Thermodynamic, HOMO-LUMO, MEP and ADMET Studies of Metronidazole and its Modified Derivatives Based on DFT

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Abstract

In this study, Metronidazole (Met) and it's modified derivatives are optimized by employing density functional theory with B3LYP/6-31g (d,p) level theory to explore their structural and thermodynamical properties. Molecular electrostatic potential (MEP) calculation has performed to calculate their possible electrophilic and nucleophilic attack. ADMET prediction was performed to search the absorption, metabolism and toxic level. Finally, this study can be helpful to design a potent candidate.

Keywords: Metronidazole; Density functional theory; HOMO-LUMO; MEP; ADMET

Abbreviation: Met: Metronidazole; DFT: Density functional theory; HOMO: Highest occupied molecular orbital; LUMO: Lowest unoccupied molecular orbital; MEP: Molecular electrostatic potential; ADMET: Absorption, distribution, metabolism, excretion, and toxicity

Introduction

Metronidazole (Met) is an antibiotic [1] and antiprotozoal drug [2]. It is widely used in the treatment of amoebiasis, trichomoniasis and giardiasis [3,4]. It has some demerits depending on the type and nature of unusual physical condition and on the limit of dose. High and long term dose can cause of leucopenia, neutropenia and peripheral neuropathy diseases [5]. Adverse effect and resistance of drugs indicate the importance of the discovery of new potential candidate. In computer aided drug design system, physicochemical, molecular docking, nonbonding interactions, and ADMET predictions are important criteria to evaluate newly designed molecules [6]. Drug modification is another alternative way to search better agent, which can increase the selective action of drug and reduce the side effect. Recently, it has been seen the trait of modifying drugs using halogens and alkyl group play important role in improving drug performance [7].

Herein, I report the optimization of Metronidazole (Met) and its modified derivatives to investigate their biochemical behavior on the basis of quantum mechanical approach. The free energy, electronic energy, enthalpy, dipole moment, HOMO-LUMO gap, hardness, softness, chemical potential and electrostatic potential have been calculated. All the newly designed derivatives show better thermodynamic properties, and some of them exhibit better chemical reactivity than parent drug. From the regarding quantum chemical studies, it's assuming that, some of the designed compounds may have profound effect as drug.

Methods and Materials

Computational Details

In computer aided drug design, quantum mechanical methods are widely used to predict thermal, molecular orbital, and molecular electrostatic potential properties [8]. Initial geometry of Metronidazole (Met) was taken from the online structure database named ChemSpider [9]. Geometry optimization and further modification of all structures carried out using Gaussian 09 program [10]. Density functional theory (DFT) with Becke's (B) [11] three-parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional [12] under Pople's 6-31g (d,p) basis set has been employed to optimize and elucidate their thermal and molecular

orbital properties [13]. Initial optimization of all compounds was performed in the gas phase. Dipole moment, electronic energy, enthalpy, free energy and electrostatic potential are calculated for all the compounds (Figure 1).

Figure 1: Chemical structure of Metronidazole (Met) and its modified analogues.
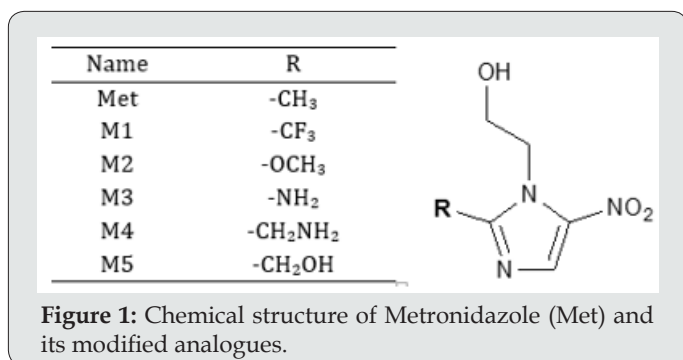
Frontier molecular orbital features HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) were calculated at the same level of theory. For each of the drugs, HOMO-LUMO energy gap, hardness (η), softness (S) and chemical potential were calculated from the energies of frontier HOMO and LUMO as reported considering Parr and Pearson interpretation [14,15] of DFT and Koopmans theorem [16] on the correlation of ionization potential and electron affinities with HOMO and LUMO energy (ε). The following equations are used to calculate hardness (η), softness (S) and chemical potential (μ);

$$\eta = \frac{[\varepsilon LUMO - \varepsilon HOMO]}{2}; \mu = \frac{[\varepsilon LUMO + \varepsilon HOMO]}{2}; S = \frac{1}{\eta}$$

In computer aided drug discovery system, computational predictions are using to explore absorption, distribution, metabolism, excretion, and toxicity (ADMET) which saves on time and investment. AdmetSAR online database was utilized to predict ADMET properties of Metronidazole and its analogues [17].

Result and Discussion

Thermodynamic Analysis

Simple modifications of molecular structure significantly influence the structural properties including thermal and molecular orbital parameters. From the free energy, and enthalpy values, spontaneity of a reaction and stability of a product can be predicted [18]. In drug design, hydrogen bond formation and non-bonded interactions also influenced by dipole moment. Increased dipole moment can improve the binding property [19]. From thermodynamic data (Table 1), the free energy of Metronidazole is -623.7600 Hartree, where M1 shows the highest negative value (-921.4882 Hartree). The –F substitution (M1) influence the free energy significantly. Highly negative free energy is favourable for stable configuration. Again, the dipole moment of Metronidazole is 4.1174 Debye where M3 shows the maximum dipole moment (5.3559 Debye) due to substitution of –NH$_2$ group (Figure 2).

Table 1: The stoichiometry, molecular weight, electronic energy, enthalpy, free energy in Hartree and dipole moment (Debye) of Metronidazole (Met) and its analogues.

Name	Stoichiometry	Molecular weight	Electronic energy	Enthalpy	Free energy	Dipole moment
Met	$C_6H_9N_3O_3$	171.154	-623.71	-623.7089	-623.76	4.1174
M1	$C_6H_6F_3N_3O_3$	225.125	-921.433	-921.4319	-921.4882	2.2061
M2	$C_6H_9N_3O_4$	187.153	-698.913	-698.9117	-698.9658	4.6665
M3	$C_5H_8N_4O_3$	172.142	-639.761	-639.7604	-639.811	5.3559
M4	$C_6H_{10}N_4O_3$	186.169	-697.035	-697.0344	-697.0881	4.677
M5	$C_6H_9N_3O_4$	187.153	-698.908	-698.907	-698.9606	4.8686
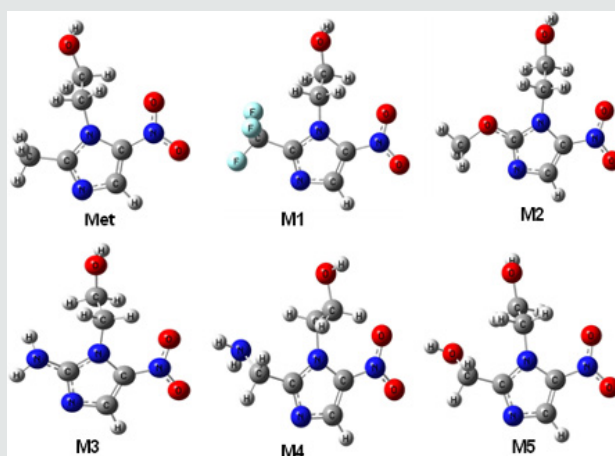
Figure 2: Most stable optimized structures of Metronidazole (Met) and newly designed analogues. Optimized with B3LYP/6-31g (d, p) level theory.

Molecular Orbital Properties

Table 2: Energy (eV) of HOMO, LUMO, gap, hardness, softness and chemical potential of the designed drugs.

| Name	εHOMO	εLUMO	Gap	Hardness (η)	Softness (S)	Chemical potential (μ)
Met	-6.9637	-2.3513	4.6124	2.3062	0.4336	-4.6575
M1	-7.7193	-2.879	4.8403	2.4201	0.4132	-5.2991
M2	-6.5345	-2.1992	4.3353	2.1676	0.4613	-4.3668
M3	-6.2749	-2.0966	4.1783	2.0891	0.4787	-4.1857
M4	-6.9482	-2.3206	4.6276	2.3138	0.4322	-4.6344
M5	-7.0513	-2.38	4.6713	2.3356	0.4281	-4.7156

The HOMO-LUMO energies, hardness, softness, chemical potential of all compounds is presented in Table 2. The electronic absorption relates to the transition from the ground state to the first excited state and mainly described by one electron excitation from HOMO to LUMO [20]. The chemical hardness, softness, and potential values depend on the energy gap of HOMO-LUMO [21,22].

Kinetic stability decreases with the decrease of HOMO-LUMO gap. As a result, removal of electrons from ground state HOMO to excited state LUMO requires less energy. In our studies, Metronidazole shows the HOMO-LUMO gap 4.6124 eV, where M3 have the lowest energy gap (4.1783 eV) with highest softness (0.4787 eV) which may contribute higher chemical reactivity (Figure 3).
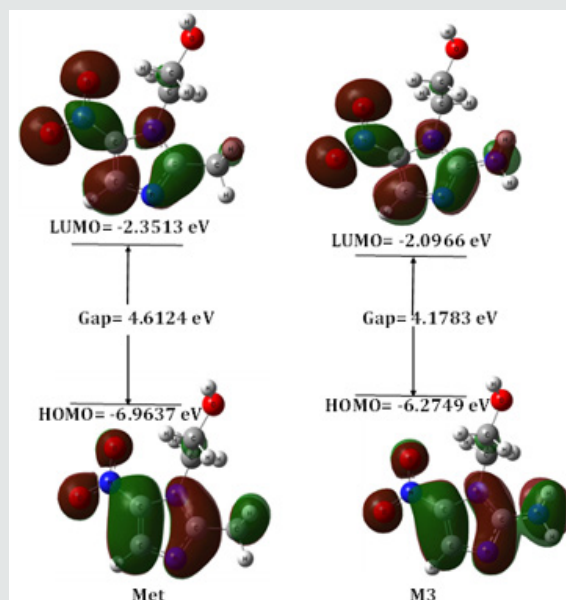
Figure 3: Frontier molecular orbital (HOMO-LUMO) and related energy of Metronidazole (Met) and M3.

Molecular Electrostatic Potential Analysis
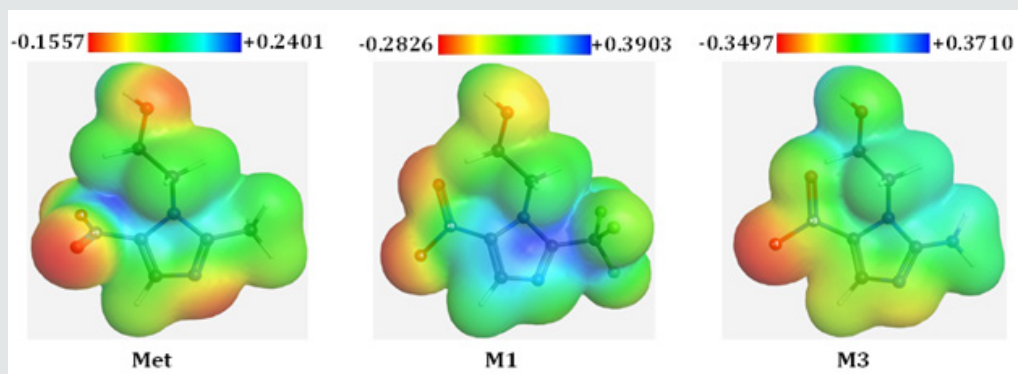
Figure 4: Molecular electrostatic potential maps of Metronidazole (Met), M1 and M3.

Molecular electrostatic potential (MEP) was calculated at B3LYP/6-31G (d,p) level of theory to forecast the reactive sites for electrophilic and nucleophilic attack of all optimized structures [23]. Red color represents maximum negative area which favorable site for electrophilic attack, blue color indicates the maximum positive area which favorable site for nucleophilic attack and green color represent zero potential area. MEP displays molecular size, shape as well as positive, negative and neutral electrostatic potential regions simultaneously in terms of color grading. It is seen from MEP map, region having the negative potential are over electronegative atom (oxygen atoms) and having positive potential are over hydrogen atoms. Here, the maximum negative potentiality is found for M3 is -0.3497 a.u (deepest red) for oxygen atoms and the highest positive potentiality of M1 is +0.3903 a.u (deepest blue) of hydrogen atoms (Figure 4).

ADMET Predictions

Table 3: Selected pharmacokinetic parameters of Metronidazole and its designed derivatives.

Name	Blood brain barrier	Human intestinal absorption	P-glycoprotein inhibitor	Carcinogen	Acute oral toxicity	Rat acute toxicity LD$_{50}$ (mol/kg)
Met	0.9381	0.9947	NI (0.8216)	NC (0.6745)	III	1.7872
M1	0.9439	1	NI (0.7477)	NC (0.6659)	III	2.3143
M2	0.9172	0.9767	NI (0.7868)	NC (0.7564)	III	2.2766
M3	0.901	1	NI (0.8946)	NC (0.8022)	III	1.9307
M4	0.8899	0.9883	NI (0.8914)	NC (0.7130)	III	2.0084
M5	0.7479	0.9422	NI (0.7692)	NC (0.7557)	III	2.0008

Here, NI= non inhibitor, NC= non carcinogenic

According to AdmetSAR data (Table 3), all the analogues are non-carcinogenic and show positive response for blood brain barrier (BBB) and human intestinal absorption criteria. All the structures show III category acute oral toxicity; as a result, they are safe for oral administration. All drugs are P-glycoprotein non-inhibitor where, P-glycoprotein inhibition can interrupt the absorption, permeability and retention of the drugs [24]. However, furthermore study of this aspect is necessary [24].

Conclusion

From quantum chemical calculations, newly designed analogues have improved thermodynamic properties than Metronidazole. M2 and M3 have smaller HOMO-LUMO gap with higher chemical reactivity than the parent drug. ADMET results predict that, all analogues are non-carcinogenic and safe for oral administration. Considering above investigation, this study can be helpful to design a new potent possible candidate for the better performance.

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