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Quantitative structure-property relationships of Taxol, Taxotere and their epi-isomers

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The current study investigates the importance of molecular structure analysis based on density functional theory (DFT) with a focus on Taxol, Taxotere, and related compounds. Numerous physicochemical parameters of these compounds with respect to their biological activity are calculated and compared. The physicochemical properties such as dipole moment, the volume of the molecule, molecular weight, total energy, solvation energy, E HOMO, E LUMO, log P, polarizability, HBD count, HBA count, area, PSA, ovality are calculated. These parameters are important for quantitative structure-property relationships (QSPR) and quantitative structure-activity relationships (QSAR) analysis. Frontier molecular orbitals energy diagram and their bandgap provide indications about chemical reactivity and kinetic stability of these compounds. Important parameters such as ionization potential, electron affinity, electronegativity, global hardness, softness, chemical potential, and global electrophilicity index are also identified. The graphical models of Taxol, Taxotere and corresponding isomers were also analyzed to evaluate the differences in the molecular charge distributions.

Keywords: Taxol, Taxotere, epi-isomers, DFT, dipole moment, AM1, HF, quantum chemical parameters.

Introduction

Taxol (Paclitaxel) is a widely used anticancer drug that derives from plants (Taxus species)[1]. Taxol is considered to be the most promising agent for cancer chemotherapy and can be used for the management of different cancers, even though it is mainly used for the treatment of ovarian and breast cancer. The promising pharmaceutical applications achieved with Taxol prompted the development of the new Taxol-related synthetic drugs. Taxotere (docetaxel) is one of the semi-synthetic derivatives of Taxol[2]. Both of these compounds share the same mechanism of action. During the interaction with cell components, both these drugs promote microtubules assembly and inhibit the disassembly process of microtubules to tubulin[3]. Although very similar in structure and mechanism, the Taxanes, (Taxol and Taxotere), have demonstrated different *in vitro, in vivo*, and clinical activities. Very interestingly an alteration of the structure of one of the asymmetric centers present in Taxol and Taxotere has created their inactive epi-isomers.

Laboratory studies have shown that Taxotere had a more potent antitumor activity than Taxol against some cancer cell lines[4] and less activity against certain cancer cell lines[5]. Over the past decade, our group had studied the synthesis and the anticancer activities of β-lactam derivatives through a series of independent studies[6]. We also had conducted computational studies on the physicochemical and structural properties of different biologically important compounds using classical mechanical and quantum mechanical methods to explore the cause of their biological activities[7].

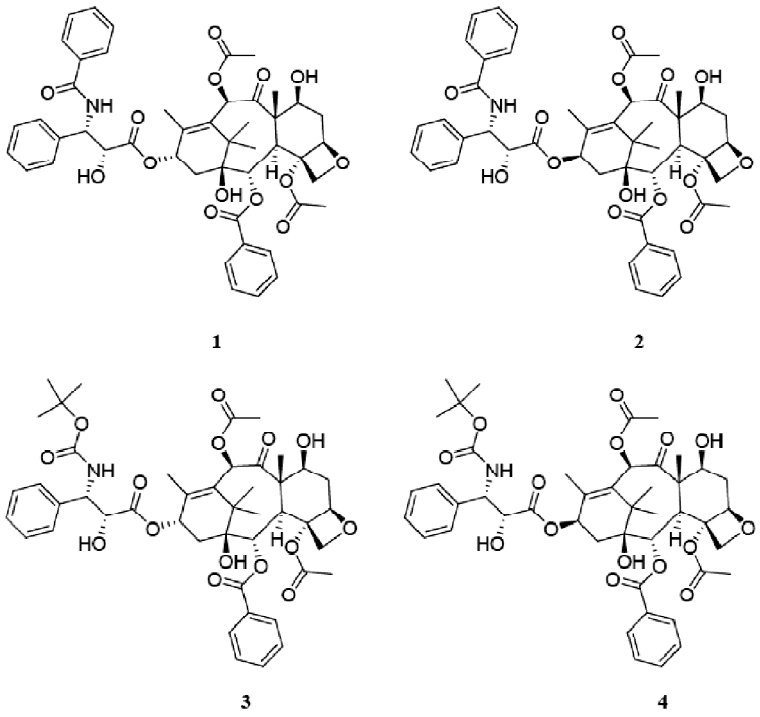
The present study is designed to calculate and compare the physicochemical parameters on the structural properties of Taxol, epi-Taxol, Taxotere, and epi-Taxotere by quantum mechanical theory. Best of my knowledge, this is a novel study on revealing the correlation between physicochemical properties and the medicinal activity of Taxol, Taxotere, and its isomers.

Materials and methods

Compounds:

Four compounds are considered in this study. The molecular structure is shown in Scheme 1.

Compound **1** is Taxol, compound **2** is epi-Taxol (an iso-



Scheme 1. Compounds used for physicochemical calculations.

mer of Taxol), compound **3** is Taxotere, and compound **4** is epi-Taxotere (an isomer of Taxotere). Taxol and Taxotere have the same core structures. But they have a difference in the C_{13} side chain.

Quantum mechanical calculations:

The quantum mechanical calculations such as full geometry optimization and calculation of the physicochemical properties were performed using the SPARTAN 18 software package. All the structures were generated first in 2D models and then converted into their 3D forms. The lowest energy conformer for each molecule was created using the molecular mechanics method with Merck Molecular Force Field (MMFF). Semi-empirical quantum mechanical methods were used to calculate the dipole moment, the simplified versions of the Hartree-Fock (HF) theory. The most successful ones and most frequently used semi-empirical methods included Austin Model 1 (AM1), Parametric Model number 3 (PM3), Recife Model 1 (RM1), and Parametric Model number 6 (PM6) methods. We used all of these methods in this study for calculating the dipole moment. All other quantum mechanical calculations were done on the energy minimized structures using the density functional theory (DFT) method[8], since DFT approach can properly describe the electron correlation effects. B3LYP, the widely employed hybrid model[9] is used for the calculation. This model includes a mixture of Hartree-Fock (HF) and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang, and Parr[10], which is parametrized by Becke[11]. Along with B3LYP, the polarization type basis set 6-31G*[12] is used in this calculation.

Results and discussion

It is highly established that organic compounds, particularly anticancer drugs and drug candidates have profound interactions on the components of cells. Many of these interactions are due to the electronic charges present in the molecules and cancer cells. Based on this simple concept, first, we calculated the ground-state dipole moment of Taxol (compound **1**), epi-Taxol (compound **2**), Taxotere (compound **3**), and epi-Taxotere (compound **4**). Table 1 showed the dipole moment values obtained from four semi-empirical methods (AM1, RM1, PM3, and PM6). All the calculations were done on the energy minimized structures.

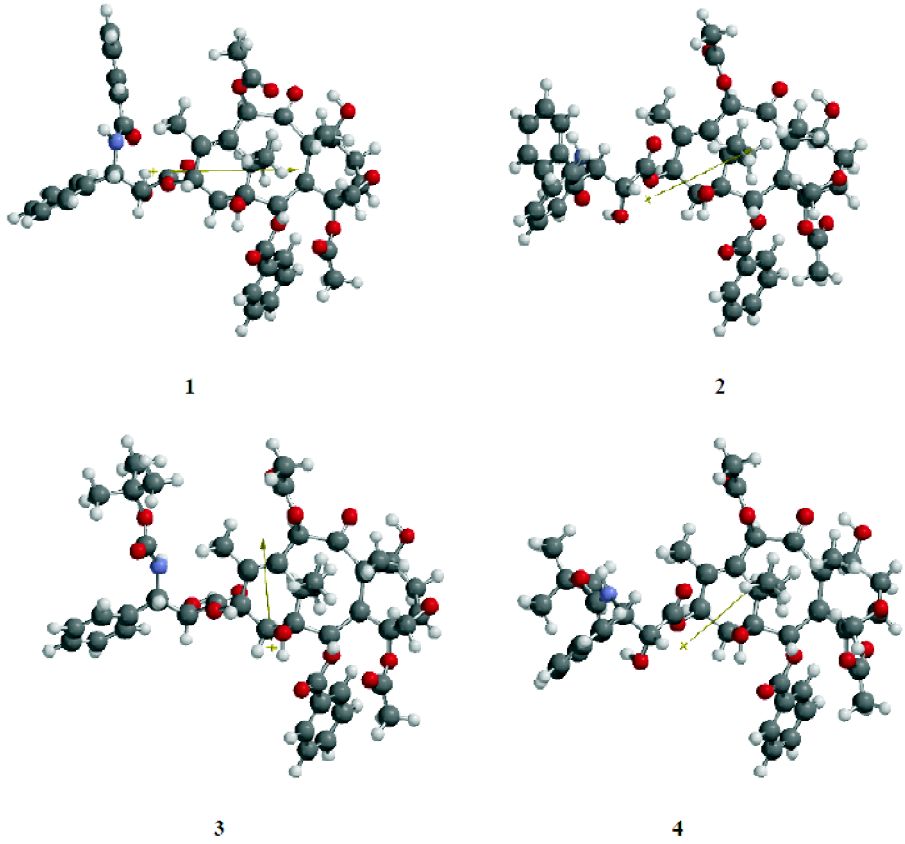
Table 1. Calculated dipole moment values using semi-empirical methods, values are in Debye (D)

Semi-empirical methods	Dipole moment values in Debye			
	Compound **1**	Compound **2**	Compound **3**	Compound **4**
AM1	6.06	2.52	5.51	3.97
RM1	7.03	4.23	6.37	5.45
PM3	6.87	4.58	6.08	5.47
PM6	6.84	3.15	5.48	4.59

It was observed that active compounds, Taxol (compound **1**) and Taxotere (compound **3**) showed a high value of dipole moment, compared to its inactive isomers (compounds **2** and **4**). Compared to other selected calculation methods, AM1 calculation gave the lowest value for dipole moment. But a similar trend was observed with all four compounds. This data indicates that the dipole moment has a significant role in the anticancer activity of Taxol and Taxotere. From the dipole moment calculation, we also found that the dipole moment of Taxol is higher than Taxotere.

The optimized structure of Taxol derivatives obtained from the DFT calculation is shown in Scheme 2. The dipole vector is represented by the arrows in Scheme 2.

The direction of the dipole vectors is different in compound **1** and compound **3**. The vectors are perpendicular to each other. In the case of epi-isomers (compound **2** and compound **4**), the direction of dipole vectors remains the same, lying in the XY plane. The dipole moment and the vector data of these compounds deserve comments. The anticancer activity of Taxol and Taxotere is due to the polar character of these molecules. The high charge density of these two molecules helps them to interact adequately with the polar components of the cells. The perpendicular nature of the vector in these two active molecules is due to the presence of a different side chain (NHCOPh and NHCOBOC) since all other groups are identical. The low dipole moment values in the epi-isomers **2** and **4** indicate that the interactions of these two molecules against the components of the cells are not to a level required for the anticancer activity. This is another



Scheme 2. The optimized structure of compounds **1** and **2** obtained from the DFT calculation.

Table 2. Calculated structural and physicochemical properties of Taxol, Taxotere and isomers

Properties	Compound **1** (Taxol)	Compound **2** (epi-Taxol)	Compound **3** (Taxotere)	Compound **4** (epi-Taxotere)
Weight (amu)	853.91	853.91	849.92	849.92
Energy (au)	–2929.31	–2929.32	–2930.76	–2930.76
Solvation energy (kJ/mol)	–172.06	–174.13	–177.38	–169.12
E HOMO (eV)	–6.21	–6.06	–6.32	–6.05
E LUMO (eV)	–1.58	–1.65	–1.77	–1.69
log P	1.17	1.17	1.53	1.53
Polarizability	107.21	107.36	107.16	107.23
HBD count	4	4	4	4
HBA count	11	11	11	11
Area ($Å^2$)	785.74	788.75	798.29	794.91
Volume ($Å^3$)	825.12	826.26	824.16	824.55
PSA ($Å^2$)	156.14	155.78	167.95	162.36
Ovality	1.85	1.85	1.88	1.87

reason that the dipole vectors of these two molecules follow an identical pattern.

The other structural and physicochemical parameters which are important for quantitative structure-property relationships (QSPR) and quantitative structure-activity relationships (QSAR) modeling analysis, were obtained using DFT calculations. The data obtained are shown in Table 2. The physicochemical and molecular properties related to electronic charge distribution such as molecular weight, total energy, solvation energy, the energy of the highest occupied molecular orbital (E HOMO), the energy of the lowest unoccupied molecular orbital (E LUMO), the octanol-water partition coefficient (log P), polarizability, the number of hydrogen bond donors (HBDs) and the number of hydrogen bond acceptors (HBAs), the surface area, volume of the molecule, polar surface area (PSA) and ovality were identified.

From Table 2 it is observed that most of the structural and physicochemical parameters of Taxol and epi-Taxol were identical. A small variation is observed in solvation energy, E HOMO, E LUMO, area, volume, and PSA. The same trend is found in the case of Taxotere and epi-Taxotere. It indicates that these parameters have less effect in controlling the bioactivity compared to the dipole moment in Taxol and Taxotere derivatives.

A noticeable change is observed in the PSA value; a higher value is observed for compound **3** (Taxotere) and compound **4** (epi-Taxotere). The higher surface areas of compounds **3** and **4** compared to compounds **1** and **2** are expected. Compounds **1** and **2** have a COPh group connected to the nitrogen at the side chain whereas a bulky BOC system is connected to the nitrogen to compounds **3** and **4**. For example, compounds **3** (798.29 $Å^2$) and **4** (794.91 $Å^2$) have more surface areas than compounds **1** (785.74 $Å^2$) and **2** (788.75 $Å^2$). Along with PSA and area, two other parameters like ovality and log P were also higher in compounds **3** and **4**. This is because of the presence of a NHBOC group in **3** and **4**. Compounds **1** and **2** have NHCOPh. The lipophilicity of **3** and **4** is higher than that of **1** and **2**. The parameter polarizability was the same for all four compounds. The polarizability of a molecule is a measure of its ability to respond to an applied electric field and acquire an electric dipole moment.

Even though compounds **2** and **4** showed identical HOMO and LUMO energies, a small variation is observed in the HOMO and LUMO energies of compounds **1** and **3**. To analyze more about this, we considered the frontier molecular orbital density distribution of the studied compounds. The molecular frontier orbitals are important descriptors related to the reactivity of molecules. The E HOMO is linked to the tendency of a molecule to donate electrons to empty molecular orbitals with low energy of convenient molecules. The E LUMO indicates the ability to accept electrons.

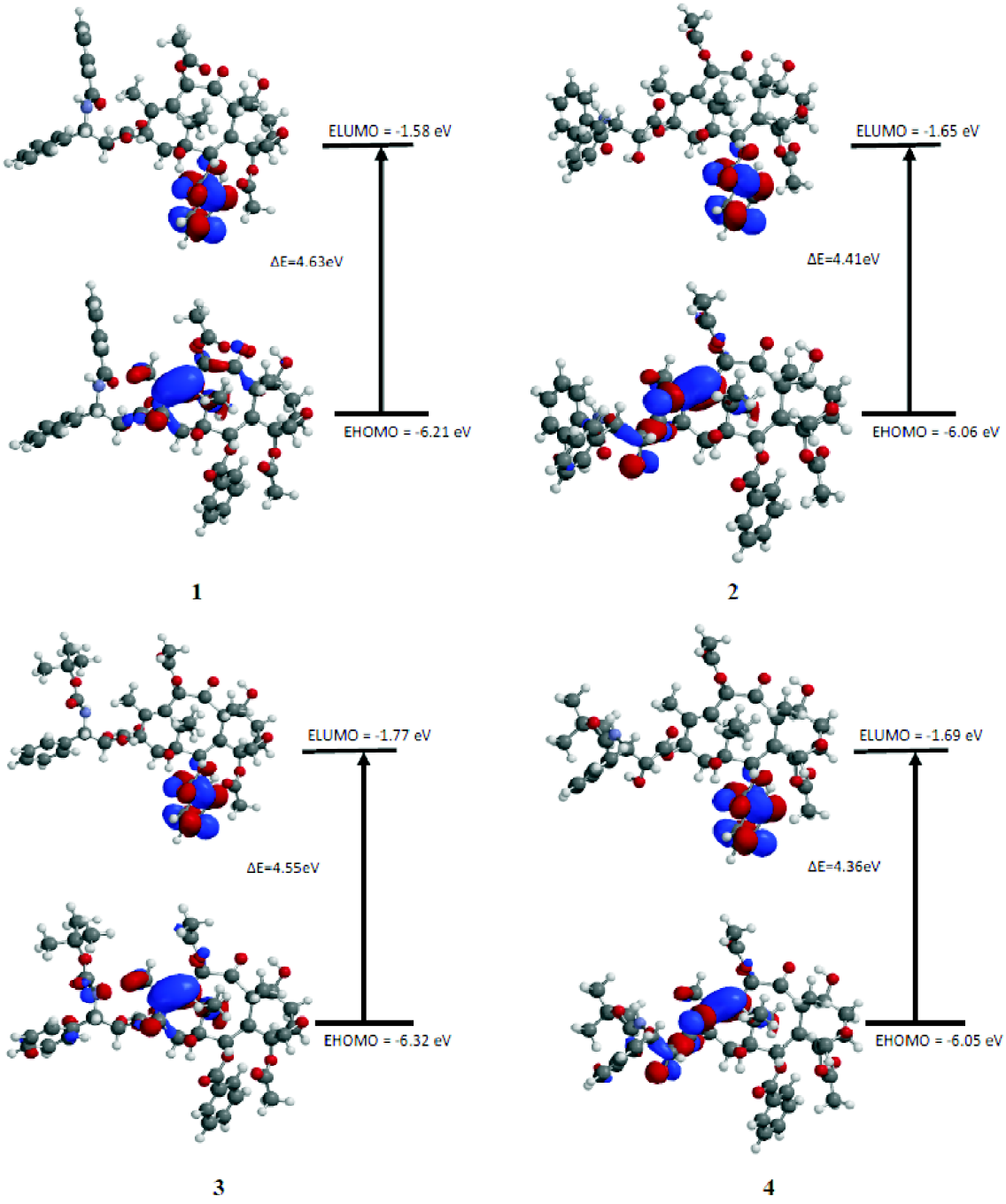


Fig. 1. HOMO-LUMO plots (ground state) and energy diagram of compounds **1**-**4**.

The calculated HOMO and LUMO electron density distributions are presented in Fig. 1. Concerning the HOMO orbital electron density, the localization was different for each compound. In epi-isomers (compound **2** and compound **4**), the electron densities of the HOMO orbitals are mostly localized on the **A** ring and are partially localized on the C_{13} side chain, a very negligible amount of localization is observed in C_{12} and C_{10} side chain also.

In compound **1**, the electron densities of the HOMO orbitals are mostly localized on the **A** ring and are partially

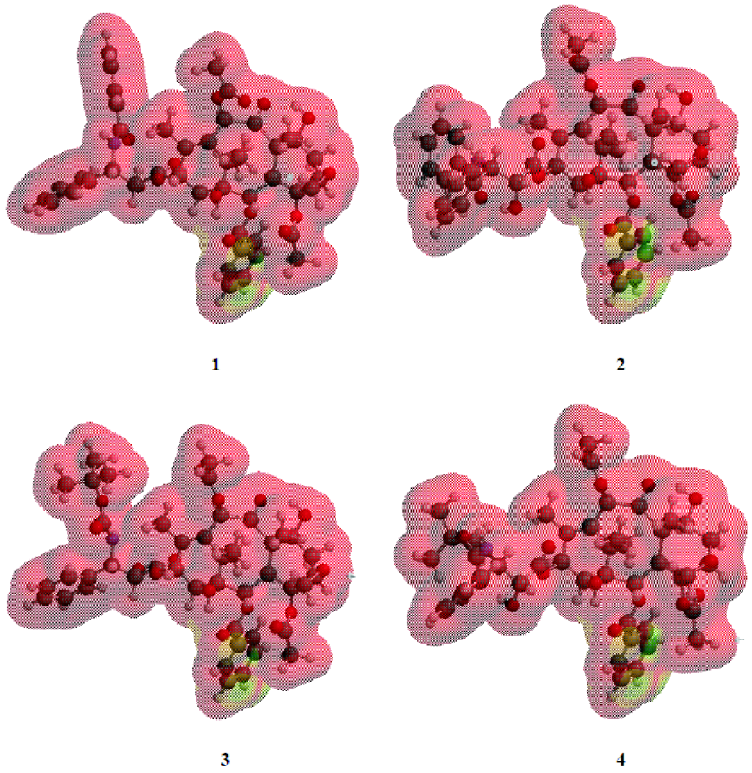


Fig. 2. |LUMO| map of compounds **1**-**4**.

localized on the B ring C_{13}, C_{12}, C_{10}, and C_9 side chains. In compound **3**, the electron densities of the HOMO orbitals are mostly localized on the **A** ring and are partially localized on the **B** ring, all over C_{13}, C_{12}, and C_{10} side chains. This data shows that stereochemistry, the orientation of the C_{13} side chain in these compounds, has an important role in controlling the electron densities of HOMO orbitals. The results show that in all four compounds the electron densities of the LUMO orbitals are localized only on the side chain and were identical. To validate this data, we also analyzed the |LUMO| maps of all the compounds.

Fig. 2 illustrates the |LUMO| maps for Taxol derivatives. Basically |LUMO| map is an indicator of nucleophilic addition and it is provided by an overlay of the absolute value of the lowest unoccupied molecular orbital (LUMO) on the electron density. From the map, it is clear that the LUMO map is identical for all the compounds. It again confirms the identical LUMO energy for all the compounds. The colors toward red indicate small (near zero) values of the LUMO.

We also had calculated other parameters such as energy gap (ΔE), ionization potential (I), electron affinity (A), electronegativity (χ), global hardness (η), softness (σ), chemical potential (μ), and global electrophilicity index (ω). These values were calculated from the HOMO and LUMO energy diagram. The obtained values are listed in Table 3.

The energy gap (ΔE) helps to characterize the chemical reactivity and kinetic stability of the compounds[13]. Even though the bandgap values of all the compounds are com-

Table 3. Calculated quantum parameters of compounds **1**-**4**

Properties	Compound **1** (Taxol)	Compound **2** (epi-Taxol)	Compound **3** (Taxotere)	Compound **4** (epi-Taxotere)
ΔE (eV)	4.63	4.41	4.55	4.36
I (eV)	6.21	6.06	6.32	6.05
A (eV)	1.58	1.65	1.77	1.69
χ (eV)	3.89	3.85	4.04	3.87
η (eV)	2.31	2.20	2.27	2.18
σ	0.43	0.45	0.44	0.45
μ	–3.89	–3.85	–4.04	–3.87
ω	3.27	3.36	3.59	3.43

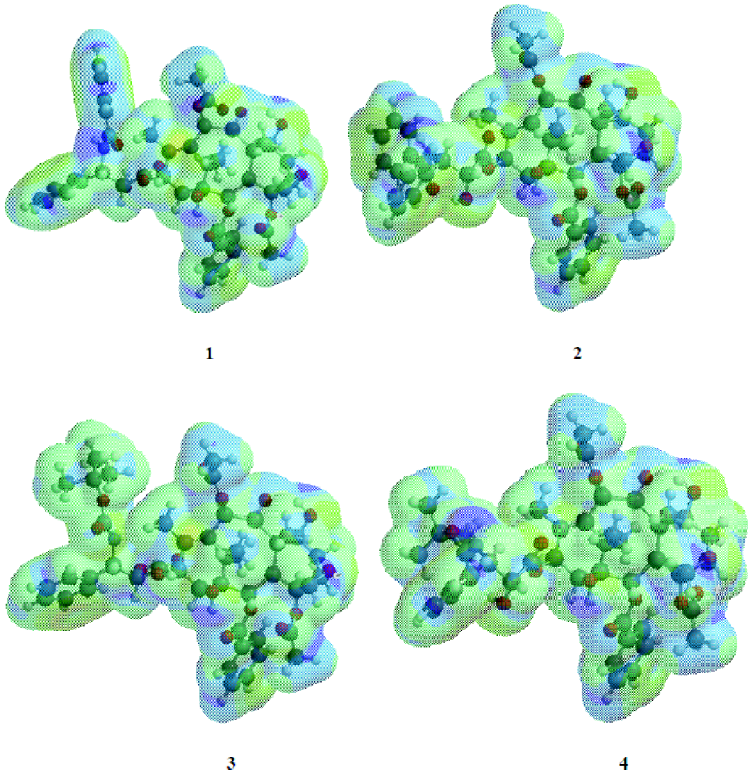


Fig. 3. Local ionization potential map of compounds **1**-**4**.

parable in this case, compound **1** showed a high value, followed by compound **3**, compound **2,** and compound **4**. The one with the highest bandgap will have low reactivity (the most chemically stable). The high ΔE value (4.63 eV) in compound **1** is due to the comparably high value of E LUMO (–1.58 eV). Low μ and high ω represent the electrophilic behavior of the compound. Also, high μ and low ω represent the nucleophilic nature of the compound.

High ionization potential (I) represents low reactive and less electron donor. Compounds **1** and **3** showed high ionization potential compared to epimers due to the low value of E HOMO. Local ionization potential maps of the compounds are represented in Fig. 3.

The ionization potential is useful to assess chemical reactivity and selectivity, in terms of electrophilic reactions. It represents an overlay of the energy of electron removal (ionization) on the electron density. For compound **1**, the energy ranges from 8.49 eV (Min) to 15.40 eV (Max); for compound **2**, the energy ranges from 9.11 eV (Min) to 15.33 eV (Max); for compound **3**, the energy ranges from 8.56 eV (Min) to 15.24 eV (Max); for compound **4**, the energy ranges from 9.09 eV (Min) to 15.30 eV (Max). The variations in these values are in accordance with the variations in their ionization energies.

The graphical quantity like electrostatic potential was also analyzed to locate the activity descriptors, along with local ionization potential and LUMO maps. These graphical quantities usually provide a visual representation of the chemically active sites and comparative local reactivity of the compound.

The electrostatic potential map is also used to analyze the chemical reactivity of a molecule. This graphical analysis is important for the identification of the reactive sites of nucleophilic or electrophilic attacks in hydrogen bonding interactions and the understanding of the process of biological recognition. The electrostatic potential map of all four compounds is shown in Fig. 4. The red region represents the highest electron density (negative potential), the blue region represents the highest positive potential, and the green region represents the neutral electrostatic potential. From Fig.

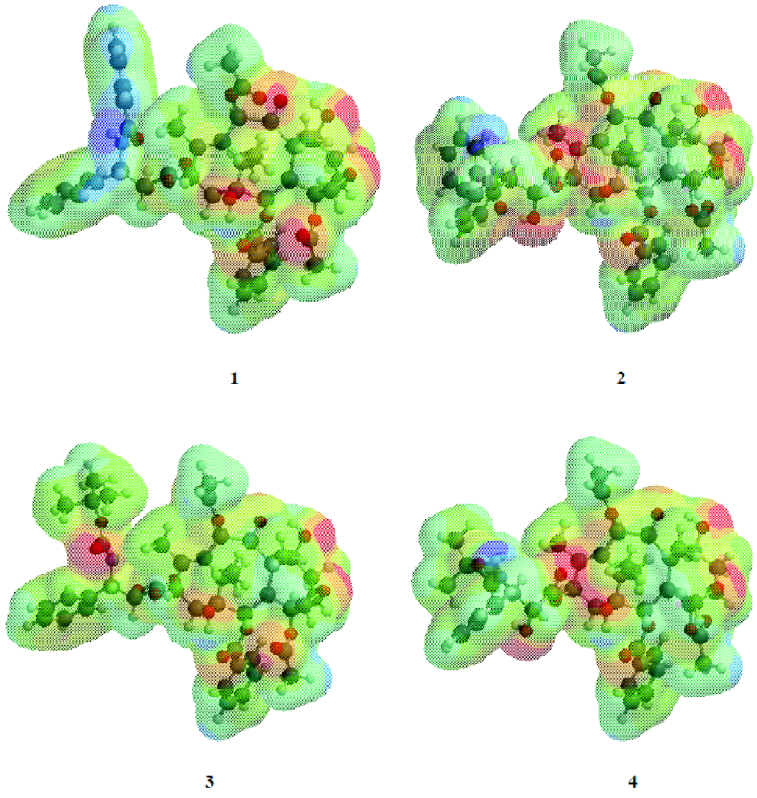


Fig. 4. Electrostatic potential map of Taxol derivatives (compounds **1**-**4**).

4, it is clear that the electrostatic potential map for all four compounds shows hydrophilic regions (negative and positive potentials) and hydrophobic regions (neutral). For compound **1**, the negative potential presents a maximum value of –202.66 kJ/mol and the positive electrostatic potential presents a maximum value of 229.32 kJ/mol. For compound **2**, the negative potential presents a maximum value of –204.61 kJ/mol and the positive electrostatic potential presents a maximum value of 219.14 kJ/mol.

For compound **3**, the negative potential presents a maximum value of –183.27 kJ/mol and the positive electrostatic potential presents a maximum value of 150.83 kJ/mol. For compound **4**, the negative potential presents a maximum value of –204.68 kJ/mol and the positive electrostatic potential presents a maximum value of 199.61 kJ/mol. Compound **3** (Taxotere) has the highest negative and lowest positive potential values compared to other compounds. Followed by compound **1**, which has the second-highest negative potential value. The negative potential of epi-isomers (compounds **2** and **4**) was identical.

Conclusion

In this work, I have analyzed the structural and physicochemical parameters of Taxol, epi-Taxol, Taxotere, and epi-Taxotere, to identify the main cause of their anticancer activity. The physicochemical properties are analyzed with DFT calculations. The physicochemical properties such as log P, polarizability, E LUMO, the volume of the molecule, solvation energy, and ovality are identical for the isomers. However, a huge difference in dipole moment value and small variation in HOMO energy is observed for active and inactive compounds. The dipole moment values are higher and HOMO energies are lower for active compounds. This study indicates that the dipole moment has a significant role in having the biological activity of these compounds. The dipole moment is the most important activity descriptor in Taxol related compounds compared to other physicochemical parameters. However, this dipole moment study does not indicate that high dipole moment controls the biological activity of Taxol derivatives. Rather, the study identified a direct cor-

relation between the dipole moment and activity. This study is unique since such explorations with Taxol derivatives and their biological activity has never been performed. The graphical quantity like electrostatic potential, local ionization potential, and LUMO maps are also analyzed to validate the data.

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