Computational Investigation on (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate using Density Functional Theory

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ABSTRACT

The theoretical calculations of the compound, (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate were calculated using Density Functional Theory (DFT) method with 6-311++G (d, p) basis set employing Gaussian 09 program package. Molecular Geometry, Vibrational analysis, Molecular Electrostatic Potential (MEP), HOMO-LUMO energy gap and Natural Bond Orbital (NBO) analysis was determined. Further, the global reactivity indices such as electron affinity, ionization energy, chemical potential, electronegativity, hardness and electrophilicity index were calculated to interpret and predict various aspects of chemical bonding and reaction mechanism. The Blood Brain Barrier (BBB) is the fundamental problem blocking progress in the development of new therapeutics for brain disorders or the development of new radiopharmaceuticals for imaging brain. This study discusses the principles of BBB drug transport and the BBB score of the title compound was determined. As a positive proof, the quality of the selected compound as a drug was also validated.

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CHAPTER 1

INTRODUCTION

1.1 MOTIVATION BEHIND THE PRESENT WORK

The present research work aims at characterization of the title compound, (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate using density functional method. Until the 18^{th} century the use of medicines(herbal) had been entirely based on empiricism (the practitioners knew what worked but not how). From the early twentieth century the science of pharmacology developed and with it the quality of life. Pharmaceutical industries are driving medical progress by researching, developing and bringing new medicines that improve the quality of life for patients around the world. Development of new drugs is the need of the hour due to new diseases, the development of drug resistance, and our understanding of health condition allowing treatment of the previously untreatable conditions. This study examines the structural, vibrational and biological properties of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.

Computational chemistry, a branch of chemistry that uses computer simulations, is a widely accepted tool to study the structure, molecular properties and reactivity of molecules. It assists in solving complex chemical problems by exploiting methods of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures, the interactions and the properties of the molecules. It has its basis from quantum theory. Quantum chemistry studies the ground state of individual atoms and molecules and the excited states and transition states that occur during chemical reaction. Quantum chemical computational techniques such as Density Functional Theory (DFT) is one of the most commonly used research tools. The vibrational frequencies were obtained by DFT calculations with B3LYP/6-311++G (d, p) [1] as basis sets. The study was conducted using the Gaussian09 program software [2].

The results obtained from this study will provide an accurate and deep knowledge of the structural composition, inter and intra molecular interaction and nature of chemical compound which is significant for further researches as well for drug manufacturing processes.

CHAPTER 2

2.1 METHODOLOGY ADOPTED FOR CHARACTERISATION

The GAUSSIAN 09 software package [3] was used to perform the whole set of theoretical computations in this study. The calculations in GAUSSIAN 09 employ basis sets, which are a set of functions used to explain electronic wave functions. B3LYP/6-311++G (d, p) has been used as the basis set for this study. Using the level of theory given above, optimised molecular structure, computation of vibrational frequencies, IR intensities, and RAMAN activities were produced. CHEMCRAFT was used to determine the geometric structure of the molecule, as well as the bond angles and bond lengths [4]. In addition, GAUSS VIEW was used as a visualisation tool in this study. It facilitates the construction of Gaussian input files as well as the execution of Gaussian calculations using a graphical interface. Using the Vibrational Energy Distribution Analysis (VEDA) tool [5], the vibrational assignments of the title compound were determined.

The electronic properties of the title molecule were determined, including the Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO), energy gap, electronegativity, electrophilicity index, chemical potential, global hardness and softness. Gauss View was used to compute the Molecular Electrostatic Potential (MEP). On the title molecule, the Natural Bonding Orbital (NBO) was calculated at the B3LYP level using the basis set 6-311++G (d, p) and the key word POP=NBO test. This study is carried out to show that stabilisation results from hyperconjugation of numerous intramolecular interactions [6-7]. Furthermore, the drug resemblance criteria of the compound often considered were examined using Lipinski's rule of five to validate its potential as a medicine. The ability of drug to penetrate the Blood Brain Barrier (BBB) is essential for the use of a compound as a drug. It helps to identify the possibility of a compound affecting the central nervous system.

2.2 COMPUTATIONAL TECHNIQUES

Computational science, known as scientific computing or scientific computation (SC), is a field in mathematics that makes use of advanced computing capabilities to understand and solve complex problems. It is an area of science that spans many disciplines, but basically, it involves the development of models and simulations to understand natural systems [8-9].

- Algorithms (numerical and non-numerical): mathematical models, computational models, and computer simulations developed to resolve science (e.g., biological, physical, and social), engineering, and humanities problems.
- Computer hardware that develops and optimizes the advanced system hardware, firmware, networking, and data management components required to solve computationally demanding problems.
- The computing infrastructure that supports both the science and engineering problem solving and the developmental computer and information science.

In practical use, it is typically the application of computer simulation and other forms of computation from numerical analysis and theoretical computer science to solve problems in various scientific disciplines. The field is unlike the theoretical and laboratory experiments, which are the traditional forms of science and engineering. The scientific computing approach is to gain understanding through the analysis of mathematical models implemented on computers. Scientists and engineers develop computer programs and application software for the model systems being studied and run these programs with various sets of input parameters. The essence of computational science is the application of numerical algorithms [10] and computational mathematics. In certain cases, these models involve massive amounts of calculations (usually floating-point) and are often executed on supercomputers or distributed computing platforms.

2.3 QUANTUM CHEMICAL CALCULATIONS

2.3.1 AB-INITIO METHODS

This type of computation is based only on theoretical principles, using no experimental data. The numerous methods have the same basic approach, but differ in the mathematical approximations used. These are the most popular type of models, despite the fact that the calculations take unbelievably long time [11-12].

Examples of Ab initio method:

HF Hartree-Fock is the basic ab initio model. It uses the approximation that Coulombic electron-electron repulsion can be averaged, instead of considering explicit repulsion interactions (central field approximation) There are two ways to compute molecular orbitals using HF: UHF (unrestricted) or RHF (restricted). UHF uses a separate orbital for each electron, even if they are paired (used for ions, excited states, radicals, etc.), RHF uses the same orbital spatial function for electrons in the same pair (good for species with paired electrons, no spin contamination). The major drawback of HF method is the exclusion of electron correlation. The following models start with an HF calculation and then correct for electron repulsion [13].

2.3.2 DENSITY FUNCTIONAL THEORY

Density-functional theory (DFT) is a computational quantum mechanical modelling method used in physics, chemistry and material science to investigate the electronic structure (or nuclear structure) (principally the ground state) of many-bodied systems, in particular atoms, molecules, and the condensed phases. Using this theory, the properties of a many-electron system can be determined by using functionals, i.e., functions of another function. In the case of DFT, these are functionals of the spatially dependent electron density. DFT is among the most popular and versatile approaches available in condensed-matter physics, computational physics, and computational chemistry [14].

DFT has been very popular for calculations in solid-state physics since the 1970s. However, DFT was not considered accurate enough for calculations in quantum chemistry until the 1990s, when the approximations used in the theory were greatly refined to better model the exchange and correlation interactions. Computational costs are relatively low when compared to

traditional methods, such as exchange only Hartree–Fock theory and its descendants that include electron correlation. Since, DFT has become an important tool for methods of nuclear spectroscopy such as Mossbauer spectroscopy or perturbed angular correlation, in order to understand the origin of specific electric field gradients in crystals [15].

Despite recent advances, using density functional theory to properly describe: intermolecular interactions (essential for understanding chemical reactions), particularly Vander Waals forces (dispersion); charge transfer excitations; transition states; global potential energy surfaces; dopant interactions and some strongly correlated systems; and calculations of the band gap and ferromagnetism in semiconductors remains a challenge. The insufficient consideration of dispersion can reduce the accuracy of DFT (at least when employed alone and uncorrected) in the treatment of systems where dispersion dominates (e.g., interacting noble gas atoms) or where dispersion competes heavily with other effects (e.g., interacting noble gas atoms) (e.g., in biomolecules). The creation of new DFT methods aimed at overcoming this problem by modifying the functional or including additive terms, is a current research topic. Classical density functional theory uses a similar formalism to calculate properties of non-uniform classical fluids [16].

Despite their current popularity, these changes or the addition of extra phrases are said to deviate from the search for the exact functional. Furthermore, because they are not functional derivatives of the exchange correlation energy with respect to the charge density, DFT potentials obtained with changeable parameters are no longer real DFT potentials. As a result, it's unclear if DFT's second theorem holds true in certain circumstances.

In condensed matter physics, computational physics, and computational chemistry, density functional theory is a computational quantum mechanical modelling tool that is one of the most popular and adaptable methods accessible. The electronic structure of numerous body systems, including atoms, molecules, and solid-state materials, is calculated using density functional theory. The Schrödinger equation is used to calculate density functionals. It's a technique for calculating an approximate solution to the Schrödinger equation for a many-body system. A functional is defined as a function of a function in mathematics. The property of a many electrons system can be determined with density functional theory using functionals. The wave function is a mathematical construct rather than a physical reality. As a result, it isn't a property of a molecule

or an atom that may be measured [17]. DFT is based on the density function of electrons rather than the wave function because electron density is a physical property shared by all molecules. DFT aims to use the electron density to compute all of the characteristics of atoms and molecules. As a result, the energy of the molecule is a function of its electron density in density functional techniques. In contrast to Hartree-Fock theory, which deals with the many-body wave function directly, the electron density is employed as the fundamental property. DFT was established as a rigorous quantum chemical approach when Hohenberg and Kohn presented two theorems in 1964. According to the first theorem, the ground state electron density function determines all properties of a molecule in a ground electronic state [18]. The electron density is a functional of the ground state energy of a many-electron system in this example. According to the second theorem, any trial electron density function will provide an energy greater than (or equal to) the real ground state energy. DFT provides a relatively efficient and impartial method for computing the ground state energy in realistic models of bulk materials and their surfaces. The creation of approximations for the exchange-correlation energy functional is required for consistency in such calculations. Dependence on local density gradients, semi-local density measurements, and non-local exchange functionals have all been introduced [19] in recent years, resulting in significant improvements in the quality of exchange correlation functionals. The GAUSSIAN 09 software [20] is one of the most extensively used programmes for calculating electrical structure. The calculations in GAUSSIAN 09 are based on the basis set. Basis sets are sets of the functions which are used to describe electronic wave functions.

2.3.3 BASIS SET

Basis sets are collections of vectors that cover a space where a problem is solved mathematically [21]. The basis set in quantum chemistry refers to any set of one-particle functions used to construct molecular orbitals. To put it another way, theoretical and computational foundations are established. In Hartree-Fock space chemistry, basis set is a set of functions that are used to represent the electronic wave function. The two different categories of basis sets are minimal basis set and extended basis set. The “extended” basis set is the ones that consider the higher orbitals of molecule and account for the shape and size of molecular charge distribution. Many methodologies are utilised in these sets, resulting in multiple sets of functions being used to

characterise part or all of the angular momentum components of a molecule. The usage of a basis set is the same as using an approximation identity resolution. The individual particle states are then expressed as linear basis function combinations. The basis set employed in this study is B3LYP/6-311++G (d, p), which belongs to the extended basis set category. The most often utilised hybrid DFT density functional, B3LYP (Becke-3-term correlation functional; Lee, Yang, and Parr exchange functional), yields excellent structural and thermochemical properties. Density is a more intuitive idea than wave functions [22], which are polarizable functions that can be applied to molecules. These are contracted primitive Gaussian functions applied to heavy atoms and hydrogen atoms, respectively, to indicate polarisation effects such as hydrogen electron density polarisation in an electric field. When we have species with a lot of valence electrons, a diffusion function like ++ is introduced [23].

2.4 INTRODUCTION TO THE COMPOUND

(5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate which belongs to Coumarins family, are lactones that occur naturally or synthetically. In various parts of the world, coumarins are used as traditional medicines. They are extracted from plant extract and sources. Coumarins can be extracted from; cassia, sweet clover, cinnamon, green tea, celery, peppermint, bilberry, honey, lavender, carrots, tobacco, wine beer, tonka bean, bison grass, and woodruff with the highest amount in the tonka bean, bison grass, and woodruff [19]. Studies show that the extracts are used to fight against bacteria. 5,7-dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate compound has a commercial name as dihedral coumarin unit comprising of the 2H-chromene giving it a planar ring system[24]. The compound has a morpholine ring with a chair conformation. It is represented as $C_{17}H_{19}NO_3S_2$. An S(7) ring is generated by a short intramolecular C-H…S contact. $R^2_2(16)$ loops are generated by the pairs of C-H…O bonds connected with inversion dimers in the crystalline structure, like any other coumarin, (5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate is used as an anti-carcinogen in the treatment of prostate cancer, renal cancer (cancer of the kidney), and leukaemia (cancer of the blood tissues) [25]. (5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate is commonly used because it has the ability to prevent or cancel the side effects caused by radiotherapy. Coumarins like, (5,7-Dimethyl-2-oxo-2H-chromen-4-yl)

methyl morpholine-4-carbodithioate have drawn a lot of attention recently because they offer both photo-chemotherapy and therapeutic applications in cancer treatment. The diagrams below represent the structure of the compound in its 3-dimensional view and chemical scheme:

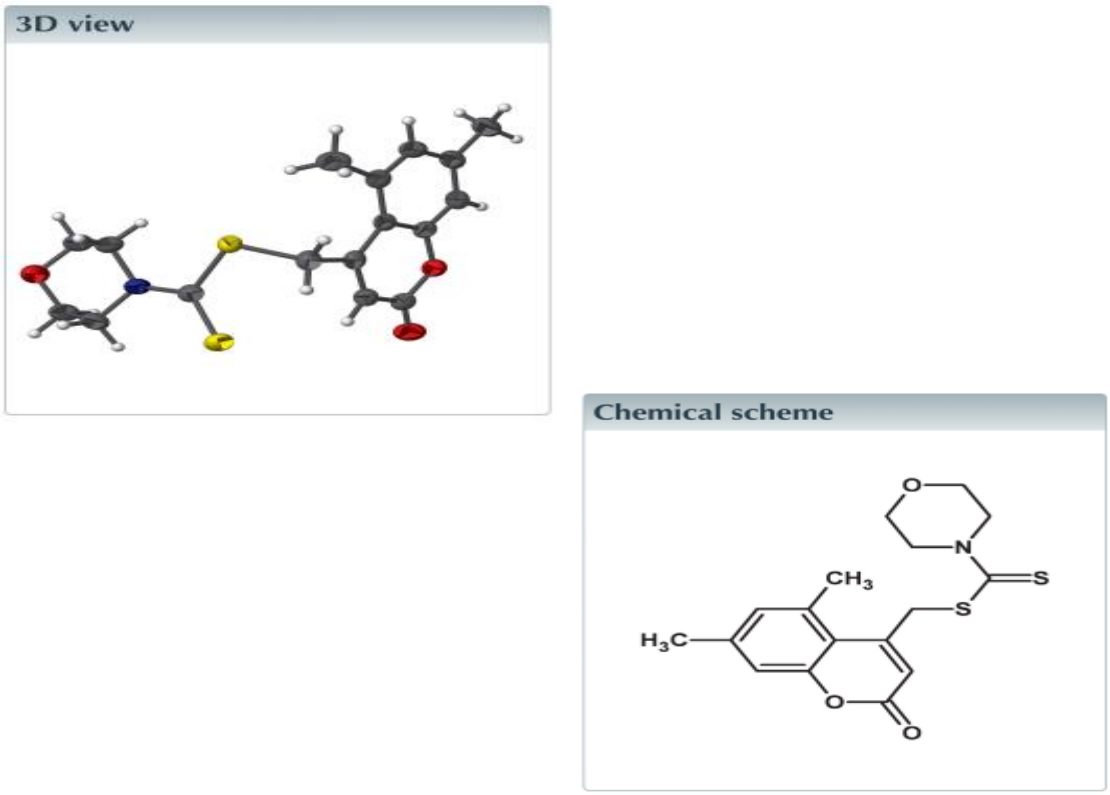

Figure 2.1: 3D view and Chemical scheme of 5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate.

According to studies, dithioacarbamic acid esters are organic molecules that are used in cancer treatments. They exist in derivatives such as chromone and thalidomide dithiocarbamates. The compound is prepared through synthesis and crystallization. It has a colourless needle in its title that is derived in a slow evaporation at room temperature in a mixed solution of EtOH/CHC_{I3} which yields 81%, m.p. 445K.

Worldwide, cancer is among the most commonly diagnosed diseases that leads to death of many people. It occurs as a result of epigenetic and genetic mutations and cell accumulation. It is treated through chemotherapy and radiotherapy. Despite these treatments, coumarins have been discovered to have a potential impact as anticancer drugs. Dithiocarbamates is an essential

pharmacophore that is used in treatment of various cancer types [26]. This compound is assimilated in antitumor agents and other compound that are used as medicines. Despite the potential of the (5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate to treat cancer, it also alleviates the risks of the disease through alteration of cell metabolism. It damages the DNA in cells interfering the biological processes in the body. Another side effect of using the compound in medicinal purposes is that the compound induces malignant and uncontrolled division that causes tumour formation. The side effects are even more including: damage to the liver in some people, nose bleeds, gum bleeds, blood in the urine, extensive bruises even though there are no accidents (also called ecchymosis), fatigue, shortness of breath, lungs may become fluidly, skin allergy due to redness and pain, damage to body organs in long-term exposure cases. Coumarins can also result to development of cognitive issues.

Coumarins like, (5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate have shown through studies that they cause liver damage in rats. Since it causes damage to rats' liver [27], it is hypothesized that similar damage can occur to human liver as well. Coumarins have also showed that they could impair cognitive development. Research showed that exposure to coumarins while the foetus is in uterus cause 90% of impairment in cognitive development especially when the exposure occurred during the third or second trimester [28].

CHAPTER 3

LITERATURE SURVEY

1. B. R. Anitha, K. R.Roopashree, K. Mahesh Kumar ,A. J. Ravi & H.C.Devarajagowda [29] did a study on (5,7-Dimethyl-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate for the geometry, crystal data, data collection, and structure refinement details.
2. Elizabeth Mathew *et al*. on their paper reports the theorical and experimental investigations of nonlinear optical properties of two novel chalcone derivatives namely (2E)-1-Anthracen-9-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (methoxy-ANC) and (2E)-1-(Anthracen-9-yl)-3-(4-ethoxyphenyl) prop-2-en-1-one (ethoxy-ANC). The theoretical calculations were performed by the aid of density functional theory. These theoretical studies were supported by the obtained experimental results. The optimized geometry, vibrational wavenumbers, HOMO-LUMO energy gap, Natural Population. Analysis (NPA), Natural Bond Orbital (NBO) analysis were computed by B3LYP level of theory with 6-311++G (d, p) basis set. The FTIR, FT-Raman and UV-visible absorption spectra were recorded and analysed. The theoretical calculations on second order hyperpolarizability were done using B3LYP and CAM-B3LYP hybrid functional. The HOMO-LUMO analysis confirms the intramolecular charge transfer interactions and suggest the better NLO response of the molecule. The NLO response of the molecule is also indicated by calculated first and second-order hyperpolarizability value These attractive nonlinear optical properties indicates that the chalcone derivatives, methoxy and ethoxy-ANC are promising potential candidates which are applicable for developing new photonic and optoelectronic devices. [30]

3. E. K. Akkol, Y. Genc, B. Karpoz, E. S. Sanchez, B. Karpuz and R. Capasso [31] investigated the structure-activity relationship studies on coumarin core inorder to design and develop new analogues with a strong anticancerous effect and reduce the potential side effects of existing therapeutics.

4. L Padmaja, C Ravikumar, D Sajan, I Hubert Joe, VS Jayakumar, GR Pettit, O Faurskov Nielsen [32] describes Combretastatin-A2 (CA2), a potential anticancer drug in advanced preclinical development that is extracted from the medicinal plant Combretum caff rum. The NIR-FT Raman and FT-IR spectral studies of the molecule were carried out and ab initio calculations performed at the B3LYP/6-31G(d) level to derive the equilibrium geometry as well as the vibrational wavenumbers and intensities of the spectral bands. The vibrational analysis showed that the molecule has a similar geometry as that of cis-stilbene, and has undergone steric repulsion resulting in twisting of the phenyl ring with respect to the ethylenic plane. Vibrational analysis was used to investigate the lowering of the stretching modes, and enhancement of infrared band intensities of the C-H stretching modes of Me2 may be attributed to the electronic effects caused by back-donation and induction from the oxygen atom. Analysis of phenyl ring modes shows that the CA2 stretching mode 8 and the aromatic C-H in plane bending mode are equally active as strong bands in both IR and Raman spectra, which can be interpreted as the evidence of intramolecular charge transfer (ICT) between the OH and OCH3groups via conjugated ring path and is responsible for bioactivity of the molecule.

5. Fernanda Borges, F Roleira, N Milhazes, L Santana, E Uriarte [33] studied Coumarins, also known as benzopyrones, are present in remarkable amounts in plants, although their presence has also been detected in microorganisms and animal sources. The structural diversity found in this family of compounds led to the division into different categories, from simple coumarins to many other kinds of polycyclic coumarins, such as furocoumarins and pyranocoumarins. Simple coumarins and analogues are a large class of compounds that have attracted their interest for a long time due to their biological activities: they have shown to be useful as anti-tumoral, anti-HIV agents and as CNS-active compounds. Furthermore, they have been reported to have multiple biological activities (anticoagulant, anti-inflammatory), although all these properties have not been evaluated systematically. In addition, their enzyme inhibition properties, antimicrobial and antioxidant activities are other foremost topics of this field of research. The present work is to survey the information published or abstracted from 1990 till 2003, which is mainly related to the occurrence, synthesis and biological importance of simple coumarins and

some analogues, such as biscoumarins and triscoumarins. Data are also highlighted, concerning the development of new synthetic strategies that could help in drug design and in the work on SAR or QSAR.

CHAPTER 4

RESULTS AND DISCUSSIONS

4.1 MOLECULAR GEOMETRY

The way atoms are joined together to form a molecule is referred to as chemical structure. Molecules are made up of a number of atoms that have been bound together. The bond length and bond angle are two crucial characteristics of this chemical bond. The distance between the nuclei (the bond length) is the distance between the centre of two atoms. The longer the bond, the easier it is to separate those two atoms. The bond length can be influenced by a variety of factors. It could be atom size, hybridization, or other factors.

Hybridization is a theory that explains chemical bonds by describing the locations of electrons in the bonds [34]. Single, double, and triple bonds are among the bonds available. Polar, ionic, and covalent bonds are the three types of bonding. The angle between the orbitals holding bonding electron pairs around the central atom in a molecule is known as the bond angle. They are measured in units of degrees. The structure of the molecule, as well as distortion effects from lone pairs of electrons on the substituent atoms, influence bond angles.

DFT-B3LYP levels with the 6-311++G (d, p) basis set were used to optimise the geometry of (5,7 Dimethyl- 2-oxo 2H chromen-4-yl) methyl morpholine-4-carbodithiote, and the results are reported in Table 4.1 according to the atom numbering method derived from CHEMCRAFT programme. Figure 4.1 depicts the optimised structure of the title compound.

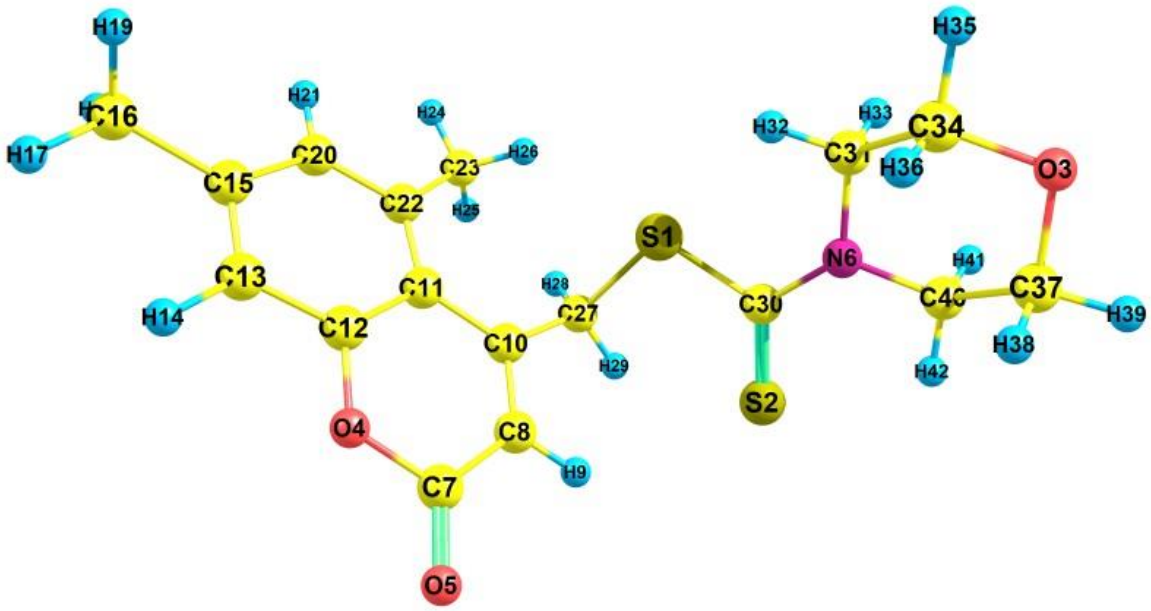

Figure 4.1 ***Optimized geometric structure with numbering of atoms of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

.

Table 4.1 ***Optimized geometric parameters of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

PARAMETERS Bond length (Å)	**B3LYP/6-311++ G (d, p)**	**PARAMETERS Bond Angle (°)**	**B3LYP/6-311++G (d, p)**
S1-C27	1.84	C27-S1-C30	103.80
S1-C30	1.82	S1-C27-C10	112.30
S2-C30	1.67	S1-C27-H28	106.10
O3-C34	1.42	S1-C27-H29	105.10
O3-C37	1.42	S1-C30-S2	123.10
O4-C7	1.39	S1-C30-N6	112.50
O4-C12	1.37	S2-C30-N6	124.30
O5-C7	1.20	C34-O3-C37	110.10
N6-C30	1.35	O3-C34-C31	111.80
N6-C31	1.47	O3-C34-H35	106.80
N6-C40	1.47	O3-C34-H36	110.10
C7-C8	1.45	O3-C37-H38	109.90
C8-H9	1.08	O3-C37-H39	106.60
C8-C10	1.36	O3-C37-C40	111.60
C10-C11	1.47	C7-O4-C12	123.00
C10-C27	1.51	O4-C7-O5	118.10
C11-C12	1.41	O4-C7-C8	115.10
C11-C22	1.43	O4-C12-C11	122.80
C12-C13	1.39	O4-C12-C13	113.90
C13-H14	1.08	O5-C7-C8	126.80

PARAMETERS Bond length (Å)	B3LYP/6-311++ G (d, p)	PARAMETERS Bond Angle (°)	B3LYP/6-311++G (d, p)
C13-C15	1.38	C30-N6-C31	125.70
C15-C16	1.51	C30-N6-C40	121.80
C15-C20	1.40	C31-N6-C40	112.10
C16-H17	1.09	N6-C31-H32	110.60
C16-H18	1.09	N6-C31-H33	108.80
C16-H19	1.10	N6-C31-C34	110.10
C20-H21	1.09	N6-C40-H41	108.30
C20-C22	1.39	N6-C40-H42	108.70
C22-C23	1.52	C7-C8-H9	115.20
C23-H24	1.09	C7-C8-C10	123.80
C23-H25	1.09	H9-C8-C10	121.00
C27-H28	1.08	C8-C10-C11	119.60
C27-H29	1.09	C8-C10-C27	115.80
C31-H32	1.09	C11-C10-C27	124.60
C31-H33	1.10	C10-C11-C12	115.60
C31-C34	1.53	C10-C11-C22	128.00
C34-H35	1.09	C10-C27-H28	113.80
C34-H36	1.10	C10-C27-H29	110.40
C37-H38	1.10	C12-C11-C22	116.40
C37-H39	1.09	C11-C12-C13	123.20
C37-C40	1.52	C11-C22-C20	119.10
C40-H41	1.10	C11-C22-C23	124.80
C40-H42	1.09	C12-C13-H14	118.00
		C12-C13-C15	120.00
		H14-C13-C15	122.00
		C13-C15-C16	121.50
		C13-C15-C20	117.80
		C16-C15-C20	120.60
		C15-C16-H17	111.40
		C15-C16-H18	111.10
		C15-C16-C19	110.90
		C15-C20-H21	118.40
		C15-C20-C22	123.40
		H17-C16-H18	108.10
		H17-C16-H19	107.90
		H18-C16-H19	107.20
		H21-C20-C22	118.20
		C20-C22-C23	116.00
		C22-C23-H24	109.40
		C22-C23-H25	112.00
		C22-C23-H26	113.20
		H24-C23-H25	107.00

4.2. VIBRATIONAL ANALYSIS

Numerous bands at particular wave numbers constitute the IR and Raman spectra. Calculating which vibrational modes cause each of the observable bands is the goal of vibrational analysis. Vibrational analysis attempts to identify the vibrational modes that give rise to each of the bands that have been detected. Frequency domains and temporal domains are used in the methodology of vibrational analysis to provide precise information on the characteristics and operating circumstances of the vibrating part. As the observed signal is divided into a series of frequency components (spectrum) by Fourier transform computations, the frequency domain is able to supply more information. The ability to associate a signature with the processed data is made possible by local analysis of the various frequency components [35].

The functional groups of the title compound can be identified by analysing the vibrational spectra. The equation n=3N-6, where N is the total number of atoms in the compound, can be used to calculate the total number of vibrational modes (n) for a non-linear system. 42 atoms make up title the compound, which also contains 120 regular vibrational modes. Vibrational assignments allow us to discriminate between different vibration types, such as stretching, bending, and torsion. To resolve the discrepancy between theoretical and experimental results, frequencies were scaled. In this work, a scaling factor of 0.962 was employed. Additionally, vibrational assignments were found using the VEDA programme.

Table 4.2 ***Vibrational frequency of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

Theoretical Frequency(cm^{-1})		IR Intensities		Raman Activity		Vibrational Assignments
Unscaled	Scaled	Relative	Absolute	Relative	Absolute	(%PED)
3206	3085	3	0	61	15	ν CH (99)
3192	3070	2	0	106	26	ν CH (99)
3175	3054	6	1	52	13	ν CH (94)
3161	3041	16	2	116	28	ν CH (99)
3137	3018	10	1	20	5	ν CH (94)
3132	3013	5	1	61	15	ν CH (94)
3111	2992	17	2	99	24	ν CH (89)
3111	2992	16	2	41	10	ν CH (94)

Theoretical Frequency(cm^{-1})		IR Intensities		Raman Activity		Vibrational Assignments
Unscaled	Scaled	Relative	Absolute	Relative	Absolute	(%PED)
3103	2985	28	4	229	56	ν CH (93)
3098	2981	27	4	154	38	ν CH (93)
3092	2975	9	1	116	29	ν CH (100)
3076	2959	13	2	115	28	ν CH (99)
3061	2945	44	6	136	33	ν CH (93)
3036	2920	21	3	226	56	ν CH (99)
3026	2911	27	4	407	100	ν CH (99)
3022	2908	76	10	239	59	ν CH (91)
3019	2904	6	1	35	9	ν CH (90)
2992	2878	32	4	184	45	ν CH (82)
2984	2871	28	4	47	12	ν CH (84)
1798	1729	760	100	167	41	ν OC (84)
1653	1590	111	15	93	23	ν CC(48)+β (10)
1639	1577	104	14	228	56	ν CC(58)
1578	1518	35	5	111	27	ν CC(63)
1525	1467	3	0	28	7	β HCH(55) + τ HCCC(10)
1502	1445	16	2	8	2	β HCH(77) + τ HCCC(13)
1500	1443	3	0	9	2	β HCH(61)
1496	1439	34	4	5	1	β HCH(63)
1495	1438	39	5	36	9	β CCC(13)+β HCH(12)+β HCC(10)
1491	1434	17	2	4	1	β HCH(39)
1487	1431	1	0	8	2	β HCH(86)
1487	1430	8	1	12	3	β HCH(76)+ τ HCCC(15)
1476	1420	26	3	14	4	β HCH(67)
1475	1419	26	3	17	4	β HCH(30)
1451	1396	259	34	2	1	ν NC(35) + βHCH(14)
1435	1381	21	3	25	6	ν CC(28) + β HCC(14)
1422	1368	1	0	13	3	β HCH(91)
1419	1365	3	0	9	2	τ HCOC(66)
1413	1360	3	0	51	13	β HCH(89)
1396	1343	36	5	25	6	β HCC(83)
1395	1342	4	1	4	1	β HCC(10)+ τ HCNC(47)
1388	1335	2	0	0	0	τ HCOC(56)
1360	1309	3	0	1	0	τ HCNC(48)+τ HCOC(16)
1350	1299	16	2	127	31	ν CC(39) + ν OC(17)
1329	1279	20	3	15	4	β HCO(67)
1309	1259	10	1	6	2	ν CC(20) + β CCC(10)
1298	1249	80	11	2	0	β CNC(11) + β HCC(18) +β HCO(10)

Theoretical Frequency(cm^{-1})		IR Intensities		Raman Activity		Vibrational Assignments
Unscaled	Scaled	Relative	Absolute	Relative	Absolute	(%PED)
1279	1230	8	1	42	10	β HCH(38) + τ HCSC(28)
1274	1225	10	1	5	1	β HCC(56)
1256	1209	173	23	13	3	ν NC(11) + β HCN(10)
1250	1202	45	6	13	3	β HCC(29)
1239	1192	41	5	9	2	β HCO(42)+β HCN(32)
1206	1160	26	3	4	1	ν NC(40) + β HCC(13)
1201	1156	9	1	87	21	ν CC(11) + β HCS(29)+τ HCSC(16)
1189	1144	15	2	7	2	β HCC(19)+ β HCS(15)
1164	1120	83	11	46	11	ν CC(21)+β HCC(19)
1132	1089	85	11	2	1	ν OC(57)
1128	1085	31	4	2	0	τ COCC(14)+τ OCCN(14)+OUT CCCN(17)
1090	1049	48	6	41	10	ν OC(22)+ ν CC(11) + β CCC(11)
1081	1040	7	1	0	0	β HCN (10) + τ OCCN (11)
1059	1019	3	0	4	1	β HCN (20) + τ HCCC (52)
1057	1017	32	4	11	3	ν CC(21)
1056	1016	4	0	3	1	β HCH (11) + τ HCCC (54)+ OUT CCCC(10)
1047	1007	53	7	4	1	β CNC(14)
1044	1004	5	1	2	1	τHCCC (50)
1021	982	5	1	17	4	ν NC(12)+ ν CC(32) + β COC(11) + β OCC(11)
1004	966	25	3	9	2	ν CC(29)
997	959	134	18	16	4	ν OC(11) + ν NC(12) + νCC(10) + ν SC(20)
983	945	12	2	3	1	ν CC(19)
915	880	20	3	4	1	ν SC(11)+ τ HCCC(17)
897	863	5	1	4	1	τ HCCC(68)
894	860	12	2	3	1	τ HCCC(74)
878	844	20	3	3	1	ν OC(23)+τ HCSC(12)
876	843	45	6	6	2	ν OC(34)
864	831	26	3	0	0	τ HCCC(70)
849	817	0	0	1	0	ν OC(12)+ν NC(15)+τ HCNC(11)
812	781	20	3	4	1	ν NC(37)+ν CC(17)+ν SC(10)

Theoretical Frequency(cm^{-1})		IR Intensities		Raman Activity		Vibrational Assignments
Unscaled	Scaled	Relative	Absolute	Relative	Absolute	(%PED)
777	748	2	0	5	1	τ CCCC(18)+τ HCOCC(13)+OUT CCCC(17)
777	748	2	0	5	1	τ CCCC(18)+τ HCOCC(13)+OUT CCCC(17)
746	718	2	0	4	1	β OCO(15)+β CCC(16)
730	702	14	2	9	2	ν SC(12)+OUT OCOC(50)
704	677	3	0	1	0	β CCC(18)+β CCO(21)
694	667	0	0	12	3	ν SC(15)
644	620	16	2	5	1	ν SC(12)+OUT CCCN(10)
635	611	9	1	1	0	ν SC(16)+OUT CCCN(10)
608	584	5	1	8	2	β OCO(13)
584	562	2	0	1	0	τ CCCC(10)+OUT OCCC(27)
559	537	1	0	14	3	ν CC(12)+ν CC(18)+β CCC(21)
551	530	4	1	2	1	OUT SNSC(10)+OUT CCCC(14)
543	522	2	0	4	1	OUT SNSC(43)
541	520	31	4	8	2	ν SC(27)+β COC(12)+OUT SNSC(20)
522	502	4	1	10	2	OUT CCCC(10)
483	464	0	0	1	0	β OCC(13)+β CCN(20)
478	460	4	0	2	0	β CCO(23)+ β CCC(21)
443	426	0	0	16	4	ν CC(13)+ν OC(11)+β COC(20)
420	404	3	0	4	1	ν SC(14)+β OCC(12)
411	396	4	1	0	0	β COC(19)+τ HCNC(11)
394	379	1	0	2	1	β OCO(12)+β CCC(15)
391	376	24	3	4	1	ν SC(14)
378	364	0	0	7	2	β CNC(33)+β SCS(11)
327	314	1	0	3	1	OUT OCCC(10)
305	293	4	0	3	1	β CCC(37)
298	287	5	1	1	0	β SCS(15)+OUT CCCN(10)
284	273	3	0	1	0	τ HCCC(32)
281	270	4	1	2	1	β SCS(15)
266	256	0	0	2	1	β NCS(17)

Theoretical Frequency(cm^{-1})		IR Intensities		Raman Activity		Vibrational Assignments
Unscaled	Scaled	Relative	Absolute	Relative	Absolute	(%PED)
245	236	2	0	2	0	β OCC(18)+ β CCC(32)
244	235	1	0	2	0	τ CCC(28)
216	208	4	1	0	0	τ OCCN(24)
184	177	2	0	0	0	τ CCCC(24)+ OUT CCCC(46)
171	165	6	1	1	0	β NCS(20)+τ CCCO(15)+τ OCCN(10)
132	127	1	0	2	0	β CCC(17) + β CSC (33)
111	107	1	0	0	0	β SCC(25)+τ CCCC(12)
92	88	1	0	0	0	τ CCCO(13)+τ CCOC(10)+ τ COCC(27)+OUT OCCC(16)
60	58	1	0	0	0	τ CCCO(13)+τ CCOC(10)+ τ COCC(27)+OUT OCCC(16)
56	54	0	0	0	0	τ HCCC(53)
49	47	1	0	3	1	T CCNC(24)+ τ CNCS(24)+ τ SCCC(14)+ τ CCCN(10)
29	28	0	0	2	0	τ CSCC(57)
19	18	1	0	5	1	τ NCSC(29) + τ SCCC(40)
14	14	0	0	5	1	τ NCSC(23)+τ CCOC(10)+τ CSCC(20)+τ SCCC(12)+OUT CCCC(11)

Abbreviations: ν - stretching, β- bending, τ- torsion.

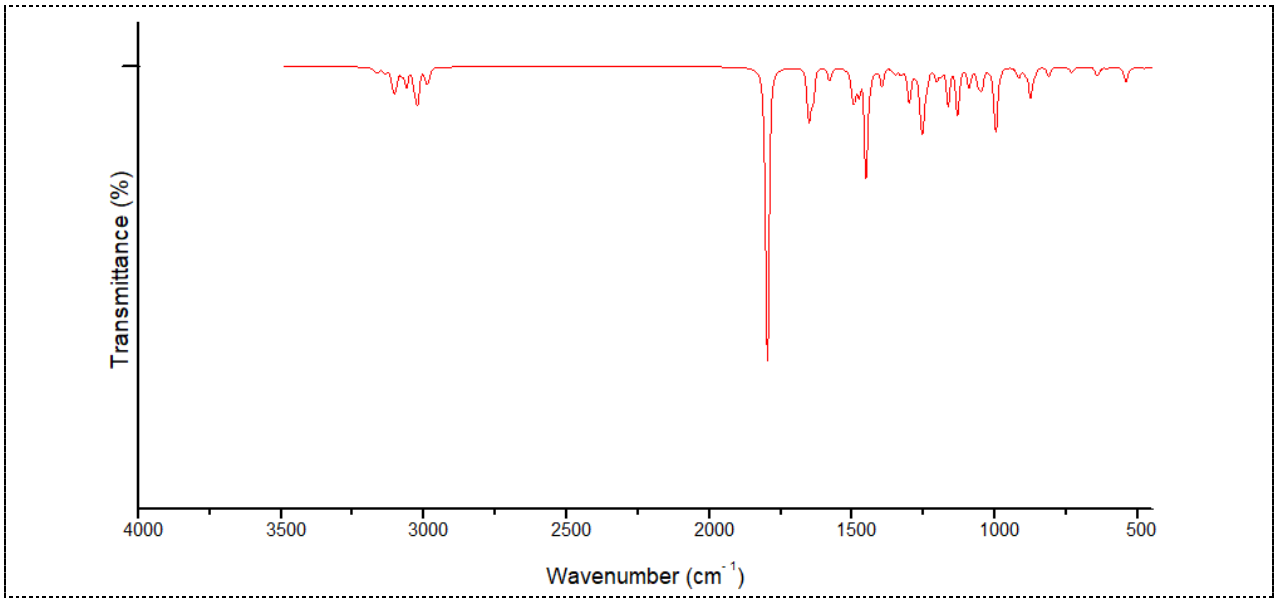

Figure 4.2: Theoretical IR spectra of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.

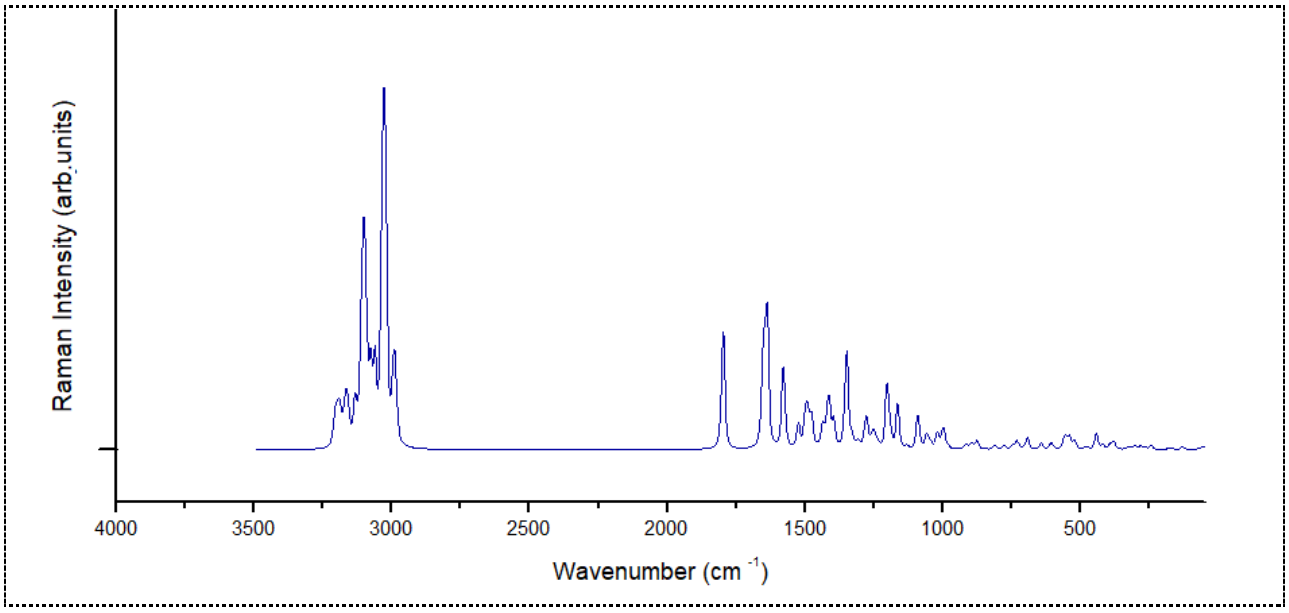

Figure 4.3: Theoretical Raman spectra of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.

C-H Vibrations

In the aromatic compounds, the C-H stretching vibrations which are the characteristic region for the identification of C-H stretching vibrations appear in the range 3100 -3000 cm^{-1} [36]. The C-H stretching and bending regions are one of the most difficult regions to interpret in infrared spectra. The nature and position of the substituent cannot affect these vibrations [37]. All the C-H stretching vibrations are of very weak intensity [38]. For the title compound, from the theoretical calculations, the peak for the mode of vibrations were obtained at 3085 cm^{-1}, 3070 cm^{-1}, 3041cm^{-1} , 3018 cm^{-1}, 3013 cm^{-1}, 2992 cm^{-1}, 2985 cm^{-1}, 2981 cm^{-1}, 2975 cm^{-1}, 2959 cm^{-1}, 2945 cm^{-1}, 2920 cm^{-1}, 2911 cm^{-1}, 2908 cm^{-1}, 2904 cm^{-1}, 2878 cm^{-1}, 2871 cm^{-1}.

O-C Vibrations

The O-C stretching vibrations are usually found in the range 1630-1695 cm^{-1} [39]. In the current study, the peaks corresponding to O-C stretching vibrations were obtained by theoretical method at 1729 cm^{-1}, 1299 cm^{-1}, 1089 cm^{-1}, 1049 cm^{-1}, 959 cm^{-1}, 844 cm^{-1},843 cm^{-1}, 817 cm^{-1}, 426 cm^{-1}.

C-N Vibrations

The C-N stretching frequency is a very tedious task since it falls in a composite region of the vibrational spectrum [40]. The C-N stretching vibrations are usually found in the range 1400-1200 cm^{-1} [41]. The theoretical C-N stretching vibrational mode was obtained at 1396 cm^{-1}, 1209 cm^{-1}, 1160 cm^{-1}, 982 cm^{-1}, 959 cm^{-1}, 817 cm^{-1}.

C-C Vibrations

Standard value of C-C stretching vibrations are in the region 1650-1100 cm^{-1} which are not significantly influenced by the nature of the substituent [42]. In this study, the bands which are of different intensities were observed at 1590 cm^{-1},1577 cm^{-1},1518 cm^{-1},1381 cm^{-1}, 1259 cm^{-1}, 1156 cm^{-1},1120 cm^{-1},1049 cm^{-1},1017 cm^{-1},982 cm^{-1},966 cm^{-1},959 cm^{-1},945 cm^{-1},781 cm^{-1}, 537 cm^{-1} and 443 cm^{-1}.

S-C Vibrations

Standard value of S-C stretching vibrations is generally found in the region 1025- 1225 cm^{-1}. In the current study the band were observed by theoretical method at 959 cm^{-1}, 880 cm^{-1},781 cm^{-1},702 cm^{-1},667 cm^{-1},620 cm^{-1},611 cm^{-1},520 cm^{-1},404 cm^{-1},376 cm^{-1} [43] .

4.3 MOLECULAR ELECTROSTATIC POTENTIAL (MEP)

The potential energy of a proton at a certain position close to a molecule is known as the molecular electrostatic potential (MEP). It shows the molecular form, size, and electrostatic potential values for the molecules in a plot of electrostatic potential that is projected on the iso-electron density surface. MEP has been employed in studies of biological recognition and hydrogen bonding interactions, as well as for predicting locations and relative reactivity towards electrophilic attack [44]. It has been demonstrated that MEP is particularly effective at describing non-covalent interactions, especially hydrogen bonds. The most likely location for electrophilic and nucleophilic attack is shown on a reactivity map using MEP. If the electron density concentration of molecule attracts the proton, the electrostatic potential is negative. In contrast, if the proton is repelled by the atomic nuclei in areas with low electron density and the nuclear charge is only partially protected, it equates to a positive electrostatic potential. By opening the optimised structure in GAUSS VIEW, the 3D plot of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate was created. The MEP surface's electron concentration is indicated using various colours. In the order listed below, electron density values rise in order:

Red > Orange > Yellow > Green > Blue.

In the current investigation, the potential ranges from -6.368eV to 6.368eV. The greatest electronegative electrostatic potential is represented by the colour red. In other words, atoms in this area have a propensity to draw electrons (electrophilic). While yellow denotes a slightly electron-rich zone, blue shows the most electropositive potential, where atoms tend to transfer electrons (nucleophilic) [45]. For the title compound, oxygen is in the zone of negative potential, whereas hydrogen is in the region of positive potential. Sulphur is in slightly electron-rich zone. Green coloration indicates areas where potentials are zero. Atoms of carbon are located in these zones of zero potential.

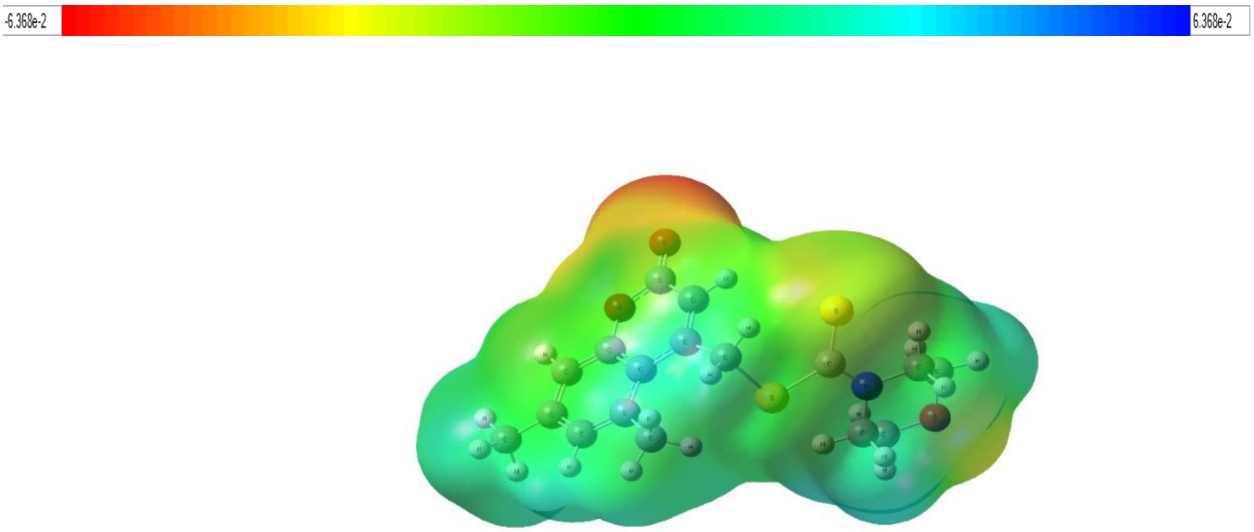

Figure 4.4 ***Molecular Electrostatic Potential map of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

4.4 HOMO-LUMO ANALYSIS

The abbreviations HOMO and LUMO stand for highest occupied molecular orbital and lowest unoccupied molecular orbital, respectively. The molecular orbital types HOMO and LUMO are also referred to as frontier orbitals. Popular quantum mechanical descriptors known as HOMO-LUMO energies have a significant impact on the regulation of a variety of chemical interactions. The Frontier Molecular Orbital provides information about the reactivity of the molecule, and the frontier orbital distribution can be used to show where the active site is [46].

Redistribution of electrons occurs during chemical reactions such as bond formation and breakage, oxidation, and reduction. The orbitals that are most likely to be engaged in chemical reactivity are HOMO and LUMO. Since HOMO is the highest energy orbital that is still occupied, it is simple to remove electrons from it energetically. This could just be acting as a Lewis base by giving electron density to create a bond, or it could be oxidation. Since the lowest orbital, or LUMO, is vacant, it is simple and energy-efficient to reduce or add additional electrons to it, acting

as a Lewis acid. The outer orbital containing an electron might be thought of as the HOMO. While LUMO has the capacity to acquire an electron, HOMO has the capacity to donate one. As a result, the ionisation potential and electron affinity are both closely related to HOMO energy and LUMO energy, respectively [47].

For the aforementioned molecule, the computed quantum chemical parameters for the highest occupied molecule (E_{HOMO}), the Lowest Unoccupied Molecular Orbital Energy (E_{LUMO}), energy gap (ΔE), Electronegativity (χ), chemical potential (μ), global hardness (η), and the softness (S) were all calculated as shown in Table 4.3.

Table 4.3 ***Calculated energy value of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

PARAMETER	VALUE
HOMO(eV)	-6.34
LUMO(eV)	-2.36
Ionization Potential	6.34
Electron Affinity	7.16
Energy Gap (eV)	4.18
Electronegativity	4.25
Chemical potential	-4.25
Chemical hardness	2.09
Chemical softness	0.24
Electrophilicity index	4.33

Each of these parameters has an associated relation [48] :

Chemical potential (μ) = 1/2 (E_{HOMO}+E_{LUMO}) (4.1)

Electronegativity (χ) = -μ = -1/2 (E_{HOMO}+E_{LUMO}) (4.2)

Global hardness (η) =1/2 (E_{HOMO}-E_{LUMO}) (4.3)

Electrophilicity =$\mu^2/2\eta$ (4.4)

The softness(S) is the inverse of the global hardness and has the formula

softness(S)=1/ η (4.5)

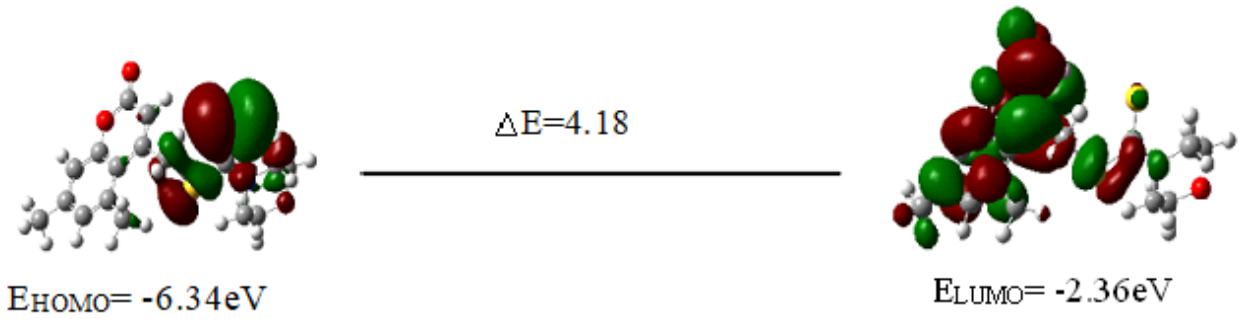

Figure 4.5 ***HOMO, LUMO energies and energy gap of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

4.5 NATURAL BOND ORBITAL (NBO)

The computational results of Schrödinger's wave equation are converted into chemical bonding concepts using a technique called natural bond orbital analysis. A given wave function is ideally transferred into localised form in NBO analysis, which corresponds to the one-centre (lone pairs) and two-centre (bonds) components of the chemist Lewis' structure picture. This technique converts the input atomic orbital basis set into natural bond orbitals (NBOs) using natural atomic orbitals (NAOs) and natural hybrid orbitals (NHOs). The two-centre bonds and lone pairs are localised in the Lewis picture, which match with the NBOs obtained in this way. These localised sets can then be converted into canonical molecular orbitals (MOs) or delocalized natural orbitals (NOs). The NBO software applications carry out these steps. Another helpful chemical concept is hyperconjugation, which explains several chemical phenomena in terms of interactions between filled-and-empty orbitals. NBO analysis can be used to quantify this phenomenon [49].

In order to assess the donor-acceptor interaction in the NBO study, the second order Fock matrix was used, and the results are given in Table 4.4. As a result of the interactions, the idealised NBO of localised Lewis structure loses its occupancy and becomes vacant. For every stabilisation energy E2 connected to the delocalization of donor (i) and acceptor (j) was estimated as,

$$E_2 = \Delta Eij = q_i \frac{(Fi,j)^2}{Ej-Ei} \qquad (4.6)$$

where E_i and E_j are diagonal elements, q_i is the donor orbital occupancy, and F(i,j) are the off-diagonal NBO fock matrix elements. The intensity of the molecular interaction between electron

donors and electron acceptors and the degree of conjugation of the overall system increase with increasing E(2) value. It is similar to stabilising donor-acceptor interaction when the electron density between occupied non-Lewis NBO orbitals delocalizes [50]. The molecule has undergone NBO analysis at the DFT/ B3LYP/ 6-311++G (d, p) level to elucidate the intramolecular, rehybridization, and delocalization of electron density. Through NBO analysis, the most significant hyper conjugative interactions that contribute to molecule stability were investigated. Delocalization of electrons from π* (C 18-C 19) to π* (C 14-C 15) and π* (C 18-C 19) to π* (C 16-C 17) in the current work resulted in large stabilisation energies of roughly 226.82 kcal/mol and 182.14 kcal/mol, respectively.

Table 4.4 ***Second order perturbation theory analysis of Fock matrix in NBO basis of* (*5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.***

Donor	Type	ED/e	Acceptor	Type2	ED/e	E(2) kcal/mol	E(j)-E(i) a.u.	F (i,j) a.u.
C 1 - C 2	σ	1.98	C 13 - C 14	σ*	0.03	3.63	1.10	0.06
C 1 - O 6	σ	1.98	C 23 - H 42	σ*	0.06	8.97	1.38	0.10
C 1 - H 24	σ	1.94	C 23 - H 42	σ*	0.06	23.14	1.06	0.14
C 2 - H 26	σ	1.98	C 1 - O 6	σ*	0.05	4.45	0.81	0.05
C 2 - H 26	σ	1.98	N 3 - C 4	σ*	0.03	3.16	0.85	0.05
C 4 - H 28	σ	1.98	C 2 - N 3	σ*	0.03	3.09	0.88	0.05
C 4 - H 28	σ	1.98	C 5 - O 6	σ*	0.02	3.86	0.83	0.05
C 5 - H 29	σ	1.98	C 1 - O 6	σ*	0.05	3.07	0.82	0.05
C 5 - H 29	σ	1.98	N 3 - C 4	σ*	0.03	3.99	0.87	0.05
C 7 - S8	σ	1.98	C 2 - N 3	σ*	0.03	4.66	0.99	0.06
C 7 - S9	σ	1.98	N 3 - C 4	σ*	0.03	3.38	1.04	0.05
C 7 - S9	σ	1.98	C 7 - S 9	π*	0.33	3.11	0.72	0.05
C 7 - S9	π	1.97	C 7 - S 9	σ*	0.11	3.37	0.69	0.04
C 7 - S9	π	1.97	C 7 - S 9	π*	0.33	5.22	0.41	0.04
C 11 - C 12	σ	1.98	C 1 - C 13	σ*	0.03	5.57	1.09	0.07
C 11 - O 20	σ	1.99	C 18 - C 19	σ*	0.02	3.57	1.32	0.06
C 11 - O 21	π	1.99	C 12 - C 13	π*	0.14	4.87	0.41	0.04
C 12 - C 13	σ	1.98	C 1 - C 13	σ*	0.03	3.24	1.18	0.05
C 12 - C 13	σ	1.98	C 13 - C 14	σ*	0.03	3.51	1.21	0.06
C 12 - C 13	π	1.85	C 1 - O 6	σ*	0.05	5.63	0.57	0.05
C 12 - C 13	π	1.85	C 11 - O 21	π*	0.24	18.28	0.30	0.07
C 12 - C 13	π	1.85	C 14 - C 15	π*	0.41	8.82	0.32	0.05
C 12 - H 34	σ	1.97	C 11 - O 20	σ*	0.15	4.12	0.76	0.05
C 12 - H 34	σ	1.97	C 13 - C 14	σ*	0.03	5.30	0.99	0.07

Donor	Type	ED/e	Acceptor	Type2	ED/e	E(2) kcal/mol	E(j)-E(i) a.u.	F (i,j) a.u.
C 13 - C 14	σ	1.97	C 12 - C 13	σ*	0.02	3.48	1.29	0.06
C 13 - C 14	σ	1.97	C 12 - H 34	σ*	0.01	3.05	1.08	0.05
C 14 - C 15	σ	1.97	C 14 - C 19	σ*	0.03	3.93	1.22	0.06
C 14 - C 15	σ	1.97	C 19 - O 20	σ*	0.03	4.00	1.05	0.06
C 14 - C 15	π	1.63	C 12 - C 13	π*	0.14	17.22	0.28	0.07
C 14 - C 15	π	1.63	C 16 - C 17	π*	0.35	14.27	0.28	0.06
C 14 - C 15	π	1.63	C 18 - C 19	π*	0.37	25.31	0.26	0.07
C 14 - C 19	σ	1.98	C 14 - C 15	σ*	0.03	3.79	1.26	0.06
C 14 - C 19	σ	1.98	C 18 - C 19	σ*	0.02	3.31	1.24	0.06
C 15 - C 16	σ	1.98	C 13 - C 14	σ*	0.03	3.11	1.12	0.05
C 15 - C 16	σ	1.98	C 14 - C 15	σ*	0.03	3.24	1.23	0.06
C 15 - C 23	σ	1.98	C 14 - C 19	σ*	0.03	3.22	1.15	0.06
C 16 - C 17	π	1.64	C 14 - C 15	π*	0.41	25.13	0.27	0.08
C 16 - C 17	π	1.64	C 18 - C 19	π*	0.37	16.54	0.26	0.06
C 16 - H 35	σ	1.98	C 14 - C 15	σ*	0.03	3.96	1.07	0.06
C 16 - H 35	σ	1.98	C 17 - C 18	σ*	0.02	3.73	1.06	0.06
C 17 - C 18	σ	1.97	C 19 - O 20	σ*	0.03	3.37	1.04	0.05
C 18 - C 19	σ	1.97	C 13 - C 14	σ*	0.03	3.30	1.13	0.06
C 18 - C 19	σ	1.97	C 14 - C 19	σ*	0.03	3.52	1.22	0.06
C 18 - C 19	π	1.65	C 14 - C 15	π*	0.41	15.87	0.28	0.06
C 18 - C 19	π	1.65	C 16 - C 17	π*	0.35	23.37	0.29	0.07
C 18 - H 36	σ	1.98	C 14 - C 19	σ*	0.03	3.99	1.05	0.06
C 18 - H 36	σ	1.98	C 16 - C 17	σ*	0.02	3.90	1.07	0.06
C 22 - H 37	σ	1.98	C 16 - C 17	π*	0.35	3.46	0.53	0.04
C 22 - H 38	σ	1.98	C 16 - C 17	π*	0.35	3.45	0.53	0.04
C 22 - H 39	σ	1.99	C 17 - C 18	σ*	0.02	4.30	1.05	0.06
C 23 - H 40	σ	1.97	C 14 - C 15	π*	0.41	3.62	0.51	0.04
C 23 - H 41	σ	1.97	C 14 - C 15	π*	0.41	3.67	0.51	0.04
C 23 - H 42	σ	1.96	C 1 - C 2	σ*	0.04	6.22	0.87	0.07
N 3	LP	1.63	C 1 - C 2	σ*	0.04	4.46	0.64	0.05
N 3	LP	1.63	C 2 - H 25	σ*	0.02	5.02	0.66	0.06
N 3	LP	1.63	C 4 - C 5	σ*	0.03	4.65	0.64	0.05
N 3	LP	1.63	C 4 - H 27	σ*	0.02	5.08	0.67	0.06
N 3	LP	1.63	C 7 - S 9	σ*	0.11	3.45	0.56	0.04
N 3	LP	1.63	C 7 - S 9	π*	0.33	39.97	0.28	0.10
O 6	LP	1.90	C 1 - C 2	σ*	0.04	4.71	0.70	0.05
O 6	LP	1.90	C 1 - H 24	σ*	0.05	7.19	0.71	0.07
O 6	LP	1.90	C 4 - C 5	σ*	0.03	4.93	0.69	0.05
O 6	LP	1.90	C 5 - H 30	σ*	0.03	5.90	0.72	0.06
O 6	LP	1.90	C 23 - H 42	σ*	0.06	8.50	0.85	0.08

Donor	Type	ED/e	Acceptor	Type2	ED/e	E(2) kcal/mol	E(j)-E(i) a.u.	F (i,j) a.u.
S 8	LP	1.98	N 3 - C 7	σ*	0.09	3.23	1.03	0.05
S 8	LP	1.89	N 3 - C 7	σ*	0.09	3.85	0.69	0.05
S 8	LP	1.89	C 7 - S 9	σ*	0.11	6.23	0.55	0.05
S 8	LP	1.89	C 10 - H 32	σ*	0.02	3.42	0.66	0.04
S 8	LP	1.89	C 10 - H 33	σ*	0.02	3.94	0.67	0.05
S 9	LP	1.98	N 3 - C 7	σ*	0.09	3.93	1.14	0.06
S 9	LP	1.98	C 7 - S 8	σ*	0.09	4.07	0.85	0.05
S 9	LP	1.84	N 3 - C 7	σ*	0.09	13.62	0.63	0.09
S 9	LP	1.84	C 7 - S 8	σ*	0.09	16.99	0.35	0.07
O 20	LP	1.96	C 11 - C 12	σ*	0.05	5.04	0.98	0.06
O 20	LP	1.96	C 14 - C 19	σ*	0.03	7.00	1.13	0.08
O 20	LP	1.75	C 11 - O 21	π*	0.24	27.35	0.33	0.08
O 20	LP	1.75	C 18 - C 19	π*	0.37	31.47	0.34	0.10
O 21	LP	1.82	C 11 - C 12	σ*	0.05	16.46	0.64	0.10
O 21	LP	1.82	C 11 - O 20	σ*	0.15	44.06	0.47	0.13
C 7 - S 9	σ*	0.11	C 2 - N 3	σ*	1.98	3.04	0.06	0.04
C 7 - S 9	σ*	0.11	N 3 - C 4	σ*	1.98	3.26	0.04	0.04
C 7 - S9	π*	0.33	C 7 - S 9	σ*	0.11	24.33	0.28	0.16
C 11 - O 20	σ*	0.15	C 11 - C 12	σ*	0.05	3.49	0.17	0.07
C 11 - O 21	π*	0.24	C 12 - C 13	π*	0.14	36.93	0.03	0.07
C 18 - C 19	π*	0.37	C 14 - C 15	π*	0.41	226.82	0.01	0.08
C 18 - C 19	π*	0.37	C 16 - C 17	π*	0.35	182.14	0.02	0.08

E(2) means energy of hyper conjugative interactions.
E(j)-E(i) is the energy difference between donor and acceptor i and j NBO orbitals.
F(i,j) is the FOCK matrix element in i and j NBO orbitals.

4.6 DRUG LIKENESS

The drug likeness of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate is examined in order to first assess its potential to be used as an active component in some new pharmaceutical product. The number of hydrogen bond donors and acceptors (HBD and HBA, respectively), AlogP, and molecular weight were analysed for the compound and has been summarised. A molecule's drug resemblance must meet the Lipinski's rule of five requirements in order for it to be considered a potential medication [51]. It can be shown from Table 4.5 that these parameters have values within acceptable ranges for the medication candidate under evaluation. Less than 5 and 10 should be the HBD and HBA, respectively. The title molecule satisfies these requirements. The AlogP, one of the most crucial metrics that reveals a molecule's

hydrophobic or lipophilic nature, is equal to 3.49, which is much below the cut-off value of 5 suggested by Lipinski's rule of five. In addition, the title compound's molecular weight of 120 is significantly less than the cut-off value of 349.08 [52]. Hence the compound is validated according to Lipinski's rule of five and can be considered as a potential medication.

4.7 BLOOD BRAIN BARRIER (BBB)

For the majority of medications to reach their target, at least one cellular membrane must be crossed. Poor membrane permeability will probably lead to a lack of efficiency even though strong binding of a therapeutic molecule to its designated target is crucial for potency. Therefore, for pharmacokinetics and rational medication design, a thorough understanding of the partitioning of solute in the membrane is crucial. A molecule can go through a membrane in one of the two ways: passively or actively [53]. A transport protein moves a molecule across a membrane through active transport by utilising energy, such as that from ATP hydrolysis.

The most frequent method of drug transit through membranes, however, is passive transport, which involves diffusion without the need for outside aid or energy expenditure. The partition coefficient of a compound between the membrane and the external medium, the diffusion coefficient of the compound across the membrane, and the gradient of the compound's concentration across the membrane are the factors that affect how quickly a chemical passively diffuses across a membrane [54]. Lipophilicity, molecular weight, and measurements of molecular polarity are significant chemical characteristics of tiny molecules for the process of membrane binding and diffusion [55].

Table 4.5: The drug similarity and BBB characteristics of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate.

Parameter	Value	Prescribed value
Molecular weight	349.08	<500
Hydrogen Bond Acceptor	5	<10
Hydrogen Bond Donor	0	<5
AlogP	3.49	<5
BBB Score	4.21	<4

The blood-brain barrier must first be crossed before medications that target the central nervous system (CNS), because of tight junctions created by lateral transmembrane proteins, a lack of openings, negative surface polarity and a high concentration of efflux transporters, especially P-glycoprotein (P-gp), the BBB, which is made up of endothelial cells that form the brain capillaries , prevents molecules from penetrating through [56].

The additional semi-permeable membrane called the blood brain barrier keeps solutes in blood from reaching the brain. The BBB score aids in determining whether a compound has a chance of impacting the central nervous system; a number below 4 is seen as having a low chance, while a score above 4 is regarded as having a high chance of penetration. The title compound's BBB score, which was calculated, was 4.21, indicating a chance that it might cross the blood-brain barrier and interact with the central nervous system [57].

The physical barrier is created by tight junctions, which greatly lessen ion and other tiny hydrophilic solute absorption through the intercellular gap (paracellular channel). Transcellular routes must be primarily used by essential molecular fluxes. Although active transport of chemicals may be more significant than initially believed, passive diffusion of tiny molecules is likely to be the most major permeability process through the BBB. Although the BBB has a protective function, the difficulty of drug molecules to pass through the BBB poses a substantial obstacle for CNS drug candidates and should be resolved as soon as possible in the drug discovery process [58]. To prevent potential CNS side effects, medicines that target peripheral organs must also be tested for BBB permeability.

CHAPTER 5

CONCLUSION AND FUTURE SCOPE

5.1 CONCLUSION

The molecular structure and vibrational analysis of (5-7 Dimethyl-2-oxo-2H chromen-4-yl) methyl morpholine-4-carbodithioate are examined theoretically in the present work. The theoretical calculations of the compound were performed using the DFT method and Gaussian 09 software package with the 6-311++G (d, p) basis set. The title molecule underwent investigation for its molecular electrostatic potential (MEP), HOMO-LUMO energy estimates, and natural bonding orbital (NBO). The global reactivity indices, such as electron affinity, ionisation energy, chemical potential, electronegativity, hardness, electrophilicity index and BBB score were estimated to analyse and predict many elements of chemical bonding and reaction mechanism.

The functional groups of the title compound can be identified by analysing the vibrational spectra. Forty-two atoms make up the compound in the name, which also contains 120 regular vibrational modes. The negative and positive portions of the molecule were visible in the expected MEP figure. For the molecule in the name, oxygen is in the zone of negative potential, whereas hydrogen is in the region of positive potential. In the current investigation, the potential ranges from -6.368eV to 6.368 eV. After calculating the HOMO and LUMO energies, the energy gap was found to be 4.18 eV. The biological activity of the chemical with the same name is described by the electrophilicity index measurement in Table 4.3. The likelihood that the title compound would be considered a significant class of compounds in medical chemistry was increased by its high electrophilicity value. Low toxicity levels linked to the computed softness value gave investigators more justification to look into biological implications of the molecule. Through NBO analysis, the most significant hyper conjugative interactions that contribute to molecule stability were investigated. Delocalizing electrons from π^* (C 18-C 19) to π^* (C 14-C 15) and π^*(C 18-C 19) to π^* (C 16-C 17) in the current work resulted in large stabilising energies of roughly 226.82 kcal/mol and 182.14 kcal/mol, respectively. Additionally, the compound's frequently used drug similarity characteristics were examined using Lipinski's rule of five to confirm its potential as a medicine.

The findings of the current study are anticipated to provide light on potential intermolecular interactions of the title molecule and may prove important for future research as well as the process of making drugs.

5.2 FUTURE SCOPE

To confirm the nonlinear optical (NLO) activity of the molecule, which is suggested by the charge transfer interactions and low HOMO LUMO energy gap, second order nonlinear optical property experiments must be carried out. The optimum binding orientation, affinity, and activity of medicinal compounds with protein targets can be predicted using molecular docking studies, which are a socially significant topic for the current day. Thus, it is possible to identify the compound's potential for treating disorders.

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