# NMR and NBO study of vinblastine as a biological inhibitor

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Vinblastine is a potent biological inhibitor that has been clinically applied against a variety of neoplasms. In this work, the molecular structure of vinblastine was optimized using HF and $B_3LYP$ level of theory with 6-31 G(d) as a basis set. Theoretical computations were performed to study thermodynamic parameters, NMR chemical shift data and NBO analysis. Accordingly, some electronic properties such as $E_{HOMO}$, $E_{LUMO}$, $E_{bg}$ (energy gap between LUMO and HOMO), atomic charges, were calculated. Moreover, thermodynamic parameters such as relative energy ($\Delta E$), standard enthalpy ($\Delta H$), entropy ($\Delta S$), Gibbs free energy ($\Delta G$) and constant volume molar heat capacity ($C_v$) values of vinblastine were evaluated. In NMR investigation, magnetic shielding tensor ($\sigma$, ppm), shielding asymmetry ($\eta$), magnetic shielding anisotropy ($\sigma_{aniso}$) and skew of a tensor (K) at various rotation angles around a characteristic rotation were estimated. Also, the calculated chemical shifts were compared with experimental data in $CDCl_3$ and DMSO. The calculated data showed in some cases acceptable agreement with experimental ones.

**Keywords**: vinblastine, NBO, *ab initio*, biological, inhibitor.

## INTRODUCTION

Alkaloids are known as biologically active molecules that originate from natural sources [1-3] as found in the late 1950s [4-7]. Since that time, more than eighty alkaloids extracted from *C. roses* have been identified. Alkaloids have shown various biological properties such as anticancer, antimicrobial, anti-hypertensive and some other biomedical activities [8] .Two alkaloids of vinblastine (VLB) and vincristine (VCR) have been obtained from the famous Madagascar periwinkle plant, formally known as *Vinca-rosea* [2, 3]. These two compounds are very similar in structure. Molecular structure of vinblastine is presented in scheme 1.

Vinblastine is a biological inhibitor that has been clinically applied against a variety of neoplasms. Vinblastine acts an anti-metabolic agent. It affects the metaphase stage of meiosis. Vincristine is also an anti-metabolic agent, but it can affect the metaphase stage of mitosis. Some differences are found between these two stages of meiosis and mitosis. But both in meiosis and mitosis, in metaphase stage, chromosomes are placed in the middle of the cell nucleus so that microtubules are attached to them very hardly and are ready to divide the chromosomes. When we use vinblastine or its analogue (vincristine), the cancer cells will not grow because these two matters bind to the microtubule and make them loose so the cell division is stopped at the metaphase stage [9-12].

Microtubules are highly dynamic polymers of heterodimers of α and β tubulin, arranged parallel to a cylindrical axis to form tubes of 25 nm diameter that may be many μm long. Polymerization of microtubules is initiated by a nucleation-elongation mechanism in which the formation of a short microtubule 'nucleus' is followed by elongation of the microtubule *via* a reversible non-covalent addition of tubulin dimers [12]. Microtubules are not simple polymers. They exhibit complex polymerization dynamics that apply energy released *via* hydrolysis of GTP. These complicated dynamics are suggested to be important for their cellular functions. Various chemical materials are bound to tubulin or microtubules that inhibit cell proliferation by acting on microtubules. Many of these bound compounds have been known as drugs that are highly applicable against various forms of cancer or are currently in clinical trials. An important class of these drugs inhibiting the microtubule polymerization at high drug concentrations is found to be the *Vinca* alkaloids [12-16]. The *Vinca* alkaloids can bind to both tubulin and microtubules, and therefore their biological activities are highly

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dependent on the drug concentration [16]. At relatively high concentrations of these alkaloids, the microtubule depolymerization is stopped, spindle microtubules are dissolved and therefore cells arrest at mitosis [18-20]. In contrast, at low concentrations, the *vinca* alkaloids decrease microtubule dynamics without depolymerizing spindle microtubules, but remain able to arrest mitosis and induce apoptosis [12]. All of these compounds can affect mitotic progression and cause apoptosis in cancer cells [21-23].

In continuation of previously experimental studies, in this work, the molecular structure of vinblastine was optimized using HF and $B_3LYP$ level of theory with 6-31 G(d) as a basis set. Theoretical computations were performed to study thermodynamic parameters, NMR chemical shift data and NBO analysis.

## THEORETICAL BACKGROUND

The chemical shift refers to the phenomenon associated with the secondary magnetic field created by the induced motions of the electrons surrounding the nucleus when it is subjected to an applied external magnetic field. The energy of a magnetic momentum, $\mu$, in a magnetic field, B, is as follow:

$$E = -\mu \cdot (1 - \sigma) \, B$$

where $\sigma$ refers to the differential resonance shift due to the induced motion of the electrons. The chemical shielding is defined by a real three-by-three Cartesian matrix, which can be divided into a single scalar term, three anti symmetric pseudo vector components, and five components corresponding to a symmetric tensor [23]. Only the single scalar and the five symmetric tensor elements can be seen in the normal NMR spectra of the solids. For brevity, these six resonance shifts are usually referred to as the shielding tensor:

$$\begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix}$$

that can be obtained by averaging the off-diagonal values of the complete tensor [24]. The chemical shielding tensor is generally referred to as the chemical shift anisotropy tensor (CSA) according to the possession of second rank properties. The measurement or calculation of the diagonal components $(\sigma_{xx}, \sigma_{yy}, \sigma_{zz})$ or $(\sigma_{11}, \sigma_{22}, \sigma_{33})$ in the principal

axis system (PAS) allows the complete description of the CSA tensor. The CSA tensor can also be illustrated by three additional parameters, as reported previously [25]. In various areas of chemical physics, a careful prediction of molecular response properties to external fields is necessary. Since the NMR data have gained substantial importance in chemistry and biochemistry, they are studied with two parameters isotropic $(\sigma_{iso})$ and anisotropic $(\sigma_{aniso})$ shielding as shown in the following relationships. If $|\sigma_{11}-\sigma_{iso}| \geq |\sigma_{33}-\sigma_{iso}|$, $\sigma$, chemical shift anisotropy, $\eta$, asymmetry parameter and $\delta$ are obtained as shown below [26]:

$$\Delta\sigma = \sigma_{11} - \frac{\sigma_{22} + \sigma_{33}}{2}$$

$$\eta = \frac{\sigma_{22} - \sigma_{33}}{\delta}$$

$$\delta = \sigma_{11} - \sigma_{iso}$$

If $|\sigma_{11} - \sigma_{iso}| \leq \sigma_{33} - \sigma_{iso}|$:

$$\Delta\sigma = \sigma_{33} - \frac{\sigma_{22} + \sigma_{11}}{2}$$

$$\eta = \frac{\sigma_{22} - \sigma_{11}}{\delta}$$

$$\delta = \sigma_{33} - \sigma_{iso}$$

For both cases, skew (K) is shown as:

$$K = \frac{3 * (\sigma_{iso} - \sigma_{22})}{\sigma_{33} - \sigma_{11}}$$

It is to be noted that the skew is a measure of the asymmetry of the probability distribution of a real-valued random variable about its mean.

### Computational Methods

Molecular structure of vinblastine was optimized using HF and $B_3LYP$ levels of theory with 6-31G(d) as a basis set. Computations were carried out to study thermodynamic parameters, NMR chemical shift data and NBO analysis [27]. All calculations were carried out using the Gaussian 09 program package. Gaussian 09 is a computational chemistry software package applicable to present interaction of electrons in atoms and molecules. It uses numerical methods to find solutions to wave functions. Molecular orbital energies, bond energies, molecular geometries and energies, and vibrational frequencies, along with many other properties are evaluable by this package. The term *ab initio* is given to calculations that are
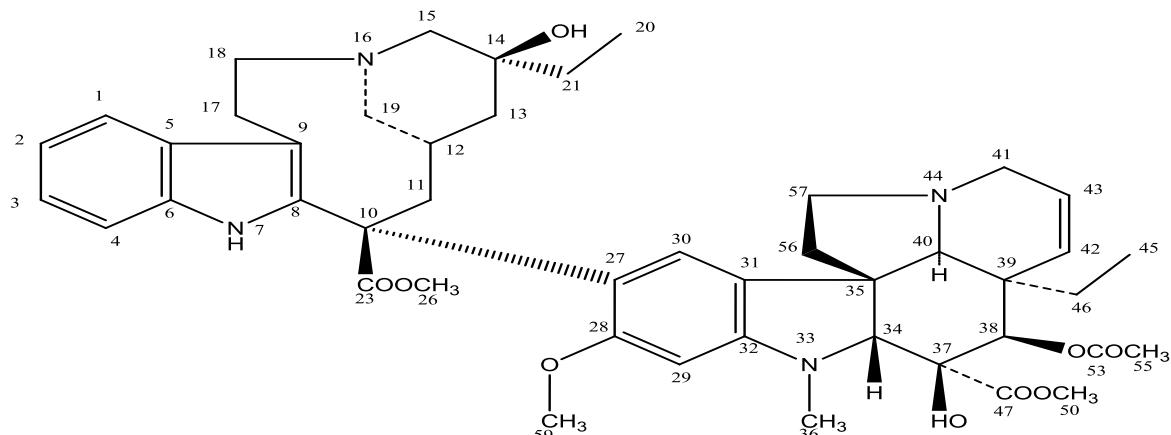
**Scheme 1**. Molecular structure of vinblastine
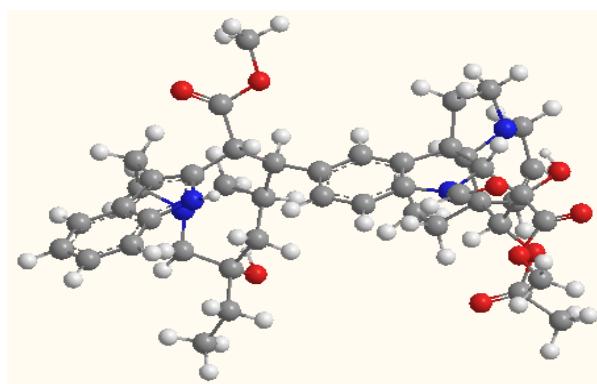


**Fig. 1.** Optimized geometric structure of vinblastine.

obtained exactly from theoretical principles without adding any experimental data [28]. The optimized geometric structure of vinblastine is shown in Fig. 1.

## RESULTS AND DISCUSSION

In this work we have theoretically studied the magnetic properties of atomic nuclei to determine physical and chemical properties of atoms in the title compound. *Ab initio* calculation of nuclear magnetic shielding has become an aid for the analysis of molecular structure. So, NMR is based on the quantum mechanical properties of the nuclei. Based on NMR study, calculated magnetic shielding tensor ($\sigma$, ppm), shielding asymmetry ($\eta$), magnetic shielding anisotropy ($\sigma_{aniso}$,ppm), the skew of a tensor (K), chemical shift anisotropy ($\Delta\sigma$) and chemical shift ($\delta$) were calculated. These results are listed in Tables 1 and 2. The graphs of these

calculated parameters *versus* the number of atoms of vinblastine were sketched as shown in Figs. 2a-2e, respectively.

As seen in Figures 2a-2e, at HF level, $O_{58}$ has a maximum value of $\sigma_{iso}$ (280.8046); $O_{24}$ has a maximum value of $\sigma_{aniso}$ (763.7363); $O_{24}$ has a maximum value of $\Delta\sigma$ (763.7363), $C_{55}$ has a maximum value of K (0.825985) and $C_{45}$ has a maximum value of $\eta$ (0.994694) and at B3LYP level $O_{22}$ has a maximum value of $\sigma_{iso}$ (246.9817); $O_{24}$ has a maximum value of $\sigma_{aniso}$ (664.3599); $O_{24}$ has a maximum value of $\Delta\sigma$ (664.3599), $C_{15}$ has a maximum value of K (0.820206), finally $C_8$ has a maximum value of $\eta$ (0.987734).

The calculated chemical shifts by HF and B3LYP methods as compared with experimental data in CDCl$_3$ and DMSO [29] are collected in Table 3. As shown in Table 3, in some cases the chemical shifts calculated by HF are close to the experimental data while in some other cases, the results computed by B3LYP are comparable with experimental data.

Moreover, some electronic properties such as energy of the highest occupied molecular orbital ($E_{HOMO}$), energy of the lowest unoccupied molecular orbital ($E_{LUMO}$), energy gap ($E_{bg}$; the gap between LUMO and HOMO energies) and atomic charges, were evaluated. The results are tabulated in Tables 4 and 5. The values of $E_{HOMO}$, $E_{LUMO}$ and $E_{bg}$ were evaluated as -0.25936, 0.12368 and 0.38304 eV, respectively. The maximum Mullikan negative charge was calculated for 58H and the maximum positive charge was computed for 47c.

**Table 1.** Magnetic shielding tensor (σ, ppm), magnetic shielding anisotropy (σ_aniso,ppm) and chemical shift anisotropy (Δσ) calculated by HF and B3LYP models with 6-31G(d) basis set for C, N, O in vinblastine.

| Atomic label | NMR chemical shielding tensors data | | | | | |
| | HF/ 6-31G(d) | | | B3LYP/ 6-31G(d) | | |
| | $\sigma_{Iso}$ | $\sigma_{Aniso}$ | $\Delta\sigma$ | $\sigma_{Iso}$ | $\sigma_{Aniso}$ | $\Delta\sigma$ |
|---|---|---|---|---|---|---|
| 1c | 82.2239 | 177.1057 | 177.10575 | 81.4572 | 155.5608 | 155.56085 |
| 2c | 86.3922 | 170.8911 | 170.89115 | 81.9852 | 152.4802 | 152.48025 |
| 3c | 80.8488 | 178.6912 | 178.69115 | 79.8344 | 155.5389 | 155.5389 |
| 4c | 93.7094 | 154.9596 | 154.95955 | 90.7186 | 136.607 | 136.607 |
| 5c | 73.1957 | 163.5265 | 163.52645 | 68.1407 | 145.5024 | 145.50245 |
| 6c | 63.9003 | 166.0338 | 166.0338 | 63.4268 | 140.3232 | 140.3232 |
| 7N | 138.4154 | 51.8364 | -75.6211 | 116.3844 | 48.4883 | -71.75595 |
| 8c | 68.5629 | 122.45 | -137.2326 | 65.238 | 102.7925 | -103.4267 |
| 9c | 85.6121 | 132.781 | 132.781 | 79.1179 | 116.9933 | 116.9933 |
| 10c | 154.2052 | 22.6749 | 22.6749 | 139.5491 | 20.9796 | -21.8936 |
| 11c | 154.7359 | 24.7421 | 24.74215 | 133.3454 | 22.3519 | 22.35185 |
| 12c | 168.6329 | 24.6203 | 24.6203 | 150.2322 | 25.4396 | 25.43955 |
| 13c | 171.3767 | 32.7447 | 32.74465 | 155.2889 | 34.6152 | 34.61515 |
| 14c | 137.8163 | 42.1837 | 42.18375 | 116.7567 | 42.1362 | 42.13625 |
| 15c | 149.6165 | 31.286 | 31.28605 | 132.3138 | 34.7518 | 34.75185 |
| 16N | 244.2934 | 47.564 | 47.56405 | 209.9096 | 51.2007 | 51.20065 |
| 17c | 181.5312 | 22.2527 | -35.2348 | 167.0131 | 25.5394 | -37.2209 |
| 18c | 160.483 | 43.4438 | 43.44375 | 143.2538 | 45.0838 | 45.08385 |
| 19c | 163.4631 | 33.0308 | 33.0308 | 146.3866 | 36.0842 | 36.08405 |
| 20c | 199.4931 | 15.4888 | 15.48885 | 187.3711 | 15.9159 | 15.91585 |
| 21c | 171.8519 | 37.7055 | 37.70545 | 155.214 | 39.0024 | 39.0023 |
| 22O | 273.5037 | 159.3895 | 159.3895 | 246.9817 | 161.2745 | 161.27455 |
| 23c | 12.5103 | 127.1395 | -186.23915 | 16.5554 | 89.0413 | -142.3802 |
| 24O | -167.7572 | 763.7363 | 763.7363 | -133.997 | 664.3599 | 664.3599 |
| 25O | 175.3948 | 211.9189 | -330.0435 | 127.8043 | 193.0803 | -316.96325 |
| 26c | 157.9504 | 62.3724 | 62.37245 | 144.5365 | 65.5015 | 65.5016 |
| 27c | 68.0566 | 170.9488 | 170.9488 | 63.2549 | 151.6022 | 151.60225 |
| 28c | 44.9724 | 134.9123 | 134.91235 | 39.9634 | 106.072 | 106.07205 |
| 29c | 98.8318 | 146.4449 | 146.44485 | 96.431 | 131.7501 | 131.75015 |
| 30c | 74.2976 | 157.3851 | 157.3851 | 73.3478 | 132.0677 | 132.0677 |
| 31c | 73.3031 | 144.0565 | 144.05655 | 67.7907 | 125.3065 | 125.30645 |
| 32c | 49.4952 | 144.72 | 144.72 | 46.1149 | 116.6732 | 116.6733 |
| 33N | 205.2028 | 82.9149 | 82.9148 | 169.211 | 80.0504 | 80.0504 |
| 34c | 132.4978 | 31.215 | 31.215 | 111.4526 | 30.3105 | 30.3105 |
| 35c | 154.2238 | 30.2564 | 30.25645 | 133.5051 | 29.9711 | 29.199 |
| 36c | 165.3309 | 59.1434 | 59.14335 | 151.3953 | 63.4749 | 63.47485 |
| 37c | 121.0346 | 21.8353 | 21.8353 | 102.1689 | 23.6388 | 23.63885 |
| 38c | 137.0632 | 37.5001 | -46.3665 | 117.5051 | 35.957 | -316.96325 |
| 39c | 165.9838 | 13.5246 | 13.52465 | 144.9849 | 14.1888 | 14.1888 |
| 40c | 147.0094 | 32.4146 | 32.41455 | 127.0656 | 35.9774 | 35.97745 |
| 41c | 160.8988 | 37.662 | 37.66205 | 143.0828 | 40.9629 | 40.9629 |
| 42c | 76.1156 | 159.1929 | -181.62215 | 70.2006 | 143.8221 | -149.7878 |
| 43c | 76.9451 | 153.362 | -176.30675 | 73.8942 | 137.5253 | -145.59015 |
| 44N | 218.0582 | 38.0472 | -67.1081 | 185.1565 | 36.8617 | -63.62375 |
| 45c | 198.666 | 13.8161 | -13.8528 | 186.5266 | 14.7872 | 14.78715 |
| 46c | 180.0201 | 22.1054 | -22.3894 | 162.9237 | 23.1603 | -24.57635 |
| 47c | 11.6178 | 134.2036 | -176.01545 | 16.6645 | 95.1436 | -134.0453 |
| 48O | -129.3067 | 711.0296 | 711.0296 | -109.4652 | 628.0083 | 628.0083 |
| 49O | 173.3682 | 207.8216 | -339.364787 | 126.1173 | 186.0971 | -322.11535 |
| 50c | 158.3326 | 61.399 | 61.399 | 144.8955 | 64.434 | 64.434 |
| 51O | 272.5608 | 57.1822 | -63.4529 | 238.7188 | 47.4807 | -51.59265 |
| 52O | 161.4416 | 183.5647 | -305.59205 | 115.4793 | 163.0053 | -295.2175 |
| 53c | 17.3794 | 125.56 | -192.1905 | 22.4825 | 87.237 | -150.53115 |
| 54O | -148.8274 | 711.1191 | 711.11915 | -119.6978 | 616.7324 | 616.73245 |
| 55c | 180.815 | 49.865 | 49.86505 | 171.534 | 47.9299 | 47.92985 |
| 56c | 163.9835 | 50.9283 | 50.9284 | 147.9227 | 52.59 | 52.59 |
| 57c | 161.0108 | 54.8761 | 54.8761 | 143.6472 | 58.7531 | 58.75315 |
| 58O | 280.8046 | 86.7669 | -128.33215 | 236.4346 | 87.2229 | -132.0352 |
| 59c | 154.7926 | 67.179 | 67.1789 | 140.8168 | 72.0584 | 72.05835 |

**Table 2.** Skew of a tensor (K) and shielding asymmetry ($\eta$) calculated by HF and B3LYP levels of theory with 6-31G(d) as a basis set for C, N, O in vinblastine.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | NMR chemical shielding tensors data | | | | | | | |
| Atomic label | HF/ 6-31G(d) | | B3LYP/ 6-31G(d) | | Atomic label | HF/ 6-31G(d) | | B3LYP/ 6-31G(d) | |
| | K | η | K | η | | K | η | K | η |
| 1c | 0.177746 | 0.776260 | 0.219067 | 0.727788 | 31c | 0.276995 | 0.661891 | 0.371120 | 0.559648 |
| 2c | 0.112513 | 0.855405 | 0.145127 | 0.815425 | 32c | 0.125273 | 0.839664 | 0.251150 | 0.691001 |
| 3c | 0.147455 | 0.812604 | 0.170245 | 0.785195 | 33N | 0.528391 | 0.400984 | 0.492250 | 0.436180 |
| 4c | 0.175871 | 0.778491 | 0.221297 | 0.725207 | 34c | 0.148045 | 0.811888 | 0.317799 | 0.616855 |
| 5c | 0.622574 | 0.312561 | 0.689458 | 0.252510 | 35c | 0.370729 | 0.560056 | 0.387924 | 0.541991 |
| 6c | 0.371780 | 0.558950 | 0.433252 | 0.495228 | 36c | 0.718357 | 0.227231 | 0.799340 | 0.158441 |
| 7N | -0.559824 | 0.370951 | -0.58051 | 0.351476 | 37c | 0.030498 | 0.959757 | 0.159907 | 0.797584 |
| 8c | -0.170777 | 0.784560 | -0.00922 | 0.987734 | 38c | -0.317158 | 0.617553 | -0.54897 | 0.218313 |
| 9c | 0.155445 | 0.802948 | 0.427788 | 0.500800 | 39c | 0.009060 | 0.987966 | 0.06443 | 0.915891 |
| 10c | 0.149083 | 0.810632 | -0.06395 | 0.916516 | 40c | 0.419833 | 0.508942 | 0.58679 | 0.345603 |
| 11c | 0.551140 | 0.379192 | 0.484246 | 0.444078 | 41c | 0.156974 | 0.801111 | 0.12501 | 0.839977 |
| 12c | 0.634505 | 0.301690 | 0.744221 | 0.204938 | 42c | -0.197431 | 0.753013 | -0.06095 | 0.920344 |
| 13c | 0.592674 | 0.340126 | 0.571183 | 0.360227 | 43c | -0.249748 | 0.759093 | -0.08545 | 0.889212 |
| 14c | 0.455015 | 0.473211 | 0.414851 | 0.514065 | 44N | -0.829084 | 0.133906 | -0.79898 | 0.158740 |
| 15c | 0.722875 | 0.223311 | 0.820206 | 0.141191 | 45c | -0.003984 | 0.994694 | 0.046761 | 0.938608 |
| 16N | 0.030366 | 0.959914 | 0.082559 | 0.892865 | 46c | -0.019144 | 0.974628 | -0.08899 | 0.884760 |
| 17c | -0.677471 | 0.263108 | -0.55838 | 0.372315 | 47c | -0.404345 | 0.524907 | -0.50920 | 0.419573 |
| 18c | 0.661427 | 0.277410 | 0.620945 | 0.314051 | 48O | 0.706988 | 0.237128 | 0.597656 | 0.335504 |
| 19c | 0.219159 | 0.727685 | 0.055836 | 0.926892 | 49O | -0.720728 | 0.225174 | -0.80292 | 0.155468 |
| 20c | 0.202640 | 0.746908 | 0.212412 | 0.735526 | 50c | 0.601598 | 0.331852 | 0.556313 | 0.374280 |
| 21c | 0.661431 | 0.277403 | 0.645588 | 0.291652 | 51O | -0.155939 | 0.802349 | -0.12451 | 0.840599 |
| 22O | 0.807507 | 0.151672 | 0.699200 | 0.243943 | 52O | -0.748394 | 0.201370 | -0.86559 | 0.104306 |
| 23c | -0.565766 | 0.365336 | -0.69145 | 0.250754 | 53c | -0.629082 | 0.306620 | -0.79860 | 0.159055 |
| 24O | 0.597302 | 0.335833 | 0.520315 | 0.408785 | 54O | 0.493689 | 0.434764 | 0.485922 | 0.442417 |
| 25O | -0.653871 | 0.284187 | -0.72866 | 0.218313 | 55c | 0.825985 | 0.136445 | 0.681357 | 0.259663 |
| 26c | 0.660716 | 0.278048 | 0.612208 | 0.322068 | 56c | 0.572955 | 0.358561 | 0.695674 | 0.247039 |
| 27c | 0.702762 | 0.240822 | 0.807988 | 0.151269 | 57c | 0.386805 | 0.543159 | 0.462369 | 0.465832 |
| 28c | 0.054552 | 0.928561 | 0.226644 | 0.719034 | 58O | -0.579711 | 0.352224 | -0.61314 | 0.321207 |
| 29c | 0.384853 | 0.545204 | 0.470383 | 0.457831 | 59c | 0.667287 | 0.272174 | 0.704061 | 0.239687 |
| 30c | 0.120913 | 0.845027 | 0.135531 | 0.827103 | | | | | |

*Thermodynamic calculations*

Thermodynamic parameters levels such as relative energy ($\Delta E$), standard enthalpies ($\Delta H$), entropies ($\Delta S$), Gibbs free energy ($\Delta G$) and constant volume molar heat capacity (Cv) values of vinblastine were computed by Freq method using HF/6-31G(d) obtained. The values are tabulated in Table 6. The resultant data show that relative energy, Gibbs free energy and standard enthalpies of vinblastine are negative indicating the stable character of its structure.

*Natural bond orbital (NBO) analysis:*

In computational chemistry, NBO is a calculated bonding orbital that contains maximum electron density. The NBO is one of a sequence of natural localized orbital sets that include "natural atomic orbitals (NAO), natural hybrid orbitals (NHO) and natural (semi-)localized molecular orbitals (NLMO). These natural localized sets are intermediate between basis atomic orbitals (AO) and molecular orbitals (MO)[30, 31]. In quantum chemistry, the distribution of electron densities on

atoms and the bonds between them are investigated by NBO analyses. NBOs contain the highest possible percentage of the electron density, ideally close to 2.000 [31-32]. This is performed by considering all possible interactions between filled donor and empty acceptor NBOs and evaluating their energetic importance by the second-order perturbation theory. For each donor NBO (i) and acceptor NBO (j), the stabilization energy E(2) associated with electron delocalization between donor and acceptor is evaluated by the equation:

$$E^{(2)} = -q_i\frac{(F)^2_{i,j}}{\varepsilon_j - \varepsilon_i}$$

where $q_i$ is the orbital occupancy, $\varepsilon_i$, $\varepsilon_j$ are diagonal characters and $F_{i,j}$ is the off-diagonal NBO Fock matrix element [32].

In this study we investigated the nature of bonding in vinblastine molecular structure (scheme 1), by the aid of NBO analyses. It is suggested that the results from NBO calculations can provide a new vision into the electronic structure of the molecule. The obtained results of NBOs analyses such as occupancy, bond orbital, coefficients and

hybrids at the HF level of theory are compiled in Table 7.
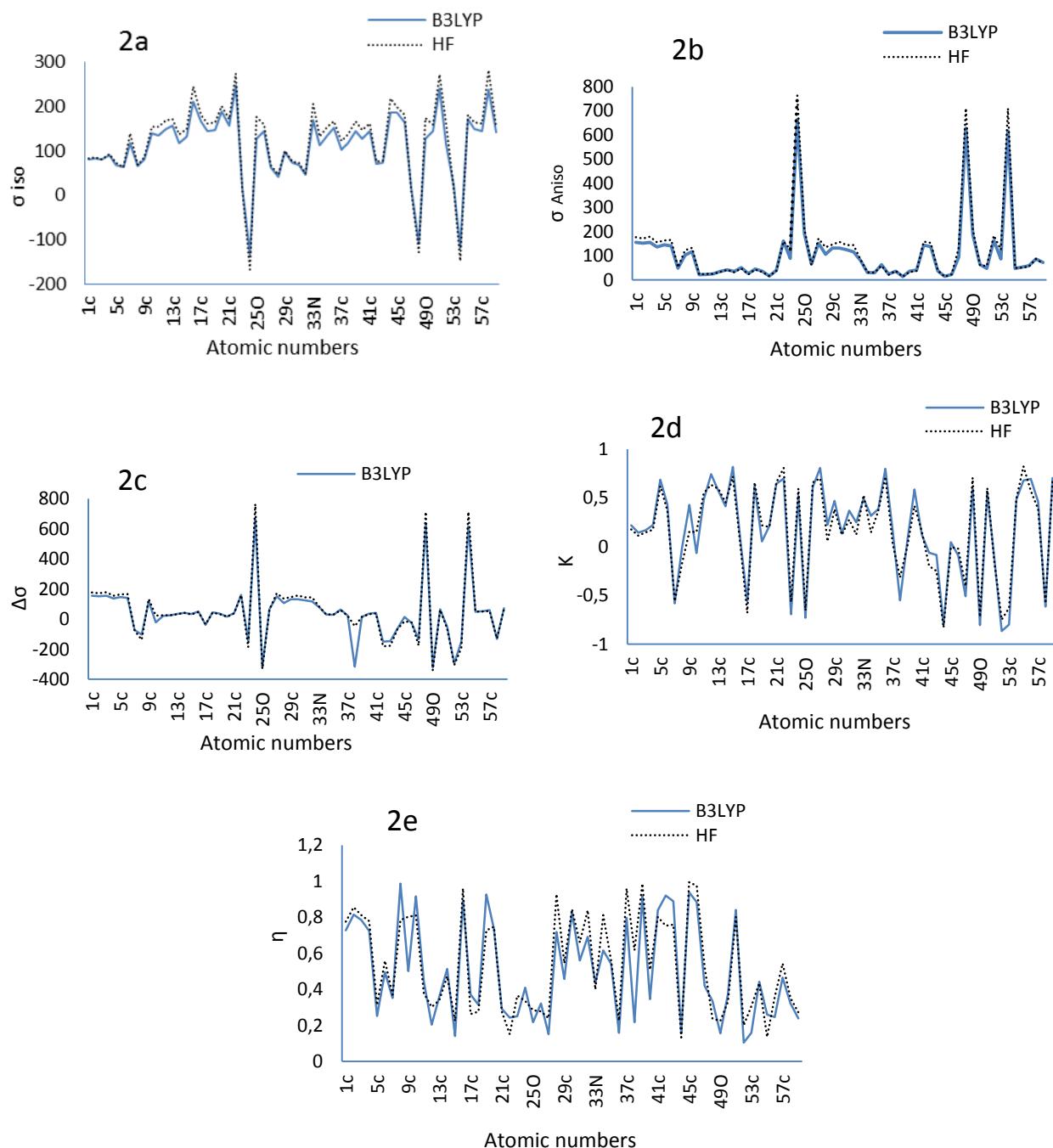


**Fig. 2.** Graphs of a) $\sigma_{iso}$, b) $\sigma_{aniso}$, c) $\Delta\sigma$ d) K, e) $\eta$ *versus* atoms of vinblastine in gas phase at the B3LYP / 6-31G (d) and HF/ 6-31G (d) basis set.

**Table 3.** Experimental (in CDCl$_3$ and DMSO) and calculated chemical shifts by B3LYP and HF levels of theory with 6-31 G(d) as basis set.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | NMR chemical shift data ($\delta$) | | | | | | | | |
| Atomic label | Calculation | | Experimental | | Atomic label | Calculation | | Experimental | |
| | HF method | B3LYP method | CDCL$_3$ solvent | DMSO solvent | | HF method | B3LYP method | CDCL$_3$ solvent | DMSO solvent |
| 1c | 118.0705 | 103.7072 | 118.5 | 117.7 | 29c | 97.6299 | 87.8334 | 94.2 | 94.2 |
| 2c | 113.9274 | 101.6535 | 118.8 | 118 | 30c | 104.9234 | 88.0451 | 123.6 | 123.8 |
| 3c | 119.1274 | 103.6926 | 122.2 | 121.1 | 31c | 96.0377 | 83.5376 | 122.7 | 122.3 |
| 4c | 103.3063 | 91.0713 | 110.5 | 111.4 | 32c | 96.48 | 77.7822 | 152.7 | 152.2 |
| 5c | 109.0176 | 97.0016 | 129.6 | 128.7 | 34c | 20.81 | 20.207 | 83.4 | 82.2 |
| 6c | 110.6892 | 93.5488 | 135.0 | 135.4 | 35c | 20.171 | 19.466 | 53.3 | 52.9 |
| 8c | -91.4884 | -68.9511 | 131.5 | 131.3 | 36c | 39.4289 | 42.3166 | 38.4 | 38.1 |
| 9c | 88.5207 | 77.9955 | 117.1 | 115.8 | 37c | 14.5568 | 15.7592 | 79.7 | 79.4 |
| 10c | 15.1166 | -14.5957 | 55.8 | 55.2 | 38c | -30.911 | -34.7096 | 76.5 | 75.9 |
| 11c | 16.4948 | 14.9012 | 34.4 | 34.2 | 39c | 9.0164 | 9.4592 | 42.7 | 42.1 |
| 12c | 16.4135 | 16.9597 | 30.2 | 29.6 | 40c | 21.6097 | 23.985 | 65.6 | 63.9 |
| 13c | 21.8298 | 23.0768 | 41.6 | 40.7 | 41c | 25.108 | 27.3086 | 50.3 | 49.5 |
| 14c | 28.1225 | 28.0908 | 69.7 | 67.3 | 42c | -121.0814 | -99.8585 | 130.1 | 130.3 |
| 15c | 20.8574 | 23.1679 | 64.4 | 63.9 | 43c | -114.5378 | -97.0601 | 124.5 | 124.0 |
| 17c | -23.4899 | -24.8139 | 28.8 | 27.9 | 45c | -9.2352 | 9.8581 | 8.4 | 7.8 |
| 18c | 28.9625 | 30.0559 | 55.8 | 56.2 | 46c | -14.9263 | -16.3842 | 30.9 | 30.7 |
| 19c | 22.0205 | 24.0562 | 48.2 | 46.9 | 47c | -117.3436 | -89.3635 | 171.7 | 171.1 |
| 20c | 10.3259 | 10.6105 | 6.9 | 7.0 | 50c | 40.9327 | 42.956 | 52.2 | 51.5 |
| 21c | 25.137 | 26.0015 | 34.4 | 34.2 | 53c | -128.127 | -100.3541 | 170.9 | 170.0 |
| 23c | -124.1594 | -94.9201 | 174.9 | 174.5 | 55c | 33.2434 | 31.9533 | 21.2 | 20.9 |
| 26c | 41.5816 | 43.6677 | 52.4 | 51.9 | 56c | 33.9523 | 35.06 | 44.6 | 44.6 |
| 27c | 113.9659 | 101.0682 | 121.2 | 121.1 | 57c | 36.5841 | 39.1688 | 50.4 | 48.9 |
| 28c | 89.9416 | 70.7147 | 158.1 | 157.6 | 59c | 44.7859 | 48.0389 | 55.8 | 56.0 |

**Table 4.** Some electronic properties of vinblastine

| E$_{HOMO}$(ev) | E$_{LUMO}$(ev) | E$_{bg}$(ev) |
|---|---|---|
| -0.25936 | 0.12368 | 0.38304 |

Table 8 collects the second-order perturbative estimations of donor-acceptor interactions. This analysis is done by considering all probable interactions between filled donor Lewis-type NBOs and empty acceptor non-Lewis NBOs, and evaluating their energetic necessity by the 2nd-order perturbation theory. Since these interactions cause a loss of occupancy from the localized NBOs of the idealized Lewis structure into the empty non-Lewis orbitals, this is known as delocalization corrections to the zero-order natural Lewis structure. The stabilization energy E$^2$ along with delocalization between donor NBO (i) and acceptor NBO (j) can be calculated based on the equation mentioned previously using the values shown in Table 8.

The strongest interaction in vinblastine is found for BD(1) C$_5$-H$_9$→ BD$^*$ (1) C$_8$-C$_{10}$ with E$^2$= 9.40 Kcal/mol and BD(2) C$_{31}$-C$_{32}$→ BD$^*$ (2) C$_{27}$-C$_{30}$ with E$^2$= 48.42 Kcal/mol.

Vinblastine molecule can be rotated around its bonds and NMR analyses are performed at each status. In this way, we changed the torsion angle around the C$_{11}$- C$_{10}$- C$_{27}$- C$_{28}$ and then NMR analyses were performed for each torsion angle. Based on these analyses, magnetic shielding tensor ($\sigma$, ppm), shielding asymmetry ($\eta$), magnetic shielding anisotropy ($\sigma_{aniso}$) and skew of a tensor (K) were evaluated and the graphs of this calculated parameters *versus* the torsion angle for some atoms were sketched, as shown in Fig. 3. As can be seen, skew parameter changes *versus* torsion angles for O$_{25}$ and N$_{44}$ obey a polynominal order 4 and Dirac delta function, respectively. The changes of $\sigma_{iso}$ and $\sigma_{Aniso}$ *versus* torsion angles for O$_{49}$ and O$_{24}$ are obtained as Dirac delta function (positive and negative, respectively) with maximum value in torsion angle of 80°. It is to be noted that this angle is the one found at the optimum structure of vinblastine. The plot of shielding asymmetry changes ($\eta$) *versus* torsion angles for O$_{24}$ is found to be of polynominal order 6.

**Table 5. C**alculated Mullikan atomic charges for all atoms in vinblastine molecular structure.

| Atomic label | Mullikan Charge | Atomic label | Mullikan Charge | Atomic label | Mullikan Charge | Atomic label | Mullikan Charge |
|---|---|---|---|---|---|---|---|
| 1c | -0.13619 | 31c | -0.02926 | 61H | 0.184648 | 91H | 0.164775 |
| 2c | -0.22792 | 32c | 0.265 | 62H | 0.186518 | 92H | 0.146818 |
| 3c | -0.21732 | 33N | -0.77152 | 63H | 0.196788 | 93H | 0.272845 |
| 4c | -0.14082 | 34c | 0.073628 | 64H | 0.43771 | 94H | 0.159914 |
| 5c | -0.21191 | 35c | -0.08953 | 65H | 0.254383 | 95H | 0.141219 |
| 6c | 0.308355 | 36c | -0.26553 | 66H | 0.230143 | 96H | 0.180493 |
| 7N | -1.00778 | 37c | 0.222878 | 67H | 0.163308 | 97H | 0.188434 |
| 8c | 0.282342 | 38c | 0.127902 | 68H | 0.21347 | 98H | 0.179906 |
| 9c | 0.154342 | 39c | -0.11579 | 69H | 0.137191 | 99H | 0.142957 |
| 10c | -0.2793 | 40c | 0.067632 | 70H | 0.168751 | 100H | 0.162479 |
| 11c | -0.16864 | 41c | -0.11388 | 71H | 0.165403 | 101H | 0.163872 |
| 12c | -0.11404 | 42c | -0.09274 | 72H | 0.197505 | 102H | 0.176901 |
| 13c | -0.26947 | 43c | -0.17035 | 73H | 0.164002 | 103H | 0.177369 |
| 14c | 0.211056 | 44N | -0.63763 | 74H | 0.158911 | 104H | 0.18265 |
| 15c | -0.02414 | 45c | -0.45698 | 75H | 0.133441 | 105H | 0.180525 |
| 16N | -0.7204 | 46c | -0.30954 | 76H | 0.172843 | 106H | 0.181985 |
| 17c | -0.32805 | 47c | 0.875485 | 77H | 0.151748 | 107H | 0.421133 |
| 18c | -0.05787 | 48O | -0.58357 | 78H | 0.148429 | 108H | 0.202064 |
| 19c | -0.09774 | 49O | -0.71443 | 79H | 0.173915 | 109H | 0.213386 |
| 20c | -0.45233 | 50c | -0.1453 | 80H | 0.154205 | 110H | 0.195012 |
| 21c | -0.31385 | 51O | -0.70344 | 81H | 0.16537 | 111H | 0.174738 |
| 22O | -0.74841 | 52O | -0.75784 | 82H | 0.141191 | 112H | 0.178543 |
| 23c | 0.785359 | 53c | 0.800234 | 83H | 0.395133 | 113H | 0.138989 |
| 24O | -0.55927 | 54O | -0.56415 | 84H | 0.188259 | 114H | 0.180177 |
| 25c | -0.72328 | 55c | -0.50742 | 85H | 0.180898 | 115H | 0.186719 |
| 26c | -0.14027 | 56c | -0.31379 | 86H | 0.177623 | 116H | 0.195058 |
| 27c | -0.03382 | 57c | -0.07669 | 87H | 0.234449 | 117H | 0.167143 |
| 28c | 0.392776 | 58H | -0.82446 | 88H | 0.227144 | | |
| 29c | -0.18419 | 59H | -0.16245 | 89H | 0.231773 | | |
| 30c | -0.20595 | 60H | 0.202366 | 90H | 0.208582 | | |

**Table 6. C**alculated thermodynamic parameters of vinblastine using HF/6-31G(d) level

| Zero point energy (Hartree) | $\Delta E$ (Hartree)[a] | $\Delta G$ (Hartree) | $\Delta H$ (Hartree) | S (cal/molK) | CV (cal/molK) |
|---|---|---|---|---|---|
| -2664.946395 | -2664.898065 | -2665.022405 | -2664.89712 | 263.683 | 197.316 |

[a] consider that 1 Hartree= 627.5095 Kcal/mol

**Table 7. R**esults of NBOs analyses at the HF level of theory with 6-31 G(d).

| $Bond^{BD}_{No.ele}$ | Coefficients hybrids | $Bond^{BD}_{No.ele}$ | Coefficients hybrids |
|---|---|---|---|
| 1 | 2 | 3 | 4 |
| $C1 - C2^{\sigma}_{1.97855}$ | $0.7096\ SP^{1.76} + 0.7046\ SP^{1.78}$ | $C17 - H73^{\sigma}_{1.98192}$ | $0.7876\ SP^{3.22} + 0.6162\ S$ |
| $C1 - C2^{\pi}_{1.74662}$ | $0.6918\ SP + 0.7220\ SP$ | $C18 - H74^{\sigma}_{1.98482}$ | $0.7836\ SP^{3.09} + 0.6213\ S$ |
| $C1 - C5^{\sigma}_{1.97347}$ | $0.6983\ SP^{1.92} + 0.7158\ SP^{1.77}$ | $C18 - H75^{\sigma}_{1.98994}$ | $0.7793\ SP^{2.94} + 0.6266\ S$ |
| $C1 - H60^{\sigma}_{1.98225}$ | $0.7868\ SP^{2.38} + 0.6172\ S$ | $C19 - H76^{\sigma}_{1.98964}$ | $0.7866\ SP^{2.96} + 0.6174\ S$ |
| $C2 - C3^{\sigma}_{1.97878}$ | $0.7059\ SP^{1.90} + 0.7083\ SP^{1.87}$ | $C19 - H77^{\sigma}_{1.98617}$ | $0.7802\ SP^{3.01} + 0.6255\ S$ |
| $C2 - H61^{\sigma}_{1.98304}$ | $0.7866\ SP^{2.38} + 0.6175\ S$ | $C20 - C21^{\sigma}_{1.99085}$ | $0.7018\ SP^{2.71} + 0.7124\ SP^{2.77}$ |
| $C3 - C4^{\sigma}_{1.97704}$ | $0.7033\ SP^{1.80} + 0.7109\ SP^{1.75}$ | $C20 - H78^{\sigma}_{1.99069}$ | $0.7841\ SP^{3.13} + 0.6207\ S$ |
| $C3 - C4^{\pi}_{1.75437}$ | $0.6965\ SP + 0.7176\ SP$ | $C20 - H79^{\sigma}_{1.99158}$ | $0.7885\ SP^{3.08} + 0.6150\ S$ |
| $C3 - H62^{\sigma}_{1.98290}$ | $0.7866\ SP^{2.40} + 0.6174\ S$ | $C20 - H80^{\sigma}_{1.99167}$ | $0.7834\ SP^{3.12} + 0.6215\ S$ |
| $C4 - C6^{\sigma}_{1.97541}$ | $0.6987\ SP^{1.97} + 0.7154\ SP^{161}$ | $C21 - H81^{\sigma}_{1.98160}$ | $0.7879\ SP^{3.21} + 0.6159\ S$ |
| $C4 - H63^{\sigma}_{1.98257}$ | $0.7865\ SP^{2.34} + 0.6176\ S$ | $C21 - H82^{\sigma}_{1.98422}$ | $0.7826\ SP^{3.34} + 0.6225\ S$ |
| $C5 - C6^{\sigma}_{1.96490}$ | $0.7073\ SP^{2.25} + 0.7069\ SP^{1.94}$ | $O22 - H83^{\sigma}_{1.98960}$ | $0.8608\ SP^{4.36} + 0.5089\ S$ |
| $C5 - C6^{\pi}_{1.61719}$ | $0.7249\ SP + 0.6889\ SP^{99.99}$ | $C23 - O24^{\sigma}_{1.99675}$ | $0.5800\ SP^{2.00} + 0.8146\ SP^{1.43}$ |
| $C5 - C9^{\sigma}_{1.96426}$ | $0.7137\ SP^{2.02} + 0.7005\ SP^{2.30}$ | $C23 - O24^{\pi}_{1.99208}$ | $0.5348\ SP^{99.99} + 0.8450\ SP^{99.99}$ |
| $C6 - N7^{\sigma}_{1.98442}$ | $0.6249\ SP^{2.64} + 0.7807\ SP^{1.95}$ | $C23 - O25^{\sigma}_{1.98208}$ | $0.5524\ SP^{2.74} + 0.8336\ SP^{2.37}$ |
| $N7 - C8^{\sigma}_{1.98134}$ | $0.7866\ SP^{2.08} + 0.6174\ SP^{2.91}$ | $O25 - C26^{\sigma}_{1.99313}$ | $0.8349\ SP^{2.43} + 0.5504\ SP^{3.91}$ |
| $N7 - H64^{\sigma}_{1.98080}$ | $0.8625\ SP^{2.51} + 0.5061\ S$ | $C26 - H84^{\sigma}_{1.99632}$ | $0.7853\ SP^{2.71} + 0.6191\ S$ |
| $C8 - C9^{\sigma}_{1.97203}$ | $0.7086\ SP^{1.47} + 0.7057\ SP^{1.79}$ | $C26 - H85^{\sigma}_{1.99624}$ | $0.7838\ SP^{2.72} + 0.6210\ S$ |
| $C8 - C9^{\pi}_{1.87436}$ | $0.7023\ SP^{99.99} + 0.7119\ SP^{99.99}$ | $C26 - H86^{\sigma}_{1.99223}$ | $0.7832\ SP^{2.86} + 0.6217\ S$ |
| $C8 - C10^{\sigma}_{1.97420}$ | $0.6982\ SP^{1.96} + 0.7159\ SP^{2.59}$ | $C27 - C28^{\sigma}_{1.97149}$ | $0.7082\ SP^{1.97} + 0.7060\ SP^{1.64}$ |
| $C9 - C17^{\sigma}_{1.97701}$ | $0.7151\ SP^{1.96} + 0.6990\ SP^{2.78}$ | $C27 - C30^{\sigma}_{1.96919}$ | $0.7097\ SP^{1.90} + 0.7045\ SP^{1.81}$ |
| $C10 - C11^{\sigma}_{1.96775}$ | $0.7196\ SP^{2.65} + 0.6944\ SP^{3.01}$ | $C27 - C30^{\pi}_{1.67501}$ | $0.7233\ SP + 0.6905\ SP$ |
| $C10 - C23^{\sigma}_{1.97450}$ | $0.7102\ SP^{3.40} + 0.7040\ SP^{1.52}$ | $C28 - C29^{\sigma}_{1.97476}$ | $0.7059\ SP^{1.61} + 0.7083\ SP^{1.91}$ |
| $C10 - H65^{\sigma}_{1.95995}$ | $0.8031\ SP^{3.53} + 0.5959\ S$ | $C28 - C29^{\pi}_{1.69659}$ | $0.6795\ SP + 0.7337\ SP$ |
| $C11 - C12^{\sigma}_{1.97338}$ | $0.7180\ SP^{2.63} + 0.6960\ SP^{2.83}$ | $C28 - O58^{\sigma}_{1.99158}$ | $0.5644\ SP^{3.23} + 0.8255\ SP^{2.17}$ |
| $C11 - C27^{\sigma}_{1.97129}$ | $0.6972\ SP^{2.89} + 0.7168\ SP^{2.13}$ | $C29 - C32^{\sigma}_{1.97041}$ | $0.7038\ SP^{1.80} + 0.7104\ SP^{1.68}$ |
| $C11 - H66^{\sigma}_{1.97329}$ | $0.7954\ SP^{3.57} + 0.6061\ S$ | $C29 - H87^{\sigma}_{1.97762}$ | $0.7917\ SP^{2.33} + 0.6109\ S$ |
| $C12 - C13^{\sigma}_{1.98056}$ | $0.7096\ SP^{2.81} + 0.7046\ SP^{2.81}$ | $C30 - C31^{\sigma}_{1.97003}$ | $0.6992\ SP^{1.83} + 0.7150\ SP^{1.73}$ |
| $C12 - C19^{\sigma}_{1.97916}$ | $0.7116\ SP^{2.94} + 0.7026\ SP^{2.71}$ | $C30 - H88^{\sigma}_{1.97988}$ | $0.7900\ SP^{2.43} + 0.6131\ S$ |
| $C12 - H67^{\sigma}_{1.97554}$ | $0.7890\ SP^{3.48} + 0.6144\ S$ | $C31 - C32^{\sigma}_{1.96735}$ | $0.7087\ SP^{2.10} + 0.7055\ SP^{1.83}$ |
| $C13 - C14^{\sigma}_{1.97846}$ | $0.7046\ SP^{2.88} + 0.7096\ SP^{2.65}$ | $C31 - C32^{\pi}_{1.65024}$ | $0.7314\ SP + 0.6819\ SP^{99.99}$ |
| $C13 - H68^{\sigma}_{1.97955}$ | $0.7966\ SP^{3.08} + 0.6045\ S$ | $C31 - C35^{\sigma}_{1.96553}$ | $0.7078\ SP^{2.21} + 0.7064\ SP^{2.87}$ |
| $C13 - H69^{\sigma}_{1.98370}$ | $0.7824\ SP^{3.28} + 0.6228\ S$ | $C32 - N33^{\sigma}_{1.98226}$ | $0.6335\ SP^{2.68} + 0.7737\ SP^{2.53}$ |

**Table 7 continued**

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| $C14 - C15^{\sigma}_{1.97286}$ | $0.7123\ SP^{2.85} + 0.7019\ SP^{2.76}$ | $N33 - C34^{\sigma}_{1.98004}$ | $0.7837\ SP^{2.54} + 0.6211\ SP^{3.75}$ |
| $C14 - C21^{\sigma}_{1.98101}$ | $0.7091\ SP^{2.59} + 0.7051\ SP^{2.75}$ | $N33 - C36^{\sigma}_{1.98375}$ | $0.7899\ SP^{2.53} + 0.6132\ SP^{3.33}$ |
| $C14 - O22^{\sigma}_{1.99275}$ | $0.5602\ SP^{4.33} + 0.8284\ SP^{2.10}$ | $C34 - C35^{\sigma}_{1.97273}$ | $0.7044\ SP^{2.64} + 0.7098\ SP^{3.16}$ |
| $C15 - N16^{\sigma}_{1.98549}$ | $0.6245\ SP^{3.26} + 0.7810\ SP^{2.38}$ | $C34 - C37^{\sigma}_{1.96735}$ | $0.6963\ SP^{2.88} + 0.7178\ SP^{2.58}$ |
| $C15 - H70^{\sigma}_{1.98379}$ | $0.7843\ SP^{3.04} + 0.6204\ S$ | $C34 - H89^{\sigma}_{1.98008}$ | $0.7999\ SP^{2.89} + 0.6001\ S$ |
| $C15 - H71^{\sigma}_{1.98834}$ | $0.7856\ SP^{2.97} + 0.6187\ S$ | $C35 - C40^{\sigma}_{1.96804}$ | $0.7141\ SP^{2.92} + 0.7001\ SP^{2.86}$ |
| $N16 - C18^{\sigma}_{1.98633}$ | $0.7847\ SP^{2.26} + 0.6199\ SP^{3.31}$ | $C35 - C56^{\sigma}_{1.96740}$ | $0.7227\ SP^{3.03} + 0.6912\ SP^{2.80}$ |
| $N16 - C19^{\sigma}_{1.98429}$ | $0.7787\ SP^{2.50} + 0.6274\ SP^{3.37}$ | $C36 - H90^{\sigma}_{1.99078}$ | $0.7912\ SP^{2.86} + 0.6115\ S$ |
| $C17 - C18^{\sigma}_{1.97913}$ | $0.7068\ SP^{2.96} + 0.7074\ SP^{2.70}$ | $C36 - H91^{\sigma}_{1.99112}$ | $0.7834\ SP^{2.96} + 0.6215\ S$ |
| $C17 - H72^{\sigma}_{1.98346}$ | $0.7918\ SP^{3.08} + 0.6107\ S$ | $C36 - H92^{\sigma}_{1.99668}$ | $0.7796\ SP^{2.89} + 0.6263\ S$ |
| $C37 - C38^{\sigma}_{1.97382}$ | $0.7110\ SP^{2.62} + 0.7032\ SP^{2.76}$ | $C46 - H103^{\sigma}_{1.98319}$ | $0.7894\ SP^{3.25} + 0.6139\ S$ |
| $C37 - C47^{\sigma}_{1.97407}$ | $0.7076\ SP^{3.23} + 0.7066\ SP^{1.57}$ | $C47 - O48^{\sigma}_{1.99697}$ | $0.5780\ SP^{1.94} + 0.8160\ SP^{1.38}$ |
| $C37 - O51^{\sigma}_{1.98942}$ | $0.5845\ SP^{3.84} + 0.8114\ SP^{2.39}$ | $C47 - O48^{\pi}_{1.99263}$ | $0.5254\ SP^{99.99} + 0.8508\ SP^{99.99}$ |
| $C38 - C39^{\sigma}_{1.96986}$ | $0.7077\ SP^{2.50} + 0.7066\ SP^{3.14}$ | $C47 - O49^{\sigma}_{1.99218}$ | $0.5550\ SP^{2.67} + 0.8319\ SP^{2.36}$ |
| $C38 - O52^{\sigma}_{1.98883}$ | $0.5475\ SP^{4.49} + 0.8368\ SP^{2.17}$ | $O49 - C50^{\sigma}_{1.98285}$ | $0.8338\ SP^{2.48} + 0.5520\ SP^{3.91}$ |
| $C38 - H93^{\sigma}_{1.97761}$ | $0.8042\ SP^{2.74} + 0.5943\ S$ | $C50 - H104^{\sigma}_{1.99123}$ | $0.7841\ SP^{2.85} + 0.6207\ S$ |
| $C39 - C40^{\sigma}_{1.97025}$ | $0.7084\ SP^{2.94} + 0.7058\ SP^{2.57}$ | $C50 - H105^{\sigma}_{1.99603}$ | $0.7838\ SP^{2.72} + 0.6210\ S$ |
| $C39 - C42^{\sigma}_{1.96975}$ | $0.7193\ SP^{2.96} + 0.6947\ SP^{2.20}$ | $C50 - H106^{\sigma}_{1.99696}$ | $0.7840\ SP^{2.72} + 0.6208\ S$ |
| $C39 - C46^{\sigma}_{1.96999}$ | $0.7219\ SP^{2.97} + 0.6920\ SP^{2.82}$ | $O51 - H107^{\sigma}_{1.98762}$ | $0.8671\ SP^{4.13} + 0.4981\ S$ |
| $C40 - N44^{\sigma}_{1.97970}$ | $0.6349\ SP^{3.57} + 0.7726\ SP^{2.58}$ | $O52 - C53^{\sigma}_{1.99158}$ | $0.8370\ SP^{2.39} + 0.5472\ SP^{2.69}$ |
| $C40 - H94^{\sigma}_{1.98178}$ | $0.7844\ SP^{3.12} + 0.6203\ S$ | $C53 - O54^{\sigma}_{1.99691}$ | $0.5800\ SP^{1.93} + 0.8146\ SP^{1.41}$ |
| $C41 - C43^{\sigma}_{1.98003}$ | $0.7106\ SP^{2.66} + 0.7036\ SP^{2.24}$ | $C53 - O54^{\pi}_{1.99310}$ | $0.5294\ SP^{99.99} + 0.8484\ SP^{99.99}$ |
| $C41 - N44^{\sigma}_{1.98515}$ | $0.6265\ SP^{3.32} + 0.7795\ SP^{2.46}$ | $C53 - C55^{\sigma}_{1.98516}$ | $0.7077\ SP^{1.57} + 0.7065\ SP^{3.01}$ |
| $C41 - H95^{\sigma}_{1.98365}$ | $0.7805\ SP^{3.04} + 0.6252\ S$ | $C55 - H108^{\sigma}_{1.98898}$ | $0.7936\ SP^{2.97} + 0.6085\ S$ |
| $C41 - H96^{\sigma}_{1.98160}$ | $0.7891\ SP^{3.02} + 0.6142\ S$ | $C55 - H109^{\sigma}_{1.98033}$ | $0.7956\ SP^{3.00} + 0.6059\ S$ |
| $C42 - C43^{\sigma}_{1.98194}$ | $0.7092\ SP^{1.52} + 0.7050\ SP^{1.53}$ | $C55 - H110^{\sigma}_{1.98239}$ | $0.7922\ SP^{3.02} + 0.6103\ S$ |
| $C42 - C43^{\pi}_{1.97100}$ | $0.7088\ SP + 0.7054\ SP$ | $C56 - C57^{\sigma}_{1.98633}$ | $0.7095\ SP^{2.94} + 0.7047\ SP^{2.78}$ |
| $C42 - H97^{\sigma}_{1.97840}$ | $0.7894\ SP^{2.45} + 0.6139\ S$ | $C56 - H111^{\sigma}_{1.98740}$ | $0.7882\ SP^{3.04} + 0.6154\ S$ |
| $C43 - H98^{\sigma}_{1.97970}$ | $0.7861\ SP^{2.37} + 0.6182\ S$ | $C56 - H112^{\sigma}_{1.98626}$ | $0.7887\ SP^{3.15} + 0.6148\ S$ |
| $N44 - C57^{\sigma}_{1.98476}$ | $0.7793\ SP^{2.61} + 0.6266\ SP^{3.41}$ | $C57 - H113^{\sigma}_{1.99091}$ | $0.7793\ SP^{2.97} + 0.6266\ S$ |
| $C45 - C46^{\sigma}_{1.99067}$ | $0.7033\ SP^{2.69} + 0.7109\ SP^{2.77}$ | $C57 - H114^{\sigma}_{1.98671}$ | $0.7886\ SP^{2.90} + 0.6149\ S$ |
| $C45 - H99^{\sigma}_{1.99164}$ | $0.7812\ SP^{3.13} + 0.6243\ S$ | $O58 - C59^{\sigma}_{1.99256}$ | $0.8320 SP^{2.58} + 0.5548\ SP^{3.85}$ |
| $C45 - H100^{\sigma}_{1.98955}$ | $0.7868\ SP^{3.13} + 0.6173\ S$ | $C59 - H115^{\sigma}_{1.99579}$ | $0.7844\ SP^{2.71} + 0.6202\ S$ |
| $C45 - H101^{\sigma}_{1.99176}$ | $0.7864\ SP^{3.09} + 0.6177\ S$ | $C59 - H116^{\sigma}_{1.98033}$ | $0.7864\ SP^{2.85} + 0.6059\ S$ |
| $C46 - H102^{\sigma}_{1.98324}$ | $0.7886\ SP^{3.23} + 0.6150\ S$ | $C59 - H117^{\sigma}_{1.98033}$ | $0.7797\ SP^{2.77} + 0.6261\ S$ |

**Table 8.** Second- order interaction energy ($E^2$, Kcal/mol) between donor and acceptor orbitals in vinblastine[a].

| Donor NBO ($i$) | Acceptor NBO ($j$) | $E_{acceptor(j)}$-$E_{Doner(i)}$ •Fack Matrix ($F_{i,j}$, a.u.) | $E^2$ (Kcal/mol) | Donor NBO ($i$) | Acceptor NBO ($j$) | $E_{acceptor(j)}$-$E_{Doner(i)}$ •Fack Matrix ($F_{i,j}$, a.u.) | $E^2$ (Kcal/mol) |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 2 | 4 | 5 | 6 | 7 | 8 |
| $C1-C2^{\sigma}$ | $C1-C5^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.79 *0.085 | 5.10 | $C12-C13^{\sigma}$ | $C14-C21^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.35 *0.031 | 2.18 |
| $C1-C2^{\pi}$ | $C3-C4^{\pi*}$ | $|\psi\rangle$= BD (2)- BD* (2)=0.50 *0.126 | 38.91 | $C12-C19^{\sigma}$ | $N16-C18^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.35 *0.032 | 3.03 |
| $C1-C5^{\sigma}$ | $C5-C9^{\sigma*}$ | $|\psi\rangle$= BD (1)- BD* (1)=1.80 *0.080 | 6.64 | $C12-H67^{\sigma}$ | $C10-C11^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.20 *0.080 | 6.63 |
| $C1-H60^{\sigma}$ | $C2-C3^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.59 *0.052 | 4.99 | $C13-C14^{\sigma}$ | $C11-C12^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.36 *0.059 | 3.21 |
| $C2-C3^{\sigma}$ | $C3-C4^{\sigma*}$ | $|\psi\rangle$= BD (1)- BD* (1)=1.79 *0.050 | 4.26 | $C13-H68^{\sigma}$ | $C12-H67^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.27 *0.030 | 2.79 |
| $C2-H61^{\sigma}$ | $C1-C5^{\sigma*}$ | $|\psi\rangle$= BD (1)- BD* (1)=1.59 *0.052 | 5.11 | $C13-H69^{\sigma}$ | $C12-C19^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.28 *0.028 | 3.64 |
| $C3-C4^{\sigma}$ | $C6-N7^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.77 *0.076 | 7.17 | $C14-C15^{\sigma}$ | $N16-C18^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.36 *0.032 | 3.51 |
| $C3-C4^{\pi}$ | $C5-C6^{\pi*}$ | $|\psi\rangle$=BD (2)-BD* (2)=0.52 *0.116 | 34.18 | $C14-C21^{\sigma}$ | $C12-C13^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.39 *0.051 | 2.34 |
| $C3-H62^{\sigma}$ | $C4-C6^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.59 *0.074 | 5.10 | $C14-O22^{\sigma}$ | $C21-H81^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.81 *0.040 | 1.19 |
| $C4-C6^{\sigma}$ | $C5-C6^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.81 *0.078 | 6.68 | $C15-N16^{\sigma}$ | $C19-H77^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.48 *0.037 | 1.95 |
| $C4-H63^{\sigma}$ | $C5-C6^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.54 *0.078 | 4.94 | $C15-H70^{\sigma}$ | $N16-C19^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.25 *0.025 | 4.60 |
| $C5-C6^{\sigma}$ | $C4-C6^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.75 *0.087 | 6.20 | $C15-H71^{\sigma}$ | $C14-O22^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.26 *0.046 | 2.29 |
| $C5-C6^{\pi}$ | $C1-C5^{\pi*}$ | $|\psi\rangle$=BD (2)-BD* (2)=0.48 *0.129 | 41.82 | $N16-C18^{\sigma}$ | $C14-C15^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.49 *0.044 | 1.87 |
|  | $N7-H64^{\sigma*}$ | $|\psi\rangle$=BD (2)-BD* (1)=1.04 *0.031 | 0.98 |  |  |  |  |
| $C5-C9^{\sigma}$ | $C8-C10^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.72 *0.047 | 9.40 | $N16-C19^{\sigma}$ | $C15-H70^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.60 *0.036 | 1.83 |
| $C6-N7^{\sigma}$ | $C8-C10^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.86 *0.070 | 3.45 | $C17-C18^{\sigma}$ | $C15-N16^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.36 *0.061 | 3.47 |
|  |  |  |  |  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=0.98 *0.059 | 3.69 |
| $N7-C8^{\sigma}$ | $C4-C6^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.82 *0.048 | 5.65 | $C17-H72^{\sigma}$ | $C5-C9^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.45 *0.075 | 4.80 |
|  |  |  |  |  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=0.89 *0.021 | 0.56 |
| $N7-H64^{\sigma}$ | $C8-C9^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.79 *0.056 | 2.16 | $C17-H73^{\sigma}$ | $C8-C9^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.61 *0.076 | 4.45 |
|  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=1.07 *0.032 | 1.09 |  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=0.89 *0.035 | 1.54 |
| $C8-C9^{\sigma}$ | $C8-C10^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.81 *0.084 | 5.95 | $C18-H74^{\sigma}$ | $N16-C19^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.27 *0.071 | 4.99 |
| $C8-C9^{\pi}$ | $C5-C6^{\pi*}$ | $|\psi\rangle$=BD (2)-BD* (2)=0.52 *0.109 | 24.23 | $C18-H75^{\sigma}$ | $C9-C17^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.35 *0.060 | 3.32 |
|  | $N7-H64^{\sigma*}$ | $|\psi\rangle$=BD (2)-BD* (1)=1.09 *0.030 | 0.96 |  |  |  |  |
| $C8-C10^{\sigma}$ | $C8-C9^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.62 *0.051 | 6.43 | $C19-H76^{\sigma}$ | $C11-C12^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.26 *0.049 | 2.36 |
| $C9-C17^{\sigma}$ | $C8-C9^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.64 *0.048 | 6.50 | $C19-H77^{\sigma}$ | $C12-C13^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.28 *0.023 | 1.94 |
| $C10-C11^{\sigma}$ | $C23-O24^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.72 *0.032 | 3.06 | $C20-C21^{\sigma}$ | $C13-C14^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.37 *0.050 | 2.32 |
|  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=1.00 *0.044 | 2.02 |  |  |  |  |
| $C10-C23^{\sigma}$ | $O25-C26^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.53 *0.052 | 3.91 | $C20-H78^{\sigma}$ | $C14-C21^{\sigma*}$ | $|\psi\rangle$=BD (1)-BD* (1)=1.26 *0.066 | 4.27 |
|  | $C8-C9^{\pi*}$ | $|\psi\rangle$=BD (1)-BD* (2)=1.08 *0.036 | 1.37 |  |  |  |  |

**Table 8 continued**

| 1 | 2 | 2 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| $C10 - H65^{\sigma}$ | $C8 - C9^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.64 *0.084 | 5.30 | $C20 - H79^{\sigma}$ | $C21 - H81^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.28 *0.024 | 3.46 |
| | $C23 - O24^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=0.84 *0.073 | 7.66 | | | | |
| $C11 - C12^{\sigma}$ | $C10 - C11^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.31 *0.034 | 1.01 | $C20 - H80^{\sigma}$ | $C21 - H82^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.29 *0.023 | 3.28 |
| | $C27 - C30^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=0.93 *0.046 | 2.43 | | | | |
| $C11 - C27^{\sigma}$ | $C27 - C28^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.34 *0.030 | 3.67 | $C21 - H81^{\sigma}$ | $C14 - O22^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.17 *0.075 | 6.03 |
| $C11 - H66^{\sigma}$ | $C27 - C28^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.31 *0.056 | 6.04 | $C21 - H82^{\sigma}$ | $C14 - C15^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1) =1.25 *0.064 | 4.10 |
| $O22 - H83^{\sigma}$ | $C14 - C15^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.47 *0.073 | 4.51 | $C36 - H90^{\sigma}$ | $C32 - N33^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.32 *0.067 | 4.16 |
| $C23 - O24^{\sigma}$ | $C10 - C23^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.99 *0.045 | 1.22 | $C36 - H91^{\sigma}$ | $N33 - C34^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.23 *0.064 | 4.17 |
| $C23 - O24^{\pi}$ | $C10 - C11^{\sigma*}$ | $\|\psi\rangle$=BD (2)-BD$^*$ (1)=1.10 *0.035 | 1.35 | $C36 - H92^{\sigma}$ | $N33$ | $\|\psi\rangle$=BD (1)-RY$^*$ (1)=1.98 *0.040 | 1.04 |
| $C23 - O25^{\sigma}$ | $C8 - C10^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.79 *0.045 | 1.39 | $C37 - C38^{\sigma}$ | $C47 - O49^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.37 *0.040 | 2.48 |
| $O25 - C26^{\sigma}$ | $C10 - C23^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.63 *0.064 | 3.09 | $C37 - C47^{\sigma}$ | $O49 - C50^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.40 *0.049 | 3.94 |
| $C26 - H84^{\sigma}$ | $O25$ | $\|\psi\rangle$=BD (1)-RY$^*$ (1)=2.22 *0.045 | 0.51 | $C37 - O51^{\sigma}$ | $N33 - C34^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.60 *0.045 | 1.56 |
| | | | | | $C47 - O48^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=1.23 *0.040 | 1.54 |
| $C26 - H86^{\sigma}$ | $C23 - C25^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.23 *0.062 | 3.81 | $C38 - C39^{\sigma}$ | $C45 - C46^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.34 *0.038 | 2.69 |
| | | | | | $C42 - C43^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=1.03 *0.040 | 1.93 |
| $C27 - C28^{\sigma}$ | $C28 - C29^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.56 *0.066 | 5.89 | $C38 - O52^{\sigma}$ | $C53 - C55^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.64 *0.041 | 2.41 |
| $C27 - C30^{\sigma}$ | $C30 - C31^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.80 *0.093 | 5.97 | $C38 - H93^{\sigma}$ | $C37 - O51^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.20 *0.076 | 5.98 |
| $C27 - C30^{\pi}$ | $C11 - C12^{\sigma*}$ | $\|\psi\rangle$=BD (2)-BD$^*$ (1)=0.92 *0.058 | 3.88 | $C39 - C40^{\sigma}$ | $N44 - C57^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.36 *0.047 | 2.37 |
| | $C28 - C29^{\pi*}$ | $\|\psi\rangle$=BD (2)-BD$^*$ (2)=0.46 *00134 | 47.35 | | | | |
| $C28 - C29^{\sigma}$ | $C27 - C28^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.57 *0.069 | 6.60 | $C39 - C42^{\sigma}$ | $C42 - C43^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.37 *0.049 | 4.53 |
| $C28 - C29^{\pi}$ | $C31 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=0.51 *0.138 | 45.08 | $C39 - C46^{\sigma}$ | $C37 - C38^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.32 *0.051 | 2.52 |
| | | | | | $C42 - C43^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=1.01 *0.050 | 3.15 |
| $C28 - O58^{\sigma}$ | $C29 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.99 *0.050 | 1.56 | $C40 - N44^{\sigma}$ | $C31 - C35^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.54 *0.064 | 3.35 |
| $C29 - C32^{\sigma}$ | $C31 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.81 *0.103 | 7.33 | $C40 - H94^{\sigma}$ | $C34 - C35^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.24 *0.069 | 4.76 |
| $C29 - H87^{\sigma}$ | $C31 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.55 *0.051 | 5.27 | $C41 - C43^{\sigma}$ | $N44 - C57^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.48 *0.027 | 3.48 |
| $C30 - C31^{\sigma}$ | $C31 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.56 *0.064 | 7.37 | $C41 - N44^{\sigma}$ | $C43 - H98^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.47 *0.047 | 2.01 |
| $C30 - H88^{\sigma}$ | $C31 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.42 *0.025 | 5.64 | $C41 - H95^{\sigma}$ | $C42 - C43^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=0.93 *0.060 | 4.85 |
| | | | | | $C42 - C43^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.69 *0.028 | 0.59 |
| $C31 - C32^{\sigma}$ | $C29 - C32^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.80 *0.100 | 6.91 | $C41 - H96^{\sigma}$ | $C40 - N44^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.25 *0.067 | 4.51 |
| | | | | | $C42 - C43^{\pi*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (2)=0.93 *0.043 | 2.52 |
| $C31 - C32^{\pi}$ | $C27 - C30^{\pi*}$ | $\|\psi\rangle$=BD (2)-BD$^*$ (2)=0.49 *0.138 | 48.42 | $C42 - C43^{\sigma}$ | $C39 - C42^{\sigma*}$ | $\|\psi\rangle$=BD (1)-BD$^*$ (1)=1.64 *0.076 | 4.40 |
| | $C35 - C56^{\sigma*}$ | $\|\psi\rangle$=BD (2)-BD$^*$ (1)=0.89 *0.065 | 5.00 | | | | |

**Table 8 continued**

| 1 | 2 | 2 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| $C31-C35^{\sigma}$ | $C30-C31^*$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.66 *0.056 | 5.49 | $C42-C43^{\pi}$ | $C41-H95^{\sigma*}$ | $\lvert\psi\rangle$=BD (2)-BD$^*$ (1)=0.95 *0.050 | 4.04 |
| $C32-N33^{\sigma}$ | $C30-C31^*$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.78 *0.051 | 3.20 | $C42-H97^{\sigma}$ | $C41-C43^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.27 *0.059 | 7.79 |
| $N33-C34^{\sigma}$ | $C29-C32^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.76 *0.085 | 5.19 | $C43-H98^{\sigma}$ | $C39-C42^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.33 *0.095 | 8.49 |
| $N33-C36^{\sigma}$ | $C31-C35^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=1.07 *0.047 | 2.13 | $N44-C57^{\sigma}$ | $C39-C40^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.47 *0.061 | 3.15 |
| $C34-C35^{\sigma}$ | $C30-C31^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.66 *0.083 | 5.15 | $C45-C46^{\sigma}$ | $C38-C39^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.33 *0.048 | 2.18 |
| $C34-C37^{\sigma}$ | $C38-O52^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.28 *0.058 | 3.25 | $C45-H99^{\sigma}$ | $C46-H103^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.38 *0.026 | 2.93 |
| | $C47-O48^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=0.96 *0.043 | 2.31 | | | | |
| $C34-H89^{\sigma}$ | $C37-C38^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.25 *0.058 | 3.34 | $C45-H100^{\sigma}$ | $C39-C46^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.24 *0.071 | 5.05 |
| $C35-C40^{\sigma}$ | $C31-C32^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=0.96 *0.035 | 1.31 | $C45-H101^{\sigma}$ | $C46-H102^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.28 *0.024 | 3.16 |
| | $C39-C40^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.37 *0.064 | 1.97 | | | | |
| $C35-C56^{\sigma}$ | $C31-C32^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=0.94 *0.050 | 2.83 | $C46-H102^{\sigma}$ | $C39-C42^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.30 *0.062 | 3.71 |
| | $C39-C40^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.35 *0.066 | 4.03 | | | | |
| $C46-H103^{\sigma}$ | $C39-C40^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.25 *0.065 | 4.21 | $C55-H108^{\sigma}$ | $O52-C53^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.22 *0.074 | 5.45 |
| $C47-O48^{\sigma}$ | $C37-C47^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.98 *0.044 | 1.17 | $C55-H109^{\sigma}$ | $C53-O54^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.54 *0.058 | 2.70 |
| | | | | | $C53-O54^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=0.87 *0.068 | 6.33 |
| $C47-O48^{\pi}$ | $C37-O51^{\sigma*}$ | $\lvert\psi\rangle$=BD (2)-BD$^*$ (1)=1.09 *0.034 | 1.99 | $C55-H110^{\sigma}$ | $C53-O54^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.54 *0.060 | 2.89 |
| | | | | | $C53-O54^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=0.87 *0.065 | 5.78 |
| $C47-O49^{\sigma}$ | $C37-C39^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.70 *0.042 | 1.30 | $C56-C57^{\sigma}$ | $C41-N44^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.43 *0.052 | 3.09 |
| $O49-C50^{\sigma}$ | $C37-C47^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.60 *0.065 | 3.26 | $C56-H111^{\sigma}$ | $C35-C40^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.27 *0.047 | 2.20 |
| $C50-H104^{\sigma}$ | $C47-C49^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.23 *0.062 | 3.79 | $C56-H112^{\sigma}$ | $C34-C35^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.24 *0.058 | 3.37 |
| $C50-H105^{\sigma}$ | $O49$ | $\lvert\psi\rangle$=BD (1)-RY$^*$ (2)=2.17 *0.036 | 0.76 | $C57-H113^{\sigma}$ | $C59-H111^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.25 *0.029 | 1.20 |
| $C50-H106^{\sigma}$ | $O49$ | $\lvert\psi\rangle$=BD (1)-RY$^*$ (2)=2.17 *0.034 | 0.66 | $C57-H114^{\sigma}$ | $C40-N44^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.25 *0.057 | 3.26 |
| $O51-H107^{\sigma}$ | $C34-C37^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.46 *0.076 | 4.87 | $O58-C59^{\sigma}$ | $C27-C28^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.88 *0.069 | 3.13 |
| | | | | | $C28-C29^{\pi*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (2)=1.20 *0.028 | 0.66 |
| $O52-C53^{\sigma}$ | $C55-H108^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.84 *0.040 | 1.07 | $C59-H115^{\sigma}$ | $C59-H116^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.42 *0.025 | 0.56 |
| $C53-O54^{\sigma}$ | $C53-C55^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=2.01 *0.041 | 1.05 | $C59-H116^{\sigma}$ | $C28-O58^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.26 *0.064 | 4.09 |
| $C53-O54^{\pi}$ | $C55-H109^{\sigma*}$ | $\lvert\psi\rangle$=BD (2)-BD$^*$ (1)=1.27 *0.024 | 1.50 | $C59-H117^{\sigma}$ | $C28-C58^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD (1)=1.27 *0.025 | 0.62 |
| $C53-C55^{\sigma}$ | $C38-O52^{\sigma*}$ | $\lvert\psi\rangle$=BD (1)-BD$^*$ (1)=1.34 *0.068 | 4.28 | | | | |

[a]BD and BD*refer to bonding and anti-bonding, respectively.
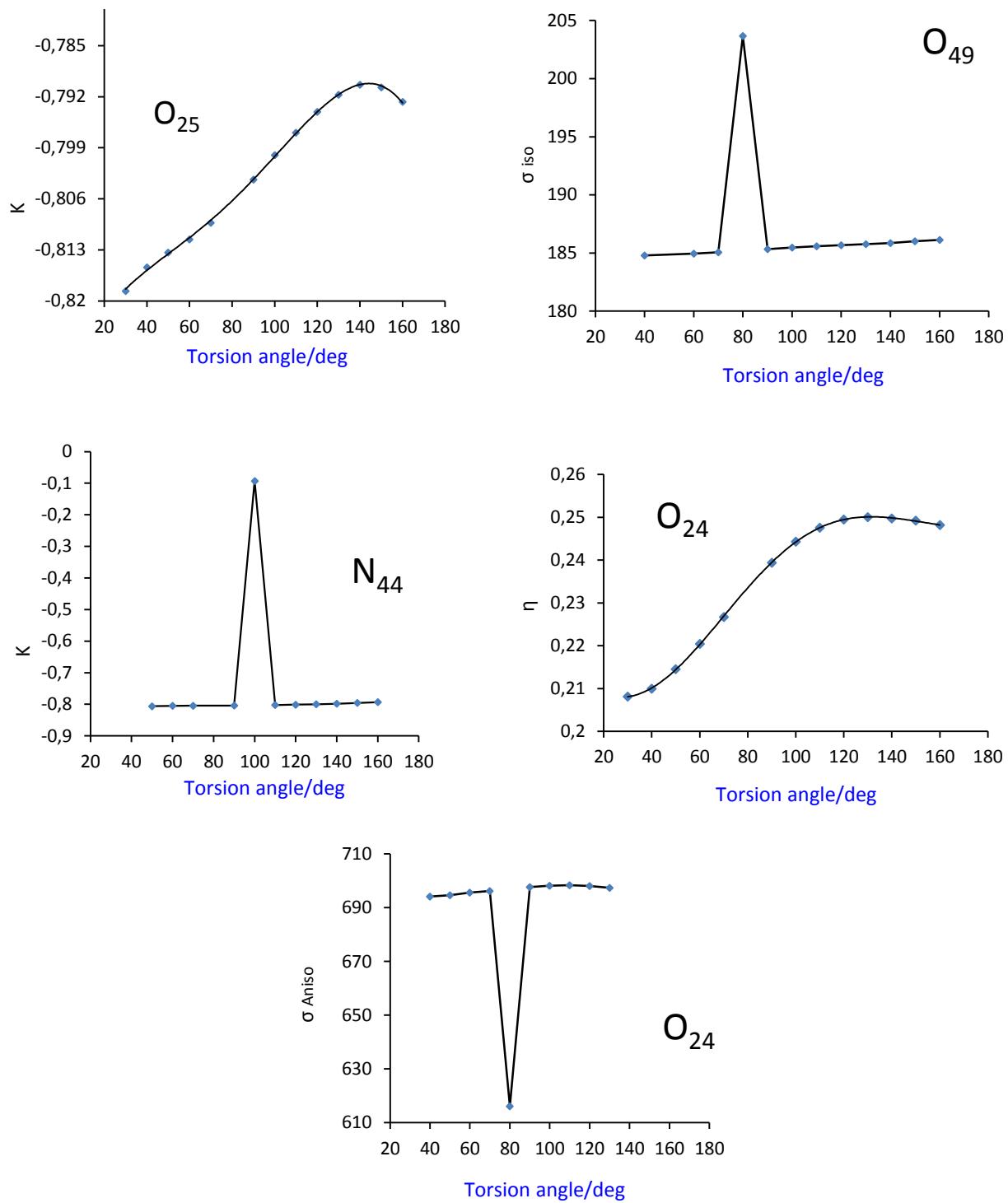
**Fig. 3** Calculated parameters of NMR (K, η, $\sigma_{iso}$, $\sigma_{Aniso}$) *versus* the torsion angle around the $C_{11}$- $C_{10}$- $C_{27}$- $C_{28}$ of the structure for some atoms of vinblastine.

CONCLUSION

In this work, we theoretically investigated the structure features of vinblastine as a biological active compound. Chemical shift anisotropy asymmetry (η), isotropy ($\sigma_{iso}$), anisotropy ($\sigma_{aniso}$), $\Delta\sigma$, K and chemical shift tensor ($\delta$) were calculated based on theoretical data obtained from BL3Y/6-31G(d) and HF/6-31G(d) levels of theory. Moreover, NBO analyses were performed and then stabilization energies, electron occupation at each bond and hybridation character around each atom were evaluated. Furthermore, Freq computation was done for investigation of thermodynamic parameters such as enthalpy, entropy, Gibbs free energy and heat capacity. Mullikan atomic charges for all atoms of the title compounds were also calculated. The values of $E_{HOMO}$, $E_{LUMO}$ and $E_{bg}$ were evaluated too. Based on the calculated results on NMR chemical shifts, it seems that the HF level has more consistency with experimental data.

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# NMR И NBO-ИЗСЛЕДВАНЕ НА ВИНБЛАСТИН КАТО БИОЛОГИЧЕН ИНХИБИТОР

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(Резюме)

Винбластинът е мощен биологичен инхибитор, който се прилага клинично срещу различни неоплазми. В тази работа е оптимизирана молекулната структура на винбластина с помоощта на флуороводород и B₃LYP-ниво на теорията с 6-31 G(d) като основна мрежа. Представени са теоретични изчисления, които да изследват термодинамични параметри, Theoretical computations were performed to study thermodynamic parameters, ЯМР-химичното отместване и NBO-анализ (естествени орбитали на връзките). Заедно с това са изчислени някои електронни свойства, като $E_{HOMO}$, $E_{LUMO}$, $E_{bg}$ (забранената зона между LUMO и HOMO) и атомните заряди. Освен това са оценени термодинамични параметри, като относителната енергия ($\Delta E$), стандартната енталпия ($\Delta H$), ентропията ($\Delta S$), термодинамичният потенциал по Гибс ($\Delta G$) и постоянният обемен моларен топлинен капацитет ($C_v$) за винбластина. В ЯМР-изследването са оценени магнитният екраниращ тензор ($\sigma$, ppm), екраниращата асиметрия ($\eta$), магнитнатно-екраниращата анизотропия ($\sigma_{aniso}$) и отместването на тензор (K) на различни ъгли на ротация около характеристичната ос на ротация. Изчислени са химическите отмествания спрямо експериментални данни с $CDCl_3$ и DMSO. Пресметнатите данни показват в приемливо съгласие с експерименталните в някои случаи.