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Computational study of Anticancer Dasatinib for drug delivery systems

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ABSTRACT: Dasatinib is a tyrosine kinase inhibitor (TKI) that is used to treat chronic myeloid leukemia and in the management of ulcerative colitis (UC) and to provide appropriate results in treatment. Dasatinib is significantly higher and faster than full cytogenetic and large molecular responses as compared to imatinib. In the recent study, using the NMR data, the frequency and thermochemical properties of the dasatinib structure and the attached form of this molecule have been explored and analyzed. In this paper, we will examine some computational studies on this subject using semi-empirical and Monte Carlo methods. The Hyperchem 8.0 and Gaussian 09 and Gauss View 5 were used to do methods for simulating molecular mechanics (MM+) and semi empirical. Quantum mechanics was calculated using B3LYP methods and the theoretical method of 6-31G. As a result, our findings indicate that the presence of Dasatinib can express the results of this molecule as anticancer agents.

Keywords: *Dasatinib, Monte Carlo, NMR, Quantum Mechanics, Semi Empirical*

INTRODUCTION

The pharmaceutical industry has steadily begun developing new drugs with the least disadvantages for the treatment of diseases in cancer cell chemotherapy. Different forms of treatment for the tumor have been widely used. However, when invasive organs and cells of the body occur, conventional treatment will not always be effective. There are some types of cancer that are specific, but cancer is a multi-factorial illness. For example, the need to control or reduce the effect of its effects on various organs and to reduce the resistance to the drug (Viana, *et al.*, 2018). The development of new therapies for diseases that are sought after therapies due to resistance is essential (Mondal, *et al.*, 2014; Giuliani, *et al.*, 2018). However, the side effects of these drugs, like other drugs, may include disadvantages, including the pharmacokinetics of these compounds, the various side effects that each drug can cause (Viana, *et al.*, 2018). The development of new therapies for diseases that are sought after therapies due to resistance is essential. Dasatinib is one of the essential medicines of the World Health Organization, which is a collection of the most effective and safe drugs for the health system. Dasotinib [N-(2-chloro-6-methylphenyl)-2-[(6-(4-(2-

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hydroxycyl)-1-piperazinyl)-2-methyl-4-pyrimidinyl) amino]-5–thiazole carboxamide Monohydrate] is the brand name of "Sprycel" and is used as a Tristin kinase inhibitor and "c-Src inhibitor" for the treatment of chronic cerebrospinal leukemia (CML), as well as specific cases of lymphatic leukemia. Dasatinib is prescribed predominantly from the mouth and distributed in wide vascular space. The drug is mainly excreted through feces and is excreted slightly in the urine. It also has a chemical formula $C_{22}H_{26}ClN_7O_2S$ and a molecular weight of 488.01 g / mol. All derivative compounds derived from TKI, which were synthesized, showed anticancer activity. In this way, the study helped to discover a new class of anti-cancer compounds (Viana, *et al.*, 2018). Dasatinib is a potent multi-functional thyvosin kinase inhibitor (TKI), and the recommended dosage of dasatinib has evolved since its initial approval for various stages of chronic myeloid leukemia (CML) treatment (Schiffer, 2018). Chronic myeloid leukemia (CML) is a chronic disease that is managed and treated with tyrosine kinase inhibitor (Talpaz, *et al.*, 2018). Protein tyrosine kinase (PTK) is a collection of enzymes that can transfer a phosphate group from ATP to a protein in a cell, which is referred to as a cancer gene transducer. Although TKIs have the potential to cure cancer, it is clear that cancer cells that are treated with TKI also have drug resistance (Wu & Fu, 2018). Because many inflammatory diseases are directly related to tyrosine kinase activity, TKIs can be useful in this regard. Despite the fact that DAS is known for the anticancer effect, it has been suggested that it can reduce inflammation of the intestine and is therefore suggested as a solution to patients with ulcerative colitis (UC) (Maher, *et al.*, 2018). Computer models and simulations have been used to determine the amount of free energy to attach dasathinib anticancer drugs to the enzyme kenase src receptor, and suggest that the ligand should destroy an energy release barrier (Mondal, *et al.*, 2014). DAS via carrier controlled by the container cassette (ATP), which is mainly glycoprotein, especially organic anion transporting polypeptide (OATP) are transferred. DAS is mainly metabolized by cytochrome enzymes (P450), which is the oxidative metabolism of phase I of most drugs in the intestine and the liver. Therefore, plasma levels of TKIs are largely influenced by the action of membrane transporter as well as the CYP450 metabolized enzyme (Maher, *et al.*, 2018). Exposure to active drugs may lead to changes in treatment efficacy or increased toxicity. Recently, drug interactions between TKIs and food, herbal medicines and beverages have been a matter of particular concern (Maher, *et al.*, 2018; Dirks, *et al.*, 2008; Karapetis, *et al.*, 2008; Bonner, *et al.*, 2006).

COMPUTATIONAL METHODS

The calculations can be made using semi-experimental replication techniques and Monte Carlo (MC) to study precisely molecular details at the atomic level, which gives us valuable assumptions about the interactions of structures. All the Monte Carlo methods are extremely complex to find a solution to solve the analysis. The molecular thermodynamic properties as well as the minimum energy structures can be defined by Monte Carlo method. This method is one of the most commonly used methods in quantum mechanics. In the Monte Carlo method, the difference in power argument is expressed by comparing the energy calculated using the OPLS force.

In this study, a quantum and molecular chemistry study was carried out using Monte Carlo simulations. All the semi-experimental calculations presented in this assay were performed using the AM1 and PM3 methods. The semi-experimental method is to reduce the cost of computation and all the parameters of the atomic position when the total energy and atomic forces are minimized. Design is proposed by optimized parameters such as total energy, binding energy, isolated atomic energy, electronics energy, core-core interaction, and heat builder for dasatinib. The computational forms used in this study are AM1, PM3. According to the semi-experimental method, the PM3 method expresses results that are higher than the AM1 method.

The molecular mechanics (Monte Carlo simulation) and molecular dynamics are the most common types of calculations, called the central field approximation. Quantum Monte Carlo (MC) is a method that makes the mistakes embarrassing. Today, these methods can be used as a precise method. B. In our study, the ki-

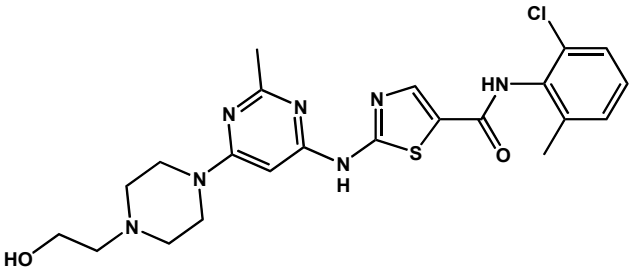

Fig. 1. Structure of Anticancer Dasatinib.

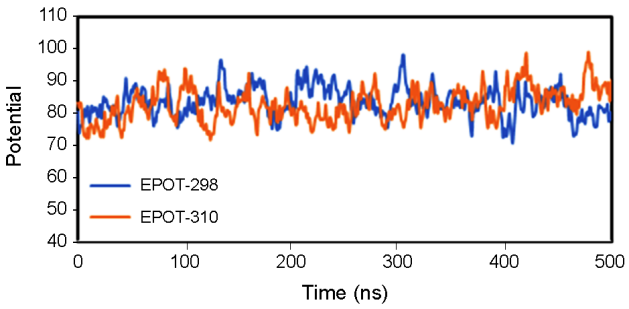

Fig. 2. The potential energy diagram, Monte Carlo simulation at 298 K and 310K.

netic energy, potential and total energy is estimated by Monte Carlo and molecular dynamics simulation (Kroese, *et al.*, 2014; Thiel, 2014; Hückel, 1931; Dewar, *et al.*, 1985; Asghari Moghaddam, 2014). In this exploration, the effects of solvent on relative energy are shown by the Monte Carlo simulation. Optimization of geostatic calculations and deastinin optimization at different temperatures (294, 298, 302, 306, 310 and 314 K) were investigated by Monte Carlo method (OPLS). To compile molecular mechanics, calculations in this study we use the deviation from total energy (D ETOT) and kinetic energy deviation (DIN) and deviation from potential energy (D EPOT) in replication.

NMR parameters are a method used to apply the magnetic properties of the atomic nucleus to the physical and chemical properties of atoms. It can also provide detailed information on the structure, chemical characteristics, and mobility of molecules. Hence, NMR is based on the quantum mechanical properties of the nucleus. It is worth noting that the theory of isotropic and anisotropic parameters of the atom is shown. The effects of different temperatures and media on the thermosetting parameters of dasatinib are presented.

RESULTS AND DISCUSSION

Dasatinib is a cancerous agent used in the process of catabolism and anabolism. NMR results are analyzed using isotropic and anisotropic analyzers. In the semi-experimental method, AM1 and PM3 were performed. Accordingly, the energy of the whole energy, the bind-

Table 1. The Potential, Total and Kinetic Energy in different Temperatures.

T (K)	EPOT	ETOT	EKIN	DEPOT	DETOT
294	76.03683	127.7416	51.70474	30.8775	30.8775
298	70.70592	123.1141	52.40821	4.573513	4.573513
302	66.5438	119.6555	53.11167	4.353386	4.353386
306	69.01325	122.8284	53.81514	3.346667	3.346667
310	71.72595	126.2446	54.5186	5.756592	5.756592
314	72.32724	127.5493	55.22207	6.716841	6.716841

Table 2. Parameters of Binding Energy, Electronic Energy, Core–Core Interaction and Heat of Formation for Dasatinib by AM1 and PM3 calculation.

Energy	AM1	PM3
Total Energy	-214.052231755	-192.117080469
Binding Energy	-5933.8366884	-5997.7330863
Isolated Atomic Energy	-128385.9832740	-114557.5699290
Electronic Energy	-1101384.1915412	-1078169.8122226
Core-Core Interaction	967064.3715788	957614.5092073
Heat of Formation	185.9033116	122.0069137

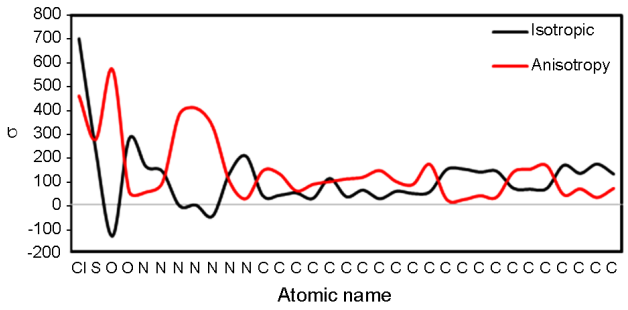

Fig. 3. NMR parameters of Dasatinib at the B3LYP/6-31G basis sets.

ing energy, the atomic energy, the electronics energy, the interaction of the core and the heat are separated. The results confirmed the findings of the initial observations. The Monte Carlo method was a modular model of MM +. Hence, this was chosen for molecular mechanics. The results are in agreement with the findings of the molecular mechanics. According to the studies, these results are matched to laboratory results that were followed by a specific and similar approach and our results were consistent with laboratory findings.

CONCLUSIONS

In other words, they confirm the theoretical and practical results of each other. We should be able to find a new theory to increase the adequacy of this drug. Dasatinib is prescribed orally and then rapidly absorbed into the tissue. In the liver and cancer cells, it is converted through an enzyme reaction. The physical and chemical properties of this drug are from the current study.

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