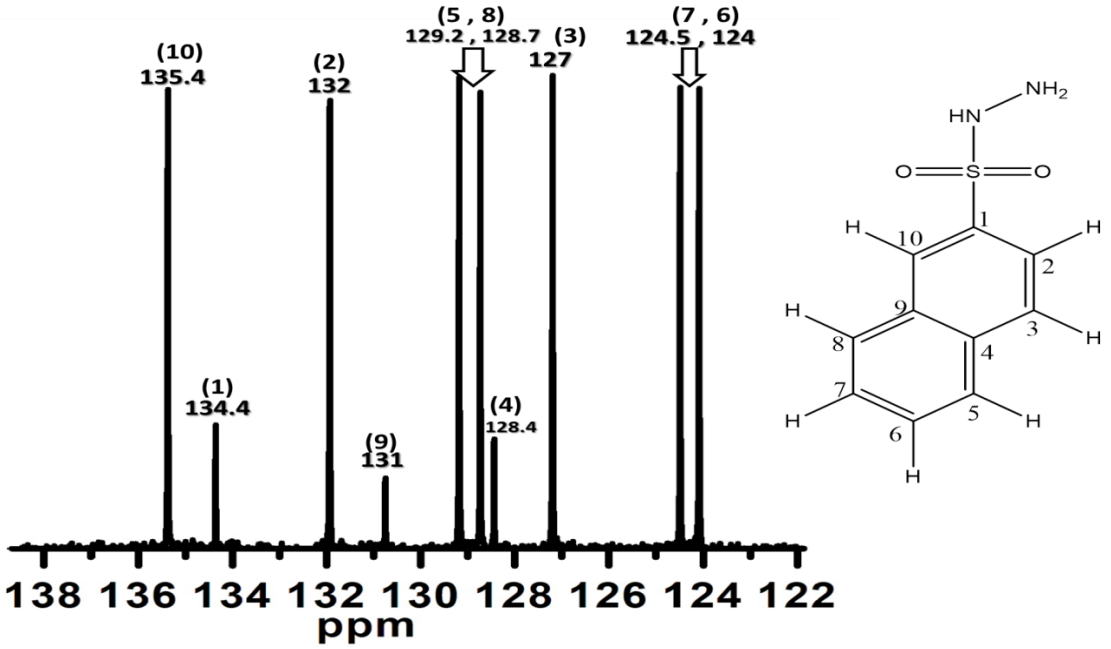


Fig. 3.4: ^{13}C-NMR spectrum of **Az** in $CDCl_3$ at room temperature.

The **Fig. 3.5.a** showed Exp. ^{1}H-NMR for **SB_1** and it has a detailed interpretation of compound. The presence of singlet (CH_3, δ= 3.6 and 3.7) ppm, singlet (C-H, δ=6.2) and doublet (C-H, 6.32 and 6.34) for benzene group, while naphthalene group has singlet (C-H, δ=7.8, 7.97 ppm), doublet (C-H, δ= 7.8, 7.9, 8.3 and 8.8)ppm and triplet (C-H, δ=7.5 and 7.6ppm), and azomethine group (C-H, δ=7.96ppm), N-H present at downfield region in 8.91ppm.

The theoretical ^{1}H-NMR was illustrated in **Fig. 3.5.b**, which was obtained from online website computation (91), and this website can't detect the NH signal. Meanwhile, the comparison between theoretical and experimental ^{1}H-NMR was plotted in **Fig. 3.5.c** which reflect agreement experimental with theoretical with R^2=0.9908.

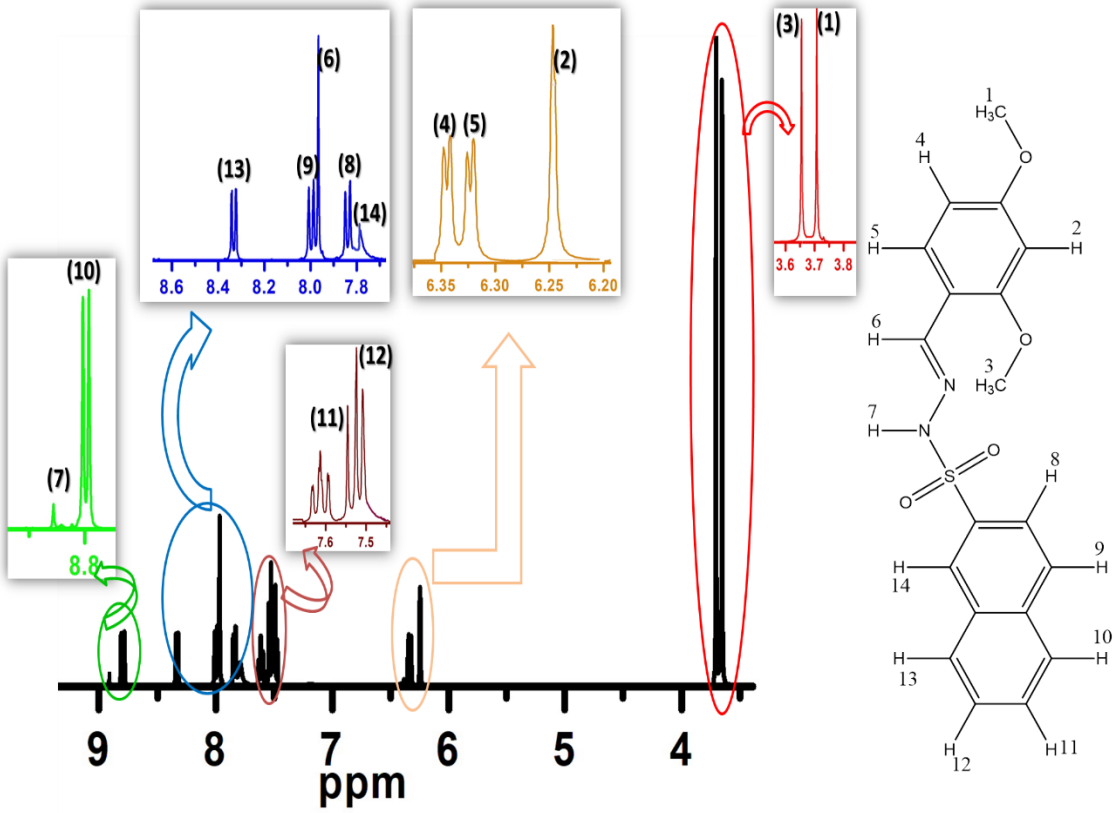


Fig. 3.5.a: Experimental ^{1}H-NMR spectrum of **SB$_1$** in $CDCl_3$ at room temperature.

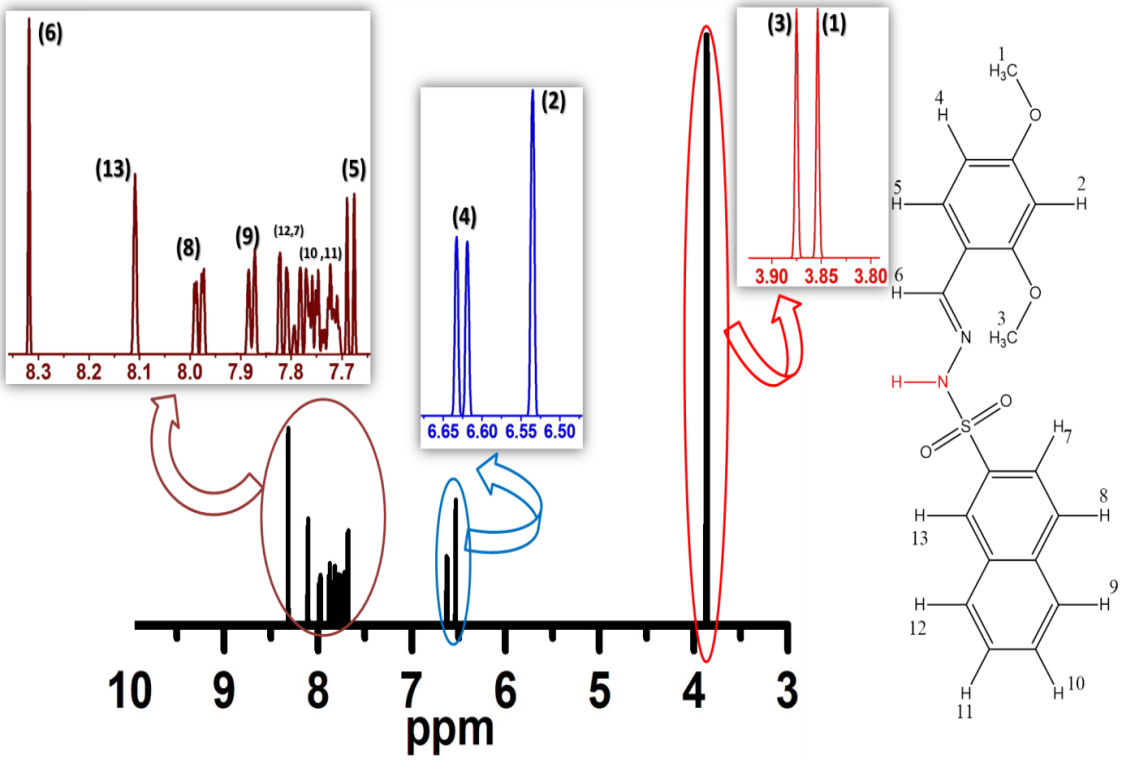


Fig. 3.5.b: Theoretical ^{1}H-NMR spectrum of **SB$_1$**.

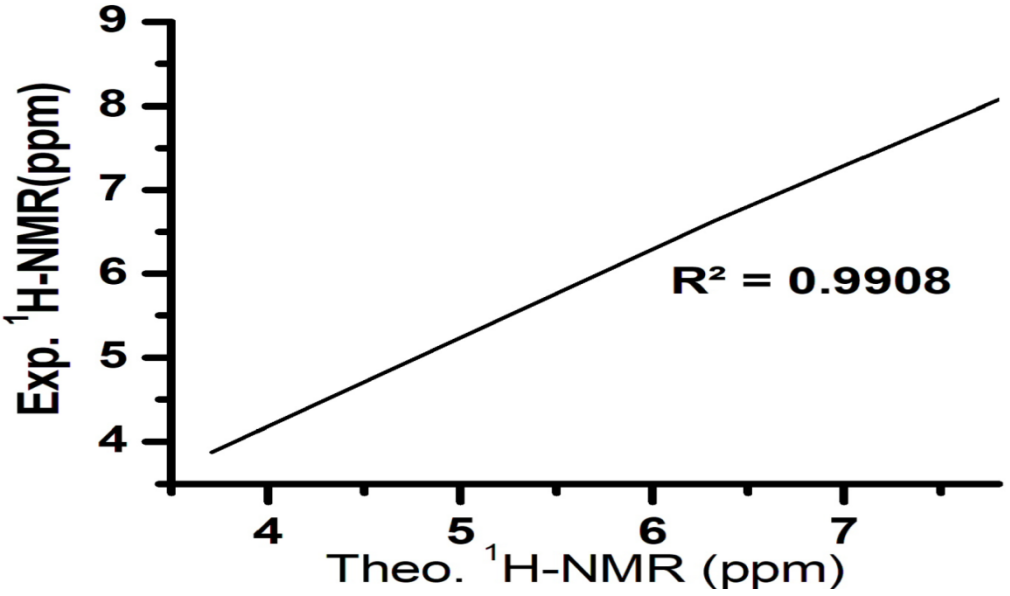


Fig. 3.5.c: Reflect the acceptable degree of agreement between experimental and theoretical ^{1}H-NMR for **SB₁**

These values confirmed that the product was Schiff base. Such results going with ^{13}C-NMR results as shown in **Fig. 3.6**. This spectrum observe 19-signals with different region one of them is azomethine carbon showed at (δ=129ppm) while other signals were shown as in **Fig.3.6** as deliberated by incremental methods.

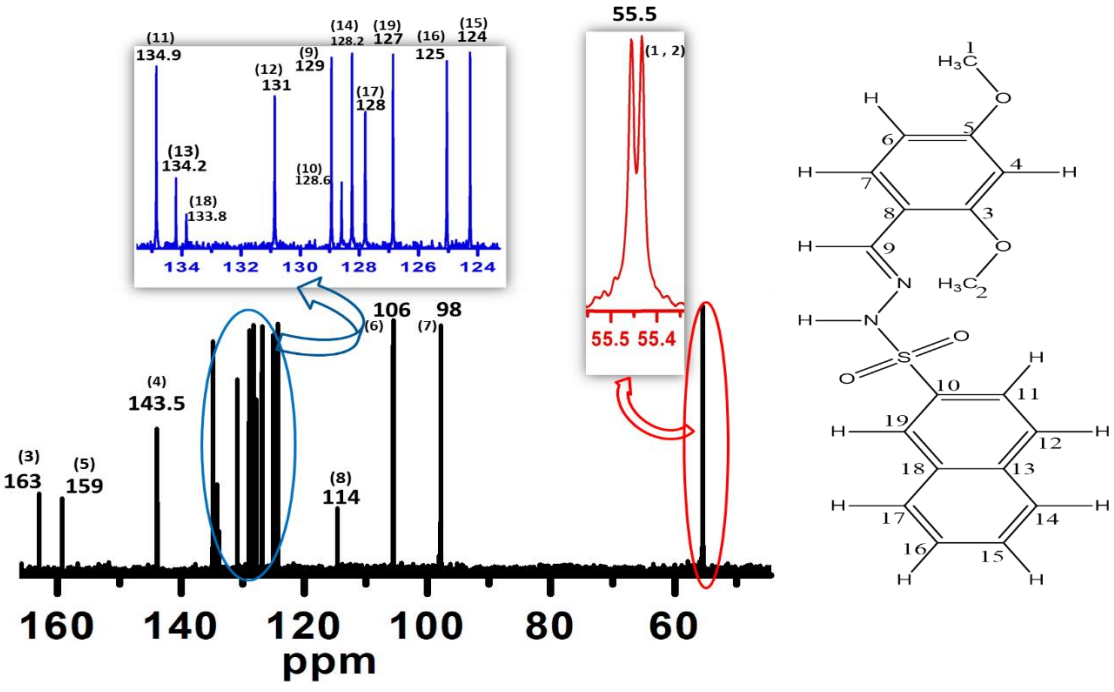


Fig. 3.6: ^{13}C-NMR spectrum of **SB₁** in $CDCl_3$ at room temperature.

3.1.1.d UV-Visible analysis of Schiff base compound:

The electron transfer behavior in the desired SB was performed in THF at room temperature. Similarly behavior for most of the prepared SB was detected, **SB_1** and it starting material electron transfer to monitor the condensation reaction as in **Fig. 3.7** illustrate the absorption of Schiff base compound between (230-450) nm, **SB_1** recorded three strong peaks at (λ_{max}=236, significantly at 278 and 317) nm.

Fig. 3.7 is another tool to ensure the produced Schiff base compound, and that's through comparison between peaks of reaction components.

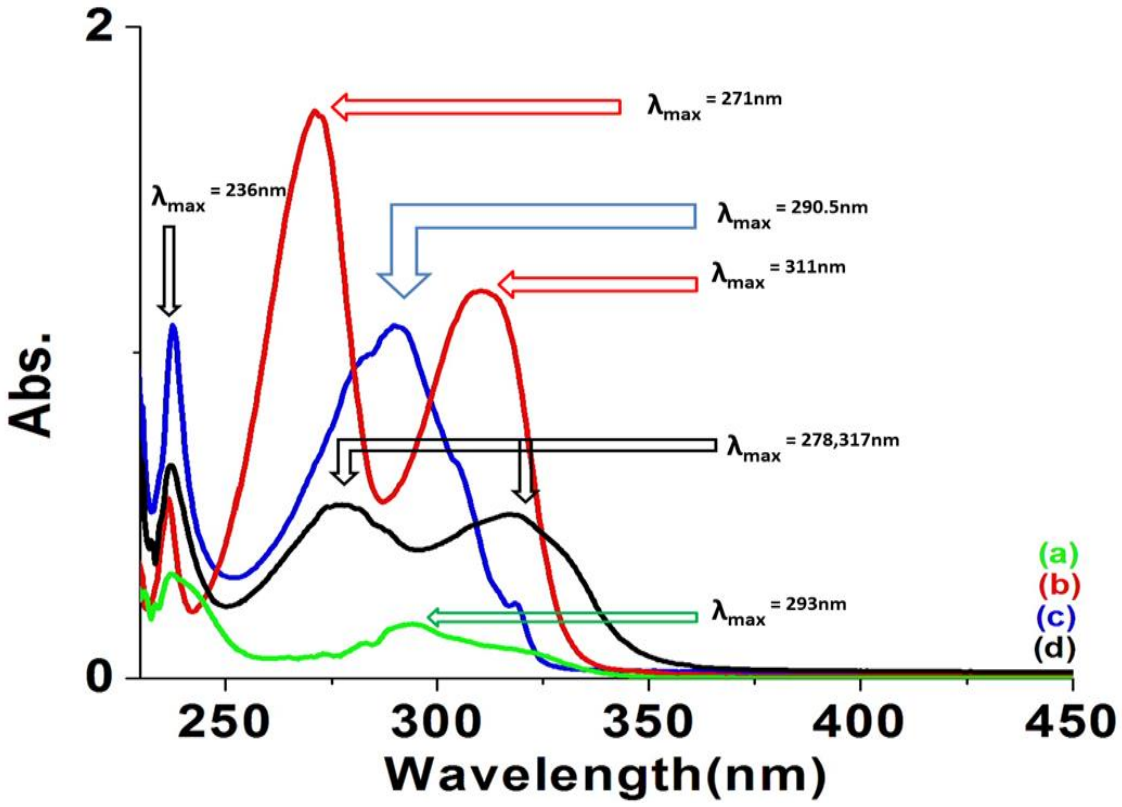


Fig. 3.7: Experimental UV-visible spectra, a) Naphthalene sulfonyl chloride , b) 2,4-Dimethoxy benzaldehyde, c) **Az**, d) **SB_1**.

3.1.2 Experimental and Theoretical results for SB_2:

3.1.2.a: NMR- SB_2:

The structure of Schiff base **SB_2** stand out *via* NMR spectra, ^{1}H-NMR as shown in **Fig.3.8** has vary regions of signals, important peaks for Schiff base showed singlet at δ= 7.83 ppm for azomethine group and singlet of N-H at 9.8ppm.

Experimentally, ^{13}C-NMR for **SB_2** was shown in **Fig. 3.9**. Another tool for confirmation **SB_2** structure as it show azomethine carbon at 140.1ppm and the rest of the peaks are clearly shown in the figure as they appeared in various places.

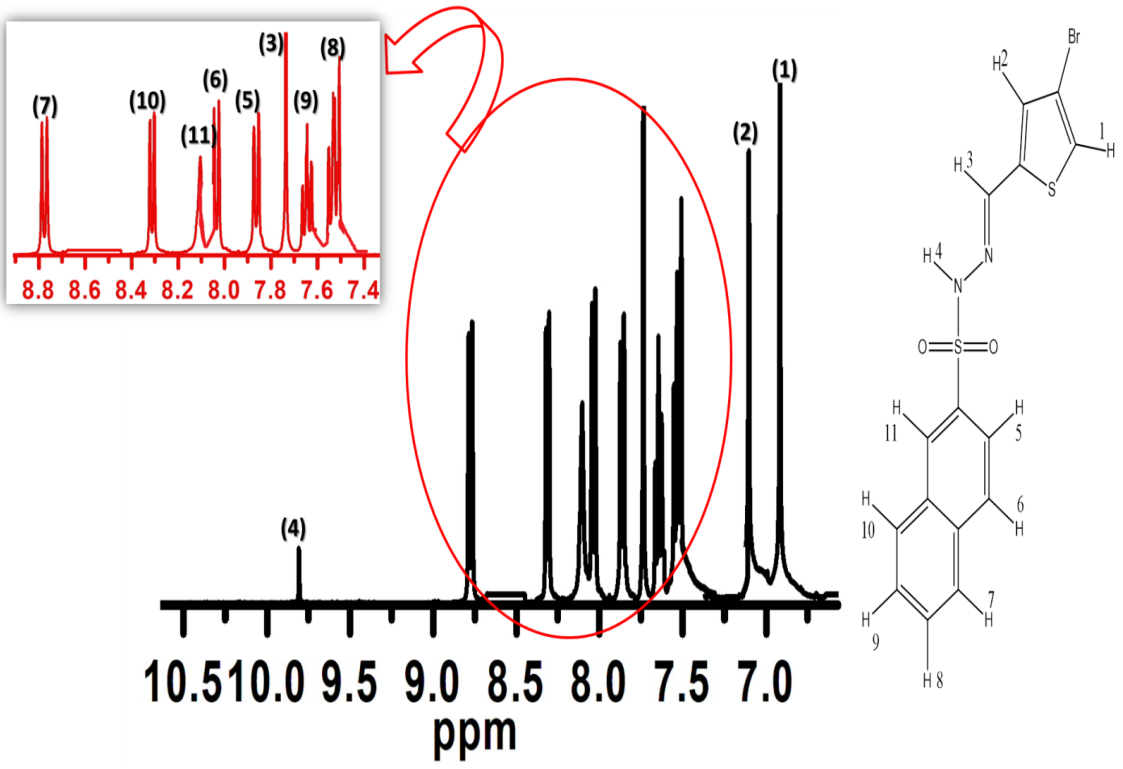


Fig. 3.8:- ^{1}H-NMR spectrum of **SB_2** in $CDCl_3$ at room temperature.

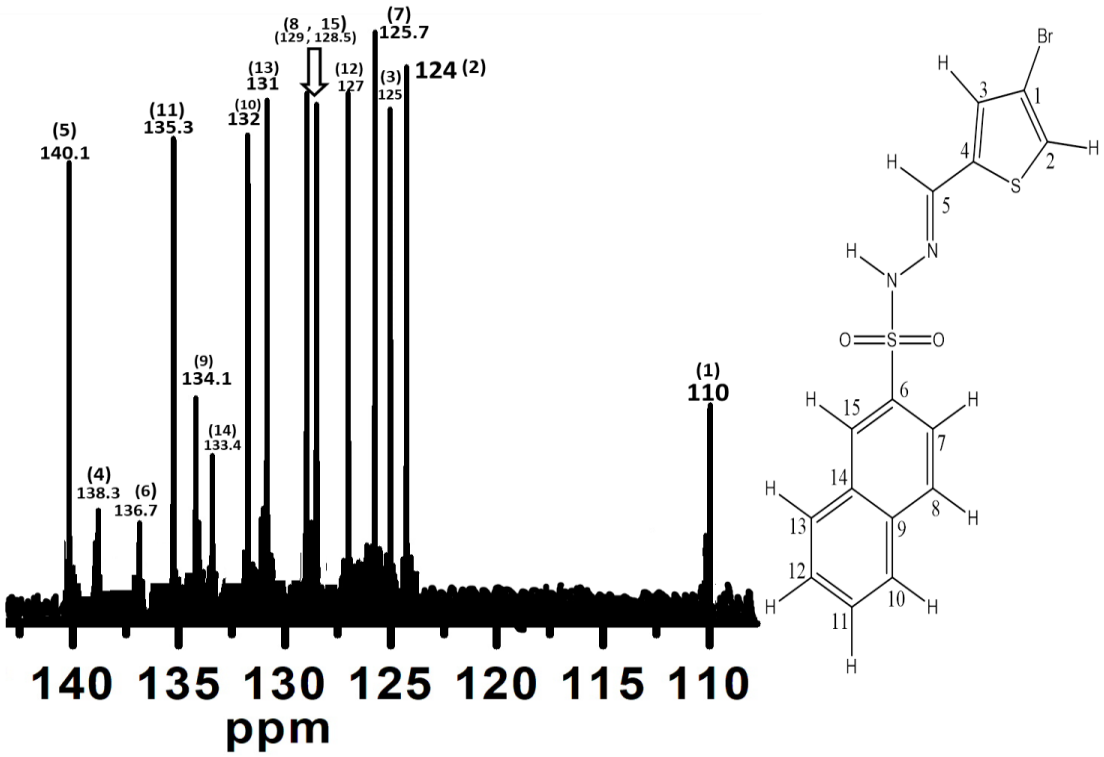


Fig. 3.9: ^{13}C-NMR spectrum of **SB_2** in $CDCl_3$ at room temperature.

3.1.2.b Optimization structure of (E/Z)-Schiff base compound:

The structure of **SB_2** was submitted to DFT- B3LYP, in the gas phase with 3-21G level basis set in order to optimize its structure, and this explain the molecular structure of E/Z-isomerization with less internal steric repulsion, as shown in **Fig.3.10.a** and **Fig. 3.10.b**

The bond lengths, bond angles and torsional angles were calculated upon structure optimization by using DFT as listed in **Table2, 3 and 4.**

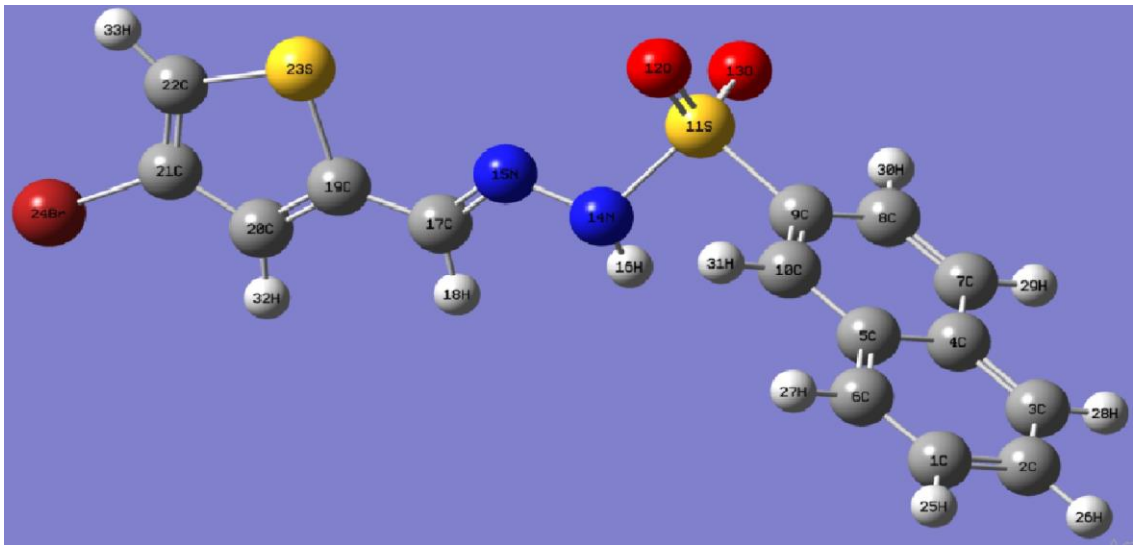


Fig. 3.10.a: DFT optimized molecular structure of *E*- **SB_2**

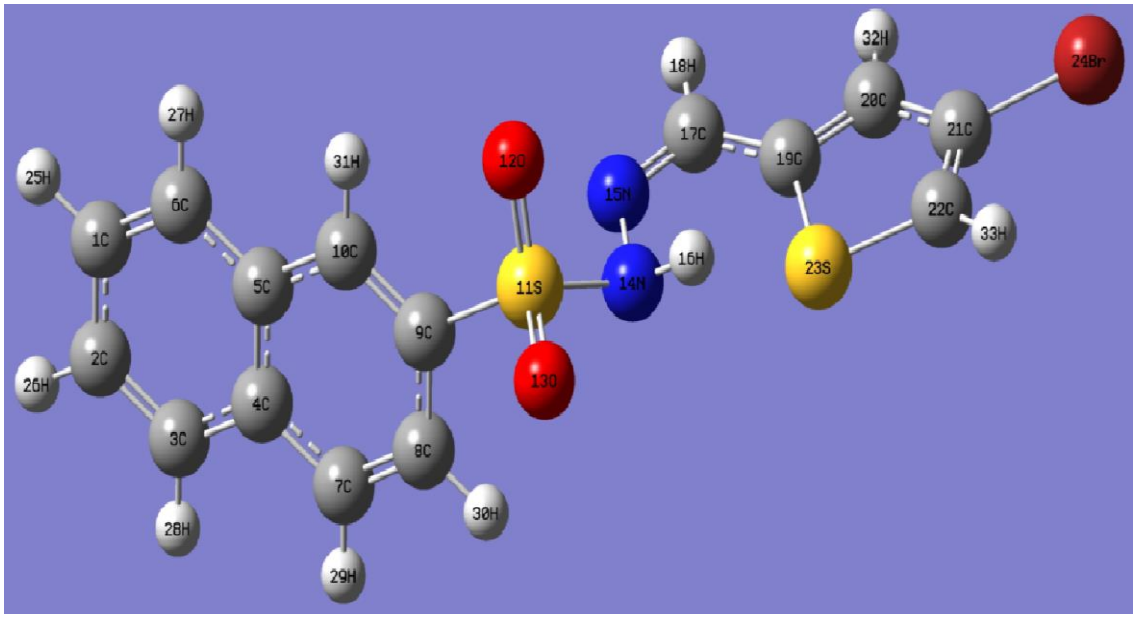


Fig. 3.10.b: DFT optimized molecular structure of *Z*- **SB_2**

Table 3.2: Bond lengths of (E/Z)- **SB_2**.

Atoms	**Bond Length(A°)**	
	E-isomer	**Z-isomer**
C1-C2	1.4187	1.4183
C1-C6	1.3755	1.3758
C2-C3	1.376	1.3766
C3-C4	1.4221	1.4216
C4-C5	1.4376	1.4361
C4-C7	1.424	1.4242
C5-C6	1.4225	1.4225
C5-C10	1.4208	1.4191
C7-C8	1.3751	1.3734
C8-C9	1.4046	1.4169
C9-C10	1.3663	1.3752
C9-S11	1.8409	1.762
S11-O12	1.5798	1.4574
S11-O13	1.5898	1.4634
S11-N14	1.8354	1.678
N14-N15	1.406	1.3915
N15-C17	1.293	1.2926
C17-C19	1.4365	1.4435
C19-C20	1.3671	1.377
C19-S23	1.8145	1.7481
C20-C21	1.427	1.4276
C21-C22	1.3551	1.3698
C21-Br24	1.9215	1.8951
C22-23	1.8032	1.7328

Table 3.3: Bond angels of (E/Z)- **SB_2**.

Atoms	Bond angles (°)	
	E-isomer	Z-isomer
C2-C1-C6	120.36	120.42
C1-C2-C3	120.56	120.42
C2-C3-C4	120.7	119.9
C3-C4-C5	118.65	119.68
C3-C4-C7	122.02	120.64
C5-C4-C7	119.33	119.68
C4-C5-C6	119.21	119.68
C4-C5-C10	118.75	119.68
C6-C5-C10	122.04	120.64
C1-C6-C5	120.52	119.9
C4-C7-C8	120.77	119.9
C7-C8-C9	118.57	120.42
C8-C9-C10	123.57	120.42
C8-C9-S11	116.58	119.79
C10-C9-S11	119.82	119.79
C5-C10-C9	118.99	119.9
C9-S11-O12	113.03	109.47
C9-S11-O13	106.65	109.47
C9-S11-N14	94.31	109.47
O12-S11-O13	120.21	109.47
O12-S11-N14	106.68	109.47
O13-S11-N14	113.02	109.47
S11-N14-N15	111.21	109.47
N14-N15-C17	117.87	120
N15-C17-C19	120.93	120
H18-C17-C19	115.8	120
C17-C19-C20	128.36	124.76
C17-C19-S23	120.26	124.77
C20-C19-S23	111.38	110.46
C19-C20-C21	113.3	113.51
C20-C21-C22	114.87	113.51
C20-C21-Br24	121.79	123.24
C22-C21-Br24	123.34	123.25
C21-C22-S23	111.36	110.46
C19-S23-C22	89.09	90.83

Table3.4: Torsional angels of (E/Z)- **SB_2**.

Atoms	Torsional angles (°)	
	E-isomer	Z-isomer
C2-C3-C4-C5	179.67	180
C3-C4-C5-C10	179.89	180
C7-C4-C5-C6	-179.64	180
C3-C4-C7-C8	179.99	-180
C10-C5-C6-C1	-179.88	-180
C6-C5-C10-C9	-179.64	-180
C7-C8-C9-S11	179.23	180
S11-C9-C10-S23	-179.31	-180
C8-C9-S11-O12	-135.16	180
C8-C9-S11-O13	-0.91	-60
C8-C9-S11-N14	114.67	60
C10-C9-S11-O13	177.33	120
C10-C9-S11-N14	-67.09	-120
C9-S11-N14-N15	175.87	59.99
O12-S11-N14-N15	60.26	-60
O13-S11-N14-N15	-74	180
S11-N14-N15-C17	157.39	150
N14-N15-C17-C19	177.09	0.01
N15-C17-C19-C20	-179.91	-179.86
N15-C17-C19-S23	0.2	-0.15
C17-C19-C20-C21	-179.84	172.21
S23-C19-S23-C22-C21	0.06	-7.54
C17-C19-S23-C22	179.83	-169.88
C20-C19-S23-C22	-0.08	9.87
C19-C20-C21-Br24	-179.88	-179.29
C20-C21-C22-S23	-0.05	7.54
Br24-C21-C22-S23	179.81	-173.17
C21-C22-S23-C19	0.07	-9.87

3.1.2.c Frontier molecular orbital (FMO) analysis:

The FMO help to predict and understanding the electronic, reactivity of chemical and optical properties of compounds. FMO analysis was carried out for **SB_2** by using B3LYP method and 3-21G level of basis set. The intermolecular charge transfer by excitation process from donor (HOMO) to acceptor (LUMO) moiety, and the tendency of the compound with largest HOMO that donate electron to acceptor with low energy and lowest LUMO that indicate the compound has tendency to accept electrons(92), as shown in **Fig.3.11**.

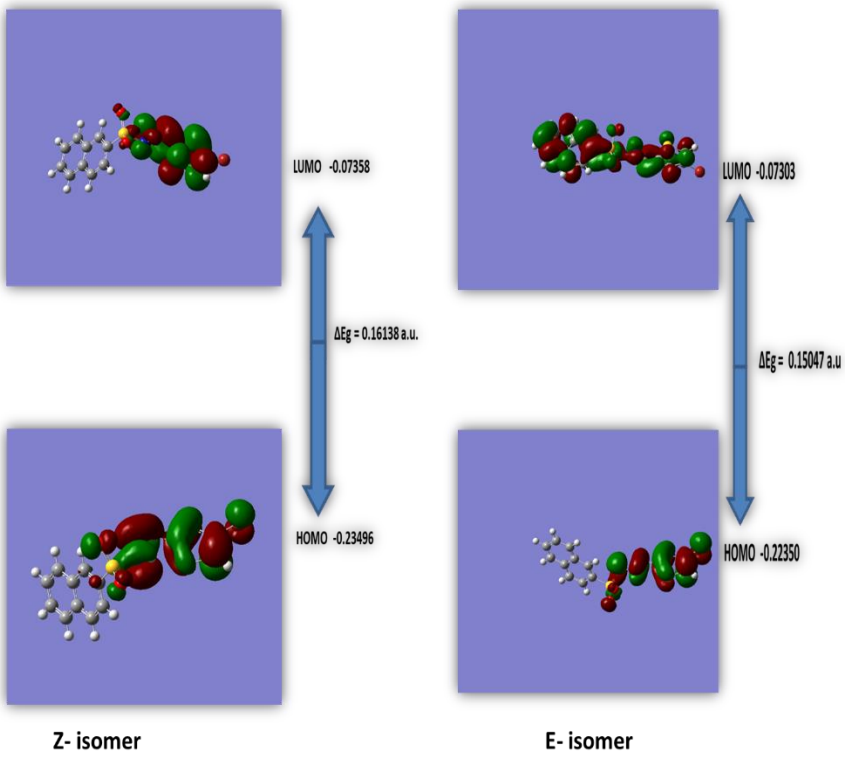


Fig. 3.11: FMO of (E/Z)- **SB_2**

3.1.2.d GRD Quantum Parameters:

GRD is theoretical analysis that helps to obtain quantum parameters for desired molecule like electrophilicity (ω), hardness (η) electronegativity (x), chemical potential (μ) and softness (σ) indexes. Such parameters can be calculated from HOMO/LUMO energy gap (93; 94) as shown in the **Table 5.**

The stability of E-isomer estimated from chemical potential value, the electronegativity and electrophilicity which describes the electronic attraction, and the hardness value for the compound. Such finding explains that the compound becomes softer with electron transfer.

Koopman's notations:

- Electronegativity (x) = $-E_{HOMO} + (-E_{LUMO}/2)$
- Chemical potential (μ) = $-x$
- Hardness (η) = $E_{LUMO} + (-E_{HOMO}/2)$
- Softness (σ) = $1/\eta$
- Electrophilicity (ω) = $\mu^2/2\eta$

Table 3.5: Calculated energy values by B3LYP/3-21G.

Basis set	B3LYP/3-21G	
	Z-isomer	E-isomer
E (a.u.)	-4187.57381681	-4187.56990333
E_{HOMO}(eV)	-6.393589635	-6.081747035
E_{LUMO}(eV)	-2.002214527	-1.98724826
ΔE(eV)	4.391375378	4.094498775
x (eV)	7.3946968985	7.075371165
μ(eV)	-7.3946968985	-7.075371165
Ƞ(eV)	1.1945802905	1.0536252575
σ(eV)	0.837114096	0.9491040509
ω(eV)	22.8873448924	23.7564906337

3.1.2.e Molecular Electrostatic Potential (MEP) Analysis:

MEP analysis is a good tool to know the possible interaction sites and reactivity of the compound. MEP diagram as shown in **Fig. 3.12** was computed by using B3LYP method and 3-21G level of basis set, the figure shows the distribution of charges that helps to determine the nature of chemical bond.

The positive moiety describes the nucleophilic sites, while negative area show the electrophilic site at MEP diagram.

The results are shown in **Fig.3.12** for both isomer (E and Z) clarify the amounts of negative charge that are above oxygen atoms (O11 and O23).

The lone pair of electrons is regarded as nucleophilic sites and are ready to attach electrophilic sites that are represented as an acidic reagent to make protonation step in the reaction.

The positive moiety described by blue color is localized around hydrogens atoms. The green region shows the zero potential of structure. The attached ribbon contains color in range -6.891x10^{-2} a.u (reddish color) and +6.891x10^{-2} a.u (dark blue) for E-isomer, and Z-isomer between (-6.090 to +6.092) x10^{-2} a.u in the attached map.

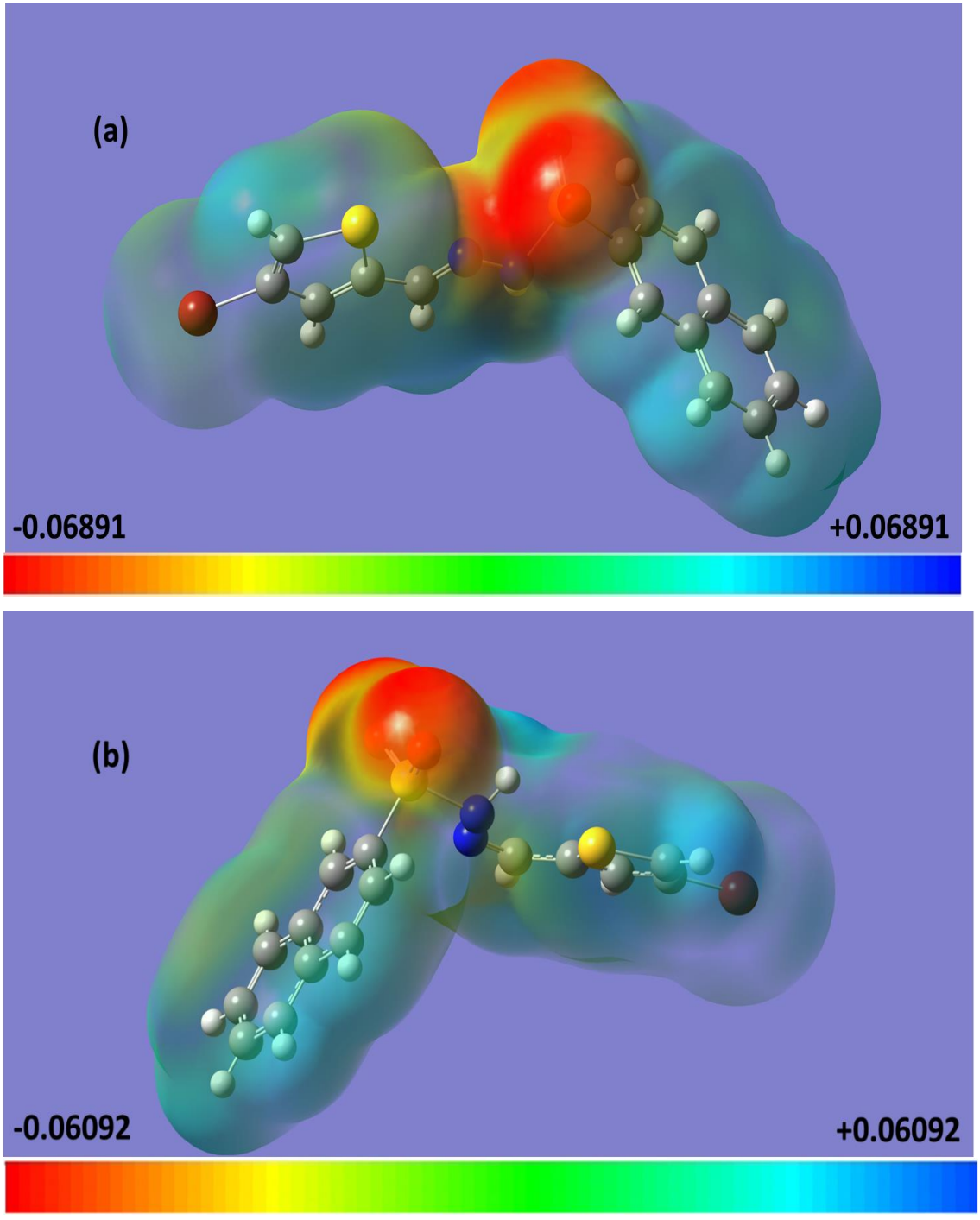


Fig. 3.12:-MEP surface of compound **SB$_2$** (a) E-isomer and (b) Z-isomer.

3.1.3 Thermal Analysis for SB_5:

The thermal behavior of product **SB_5** was analyzed by TG/DTG in range of (0-800°C) temperature in open air atmosphere with 10°C min^{-1} as heat rate, **Fig. 3.13**, describe composition and decomposition of the components and it important to show the purity of compound.

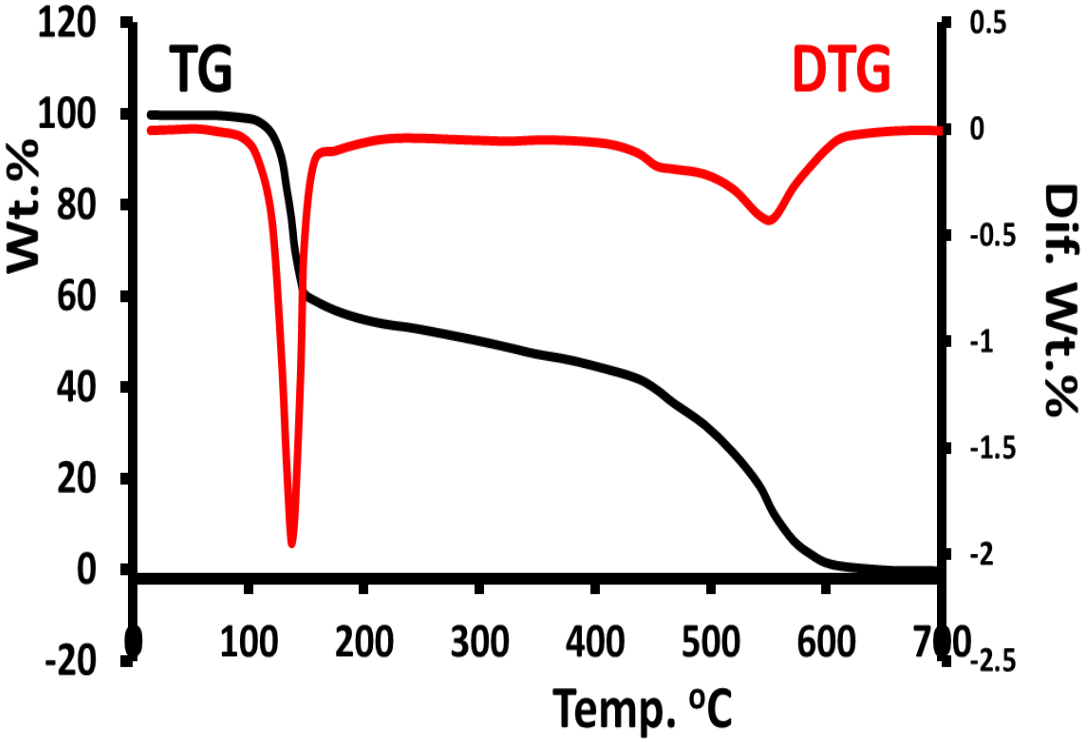


Fig. 3.13:- TG/DTG thermal curve of **SB_5**

The **Fig.3.13**, 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.

Part Two

Biological part

(Biological activity, Lipase inhibition and Auto-Docking)

3.2.1 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 (95). Therefore, the current study was conducted to explore the antibacterial potential of newly synthesized Schiff bases which are **SB_1**, **SB_2**, **SB_3**, **SB_4**, **SB_5** and **Az**. The antibacterial activity was examined by measuring the MIC and MBC values for all the previously mentioned Schiff bases.

In addition to that, the inhibition zone diameter was also measured. The later measurement showed weak antibacterial behavior for most of the tested compounds, this may be due their low solubility and consequently their low diffusion rate.

a-Disc Diffusion Method:

The Schiff bases activity was assessed using the disc diffusion method. Only (**SB_2**, **SB_3** and **SB_5**) Schiff bases compounds were showed an effect only on Gram-positive bacteria (*MRSA* and *S. aureus* bacteria) showed an obvious inhibition zone to be measured. The largest inhibition zone was assessed by compound **SB_5** on *MRSA* bacteria**.. SB_3** and **SB_5** compounds did not give any activity against *S. aureus,* although, it was effective on *MRSA*. The diameter of the inhibition zone was documented in **Table6** below.

Table 3.6. Results of disc diffusion method on *S.aureus* and *MRSA* bacterial species .

The Schiff bases compounds	**IZD**	
	MRSA (mm)	***Staphylococcus aureus (mm)***
12	11	**SB_5**
9	0	**SB_2**
15	0	**SB_3**

b- **MIC and MBC methods:**

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

The obtained MIC results revealed that compound **SB_3** exhibited an excellent inhibitory activity against all studied bacterial isolates. The promising bacteriostatic effect of this compound was against gram negative bacteria as the MIC values against *P. aeruginosa* and *K. pneumoniae* were 7.8125 µg/ml and 15.625 µg/ml respectively.

Meanwhile, compound **Az** had moderate bacteriostatic effect against all bacterial isolates under investigation with MIC values range (500 µg/ml -100 µg/ml). *MRSA* growth was also inhibited by **SB_2**, **SB_5** and **AZ** compounds with MIC values range from 125 µg/ml to 500 µg/ml. In this experiment, the obtained MIC results indicated that compound **SB_1** were effective against Gram negative bacterial isolates, as **Table7** as shown as results value. Besides MIC measurements, MBC measurements for all

Schiff bases was also investigated. The MBC results revealed that **SB_5** compound worked as bactericidal agents at a concentration range between 250 µg/ml and 1000 µg/ml against all tested bacteria except *E. coli*, and also compound **SB_3** was the most potent bactericidal agent, as it killed all the studied bacterial isolates at a concentration range (125 µg/ml -250 µg/ml), as these results was shown in **Table8**. It is interesting to find compounds like **SB_2**, **SB_3** and **SB_5** which provided powerful antibacterial activity even more effective than the broad spectrum antibiotic tetracycline.

The **Fig. 3.14** and **Fig**. **3.15** are used to illustrate the MIC and MBC respectively value for each (**SB_{1-5}**), **Az** and TE antibiotic against Gram-negative bacteria.

Table3.7: The MIC for **$SB_{(1-5)}$**, **Az** and TE antibiotic.

Compounds / **Types of Bacteria**	**SB_1**	**SB_2**	**SB_3**	**SB_4**	**SB_5**	**Az**	**TE**
MRSA	0	250	21.25	0	125	500	250
S. aureus	0	1000	62.5	0	1000	1000	500
Escherichia Coli	1000	1000	15.625	0	0	1000	500
Pseudomonas aeruginosa	500	500	7.8125	1000	500	500	500
Klebsiella pneumonia	0	0	250	0	125	1000	500

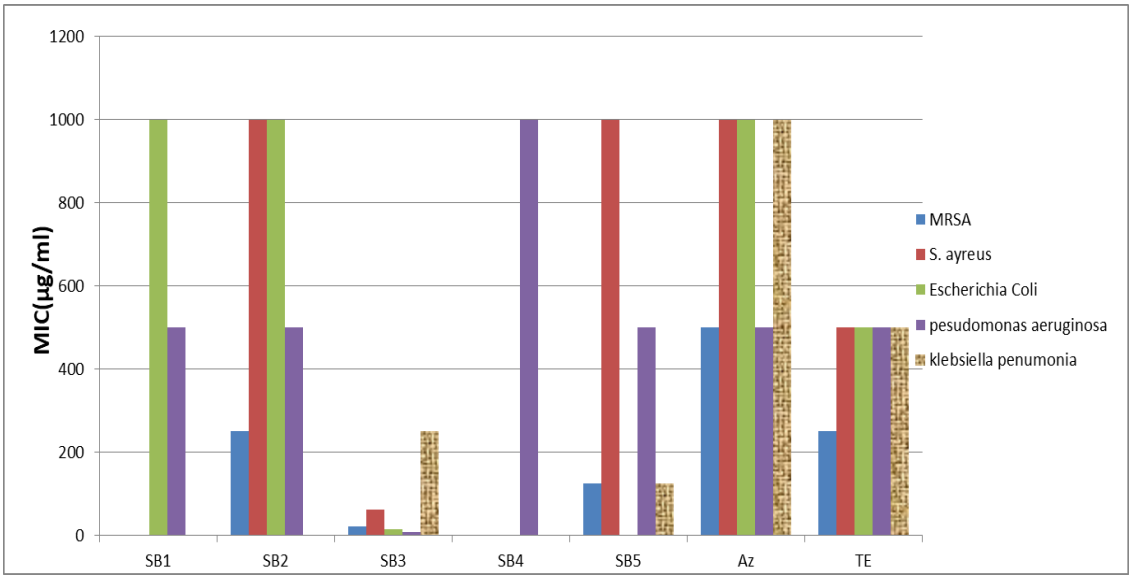


Fig. 3.14: Antibacterial activity for **SB$_{(1-5)}$** and **Az** against *MRSA*, *S. aureus*, *E.coli*, *P. aeruginosa* and *K. pneumoniae* using micro-broth dilution method; MIC (µg/ml).

Table 3.8: The MBC for **SB$_{(1-5)}$**, **Az** and TE antibiotic.

Compounds / Types of Bacteria	SB$_1$	SB$_2$	SB$_3$	SB$_4$	SB$_5$	Az	TE
MRSA	0	1000	250	0	250	1000	500
S. ayreus	0	0	250	0	1000	1000	1000
Escherichia coli	0	0	250	0	0	0	1000
pesudomonas aeruginosa	0	0	125	0	1000	0	1000
klebsiella penumonia	0	0	250	0	1000	0	1000

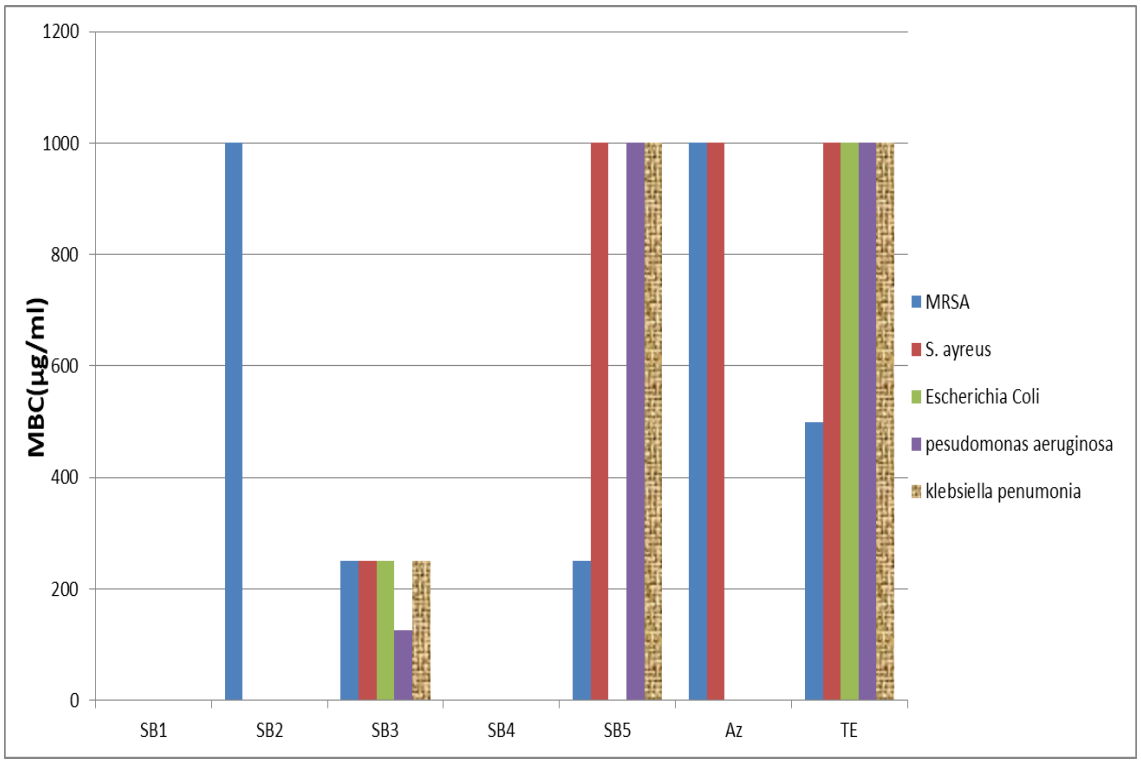


Figure 3.15: Antibacterial activity for **SB(1-5)** and **Az** against *MRSA, S. aureus, E.coli, P. aeruginosa* and *K. pneumoniae* using micro-broth dilution method; MBC (µg/ml).

3.2.2 Lipase enzyme inhibition activity for Schiff base compounds:

The compounds **SB_1**, **SB_3, SB_4** and **SB_5** were estimated with taking inconsideration pancreatic lipase inhibitory activity showed anti-lipase activities at various concentrations in **Table9**.There wasn't remarkable inhibitory effect which was detected for other compounds.

Table 3.9: IC50 value for lipase inhibition for **SB_1**, **SB_3**, **SB_4** and **SB_5** compounds.

Compounds	IC50 value for lipase inhibition assay (µg/ml), ±SD
SB_5	42.65±0.97
SB_3	125.89±1.44
SB_1	45.7±2.2
SB_4	75.85±0.8
Orlistat	12.3±0.35

Dose-dependent pancreatic lipase inhibitory activity for the four active compounds are shown in **Fig.3.16** Among all the given compounds **SB_5** was distinguished as the best anti-lipase activity. The compound inhibited pancreatic lipase activity at a concentration of 42.65µg/ml.

Orlistat is known as pancreatic lipase inhibitor which is perfectly used as anti-obesity drug, Orlistat and compound of **SB_5** the IC50 values were calculated as (12.3±0.35)and (42.65±0.97) µg /mL, respectively as shown in **Table**. And the **SB_1** has also potent inhibition at 45.7 µg/ml. The compounds **SB_2**, **SB_3**, and **SB_4** showed moderate inhibitory activity compared to orlistat, hence, these compound can be strongly suggested as an alternative to orlistat.

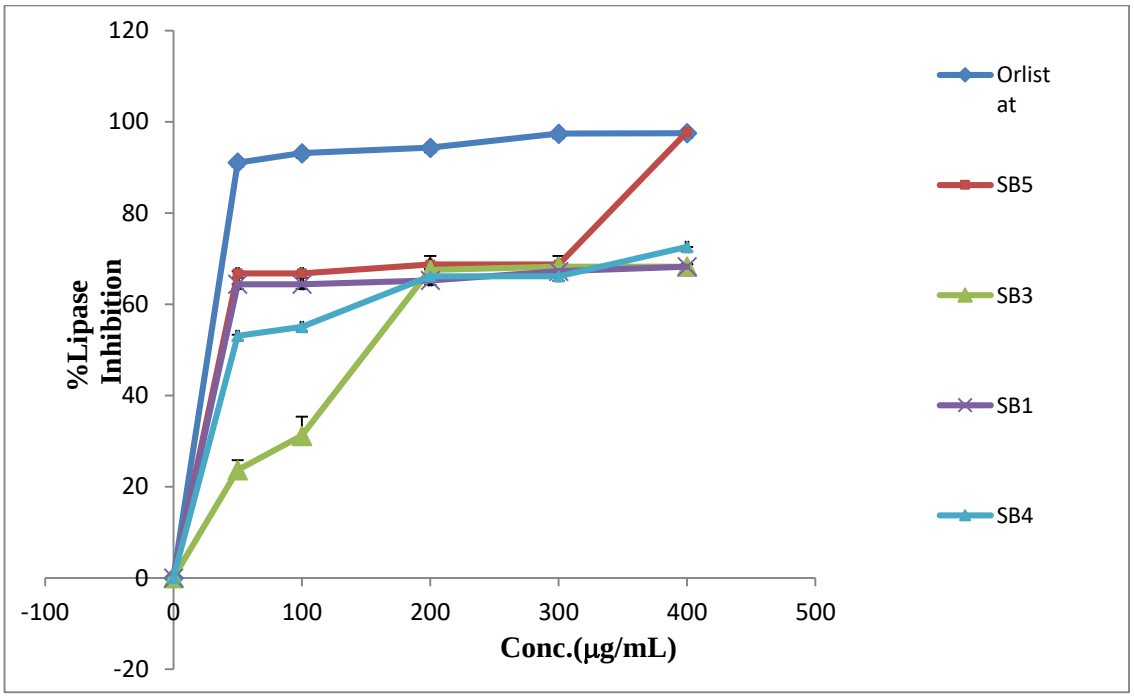


Fig. 3.16:- IC_{50}(µg/mL) values for compounds comparing with Orlistat (IC_{50} = 12.3µg/mL) as reference

3.2.3 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 **SB_5** and lipase since such compound reflected a high lipase inhibition experimentally.

The docking result was illustrated in **Fig.3.17**, the figure reflected the desired **SB_5** as a strong binder. Three strong hydrogen bonds exist between lipase and **SB_5**, 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_5** was the shortest among the three hydrogen bond distances, as seen in **Fig. 3.17.(c 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.

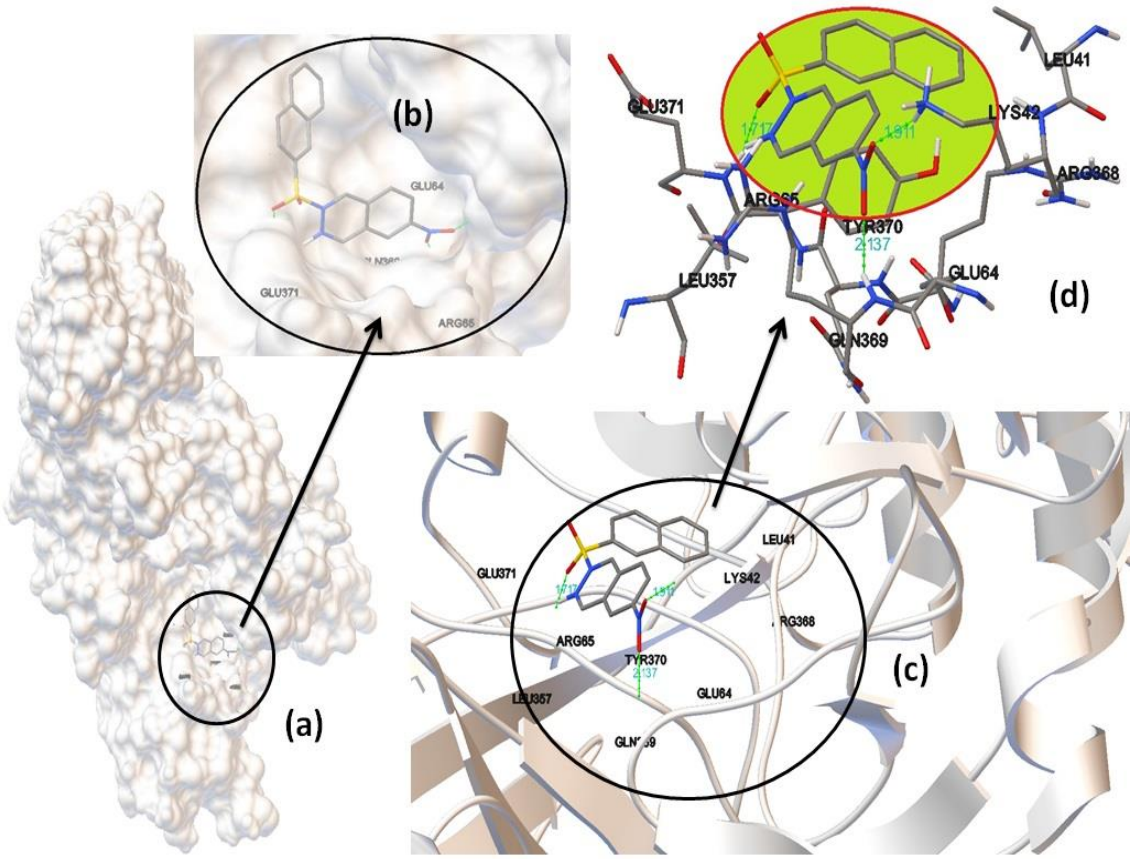


Fig.3.17:-Detailed view of the docked poses of **SB**$_5$ derivatives and the corresponding interacting amino acids within the binding site of pancreatic lipase enzyme.

Chapter four

Conclusion

Five novel Schiff base compounds containing Sulfonylhydrazide functional group were synthesized in very good yield via condensation of naphthalene-2-sulfonylhydrazide with several types of aldehydes. The structures of desired ligands were identified using FT-IR and NMR spectroscopy, then the products were confirmed also by UV-Vis spectrophotometry, Elemental analysis and GC/Ms.

Furthermore, DFT studies were carried out for one desired E/Z-**SB**, the FMO, MEP, GRD. Excellent correlation ratios were detected when theoretical IR and NMR were compared to their experimental relatives.

Such characters are valuable for biological applications. The results of the biological activities including antibacterial and Lipase enzyme inhibition activity revealed their importance in the field biological science.

The molecular docking was studied for **SB_5** with the most enzyme inhibitor, related porcine pancreatic lipase, the theoretical docking result explained the experimental one since several hydrogen bonds between the **SB_5** and amino acids formed the lipase were detected.

Sugesstion and Future work:

1. Obtaining crystall from these schiff base comounds is a great acheivment for future to be fullfilled and characterize their structure through X-ray diffraction.

2. Produce many complexes from these schiff bases by using several metals and studying their properties by using many techiniques (IR, UV-Vis., TGA, EA, GC/Ms and NMR) and testing their biological activity.

3. Testing these compound for antioxidant, antivirial, antifungal and for anthore bacteria. And applying these compounds in medical fields.

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جامعة النجاح الوطنية

كلية الدراسات العليا

تحضير وتشخيص قواعد شيف من نوع سلفنيل هيدرازيد ودراسة الأثر البيولوجي والترابط الجزيئي النظري لها

إعداد

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إشراف

أ. د. إسماعيل وراد

أ. د. محمد النوري

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في الكيمياء بكلية الدراسات العليا في جامعة النجاح الوطنية، نابلس- فلسطين.

2019

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أ. د. محمد النوري

الملخص

العمل في هذه الأطروحة يتركز في تكثيف (naphthalene-2-sulfonylhydrazide)، كماده اوليه مع العديد من الالدهايدات، من أجل إنتاج خمسة من المركبات الجديدة من قواعد شيف، حيث يتم فصلها وتنقيتها ومن ثم دراسة خصائصها من خلال إجراء امتصاص الاطياف الفوق البنفسجية (.UV-Vis)، جهاز مطياف الكتلة (GC/Ms)، اطياف تحت الحمراء(FT-IR), الرنين المغناطيسي النووي (NMR). ودراسة لواحد من المركبات للتحليل الحراري الكتلي (TGA).

E/Z– النظير البنائي لواحد من قواعد شيف المرغوب به سوف يتم الحصول عليها من خلال B3LYP. العديد من قياسات DFT المحوسبة مثل ,MEP,GRD,IR/B3LYP, (FMO HMO-LUMO) التي تم حسابها.

لقد تم فحص فعالية مركبات شيف من عدة أنواع من البكتيريا بواسطة تجربة (disk) diffusion باستخدام (TE) كمرجع لهذه التجارب، ولقد اظهرت هذه الفحوصات نتائج ايجابية.