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Synthesis, Molecular Structure, Spectral (IR, UV-Vis, ^{1}H-NMR) and Molecular Docking Analysis of 4-Amino-5-(Naphth-2-Oyl)-2-Methyl-Phenylaminothiazole: DFT Technique

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ABSTRACT

The aim of the work is to synthesis and examines novel 4-amino-5-(naphth-2-oyl)-2-methyl-phenylaminothiazole by experimental and theoretical spectroscopic investigations and to identify its structural and biological properties. The vibrational behaviour of the title molecule was extracted by using Fourier transform infrared analysis. The experimental FT-IR (400–4000 cm^{-1}) spectrum of 4-amino-5-(naphth-2-oyl)-2-methyl-phenyl-aminothiazole has been recorded in the solid phase. The UV-visible spectrum was recorded by using a UV-Visible spectrophotometer and correlated with the TD-DFT method. Hydrogen (^{1}H) nuclear magnetic resonance spectrum was also recorded. The geometry optimization has been performed to analyze the 4-amino-5-(naphth-2-oyl)-2-methyl-phenyl-amino-thiazole active sites with bonding features. For identifying the bio-activity of the title molecule, docking studies have been performed by using molecular docking software.

Keywords : FT-IR, UV-Vis, NMR, DFT, Molecular Docking.

Introduction

Benzothiazole derivatives are fascinating chemical products used in the field of medicine as they have been found to possess a wide spectrum of biodynamic properties. Literature survey reveals derivatives of benzothiazole unit having a useful pharmacophore moiety and exhibit anticancer [1] anti-inflammatory [2] anti-bacterial [3] antifungal [4] anti-tubercular [5] and antioxidant activities [6]. Patil et al. reported the DFT study on dihydroxyphenyl benzothiazole by using B3LYP/6-31G(d)[7]. Hakan Arslan studied the molecular structure and vibrational frequencies of 2-(4-methoxyphenyl)benzothiazoles derivatives implementing the standard 6-311G(d,p) set in the ground state have been investigated with ab initio/HF and density functional methods BLYP, B3LYP, B3PW91 and PW1PW91[8]. Inspite of the existing studies, there are still lack of information about structural and energetic properties of 4-amino-5-(naphth-2-oyl)-2-methyl-phenyl-aminothiazole molecule have been computationally investigated by using DFT method.

Synthesis

4-amino-5-(naphth-2-oyl)-2-methyl-phenylaminothiazole was framed through the reaction of (1-aryl-3-N-nitroamidino)thiourea (1mmol) in DMF (2ml) and 2-bromoacetyl naphthalene (1mmol)in DMF(2ml). The resultant reaction mixture was stirred well and triethylamine (1mmol) was added. Then the whole mixture was warmed to about 80-85°C for 15 mins. It was then cooled in ice–cold water with constant stirring. The derived orange precipitate was filtered, washed well with water and dried well. The crude product was re-crystallised from ethanol-water (2:1) ratio to give a yellow orange crystalline solid.

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Experimental Details

4-amino-5-(naphth-2-oyl)-2-methyl-phenylaminothiazole (4PMN) FT-IR spectrum was recorded in the 4000-400cm^{-1} range using the KBr pellet technique (Perkin Elmer Spectrum). In solvent phase, the UV-Visible spectrum of the compound was recorded in the range of 250-600 nm using UV-Visible Spectrophotometer (Perkin Elmer Lambda 950). The spectroscopy of nuclear magnetic resonance (NMR) is a very powerful non-invasive technique that provides detailed structural information in different molecular systems. On a Bruker Avance III500 MHZ (AV500), the ^{1}H NMR spectrum was recorded.

Computational Details

By using the Gaussian 09 [9] software package, vibrational wavennumber, computed vibrational assignments and the optimized structure of 4PMN molecule were performed using the standard base set B3LYP/6-311G (d,p). The assignment of the calculated wave numbers is supported by the GAUSSVIEW animation option, which provides a visual presentation of the vibrational modes [10]. The time-dependent DFT approach was used to calculate the electronic transitions of major assignments, maximum absorption, excitation energy, band gap energy, and oscillator strengths [11]. The isotropic shielding of ^{1}H-NMR has been calculated using the GIAO method [12]. The docking studies were carried out using Auto Dock4.2 [13] molecular docking software.

Results and Discussions

Optimized Geometry

The optimized molecular structure along with numbering of compound is shown in Fig.1. The basic parameters such as bond length, bond angle, dihedral angle are calculated by DFT/B3LYP method with 6-311G (d,p) basis set. Table 1 summarizes the selected geometrical parameters of the 4PMN compound. The molecule contains three rings (naphthalene, thiazole and NHAr rings) connected by a keto group, the thiazole and aromatic group connected by NH group. The bond length of (N28-C30 =1.410 Å) corresponds to single bond. It is observed that carbon-carbon bond lengths for the phenyl ring of the 4PMN molecule tend to be intermediate between 1.389-1.401 Å and the C-H bond lengths of a phenyl ring varies through 1.080-1.088 Å arises from B3LYP level of calculation which in turn good agreement with literature [14]. Several authors have reported the changes in frequency or bond length of the C-H bond on substitution due to change in charge distribution on the carbon atom of the benzene ring; mainly the substituents are electron withdrawing groups or electron donating groups [15]. From the above we can conclude that electron donating substituents activate the benzene ring toward electrophilic attack, electron with drawing substituents deactivates the ring. The C=O group bond length is experimentally calculated as 1.23 Å as a results of our compound exhibit the same value 1.23 Å. The bond length of C4-N25 is 1.363 Å while the nearest bond length C4-N3 is 1.373 Å experience a slight deviation which in turn the strong hydrogen bonding interaction of C31-H36...N3. The reported value for the C-S bond length is in the range of 1.765 Å -1.864 Å; For our title compound the C-S bond length is S1-C2 =1.760 Å which are in close agreement with the literature [16] and the difference between calculated and reported value is due to the presence of adjacent C-N present in the heterocyclic ring. In the 4PMN molecule, the bond angles S1-C2-N3, C2-N3-C4, N3-C4-C5 are as 115.9˚,110.7˚, 116.3˚ respectively therefore it is slightly deviated from the normal bond angle value due to the electron withdrawing groups nitrogen and sulphur present in the thiazole ring. The interaction between thiazol sulphur and amine hydrogen makes bond angle drifted to 130.4˚ (C2-N28-C30) leads to elongation. The bond angle C4-C5-C6 = 135˚ rises by the bis substituted nitrogen group and oxygen atom which gets slightly flipped and affects the planarity of the structure.

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Table 1. Optimized geometric parameters

Bond length	Calculated values(Å)	Bond angle	Calculated values (˚)
S_1-C_2	1.760	S_1-C_2-N_3	115.9
C_2-N_3	1.313	C_2-N_3-C_4	110.7
N_3-C_4	1.373	N_3-C_4-C_5	116.4
C_4-C_5	1.399	C_4-C_5-C_6	135.0
C_8-H_{23}	1.086	C_5-C_6-O_{24}	120.6
C_6-O_{24}	1.236	N_3-C_4-N_{25}	115.6
C_4-N_{25}	1.363	C_4-N_{25}-H_{26}	119.7
N_{28}-H_{29}	1.009	C_2-N_{28}-C_{30}	130.4
N_{28}-C_{30}	1.410	N_{28}-C_{30}-C_{31}	124.0
C_{30}-C_{31}	1.401	C_{30}-C_{31}-C_{32}	119.3
C_{31}-C_{32}	1.395	C_{31}-C_{32}-C_{33}	122.3
C_{32}-C_{33}	1.399	C_{32}-C_{33}-C_{34}	117.3
C_{33}-C_{34}	1.401	C_{33}-C_{34}-C_{35}	121.3
C_{34}-C_{35}	1.389	C_{30}-C_{31}-H_{36}	119.5
C_{31}-H_{36}	1.080	C_{31}-C_{32}-H_{37}	118.4
C_{32}-H_{37}	1.087	C_{32}-C_{33}-C_{38}	121.4
C_{33}-C_{38}	1.510	C_{33}-C_{34}-H_{39}	119.6
C_{34}-H_{39}	1.087	C_{34}-C_{35}-H_{40}	119.6
C_{35}-H_{40}	1.088	C_{33}-C_{38}-H_{41}	111.4

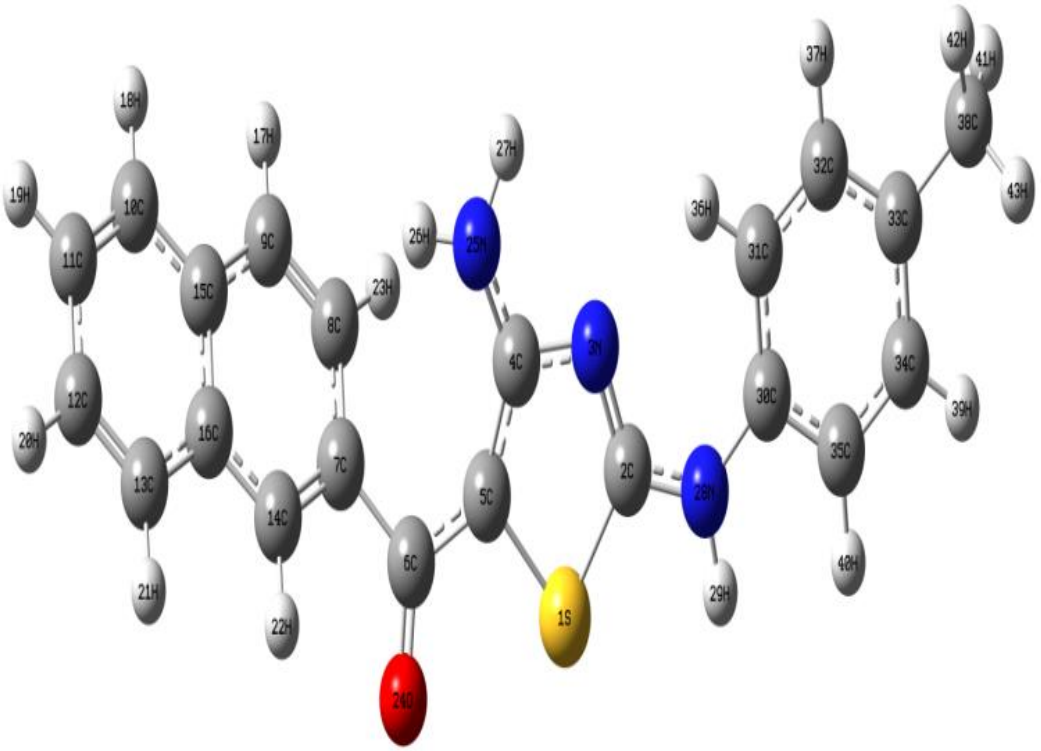

Fig.1: The optimized structure of 4PMN molecule.

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Vibrational analysis

The recorded FTIR spectrum of 4PMN molecule was shown in Fig.2. The asymmetric stretching vibration of NH_2 ranges from 3500 to 3420 cm^{-1} and the symmetrical stretching of NH_2 ranges from 3420 to 3340 cm^{-1} [17]. In the present work, the wavenumber observed at 3453 cm^{-1} in the FT-IR spectrum corresponds to NH_2 asymmetric stretching mode. The wavenumber observed at 3344 cm^{-1} in the infrared spectrum is assigned to symmetric NH_2 stretching mode. NH_2 modes are expected to be in the range 1640-1580 cm^{-1} (deformation modes), 1170-1080 cm^{-1}(rocking modes), and 730-610 cm^{-1}(wagging) according to the literature [18-21]. A band in IR at 1590 cm^{-1} is assigned to NH_2 deformation mode of 4PMN molecule. Based on Roeges [18] the rocking NH_2 mode is expected in the range 1160 ± 140 cm^{-1}. In the present work, the NH_2 rocking mode is observed at 1041 cm^{-1} in the FT-IR spectrum. In general the N-H stretching vibration occurs in the range of 3500-3300 cm^{-1} [22]. A medium band observed at 3396 cm^{-1} in the IR spectrum accounted for N-H stretching vibration.

The carbonyl stretching frequency has been most extensively studied by infrared spectroscopy [23]. The strong band of C=O stretching vibration mode exhibits in the range of 1600-1750 cm^{-1} [18]. It is assigned for the title compound at 1689 cm^{-1} in the IR spectrum. Basically, the spotting of carbon and nitrogen vibration is a hard burden because they fall in the convoluted region of the vibrational spectrum so mixing of several bands likely to be happening in this region [24]. The C-N stretching vibration of the amide group is expected in the range 1385±85 cm^{-1} and it is difficult to detect [25]. The band observed at 1397 cm^{-1} corresponds to C–N stretching vibration.

The C-S stretching frequency is quite compatible for many different types of compounds that contain the C-S moiety [26]. Generally, the C-S stretching vibration was reported at 750-600 cm^{-1}[27]. In the present work, the C-S stretching vibration specified at 743 cm^{-1} consecute the medium FT-IR band in the spectrum. The C-C aromatic stretching vibration attributes bands in observed FT-IR spectrum, causing the spectral range from 1600-1200 cm^{-1}. The real spot of these modes is determined not so much by the nature of the substituents yet by the form of substitution throughout the ring [28]. The title compound manifested bands of different intensities at 1553, 1521, 1468 and 1365 cm^{-1} set for stretching vibration of C-C mode with the substituents in the benzene ring.

The C-H stretching vibration noticed in the frequency range of 3200-2850 cm^{-1} for heteroaromatic compounds [29, 30]. The bands captured at 3198, 3067, 3053, 3000, 2939cm^{-1} successively in IR spectrum were assigned for C-H stretching vibration of our title compound. The C-H in plane bending vibration appears in the region 1300-1000 cm^{-1} [31]. Here the C-H in plane bending vibration of our compound observed at 1227, 1157 cm^{-1} in the FT-IR spectrum. The C-H out of plane bending vibration arises within the region 900-675 cm^{-1} [32-34]. The medium band observed at 811 cm^{-1} in IR spectrum is assigned to CH-out of plane bending vibration. The methyl group C–H stretching vibrations were reported in the region of 3000–2800 cm^{-1} [35]. The C–H stretching vibration was observed at 3000, 2939 cm^{-1} in the FT IR spectrum and the theoretical value identified at 2920 cm^{-1} noted to C–H stretching mode with 97% PED output. The CH3 rocking vibrations are usually found at 1070–1010 cm^{-1} [36]. The medium IR band observed at 1026 cm^{-1} is ascribed to CH3 rocking vibration. The asymmetric and symmetric bending vibrations of methyl groups normally appear in the region 1470–1440 cm^{-1} and 1390–1370 cm^{-1} respectively. The bands predicted at 1443 cm^{-1} and 1385 cm^{-1} were assigned for CH_3 bending mode.

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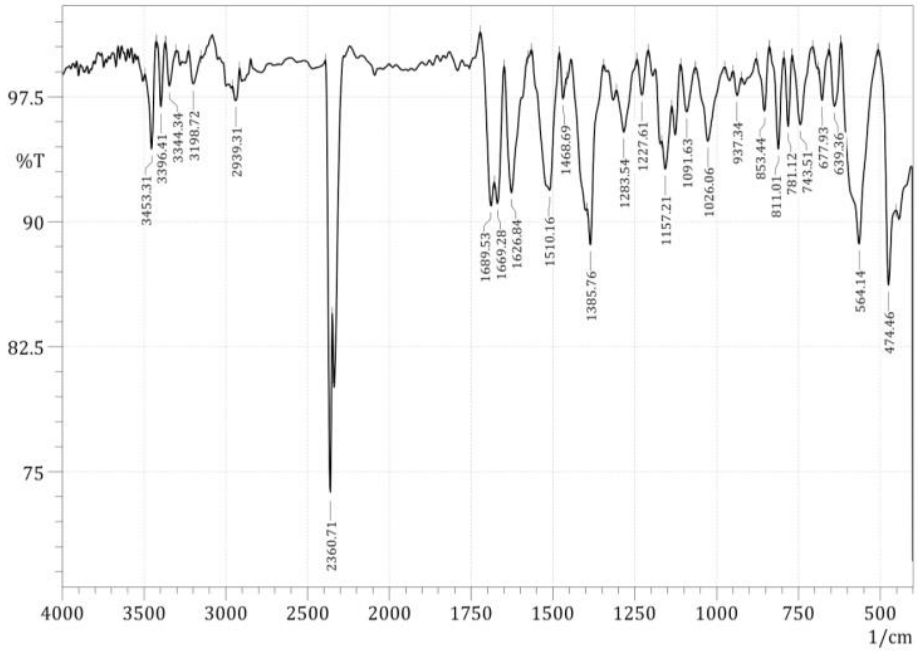

Fig.2: FT-IR Spectrum of 4PMN molecule

UV-Visible analysis

The UV–Vis spectrum of the title molecule was recorded in the wavelength range 250–800nm as shown in Fig.3, and methanol is used as solvent for both theoretical and experimental analysis. The computational UV-visible absorption spectra were calculated using the TD–DFT method based on the B3LYP/6–311G (d,p) level of theory. The observed and computed wavelength (λ), the corresponding electronic excitation energies, oscillator strength (*f*) and the transition nature are listed in Table 2. The electronic spectrum of 4PMN molecule shows the three transitions state as 378nm, 324nm and 300nm and the calculated UV absorption result has also three excited states 383.77nm, 342.05nm, 334.76nm and their corresponding excitation energies are 26056.7, 29235.3 and 29871.7cm-1, respectively. The strong transition show maximum absorption wavelength at λ_{max} =383.77nm (Cal) & 378nm (Exp) with an oscillator strength f= 0.419 in solvent phase was assigned to n–π* transition. Considering calculated absorption spectra, the most extreme absorption wavelength relates to the electronic transition from HOMO to LUMO with 98% contribution. The HOMO to LUMO 98% maximum contribution shows the transfer of electron from thiazole ring to naphthalene ring.

Table 2. UV-Visible datas

Exp	**Theoretical**			**Assignments**
($\boldsymbol{\lambda}_{max}$) nm	($\boldsymbol{\lambda}_{max}$) nm	Energy (Cm^{-1})	Oscillator Strength(F)	Major Contribution
378	383.7	26056.7	0.419	HOMO→LUMO (98%)
324	342.0	29235.3	0.228	HOMO→LUMO+1 (56%)
300	334.7	29871.7	0.084	HOMO→LUMO+1 (39%)

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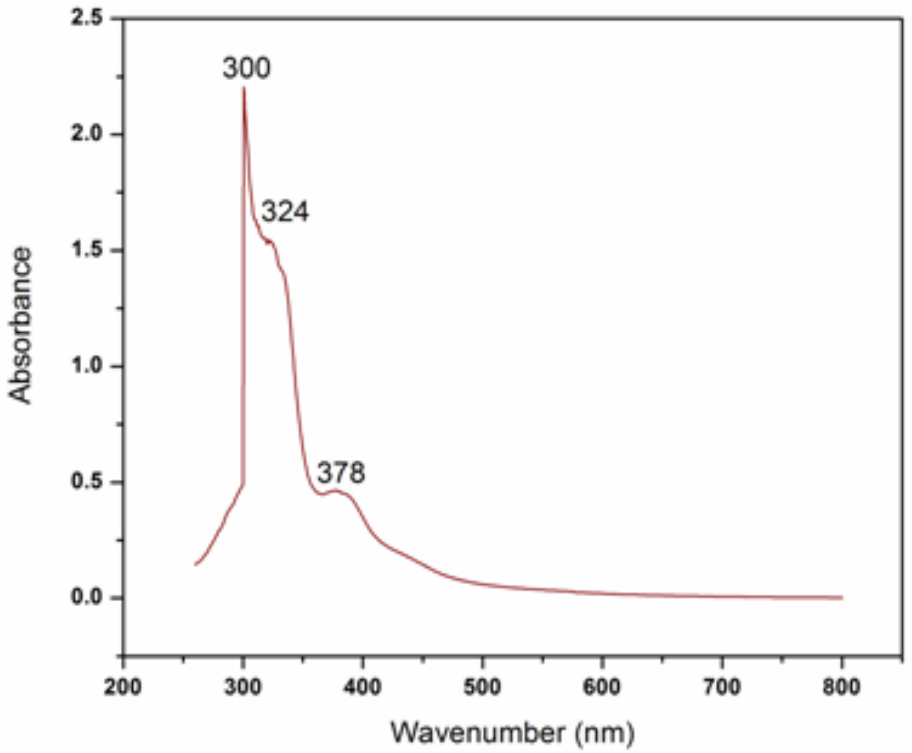

Fig.3: UV-Vis Spectrum of 4PMN molecule

NMR analysis

The computed and experimental value of ^{1}H NMR chemical shifts of title molecule is listed in Table 3. The observed ^{1}H NMR spectrrum of the title molecule is shown in Fig.4. The B3LYP/GIAO model calculated the absolute isotropic chemical shielding of the title molecule [37]. Relative chemical shifts were then estimated using the corresponding TMS shielding: σ_{calc} (TMS) is calculated in advance at the same theoretical level. Numerical values of chemical shift δpred = σ calc (TMS) - σ_{calc} together with the calculated and experimental δ values are given in Table 3.

^{1}H chemical shifts of 4PMN molecule were obtained by complete analysis of their NMR spectra and interpreted critically in an attempt to quantify the possible different effects acting on the shielding constant of protons. Aromatic protons signals normally absorb around 6.2–8.2 ppm; In 4PMN molecule the chemical shift values of aromatic protons are in the range 6.332–8.758 ppm and their corresponding calculated values are in the range 6.624-8.977 ppm. The highest chemical shift of H36 atom shows C31-H36….N3 hydrogen bond interaction. The amino group hydrogen has a highly variable signal in the 1H NMR spectrum of amides between 5 and 9 ppm [38]. In the present study, the 1H-NMR spectrum of title molecule gives different δ values of amide group NH2 proton such as δ 5.074 for H26 and δ 4.946 for H27. Most of the calculated NMR chemical shifts are in agreement with the observed experimental results.

Table 3. ^{1}H NMR datas

Atoms	Calculated	Experimental
H_{17}	8.032	8.041
H_{18}	8.064	8.075
H_{19}	7.871	7.807
H_{20}	7.876	7.837
H_{21}	8.202	8.121

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H_{22}	8.474	8.141
H_{23}	8.013	8.019
H_{26}	4.718	5.074
H_{27}	4.344	4.946
H_{29}	6.365	6.065
H_{36}	8.977	8.758
H_{37}	7.457	7.463
H_{39}	7.312	7.325
H_{40}	6.624	6.223
H_{41}	1.931	1.641
H_{42}	1.830	1.626
H_{43}	1.250	1.108

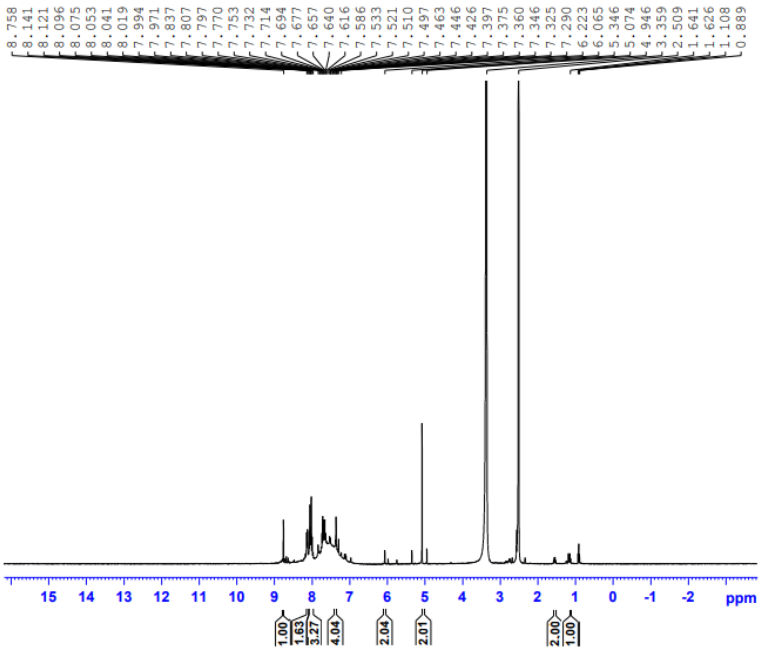

Fig.4: ^{1}H NMR spectrum of 4PMN molecule.

Molecular Docking

Molecular docking approach can be used to model the interaction between a ligand and a protein at the atomic level. In the present study, molecular docking studies were performed using AutoDockVina [13]. The three dimensional structure of proteins was taken from Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. The PDB ID of the target proteins are 1N50, 2PSQ and 5CQD. For docking, all water molecules were removed and polar hydrogen atoms were added to the refined model using AutoDock tools. The best confirmation between the ligand and protein was selected using Lamarkaina Genetic Algorithm (LGA). The hydrogen bond interaction between the compound and protein is visualized using PyMOL viewer [39]. For identifying anti-cancer activity of title molecule BRCA1-BRCT missense mutation, (FGFR2) kinase domain and cancer genomic DNA mutator APOBEC3B type proteins are selected. The binding affinity of the 4PMN molecule with the target proteins was analyzed using molecular

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docking studies. The interaction between the protein 1NO5 and ligand 4PMN was studied using Pymol viewer and shown in Fig.5. The binding mode of the 4PMN molecule with the target protein was analyzed using Autodock Vina. Evaluation of binding affinity revealed the 4PMN molecule was capable of inhibiting all the selected target proteins. In 4PMN molecule the protein 1N5O exhibited five hydrogen bond interactions with a binding affinity of -7.8 Kcal/ mol (Table 4). The least binding score revealed 4PMN molecule highly inhibit cancer genomic DNA mutator APOBEC3B type protein. From the studies, it is evident the compound exhibited a similar response against all three selected target and thus further investigation of the stability of the interaction would help in evolving an effective lead compound against the target proteins.

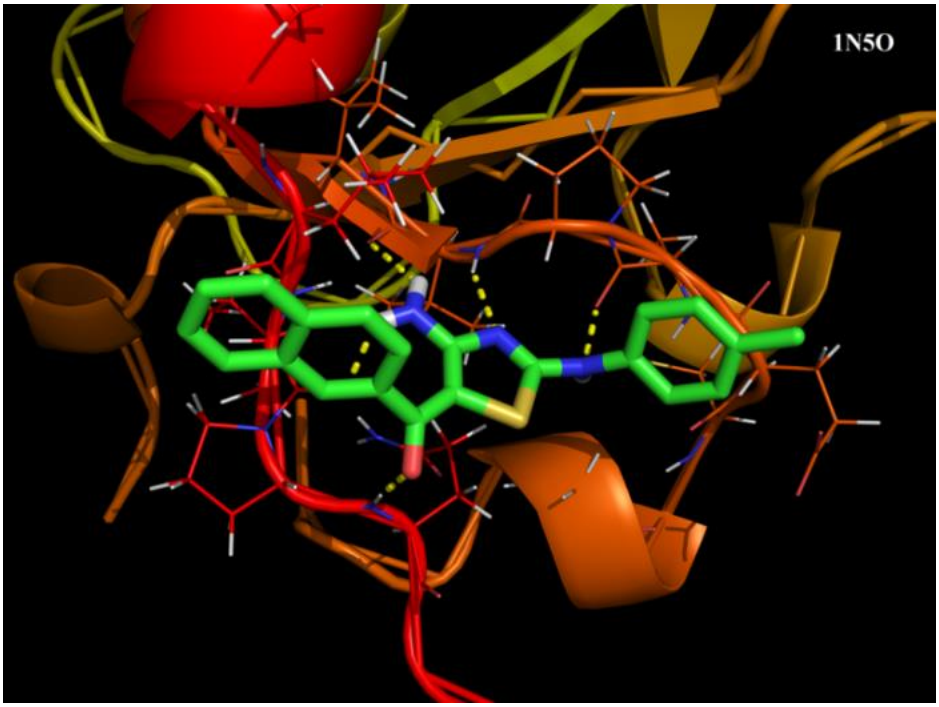

Fig.5: 4PMN molecule interact with protein 1N5O

Table 4. 4PMN molecule interact with different proteins

Protein (PDB:ID)	Binding Residue	Bond Distance (Å)	Incubation Constant (Mm)	Binding Affinity (K/Cal)
1N5O	ALA 1830 VAL 1832 VAL 1832 ILE 1855 GLN 1857	2.10 2.15 2.33 1.98 1.72	1.91	-7.8
2PSQ	GLY 490 ASP 644	2.19 1.81	12.69	-6.68
5CQD	GLN 233	1.89	33.4	-6.11

5 Conclusion

Attempts have been made in this paper to study the vibrational assignments of 4PMN molecule using DFT method (B3LYP) with 6-311G (d,p) basis set. The optimized molecular

geometry, mulliken charges in the ground state were also calculated .The results indicate that the B3LYP Method is able to provide satisfactory results for predicting vibrational frequencies and structural parameters. The maximum UV-Vis absorption result show electron transfer from thiazole to naphthalene ring. The observed ^{1}H-NMR chemical shifts are agreed with the calculated values. The 4PMN molecule highly inhibits cancer genomic DNA mutator APOBEC3B type protein with binding score -7.8 kcal/mol which reveals efficient anti-cancer activity. All the spectral, structural and reactive properties are accountable for bio-activity of 4PMN molecule.

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