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Full Length Research Paper

DFT studies of nano anticancer on vinblastine and vincristine molecules

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Medicinal chemistry depends on many other disciplines ranging from organic chemistry and pharmacology to computational chemistry. Typically, medicinal chemists use the most straightforward ways to prepare compounds. The validation of any design project comes from the biological testing. The investigation of vinblastine and vincristine have been studied by theoretical methods. It has been established the best structural and functional of vinblastine and vincristine. In this study, we have extracted information of vinblastine and vincristine with hybrid density functional theory (B3LYP,BLYP) and hartree-fock (HF) methods by different basis sets, and then total energy, band gap, dipole moment, NMR parameter of VCR and VLB have been studied. Also, the information gathered in this investigation from the atomic structure of tubulin involved dynamic instability of microtubules, gives additional help in determining crucial binding site for the activity of potent antimitotic drugs.

Key words: Hybrid density functional theory (B3LYP, BLYP) and hartree-fock (HF), vinblastine, vincristine, drug.

INTRODUCTION

Alkaloids are biologically effective molecules taken from natural sources (Sen and Maiti, 1994; Chen et al., 2005; Qin et al., 2006). The alkaloids began in the late 1950s. Since then, more than eighty alkaloids have been isolated from C. roseus. Alkaloids are known to have anti cancerous, antimicrobial, antihypertensive and multiple other biological activities (Blaskó and Cordell, 1990; Bölcskei, 2005). Vinblastine and vincristine are a vinca alkaloid obtained from the famous Madagascar Periwinkle plant, an evergreen plant known more formally as Catharanthus roseus (Sen and Maiti,1994; Chen et al., 2005; Qin et al., 2006). They are an anticancer drug used to treat certain kinds of cancer (Nakagawa et al., 2005).

Vinca alkaloids (vinblastine, vincristine, and more recently, vinorelbine) are antimitotic, anticancer agents that induce tubulin to form spiral polymers at physiological protein concentrations. Sedimentation velocity to investigate the effects of six vinca alkaloids on tubulin spiraling. Thermodynamic analysis of LnK_1K_2 data demonstrates large and positive ΔS values, indicating that tubulin spiral formation is entropically-driven (Lobert et al., 2006).

Quantitatively examined the Additivity of Dilantin and Vinblastine Inhibitory Effects on Microtubule Assembly1 (Lobert et al., 1999). The interaction of vinblastine with calf brain tubulin has been studied by velocity sedimentation, gel filtration, and fluorescence (Lee et al.,1975).Then discuss the Physiochemical Aspects of Tubulin- interacting Antimitotic Drugs (Correia and Lobert ,2001).The interactions of vinblastine with tubulin heterodimers and microtubules have been studied extensively, and in Vitro studies have shown that at low ionic strengths vinblastine induces spiral formation by a mechanism involving ligand-mediated plus ligand-facilitated isodesmic self-association (Lobert et al.,1996).Tryptic hydrolysis identifies a single fluorescent β-peptide coinciding with residues 175–213 (Rai and Wolff, 1996).

Vincristine (VCR) a natural constituent of C.roseus which is produced in practice semisynthetically from VLB, is used mainly for acute lymphoblastic leukaemia and non-Hodgkin's lymphomas as well asother neoplastic

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disorders like Wilms' tumor, neuroblastoma, Kaposi sarcoma and rhabdomyosarcoma (Pearce,1990 ;Kuehne and Markó , 1990;Va et al.,2010; Sasaki et al., 2010). Vinblastine is an anti-metabolic agent. It effects on the metaphase stage of meiosis. Vincristine is an anti-metabolic agent, too but it effects on the metaphase stage of mitosis (Smith,1997; Peters et al., 2000). There are several differences between meiosis and mitosis (Eric Hall, 2006). But in both case, in metaphase stage, chromosomes are placed in middle of Cell nucleus then microtubules attached to them very hardly and are ready to divide the chromosomes (Mitchison and Poleward,1989; Mitchison and Kirschner,1984; Margolis and Wilson,1998;Rodionov et al.,1999; Rudner and Murray, 1996). This doesn't happen if we use of vinblastine or vincristine because these two factors are binding to the microtubule and make them loose so the cell division stops at this stage and the cancer cells will not grow (Vale, 2003; Howard and Hyman, 2007; Jordan and Leslie, 2004).

The most of works in related to these molecules were experimentally that has been based on its performance on DNA and get evidence of their effects (Howard and Hyman, 2007; Jordan and Leslie, 2004; Jordan and Wilson, 1999).In view of their structural and biological similarities it is of considerable interest that in their use as anticancer agents VLB and VCR differ markedly in their spectra of oncolytic activity, the dosages which are tolerated and the symptoms of toxicity they elicit. VLB, for example, is one of the more useful drugs for treating Hodgkin's disease but has only minimal effects against acute leukemia; VCR, on the other hand, is a valuable drug in the treatment of acute leukemia, particularly in children, and is also effective against certain lymphomas and neuroblastomas (Hooker and Bogdanich, 2008).

Also, the equilibrium geometry, various bonding features, and harmonic vibrational wavenumbers and NMR analysis have been investigated with the help of density functional theory (DFT) calculations (Mollaamin et al., 2011; Monajjemi et al., 2010).

But we tried to check the stability of the molecules by information obtained from computational methods and modeling. In computational methods you will be able that check in very small dimensions and this gives us the opportunity to examine the chemical properties of the individual atoms.

However, the vinblastine and vincristine compounds have been displayed different spectrum by GIAO approximations, which appears the results of the determination of the number of active sites in vinblastine and vincristine using the DFT and HF methods with STO-3G, 3-21G,6-31G, 6-31G*, 6-31G** basis sets. These simulations provide an atomistic analysis of the vinblastine and vincristine compounds strategy and their implications for further investigations of microtubule.

Theoretical Background

The chemical shift refers to the phenomenon which associated with the secondary magnetic field created by the induced motions of the electrons that surrounding the nuclei when in the presence of an applied magnetic field. The energy of a magnetic moment **μ**, in a magnetic field, **B**, is as follow:

$E = -\mu . (1 - \sigma) B$

where the shielding *σ,* is the differential resonance shift due to the induced motion of the electrons. The chemical shielding is characterized by a real three-by-three Cartesian matrix, which can be decomposed into a single scalar term, three anti symmetric pseudo vector components, and five components corresponding to a symmetric tensor (Facelli, 2002). Only the single scalar and the five symmetric tensor elements can be observed in the normal NMR spectra of the solids. For brevity, these six values 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 (Sefzic and Turco, 2005).

The chemical shielding tensor is commonly referred to the chemical shift anisotropy (CSA) tensor according to the possession of second rank properties. The measurement or calculation of the diagonal components (σ_{xx} , σ_{yy} ,σ_{zz}) or (σ_{11} , σ_{22} ,σ_{33}) in the principle axis system (PAS) allows the complete description of the CSA tensor [sandia].The CSA tensor can also be described by three additional parameters ,

a: The isotropic value (or trace portion of the CSA tensor) σ_{iso} , of the shielding tensor which is defined as

$\sigma_{iso} = 0.33(\sigma_{11} + \sigma_{22} + \sigma_{33})$

b: The anisotropy (Δσ) of the tensor, due to the following expression:

$\Delta\sigma = \sigma_{33} - 0.5(\sigma_{11} + \sigma_{22})$

And

c: The shielding tensor asymmetry parameter (η)

$$\eta = \frac{|\sigma_{22} - \sigma_{11}|}{|\sigma_{33} - \sigma_{iso}|}$$

computational Methods

We report the results of optimization and nuclear magnetic resonance (NMR) on VLB and VCR. Vinblastine and vincristine theoretically were investigated

Table 1. total energy (Kcal/mol) of vinblastine and vincristine in (B3LYP, BLYP, HF) methods with sto-3g,3-21g,6-31g,6-31g*,6-31g** basis sets.

Total energy of vinblastine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	-1662873.96	-1674885.17	-1683589.764	-1684078	-1684147.388
BLYP	-1662019.2	-1674190.393	-1682943.514	-1683379	-1683436.779
HF	-1652943.84	-1664416.991	-1672960.903	-1673677	-1673742.364
Total energy of vincristine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	-1708561.651	-1720996.651	-1729947.003	-1730540.469	-1730596.861
BLYP	-1707720.927	-1720310.329	-1729310.566	-1729845.889	-1729901.68
HF	-1698417.326	-1710304.423	-1719195.685	-1719939.609	-1720003.403

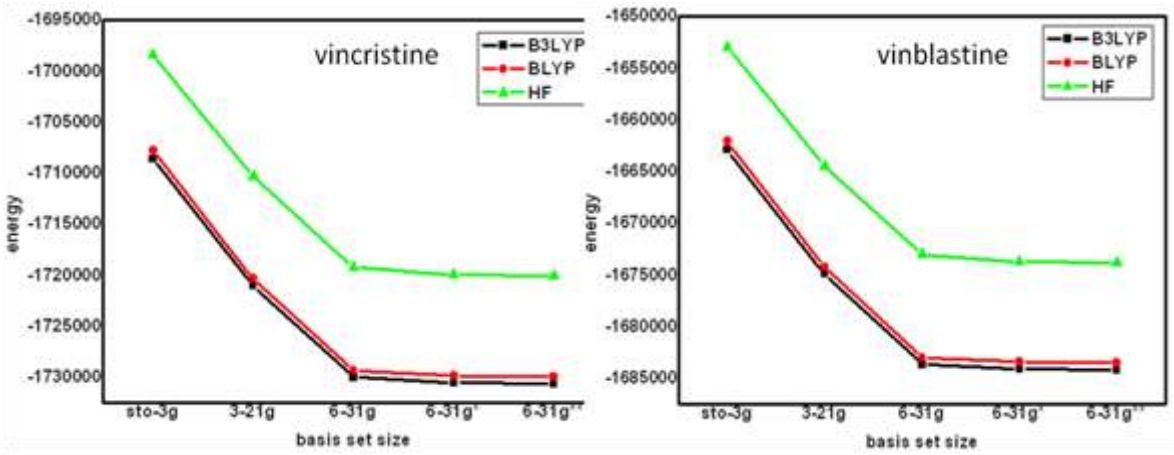

Figure 1. Energy of vincristine and vinblastine versus basis sets in (B3LYP, BLYP and HF).

by using density functional theory and Hartree–Fock levels of theory with the standard STO-3G, 3-21G,6-31G, 6-31G*, 6-31G**, basis sets employed Gaussian 98 (Frisch et al.,1998). The aim of investigation is comparisons between vincristine and vinblastine in properties of thermodynamics data obtained from NMR chemical shift values.

RESULTS AND DISCUSSION

Energy

To investigate the structural stability, at first we have optimized the structures of vinblastine and vincristine with hybrid density functional theory (B3LYP,BLYP) and Hartree-Fock (HF) methods with sto-3g,3-21g,6-31g,6-31g*,6-31g** basis sets .Optimized energy for vinblastine and vincristine structures with different methods and basis sets are presented in table 1. By investigation on data We have seen that vincristine is more stable than vinblastine.

According to the Figure1, we see that both molecules with increase the size of basis sets the molecules energy is reduced and is close to its limit value. Also, mentioned trend is correct for all methods (B3LYP, BLYP and HF).

We can be seen, in large basis sets (6-31g, 6-31g*, 6-

Table 2. band gap energy of vinblastine and vincristine in (B3LYP, BLYP, HF) methods with sto-3g,3-21g,6-31g,6-31g*,6-31g** basis sets.

Band gap energy of vinblastine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	0.15752	0.13093	0.12302	0.14959	0.14969
BLYP	0.07856	0.06651	0.0593	0.08036	0.08061
HF	0.46083	0.39312	0.39573	0.39204	0.39179
Band gap energy of vincristine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	0.0871	0.08142	0.07354	0.13611	0.13611
BLYP	0.01417	0.01722	0.01139	0.06991	0.0701
HF	0.37871	0.33101	0.36905	0.37612	0.37577

Table 3. Dipole moment (Debye) of vinblastine and vincristine in (B3LYP, BLYP, HF) methods with sto-3g,3-21g,6-31g,6-31g*,6-31g** basis sets.

Dipole moment of vinblastine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	6.9863	8.6208	9.0668	7.86	8.026
BLYP	6.9951	7.6449	7.7057	7.8107	7.8107
HF	5.9561	8.3616	10.0082	9.047	9.1093
Dipole moment of vincristine					
basis sets / methods	sto-3g	3-21g	6-31g	6-31g*	6-31g**
B3LYP	6.3131	5.1827	5.9815	7.9861	7.9601
BLYP	6.4239	4.5618	5.7558	7.3849	7.4014
HF	5.3897	8.6665	8.4569	7.6979	7.7282

31g**) in all methods which energy of molecules are almost identical.

Band Gap energy of the molecules

The LUMO-HOMO band gap is a gap between the LUMO (the lowest unoccupied molecular orbital) and HOMO (the highest occupied molecular orbital).
It has been shown the band gap energy in all methods and basis sets in two systems and we have resulted that the most stabilized molecule is vincristine in comparison to vinblastine molecule in HF method (Table 2).

Dipole moments of molecules

The central quantity in the physics of dielectrics is the polarization of the material **P**. The polarization **P** is defined as the dipole moment **p** per unit volume. The dipole moment of a system of charges is given by
$\mathbf{p} = \sum q_i \, r_i$
Where r_i is the position vector of charge q_i. The value of the sum is independent of the choice of the origin of system, provided that the system in neutral.
The two compounds are very similar in structure and apparently also in their primary biological action. Thus the toxicity of VLB and VCR can in many cases be linked to

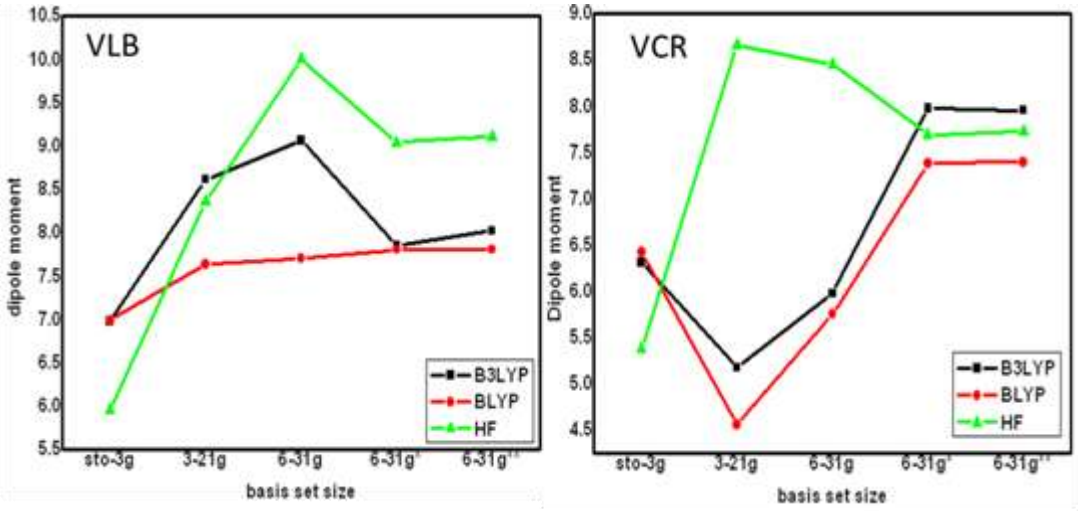

Figure 2. Dipole moment of vincristine and vinblastine versus basis sets size in (B3LYP, BLYP and HF)

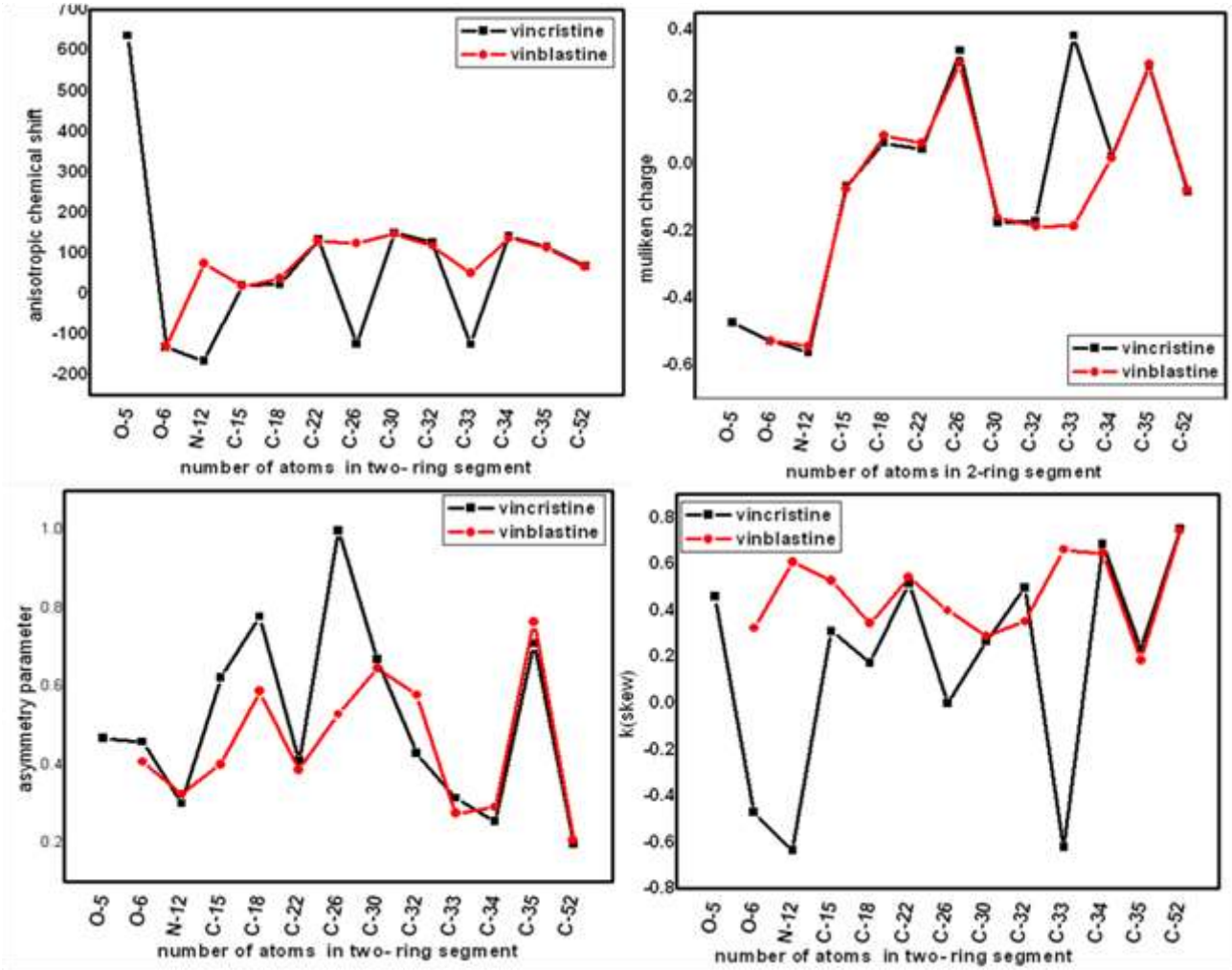

Figure 3. Muliken charge, Anisotropic chemical shift, Asymmetric and Skew parameters versus number of atoms in two-ring segment

disturbances in intracellular microtubular structures resulting from the binding of the alkaloids to a common target molecule, tubulin, the protein subunits from which microtubules are assembled (Vale , 2003).

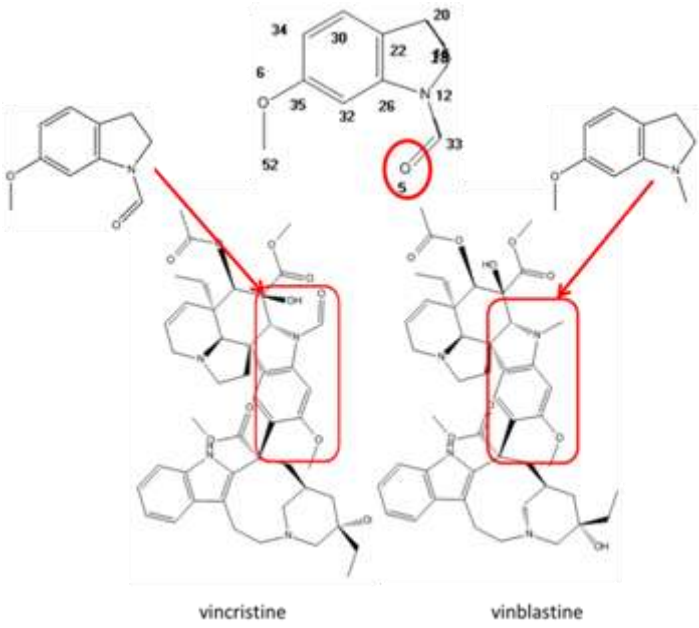

Figure. 4. vincristine structure, vinblastine structure and two ring segments of the molecules have been studied and No. of atoms.

Dipole moment of the molecules can be important factor in the binding of the alkaloids to target molecule. Dipole moment of molecule VLB almost in all methods is more than VCR then Inhibition of tubulin polymerization by vinblastine is more than VCR. The inhibition in bothpositive and negative ends of tubules is related to interactions and polarity of drug. Whether the interactions between the drugs are locally determined at the central portion of the b-monomer or globally or at long range, or both, is difficult to ascertain. But we know, if the molecular dipole moment is high, then increase the intermolecular force, therefore at high concentrations, the number of active sites decreased and the pharmacological effects also is reduced. Empirical studies also approved that this topic [25, 26] .

According to table 3, dipole moment vinblastine and vincristine in (B3LYP, BLYP, HF) methods with sto-3g,3-21g,6-31g,6-31g*,6-31g** basis sets have been measured

In Figure 2 we can be seen that dipole moments are different with the various methods and basis sets. For example dipole moment of VCR molecule, in both DFT methods (B3LYP,BLYP) are the same but in HF in three small basis set we see that the dipole moment changes is the opposite of DFT methods and in the larger basis sets of HF ,values remained constant and approximately between the values of DFT. In diagram dipole moment of VLB molecule can be seen, dipole moment increases with increasing size of STO-3G to 6-31G and the two basis sets of larger 6-31G* and 6-31G**, Dipole moment decreases and remains constant. In the largest basis set 6-31G**, average values of dipole moment are 8.3153 in VLB and 7.6965 in VCR.

Within the Gaussian 98 software suite there is a sub function that uses a calculation method called GIAO (gauge including atomic orbitals) (Jordan and Leslie ,(2004) to calculate isotropic NMR shielding values, from which computed chemical shifts may be derived.

In the standard convention, the principal components of the chemical shift tensor, $(\delta_{11}, \delta_{22}, \delta_{33})$, are labeled according to the IUPAC rules (Jordan and Wilson ,1999). They follow the high frequency-positive order. Thus, δ_{11} corresponds to the direction of lowest shielding, with the highest frequency, while δ_{33} corresponds to the direction of highest shielding, with the lowest frequency.

It is useful to define the span, Ω, and the skew, κ, of a CS tensor. The span is defined as

$\Omega = \delta_{11} - \delta_{33} = \sigma_{33} - \sigma_{11}$ and indicates the width of the NMR line shape for a nonspinning, stationary, sample. The skew is defined as

$$\kappa = \frac{3(\delta 22 - \delta iso)}{\Omega} = \frac{3(\sigma iso - \sigma 22)}{\Omega}$$

And provides information on the symmetry of the line shape. For example, κ values of ±1 imply axial symmetry.

For nuclear magnetic resonance study of these two molecules, first the same part of the two molecules were removed and then the NMR study was performed on a two-ring segments of the system (the segments are shown in Figure. 3). The NMR shielding constants and correspond-

Table 4. NMR shielding constants and corresponding parameters for two-ring segments of the vincristine and vinblastine

VINBLASTINE													
	Atomic Name	O	O	N	C	C	C	C	C	C	C	C	C
	Atomic Number	5	11	14	16	21	24	29	30	31	33	34	50
B3LYP 6-31G**	Mulliken atomic charges	-0.52773	-0.54373	-0.07535	0.083695	0.062306	0.301014	-0.15839	-0.18483	-0.1864	0.018686	0.296574	-0.0779
	Δσ (ppm)	-129.755	75.33645	19.3001	38.0018	131.0034	125.6734	147.9928	51.65965	118.4682	137.0725	114.3984	66.7453
	η (ppm)	0.408032	0.325279	0.400911	0.587902	0.386403	0.529312	0.647346	0.276061	0.579383	0.291528	0.765017	0.206707
	k	0.324934	0.60872	0.528472	0.344576	0.543583	0.400095	0.290064	0.662933	0.352533	0.645724	0.187235	0.742156
BLYP 6-31G**	Mulliken atomic charges	-0.48378	-0.4762	-0.0044	0.045022	0.072121	0.328215	-0.20687	-0.16552	-0.18283	0.040954	0.263044	-0.05554
	Δσ (ppm)	-138.227	80.28645	23.5453	-14.4024	126.0442	124.9593	152.0842	51.19735	109.4646	119.4541	104.5893	68.1544
	η (ppm)	0.395234	0.44133	0.687168	0.749604	0.497975	0.533235	0.57986	0.357097	0.602539	0.325997	0.627791	0.22125
	k	-0.53437	0.487024	0.254526	-0.20034	0.430558	0.396321	0.352087	0.574515	0.330983	0.607939	0.307797	0.72526
HF 6-31G**	Mulliken atomic charges	-0.6765	-0.78064	-0.17766	0.148003	-0.05244	0.375853	-0.11091	-0.11856	-0.2544	-0.16778	0.433562	-0.0258
	Δσ (ppm)	-128.88	83.38765	23.73695	-20.0899	135.8804	155.0965	184.2009	50.9989	124.757	137.2972	135.0151	60.21815
	η (ppm)	0.359506	0.139706	0.442823	0.176873	0.70025	0.750048	0.637729	0.082178	0.655365	0.429098	0.918539	0.116275
	k	-0.57195	0.822013	0.485516	-0.7773	0.243024	0.199959	0.298761	0.893349	0.282844	0.499462	0.062367	0.850753

VINCRISTINE														
	Atomic Name	O	O	N	C	C	C	C	C	C	C	C	C	C
	Atomic Number	5	6	12	15	18	22	26	30	32	33	34	35	52
B3LYP 6-31G**	Mulliken atomic charges	-0.47238	-0.52903	-0.56205	-0.06536	0.062263	0.044474	0.338623	-0.17388	-0.16955	0.383023	0.021955	0.292674	-0.08333
	Δσ (ppm)	636.8996	-131.639	-164.273	21.69255	24.2524	133.8436	-122.957	150.8043	127.5482	-124.715	141.3472	116.1762	67.91265
	η (ppm)	0.469009	0.458414	0.301535	0.623765	0.77908	0.410662	0.998901	0.670839	0.429673	0.314834	0.255445	0.710429	0.196521
	k	0.459202	-0.4698	-0.63467	0.311473	0.175371	0.518378	-0.00083	0.269007	0.498877	-0.62009	0.686133	0.234126	0.754082
BLYP 6-31G**	Mulliken atomic charges	-0.43953	-0.4866	-0.49153	-0.04499	0.048121	0.087566	0.318918	-0.20412	-0.15174	0.340475	0.047403	0.262065	-0.06338
	Δσ (ppm)	622.908	-139.148	-163.057	20.08455	24.3696	127.6673	115.4491	152.9592	122.403	-121.745	128.8202	106.4833	69.7702
	η (ppm)	0.485288	0.449281	0.219846	0.799816	0.824663	0.384625	0.977117	0.602434	0.429135	0.203854	0.27669	0.581559	0.201494
	k	0.443044	-0.47899	-0.72688	0.158047	0.137532	0.545445	0.017263	0.33108	0.499424	-0.74549	0.662233	0.350496	0.748248
HF 6-31G**	Mulliken atomic charges	-0.63865	-0.57796	-0.67913	-0.82486	-0.17604	0.158754	-0.07308	0.405827	-0.23593	0.570876	-0.16778	0.427386	-0.03331
	Δσ (ppm)	644.3693	-129.312	-156.008	22.46035	-25.1401	139.6721	-152.155	183.0262	132.43	-134.574	140.6178	136.202	61.6229
	η (ppm)	0.392775	0.386734	0.502218	0.195911	0.402106	0.617074	0.949259	0.640605	0.497683	0.505146	0.410294	0.87949	0.108184
	k	0.536928	-0.54324	-0.4264	0.754793	-0.52723	0.317598	-0.03854	0.296156	0.430844	-0.42354	0.518757	0.093191	0.860777

ing parameters for two-ring segments of the vincristine and vinblastine are shown in Table 4.

We first consider the B3LYP method and the two molecules were compared in terms of muliken charge, isotropic chemical shift, asymmetric and skew parameters (Figure 3).In the diagrams in Figure 4 can be seen, because there is oxygen No.5 only in vincristine molecule, so, in atom No.33, muliken charge is different from vinblastine and anisotropic chemical shift in atoms with No.33, 12, 26 of vincristine molecule is more negative than vinblastine molecule. Also, we see in Figure. 4 that in general the asymmetry parameter in the atoms of vinblastine molecule is less than vincristine and in atom No.35, two molecules have similar asymmetry parameter but the skew parameter for atoms vincristine is less than vincristine even in the atoms No.6, 12 and 33 is negative.

CONCLUSION

The study of Energy, between the two molecules showed that vincristine structure is more stable from vinblastine and also, calculated energy of molecules with the large basis sets (6-31g, 6-31g*, 6-31g**) in all methods , are almost identical. In the band gap energy for all methods and basis sets, we saw that vinblastine molecule is more than vincristine molecule. The band gap energy calculation with the method of HF has been the highest values. Dipole moment of molecule VLB almost in all methods is more than VCR then Inhibition of tubulin polymerization by vinblastine is more than VCR. The inhibition in both positive and negative ends of tubules is related to interactions and polarity of drug so, at the initial moment that the concentration of the drug is low, Inhibition effect of VLB is more. In NMR study, we concluded that due to an additional oxygen atom on the ring of the vincristine, charges of atoms and chemical shift of atoms is different from vinblastine.

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