Heterocyclic Letters
Vol. 13| No.1|17-26|November -January|2023
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

COMPUTATIONAL STUDIES OF PHYSICOCHEMICAL PARAMETERS ON OPTICALLY ACTIVE ANTICANCER BETA-LACTAMS

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ABSTRACT:
The current study investigates the correlation between *in vitro* anticancer activity and physicochemical parameters of a few specific optically active β-lactams. Theoretical studies on enantiomeric *trans*-β-lactams were performed using different quantum mechanical and classical mechanical methods. The computational methods used in this study include Density Functional Theory (DFT) method, Møller–Plesset (MP) method, Hartree-Fock (HF) method, Semi-empirical method, and Molecular Mechanics (MM) method. Physicochemical and geometrical parameters such as weight, total energy, solvation energy, dipole moment, the energy of the highest occupied molecular orbital (E HOMO), the energy of the lowest unoccupied molecular orbital (E LUMO), polarizability, the octanol-water partition coefficient (Log P), polar surface area (PSA), the number of hydrogen bond donors (HBDs), the number of hydrogen bond acceptors (HBAs), the surface area, volume of the molecule, ovality, energy gap (ΔE), ionization potential (I), electron affinity (A), electronegativity (χ), global hardness (η), softness (σ), chemical potential (μ) and global electrophilicity index (ω) are analyzed to identify a correlation with experimental anticancer activity of β-lactams. To the best of our knowledge, this is the first report on the relationships between physicochemical parameters and anticancer activities of optically active β-lactams.

KEYWORDS: β-Lactam, QSAR, Anticancer, Dipole Moment, DFT, HF, AM1, RM1, PM3, PM6, and MNDO

INTRODUCTION

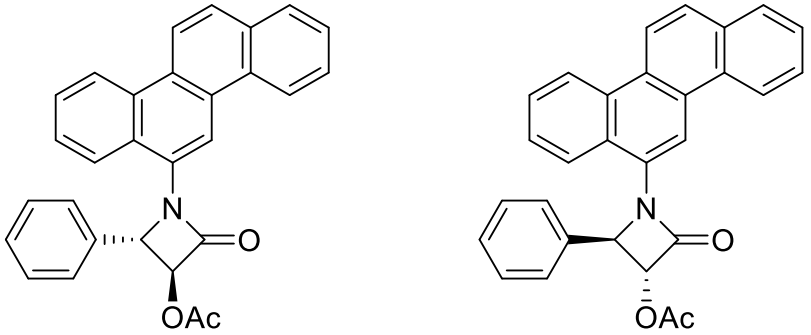
Beta-Lactams are pharmaceutically important compounds. These compounds have a wide spectrum of biological activities. These include anticancer [1-10], antifungal [11], antibacterial [12], anti-inflammatory [13], antihepatitis [14], cholesterol absorption inhibitors [15-18], analgesic properties [19] and antihyperglycemic [20]. Over the past decade, our

group has widely studied the synthesis and the anticancer activities of β-lactam derivatives through a series of independent studies [1-10, 21, 22].

A slow success rate of other chemotherapeutic agents has led to increased interest in the development of novel β-lactam-based anticancer drugs. It is well known that an optically active isomer of a racemic compound has higher and much selective biological activity. The anticancer activity studies of our racemic β-lactams had prompted us to devise a method for the preparation of the optically active analogues. Our group had reported for the first time the synthesis and biological evaluation of optically active anticancer β-lactams [10]. We realize that theoretical studies on the physicochemical and geometrical properties of β-lactams using quantum mechanical or classical mechanical methods may be one of the ways to understand the cause of their anticancer activities. We report here physicochemical and geometrical parameters including weight, total energy, solvation energy, dipole moment, the energy of the highest occupied molecular orbital, the energy of the lowest unoccupied molecular orbital, polarizability, the octanol-water partition coefficient, polar surface area, the number of hydrogen bond donors, the number of hydrogen bond acceptors, the surface area, volume of the molecule, ovality, energy gap, ionization potential, electron affinity, electronegativity, global hardness, softness, chemical potential and global electrophilicity to identify a correlation with anticancer activity of β-lactams.

MATERIALS AND METHODS

Two optically active β-lactams used for the theoretical calculation are shown in **Scheme 1**. These β-lactams have a chrysene group linked to N_1 position of the ring, oxygen at the C_2 position, an acetoxy group at the C_3 position of the ring and a phenyl group at the C_4 position. Both are *trans*-β-lactams and the compound (+)-**2** is the chiral isomer of compound (-)-**1**.



1 **2**

Scheme 1: β-lactam isomers used for the theoretical calculation

Theoretical calculations for the compounds were obtained using the SPARTAN 18 software package. The following five different calculation methods including quantum mechanical and classical mechanical methods are used for the calculations.

Semi-empirical method:

Semi-empirical methods are based on quantum mechanics. These methods are simplified versions of the Hartree-Fock theory. Due to the use of the zero differential overlap approximation, calculations based on these methods are much faster than their ab initio counterparts. The most successful ones and most frequently used Semi-empirical methods are modified neglect of differential overlap (MNDO) [23], Austin Model 1 (AM1) [24] and Parametric Model number 3 (PM3) [25]. All three methods are based on the Neglect of Differential Diatomic Overlap (NDDO) integral approximation. New versions of the NDDO methods such as Recife Model 1 (RM1) [26] and Parametric Model number 6 (PM6) [27] methods have been developed by reparametrized the existing methods. In this study, we have used all these methods for calculating the dipole moment. All the calculations were

performed with equilibrium geometry at the ground state by changing AM1, RM1, PM3, PM6, and MNDO Hamiltonians. All the structures were drawn in 2D and then converted into their 3D forms using the same software.

Molecular Mechanics (MM) method:

The molecular mechanics method is based on classical mechanics. This method, using classical force fields, is a highly efficient way to calculate molecular energies and other physicochemical parameters. In this study, we used molecular mechanics with Merck Molecular Force Field (MMFF) for dipole moment calculation. All the structures were drawn in 2D and then converted into their 3D forms using the same software followed by their energy minimization procedure and the optimization was done using MMFF94.

Hartree-Fock (HF) method:

The Hartree-Fock (HF) method is a variational method for the determination of the energy and the wave function of a quantum many-body system. HF models follow from the Schrödinger equation by requiring that the electrons be independent particles, the Hartree-Fock approximation. For the dipole moment calculation, after the energy minimization procedure, the geometry optimization was done using the 6-31G* basis sets.

Density Functional Theory (DFT) method:

Correlated models are the models that lessen the effects of the Hartree-Fock approximation. Those are divided into two broad categories, density functional models and wave function-based models. Density functional theory (DFT) is a quantum mechanical modelling method. It is mainly used to investigate the electronic structure (or nuclear structure) of many-body systems, in particular atoms, molecules, and the condensed phases. DFT is presently the most successful and the most promising approach to compute the electronic structure of matter. It is possible to make the DFT calculations at a different level using different basis sets. In this study, after the energy minimization procedure, the structures were optimized using the 6-31G* basis sets at the B3LYP level. This results in the most stereochemically stable structure of each compound.

Møller–Plesset (MP) Method:

Møller–Plesset perturbation theory (MP) method is a quantum chemistry post-Hartree–Fock ab initio methods in the field of computational chemistry [28]. MP method improves on the Hartree–Fock method by adding electron correlation effects by means of Rayleigh–Schrödinger perturbation theory (RS-PT). Mainly, second (MP2), [29] third (MP3), [30, 31] and fourth (MP4) [32] order Møller–Plesset calculations are standard levels used for calculation of basic systems. In current work, we have used the 6-31G* basis sets at the MP2 level for optimization.

RESULTS and DISCUSSIONS

We tested these optically active β-lactams **1** and **2** against human cancer cell lines and observed a considerable difference in the anticancer activities. Anticancer activities of these β-lactams are shown in **Table 1**. Tests were done against seven human cancer cell lines. MDA-231 is human breast cancer cells; BRO is human melanoma cells; SKOV-3 is human ovarian cancer cells; HT-29 is human colon cancer cells; PC-3 is human prostate cancer cells; HL-60 and K-562 are human blood cancer cells. The details of synthesis and anticancer activity were discussed before [10]. The data from cisplatin, the anti-cancer chemotherapy drug, is included in **Table 1** as a reference.

	Cisplatin	**1**	**2**
MDA-231	12.33	1.8	8.5
BRO	7.66	6.1	22
SKOV-3	5.99	6.8	8.5

HT-29	16.99	0.7	8.3
PC-3	4.66	1.4	15.5
HL-60	1.66	0.7	5.4
K-562	2.33	1.1	6

Table 1: In vitro cytotoxicity of β-lactams on seven human cancer cell lines (μM)

The cell growth inhibition data (IC_{50}) suggests that the β-lactams, (-)-**1**, demonstrate significantly increased activity against six human tumor lines compared to cisplatin and compound (+)-**2**. The results also showed that the activity of **1** is not uniform against all tumor lines, which suggests that the target of the action of this compound is highly specific. Compound **1** showed the highest activity against colon cancer cell line (HT-29) and blood cancer cell line (HL-60). Even though the compound **2** showed activity against all seven human cancer cell lines, it was weak compared to cisplatin and compound **1**. Computational molecular analysis is the best way to explain this activity difference in these isomers.

It is known that organic compounds, particularly anticancer drugs and drug candidates have intense interactions on the components of cells. The main reason for these interactions is the electronic charges present in the drug molecules and cancer cells. Based on this known concept, first we calculated the dipole moment of these β-lactams. The ground-state dipole moment values were calculated for compounds **1** and **2** is shown in **Table 2**. The values were calculated using five Semi-empirical methods (AM1, RM1, PM3, PM6, and MNDO). It was observed that trans β-lactam **1** showed a high value of dipole moment, ranging from 7D to 6D. The dipole moment value of trans β-lactam **2** was in the range of 4.34 D to 5.12D. Compared to other selected calculations methods, MNDO calculation gave the lowest value for dipole moment. But a similar trend was observed with compounds **1** and **2**.

Semi-empirical methods	**Dipole moment Values**	
	Compound 1	**Compound 2**
AM1	7.1	5.12
RM1	6.93	5.02
PM3	6.65	4.82
PM6	7.14	4.63
MNDO	6	4.34

Table 2: Calculated dipole moment values using semi-empirical methods, values are in Debye (D).

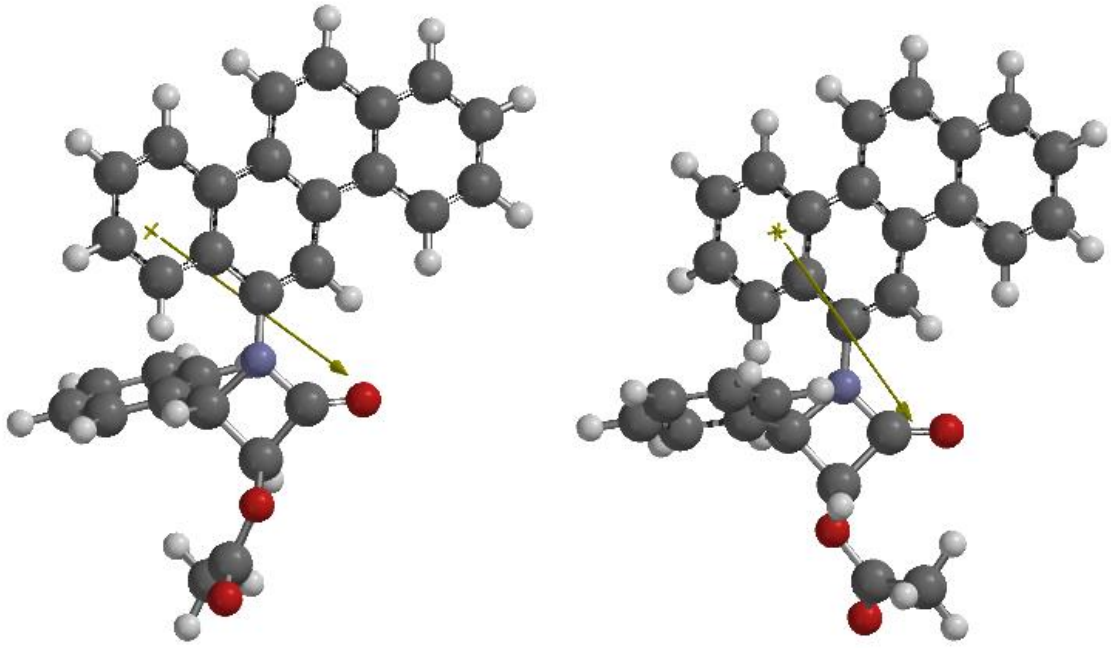
To confirm the result, the dipole moment calculations were also done using other quantum mechanical methods such as Hartree-Fock (HF) method, Density Functional Theory (DFT) method, Møller-Plesset (MP) Method and a classical mechanics method, and the Molecular Mechanics (MM) method. The results obtained were shown in **Table 3**. The values obtained from the AM1/semi-empirical method were also included for comparison. The results again proved that compound **1** has a higher dipole moment than its chiral isomer **2**. Compared to other selected calculations methods, the MM method showed the highest value for the dipole moment. MP method took more CPU time for the successful completion of the calculation compared to other methods.

It is understandable that optical isomers should not differ in their dipole moment values regardless of these values. However, some differences of dipole moment values are seen in the calculation of five different methods.

Methods	**Dipole moment Values**	
	Compound 1	**Compound 2**
AM1	7.1	5.12
DFT	6.75	5.92
MM	6.93	5.95
HF	7.17	6.04
MP	7.10	6.01

Table 3: Calculated dipole moment values using different methods, values are in Debye (D).

The compound **1** showed high anticancer activity than compound **2**.
The optimized structure of β-lactams **1** and **2** obtained from the DFT calculation is shown in **Scheme 2**. The arrows in the scheme represent the dipole vector. The dipole vector of isomers is in a different direction. In compound **2**, the vector arrow is not fully directed to the oxygen atom of the β-lactam carbonyl group. In contrast, the vector arrow is fully directed to the carbonyl group of the β-lactam ring in compound **1**. The optimized structures of **1** and **2** indicate that the distance between the phenyl group at C_4 and the acetoxy group at C_3 in **1** is less than that of **2**.



1 **2**

Scheme 2: The optimized structure of β-lactams **1** and **2** obtained from the DFT calculation

The other physicochemical parameters which are important for the structure activity relationship (SAR), structure property activity relationship (SPAR) and quantitative structure activity relationship (QSAR) were also calculated. To check the authenticity of the data we used three different calculation methods such as Density Functional Theory (DFT) method, Hartree-Fock (HF) method and Møller–Plesset (MP) Method. The physicochemical and molecular properties 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), polarizability, the octanol-water partition coefficient (Log P), polar surface area (PSA), the number of hydrogen bond donors (HBDs), the number of hydrogen bond acceptors (HBAs), the surface area, volume of the molecule, and ovality were identified. The obtained data are shown in **Table 4**.

From **Table 4** it is observed that most of the structural and physicochemical parameters of compounds **1** and **2** were identical. A very negligible variation is observed in E HOMO, E LUMO, area, volume, and PSA. The same trend is found in all the calculation methods. It indicates that these parameters have less effect in controlling the bioactivity compared to dipole moment.

Properties	**DFT**		**MP**		**HF**	
	1	**2**	**1**	**2**	**1**	**2**
Weight (amu)	431.49	431.49	431.49	431.49	431.49	431.49
Energy (au)	-1398.18	-1398.18	-1393.85	-1393.86	-1389.48	-1389.49
E HOMO (eV)	-5.53	-5.57	-7.14	-7.17	-7.57	-7.60
E LUMO (eV)	-1.58	-1.63	1.79	1.76	2.06	2.03
Log P	5.32	5.32	5.32	5.32	5.32	5.32
Polarizability	76.66	76.63	75.33	75.34	75.06	75.05
HBD count	0	0	0	0	0	0
HBA count	3	3	3	3	3	3
Area ($Å^2$)	445.34	442.51	435.02	436.58	444.74	443.05
Volume ($Å^3$)	446.49	446.11	444.54	444.68	443.23	443.05
PSA ($Å^2$)	36.83	36.16	37.28	36.44	36	35.61
Ovality	1.58	1.57	1.54	1.55	1.58	1.58

Table 4: Calculated structural and physicochemical properties of β-lactams **1** and **2**

We also had calculated the reactivity descriptors 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) at the B3LYP/6-31G* level of theory. The obtained values are listed in **Table 5**. Both the compounds showed comparable values.

Properties	**β-lactam 1**	**β-lactam 2**
ΔE (eV)	3.95	3.94
I (eV)	5.53	5.57
A (eV)	1.58	1.63
χ (eV)	3.55	3.6
η (eV)	1.97	1.97
σ	0.25	0.25
μ	-3.95	-3.94
ω	3.96	3.94

Table 5: Calculated quantum parameters of β-lactams **1** and **2.**

We also analyzed some useful graphical models, such as local ionization potentials, LUMO map, and electrostatic potentials, to insight the electron density, nucleophile regions, and electrophile regions.

The most commonly employed and (to date) most important property map is the electrostatic potential map. It provides an indicator of charge distribution in a molecule. 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 attack in hydrogen bonding interactions and the understanding of the process of biological

recognition. The electrostatic potential map of β-lactam isomers is shown in **Figure 1**. 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 **Figure 1**, it is clear that the electrostatic potential map for all the two compounds shows hydrophilic regions (negative and positive potentials) and hydrophobic regions (neutral) and are comparable.

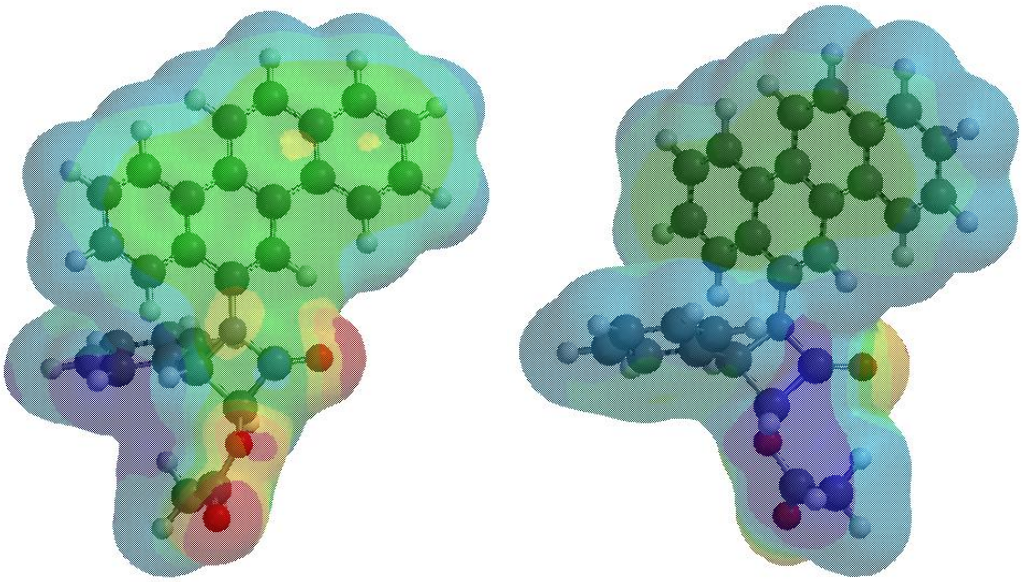


Figure 1: Electrostatic potential map of Compound **1** and **2**

For Compound **1**, the negative potential presents a maximum value of -273.80 kJ/mol and the positive electrostatic potential presents a maximum value of 136.72 kJ/mol. For Compound **2**, the negative potential presents a maximum value of -284.61 kJ/mol and the positive electrostatic potential presents a maximum value of 134.52 kJ/mol.

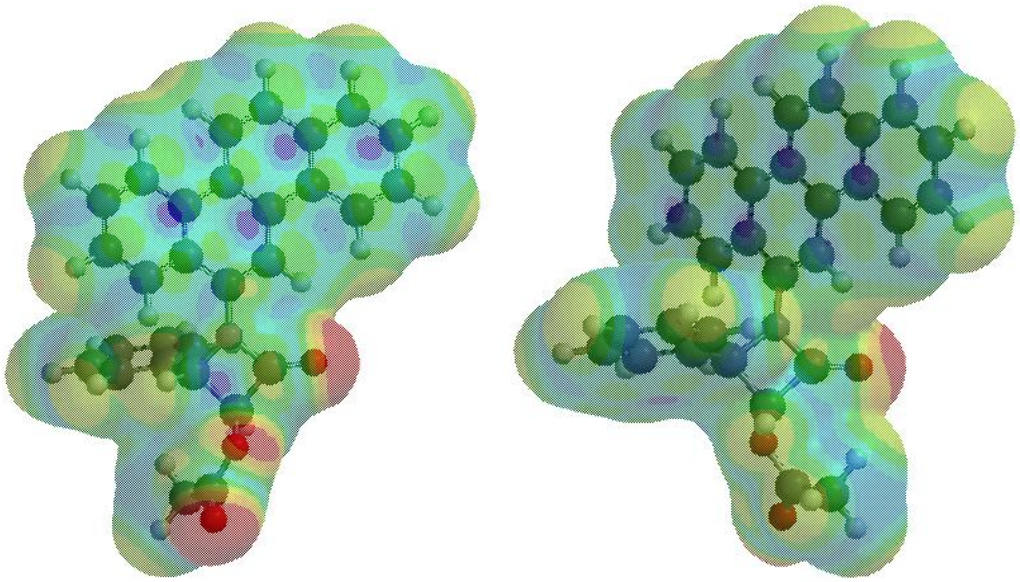


Figure 2: Local ionization potential map of compounds **1** and **2**

Mapping the local ionization potential onto a size surface reveals those regions from which electrons are most easily ionized. Local ionization potential maps of the compounds are represented in **Figure 2**. The ionization potential is also 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 13.74eV (Min) to 42.94eV(Max); for compound **2**, the energy ranges from 12.99eV (Min) to 43.39eV(Max). No variations observed in the map and energy range values.

Figure 3 illustrates the |LUMO| maps for β-lactams isomers. Basically |LUMO| map reveals the most electron-deficient sites on a molecule, that is, those which are most susceptible to attack by a nucleophile. That is, it 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 two compounds. It again confirms the identical LUMO energy for all the compounds. The colors toward red indicate small (near zero) values of the LUMO.

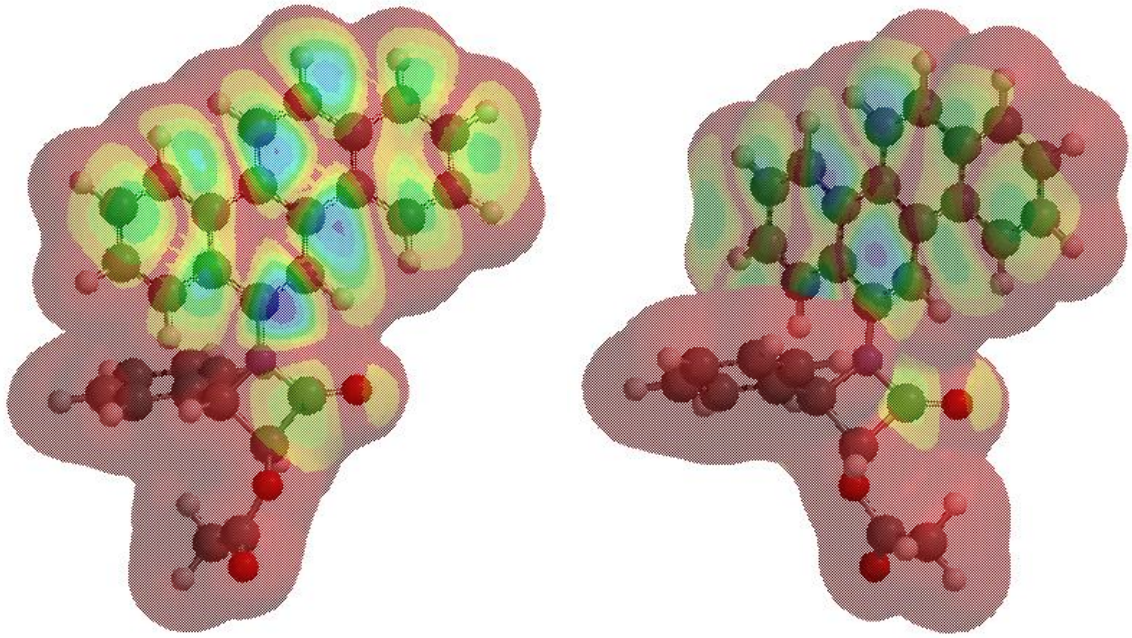


Figure 3: |LUMO| map of compounds **1** and **2**.

CONCLUSIONS

In this work, we have calculated the physicochemical and geometrical parameters such as weight, total energy, solvation energy, dipole moment, E HOMO, E LUMO, polarizability, Log P, PSA, HBD, HBA, surface area, volume of the molecule, Ovality, energy gap (ΔE) ionization potential (I), electron affinity (A), electronegativity (χ), global hardness (η), softness (σ), chemical potential (μ) and global electrophilicity index (ω) of optically active β-lactams. This study is unique since such explorations with optically active *trans*-enantiomeric β-lactams and their anticancer activity have never been performed. The graphical quantity like electrostatic potential, local ionization potential, and LUMO maps were also analyzed to validate the data.

CONFLICT OF INTEREST

The authors confirm that this result has no conflict of interest.

ACKNOWLEDGEMENTS

AD and BKB are grateful to Prince Mohammad Bin Fahd University for support. BKB is also grateful to US NIH, US NCI and Kleberg Foundation of Texas for financial support.

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Received on November 25, 2022.