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Benchmark Study of Computational Methods for Predicting Partition Coefficient of Chlormethiazole

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Abstract: The present study contains the evaluations of lipophilicity estimation, HOMO-LUMO analysis, and electrostatic surface properties of Chlormethiazole molecule by using quantum chemical calculation techniques. All geometrical optimizations, energy and frequency calculations were carried out with six different basis sets by choosing the Hartree-Fock (HF) method and two different Density Functional Theory (DFT) functionals B3LYP and B3PW91. All calculations were repeated for the water and n-octanol phases by using SMD solvation model in order to investigate the solvent effect and also to obtain the Gibbs free energies of solvation that help to estimate partition coefficients. As a result, among the applied theoretical methods, the best agreement with the experimental logP value was obtained with the HF/6-31G(d,p) method. Also, it is concluded that the forecast performance of the computational methods decreases in the following order: HF> B3LYP> B3PW91.

Keywords: Chlormethiazole, DFT, HOMO-LUMO, Lipophilicity

Klormetiyazol'ün Partisyon Katsayısının Tahmin Edilmesi için Hesaplamalı Yöntemlerin Kıyaslama Çalışması

Öz: Bu çalışma, kuantum kimyasal hesaplama teknikleri kullanılarak Klormetiyazol molekülünün lipofiliklik tahmini, HOMO-LUMO analizi ve elektrostatik yüzey özelliklerinin değerlendirmelerini içermektedir. Tüm geometrik optimizasyonlar, enerji ve frekans hesaplamaları, Hartree-Fock (HF) yöntemi ve iki farklı Yoğunluk Fonksiyonel Teori (YFT) fonksiyoneli B3LYP ve B3PW91 seçilerek altı farklı temel set ile gerçekleştirilmiştir. Çözücü etkisini araştırmak ve ayrıca partisyon katsayılarını tahmin etmeye yardımcı olan Gibbs solvasyon serbest enerjilerini elde etmek için tüm hesaplamalar su ve n-oktanol fazları için SMD solvasyon modeli kullanılarak tekrarlanmıştır. Sonuç olarak, uygulanan teorik yöntemler arasında deneysel logP değeri ile en iyi uyum HF/6-31G(d,p) yöntemi ile elde edilmiştir. Ayrıca hesaplamalı yöntemlerin tahmin performansının HF> B3LYP> B3PW91 sırasıyla azaldığı sonucuna varılmıştır.

Anahtar Kelimeler: Klormetiazol, DFT, HOMO-LUMO, Lipofiliklik

1. Introduction

Pharmacokinetics examines the processes of absorption, distribution, metabolism and excretion (ADME) of a drug in the body. The extent of the ADME process largely depends on the structural and physicochemical properties of the drug such as shape, lipophilicity, solubility, dissociation constant, protein binding, hydrogen bonding, and molar refractivity. Lipophilicity is a crucial determinant of the utility of a drug candidate that may have a remarkable impact on the pharmacokinetic properties [1]. Many studies have interpreted the correlation between lipophilicity and pharmacokinetic properties [2-5]. In order to carry through the desired selectivity and

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effectiveness of drugs, the development of highly lipophilic drugs is increasingly demanded as a result of the lipid character of biological targets [6]. Expressing the lipophilic character with a numerical scale in drug design studies is very advantageous in terms of providing a prediction of how hydrophilic and how hydrophobic the designed drug is. The quantitative expression of the lipophilicity is logarithm of the partition coefficient (logP) that acquired by measuring the partitioning of a solute between two immiscible solvents system. The water/n-octanol solvent system is the most commonly used system [7]. Therefore, the prediction and evaluation of partition coefficients for a particular drug class plays an influential role for the pharmacological sciences. At this point, it is a quite advantageous choice to use the quantum chemical computation techniques, which provide much information about the drug candidate while it is still in the synthesis stage. The rapid advancement of computational techniques has made computer-aided drug design (CADD) a progressively beneficial tool for the modelling, analysis and management of drug candidates [8]. For data modelling of drugs, quantitative structure–activity relationship (QSAR) and quantitative structure–property relationship (QSPR) studies have been performed frequently over years with a wide variety of biological and physicochemical data [9-11]. The reliability and validity of the property/activity predictive power of a QSPR/QSAR model vary depending on the convenience of calculated molecular descriptors. Many molecular descriptors can be found through quantum chemical calculations.

In this study, the partition coefficient was estimated for the chlormethiazole molecule by using quantum chemical calculations. Chlormethiazole (also called clomethiazole or heminevrin; 5-(2-chloroethyl)-4-methyl-1,3-thiazole, CMZ) is a thiazole derivative that is generally used as sedative, hypnotic and anticonvulsant [12]. It is chemically interrelated to vitamin B1. It has been in medical use for years primarily as a treatment for acute ethanol withdrawal and seizures. Additionally, there are several clinical studies on a variety of animals and it is supposed that the bioactivity parallels the drug concentration in the brain [13-14]. LogP survey was performed for some hypnotics which have been in clinical use including CMZ, and it was observed that the n-octanol-water partition coefficients were close to 2 [4].

2. Computational Methods

All quantum chemical calculations were carried out by using GAUSSIAN 09W software package [15] and also, 3D HOMO-LUMO diagrams and ESP maps were visualized by using GAUSSVIEW 5 molecular visualization software [16]. The geometrical optimization and frequency calculations of CMZ have been performed by using both Density Functional Theory methods B3LYP/ B3PW91 [17-20] with six different basis sets and Hartree-Fock [21] methods with same basis sets. No imaginary frequencies were found from vibration frequency analysis. In order to estimate partition coefficient of CMZ, Gibbs free energies of solvation were calculated in water and n-octanol phases. SMD solvent model was used to simulate the solvent media [22]. In addition, electrostatic surface properties examination and frontier molecular orbital analysis were performed by using same methodologies. The ionization energy ($I = -E_{HOMO}$) and electron affinity ($A= -E_{LUMO}$) values which are introduced by the Koopmans' Theorem [23] are calculated by means of the energies of frontier molecular orbitals. Accordingly, some quantum chemical descriptors used to determine the chemical reactivity behavior of CMZ were calculated with the data obtained from the HOMO-LUMO analysis [24-26].

3. Results and Discussion

3.1. LogP Calculation of CMZ

The partition coefficient can be obtained experimentally by applying the shake-flask method [27], generator column method [28] and reverse phase high performance liquid chromatography [29]. In

turn, the $logP_{ow}$ can be stated in terms of the transfer free energy between the n-octanol and water phase theoretically [30]. In pharmaceutical screening, it is highly beneficial to use computational methods to predict the logP values instead of using expensive and time-consuming experimental methods. By using Gibbs free energies of solvation in water and n-octanol phases, one can calculate the partition coefficient, according to the expression given below:

$$LogPow = \frac{\Delta Gwater - \Delta Gn - octanol}{2.303RT} \quad (1)$$

In the formula, R and T represent gas constant and temperature, respectively.

Table 1. Calculated solvation free energies and $logP_{ow}$ values of CMZ

		ΔG_{solv} (kcal/mol)			
	Basis Set	ΔG_{water}	$\Delta G_{octanol}$	**$LogP_{ow}$ (calc.)**	**Residual**
B3LYP	**6-31G (d,p)**	-5.64	-8.04	**1.76**	**0.36**
	6-311G (d,p)	-5.28	-7.60	1.70	0.42
	6-31+G (d,p)	-5.76	-8.05	1.67	0.45
	6-311+G (d,p)	-5.73	-7.98	1.65	0.47
	6-31++G (d,p)	-5.74	-8.04	1.69	0.43
	6-311++G (d,p)	-5.74	-8.03	1.67	0.45
B3PW91	**6-31G (d,p)**	-4.78	-7.18	**1.75**	**0.37**
	6-311G (d,p)	-5.26	-7.54	1.67	0.45
	6-31+G (d,p)	-5.72	-7.95	1.64	0.48
	6-311+G (d,p)	-5.62	-7.82	1.61	0.51
	6-31++G (d,p)	-5.69	-7.94	1.65	0.47
	6-311++G (d,p)	-5.65	-7.86	1.62	0.50
HF	**6-31G (d,p)**	-5.86	-8.58	**2.00**	**0.12**
	6-311G (d,p)	-5.98	-8.68	1.98	0.14
	6-31+G (d,p)	-6.57	-9.11	1.86	0.26
	6-311+G (d,p)	-6.28	-8.91	1.93	0.19
	6-31++G (d,p)	-6.54	-9.06	1.85	0.27
	6-311++G (d,p)	-6.29	-8.90	1.92	0.20

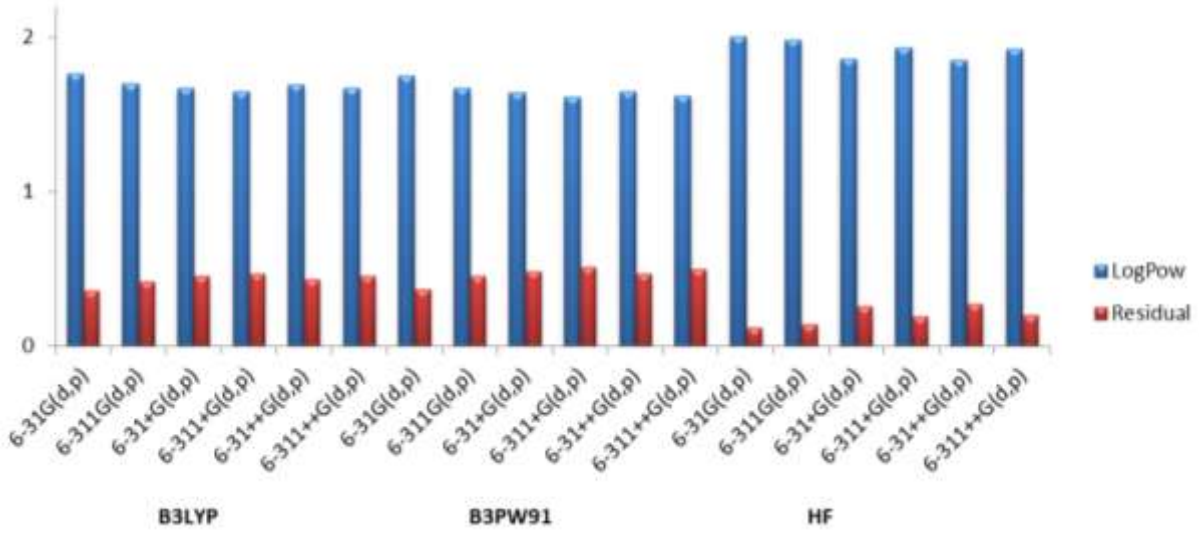


Figure 1. Calculated $logP_{ow}$ values and deviations

Frequency calculations have been performed at the Hartree-Fock, B3LYP, B3PW91 level of theory

using 6-31G(d,p), 6-311G(d,p), 6-31+G(d,p), 6-311+G(d,p), 6-31++G(d,p), 6-311++G(d,p) basis sets in gas phase and also in water and n-octanol phases. In order to take into account of solvent effects, SMD universal model (**S**olvation **M**odel based on **D**ensity) was utilized [22].

The calculated solvation free energies, $logP_{ow}$ values and differences from the value given in the literature were represented in Table 1. The logarithm of partition coefficient of CMZ ($logP_{ow}$=2.12) was taken from reference [4]. According to the Table 1, the closest result to the value given in the literature was obtained by HF/6-31G (d,p) level. Also, among other DFT functionals B3LYP and B3PW91, the closest results were obtained with 6-31G (d,p) basis set. When comparing the calculated $logP_{ow}$ values with the value given in the literature, deviations range between 0.51 and 0.12 logarithmic units. Figure 1 demonstrates the graphical presentation of these values. According to Figure 1, the predictive power of the computational methods decreases in the following order: HF > B3LYP > B3PW91. In addition, it is observed that calculations with basis sets including diffuse functions tend to produce lower solvation free energies not only in water but also in n-octanol phases.

3.2. Frontier Molecular Orbital Analysis of CMZ

The frontier molecular orbitals (FMOs) refer to the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and it is commonly known that HOMO and LUMO energy levels are useful descriptors that help to explain the chemical reactivity behaviors of molecules.

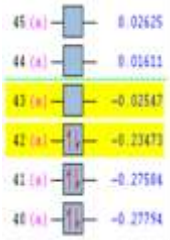
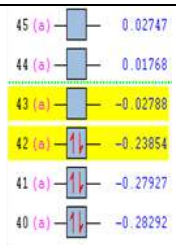
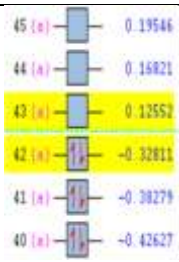
METHOD	HOMO	MOED	LUMO
DFT/B3LYP/ 6-31G(d,p)		 ΔE=5.69426 eV	
DFT/B3PW91/ 6-31G(d,p)		 ΔE=5.73236 eV	
HF/6-31G(d,p)		 ΔE=12.34391eV	

Figure 2. 3D diagrams of the frontier orbitals and molecular orbital energy level diagrams for CMZ in water

Besides, the gap between the HOMO and LUMO orbitals (ΔE) indicates the stability of the molecule. HOMO and LUMO energy values were taken from the molecular orbital energy level diagrams (MOED) of CMZ as shown in Figure 2. Additionally, the 3D diagrams for HOMO-LUMO energy levels and energy gap values of CMZ are represented in Figure 2. Figure 3 represents the ΔE values of CMZ according to changing dielectric media. No sharp increases or decreases in energy gap values were observed on going from gas phase to solvent phase. However, an increase was observed in ΔE values at HF methods compared to DFT/B3LYP and DFT/B3PW91 methods. Some quantum chemical descriptors such as Chemical Hardness (ɳ), Softness (σ), Electronegativity (χ), Chemical Potential (μ) and Electrophilicity index (ω) were calculated according to equations given in literature [31].

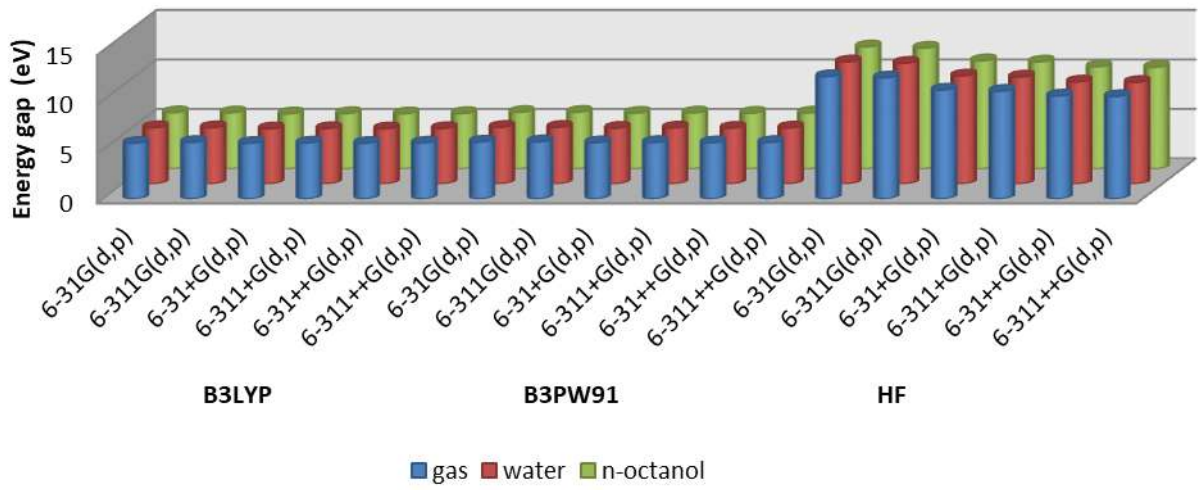


Figure 3. Energy gap values of CMZ according to changing basis set and dielectric media

Table 2. Calculated quantum chemical descriptors for CMZ in gas phase

GAS PHASE								
Basis Set / **B3LYP**	**E_{HOMO} (eV)**	**E_{LUMO} (eV)**	**ΔE (eV)**	**Chemical Hardness (ɳ) (eV)**	**Softness (σ) (eV^{-1})**	**Chemical Potential (μ) (eV)**	**Electronegativity (χ) (eV)**	**Electrophilicity index (ω) (eV)**
6-31G (d,p)	-6.5947	-0.9592	5.6355	2.8177	0.1775	-3.7769	3.7769	2.5313
6-311G (d,p)	-6.8380	-1.1070	5.7310	2.8655	0.1745	-3.9725	3.9725	2.7535
6-31+G (d,p)	-6.8532	-1.2199	5.6333	2.8167	0.1775	-4.0365	4.0365	2.8924
6-311+G (d,p)	-6.8956	-1.2354	5.6602	2.8301	0.1767	-4.0655	4.0655	2.9201
6-31++G (d,p)	-6.8527	-1.2226	5.6300	2.8150	0.1776	-4.0376	4.0376	2.8956
6-311++G (d,p)	-6.8954	-1.2379	5.6575	2.8288	0.1768	-4.0666	4.0666	2.9231
B3PW91								
6-31G (d,p)	-6.7063	-0.9358	5.7705	2.8852	0.1733	-3.8210	3.8210	2.5302
6-311G (d,p)	-6.8695	-1.0947	5.7748	2.8874	0.1732	-3.9821	3.9821	2.7459
6-31+G (d,p)	-6.8766	-1.1900	5.6866	2.8433	0.1759	-4.0333	4.0333	2.8606
6-311+G (d,p)	-6.9098	-1.1968	5.7130	2.8565	0.1750	-4.0533	4.0533	2.8757
6-31++G (d,p)	-6.8758	-1.1908	5.6850	2.8425	0.1759	-4.0333	4.0333	2.8614
6-311++G (d,p)	-6.9093	-1.1987	5.7106	2.8553	0.1751	-4.0540	4.0540	2.8779
HF								
6-31G (d,p)	-9.1923	3.1946	**12.3869**	6.1935	0.0807	-2.9988	2.9988	0.7260
6-311G (d,p)	-9.2674	2.9805	12.2479	6.1239	0.0817	-3.1435	3.1435	0.8068
6-31+G (d,p)	-9.2894	1.7328	11.0222	5.5111	0.0907	-3.7783	3.7783	1.2952
6-311+G (d,p)	-9.2973	1.6027	10.9001	5.4500	0.0917	-3.8473	3.8473	1.3579
6-31++G (d,p)	-9.2875	1.1255	10.4130	5.2065	0.0960	-4.0810	4.0810	1.5994
6-311++G (d,p)	-9.2968	1.0653	10.3621	5.1811	0.0965	-4.1157	4.1157	1.6347

Table 3. Calculated quantum chemical descriptors for CMZ in water phase

WATER PHASE								
Basis Set / **B3LYP**	**E_{HOMO} (eV)**	**E_{LUMO} (eV)**	**ΔE (eV)**	**Chemical Hardness (η) (eV)**	**Softness (σ) (eV^{-1})**	**Chemical Potential (μ) (eV)**	**Electro-negativity (χ) (eV)**	**Electrophilicity index (ω) (eV)**
6-31G (d,p)	-6.38733	-0.69307	5.69426	2.84713	0.17562	-3.54020	3.54020	2.20099
6-311G (d,p)	-6.57999	-0.88981	5.69018	2.84509	0.17574	-3.73490	3.73490	2.45150
6-31+G (d,p)	-6.58489	-1.00165	5.58324	2.79162	0.17911	-3.79327	3.79327	2.57716
6-311+G (d,p)	-6.64149	-1.02696	5.61453	2.80727	0.17811	-3.83423	3.83423	2.61843
6-31++G (d,p)	-6.58516	-1.00328	5.58188	2.79094	0.17915	-3.79422	3.79422	2.57908
6-311++G (d,p)	-6.64067	-1.02778	5.61289	2.80645	0.17816	-3.83423	3.83423	2.61920
B3PW91								
6-31G (d,p)	-6.49101	-0.75865	5.73236	2.86618	0.17445	-3.62483	3.62483	2.29214
6-311G (d,p)	-6.64176	-0.90342	5.73834	2.86917	0.17427	-3.77259	3.77259	2.48024
6-31+G (d,p)	-6.64230	-1.00002	5.64228	2.82114	0.17723	-3.82116	3.82116	2.58783
6-311+G (d,p)	-6.68666	-1.01499	5.67167	2.83584	0.17631	-3.85083	3.85083	2.61455
6-31++G (d,p)	-6.64149	-1.00029	5.64120	2.82060	0.17727	-3.82089	3.82089	2.58796
6-311++G (d,p)	-6.68557	-1.01526	5.67031	2.83516	0.17636	-3.85042	3.85042	2.61462
HF								
6-31G (d,p)	-8.92833	3.41558	**12.34391**	6.17196	0.08101	-2.75638	2.75638	0.61549
6-311G (d,p)	-8.99228	3.22156	12.21384	6.10692	0.08187	-2.88536	2.88536	0.68163
6-31+G (d,p)	-9.01541	1.91732	10.93273	5.46637	0.09147	-3.54905	3.54905	1.15211
6-311+G (d,p)	-9.02929	1.78507	10.81436	5.40718	0.09247	-3.62211	3.62211	1.21317
6-31++G (d,p)	-9.01378	1.31023	10.32401	5.16201	0.09686	-3.85178	3.85178	1.43706
6-311++G (d,p)	-9.02820	1.24411	10.27231	5.13616	0.09735	-3.89205	3.89205	1.47465

Table 4. Calculated quantum chemical descriptors for CMZ in n-octanol phase

N-OCTANOL PHASE								
Basis Set / **B3LYP**	**EHOMO (eV)**	**ELUMO (eV)**	**ΔE (eV)**	**Chemical Hardness (η) (eV)**	**Softness (σ) (eV^{-1})**	**Chemical Potential (μ) (eV)**	**Electronegativity (χ) (eV)**	**Electrophilicity index (ω) (eV)**
6-31G (d,p)	-6.41237	-0.71620	5.69617	2.84809	0.17556	-3.56429	3.56429	2.23029
6-311G (d,p)	-6.60638	-0.91458	5.69180	2.84590	0.17569	-3.76048	3.76048	2.48449
6-31+G (d,p)	-6.61237	-1.02478	5.58759	2.79380	0.17897	-3.81858	3.81858	2.60963
6-311+G (d,p)	-6.66679	-1.04873	5.61806	2.80903	0.17800	-3.85776	3.85776	2.64901
6-31++G (d,p)	-6.61264	-1.02669	5.58595	2.79298	0.17902	-3.81967	3.81967	2.61188
6-311++G (d,p)	-6.66598	-1.04954	5.61644	2.80822	0.17805	-3.85776	3.85776	2.64978
B3PW91								
6-31G (d,p)	-6.51223	-0.77825	5.73398	2.86699	0.17440	-3.64524	3.64524	2.31737
6-311G (d,p)	-6.66353	-0.92356	5.73997	2.86999	0.17422	-3.79355	3.79355	2.50715
6-31+G (d,p)	-6.66489	-1.01880	5.64609	2.82305	0.17711	-3.84185	3.84185	2.61416
6-311+G (d,p)	-6.70761	-1.03267	5.67494	2.83747	0.17621	-3.87014	3.87014	2.63932
6-31++G (d,p)	-6.66434	-1.01934	5.64500	2.82250	0.17715	-3.84184	3.84184	2.61466
6-311++G (d,p)	-6.70652	-1.03322	5.67330	2.83665	0.17626	-3.86987	3.86987	2.63971
HF								
6-31G (d,p)	-8.95690	3.39626	**12.35316**	6.17658	0.08095	-2.78032	2.78032	0.62577
6-311G (d,p)	-9.02221	3.20251	12.22472	6.11236	0.08180	-2.90985	2.90985	0.69263
6-31+G (d,p)	-9.04453	1.90534	10.94987	5.47494	0.09133	-3.56960	3.56960	1.16367
6-311+G (d,p)	-9.05813	1.77065	10.82878	5.41439	0.09235	-3.64374	3.64374	1.22607
6-31++G (d,p)	-9.04262	1.29581	10.33843	5.16922	0.09673	-3.87341	3.87341	1.45121
6-311++G (d,p)	-9.05704	1.22996	10.28700	5.14350	0.09721	-3.91354	3.91354	1.48885

Calculated values for gas, water and n-octanol phases are given in Tables 2, 3 and 4, respectively. When the tables are examined, the highest energy gap values of CMZ are obtained by using HF/6-31G (d,p) method and the values are equal to 12.3869 eV, 12.3439 eV and 12.3532 eV for gas,

water and n-octanol phases respectively. These high energy values point out good stability and low reactivity of CMZ molecule. Also, chemical hardness, softness and energy gap values are notions related to each other. The highest chemical hardness value and the lowest softness value are belong to again HF/6-31G (d,p) method.

3.3 Molecular Electrostatic Potential (MEP)

Molecular electrostatic surfaces illustrate the 3D charge distributions within the molecule. These surfaces give a visual representation of variably charged regions of a molecule [32]. The electrostatic surface potential maps were calculated in order to estimate reactive sites of electrophilic or nucleophilic attack for CMZ at DFT/B3LYP/6-31G (d,p), DFT/B3PW91/6-31G(d,p) and HF/6-31G(d,p) levels of theory. The calculated MEP maps and 2D contours of CMZ are displayed in Figure 4. The red color indicates the lowest electrostatic potential energy, and blue indicates the highest electrostatic potential energy. Red regions are characterized by an abundance of electrons as well as blue regions are characterized by a relative absence of electrons. The MEP maps are in the ranges −5.000 a. u. red and 5.000 a. u. blue for CMZ. The electrostatic potential decreases according to the order blue > green > yellow > orange > red.

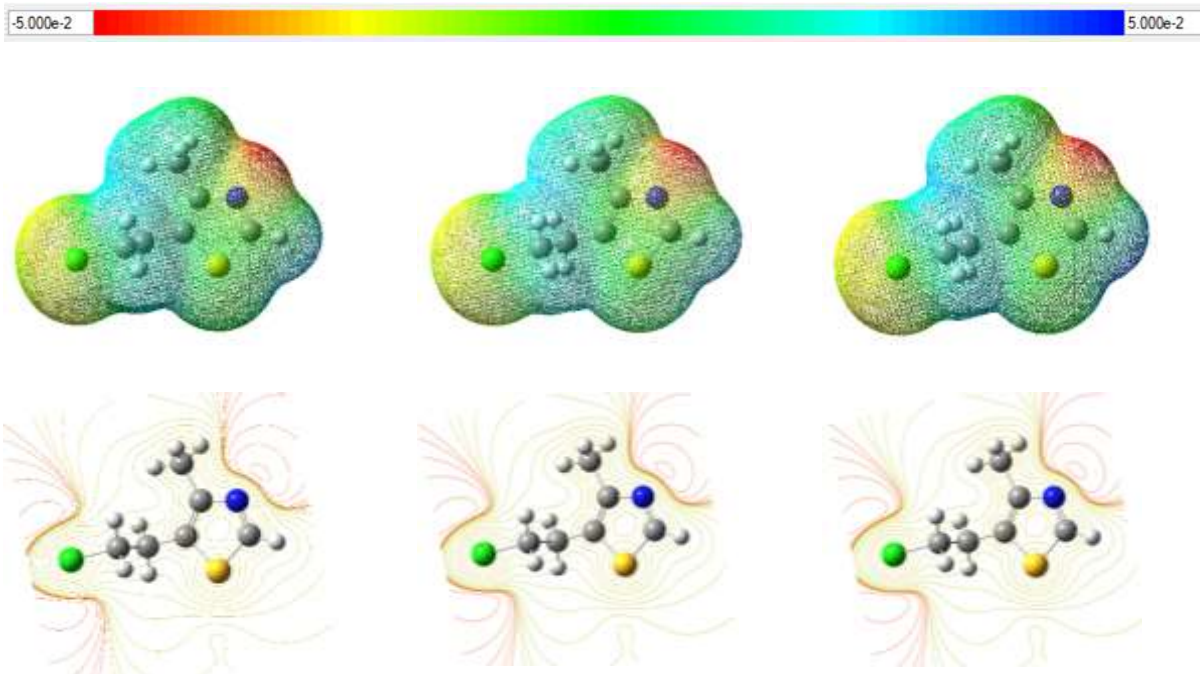


Figure 4. Molecular electrostatic potential (MEP) and 2D contour maps of CMZ

4. Conclusions

It is widely admitted that the lipophilic character of drugs has a great influence on the bioavailability and pharmacological activity, and is connected with the ability of the central nervous system penetration. In addition, information about the toxicity of the drug, which is an important parameter, can be obtained. Therefore, the study of partition coefficients for a particular drug class plays an influential role for the pharmacological sciences. The advantage of using the computational methods is the probability to predict partition coefficient, $\log P_{ow}$, during the design of drug candidates previous to synthesis step. In this study, for $\log P_{ow}$ prediction of Chlormethiazole, we were utilized quantum chemical calculations with eighteen different methodologies consist of HF,

DFT/B3LYP, DFT/B3PW91 functionals with 6-31G(d,p), 6-311G(d,p), 6-31+G(d,p), 6-311+G(d,p), 6-31++G(d,p), 6-311++G(d,p) basis sets. The closest result with the experimental logP value was achieved by the HF/6-31G (d,p) level with the SMD model. Besides, it is observed that the forecast performance of the computational methods decreases in the following order: HF > B3LYP > B3PW91. Additionally, HOMO-LUMO analyses were performed for not only gas phase but also solvent phases. Based on HOMO-LUMO energies, the related quantum chemical descriptors were calculated for all three phases by eighteen methodologies. MEP maps of CMZ demonstrate that the positive sites are around the hydrogen atoms while the negative sites are on chlorine and nitrogen atom.

Authors' Contributions

SS and AB wrote up the article. Both authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

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