

Full Length Article

Molecular structure, electronic, topology and non-covalent interaction of 4-(Bis(2-chloroethyl)amino)-L-phenylalanine- Anti-blood cancer activity

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ABSTRACT

In this study, it is attempted to scrutinize the global minimum energy structure of anti-blood cancer drug 4-(Bis(2-chloroethyl)amino)-L-phenylalanine (4B2CA-LPA) and functionalized density functional theory (DFT) calculations regarding their geometries, topological features of covalent, non-covalent interactions with employing Atoms in molecule (AIM) and Reduced density gradient (RDG) studies. As per the topological results, a new type of non-covalent attraction forces of hydrogen-hydrogen interaction was found in this molecule. Electrostatic potential variation as well as global reactive descriptor energy variations in the solvation phases was carried out by molecular electrostatic potential (MEP) and frontier molecular orbitals (FMOs) analysis. Moreover, the electronic excitations in liquids of 4B2CA-LPA were evaluated in UV-Vis absorptions. The local bonding electron transitions and optical properties of the compound were examined with natural bond orbital (NBO) studies. The 4B2CA-LPA molecule can serve as lead molecules for the growth of anti-blood cancer drugs. Molecular docking investigation has also been carried out to determine the ability of target molecules to bind with Hematopoietic inhibitors in blood cells.

1. Introduction

Blood cancer is a malignant class of cancer disease that can develop in complete organs of the body because of the unregulated proliferation of abnormal cells. The introduction of novel medication classes [1–4], such as novel treatments for multiple myeloma (blood cell cancer), including proteasome blockers, immunoregulatory drugs, and monoclonal antibodies, have significantly changed exactly how the disease is treated, over the past 20 years [3,5–8]. The levels and degree of responsiveness, as a result, increased by including these medications in treatment regimens for patients with newly diagnosed multiple myeloma [8,9]. Further research is necessary to determine the advantages of consolidating treatment based on innovative medications following the intensifying stage [10,11], as not all studies have

supported the use of consolidation treatment after transplantation [12]. The 4-(Bis(2-chloroethyl) amino)-L-phenylalanine (**4B2CA-LPA**) and also known as Alkeran is anti-blood cancer (multiple myeloma) drug and it was approved melphalan by USA Food and Drug Administration five decades ago [13–16]. It functions by preventing the growth of cancer cells, which are then subsequently eliminated by the body. Melphalan may also influence the proliferation of healthy cells, therefore other negative consequences will also manifest [17–20]. Several works have already reported how the 4B2CA-LPA chemical was synthesized using many different approaches [21–23]. According to the literature, the common process for producing the title chemical, when 4-Nitro-L-phenylalanine was heated with phthalic anhydride, it was converted to phthalimide, which was subsequently modified into its ethyl ester. Catalytic hydrogenation was used to produce similar aniline. The

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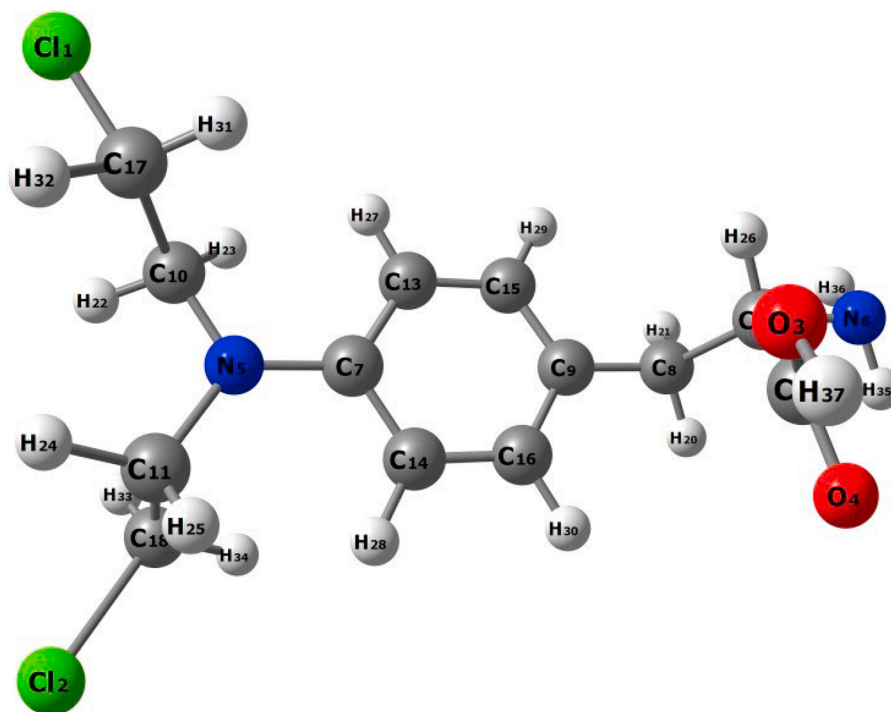


Fig. 1. Optimized stable Structure 4B2CA-LPA in the gas phase.

Table 1

Optimized parameters of the title compound: bond lengths (Å) bond angles (°).

Parameter	Bond Length (Å)		Parameter	Bond Angle (°)	
	DFT	Lit. ^a		DFT	Lit. ^a
Cl1-C17	1.817	1.787	Cl1-C17-C10	110.4	110.8
Cl2-C18	1.817	1.807	O3-C19-O4	123	126.2
O3-C19	1.348	1.266	O3-C19-C12	113	112.2
O3-H37	0.97	1.006	O4-C19-C12	124	121.6
O4-C19	1.207	1.228	C7-N5-C10	121.5	121.33
N5-C7	1.399	1.471	C7-N5-C11	121.5	122.58
N5-C10	1.455	1.451	N5-C7-C13	121.5	121.12
N5-C11	1.455	1.474	C10-N5-C11	116.9	116.4
N6-C12	1.463	1.485	N5-C10-C17	111.8	110.8
N6-H35	1.016	1.063	N5-C11-C18	111.8	110.9
N6-H36	1.015	1.029	N6-C12-C8	114.5	-
C7-C13	1.41	1.391	N6-C12-C19	106.6	-
C7-C14	1.409	1.372	C13-C7-C14	116.9	115.97
C8-C9	1.511	1.442	C7-C13-C15	121	121.91
C8-C12	1.557	1.499	C7-C13-H27	120.8	119.0
C9-C15	1.398	1.398	C9-C8-C12	115	115.97
C9-C16	1.397	1.360	C9-C8-H20	110.3	119.0
C10-C17	1.531	1.495	C8-C9-C15	121.5	-
C11-C18	1.531	1.504	C8-C12-C19	109.8	-
C12-C19	1.523	-	C15-C9-C16	116.9	118.78
C13-C15	1.39	1.391	C9-C15-C13	122.1	125.06
C14-C16	1.391	1.372	C9-C16-C14	122	124.63

^a Literature values are taken from Ref. [33,34]

bischloride was created by heating oxirane in acid and then treating it with phosphorus oxychloride, finally 4-(Bis(2-chloroethyl)amino)-L-phenylalanine (Melpalan) was produced by removing the protecting groups in hydrochloric acid.

Melpalan (Alkeran) is a medication that can be used to treat multiple myeloma. To prepare patients for stem cell transplantation, it serves as a conditioning therapy. For individuals who are unable to take melpalan orally, there is also an available liquid form of melpalan (melpalan hydrochloride). Hence the researchers need more about the physicochemical properties of 4B2CA-LPA and the influence of molecule in liquid phases (solvent effects), Melpalan is used in advanced therapy

for the treatment of developing medication carriers for multiple myeloma that minimize the toxicity, the chemical and biological modifications of the 4B2CA-LPA molecule to increase anticancer activity and integrating therapies to improve the efficiency of cancer treatment. Due to fact that the use of 4B2CA-LPA in the treatment of different tumor cell types is currently being researched and a large number of research articles have been published. To the best of my knowledge, no DFT investigations using topological analysis, solvation effects, reactivity-based descriptor analyses and vibrational studies have ever been conducted on this drug. In recent years, the study of theoretical modeling of cancer drug molecules with medical significance has benefited from the development of computer simulators, and it is now able to assess the important physical and chemical properties of approved drug compounds for cancer treatment using a range of theoretical methodologies [24]. Density functional theory (DFT) has advanced with the establishment of a much more accurate exchange-correlation function and has developed into a magnificent tool in comparison to other traditional approaches because of its low processing cost and excellent accuracy [25].

In the present investigation, the focus of our study has been on figuring out how to drug material's molecular geometry by connecting the desired attributes from an experimental assessment with the expected theoretical parameters of DFT. The physicochemical properties of vibrational assessment with IR and Raman spectra, topological analysis (RDG, LOL, ELF & AIM), solvation effects on reactivity descriptors (MEP & FMOs), natural bond orbital studies, and electronic structure assessments (UV-Vis, MEP & FMOs) in various liquids are all being investigated using the DFT methods. Finally, molecular docking was carried out using three different blood cancer proteins (PDB codes: 4FVR, 3WIX, & 5UUT) based on the PASS Online tool's prediction with the highest probability activity (Pa). We chose them for the current studies based on the literature review since the title chemical 4B2CA-LPA has not been previously investigated with these specific blood cell proteins.

2. Quantum computational details

The compound's complete molecular geometry optimization was

Table 2Topological parameters of the **4B2CA-LPA** for covalent and non-covalent interactions in gas phases.

BCP	$\rho(r)$ (a.u)	$\nabla^2\rho(r)$ (a.u)	$V(r)$ (a.u)	$G(r)$ (a.u)	$H(r)$ (a.u)	$-(G/V)$	ϵ
C10 - C17	0.2454	-0.5626	-0.2516	0.0555	-0.1961	0.2204	0.0650
C10 - H22	0.2813	-0.9582	-0.3170	0.0387	-0.2783	0.1221	0.0276
C10 - H23	0.2825	-0.9647	-0.3173	0.0381	-0.2792	0.1199	0.0268
C11 - C18	0.2454	-0.5627	-0.2516	0.0554	-0.1961	0.2204	0.0651
C11 - H24	0.2813	-0.9578	-0.3168	0.0387	-0.2781	0.1221	0.0276
C11 - H25	0.2825	-0.9649	-0.3172	0.0380	-0.2792	0.1198	0.0267
C12 - C19	0.2554	-0.6309	-0.2713	0.0568	-0.2145	0.2092	0.0387
C12 - H26	0.2841	-0.9767	-0.3194	0.0376	-0.2818	0.1178	0.0192
C13 - C15	0.3092	-0.8574	-0.4193	0.1025	-0.3168	0.2444	0.2239
C13 - H27	0.2818	-0.9607	-0.3244	0.0421	-0.2823	0.1298	0.0291
C14 - C16	0.3087	-0.8547	-0.4174	0.1019	-0.3155	0.2440	0.2203
C14 - H28	0.2818	-0.9607	-0.3244	0.0421	-0.2823	0.1298	0.0292
C15 - H29	0.2801	-0.9572	-0.3178	0.0392	-0.2785	0.1235	0.0173
C16 - H30	0.2813	-0.9659	-0.3181	0.0383	-0.2798	0.1204	0.0172
C17 - H31	0.2854	-0.9874	-0.3199	0.0365	-0.2834	0.1142	0.0237
C17 - H32	0.2841	-0.9787	-0.3188	0.0371	-0.2817	0.1163	0.0243
C18 - H33	0.2841	-0.9785	-0.3188	0.0371	-0.2817	0.1163	0.0243
C18 - H34	0.2854	-0.9872	-0.3199	0.0365	-0.2833	0.1142	0.0237
C7 - C13	0.2997	-0.8095	-0.3931	0.0954	-0.2977	0.2426	0.2172
C7 - C14	0.3001	-0.8114	-0.3946	0.0959	-0.2987	0.2430	0.2189
C8 - C12	0.2306	-0.4840	-0.2288	0.0539	-0.1749	0.2356	0.0368
C8 - C9	0.2496	-0.5833	-0.2625	0.0584	-0.2042	0.2223	0.0422
C8 - H20	0.2762	-0.9210	-0.3133	0.0415	-0.2718	0.1325	0.0070
C8 - H21	0.2739	-0.9064	-0.3126	0.0430	-0.2696	0.1376	0.0078
C9 - C15	0.3070	-0.8467	-0.4111	0.0997	-0.3114	0.2425	0.2102
C9 - C16	0.3071	-0.8467	-0.4116	0.1000	-0.3117	0.2429	0.2125
Cl1 - C17	0.1686	-0.1849	-0.1591	0.0564	-0.1027	0.3547	0.0067
Cl2 - C18	0.1687	-0.1852	-0.1592	0.0564	-0.1027	0.3546	0.0066
H23 - H27	0.0139	0.0544	-0.0087	0.0111	0.0025	1.2825	0.7384
H25 - H28	0.0139	0.0543	-0.0087	0.0111	0.0025	1.2828	0.7486
N5 - C10	0.2623	-0.6827	-0.4175	0.1234	-0.2941	0.2956	0.0482
N5 - C11	0.2622	-0.6823	-0.4174	0.1234	-0.2940	0.2957	0.0482
N5 - C7	0.2916	-0.8053	-0.5407	0.1697	-0.3710	0.3138	0.1153
N6 - C12	0.2656	-0.6845	-0.3783	0.1036	-0.2747	0.2739	0.0532
N6 - H35	0.3362	-1.5132	-0.4963	0.0590	-0.4373	0.1189	0.0492
N6 - H36	0.3368	-1.4872	-0.4934	0.0608	-0.4326	0.1232	0.0499
O3 - C19	0.3001	-0.4745	-0.7506	0.3160	-0.4346	0.4210	0.0324
O3 - H37	0.3581	-2.4988	-0.7577	0.0665	-0.6912	0.0878	0.0167
O4 - C19	0.4173	-0.1744	-1.3767	0.6666	-0.7102	0.4842	0.0737
RCP ^a	$\rho(r)$ (a.u)	$\nabla^2\rho(r)$ (a.u)	$V(r)$ (a.u)	$G(r)$ (a.u)	$H(r)$ (a.u)	$-(G/V)$	ϵ
R1	0.0215	0.1560	-0.0243	0.0316	0.007	1.300	-
R2	0.0135	0.0666	-0.01040	0.0135	0.003	1.298	-
R3	0.0134	0.0664	-0.01037	0.01349	0.003	1.301	-

^a [R1- RCP1 (C7 C13 C15 C9 C16 C14); R2 – RCP2 (N5 C7 C13 H27 H23 C10); R3- RCP3 (N5 C7 C14 H28 H25 C11)]

done using the Gaussian 09W desktop programme and DFT at the B3LYP/6-311++G(d,p) level basis set [26]. The vibrational frequencies of the optimized molecule were evaluated at the same theoretical level, and the scaled wavenumbers were obtained by applying the standard scaling factor of 0.96 [27]. PED prediction was performed using the VEDA programme [28]. TD-DFT methodology in the gas phase, ethanol, chloroform, DMSO, methanol, and water was used to detect the electronic excitations of the title chemical. Moreover, the Multiwfn 3.6 tool was used to analyze the solvent effect on the ESP surface map as well as the topological properties of the ELF, LOL, RDG, and AIM studies [29]. Before Molecular docking, the title molecule's lower energy structure was designed then it was saved as a single document in PDB format using the PyMol programme [30]. The selected protein (PDB code: 4FVR, 3WIX & 5UUT) was then downloaded in PDB format from the online tool, then docking was performed by Autodock tools 1.5.6 [31].

3. Results and discussion

3.1. Molecular geometry

The compound **4B2CA-LPA** has the C1 point group and the chemical formula is C₁₃H₁₈Cl₂N₂O₂. In this present work, the optimized structure of the compound was obtained by DFT at the B3LYP level and the 6-

311++G(d,p) basis set [32]. This ideal structure was found by the lowest global minimum energy of -1686.85890 Hartree (-2.6882 kcal/mol) with dipole moment 1.5384557 Debye and it was shown in Fig. 1. For the comparison of theoretical values of bond length and bond angles as the structure of the compound **4B2CA-LPA** was not studied through XRD crystal investigations, hence we selected two structurally similar compound's parameters, which are listed in Table 1 [33,34]. As per the optimized result, the longest bond distance 1.817 Å, was calculated for Cl1-C17 & Cl2-C18 because the heavier chlorine molecule was attached at positions Cl1 and Cl2 and since these bonds are considered to be the weakest site in this molecule, which are good agreement with literature values (1.787 & 1.807 Å). Usually, the Cl-C bond range is 1.77-1.78 Å however, it is significantly longer and the calculated adjacent C-C bonds (C10-C17 & C11-C18) are consequently shorter (1.531 Å) because of the electronegativity difference between the atoms. Similar to this, the strongest calculated bonds in the molecule were found at O3 and C19, which had a dual attachment between them, hence the shortest distance for O3-H37 & O4-C19 are 0.97 & 1.207 Å respectively, which is also consistent with the values of literature (1.006 & 1.228 Å). This carbonyl and hydroxyl (C=O, CO & OH) groups with one aromatic ring combine to form an L-phenylalanine group in the title chemical **4B2CA-LPA**. Moreover, the important calculated nitrogen attached bonds are N5-C7, N5-C10, N5-C11, N6-C12, N6-H35, and

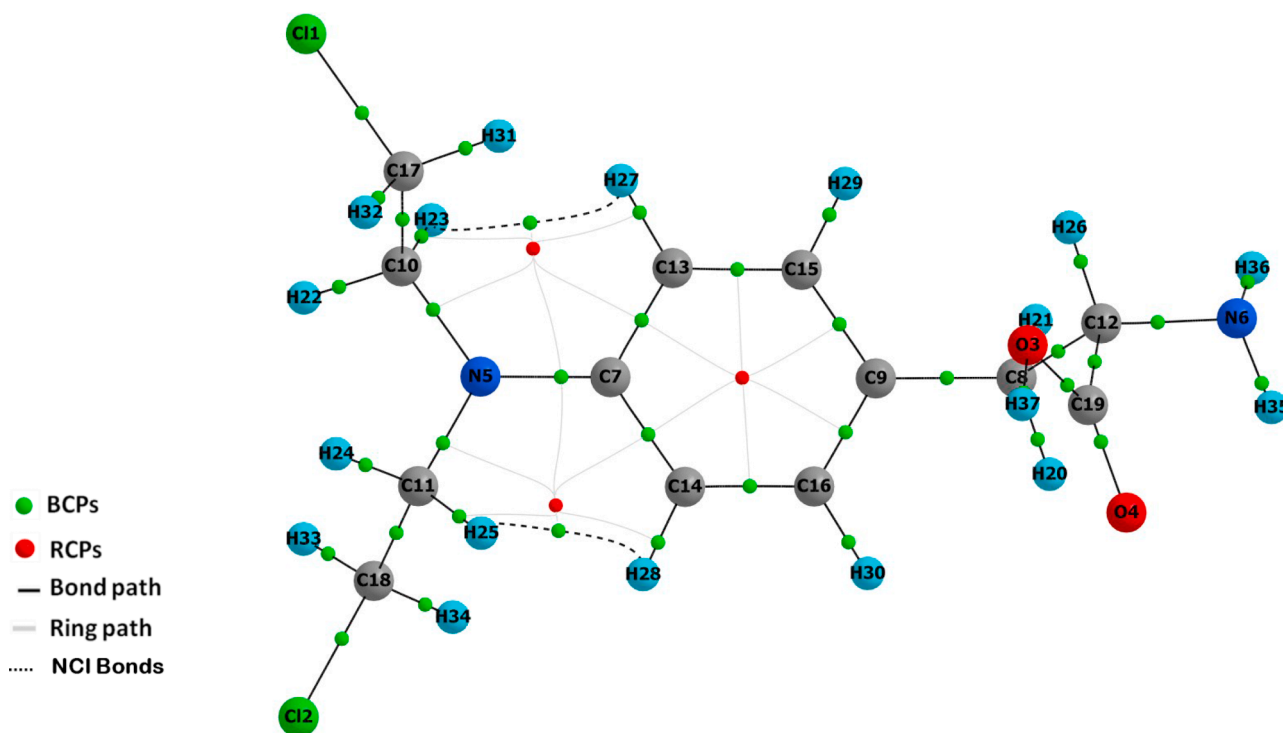


Fig. 2. AIM Molecular graph of **4B2CA-LPA**: green tiny spheres (BCPs), small red spheres (RCPs), black lines (bond paths), ash color solid lines (RCP to BCP ring path), and black dotted lines (non-covalent interactions (NCI)) are illustrated in this figure.

N6-H36 with distances 1.399, 1.455, 1.455, 1.463 1.016 and 1.015 Å respectively, while the CC bonds in the benzene ring are C9-C15, C9-C16, C13-C15, C14-C16, C7-C13 C7-C14 of 1.398, 1.397 1.39, 1.391 1.41 and 1.409 Å respectively.

The 2-chloroethyl chains from N5 are stretched and separate from one another between the N5-C10 and N5-C11 bonds, with the distance found between Cl1 and Cl2 being 6.699 Å and the angle of C11-N5-C10 being 116.9°. Most of the bond angle values are very close to those that are frequently seen in structures with similar compound structures, therefore extensive discussion is not required.

3.2. Topological analysis

3.2.1. AIM analysis

Table 2 shows the **4B2CA-LPA** parameters for all BCPs in the compounds under study. Fig. 2 exhibits the atomic diagram of **4B2CA-LPA** as illustrated in this figure ring critical points RCP's (in a small sphere in red color), bond routes (in black color solid lines for covalent; and black color dotted lines for non-covalent paths), bond critical points BCP's (in green color small spheres with $\nabla^2\rho(r)$ values mentioned) [35,36]. As a result, BCPs H23...H27 and H25...H28 are subsequently formed as intramolecular hydrogen bonds in the molecular surface during optimization, and they can be identified by their positive $\nabla^2\rho(r)$ values (0.0544 & 0.0543 a.u.) and lowest $\rho(r)$ values (0.0139 & 0.0139 a.u.). Other BCPs are identified as covalent bonds by the range of $\rho(r)$ (0.1686 to 0.4173 a.u.) and all negative (-2.4988 to -0.1744) values of $\nabla^2\rho(r)$. Moreover, this AIM result shows that O4=C19 ($\rho(r)$ = 0.4173 a.u.) has the highest computed electron density while H2-H27 and H25-H28 (ϵ = 0.7486 & 0.7384 a.u.) had the highest degree of electron distribution asymmetry. This may be because of the non-covalent (intramolecular hydrogen) bonds that were formed at these BCPs. In this case, three RCPs (ring critical points) were also found at R1(C7 C13 C15 C9 C16 C14), R2 (N5 C7 C13 H27 H23 C10) and R3 (N5 C7 C14 H28 H25 C11) with positive $\nabla^2\rho(r)$ (0.1560, 0.0666, & 0.0664 a.u.) and $\rho(r)$ (0.0215, 0.0135 & 0.0134 a.u.) values respectively. According to this result, the

higher values of $\nabla^2\rho(r)$ & $\rho(r)$ of R1 in comparison to the other two RCPs indicate the strongest repulsive steric effect in this aromatic ring, and it was confirmed by the RDG-NCI investigation.

3.2.2. LOL and ELF studies

Fig. 3 (a-d) shows color-filled and contour line maps of ELF and LOL of the chemical **4B2CA-LPA** respectively. A high value (or red color region) in that area denotes a strong localization of electrons caused by the presence of a nuclear shell [36]. In the present case, the maximum ELF regions are seen at H28 & H26 and show the localized electron bind between the atoms regions. The blue regions around a few atoms of chlorine and carbon atoms of Cl1, Cl2 & C11, show the delocalized electron cloud around it.

From Fig. 3(b) & (d), ELF & LOL contour map with gradient lines conveys a more definite and clearer picture of **4B2CA-LPA** whether the electron depletion region with dark blue circles at Cl1, & Cl2. Since the strongest delocalization regions are around Cl1-C17-C10 and Cl2-C18-C11 and they are visualized in Fig. 4 (a & b) respectively.

3.2.3. RDG-NCI analysis

The red peaks at 0.05 to 0.23 a.u. in Fig. 5 (a) demonstrate the existence of strong steric repulsion influences at the center of the aromatic ring of the title molecule, while the green spikes at closely -0.01 a.u. is a clear indication that the interactions of van der Waals forces between the atoms H28 & H38 and NH₂ increase the compound's stability. By demonstrating the strong attraction of two hydrogen-hydrogen interactions (H23...H27 and H25...H28) the dark green with slit blue color spikes at -0.016 a.u improve the compound's stability and significant biological affinity. Additionally, the existence of weak contacts was confirmed in this investigation by Fig. 5 (b), which shows circular slabs with colored green, red, and dark green with blue among the atoms

3.3. Vibrational assignment

Vibrational spectra have been used to identify the **4B2CA-LPA**

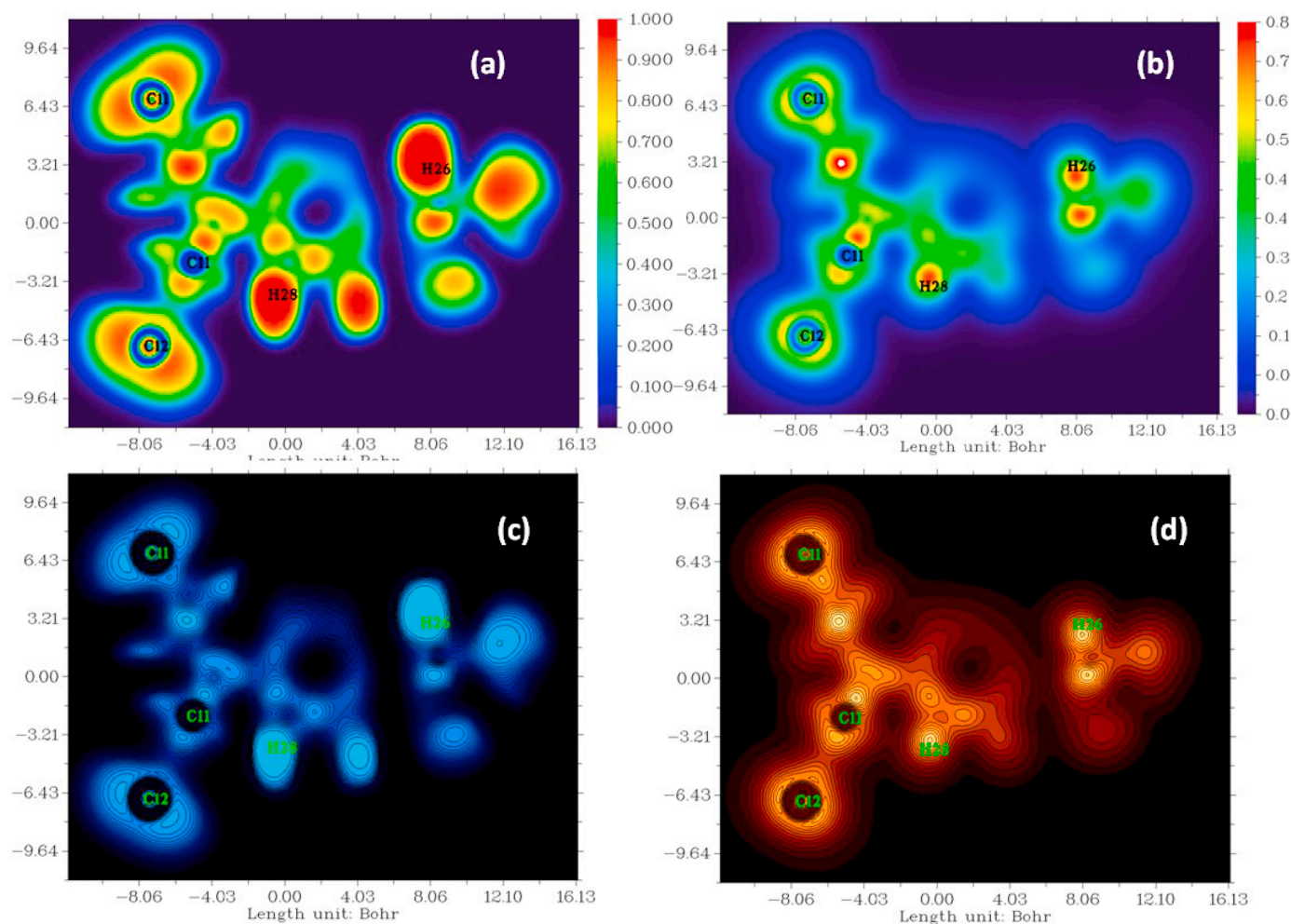


Fig. 3. (a) Electron localization function (ELF) map, (b) Localized orbital locator (LOL) map (c) contour surface of ELF, and (d) contour surface of LOL for the 4B2CA-LPA in the gas phase.

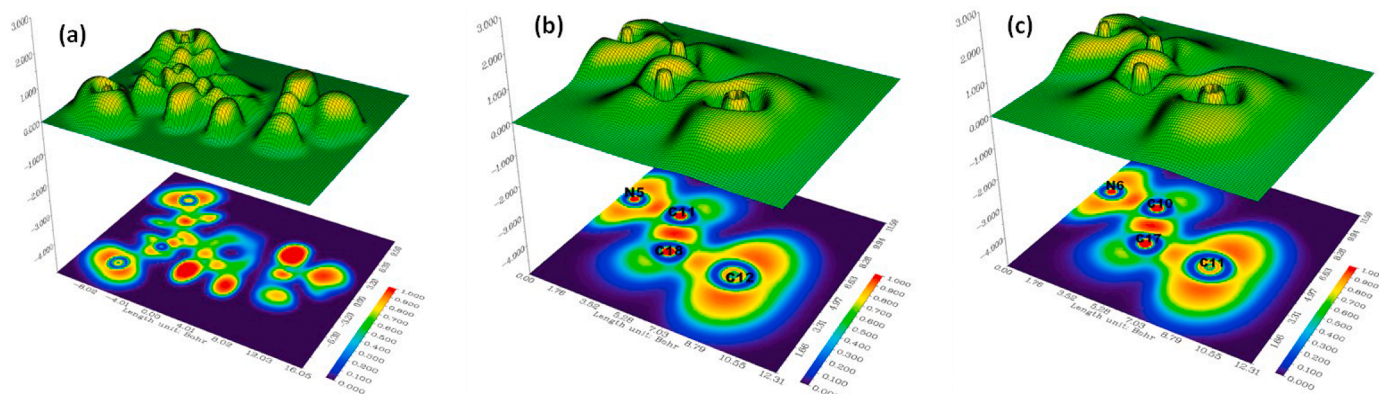


Fig. 4. The ELF map with an electronic environment shows that the highest delocalization region (a) entire molecule (b) C12-C18-C11 (c) C11-C17-C10 of 4B2CA-LPA.

molecule's functional groups in this study. For gaseous phases with the same optimization basis level, theoretical Raman and IR spectra of 4B2CA-LPA were calculated [37,38] and are shown in Fig. 6. The molecule has 37 atoms and 45 normal modes of fundamental vibrations. The calculated vibrational frequencies were scaled using a scaling factor of 0.96 for all unscaled wavenumbers of 3744 to 18 cm^{-1} [25], and the corresponding assignment with PED values is given in Table 3.

The different modes of OH stretching vibrations generally appear

between 3200 and 3650 cm^{-1} [39]. In this case, the calculated IR spectrum bands in the molecule identified at 3594 cm^{-1} and have 100% PED (mod no. 105) contribution. NH stretching typically varies from 3500 to 34000 cm^{-1} [40]. The N6-H36 & N6-H35 atoms, which have 3438, and 3357 cm^{-1} and a potential energy distribution of 100% for both (mode no. 103 & 104) are the cause of the stretching vibration of the amine (NH_2). Typically, the functional group C=O arises between 1850 and 1550 cm^{-1} . [41]. In this instance, the carbon atom C19

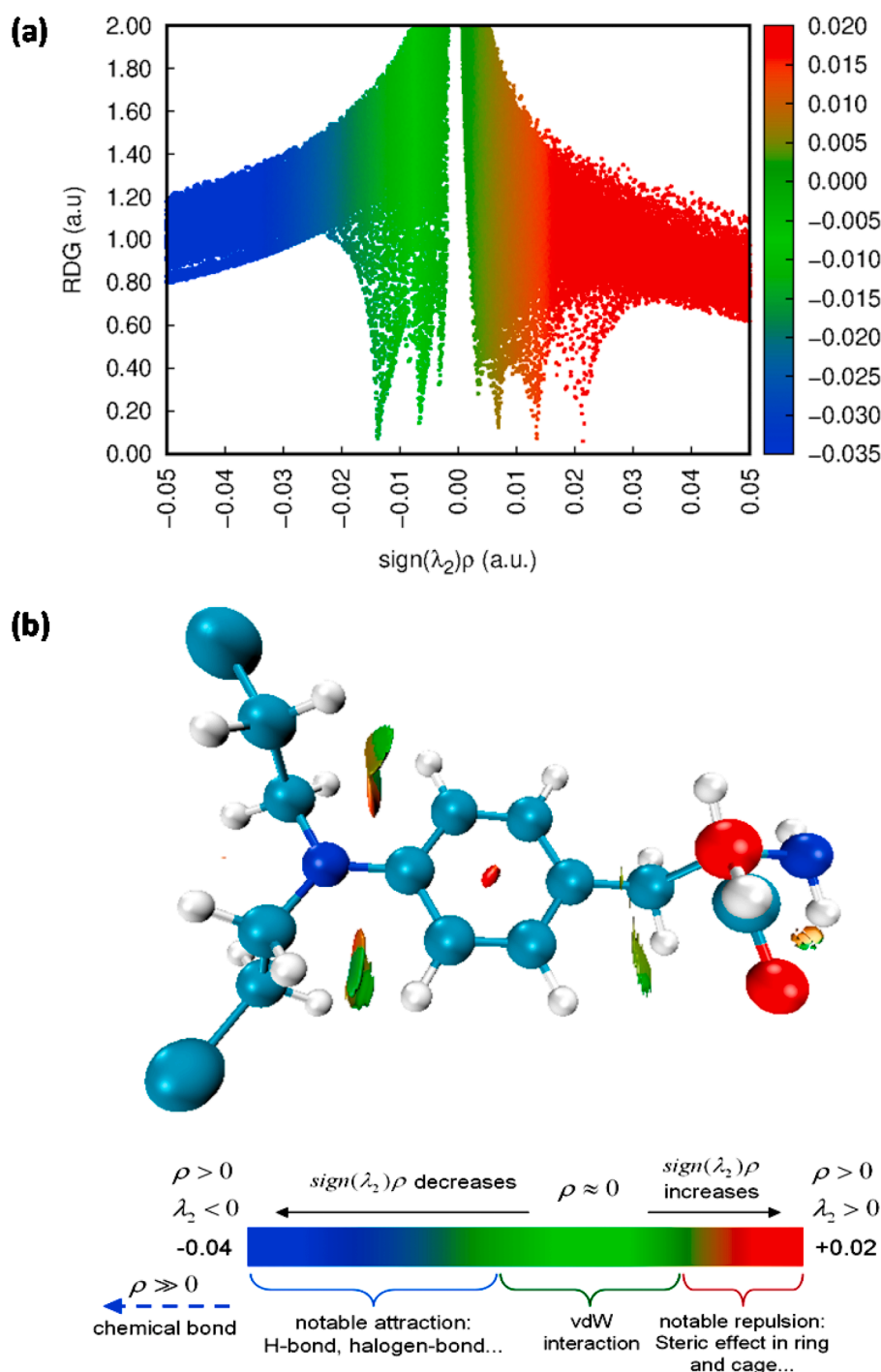


Fig. 5. RDG Plots versus the electron density ρ multiplied by the sign of λ_2 of the title compound in the gas phase.

produced a double bond with the oxygen atom O4 at a current stretching vibration of 1735 cm^{-1} with a contribution from PED of 82% (mode no. 87). In vibrational analysis, the C-O stretching phase was usually found between 1180 and 989 cm^{-1} . With maximum PED 56%, **4B2CA-LPA** (CO) stretching was seen at 1153 , 1104 , 1033 & 991 cm^{-1} (mode no. 59, 56, 53, & 51).

Aromatic compounds exhibit C-H stretching vibrations between 3000 and 3100 cm^{-1} and 3280 and 3340 cm^{-1} [42,43]. In this work, these vibrations were found at 3074 , 3073 , & 3036 cm^{-1} with PED contribution 100% for all (mode no. 102-100). The CH_2 stretching was also found at 3029 , 3028 , 3026 , 2973 , 2971 , 2968 , 2967 , 2961 , 2943 , 2936 , and 2928 cm^{-1} with PED contributions 100%, 100%, 52%, 98%,

100%, 100%, 57%, 57%, 100%, 100% (mode no. 99-88). The C-C harmonic stretching in aromatic compounds between 1650 and 800 cm^{-1} has been reported [44].

Evidence of possible $\text{C}=\text{C}_{\text{ring}}$ stretching in this title molecule at 1441 , 1428 , 1181 , 987 , & 984 cm^{-1} with PED contribution of 56%, 58%, 33%, 45%, & 52% (mode no. 81, 80, 61, 50 & 49) was calculated. The actual C-C-C bending vibrations mode has drawn attention in this study, and the maximum PED for CC vibrations is predicted to be 46%. Although stretching harmonics (CH) also contribute, their effects are less noticeable than those of (CC). These have a smaller PED rapport but influence C-C stretching. It follows that molecule vibrating modes were not at all affected by other vibrational modes since all reasonable frequency

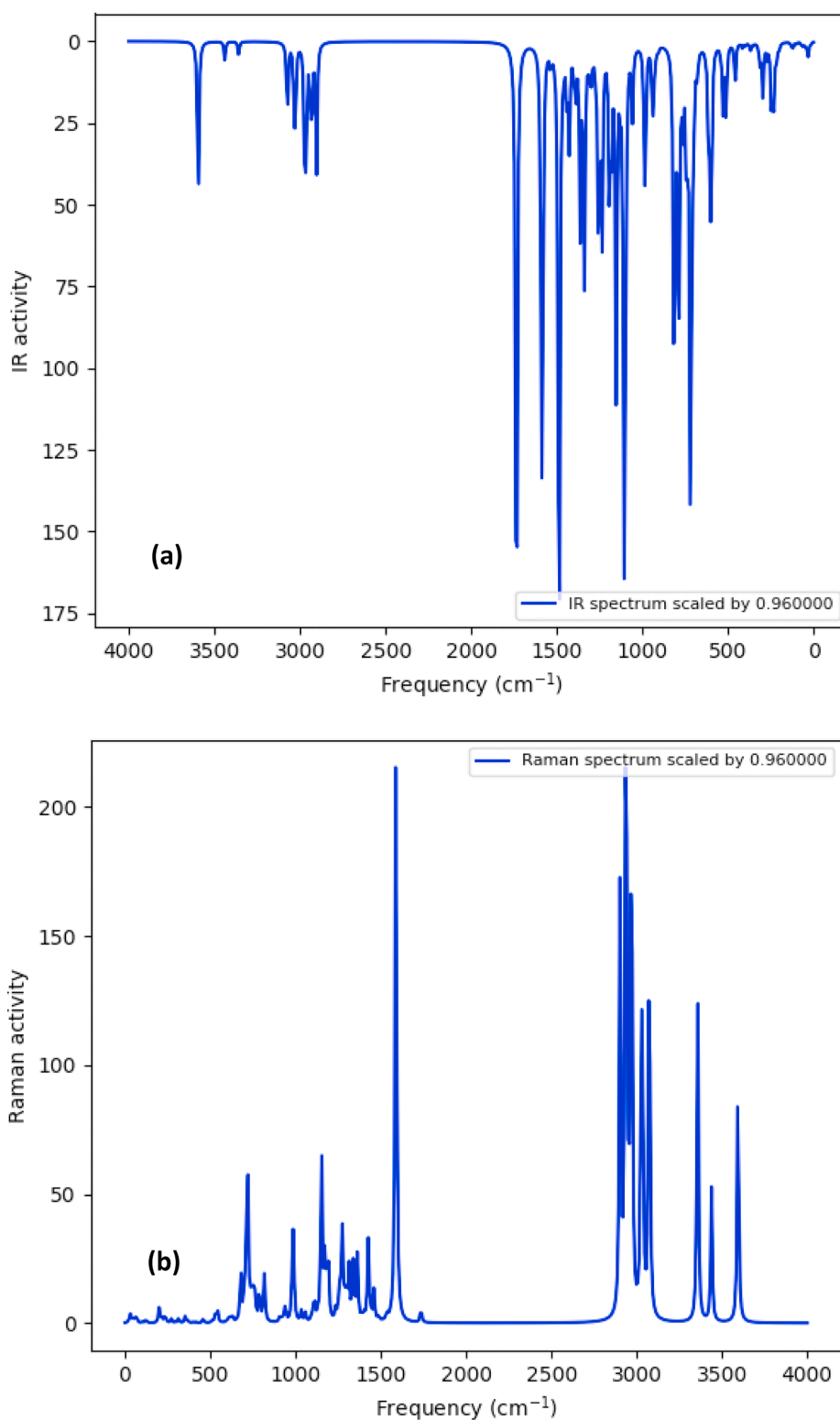


Fig. 6. Theoretical spectra of (a) IR spectrum (b) Raman spectrum of 4B2CA-LPA.

modes remained within the most expected range.

The C-N vibrations can be seen between 1670 and 1600 cm^{-1} [45], but in the presently calculated at 1255 & 1058 cm^{-1} PED values are 62%, & 11% (modes no. 66 & 54). Since a reduction in molecular symmetry and the presence of heavy atoms on the material's 4B2CA-LPA enable frequency coupling possible, it is important to take into account the vibrations associated with the link between the carbon atoms of two

CH_2 and two halogen atoms (Cl) in this situation. Usually, wide bands are produced by the C-Cl stretching mode in the range of 710 - 505 cm^{-1} and this case at 702 & 679 cm^{-1} with PED values of 40%, & 41% (mode no. 33 & 32).

Table 3

Vibrational frequencies (cm^{-1}) with assignment, IR intensities (I_{IR} ; km mol^{-1}), Raman scattering activities (S_{Raman} ; $\text{A}^4\text{amu}^{-1}$) of 4B2CA-LPA were calculated using B3LYP/6-311++G(d,p) basis set in the gas phase.

Mode no.	DFT/B3LYP/6-311++G(d,p)				Vibrational Assignment [% PED] ^b
	Freq. Unscale ^a	Freq. Scaled	I_{IR}	S_{Raman}	
105	3744	3594	55.42	106.46	105 $\nu_{\text{OH}}(100)$
104	3582	3438	5.71	52.77	104 $\nu_{\text{asy}}\text{NH}_2(100)$
103	3497	3357	4.28	134.11	103 $\nu_{\text{sy}}\text{NH}_2(100)$
102	3202	3074	11.39	135.81	102 $\nu_{\text{ring}}\text{CH}(100)$
101	3201	3073	13.83	41.71	101 $\nu_{\text{ring}}\text{CH}(100)$
100	3162	3036	8.67	60.93	100 $\nu_{\text{ring}}\text{CH}(100)$
99	3155	3029	9.93	15.43	99 $\nu_{\text{asy}}\text{CH}_2(100)$
98	3154	3028	0.79	35.79	98 $\nu_{\text{asy}}\text{CH}_2(99)$
97	3152	3026	19.02	70.42	97 $\nu_{\text{ring}}\text{CH}(46)+\nu_{\text{asy}}\text{CH}_2(52)$
96	3097	2973	2.21	80.08	96 $\nu_{\text{sy}}\text{CH}_2(100)$
95	3095	2971	32.72	6.02	95 $\nu_{\text{sy}}\text{CH}_2(100)$
94	3091	2968	11.89	95.49	94 $\nu_{\text{sy}}\text{CH}_2(98)$
93	3090	2967	2.37	34.13	93 $\nu_{\text{asy}}\text{CH}_2(100)$
92	3085	2961	19.18	16.83	92 $\nu_{\text{CH}}(41)+\nu_{\text{asy}}\text{CH}_2(57)$
91	3065	2943	2.39	73.64	91 $\nu_{\text{CH}}(41)+\nu_{\text{asy}}\text{CH}_2(57)$
90	3059	2936	16.11	227.67	90 $\nu_{\text{sy}}\text{CH}_2(100)$
89	3050	2928	18.51	15.83	89 $\nu_{\text{sy}}\text{CH}_2(100)$
88	3024	2903	40.78	170.80	88 $\nu_{\text{sy}}\text{CH}_2(100)$
87	1808	1735	251.78	5.87	87 $\nu_{\text{C=O}}(82)$
86	1655	1589	129.38	237.40	86 $\nu_{\text{CC}}(68)+\beta\text{HCC}(20)$
85	1646	1580	50.90	5.88	85 $\beta\text{HNNH}(33)+\beta\text{HCC}(21)$
84	1600	1536	5.62	2.65	84 $\nu_{\text{CC}}(68)+\beta\text{HCO}(22)$
83	1548	1486	250.81	2.07	83 $\nu_{\text{CC}}(80)+\beta\text{HCC}(10)$
82	1521	1460	2.43	12.47	82 $\beta\text{HNNH}(36)+\beta\text{HCC}(51)$
81	1501	1441	16.11	1.87	81 $\nu_{\text{C=C}}(56)+\beta\text{CH}(22)+\beta\text{NH}(20)$
80	1488	1428	8.56	15.31	80 $\nu_{\text{C=C}}(58)+\beta\text{CH}(18)$
79	1486	1426	17.24	11.12	79 $\text{CH}_2\text{scis}(67)$
78	1484	1424	6.29	8.76	78 $\text{CH}_2\text{scis}(77)$
77	1460	1401	4.77	2.44	77 $\text{CH}_2\text{scis}(78)$
76	1448	1390	17.83	1.93	76 $\text{CH}_2\text{scis}(37)$
75	1420	1363	56.55	25.64	75 $\text{CH}_2\text{twist}(32)+\beta\text{CH}(56)$
74	1395	1340	72.14	21.54	74 $\text{CH}_3\text{twist}(28)+\beta\text{CH}(29)$
73	1389	1333	4.73	3.13	73 $\text{CH}_2\text{twist}(40)$
72	1368	1314	2.84	21.03	72 $\text{CH}_3\text{twist}(38)$
71	1357	1302	12.49	4.37	71 $\beta_1\text{CH}_{\text{ring}}(28)$
70	1348	1294	2.81	11.84	70 $\text{CH}_2\text{twist}(29)+\beta\text{CH}(46)$
69	1328	1275	4.68	34.98	69 $\beta\text{NCO}(62)+\beta\text{CH}(23)$
68	1317	1265	4.33	8.05	68 $\text{CH}_2\text{wag}(78)$
67	1310	1258	4.44	4.60	67 $\text{CH}_2\text{wag}(48)+\beta\text{CH}(29)+\beta\text{NCO}(10)$
66	1307	1255	68.25	6.20	66 $\nu_{\text{CN}}(62)+\beta\text{CH}(32)+\beta\text{NCO}(26)$
65	1288	1237	28.50	2.62	65 $\text{CH}_2\text{wag}(87)+\beta\text{CH}(11)$
64	1287	1235	36.04	2.23	64 $\text{CH}_2\text{wag}(59)+\beta\text{CH}(12)$
63	1243	1194	35.24	1.87	63 $\beta\text{CH}(26)+\beta\text{CCO}[28]$
62	1241	1191	11.13	26.30	62 $\beta\text{CCC}(28)+\beta\text{CH}(12)$
61	1230	1181	33.62	7.53	61 $\text{CH}_2\text{twist}(62)+\nu_{\text{C=C}}(33)$
60	1220	1172	0.78	22.86	60 $\text{CH}_2\text{rock}(48)+\beta\text{CH}(18)$

Table 3 (continued)

Mode no.	DFT/B3LYP/6-311++G(d,p)				Vibrational Assignment [% PED] ^b
	Freq. Unscale ^a	Freq. Scaled	I_{IR}	S_{Raman}	
59	1201	1153	119.07	69.63	59 $\nu_{\text{CO}}(22)+\beta\text{HCO}(24)$
58	1176	1129	10.48	2.17	58 $\text{CH}_2\text{wag}(66)+\beta\text{CH}(38)$
57	1157	1111	38.72	8.90	57 $\text{CH}_2\text{wag}(58)+\beta\text{NH}(39)$
56	1150	1104	174.89	1.83	56 $\nu_{\text{CO}}(14)+\beta\text{HCC}(10)$
55	1140	1095	14.78	1.97	55 $\beta\text{COH}(68)+\beta\text{CH}(24)$
54	1102	1058	21.35	3.45	54 $\nu_{\text{CN}}(11)+\tau\text{HCCC}(10)$
53	1076	1033	0.04	4.30	53 $\nu_{\text{CO}}(19)+\beta\text{HCO}(16)$
52	1033	991	10.21	1.92	52 $\text{CH}_2\text{wag}(55)+\beta\text{CH}(33)$
51	1031	990	0.63	11.87	51 $\nu_{\text{CO}}(56)+\beta\text{NH}(32)+\beta\text{CH}(11)$
50	1028	987	1.97	0.38	50 $\nu_{\text{C=C}}(45)+\beta\text{CH}(26)$
49	1025	984	29.57	25.99	49 $\nu_{\text{C=C}}(52)+\beta\text{NH}(22)+\beta\text{CH}(36)$
48	1023	982	15.00	6.72	48 $\beta_0\text{CH}_{\text{ring}}(32)$
47	980	940	24.95	6.86	47 $\beta_0\text{CH}_{\text{ring}}(28)$
46	968	929	5.44	0.67	46 $\beta\text{CCC}_{\text{ring}}(50)+\beta\text{CH}(29)$
45	962	924	1.08	1.12	45 $\text{CH}_3\text{ rock}(32)$
44	947	909	1.99	2.59	44 $\beta_0\text{CH}_{\text{ring}}(56)$
43	851	817	75.75	18.03	43 $\beta_0\text{CH}_{\text{ring}}(32)$
42	842	809	52.86	1.40	42 $\beta_0\text{CH}_{\text{ring}}(28)+\text{CH}_2\text{ rock}(32)$
41	822	789	94.06	12.87	41 $\text{CH}_2\text{ rock}(53)$
40	817	785	13.19	0.43	40 $\text{CH}_3\text{ rock}(56)$
39	796	764	24.82	5.21	39 $\nu_{\text{CO}}(44)+\beta\text{HCC}(10)$
38	788	757	0.66	12.91	38 $\text{CH}_2\text{ rock}(58)$
37	775	744	13.74	3.58	37 $\beta_0\text{CH}_{\text{ring}}(12)+\beta\text{CHH}(25)$
36	772	741	32.42	8.91	36 $\beta_0\text{CH}_{\text{ring}}(28)+\beta\text{CH}(18)$
35	752	721	87.94	31.14	35 $\beta_0\text{CH}_{\text{ring}}(19)$
34	747	717	87.37	44.20	34 $\text{CH}_3\text{ rock}(28)+\beta_0\text{CH}_{\text{ring}}(21)$
33	732	702	31.82	13.89	33 $\nu_{\text{CCl}}(40)+\beta\text{HNNH}(36)+\beta\text{HCC}(21)$
32	708	679	7.65	19.98	32 $\nu_{\text{CCl}}(41)+\beta\text{HNNH}(48)+\beta\text{HCC}(18)$
31	656	629	1.32	2.89	31 $\beta\text{CCC}_{\text{ring}}(68)+\beta\text{CNH}(21)$
30	639	613	38.79	2.46	30 $\beta\text{NH}(18)+\beta\text{CH}(70)$
29	623	598	65.54	0.70	29 $\beta\text{NH}(11)+\beta\text{CH}(80)$
28	565	542	1.54	5.60	28 $\beta\text{HCN}(60)+\beta\text{NH}(11)$
27	552	529	20.22	2.70	27 $\text{NH}_2\text{wag}(68)+\beta\text{OH}(22)$
26	532	511	23.93	0.79	26 $\beta\text{CH}(12)+\beta\text{NHH}(60)$
25	478	459	13.06	1.60	25 $\beta\text{COH}(12)+\beta\text{CNC}(48)$
24	434	416	1.49	0.35	24 $\text{CH}_2\text{rock}(23)+\beta\text{CH}_{\text{ring}}(22)$
23	416	399	0.95	0.32	23 $\text{NH}_2\text{rock}(78)+\beta\text{COH}(11)$
22	386	370	2.40	0.71	22 $\text{NH}_2\text{rock}(68)+\beta\text{COH}(32)$
21	369	354	0.78	2.86	21 $\text{NH}_2\text{rock}(58)+\beta\text{COH}(12)$
20	328	314	6.88	1.78	20 $\beta\text{CH}_{\text{ring}}(20)+\beta\text{CHHC}(16)$
19	309	297	16.24	0.28	19 $\beta\text{CNC}(58)+\beta\text{COH}(22)$

(continued on next page)

Table 3 (continued)

Mode no.	DFT/B3LYP/6-311++G(d,p)				Vibrational Assignment [% PED] ^b
	Freq. Unscale ^a	Freq. Scaled	I _{IR}	S _A Raman	
18	284	272	4.23	1.51	18 β CCO(54)+ β CHring(18)
17	258	247	18.64	0.17	17 β HCCH(40)+ β OCO(20)
16	248	238	9.78	1.60	16 β CO(44)+ β CHring(15)
15	242	233	14.19	1.37	15 β CCCring(58)+ β CCC(25)
14	228	219	3.53	1.00	14 β CCH(42)+ β CNO(17)
13	222	213	1.93	1.31	13 β CHring(42)
12	209	201	1.37	5.73	12 β CO(48)+ β CHring(28)
11	136	131	0.92	0.31	11 β CO(38)+ β CHring(28)
10	127	122	1.91	1.04	10 β CH ₂ (22)+ β CHring(10)
9	106	102	0.66	0.45	9 β CCN(28)+ β CNH(22)
8	74	71	0.71	1.21	8 β CO(21)+ β CHring(47)
7	64	61	1.30	2.25	7 β CCCring(68)
6	51	49	0.72	1.00	6 β CH(15)+ β OH(12)
5	37	36	0.38	1.45	5 β CNH(11)+ β CHring(13)
4	35	34	4.43	0.89	4 β CO(25)+ β CHring(22)
3	32	31	0.36	1.81	3 β CCN(34)+ β CNH(12)
2	25	24	0.21	0.26	2 β CHCring(38)+ β COH(26)
1	18	17	0.55	0.25	1 β CCN(11)+ β CNH(22)

^a [Scaling factors of 0.96 are used to scale down calculated wavenumbers for all frequencies]

^b [% PED- Percentage of potential energy distribution; ν -stretching, ν_{sy} -symmetric stretching, ν_{asy} -asymmetric stretching, β -bending, scis-scissoring, wag-wagging, twist-twisting, rock-rocking & τ - torsion].

3.4. FMOs analysis: HOMO-LUMO energy prediction

The 4B2CA-LPA molecule's pharmacokinetics and stabilization can be understood by using energy values of filled and empty orbitals (HOMO & LUMO). Soft chemicals are compounds with a narrow FMO

band gap and high chemical excitability [46]. To explore 4B2CA-LPA better, the effect of the solution was studied in this instance. Fig. 7 and Table 4 provide an understanding of the spectral gap (ΔE) with different solvents. The band gap energies of various solvents are 4.9781, 4.9441, 4.9463, and 4.9420 eV, whereas the chemical potential differences in solvents are -3.1808, -3.1630, -3.1635, and -3.1627 eV (for chloroform, DMSO, methanol, and water, respectively) indicating that the molecule is significantly more reactive in water compared to other solutions. This was determined by the discovery of the minimum energy in the water phase. For chloroform, DMSO, methanol, and water, respectively, the softness energies are 0.2009, 0.2023, 0.2022, and 0.2023 eV; the hardness 2.4891, 2.4721, 2.4732, & 2.4710 eV. Since the 4B2CA-LPA was less harmful in these phases because DMSO and water had the highest levels of softness and minimal hardness, demonstrating the compound's good biological properties.

3.5. MEP analysis

The MEP prediction predicted the comparative reactivity sites of a molecule for electrophilic and nucleophilic attacks [47]. Employing the optimized structure was used to calculate the MEP surface analysis in gas and various solvent of chloroform, DMSO, methanol, and water of the 4B2CA-LPA. Fig. 8 shows the mapped ESP surface of the investigated chemical 4B2CA-LPA. The position of nucleophilic, and electrophilic assaults concerning the colors of blue, and red in the range from +100.00 to -100.00 in Fig. 8.

The MEP results indicate that on the surface of molecules, 14 surface maxima (positive values) and 7 surface minima (negative values) were acquired in all phases. The more negative values or minimum electrostatic energies were found at NH₂ (-32.845, 35.34, -36.52, -36.45 & -36.58 kcal/mol) and O4 (-19.115, -34.31, -35.55, -35.49 & -35.62 kcal/mol) regions with red color regions in gas, chloroform, DMSO, methanol, and water respectively. The maximum electrostatic energies or more positive values were found at CH₂ (C8-H20-H-21; 48.642, 51.77, 52.90, 52.85 & 52.95 kcal/mol) with blue regions in gas, chloroform, DMSO, methanol, and water respectively. Since this result shows that the maximum possibility of a strong nucleophilic attack region is NH₂ and among the solvents, water has the highest energy -36.58 kcal/mol compared to other solvents, whereas the maximum possibility of the strongest electrophilic attack region is CH₂ (C8-H20-H-21) and among the solvent, the solvent water has the highest energy 52.95 kcal/mol compared to other solvents.

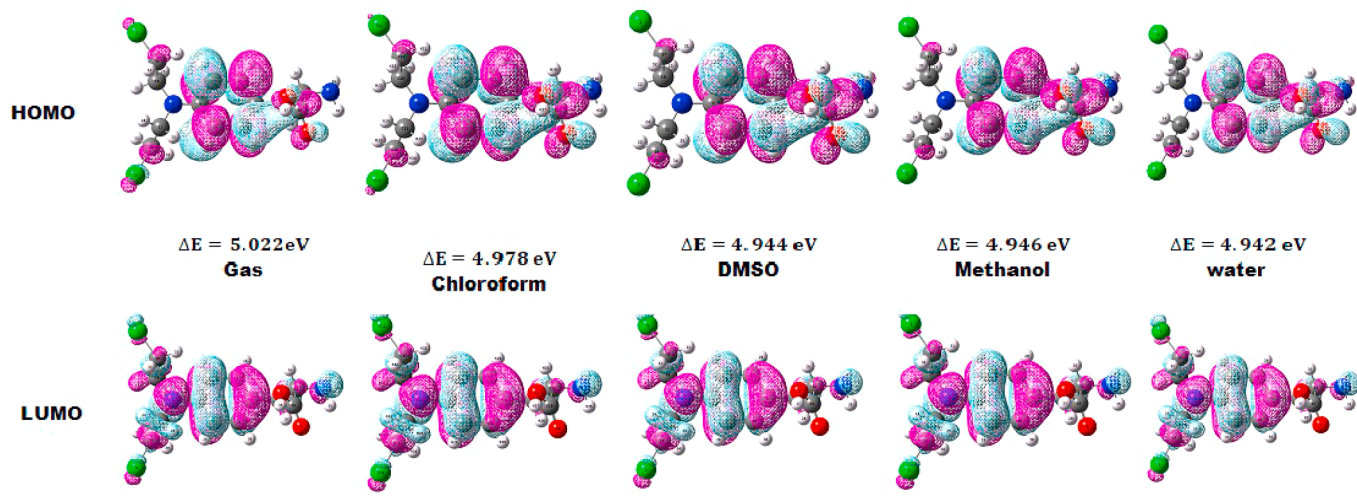
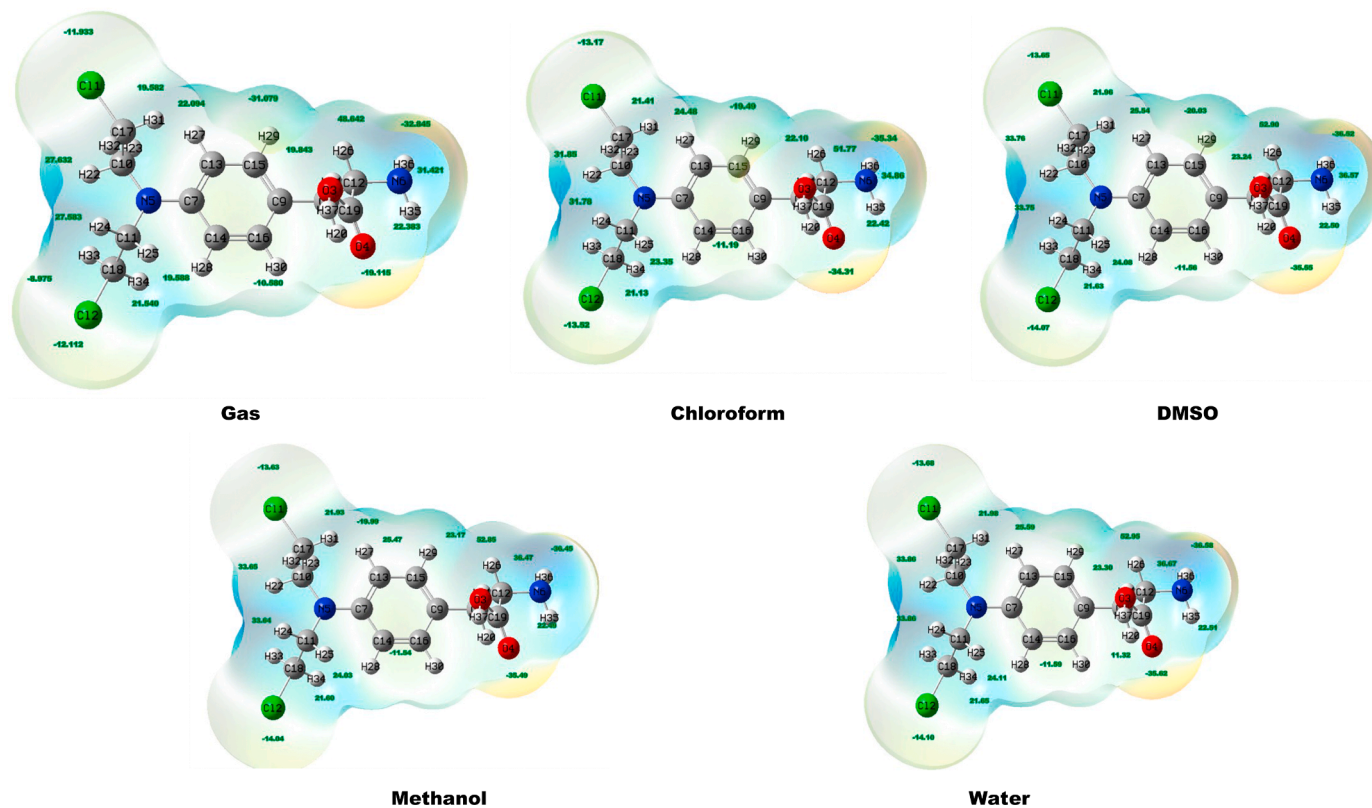


Fig. 7. The Frontier molecular orbitals (HOMOs & LUMOs) in the gas and solvent phases of the title compound.

Table 4

Calculated Frontier Molecular Orbital (FMO) energy parameters (all in eV) highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), Energy gap (ΔE_g), Ionization potential (I_p), Electron affinity (E_a), chemical hardness (η), chemical softness (S), electro negativity (χ), chemical potential (μ), and electrophilicity index (ω) of the title compound in different mediums.

Medium	E_{HOMO}	E_{LUMO}	ΔE	I_p	E_a	η	S	χ	μ	ω
Gas	-5.8175	-0.7956	5.022	5.8175	0.7956	2.5110	0.1991	3.3066	-3.3066	2.1771
Chloroform	-5.6698	-0.6917	4.978	5.6698	0.6917	2.4891	0.2009	3.1808	-3.1808	2.0323
DMSO	-5.6350	-0.6909	4.944	5.6350	0.6909	2.4721	0.2023	3.1630	-3.1630	2.0235
Methanol	-5.6367	-0.6903	4.946	5.6367	0.6903	2.4732	0.2022	3.1635	-3.1635	2.0233
Water	-5.6337	-0.6917	4.942	5.6337	0.6917	2.4710	0.2023	3.1627	-3.1627	2.0240

**Fig. 8.** Molecular Electrostatic Potential (MEP) surface map of 4B2CA-LPA in gas and different solvents phases.**Table 5**

S-order perturbation theory of Fork matrix selected NBO analysis of title compound based on B3LYP/6-311++G(d,p) basis set.

Donor (i)	Acceptor (j)	Type of Transition	Occupancy (ED/e) Donor (i) Acceptor (j)	Energy $E^{(2)a}$ KJ/mol	Energy difference $E(j)-E(i)^b$ a.u	Polarized energy $F(i,j)^c$ a.u
O3-C19	C18-H34	$\sigma-\sigma^*$	1.99531 0.01951	141.6	3.71	0.649
O3-H37	C18-H34	$\sigma-\sigma^*$	1.98695 0.01951	130.7	3.50	0.605
LP(n)N6	C18-H34	LP (n)- σ^*	1.95124 0.01951	75.4	3.00	0.428
LP(n)C12	C18-H34	LP (n)- σ^*	1.99713 0.01951	53.7	3.61	0.395
LP(n)O3	O4-C19	LP (n)- π^*	1.81196 0.20186	49.6	0.32	0.113
LP(n)C12	C18-H34	LP (n)- σ^*	1.97772 0.01951	40.1	3.05	0.312
LP(n)N5	C7-C14	LP (n)- π^*	1.7435 0.42081	39.5	0.27	0.097
LP(n)O3	C18-H34	LP (n)- σ^*	1.97666 0.01951	38.2	3.41	0.322
LP(n)O4	O3-C19	LP (n)- σ^*	1.84924 0.0985	32.7	0.62	0.129
LP(n)O3	C18-H34	LP (n)- σ^*	1.81196 0.01951	30.8	3.08	0.287
LP(n)O4	C18-H34	LP (n)- σ^*	1.97839 0.01951	29.1	3.44	0.283
C9-C16	C13-C15	$\pi-\pi^*$	1.6597 0.34599	23.7	0.28	0.072
C7-C14	C9-C16	$\pi-\pi^*$	1.63867 0.37046	23.2	0.29	0.074
O3-H37	C18-H33	$\sigma-\sigma^*$	1.98695 0.01966	22.0	1.26	0.149

3.6. NBO analysis

The second-order Fock matrix was utilized in the NBO technique to assess the acceptor-donor interactions of 4B2CA-LPA [48]. The

calculated NBO parameters for 4B2CA-LPA are listed in Table 5. From this table, the highest stabilization was found for the transition of $\sigma-\sigma^*$ between the natural bonds of (O3-C19) and (C18-H34) with an energy value of 141.6 kJ/mol. And the next strongest transition identified for

Table 6

Electronic excitations of **4B2CA-LPA** obtained by experimental and TD-DFT/B3LYP/6-311++G(d,p) method.

Medium	TD-DFT/B3LYP/6-311++G(d,p)				Major contribution ^a
	λ_{max} (nm)	Band gap ΔE (eV)	Energy (cm ⁻¹)	Oscillator Strength (f)	
Gas	241.31	5.139	41441	0.2608	H → L+1 (28%), H → L+2 (23%), H → L+3 (16%), H → L+9 (14%)
Chloroform	242.90	5.105	41169	0.3975	H → L+1 (36%), H → L+2 (10%), H → L+3 (10%), H → L+9 (25%)
DMSO	243.02	5.102	41149	0.4135	H → L+1 (49%), H → L+9 (24%)
Ethanol	242.65	5.110	41212	0.3951	H → L+1 (50%), H → L+9 (24%)
Methanol	242.70	5.109	41203	0.3951	H → L+1 (50%), H → L+9 (24%)
Water	242.74	5.108	41196	0.3984	H → L+1 (50%), H → L+9 (24%)

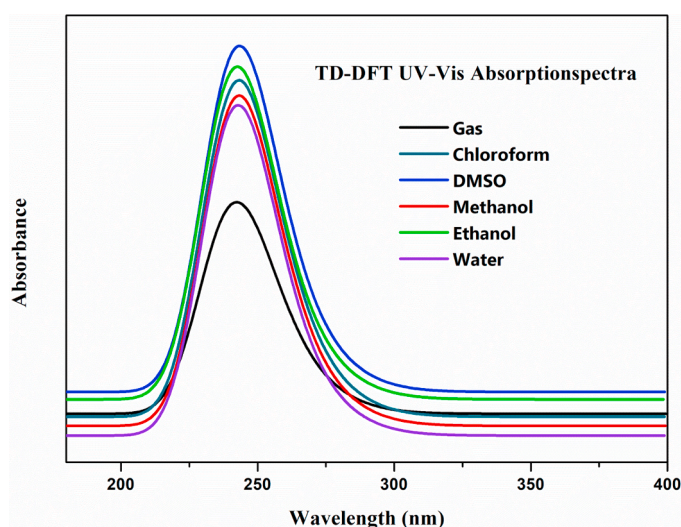


Fig. 9. The UV-Visible absorption spectrum of theoretical TD-DFT spectra for different mediums.

σ - σ^* between the natural bonds of (O3-H37) and (C18-H34) with an energy value of 130.7 kJ/mol. Interactions are largely caused by lone pairs of nitrogen, chlorine, and oxygen ions (e.g., N6, Cl2, O3, N5, O3, & O4) and anti-bonding σ^* and π^* groups with better interaction energies, which stated that the charge transfer among natural bonds and increase molecular stability. E.g. the lone pair transitions are LP(n)N6 → (C18-H34), LP(n)Cl2 → (C18-H34), LP(n)O3 → (O4-C19), LP(n)Cl2 → (C18-H34), LP(n)N5 → (C7-C14), LP(n)O3 → (C18-H34), LP(n)O4 → (O3-C19), LP(n)O3 → (C18-H34) and LP(n)O4 → (C18-H34) with energies are 75.4, 53.7, 49.6, 40.1, 39.5, 38.2, 32.7, 30.8, & 29.1 kJ/mol respectively.

Table 7

Molecular docking results of binding energy (in kcal mol⁻¹), inhibition constant (in μ m), electrostatic energy (in kcal mol⁻¹) intermolecular energy (in kcal mol⁻¹), and RMSD values (in Å) for the compound **4B2CA-LPA** with three different proteins (PDB code: 4FVR, 3WIX & 5UUT).

Protein (PDB code)	Type of organism	ligand molecule	Binding affinity (Kcal mol ⁻¹)	Inhibition constant (μ m)	Electrostatic energy (Kcal mol ⁻¹)	Inter molecular energy (Kcal mol ⁻¹)	Reference RMSD (Å)
4FVR	Homo sapiens	4B2CA-LPA	-6.78	311.57	-1.19	-7.77	23.26
3WIX	Homo sapiens	4B2CA-LPA	-7.30	4.45	-0.87	-10.28	55.92
5UUT	Homo sapiens	4B2CA-LPA	-5.10	181.31	-1.00	-8.09	30.99

3.7. UV-Vis absorption studies

The electronic transition of **4B2CA-LPA** was theoretically obtained with different solutions of chloroform, DMSO, ethanol, methanol, and water, as well as for the gaseous state, using the approach TD-DFT with the same basis set level. The findings are provided in [Table 6](#) and shown in [Fig. 9](#). The gas phase has the longest wavelength of 241.31 nm and energy of 5.139 eV which is greatly helped by the electronic absorption of **4B2CA-LPA** from the frontier orbitals [49] with a 28% maximum contribution of HOMO-LUMO+1 transition. Among the solvent phases, the DMSO's lowest energy is 41149 cm⁻¹ with maximum wavelengths of 243.02 nm, respectively. Band gap values of chloroform, DMSO, ethanol, methanol, and water are 5.139, 5.105, 5.102, 5.110, 5.109, and 5.108 eV, respectively. This shows that the molecule in DMSO solvent has greater electronic characteristics and less kinetic stability.

3.9. Molecular docking studies

Computerized drug design and basic molecular biology both have an advantage in the study of molecular docking [50]. The drug Alkeran is one of the most effective therapies for multiple myeloma currently available. Myeloma is often referred to as plasma cell cancer or blood cancer. Also based on PASSOnline tool prediction for **4B2CA-LPA**, the highest probability activity (Pa = 0.921) was found for Hematopoietic inhibitor and it is given in [Table S1 \(supplementary file\)](#). Blood cell production is increased by hematopoietic drugs. The terms "hema" and "poiesis" both refer to blood. The generation of serum, or red blood cells, phagocytes, which are tiny pieces of a bigger cell called a megakaryocyte that forms clots, is particularly increased by hematopoietic medicines.

Since this investigation for **4B2CA-LPA**, we selected three different blood cell-related cancer proteins (PDB codes: 4FVR, 3WIX, & 5UUT) for molecular docking with the title chemical **4B2CA-LPA**. The focus of this research was to determine which of these three blood cancer cells had the best docking score with the greatest binding energy and the most residues in non-covalent interaction; (a) **4FVR**: Janus kinase 2 (JAK2) mutants V617F is a protein tyrosine kinase that regulates signaling via several cytokine receptors in blood cancer cells. (b) **3WIX**: The human myeloid leukaemia cell development protein (hMcl-1) is a number of co-anti-apoptotic enzymes that belongs to the B-cell lymphoma-2 (Bcl-2) family proteins. it is a key pharmacological target in blood tumors. (c) **5UUT**: N-myristoyl-transferase 1 (NMT) protein is involved in the malignant progression of prostate cancer in blood cells and enables cell localization [51–53].

The Auto Dock software, which can find the optimal binding pose for Protein couplings, was used to execute this docking research. Binding characteristics including reference RMSD rate, binding energy, electrostatic energy, intramolecular energy, inhibit activity, and others are included in both [Table 7](#) and [Fig. 10](#).

As a docking result, the title compound **4B2CA-LPA** interacted well with all targeted proteins with good binding energy (-6.78, -7.30 & -5.10 kcal/mol) for proteins 4FVR, 3WIX, and 5UUT. The highest binding energy -7.30 kcal/mol with many weak interactions was found for **3WIX**: The human myeloid leukaemia cell development protein (hMcl-1) with the compound **4B2CA-LPA**. The Non-covalent weak interactions between **4B2CA-LPA** and targeted proteins (a) **4FVR**, (b) **3WIX**, & (c) **5UUT**

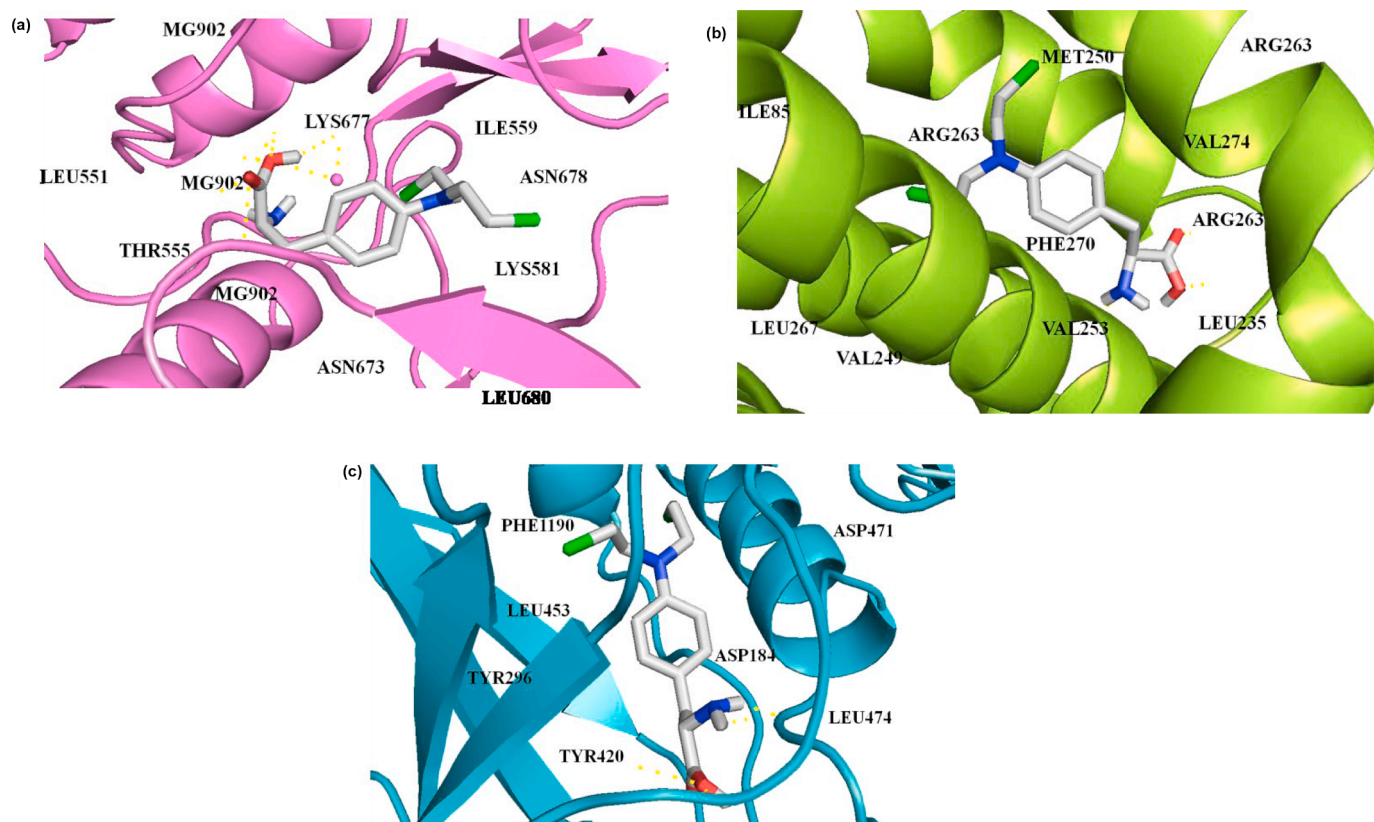


Fig. 10. The protein-ligand interaction surface with the best-docked pose of 4B2CA-LPA with targeted proteins (a) 4FVR, (b) 3WIX, & (c) 5UUT.

Table 8

The Non-covalent weak interactions between the ligand 4B2CA-LPA and three different proteins 4FVR, 3WIX & 5UUT.

Ligand	Protein	Binding Energy (kcal mol ⁻¹)	Ligand group	Protein Residues	*Type of interaction	Distance (Å)
4B2CA-LPA	4FVR	-4.78	C=O	LYS677	COHB	5.63
			C=O	THR555	COHB	3.93
			OH	ASN678	COHB	4.39
			OH	ASN673	COHB	4.86
			OH	MG902	UNMD	2.03
			C-Cl	MG902	MAC	5.47
			BEN	LYS581	PCA	6.33
			BEN	MG902	PCA	3.39
			BEN	ILE559	AKL	5.47
			CH ₂	LEU680	PAL	5.2
			CH ₂	LEU551	PAL	4.8
			NH ₂	ARG263	COHB	4.76
			NH ₂	ARG263	COHB	4.04
			OH	ARG263	COHB	2.21
			OH	ARG263	COHB	3.67
4B2CA-LPA	3WIX	-7.30	C=O	ARG263	COHB	4.05
			BEN	PHE270	PPTS	4.58
			CH ₂	ILE85	AKL	5.11
			CH ₂	VAL249	AKL	4.7
			CH ₂	LEU235	AKL	3.43
			CH ₂	MET250	PAL	4.58
			CH ₂	VAL274	PAL	5.5
			BEN	LEU267	PAL	5.18
			BEN	VAL253	PAL	6.39
			NH ₂	ASP184	COHB	4.1
			NH ₂	ASP471	COHB	3.77
			BEN	PHE1190	PPTS	6.51
			CH ₂	LEU453	AKL	5.38
			CH ₂	TYR420	AKL	5.96
			CH ₂	LEU474	PAL	5.68
4B2CA-LPA	5UUT	-5.10	CH ₂	TYR296	PAL	5.26

* [COHB - Conventional Hydrogen bond; UFDD - Unfavourable Donor-Donor; AKL-Alkyl; PCA- π -Cation; PAN- π -Anion; PAL- π -Alkyl; PPS - π - π Stack; PPTS- π - π T shaped; APS- Amide π -stacked; UNMD- Unfavourable Metal-Donor; MAC- Metal Acceptor]

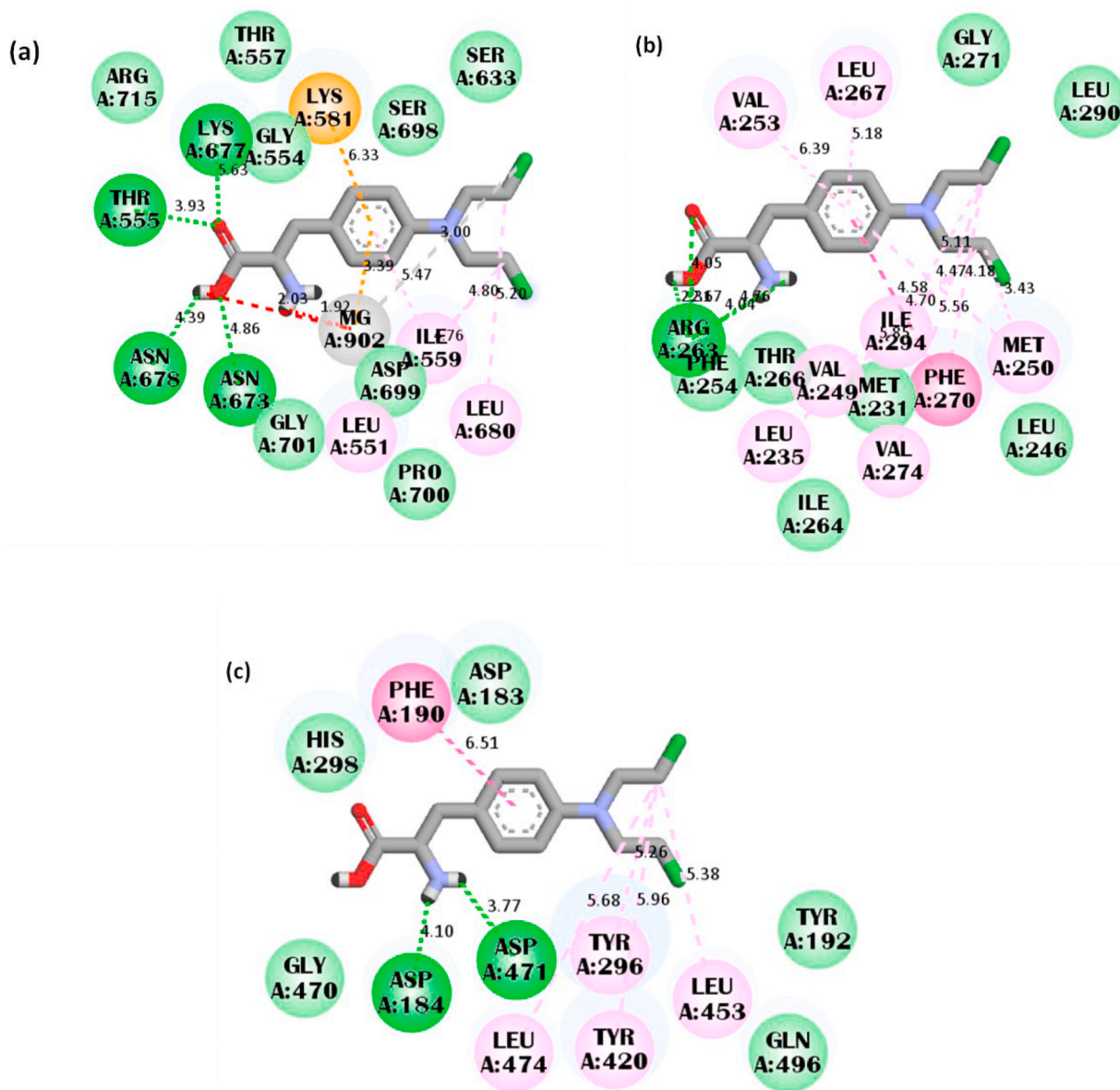


Fig. 11. The Non-covalent weak interactions between 4B2CA-LPA and targeted proteins (a) 4FVR, (b) 3WIX, & (c) 5UUT.

are presented in Table 8 and Fig 11. For this complex, the five conventional carbonyl H-bonds were found between the residues of protein at only ARG263 and the functional groups of NH_2 , OH, & $\text{C}=\text{O}$ of the ligand with distances 4.76, 4.04, 2.21, 3.67, & 4.05 Å respectively. One π - π T-shaped interaction was found at PHE270 and the benzene ring of the 4B2CA-LPA with a distance of 4.58 Å. Three alkyl bonds were identified at ILE85, VAL249, & LEU235 with the CH_2 group of the ligand with distances 5.11, 4.7 & 3.43 Å respectively.

4. Conclusion

In this study, we obtained the global minimum energy structure of anti-blood cancer drug 4-(Bis(2-chloroethyl)amino)-L-phenylalanine and functionalized density functional theory (DFT) calculations. As per these topological results, a novel type of non-covalent interaction of hydrogen-hydrogen attraction forces was found in this molecule by AIM analysis. The strongest delocalization regions are around C11-C17-C10 and C12-C18-C11 and they are visualized by the ELF map and LOL map respectively. As per the FMOs study, the 4B2CA-LPA was less harmful in these phases because DMSO and water had the highest levels

of softness and minimal hardness, demonstrating the compound's good biological properties. the maximum possibility of a strong nucleophilic attack region is NH_2 , and water has the highest negative energy -36.58 kcal/mol when compared to other solvents, the maximum possibility of a strong electrophilic attack region is CH_2 (C8-H20-H-21), and water has the highest positive energy 52.95 kcal/mol when compared to other solvents. According to the Molecular docking results title compound with the highest binding energy -7.30 kcal/mol was found for 3WIX: The human myeloid leukaemia cell development protein (hMcl-1) with the compound 4B2CA-LPA. Molecular docking studies predicted the anti-cancer activity of the title molecule and future experiments to be tested

CRediT authorship contribution statement

K. Parveen Begaum: Validation, Visualization, Writing – original draft, Writing – review & editing. **T. Prabhu:** Conceptualization, Supervision, Data curation, Formal analysis, Funding acquisition, Investigation. **M. Thirunavukkarasu:** Supervision, Validation, Visualization, Resources. **P. Sangeetha:** Data curation, Formal analysis, Funding acquisition, Investigation. **Saleem Javed:** Conceptualization, Data

curation, Formal analysis, Funding acquisition, Software. **Jamal M. Khaled:** Validation, Visualization, Resources. **Ghulam Abbas:** Investigation, Methodology, Project administration. **S. Muthu:** Investigation, Methodology, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.chphi.2023.100272](https://doi.org/10.1016/j.chphi.2023.100272).

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