Computational study of Sulphadoxine based Schiff base and its metal complexes

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DECLARATION

I hereby declare that this thesis work, titled Title Computational study of Sulphadoxine based Schiff base and its metal complexes, was carried out by me under the supervision of Dr. Uzma Habib at the School of Interdisciplinary Engineering and Sciences (SINES) at the National University of Sciences and Technology (NUST). I solemnly declare that this is my original work to the best of my knowledge. It contains no material that has been accepted for the award of other degrees in my name or any other university. Also, no material previously published or written by any other person has been included in this thesis except where due reference has been made to the previously published work.

Hafsa Khan

MS Computational Science & Engineering

Dedicated to

My Parents and Family

ACKNOWLEDGEMENTS

"Thank you, my dear ALLAH, for everything."

Then I would like to acknowledge the National University of Science and Technology Islamabad for providing me with the opportunity to complete the MS degree.

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1.Table of Contents

Table of Figures 11

Abstract 13

Chapter 1 14

1.1 Sulphadoxine 14
1.2 Malaria 15
1.3 Malarial Pathway in Humans 15
1.4 Mechanism of Sulphadoxine action 16
1.5 Anti-malarial Drugs 17
1.6 Resistance against Anti-Malarial Drugs 17
1.7 Schiff Base 18
1.8 Computational Analysis 19
1.8.1 Classical Mechanical Methods 19
1.8.2 Quantum Mechanical Methods 19
Chapter 2 25

Literature Review 25

Problem Statement 33

Methodology 34
3.1 Molecular Modelling 35
3.2 Quantum Mechanical Calculations: Density Functional Theory (DFT) 35
Chapter 4 37

Results 37

Chapter 5 49

Discussions 49

Chapter 6 52

Conclusion 52

References 53

Table of Figures

FIGURE 1.1 2D STRUCTURE OF SULPHADOXINE 14

FIGURE 1.2 FOLIC ACID..... 15

FIGURE 1.3 FOLATE BIOSYNTHESIS PATHWAY IN ORGANISMS..... 16

FIGURE 1.4 STRUCTURAL SIMILARITY OF PABA AND SULFONAMIDE..... 17

FIGURE 1.5 FIGURE 1- 5 BASIC STRUCTURE OF SCHIFF BASE 18

FIGURE 1.6 BALL AND SPRING TREATMENT..... 20

FIGURE 1.7 CLASSIFICATION OF COMPUTATIONAL METHODS..... 24

FIGURE 2.1 SCHIFF BASE METAL (II) COMPLEXES [37].... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 2.2 SULFADIAZINE 30

FIGURE 2.3 SULFAMETHOXAZOLE 31

FIGURE 2.4 COTRIMOXAZOLE..... 32

FIGURE 4.1 HEXADENTATE POCKETS..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 4.2 PROPOSED STRUCTURE FOR THE SCHIFF-BASED METAL COMPLEX OF SULPHADOXINE ..... **ERROR! BOOKMARK NOT DEFINED.**

FIGURE 4.3 OPTIMIZED STRUCTURE OF COBALT-BASED SCHIFF BASE SULPHADOXINE COMPLEX..... 40

FIGURE 4.4 OPTIMIZED STRUCTURE OF COPPER-BASED SCHIFF BASE SULPHADOXINE COMPLEX..... 40

FIGURE 4.5 OPTIMIZED STRUCTURE OF IRON-BASED SCHIFF BASE SULPHADOXINE COMPLEX..... 41

FIGURE 4.6 OPTIMIZED STRUCTURE OF NICKEL-BASED SCHIFF BASE SULPHADOXINE COMPLEX 41
FIGURE 4.7 OPTIMIZED STRUCTURE OF MANGANESE-BASED SCHIFF BASE SULPHADOXINE COMPLEX 42
FIGURE 4.8 OPTIMIZED STRUCTURE OF ZINC-BASED SCHIFF BASE SULPHADOXINE COMPLEX 42
FIGURE 4.9 RELATIVE ENERGIES OF OPTIMIZED COMPLEXES 43
FIGURE 4.10 PROPOSED STRUCTURE FOR SCHIFF-BASED METAL COMPLEX OF SULPHADOXINE……..…44
FIGURE 4.11 SCHEME FOLLOWED FOR THE MEASUREMENT OF BOND LENGTHS…….44
FIGURE 4.12 UV-ABSORPTION SPECTRA OF SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES……46
FIGURE 4.13 IR SPECTRA FOR SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES……48
FIGURE 4.14 DOS SPECTRUM FOR SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES……49
FIGURE 5.1 METAL-BASED SULPHADOXINE SCHIFF BASE COMPLEX 50

Abstract

Sulphadoxine is an antibacterial drug whose effectivity decreases with time due to the bacterial resistance. Formation of Schiff base metal complexes is one of the solution as the chelating structure of Schiff base ligand, containing N, S, and O donor atoms, increases the biological activity. Therefore, in this study, Schiff base of Sulphadoxine and their metal complexes were designed and optimized to minima using B3LYP/LANL2DZ level of Density Functional Theory method. Frequency calculations were performed to validate the energy minimization of all the optimized geometries. To compute the relative energies for the Metal-Schiff base complexes, single point energies were performed in the gas as well as solvent phase using the same level of DFT method. For characterization purpose, UV spectra, IR spectra and the DOS spectrum were analyzed. According to the computed results, the Iron Schiff base metal complex was found to be most stable complex among all the six metal ligand complexes that were studied. In future perspectives, the iron Schiff based complex could be studied in the wet lab for deeper understanding.

Chapter 1
Introduction

1.1 Sulphadoxine

Sulphadoxine is a derivative of the sulfa drug (Figure 1-1), a class of synthetic antimicrobial compounds consisting of aminobenzenesulfonamide and varying functional groups. The molecular formula of Sulphadoxine is C12H14N4O4S, and the chemical formula is 4-amino-N-(3,5-dimethoxypyrimidin-4-yl) benzene sulfonamide. Sulphadoxine is a bacteriostatic agent that inhibits folate synthesis, acting as a competitive inhibitor of para-aminobenzoic acid.[1] Due to the bacteriostatic effect, Sulphadoxine is used as an antimicrobial drug to treat urinary tract infections and malaria. Sulfa drugs used to treat intestinal infections and ulcerative colitis cannot absorb properly. Topical Sulfa drugs can be applied in the form of ointments for the treatment of eye infections such as bacterial conjunctivitis.[2] Sulphadoxine is an anti-parasitic drug.[3]

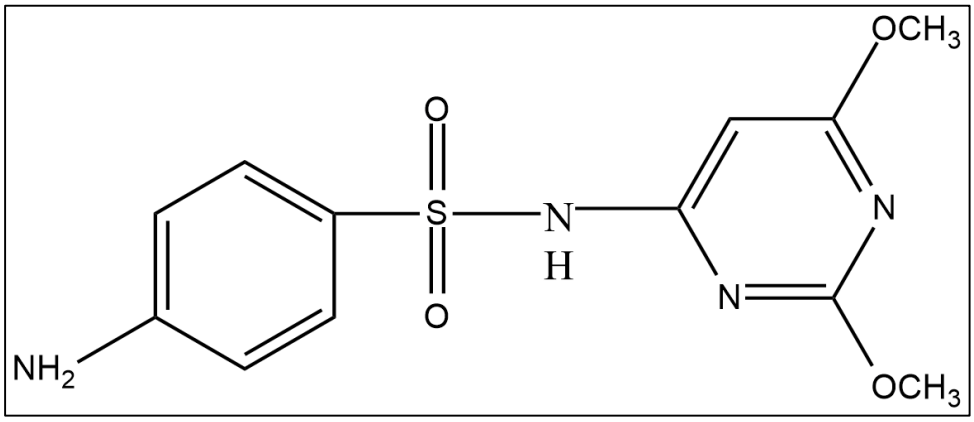


Figure 1.1 2D Structure of Sulphadoxine

1.2 Malaria

Malaria is one of the world's most widely spread, vector-carried diseases [4]. This disease has been around for over 10,000 years and spreads through the anopheles mosquito [5]. It has various symptoms, but the most common symptoms include high fever and body aches. Different treatments are devised to target the malarial pathogen plasmodium's reproduction pathway in the human body.

1.3 Malarial Pathway in Humans

The reproduction of malarial parasites depends on an intricate Folate Biosynthesis pathway[6]. Folates serve as coenzymes in 1-carbon transfer reactions of purines and pyrimidines for DNA synthesis, in the biosynthesis of methionine, serine, and glycine, and in the initiation of protein synthesis, required for bacterial growth. Folic acid constitutes three subunits: a pteridine portion, p-aminobenzoic acid (PABA), and one molecule of L-glutamic acid(Figure1.2). [7][8]

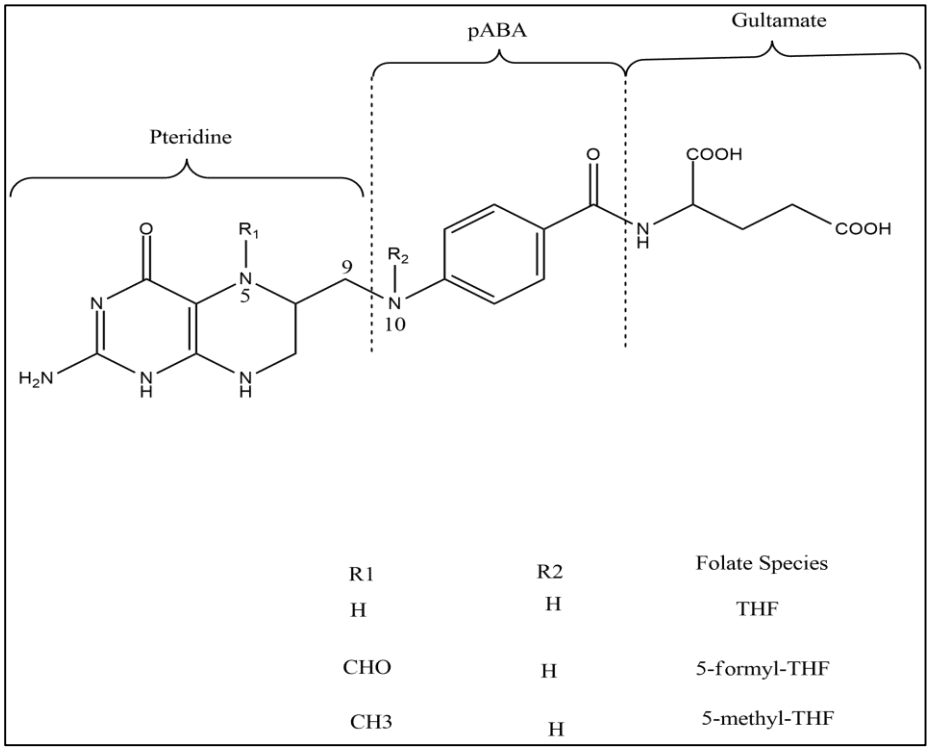


Figure 1.2 Folic Acid

In nature, microorganisms can synthesize folates from the precursors; guanosine triphosphate (GTP), PABA, and L-glutamate. The pterin is added with PABA to form dihydropteroate. In the next step, glutamic acid is added to form dihydrofolate (DHF) with the help of dihydrofolate synthase (DHFS) (Figure 1.3). DHFR is an enzyme that participates in the recycling of folates where dihydrofolate reduces to tetrahydrofolate. The tetrahydrofolate is then oxidized back to dihydrofolate. The dihydrofolate then participates in biosynthetic reactions (e.g., thymidylate synthase). Inhibiting DHFS or the formation of thymidylate lead to deadlocks in DNA synthesis and subsequent parasite death.[9][10]

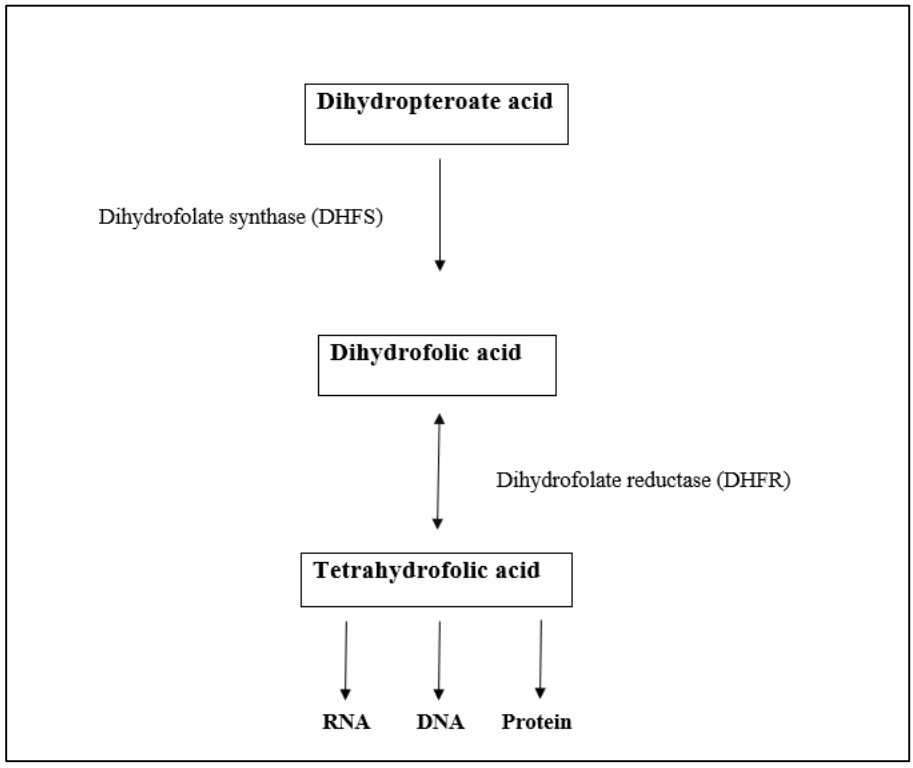


Figure 1.3 Folate Biosynthesis pathway in organisms

1.4 Mechanism of Sulphadoxine action

Sulphadoxine is a competitive inhibitor of para-aminobenzoic acid (PABA), the essential compound for folic acid synthesis, which is the precursor to bacterial genetic material.

Sulphadoxine stops the growth of folic acid; that is why sulfa drugs are bacteriostatic. The basis of inhibitory action is a structural analogy between PABA and sulfa drugs (Figure 1.4). [2]

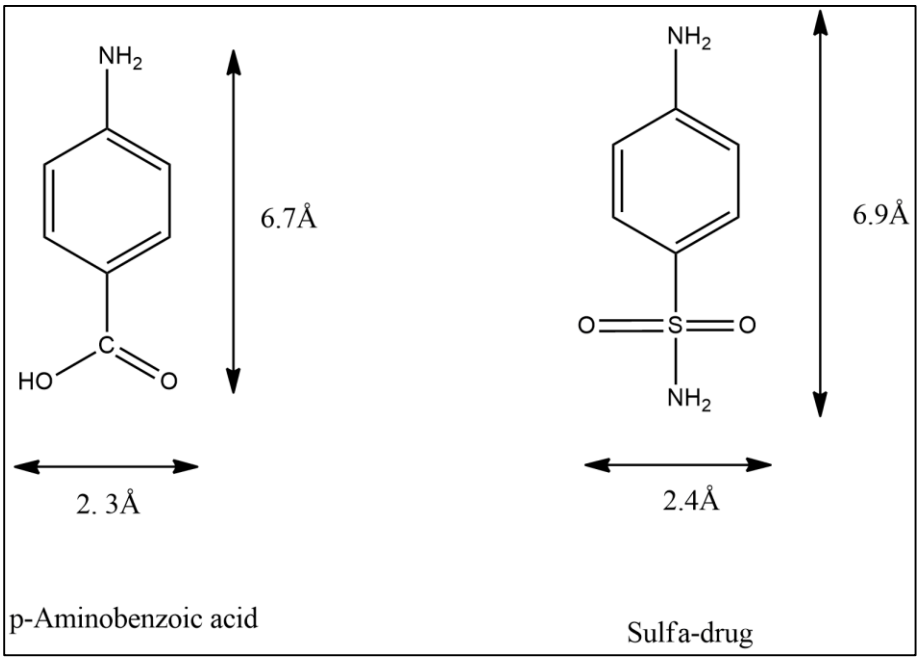


Figure 1.4 Structural Similarity of PABA and Sulfonamide

1.5 Anti-malarial Drugs

The first administered anti-malarial drug was Quinine, derived from the tree bark of the Cinchona calisaya. These anti-malarial drugs worked wonders when introduced to the world [11]. Sulfonamides, an anti-malarial drug in combination with other medicines, was used. Sulfa drugs act as folate inhibitors and inhibit the growth of dihydropteroate by dihydropteroate synthetase.[12] Gradually the efficiency of these drugs decreased as, with time, the plasmodium pathogen formed a resistance against the anti-malarial drug.

1.6 Resistance against Anti-Malarial Drugs

The earliest recorded malarial parasite resistance against the Quinine is seen in the early twentieth century[4]. The pfert is the critical gene responsible for causing resistance against

Quinine. It resides on chromosome 7 and encodes a 49 kDa protein with ten predicted transmembrane domains. This gene exhibits mutations that ultimately link to malaria quinine resistance [13]. For this reason, different approaches were taken to form a new and better anti-malarial drug. Many derivatives of Quinine are present in the market, which offer defense against the fatal symptoms of malaria. Among them, Schiff Bases-based drugs are the most viable options [14].

1.7 Schiff Base

Schiff bases are azomethine (-CH=N-) containing compounds formed by the condensation of aldehydes and ketones with primary amines. Hugo Schiff first reported these compounds in 1864. A Schiff base (Figure 1.5) is a nitrogen analog of aldehyde or ketone in which an imine or azomethine group replaces the carbonyl compound.[15]

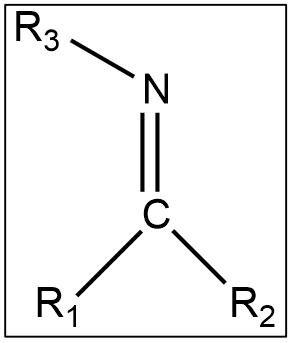


Figure 1.5 Basic Structure of Schiff Base

Schiff bases are one of the most versatile organic compounds. They are used as catalysts, pigments, dyes, and intermediates in organic synthesis. Schiff bases exhibit various biological activities, like antifungal, anti-bacterial, anti-malarial, anti-inflammatory, antiviral, and antipyretic[16]. They are used as cancer-resistant and anti-malarial drugs.[17]

1.8 Computational Analysis

The computational analysis covers a broad area that uses algorithms and hardware to solve scientific problems. Computational analysis techniques are used in all scientific and non-scientific disciplines. One such scientific discipline is Computational Chemistry, which uses computational algorithms to solve and calculate chemical behavior and the effect of chemicals[18]. The most defined and important computational chemistry methods are density functional, molecular mechanics, molecular dynamics, semi-empirical, and ab initio.

Broad-spectrum computational methods are further divided into two main categories:

1.8.1 Classical Mechanical Methods

1.8.2 Quantum Mechanical Methods

1.8.1 Classical Mechanical Methods

There are two categories of classical mechanical methods:

1.8.1.1 Molecular Mechanics Methods

Molecular Mechanics (MM) methods use the mathematical basis of classical mechanical methods to calculate and model molecular systems. These methods use force-field to calculate the minimum energy of the molecular system. The molecular mechanic's method treats atoms as balls and bonds as springs (Figure1.6) without explicitly treating electrons. This method models small and large molecules consisting of thousands of atoms. [18]

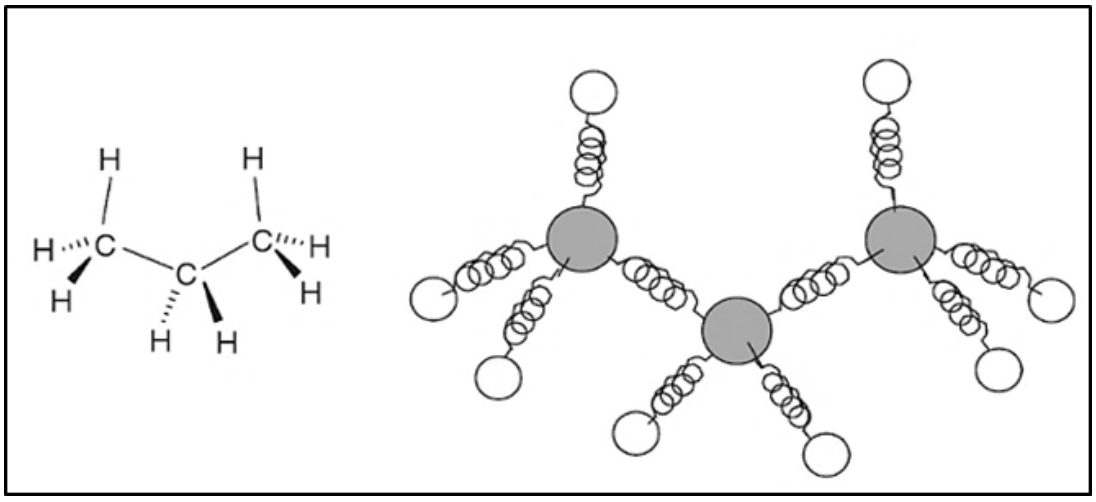


Figure 1.6 Ball and spring treatment

We can calculate the active site coordinates and binding constants using molecular mechanics.[20] It is one of the most time-efficient methods for computational analysis using limited computer resources. MM looks at molecules as balls held together through springs [21]. This method is interesting as it considers the Born-Oppenheimer Approximation.

In classical mechanical methods, MM2 (Molecular mechanics 2) and MM3 (Molecular mechanics 3) methods are used for accurate force field for organic molecules, whereas AMBER (Assisted model building with energy refinement), CHARMM (Chemistry at Harvard Macromolecular Mechanics), and GROMOS (Groningen molecular Simulation) used for calculating force field for macromolecules[22].

1.8.1.2 Molecular Dynamics Method

Molecular Dynamics is a form of Computational Analysis that considers the changes molecules and atoms undergo over time, hence the name dynamics. This method calculates the positional properties by solving Newton's second law of motion (F=ma). It is mainly used to calculate systems containing a single atom or a large group of atoms.[23]

The following equations express the total energy in the classical mechanical method: total energy is the sum of bonded forces' total energy of bonded forces' total energy of non-bonded forces. [24]

$$\mathbf{E_{(Total)} = E_{(bonded)} + E_{(non\text{-}bonded)}}$$

$$\mathbf{E_{(bonded)}} = E_{angle} + E_{bond} + E_{dihedral}$$

$$\mathbf{E_{(non\text{-}bonded)}} = E_{Van\ der\ Waal} + E_{electrostatic}$$

1.8.2 Quantum Mechanical Method

Quantum Mechanical (QM) methods are based on solving the Schrödinger wave equation. This equation governs the wave function of single electrons. The limitation of the Schrödinger wave equation is that it can only be solved for one electron in a molecule[25]. The interactions taken into consideration are electron-electron and electron-nuclei interactions. This method is further divided into three methods:

1.8.2.1 Ab Initio Method

1.8.2.2 Semi-empirical Method

1.8.2.3 Density Functional Theory Method

1.8.2.1 Ab Initio Method

The Ab-initio method is one of the most famous for modeling chemical systems. The Ab initio method solves Schrödinger's equation by using wave functions to describe atomic orbitals for calculating molecular properties. This method can only be used effectively for a small number of atoms. [26]

In this method, electrons are treated explicitly, which invokes the wave function Ψ. The system's energy in the ab-initio method is calculated by solving the Schrödinger equation.

$$\hat{H}\,\Psi = E\Psi$$

The methods used in ab-initio are Hartree-Fock (HF) and post Hartree-Fock. In the HF method, only the average effect of electron repulsion is included. Moller-Plesset perturbation theory (MP) and coupled cluster (CC) methods are examples of post-HF methods.[27]

1.8.2.2 Semi-empirical Method

The semi-empirical method is also based on the Schrödinger wave equation but requires experimental value or empirical parameters [22]. This method can be used for many atoms at a given time. This method is more efficient than the ab Initio method. Different types of semi-empirical methods are used for computational calculations. John Pople introduced the INDO (Intermediate neglect of differential overlap), NDDO (neglect of diatomic differential overlap), and CNDO (complete neglect of differential overlap) methods. Other methods, including MINDO (modified Intermediate neglect of diatomic overlap), MNDO (modified neglect of diatomic overlap), AM1 (Austin model 1), PM3 (parametric method 3), and PM6 are also used in which experimental data or experimental parameters are considered. The experimental data include results from heat of formation, ionization potential, dipole movements, and geometries. For the calculation of excited states and electronic spectra prediction, ZINDO and SINDO methods are used.

1.8.2.3 Density Functional Theory Method

This method is also based on the Schrodinger equation.

$$\hat{H}\,\Psi = E\Psi$$

The left side of the equation explains the kinetic energy of electrons and nuclei. In contrast, the right side of the equation tells about the attractive interaction of nuclei-electron and repulsion potential between the electron-electron and nucleus-nucleus. [28]

This method uses electron density instead of solving complicated many-electron wave functions. In this method, energy is minimized concerning electron density. This method uses electron density functions other than solving the wave equation. [29] DFT simulation algorithms can calculate structural, chemical, optical, spectroscopic, elastic, vibrational, and thermodynamic properties[30].

Nowadays, DFT methods are the most successful technique for finding the molecule's electronic structure. DFT provided the ground state properties of a molecular system. It also predicts:

a) Geometry optimization

b) Single-point energy calculations

c) Spectroscopic analysis

d) Frequency calculations

e) Dipole moments

f) Atomic charges

g) Electrostatic potential

h) Polarizabilities, etc.

DFT calculations are relatively computationally less expensive and offer a wider variety of density functions like BLYP, B3LYP, BPLYP, BP86, and PBE0. All of which have unique properties and directions of use[31].

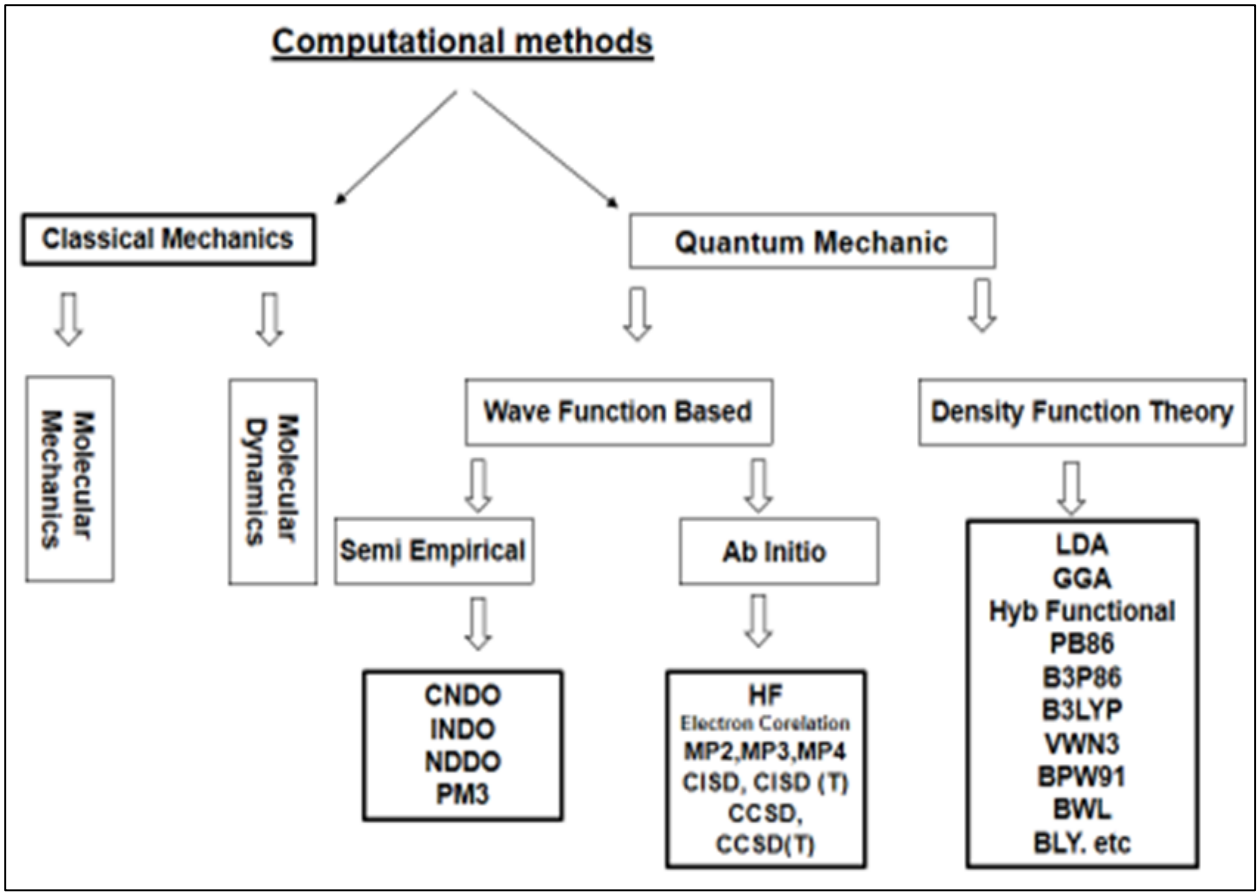


Figure 1.7 Classification of Computational Methods

1.8.2.3.1. Gaussian

Gaussian-09 is computer software for computational chemistry, which the now late John Popel released in 1970. John Popel belonged to the esteemed Carnegie -Mellon University. The initial launch of the software was as Gaussian 70, and with time various new versions and updates were released. The most up-to-date and used Gaussian is Gaussian 09 now. The software can also predict various properties of molecules and their reactions, molecular energies and structures, IR, NMR, Raman, and UV. The advantage of using this software is that the results are very accurate compared to the experimental data. This software can be used with windows and Linux, which is also a big plus.

Chapter 2

Literature Review

In the world today, many anti-malarial drugs previously used are discontinued. The reason is that the malarial parasite has evolved into a more potent and resistant parasite not affected by the drug. For this reason, there is a continuous need for new and better anti-malarial drugs that can be used against this bacterium optimally. Schiff bases with their base as Sulphadoxine are a promising candidate for diminishing bacterial growth.

Schiff base ligands have attracted the attention in coordination chemistry due to their ability to coordinate with many transition metals and stabilize them in their various oxidation states. The stability of Schiff base complexes has dramatically increased due to the chelating nature of the polydentate ligands. This exceptional chelating ability of Schiff Bases has been increased due to azomethine nitrogen, which transports a lone pair of electrons in a sp2 hybrid orbital [31]. The performance of Schiff bases as coordinating agent is increased due to the presence of O-H or S-H functional group(s) within 2–3 atomic distances from the azomethine group [32].

Schiff bases have been widely tested as anti-bacterial since the 2000s. The first ever Schiff base used as an anti-bacterial was Ancistrocladidine. It is a secondary metabolite produced by plants belonging to the families of Dioncophyllaceae and Ancistrocladaceae. They have an imine group in their molecular scaffold. It was used to treat diseases caused by P. falciparum K. [32]

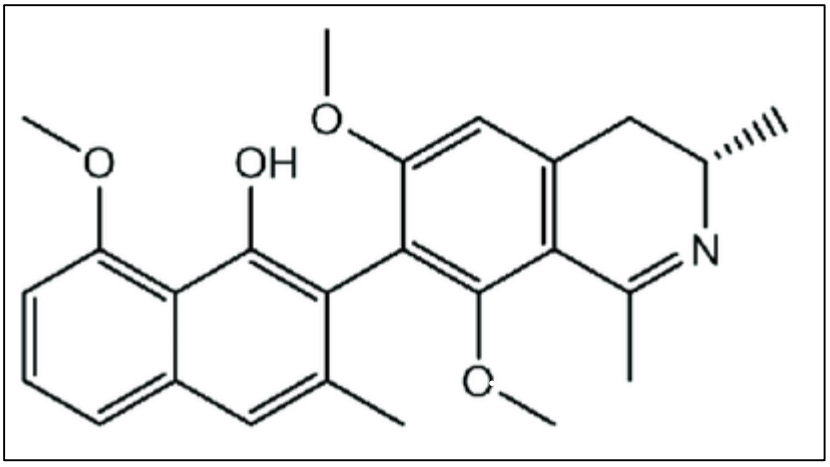


Figure 2.1 Ancistrocladidine

Schiff bases have the following applications.

Anti-bacterial: Schiff bases are anti-bacterial agents. For example, N-(Salicylidene)-2-hydroxyaniline is active against Mycobacterium tuberculosis [33].

Antifungal: Fungal infections are not limited to the contamination of surfaces. There was an incidence of recurring fungal infections, which are life-threatening. Schiff bases are considered antifungal agents. Some of them, such as imine derivatives of quinazolinones, having antifungal properties against Candida albicans, Trichophyton rubrum, T. mentagrophytes, Aspergillus niger, and Microsporum gypseum.[34].

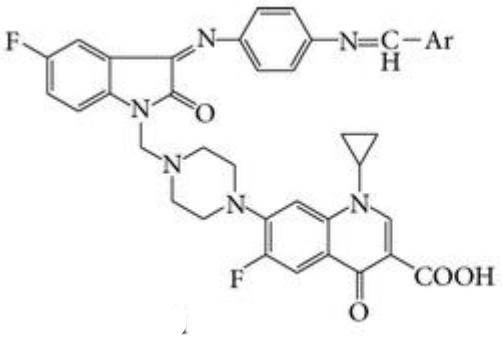
Biocidal Property: Schiff bases obtained by synthesizing o-aminobenzoic acid and β-keto esters have been discovered to be effective biocides against S. epidermidis, E. coli, B. cinerea, and A. niger [35]. Antiviral Property: Isatin Schiff base ligands show antiviral activity and are used to treat AIDS [36]. Schiff bases containing 2-hydroxybenzaldehydes are famous antimicrobial agents in the free and chelated form in metal complexes. Biological actions are reported for various

Schiff bases of sulfonamides. Sulfamethoxazole has exhibited action against Mycobacterium tuberculosis [37].

World Health Organization (WHO) claims that recently approved drugs offer very modest advantages over currently employed practices; about 75% of the antimicrobials now in research are derivatives of previously well-known and widely-used compounds in the market. [35].

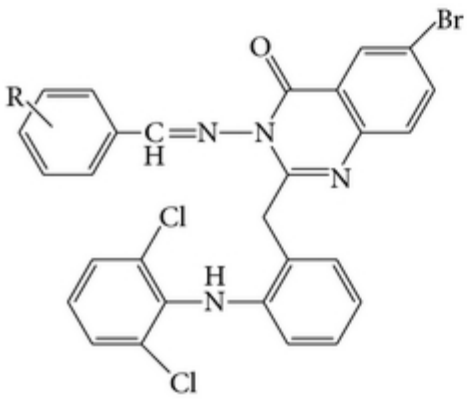
Schiff bases as anti-bacterial is an exciting concept. These unusual compounds have been showing increasing cytotoxic and cytostatic activity against bacterial agents, which is why in the newest formed anti-bacterial, Schiff bases are commonly used. Other than that, there are uncountable possibilities for forming combinations of and with Schiff bases, making it unique and usable[33][34]. Some of the most famous series of anti-bacterial Schiff base medicines are as follows:

1. 6-bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(substitutedbenzylideneamino)-quinazolin-4(3H)-one



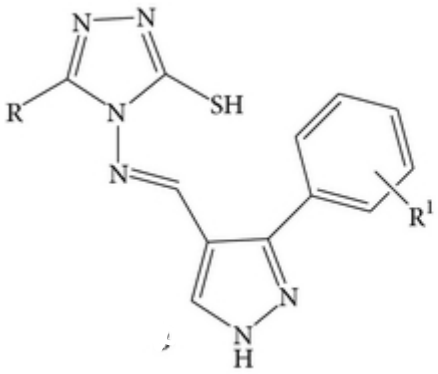
1	Ar	1	Ar
a	$-C_6H_5$	g	$-4CH_3-C_6H_4$
b	$-4Cl-C_6H_4$	h	$-3,4,5(OCH_3)_3-C_6H_4$
c	$-4OH-C_6H_4$	i	$-4OH, 5-OCH_3-C_6H_4$
d	$-4OCH_3-C_6H_4$	j	$-5NO_2-C_6H_4$
e	$-4NO_2-C_6H_4$	k	$-4N(CH_3)_2-C_6H_4$
f	$-6OH-C_6H_4$	l	$-CH=HC-C_6H_4$

2. 4-[(3-substituted-1H-pyrazol-3-yl)methyleneamino]-5-substituted-4H-1,2,4-triazole-3-thiols



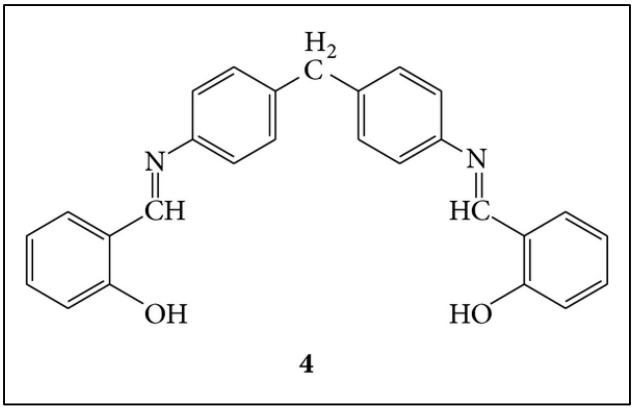
2	R	2	R
a	2-NO_2	**g**	4-OCH_3
b	3-NO_2	**h**	3,4,5-$(OCH_3)_3$
c	2-OH	**i**	2-OH, 4-OCH_3
d	4-OH		
e	2-Cl	**j**	4-$N(CH_3)_2$
f	4-Cl	**k**	2-OH, 4-$N(C_2H_5)_2$

3. Condensed salicylaldehyde and o-vanillin with 4,4′-diaminodiphenylmethane, 4,4′-diamino diphenyl sulfide, and diethyl ester of terephthalic acid



3	R	R^1	3	R	R^1
a	$-C_2H_5$	H	**f**	H	H
b	$-C_2H_5$	4-OCH_3	**g**	H	4-OCH_3
c	$-C_2H_5$	4-F	**h**	H	4-F
d	$-C_2H_5$	4-Cl	**i**	H	4-Cl
e	$-C_2H_5$	2,4-Cl_2	**j**	$-C_3H_7$	4-F

4. 4-hydroxy-3-(1-{2-(2-hydroxy-benzylidene)-amino-phenylimino}-ethyl)-6-methyl-pyran-2-ones



4

These Schiff bases are very famously used in the anti-bacterial world. The only changes are made on the bases of the metal they are bonded to[35].

Schiff base contains chelating agents that can coordinate with metal ions to form metal complexes, i.e., cobalt (II), copper (II), iron (II), manganese (II), nickel (II), and zinc (II). These metal Schiff-based complexes could treat biological infections [39]. A novel Schiff base was prepared by condensation of Sulphadoxine and 2-carboxybenzaldehyde [38]. Researchers have been interested due to their potential antibacterial activity, in N-donor ligand derivatives, carboxylate derivatives, and the Zn (II) cation. Cu(II) and Zn(II) are two d-block metal ions that have potential anti properties. The only metal that can be found in all types of enzymes is zinc, which is the second most common trace element in our body after iron.

Studies have revealed that Zn (II) metal ions have essential anti-bacterial and antiviral effects. Moreover, it is distributed in the human body's blood, kidney, liver, and bone. In addition, several bacteria, including Escherichia coli, Streptococcus faecalis, as well as many soil pathogenic bacteria, are hindered by zinc. [40]. Mass spectroscopy (MS) and nuclear magnetic

resonance (NMR) spectroscopy were performed for the structural characterization of Schiff base metal complexes [38].

Sulfonamides are a group of synthetic antibiotics. They contain a sulfanilamide molecular structure and are widely used as anti-malarial drugs because of their structural similarity to Para-amino Benzoic Acid (PABA). Normally PABA binds with Dihydropteroate Synthetase (DHPS) to form dihydrofolic acid in the folate biosynthetic pathway. Since Sulfonamides are structural analogs of PABA, they bind with DHPS, blocking the pathway from going any further. There are many Sulfonamides based drugs on the market. Some of them are Sulfadiazine, Sulfamethoxazole, Trimethoprim, and Cotrimoxazole.

Sulfadiazine:

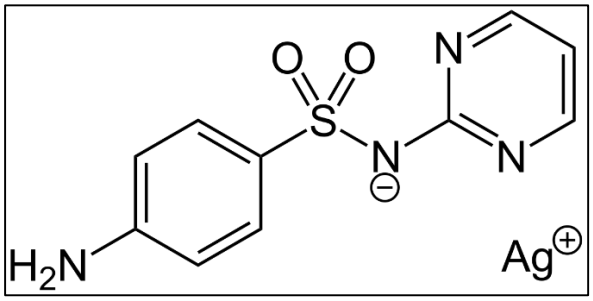


Figure 2.2 Sulfadiazine

Sulfadiazine is a dihydrofolate reductase inhibitor that works with pyrimethamine. The common side effects of using this drug include nausea, diarrhea, rash, fever, and depression. The drug belongs to the class of sulfa drugs and is a known anti-malarial. It is sold under many names in the market, for example, Lantrisul, Neotrizine, Sulfa-Triple #2, Sulfadiazine, Sulfaloid, Sulfonamides Duplex, Sulfose, Terfonyl, Triple Sulfa, Triple Sulfas, and Triple Sulfoid. This drug was discovered in the 1960s when malaria was rising in European countries. This medicine is also on the list of essential medicines of the World Health Organization (WHO)[36].

This drug was discontinued in 1994 by the United States of America because the consequent abuse of this medicine in practicing hospitals caused resistance to malarial parasites.

Sulfamethoxazole:

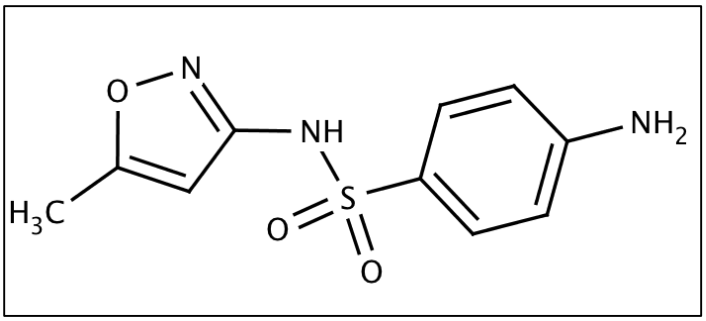


Figure 2.3 Sulfamethoxazole

This drug was discovered in 1932 and has been used extensively in various clinical indications. Sulfamethoxazole and trimethoprim are two drugs sold in combination as an antibiotic for malaria and other infections[37]. This combination of medicines works best for bacterial infections and does not affect viral infections, colds, and flu.

Cotrimoxazole:

This drug is deemed the wonder drug for resistance. It helps treat many bacterial infections, including skin infections, chest infections, and bladder infections[36]. The drug was introduced in 1969 in the United States of America. Many countries later adopted it, and it has since been used for treatment.

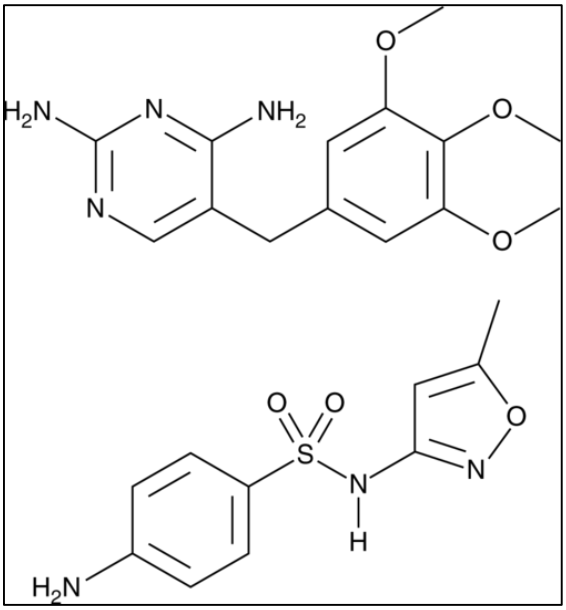


Figure 2.4 Cotrimoxazole

With time the malarial parasite has shown resistance to most synthetic malarial drugs. The degree of resistance varies for each drug. It is only a matter of time before the malarial parasite forms complete resistance to synthetic anti-malarial drugs [38]. Due to antibiotic resistance in the United States, every year, around 2.8 million people suffer, resulting in more than 35000 deaths. In Europe, around 33000 deaths are due to antibiotic resistance [39].

Schiff bases are pharmacophores that cave metal ions into their structure due to the presence of donor atoms. The metal complexes of Schiff bases provide a new line of anti-bacterial which will act as a first-line defense against the malarial parasite Plasmodium. Much research has been carried out for decades on Schiff base metal complex production and pharmacology. Many different metal complexes of Schiff bases are being synthesized in the laboratories. Generally, Transition metal Schiff base complexes are formed by chelation due to the vacant d orbital of transition metals. Chelation makes the complexes more stable by delocalization of electrons[40].

Metal-based medicines are capable of replacement for several existing medicines. Transition metal complex enhanced the antimicrobial performance as compared to parent

medicine. The effectiveness of metallic-based compounds is greater than the free Schiff base ligands[41]. Schiff Base derived from ethylenediamine and 2-hydroxyphenylacetone and its Cu(II) complex were found to forcefully stop the growth of different cancer-causing cells by several mechanisms[42]. The Schiff base ligands derived from amoxicillin (AMX) and picolinaldehyde (PC2) were tested against human pathogenic clinical strains of microbes. The result showed that the antimicrobial activity of microbes was suppressed[43].

Problem Statement

The malarial pathogen, Plasmodium has become ever-resistant to the present anti-malarial drugs. As a result, the drugs on the market have lost their viability against the parasite. There is a strong need to design a new anti-resistant drug for malaria. Schiff-based ligands of many drugs proved to be very effective against resistance. Therefore, in this research, Schiff-based ligands of Sulphadoxine and their complexes with metals were designed and studied computationally.

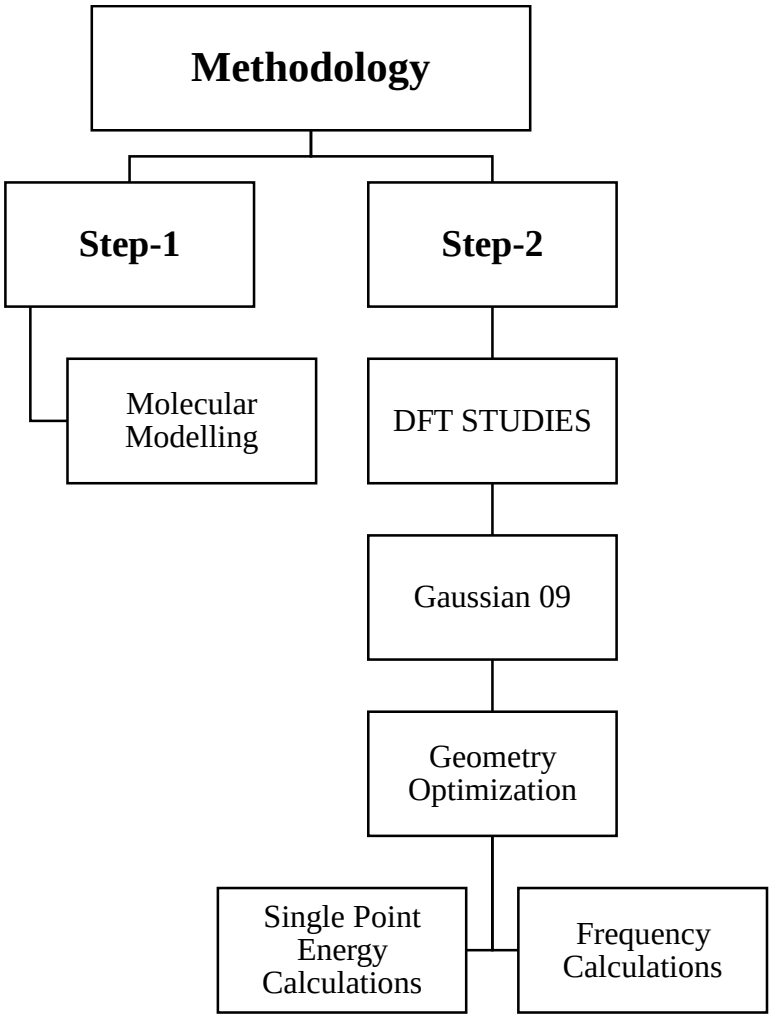
Objectives

The objective of this research is to design and analyze the Schiff-based ligands of Sulphadoxine and their metal complexes. This will be done in order to identify the most stable Metal-Schiff-based ligand complex.

Chapter 3

Methodology

The main aim of this research was to identify the most stable Sulphadoxine based Schiff base metal complexes to be used as an anti-malarial drug because of the current resistance of malarial parasites against them. The research was carried out in the following two significant steps:



3.1 Molecular Modelling

Molecular modeling is the science of representing a molecule's structure in a space with x, y, and z coordinates. The structures are modeled and then subjected to optimization studies. The structure is modeled to fulfill the basic chemical laws and theories.

The field of molecular modeling is vast and undoubtedly has the utmost potential. Over the last ten years, molecular modeling has expanded to optimizing, predicting, simulating, and analyzing the behaviors of molecules in real and passive time. This technique has dramatically enhanced the computation and science of solving chemical problems and has given a brand-new discipline in the world to excel.

Using molecular modeling in disease sciences has led to the real-time innovation and study of multiple disease facets. Without the advent of this technique, scientists and researchers would have to be exposed to various chemicals, pathogens, and viruses, daily.

The Sulphadoxine-based Schiff bases and their complexes were designed using molecular modeling.

3.2 Quantum Mechanical Calculations: Density Functional Theory (DFT)

Density Functional Theory (DFT) is a computational method to investigate the electronic structure of atoms and molecules with the help of a hybrid function of electron density. Electron density is a function of electron position in x, y, and z coordinates. For DFT studies, Gaussian 09 software [44] was extensively used. Molden [43] program was used to visualize the output geometries. Gaussian is a general-purpose computational chemistry software package initially released in 1970 by John Pople. The Gaussian package is widely used in molecular mechanics, semi-empirical methods, and density functional theory studies. For this research, Gaussian-09 was used to perform all the simulations. Using DFT following steps were performed:

3.2.1 Geometry Optimization

3.2.2 Frequency Calculation

3.2.3 Single Point Energy Calculations

3.2.1 Geometry Optimizations

Geometry optimization is optimizing the system's geometry, including the atoms' nuclear coordinates, to get the most negligible possible energy for the molecule. Geometry optimization is performed on all the modeled geometries using hybrid density functional B3LYP and LANL2DZ levels of energy.

3.2.2 Frequency Calculations

For validation purposes, frequency calculations were performed on all the optimized geometries to ensure that the minimized geometry has no imaginary or negative frequency.[46] Zero-point correction energies were also obtained from the frequency calculations.

3.2.3 Single Point Energy Calculations

Single Point Energies in the gas phase and Self-Consistent Reaction Field calculations using water as a solvent were performed on all the optimized geometries to calculate the electronic energy of a specific arrangement of atoms. For all optimized geometries, the single-point energy calculations were performed using Stuttgart Dresden's effective core potential in the gas and solvent phase.[47]

3.2.4 Molden

The Molden software package is used to visually analyze electronic and molecular properties from Gaussian output files [43]. Molden software is used for post and pre-evaluation of computational results. It displays molecular density and is widely used in computational chemistry.

Chapter 4

Results

The resistance of bacterial strains against anti-bacterial drugs is an ever-growing concern. These bacterial strains have become stronger than before by improving their genetic makeup, which renders the potency of anti-bacterial drugs useless. Many different types of drugs have been synthesized to cope with this problem at hand. Among these, Sulfa drugs can lose their effectiveness against bacteria. Sulfa drugs, also called Sulfonamide, are a type of synthetic antibiotic drug containing a chemical group called Sulfanilamide.

Sulphadoxine s are bacteriostatic, which means they do not kill the bacteria but halt their production. Bacteria reproduce in the human body by utilizing the available simpler biomolecules. One of the essential constituents of the bacterial body is the vitamin B complex. This complex controls the production of bacterial DNA and RNA needed for reproduction. The production of this complex is through an intricate folate biosynthetic pathway.

The Folate pathway is three-stepped. The first step starts with p-Amino Benzoic Acid (PABA). This PABA is converted into Dihydropteroate Acid by Dihydropteroate Synthase (DHPS). In the second step, Dihydropteroate Acid is converted into Dihydrofolic Acid with the help of Dihydrofolate Synthase (DHFS). A reversible reaction is the third and final step in the folate biosynthetic pathway. In this step, Dihydrofolic Acid converts into Tetrahydrofolic Acid with the

help of Dihydrofolate Reductase (DHFR). This tetrahydrofolate synthesizes DNA, RNA, and amino acids as it is an essential coenzyme. So technically, if the production of the bacteria is to be halted, this pathway should be targeted.

Sulfonamides act as structural analogs for PABA, thus binding with the DHPS. As a result, the reaction stops going further, meaning no tetrahydrofolate is synthesized. Since this approach has been in use for a long time, the bacterial strains have become resistant to Sulfonamides. For resistance against Sulfonamides, they have been complexed with structures to increase their potency. These new complexes keep the structural integrity of Sulfonamides intact because they are supposed to be PABA analogs. As these analogs become resistant to bacteria, there was a need to modify these analogs to fight the bacteria.

This study aimed to model the Schiff-based Sulfonamide and their metal complexes (Co, Cu, Fe, Ni, Mn, and Zn) as the structural analog that can take the place of PABA in the folate biosynthetic pathway. These Schiff-based ligands (Figure 4.1) and their complexes with Co, Cu, Fe, Ni, Mn, and Zn metals were designed/ modeled. The proposed metal-ligand complex is presented in Figure 4.2.

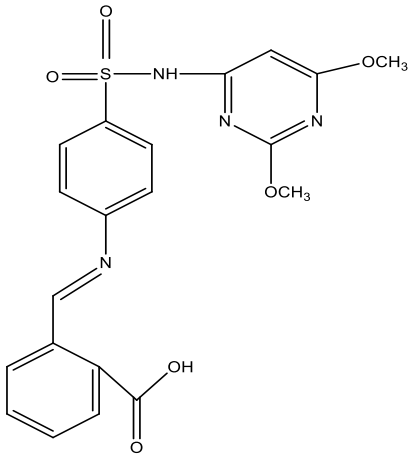


Figure 4.1 Schiff Based Ligand

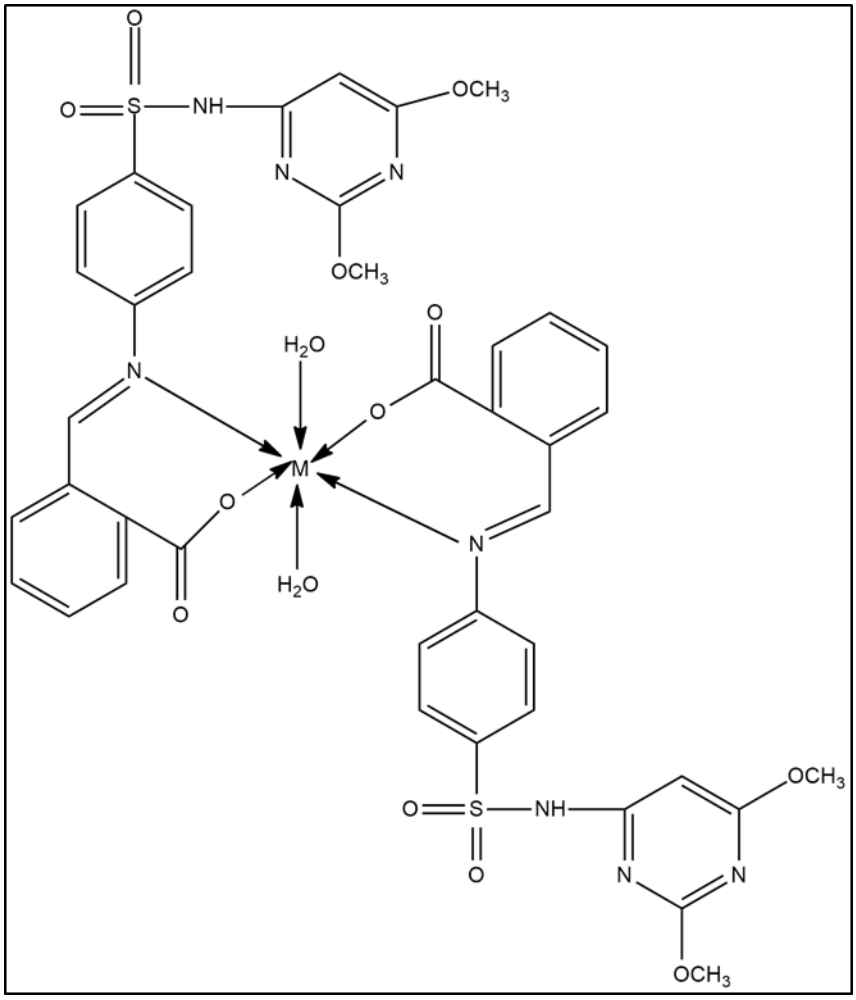


Figure 4.2 Metal Ligand Complex

All the modeled geometries were then optimized using a hybrid functional B3LYP and LANL2DZ basis set. The optimized structures were then subjected to SCRF calculations with the solvent kept as water.

Order of Stability

According to the computed data, the energy required for forming Co-Schiff-based Sulfonamide is -104 kcal/mol (in solvent) relative to the separate Schiff-based ligands and a metal salt. The energy required for forming Cu-Schiff-based Sulphadoxine is -68.4 kcal/mol relative to the separate Schiff-based ligand and metal salt. Ni-Schiff-based Sulphadoxine formation requires -90.8 kcal/mol energy, Mn-Schiff-based Sulphadoxine requires -114 kcal/mol, and Zn-Schiff based

Sulphadoxine requires -125 kcal/mol, for Fe-Schiff based Sulphadoxine requires -134 kcal/mol energy relative to the separate Schiff-based ligand and a metal salt.

The order of stability is Fe-SB > Zn-SB > Mn-SB > Co-SB > Ni-SB > Cu-SB.

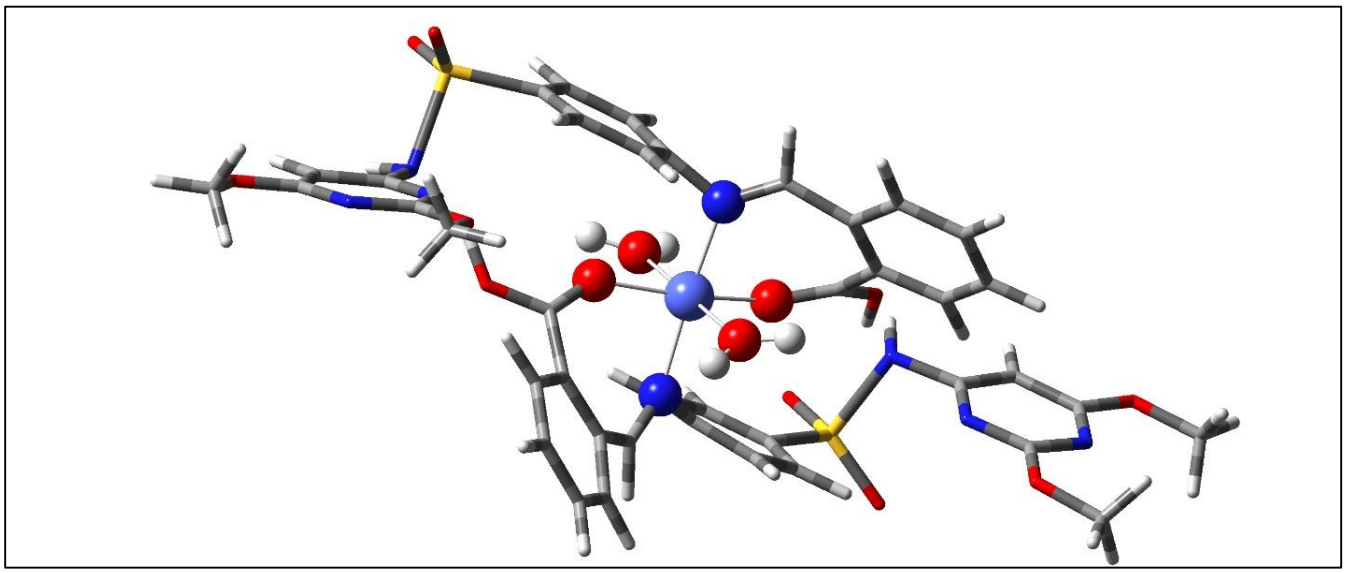


Figure 4.3 Optimized Structure of Cobalt-based Schiff Base Sulphadoxine Complex

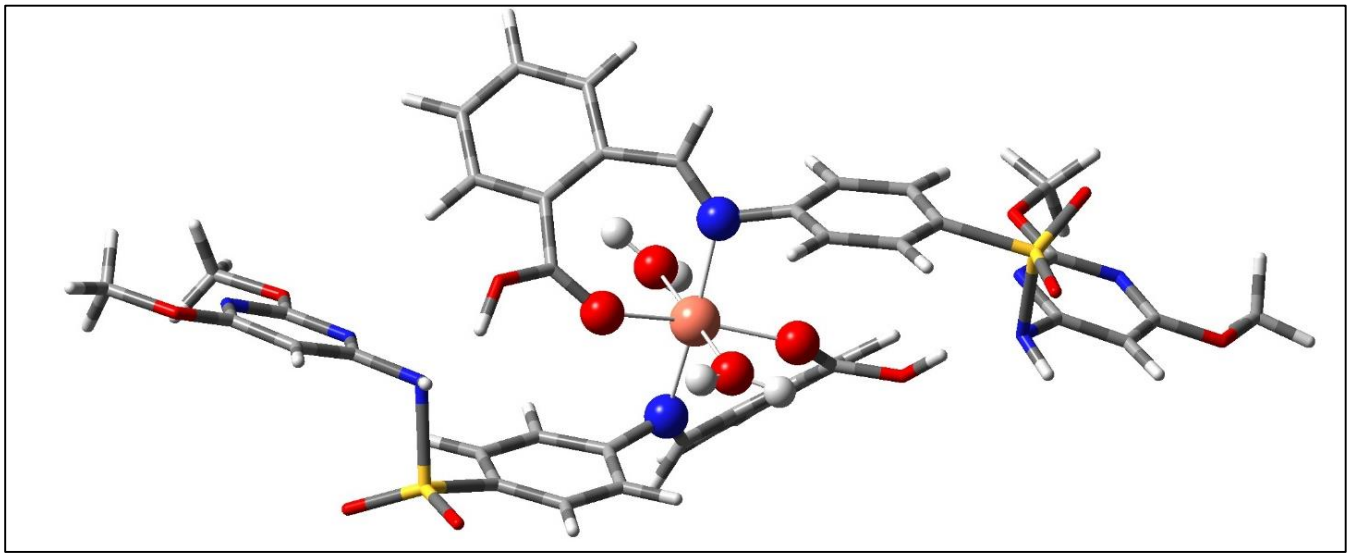


Figure 4.4 Optimized Structure of Copper-based Schiff Base Sulphadoxine Complex

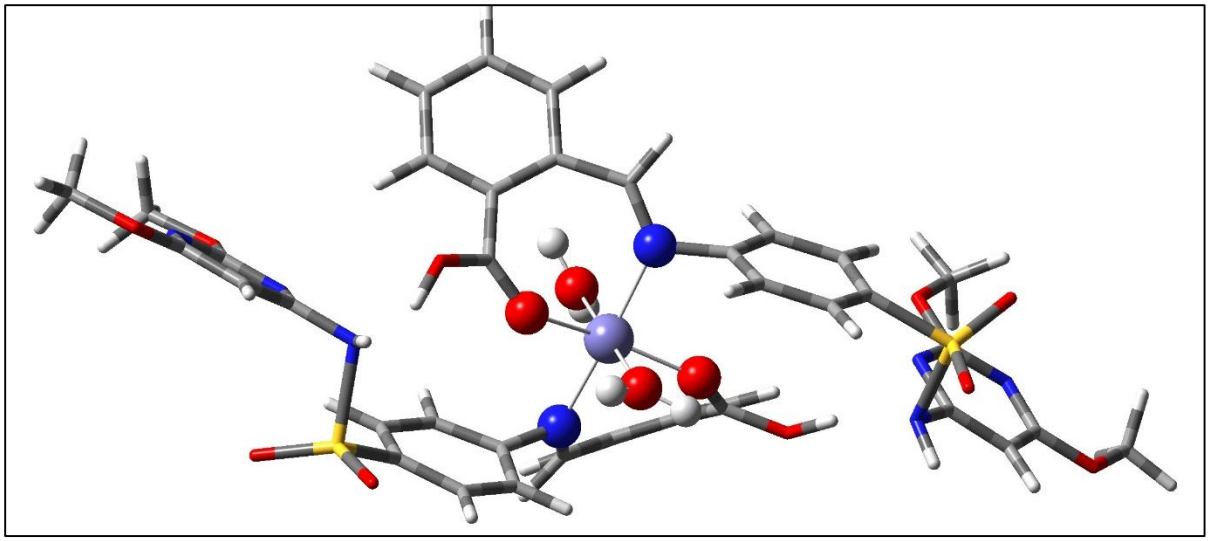


Figure 4.5 Optimized Structure of Iron-based Schiff Base Sulphadoxine Complex

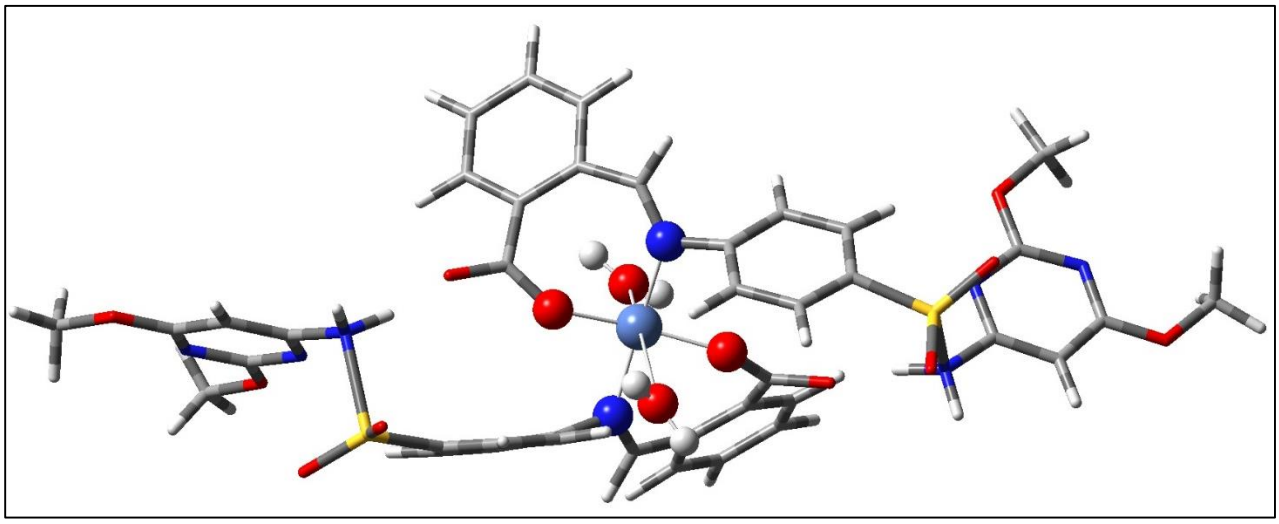


Figure 4.6 Optimized Structure of Nickel-based Schiff base Sulphadoxine Complex

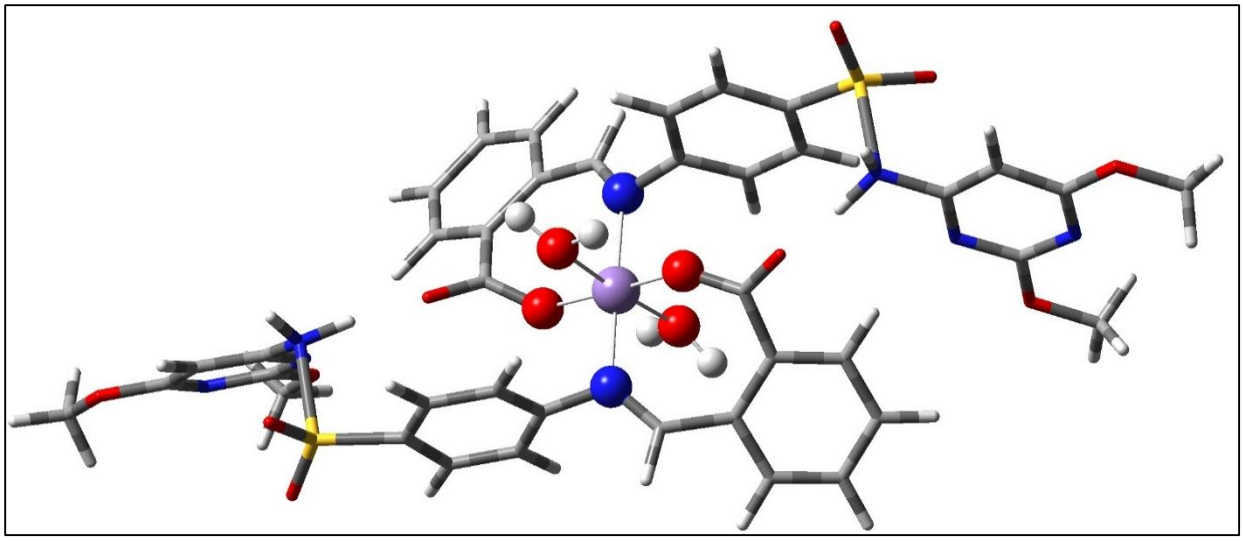


Figure 4.7 Optimized Structure of Manganese-based Schiff Base Sulphadoxine Complex

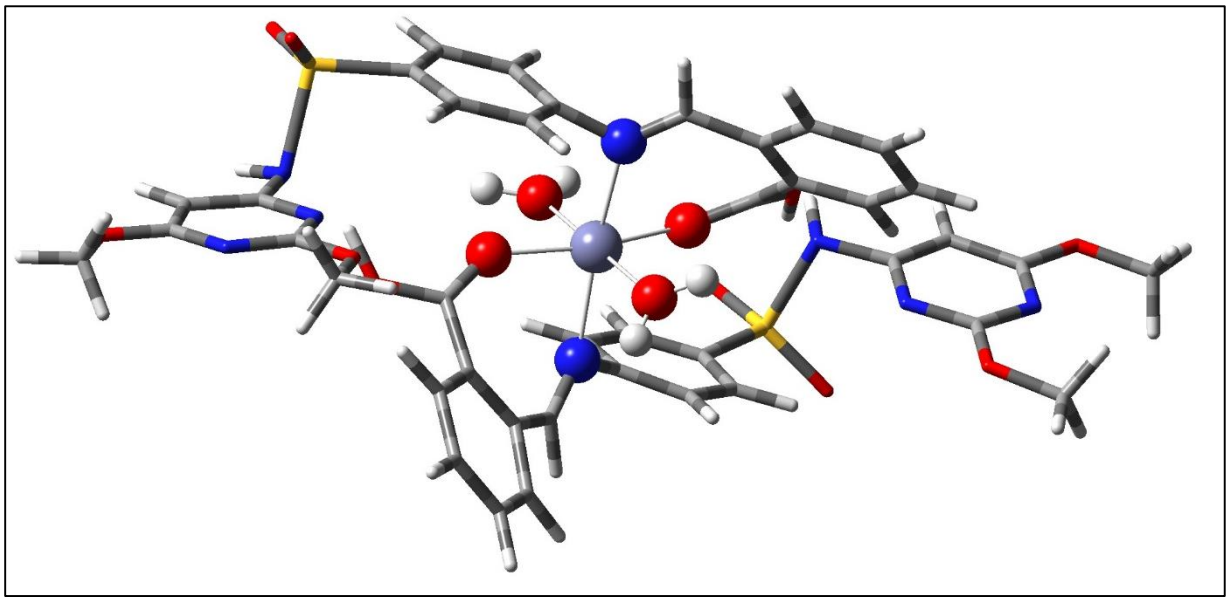


Figure 4.8 Optimized Structure of Zinc-based Schiff Base Sulphadoxine Complex

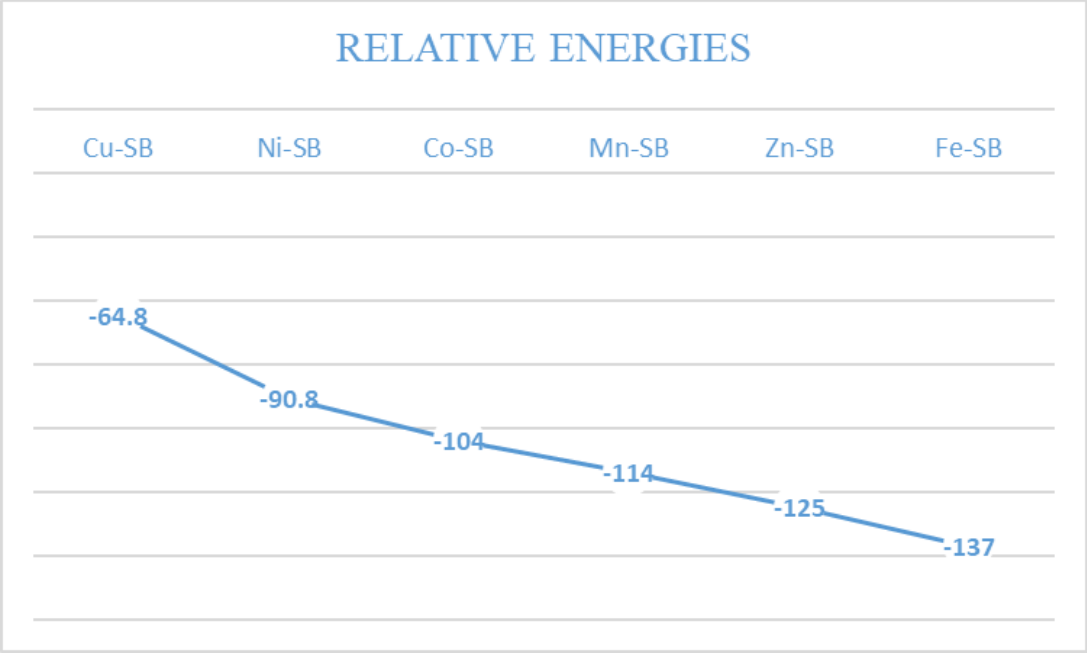


Figure 4.9 Relative Energies of Optimized Complexes

Table 4.1 Relative Energies of Optimized Complexes

Complexes	SB(kcal/mol)
Cu-SB	-64.8
Ni-SB	-90.8
Co-SB	-104
Mn-SB	-114
Zn-SB	-125
Fe-SB	-137

Geometric parameters

The geometric parameters are an essential factor in identifying the stability of complexes. In all the model metal complexes, metal is chelated with the two bidentate ligands and two water molecules in the complex. The bond length of metals with each coordinating group in all

complexes also represents the strength of complexes. All the bond lengths measured are presented in Table-2. The scheme followed for measuring the bond length is presented in Figure 21.

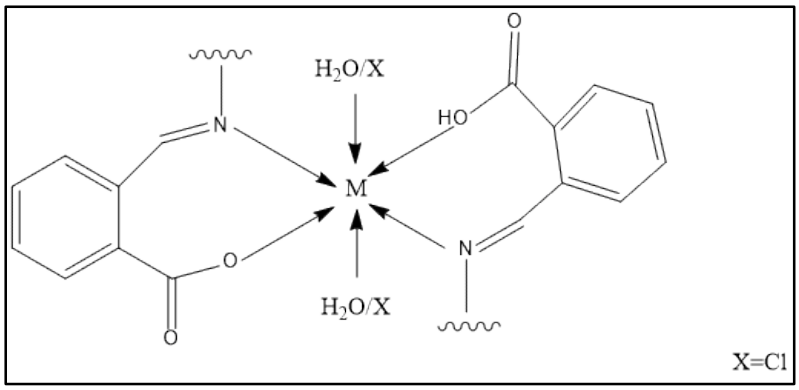


Figure 4.10 Proposed Structure for Schiff-Based Metal Complex of Sulphadoxine

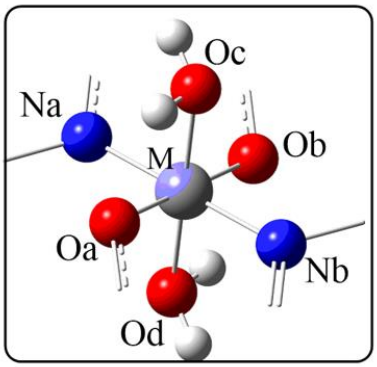


Figure 4.11 Scheme followed for the measurement of bond lengths

Table 4.1 Measured Bond Lengths of Optimized Complexes

	Cu-SB	Co-SB	Zn-SB	Ni-SB	Mn-SB	Fe-SB
M-Na	2.057	2.001	2.175	1.958	2.116	2.04
M-Nb	2.056	2.001	2.175	1.958	2.042	2.04
M-Oa	2.033	1.993	2.089	1.872	1.959	1.996
M-Ob	2.031	1.994	2.089	1.872	1.992	1.996
M-Oc	2.263	2.185	2.09	4.527	2.088	2.003
M-Od	2.349	2.219	2.146	2.512	2.082	2.03

Spectroscopic data

Using the TDFT method, the Schiff base ligands' electronic spectrum and their metal complexes were calculated from 300 -800nm. For the Schiff base, the UV spectra show the λmax at 345.8 nm with an absorption intensity of 19640.02 cm-1 (Table- 3). The UV spectra of its metal (Co, Co, Fe, Mn, Ni, and Zn) complexes show varied results. Co-complex and Cu-complex show hypsochromic (shorter λmax) and hyperchromic effects (greater absorbance), whereas Fe, Mn, Ni, and Zn complexes show bathochromic (longer λmax) and hypochromic (lower absorbance) effects.

On analyzing Schiff bases and metal complexes spectra, it has been observed that the metal complexes exhibit intense bands in the 300–700 nm region, which could be assigned to n→π* and π→π* transitions (Table 4.3).

Table 4.2:Electronic absorption values for Schiff base ligands and their metal complexes

	UV Absorption	
	Wavelength (nm), λ_{max}	Absorption (mol-1cm-1)
Ligand, SB	345.8m	19640.02
Co	318.7s	32695.92
Cu	317.9s	34657.5
Fe	417.4m	18900.15
Mn	406.8s	17911.69
Ni	625m	19043.22
Zn	415.2m	16007.54

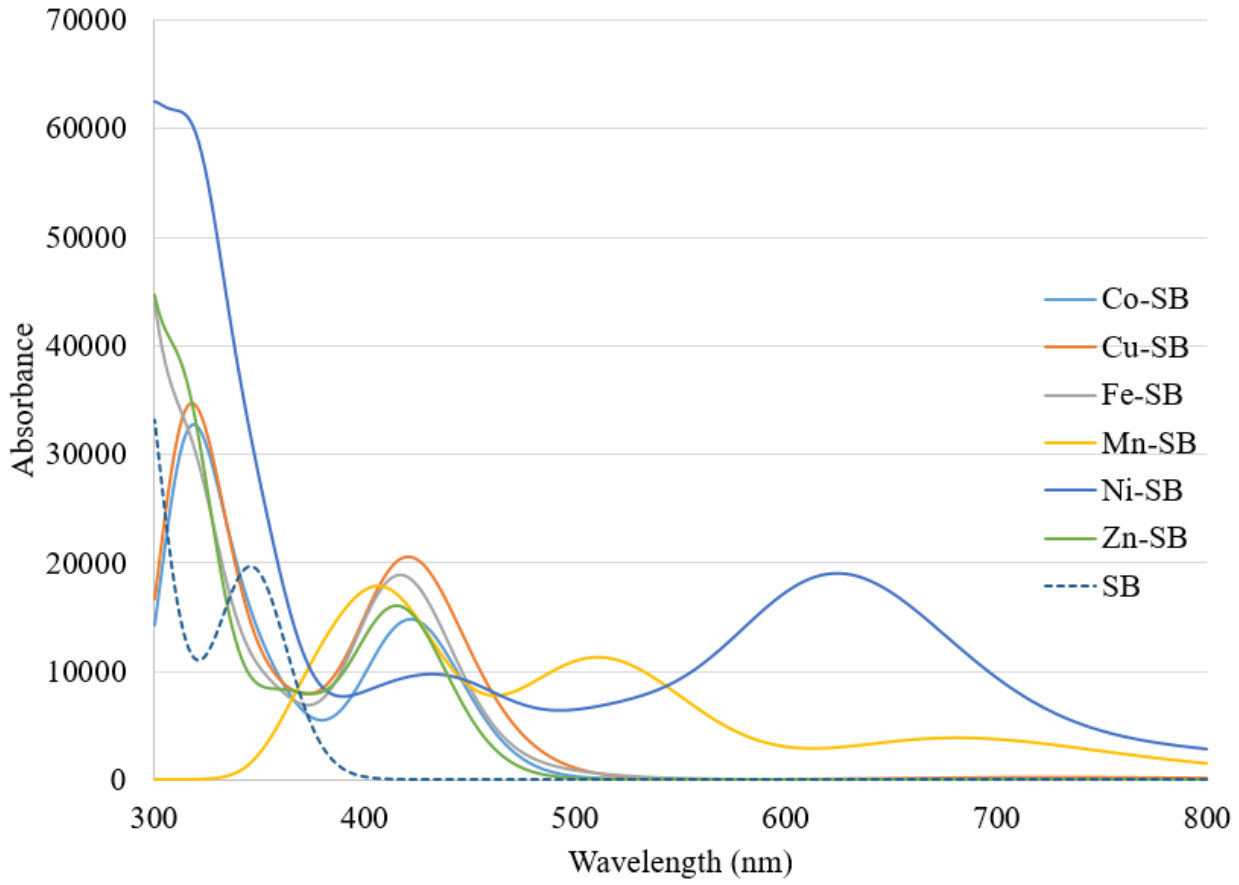


Figure 4.12 UV-Absorption spectra of Schiff base ligands and their metal complexes

FT-IR

The computational analyses obtained IR spectra for the SB ligand and corresponding transition metals in the 0–4000 cm-1 region. The main/intense peaks of the SB ligand are at 3640, 1608, and 1568 cm-1, where the 3640 cm-1 peak corresponds to the O-H bond of the benzoic group, 1608 cm-1 (1624 cm-1 experimental value) to the HC=N of azomethine, and 1568 cm-1 to the oxygen of phenolic/benzoic ring.

The O-H bond of the benzoic group, the HC=N of the azomethine, and the C=N of the pyrimidine ring is represented by the main/intense peaks of the SB ligand's IR spectrum at 3640, 1608, and 1568 cm-1, respectively. The peak responsible for the O-H bond is shifted from 3640 cm-1 to 2800 - 2312 cm-1 due to the oscillation of benzoic hydrogen between the oxygen of the carboxylic group and nitrogen of the NH attached to the pyrimidine ring. The HC=N peak is shifted to 1600 cm-1, according to a comparison of the SB IR spectra with those of its metal complexes. It is crucial to emphasize that coordination involves the oxygen atom from benzoic acid's C=O structure. The IR spectra of SB metal complexes also exhibit peaks in the 350–700 cm-1 region that were not visible in the IR spectra of SB. This indicates that new M-O and M-N bonds have formed in SB's coordination complexes.

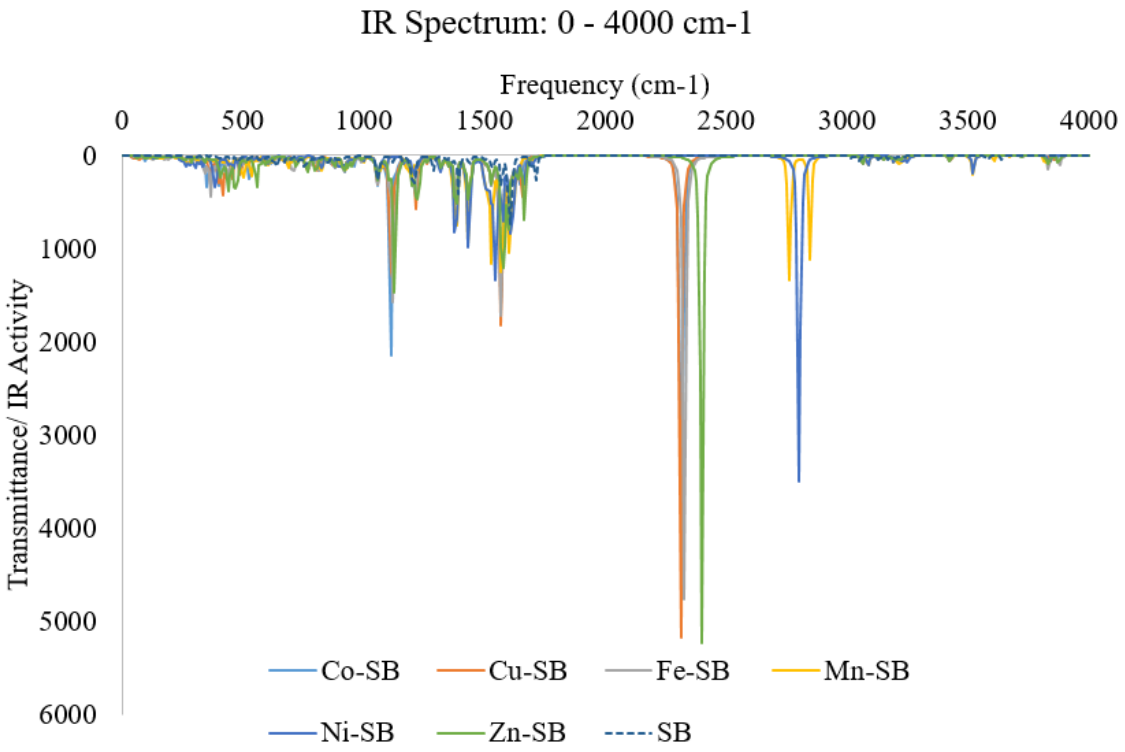


Figure 4.13 IR spectra for Schiff base ligands and their metal complexes

Additionally, the density of states (DOS), which defines the availability of states at various energies, was computed. A high DOS value indicates the most states possible for electron occupation or transition. The DOS spectrum for the ligands, SB, and their metal complexes is shown in Figure 4.14. The Fe-SB and Zn-SB complexes for SB metal complexes have the highest DOS values.

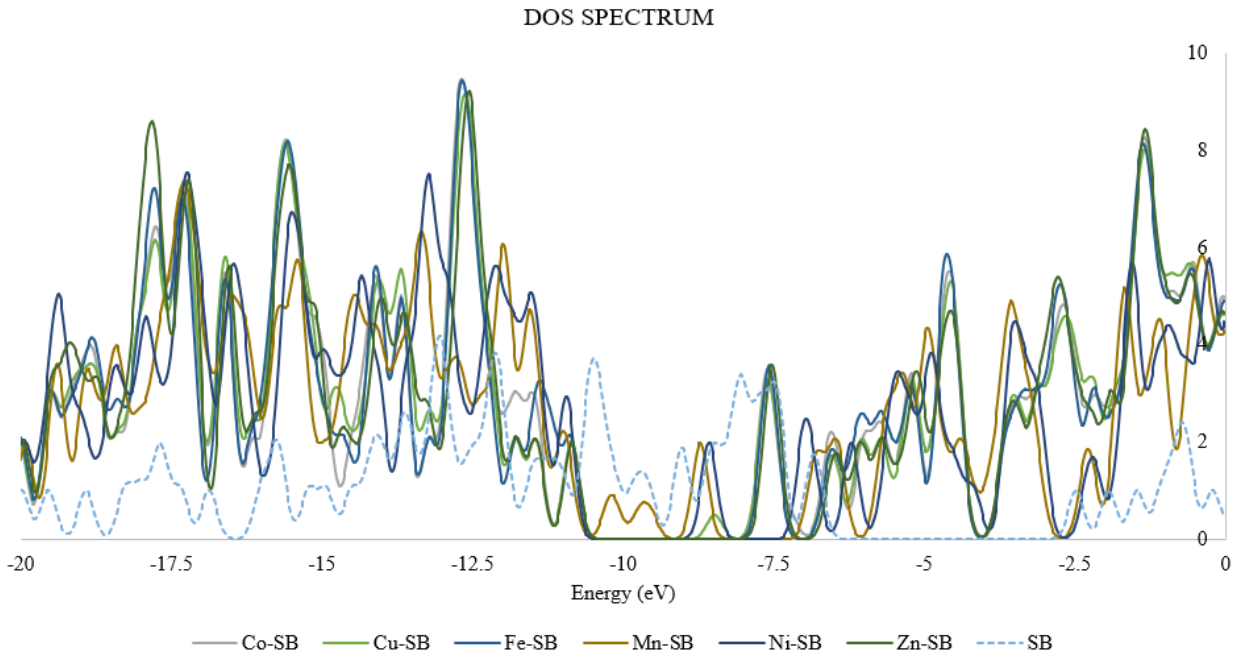


Figure 4.14 DOS spectrum for Schiff base ligands and their metal complexes

Chapter 5

Discussion

Sulphadoxine is a class of synthetic antimicrobial drugs that act as bacteriostatic. Structural analog to para-aminobenzoic acid (PABA), which is the precursor to bacterial genetic material, stops the growth of microbes.[12] Sulphadoxine is used to treat intestinal infections, urinary tract infections, malaria, and many other microbial infections.[8] With time microbes shows resistance to Sulphadoxine. To increase the antibacterial activity of Sulphadoxine, derivatives are formed by keeping the structural integrity of Sulphadoxine intact because these are analog to PABA.

There are many Sulfonamides on the market; Sulphadoxine was used for this research. Sulphadoxine is a sulfonamide with the chemical formula of $C_{12}H_{14}N_4O_4S$. Sulphadoxine is complexed with transition metals: Zn, Co, Cu, Fe, Ni, and Mn. This work's novelty is adding Schiff base to metal-based Sulfonamide. Schiff bases add potency to metal-based Sulfonamide. The proposed structure of metal-based Sulphadoxine Schiff base (Figure 5-1). Figure 5-1 is reproduced as Figure 6-1 for reference. To find the most stable complex computational study was performed.

For Computational Analysis, the hybrid density function method B3LYP was used along with the basis set LANL2DZ. According to the literature, the LANL2DZ basis set produces more accurate results for Transition metals. All geometry optimizations and single-point energy calculations in the gas phase on the optimized geometries were performed using the B3LYP/LANL2DZ level of DFT, followed by frequency and Single point energy calculations.

The relative energies and bond lengths of all optimized structures were calculated. The results revealed that the Fe-based Schiff base Sulphadoxine complex is the most stable, with an energy of -137kcal/mol. The order of stability of the six complexes is as follows: Fe-SB > Zn-SB > Mn-SB > Co-SB > Ni-SB > Cu-SB. So, the Fe-based Schiff base Sulphadoxine complex was seen to be the most promising Schiff base in the pool. This Schiff base will be the perfect anti-malarial drug from the above-mentioned Schiff bases. This offers the basis for further studies where the interaction of the Schiff base can be analyzed with the target molecule in the folate synthesis in real time.

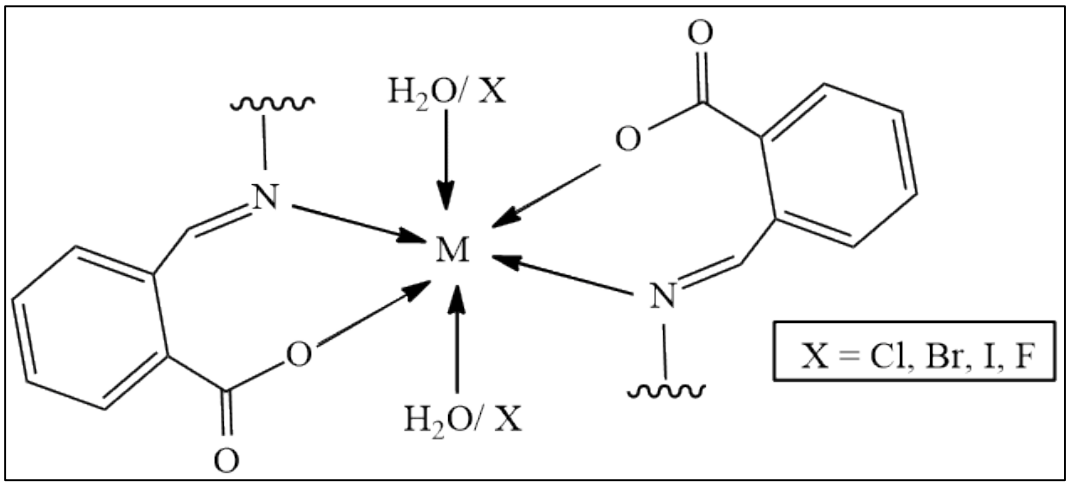


Figure 5.1 Metal-based Sulphadoxine Schiff Base Complex

Moreover, optimized geometries were used for spectroscopic calculations (UV, IR & DOS) for structural analysis. For this purpose, UV calculations were simulated with the help of time-dependent DFT (TD-DFT) using B3LYP/ LANL2DZ functional and TD-SCF methods. On analyzing Schiff bases and metal complexes spectra, it has been observed that the metal complexes exhibit intense bands in the 300–700 nm region. IR data confirms the formation of metal complexes. The IR of SB metal complexes also shows peaks in the range of 350 – 700 cm-1 which

were not present in the IR spectra of SB. This confirms the formation of new M-O and M-N bonds in the coordination complexes of SB.

Chapter 6

Conclusion

Malaria is an ever-growing problem in third-world countries. Humankind has tried to eradicate this disease by employing open-air sprays and intravenous drugs. With time, the environment has given malarial parasites the power to evolve and render our drugs useless. As the Schiff bases are known for their antibiotic properties and metals to add their chemical character, the Schiff-based ligand of Sulphadoxine, a structural analog of PABA, and their metal (Cu, Co, Fe, Mn, Zn, and Ni) complexes were designed and studied computationally to identify the most stable complex.

According to this study, Sulphadoxine-based Schiff Base metal complexes were modeled, characterized, and validated using density functional studies. By this study, it can be concluded that iron-based Schiff base ligands can be used for antimicrobial activity. Schiff base ligand showed maximum stability when complexed with iron and minimum stability with copper. The DOS spectrum also supported this conclusion.

This study will add greatly to the existing information of resistance shown by the microbes to the Sulphadoxine. The most stable complex found, Iron complex could be subjected to the in-depth analysis for test trials and a potential antimalarial drug.

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