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Structure, Biological activity, IR UV spectra of sulfur derivative of pyrazine using DFT method

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Abstract
In this paper we study structure stability of sulfur derivative of pyrazine using combination of DFT/B3LYP method and 6-311G (d, p) basis set. To know transition spectra from ground level and other higher energy level we also studied TDDFT of title molecule and calculated UV spectrum is compared with experimental spectra of pyrazine available on NIST book. Calculated IR after scaling also compared with experimental spectra of pyrazine available on NIST book to know performance of DFT/B3LYP method. To know chemical activity we study electronic parameter like HOMO-LUMO etc. The main aim of this paper to calculate several biological parameter and DOCKING with appropriate protein suggested by Swiss dock online server. In this study we find that sulfur increase toxicity as well as biological activity of title compound as compared to pyrazine.

Keywords: DFT, TDDFT, HOMO, LUMO

Introduction

Pyrazine with chemical formula $C_4H_4N_2$ is a heterocyclic aromatic organic compound having point group D_{2h}. The basicity of Pyrazine is less than pyridine, and pyrimidine [1]. Derivatives such as phenazine are well known for their antitumor, antibiotic anddiuretic activities Tetramethyl-pyrazine (also known as ligustrazine) is reported to scavenge superoxide anion and decrease nitric oxide production in human polymorphonuclear leukocytes [1], and is a component of some herbs intraditional Chinese medicine [2]. In the Staedel–Rugheimer pyrazine synthesis (1876) 2-chloroacetophenone is reacted with ammonia to the amino ketone, then condensed and then oxidized to a pyrazine [3]. A variation is the Gutknecht pyrazine synthesis (1879) also based on this self condensation, but differing in the way the alpha-ketoamine is synthesised [4] Sulfur is an essential component of all living cells. Amino acids cysteine and methionine contain most of the sulfur in plants and animals. Sulfur is very important member in pharmaceutical skin preparations for the treatment of acne and other conditions. Sulfur is also known as keratolytic agent because this kills bacteria, fungi, scabies mites and other parasites [4]. Precipitated sulfur and colloidal sulfur are used, in form of lotions, creams, powders, soaps, and bath additives, for the treatment of acne vulgaris, acne rosacea, and seborrhoeic dermatitis [5]. Common adverse effects include irritation of the skin at the application site, such as dryness, stinging, itching and peeling [6]. In this paper we discuss stability structure and biological activity of sulfur derivatives of Pyrazine with help of combination of DFT/B3LYP method and 6-311G(d, p)

Computational Methods

All the calculations were performed by the using combination of DFT/B3LYP method and 6-311G (d, p) basis set [7-10]. All computations were carried out with the GAUSSIAN 03 package [11] by combining the results of the GAUSSVIEW'S program [12] with symmetry considerations. Vibrational frequencies are scaled with 0.963 with calculated frequency [13].

Result and Discussion

The optimized Structure parameters of pyrazine calculated by B3LYP method with the 6-311G (d, p) basis set are listed in Table 1 are in accordance with the atom numbering scheme as shown in Figure 2, respectively. To find global minima we scan PES with respect N8-C4-S10-H11 20^0 with five step and after that most stable conformer is shown in fig-1.After geometry optimization local minimum energy obtained for surfur derivative pyrazine with combination of DFT/B3LYP method and 6-311G (d, p) basis set is approximately -652.61218705 (a.u.). In this structure nitrogen atom displaced $5^0$with plane ring to reduce anti-bonding repulsion. The (C-N) bond length lies between 1.3657Å- 1.3511Å, while (N-H) bond length lies between 1.3511Å- 1.3207Å.The (C-N-C) bond angle lies from 114.9427^0- 115.0899^0 while (C-N-H) lies between 118.965^0-116.0512^0.

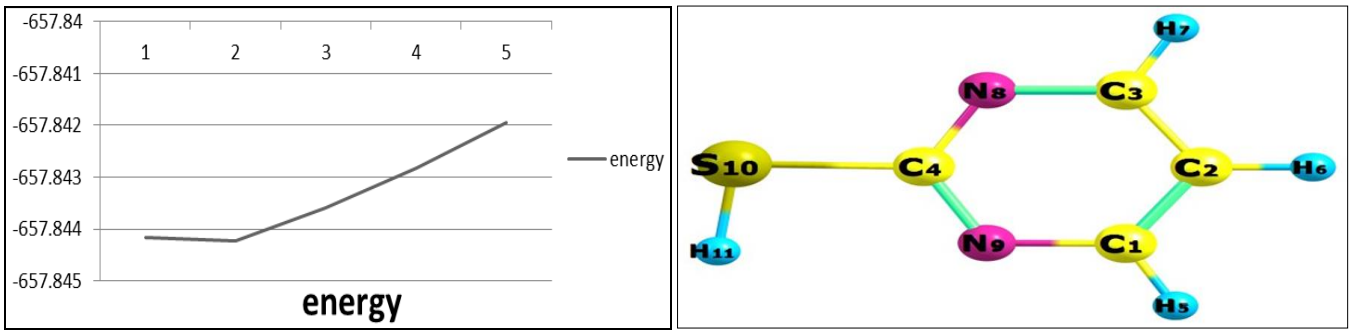

Fig 1: Model molecular structure of title molecule

Table 1: Bond Length (Å) and Bond Angle of title molecule

Bond Length			"BOND ANGLE		
S. No.	**Parameter**	**Calculated Value**	**S. No.**	**Parameter**	**Calculated Value**
1.	C_1-C_2	1.3872	12.	C_2-C_1-C_4	116.9277
2.	C_1-C_4	1.3852	13.	C_2-C_1-H_5	121.5231
3.	C_1-H_5	1.0797	14.	C_4-C_1-H_5	121.5492
4.	C_2-H_6	1.0883	15.	C_1-C_2-H_6	120.725
5.	C_2-N_9	1.3484	16.	C_1-C_2-N_9	123.0832
6.	C_3-N_8	1.3628	17.	H_6-C_2-N_9	116.1918
7.	C_3-N_9	1.3657	18.	N_8-C_3-N_9	126.7382
8.	C_3-S_{10}	1.7399	19.	N_8-C_3-H_{10}	118.965
9.	C_4-H_7	1.0883	20.	N_9-C_3-S_{10}	114.2968
10.	C_4-N_8	1.3511	21.	C_1-C_4-H_7	120.7304
11.	S_{10}-H_{11}	1.3207	23.	H_7-C_4-N_8	116.0512
			24.	C_3-N_8-C_4	114.9427
			25.	C_2-N_9-C_3	115.0899

Table 2: Total Energy, HOMO, LUMO, Energy Gap and Dipole Moment of Title Molecule

S. No.	Parameter	Value
1.	Total Energy E (a.u.)	-652.61218705
2.	HOMO	201.3728
3.	LUMO	3755.6296
4.	Frontier Orbital Energy Gap	-3554.2568
5.	Dipole Moment	1.2934 Debye

Electronic Properties and UV spectra

The FHOMO and FLUMO determine the way a molecule interacts with other species. The frontier orbital gap helps describe the chemical reactivity and kinetic stability of the molecule. Lesser frontier orbital gap makes a molecule more polarizable and is generally associated with a high chemical reactivity, low kinetic stability [13-14]. HOMO shows considerable anti bonding character. HOMO located over whole pyrazine ring however LUMO located specially on Sulfur group. HOMO acts primarily donor and LUMO act primarily acceptor so electron transfer from sulfur to ring to stabilize this system. TD–DFT method is significant tool for grinding the nature of the transitions of UV–Vis spectrum of the title compound. TD–DFT calculations demonstrate that the calculated bands at 210nm, 290 nm originate mainly due to H-3→L,H-1→L transitions respectively are not exactly match with experimental UV of pyrazine molecule [15] because presence of sulfur change slight difference in between calculated and experimental transition. On the basis of the calculated molecular orbital coefficients analyses electronic transition are assigned $n_p \rightarrow \sigma^*$ and $n_p \rightarrow \pi$ respectively

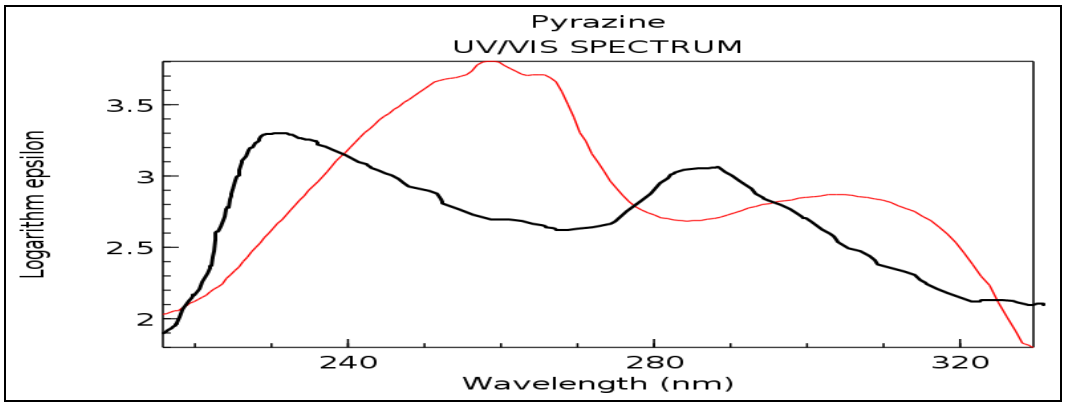

Fig 2: Comparative study of calculated UV spectra of title molecule and UV spectra of Pyrazine

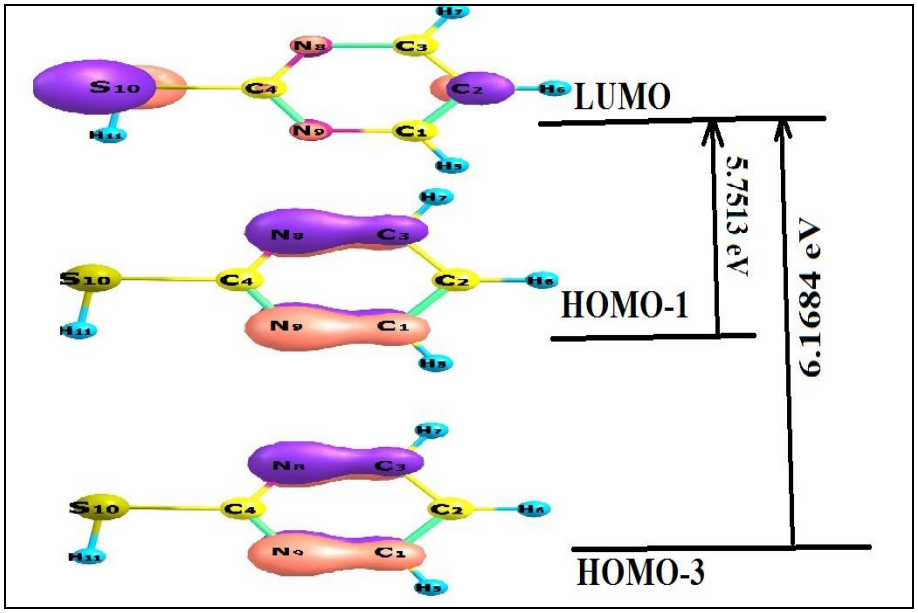

Fig 3: Various UV transition of title Molecule

Table 3: Calculated Wave Numbers and its respective I.R. Intensity of Title molecule

S.N.	Frequency	I.R. Intensity	Vibrational Assignment
1.	193	4.2099	β(Whole molecule)
2.	278	4.4782	β(Whole molecule)
3.	331	2.1792	γ((S-H)
4.	438	0.0038	γ((S-H)
5.	474	0.1468	μ (whole molecule)
6.	531	0.0758	Twist(whole molecule)
7	1059	0.5387	μ(C-N)[54%]
8.	1102	0.0001	β(C-H)[39%]
9.	1120	16.0910	β(S-H)[43%]
10.	1127	0.8180	γ(C-H)[54%]
11.	1195	1.8455	β(C-H)[64%]
12.	1236	2.8197	β(C-H)[76%]
13.	1375	49.0972	β(C-H)[54%]
14.	1384	11.5078	β(C-H)[61%]
15.	1531	246.5258	μ(C-N)[86%]
16.	1612	12.2733	μ(C-N)[79%]
17.	1756	60.5181	μ(C-C-N)[69%]
18.	1804	62.0859	μ(C-C-N)[65%]
19.	2962	3.4161	μ(C-H)[100%]
20	3044	0.4385	μ(C-H)[74%]
21	3055	3.8806	μ(C-H)[89%]
22	3205	22.0971	μ(C-H)[100%]

Where The Symbols Are:- μ=Stretching, β=In Plane Banding. ω=Wagging. R=Rocking. τ=Toque. γ=Out Plane Banding.

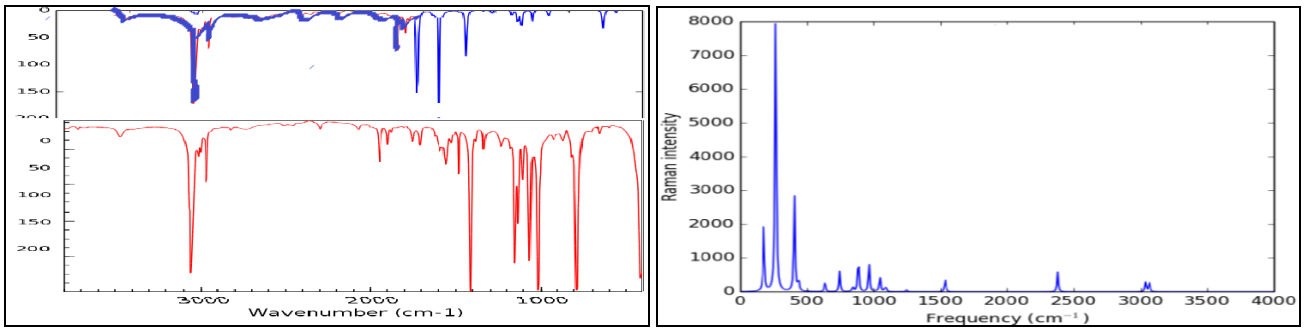

Fig 4: Comparative study of calculated IR spectra of title molecule and IR spectra pyrazine

Assignment of fundamentals

Pyrazine has 12 atoms 30 normal modes of vibration. We made a reliable one-to-one correspondence between the fundamentals and the frequencies calculated by DFT (B3LYP). The relative bands intensities are also vary satisfactory along with their positions. Some important modes are discussed here after.

Vibrational modes discription

Change in geometry reflected by change in frequency. The aromatic structure of title molecule shows that C–H stretching vibrations in the region 3200-3000 cm^{-1}, which is the characteristic region for the ready identification of the C–H stretching vibration. An intense polarized peak appears at 3255 cm^{-1} corresponding to C-H stretching with 100% PED is obtained. This band are well mathced with experimental IR spectra of pyrazine molecule [15] Two less intense polarized mode are obtained at 3055 cm^{-1}, 3044 cm^{-1} are also lies in this range. In this study two intense polarized mode corresponding to bending of C-C-N is obtained at 1756 Cm^{-1}, and 1804 Cm^{-1}. An intense polarized peak corresponds to C-N stretching mode are obtained at 1531 Cm^{-1}.

Biological Activity

Pyrazine and related heterocyclic compounds are used in tuberculosis and other conditions. Pyraines also shows biological activities in various disease such as antimycobacterial, antibacterial, fungicidal etc. Pyrazinamide, a derivative of pyrazine is an important antitubercular agent used as first line drug for tuberculosis therapy. Tuberculosis is a chronic disease triggered by Mycobacterium tuberculosis. The main problem of tuberculosis therapy is the growth of drug confrontation. In this section we have calculate various biological parameter and docking character of sulphur derivative of pyrazine with various protein. Along with docking we discuss the biological activity of title compound predicted by PASS software [16]. This prediction is based on the analysis of SAR for the exercise set with more than 46,000 drugs, drug-candidates and lead compounds with known biological active compound. PASS deductions 900 pharmacological constraints, molecular mechanisms of action, mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity. Nearly 85% accuracy of prediction in leave one- out cross-validation [17]. In our study we calculate biological parameter for Pa > 70%. In this range molecules will most likely display these activities in the experiment Table - 4 lists the foretold activities of title compound. Title compound is found active against Gluconate 2-dehydrogenase (acceptor) inhibitor substrate. Gluconate 2-dehydrogenase (acceptor) inhibitor belongs to cytochrome family whose expression is liver-specific and regulated at the transcriptional level by growth hormone [18]. Nitrate reductase (cytochrome) inhibitor is the first enzyme in nitrate assimilation pathway. During drop of nitrate to nitrite, it uses pyridine nucleotides, and benzyl viologen as electron donor [19]. It performances as dominant point for addition of metabolism by nursing flux of condensed nitrogen in plants, algae and fungi [20]. The value of this parameter having value 0.422 shows activity of this drug is good. The value of this parameter having the value 0.590 so title compound is a utilizing source for nitrogen reducing element [22]. Designing new tuberculosis agents requires the identification of targets which when inhibited can kill the effected cells. Swiss dock online server predict efficient target MAKP8, MAKP9 MAKP10, MAKP11 MAKP14 based on this we performed the molecular docking simulation of the compounds with Swiss Dock online server [23]. The three dimensional (3D) crystal structure of target protein was obtained from Protein Data Bank (PDB file protein data bank). Swiss Dock Online server can calculate protein-ligand docking, assuming the legend is rigid, and it can superimpose pairs of molecule using only knowledge of their 3D shapes. The docking score can be approximated to an interaction energy value (*e*-value), which we seek to minimize. The more negative the *e*-value, the more efficient will be the docking process. We have performed the molecular docking studies to get insight into the potential target of MAPK series receptor for binding with title molecules. Note that it is merely a model that may provide the binding affinity of a particular site in terms of *e*-value. The docking of title compounds into MAKP series receptor is displayed in Figure 4 and Figure 5. The total *e*-value obtained is in this process favour title compound to dock with MAPK11 protein as compared with other protein.

Table 4: Docking protein with full fitness energy and change in Gibes free energy in this process

Protein	MAKP9	MAKP10	MAKP11	MAKP14	MAKP8
E (Kcal/Mol)	-1887.5259	-1968.0687	-1958.9841	-1887.5259	-1958.9841
ΔG((Kcal/Mol)	-5.74	--7.61	-6.52	-5.91	-6.73

Biological activity of Title molecule predicted by PASS program with Pa > 0.7

Table 5

Biological Activity	Title molecule
Nitrate reductase (cytochrome) inhibitor	0.590
Gluconate 2-dehydrogenase (acceptor) inhibitor	0.517
Antineoplastic	0.423
CYP2C12 substrate	0.607

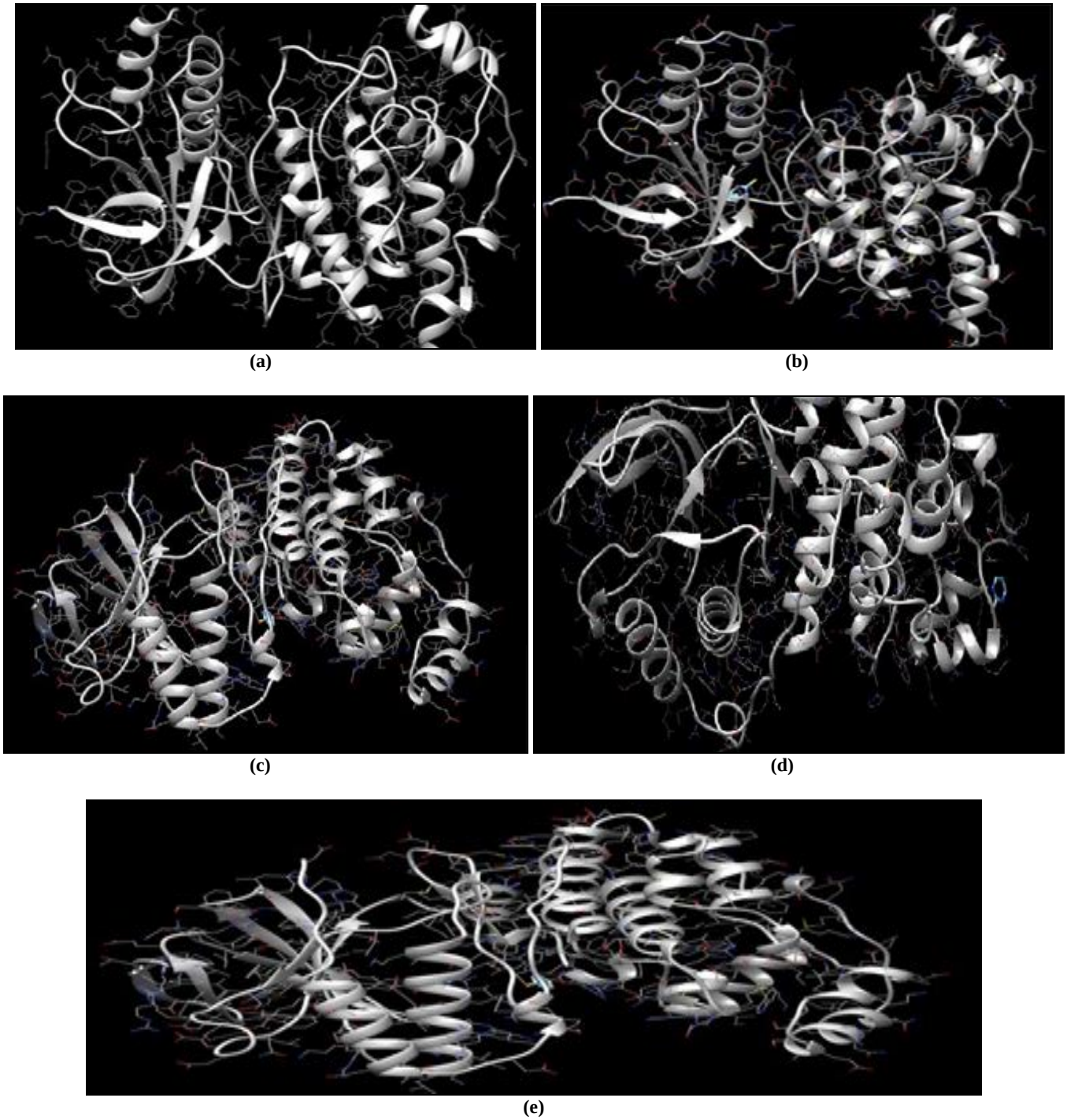

Fig 5: Docking with MAKP8 (a), MAKP9 (b), MAKP10 (c), MAKP11 (d), MAKP14 (e) Protein with Title molecule

Conclusion

In this paper we study DFT and TDDFT calculation with 6-311G (d, p) basis set. Normal mode analyses are done on title molecule have also been carried out and detailed assignments are offered to the significant vibrational modes. The electronic reactivity of title molecule are also evaluated with the help HOMO, LUMO. The biological activity of title molecule has also been predicted with help of several parameter calculated PASS software. To model new drug we also make docking of title molecule with several MAKP series protein and our finding is MAKP14 having lowest e-value for docking.

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