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THERMODYNAMIC INVESTIGATION OF PROMETHAZINE, LORATADINE, CETIRIZINE AND BUCLIZINE AS ANTIHISTAMINE DRUGS; MONTE CARLO AND SEMI-EMPIRICAL STUDIES

INVESTIGACIÓN TERMODINÁMICA DE PROMETAZINA, LORATADINA, CETIRIZINA Y BUCLIZINA COMO MEDICAMENTOS ANTIHISTAMÍNICOS; MONTE CARLO Y ESTUDIOS SEMI-EMPÍRICOS

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ABSTRACT

In this article, we discussed about four antihistamine drug called promethazine, loratadine, cetirizine and buclizine. Promethazine in this list is the only one in first generation antihistamine classification with CNS sedation effect and the other three belongs to second generation antihistamine group which are non-sedation and used to treat in many different anti-allergenic fields. In the following we optimized potential, kinetic and total energy of these molecules at body temperature (310 k˚) and environment temperature (298 k ˚) using Mont Carlo method in Amber force field in 500 ns. The quantum mechanics calculations and molecular structure of these molecules investigated using B3LYP level of theory with 6-31 G (d) as a basis set. Theoretical computations were performed to study thermodynamic parameters and frequency analysis. Electronic, thermal, zero point and gibs free energy and enthalpy were estimated in frequency analysis. Semi empirical computations were summarized to pm3 method and different energy parameters (total energy, Binding Energy, Isolated Atomic Energy, Electronic Energy, Core–Core Interaction and Heat of Formation.

Keywords: Promethazine; Loratadine; Cetirizine and Buclizine; Monte Carlo; Semi empirical

RESUMEN

En este artículo, discutimos sobre cuatro medicamentos antihistamínicos llamados prometazina, loratadina, cetirizina y buclizina. La prometazina en esta lista es la única en la clasificación de antihistamínicos de primera generación con efecto de sedación del SNC y los otros tres pertenecen al grupo de antihistamínicos de segunda generación que no son sedantes y se usan para tratar en muchos campos antialérgicos diferentes. A continuación, optimizamos la energía potencial, cinética y total de estas moléculas a temperatura corporal (310 k˚) y temperatura ambiente (298 k ˚) utilizando el método Mont Carlo en el campo de fuerza ámbar en 500 ns. Los cálculos de la mecánica cuántica y la estructura

molecular de estas moléculas se investigaron utilizando el nivel de teoría B3LYP con 6-31 G (d) como conjunto de bases. Se realizaron cálculos teóricos para estudiar los parámetros termodinámicos y el análisis de frecuencia. Electrónica, térmica, punto cero y energía libre de gibs y entalpía se estimaron en análisis de frecuencia. Los cálculos semiempíricos se resumieron en el método pm3 y diferentes parámetros de energía (energía total, energía de enlace, energía atómica aislada, energía electrónica, interacción núcleo-núcleo y calor de formación).

Palabras clave: Prometazina; Loratadina; Cetirizina y buclizina; Monte Carlo; Semi empirico

1. INTRODUCTION

Promethazine is in a group of drugs called phenothiazine (FEEN-oh-THYE-a-zeens) ,with $C_{17}H_{20}N_2S$ molecular formula and 284.42 g·mol^{-1} molecular mass, known by a first-generation antihistamine and blocks the effects of the naturally occurring chemical histamine in our body (Monajjemi et al, 2018 & Scherl ER et al, 1995).

In the treatment of allergenic prepuces ,Promethazine is used to cure allergy symptoms such as itching, migraine episodes (Buzdar et al, 1994), cancer Chemotherapy (Philpot et al,2000), runny nose, sneezing, itchy or watery eyes, hives, and itchy skin rashes and in some cases it also famous in prevention of motion sickness, and treats nausea , vomiting or pain after surgery and as a sedative or sleep aid (Davis et al, 1973), although the sedation related to first generation antihistamine use has been shown some compromise performance at school and at work, distracting during driving and the ability to handle tasks that require a high degree of concentration and alertness (Hughes et al, 1972).

In addition, studies of promethazine have been shown of this drug has the modification effects on the electrical activity in cardiac tissues and blocks the histamine-induced positive chronotropic response in rabbit atria (Mutschler et al, 2001).

Along with its needed effects, promethazine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, they may need medical attention such as Convulsions(Monajjemi et al, 2019), difficult or unusually fast breathing, fast heartbeat or irregular pulse, high fever, high or low (irregular) blood pressure, increased sweating, loss of bladder control (Scherl ER et al 1995).

Loratadine with $C_{22}H_{23}ClN_2O_2$ Molecular Formula and 382.88 g/mol g·mol^{-1} molecular mass known as a tricyclic antihistamine, which acts as a selective inverse agonist of peripheral histamine H1 receptors, orally effective, long-acting, and free of significant central and autonomic nervous system activity (Monajjemi et al, 2020), is a medication used to treat allergies such as allergic rhinitis (hay fever) and hives , treat sneezing, runny nose, watery eyes, hives, skin rash, itching, and other cold or allergy symptoms, treatment of allergic cough, as well as in rhino conjunctivitis (Fischer et al, 2006).

Loratadines safety and efficacy were evaluated in a 28-day study conducted in patients with chronic idiopathic urticaria (Barbey et al, 1999).

Loratadine was discovered in 1980 and came to market in 1988 (Kosoglou et al, 2000). It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system (Roth et al, 1987), but recently studies shown that Patients with severe hepatic would better start with a lower dose (Meltzer et al, 1995) and in 1993 was approved by the FDA. The drug continued to be available only by prescription in the U.S. until it went off patent in 2002 (Fischer et al, 2006).

Loratadine metabolized primarily by the cytochrome P450 hepatic enzyme, CYP3A4, and secondarily by CYP2D6 quickly in the liver to desloratadine combination (Portnoy et al, 2004).

About the presence of compatible doses of loratadine in the blood , substances that act as inhibitors of the CYP3A4 enzyme such as ketoconazole, erythromycin, cimetidine, and furanocoumarin derivatives (found in grapefruit) lead to increased plasma levels of loratadine and desloratadine which this had clinically significant effects in controlled trials of higher-than-usual doses of loratadine (20 mg) (Tillementa et al, 2003) Loratadine is a tricyclic antihistamine, which has a threefold greater affinity for peripheral as compared with central histamine1-receptors.

Loratadine and cetirizine are the most commonly prescribed second-generation antihistamines and in comparison, with first generation antihistamine at recommended doses have been shown to lack the CNS depressant effects associated with traditional antihistamines by having low affinity for H1-receptors in the CNS in vitro or in vivo (Safi et al, 2015).

Sedating antihistamines can worsen these effects. Therefore, nonsedating antihistamines are the best treatment choice for allergic conditions. However, although most antihistamines designated to be nonsedating at the recommended dose, sedation can occur when higher doses are used (Martindale, 1996).

Loratadine is a promising antihistamine for individuals involved in skilled activity studies a single daily dose of 10 mg is unlikely to impair performance and such these clinical usefulness studies have made possibility of the treatment of patients in sensitive occupations such as those in control of public service vehicles (Scherl ER et al, 1995).In as much as the deficiency of CNS effects is superior when choosing an antihistamine for an ambulant patient, it is also important that a clinically effective dose regimen is utilized (Buzdar et al, 1994).Cetirizine with $C_{21}H_{25}ClN_2O_3$ and 388.89 $g \cdot mol^{-1}$ respectively as molecular formula and molecular mass ,known as an antiallergic treatment and the carboxylic acid metabolite of hydroxyzine crosses the blood–brain barrier only slightly, and for this reason, it considered sedating by the FDA, as reflected in its cautionary labelling with regard to driving or operating potentially dangerous machinery while taking it ,although as it said before in a much lesser degree than older antihistamines such as promethazine and has 600-fold or greater selectivity for the H_1 receptor in comparison with a wide variety of other sites, such as muscarinic acetylcholine, serotonin, dopamine, and α-adrenergic receptors, among many others (Mutschler et al, 2001) and bound to albumin with high affinity, while α_1-acid glycoprotein and lipoproteins contribute much less to total plasma protein binding (Monajjemi et al, 2020 & Portnoy et al, 2004).

Cetirizine and its R-isomer (Levocetirizine) has the same activity base on Pharmacodynamic studies and in the skin when a weal and flare reaction was induced by histamine (100 mg/ml), single doses of 2.5 mg L-CTZ and 5 mg CTZ produced equivalent inhibition (Mutschler et al, 2001).studies have revealed that the antihistaminergic activity of the racemate is primarily due to levocetirizine (Portnoy et al, 2004). Hepatic metabolism of cetirizine is insignificant. Even so, the pharmacokinetics of cetirizine in patients with hepatic dysfunction are modified (Safi et al, 2015).

For the reason of the fact which Cetirizine cannot metabolized by the cytochrome P450 system, agents which inhibit or induce cytochrome P450 enzymes including theophylline, erythromycin, clarithromycin, cimetidine, or alcohol cannot interact with drug (Mutschler et al, 2001).

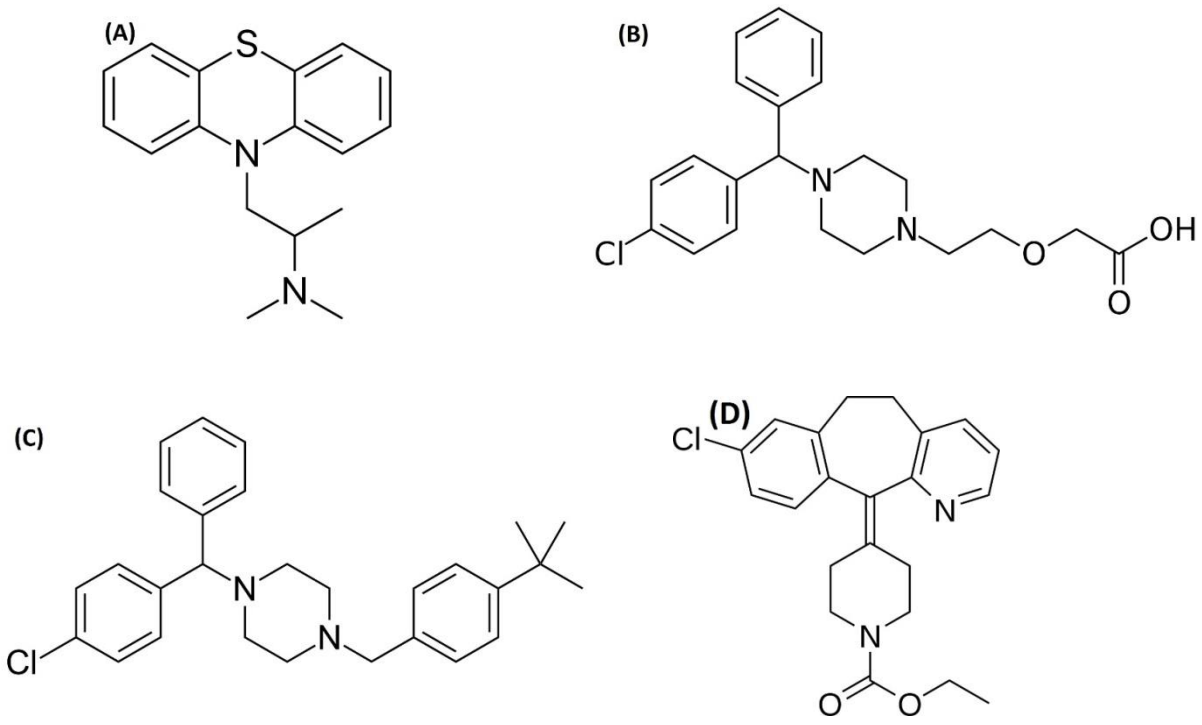

Figure 1. Promethazine (a), cetirizine (b), buclizine(c) and loratadine (d) structures

Moreover, the non-renal (mostly hepatic) clearance of levocetirizine is also significantly lower than that of dextrocetirizine (11.8 mL min^{-1} vs. 29.2 mL min^{-1}). By the fact that levocetirizine is indeed the eutomer of cetirizine (Portnoy et al, 2004) also Cetirizine did not cause any severe adverse events and no patient was recede from treatment because of a harmful event Tillementa et al, 2003).

Buclizine with $C_{28}H_{33}ClN_2$ molecular formula and 433.028 g/mol $g \cdot mol^{-1}$ molecular mass is a piperazine histamine H1 receptor antagonist with mainly antiemetic and antivertigo activities, binds to and blocks the histamine H1 receptor and so on preventing the symptoms of histamine activity. Buclizine apply its anti-emetic effect by binding to and blocking the muscarinic and histamine receptors in the vomiting center of the central nervous system (CNS), thereby this may prevent activation of the chemoreceptor trigger zone (CTZ) and may reduce nausea and vomiting (Martindale, 1996).

Studies demonstrated Buclizine is an N-alkylpiperazine carrying (4-chlorophenyl) (phenyl) methyl and 4-tert-butylbenzyl groups. It was manufactured by Stuart Pharms and initially approved by the FDA in 1957. So on, it was admitted to be effective as an appetite stimulant in children when carried out in the syrup form, however, this symptom has not been validated. In addition to the above benefits, buclizine also has been studied in the treatment of migraine attacks (the drug is given in usual doses of 12.5 mg at the start of an attack or when one is known to be imminent) and in the treatment of nausea and vomiting during pregnancy (Portnoy et al, 2004) and also been used in the treatment of vertigo associated with disorders of vestibular system, although its value in these conditions remains to be established (Mutschler et al, 2001).

Morren and Strubbe prepared buclizine by mixing hydrochloric acid with 0.5 mol of 1-(p-tert-butyl benzyl)-piperazine 1, adding 0.5 mol p-chlorobenzaldehyde 2, and adding dropwise aqueous 0.55 M potassium cyanide, then heating on a water bath for 2 h, yields an addition product which is separated in toluene and dried before reaction with phenyl magnesium bromide 3 to give buclizine 4 (Portnoy et al, 2004).

Molecular mechanics calculations use to to predict the structure and properties of molecules features from classical physics rules, based on the descriptive model of the ball and spring, and are better interpreted for geometrical equilibrium than plastic models. It is low cost and limited to geometric equilibrium. (Tillementa et al, 2003).

All-atomistic molecular mechanics methods have the following properties:

- Each atom is simulated as one particle
- Each particle is assigned a radius (typically the van der Waals radius), polarizability, and a constant net charge (generally derived from quantum calculations and/or experiment)
- Bonded interactions are treated as springs with an equilibrium distance equal to the experimental or calculated bond length

These equations together with the data (parameters) required to describe the behavior of different kinds of atoms and bonds, is called a force-field. Many different kinds of force-fields have been developed over the years. Some popular force fields such as Mm, Opls, Amber and bio+ will investigated in this article(Tillementa et al, 2003). Quantum mechanics (QM; also known as quantum physics, quantum theory, the wave mechanical model, or matrix mechanics), including quantum field theory, is a fundamental theory in physics which describes nature at the smallest including atomic and subatomic – scales (Naghsh et al, 2018). Classical physics, the description of physics existing before the formulation of the theory of relativity and of quantum mechanics, describes nature at ordinary (macroscopic) scale. Most theories in classical physics can be derived from quantum mechanics as an approximation valid at large (macroscopic) scale (Safi et al, 2015).

2. COMPUTIONAL METHODS

The molecular structure, quantum mechanics and Theoretical computations, charges distribution and electronic, thermal, zero point and gibs free energy for Promethazine, Loratadine, Cetirizine, Buclizine at Frequency method (Monajjemi et al, 2019) calculated using B3LYP level of theory with 6-31 G (d) basis set with the gaussian 09 program. Gaussian 09 is a computational chemistry software package appropriate to demonstration interaction of electrons in atoms and molecules. Molecular orbital energies, bond energies, molecular geometries and energies, and vibrational frequencies are the other features can be found in this program (Pham et al, 2019 & Safi et al, 2015).

Kinetic and thermodynamic investigations, geometry optimization, Monte Carlo and vibrational analysis done by using HyperChem 8.0.8 software which is appropriate in both molecular mechanics (MM) and quantum mechanics (QM) computations and known by its sophisticated molecular modeling environment including, its quality, Flexibility, and ease of use and 3D embodiment (Portnoy et al, 2004).
There will be three steps ahead in any quantum mechanical calculation in HyperChem 7.0 program package (Mutschler et al, 2001).

In the beginning, the molecule must be prepared by an appropriate starting geometry and compatible format (pdb, mol). Second, a calculation method and its associated (Setup menu) options must be chosen. At the end, there must be choosing of the type of calculations such as single point, geometry optimization, Monte Carlo and vibrational analysis (Portnoy et al, 2004).

Three important parameters including total energy, potential energy and kinetic energy in time of simulations 10 ns at two temperature (298 and 310 K degree) and in the Amber force field were also optimized data we extraction from Monte-Carlo simulation.

Parameters such as Total Energy, Binding Energy, Isolated Atomic Energy, Electronic Energy, Core–Core Interaction and Heat of Formation are the best vibration analysis of molecules using a quantum mechanical approach that was obtained via pm3 method in Semi-empirical calculations (Mutschler et al, 2001).

3.RESULT AND DISCUSSION

In this article theoretically and geometry calculations, physical and chemical preparties of nuclear optimized by using three methods such as Mont Carlo, semi empirical and frequency.in the first section total, potential and kinetic energy in Mont Carlo calculations optimized in two different temperature 298, 310 kelvin degree (respectively environment and body temperature) in Amber force field and at 500 steps which came in table 1,2.

According to semi empirical-based calculations, our results were summarized to computation of total energy, Binding Energy, Isolated Atomic Energy, Electronic Energy, Core–Core Interaction and Heat of Formation obtained by pm3 method (table3). Computations were carried out to study thermodynamic parameters, frequency method and optimized geometrical parameters investigated using gaussian 09, B3LYP method and Uff/6-31G as the basis set that are listed in Table (table 4).

ε0 in frequency has been used to calculate total electronic energy:
Sum of electronic and zero-point energies= ε0 + EZPE
Sum of electronic and thermal energies= ε0 + Etot
Sum of electronic and thermal enthalpies= ε0 + Hcorr
Sum of electronic and thermal free energies= ε0 + Gcorr

In the general look at the table 1 in 298 k˚, the kinetic energy in promethazine is the lowest one and after that loratadine with 44.4 kcal/mol, cetirizine with 46.1 kcal/mol and then buclizine with 56.8 kcal/mol are located. For potential energy, there is the minimized energy amount at the beginning of processing of cetirizine, promethazine and loratadine but with the steppes increasing, the more stability we get as it shown in table 1 these amounts for cetirizine in step 0 and 500 respectively is equal to 12.7 and 61.9 kcal/mol, for promethazine 23.1 and 53.9 kcal/mol and for loratadine23.9 and 64.5 kcal/mo. Indeed, potential energy at the step zero for buclizine 76.4 kcal/mol and at step 500 is 73.5 kcal/mol and the most value of this parameter is 92.2 kcal/mol in step 430.

For total energy in step 0 and 500 buclizine there is a value of 133.2 and 130.4kcal/mol, in cetirizine it is about 58.9and 108.1 kcal/mol, in loratadine 68.3 and 108.9 kcal/mol and for promethazine it is equal to 58.6 and 89.5 kcal/mol .Buclizine at the step 500 has the biggest value of total energy.

Also, we can figure out that the most value of total energy in buclizine belongs to step 10 (143.4 kcal/mol), in cetirizine belongs to step 370 (107.3 kcal/mol) and for loratadine it belongs to step 140 (115.7 kcal/mol) and for promethazine belongs to step 370 (103.4 kcal/mol).

Based on table 2 ate 310 kelvin degree (the body temperature and the most important part of this investigation) kinetic energy in order from high to low value is equal to 59.13 kcal/mol (in buclizine) ,48.05 kcal/mol (in cetirizine), 46.2 kcal/mol (in loratadine) and 36.9 kcal/mol in promethazine.

For buclizine the minimized value of potential energy is in step 0 (73.6kcal/mol) and the maximum value is in step 230 (83.2 kcal/mol) and in step 500 is 67.6 kcal/mol .Also total energy in the beginning is 132.7 kcal/mol and at the end 126.7 kcal/mol and the maximum value is also in step 230 (142.4 kcal/mol).

Except buclizine with a reduction behavior of potential and total energy, cetirizine, loratadine and promethazine have opposite behavior as In cetirizine potential and total energy in step 0 respectively is equal to 61.9 and 110.3 kcal/mol and in step 500 is equal to, 62.6 and 110.6 kcal/mol and the maximum value with this order is 63.6 kcal/mol (in step 50) and 112.3 kcal/mol (in step 170).

In loratadine potential energy in step 0 has a value of 64.51 kcal/mol and in step 500 has a value of 64.53 kcal/mol and total energy in these steps is 110.71 and 110.74 kcal/mol.

Potential energy in step 0 in promethazine has a value of 53.9 kcal/mol and in step 500 has a value of 59.5 kcal/mol and total energy in step 0 in has a value of 90.9 kcal/mol and in step 500 has a value of 96.9 kcal/mol and the both maximum amount of potential and total energy belongs to step 150 (67.5 and 102.7 kcal/mol).

Semi empirical results in the table 3 obtained that maximum energy of total and binding energy belongs to promethazine (respectively is -65270.2 and -4134.2 cal/mol) and minimum value of these energies belongs to buclizine (-102925.2 and-6616.2 cal/mol).

The next parameters have been checked in semi empirical are isolated atomic energy ,electronic energy ,heat of formation and core-core interaction which the maximum value of the amounts belongs to buclizine and respectively are equal to -96309.008 ,-963841.6 ,143.002 and 860916.4 cal/mol and the minimum values also are -327771.06 , -61135.9 , 105.181 and 446322.6 cal/mol and belong to promethazine .

As it figures out in figure 2, R^2 parameter in semi empirical method for our antihistamine molecules has a value of =0.97 for total energy, =0.90 for core-core interaction, heat of formation and binding energy, =0.82 for isolated atomic energy, = 0.92 for electronic energy.

In table 4, it has been observed that the most positive value of ΔG (Gibbs free energy), ΔH (enthalpy) for buclizine was 0.67and 0.75 which was obtained from the B3LYP/6-31G method. But the highest total energy (Etot) of buclizine was also computed by B3LYP/6-31G basis set and the calculated amount was 0.61 (Kcal/mol). Buclizine has also the maximum value of E_{zpe} (0.59, H_{corr} (0.61) and G_{corr}(0.54).

Table 1. Comparison of Mont Carlo parameters (Energy: kcal/mol) at 298 K˚ in amber force field for Buclizine, Loratadine, Cetirizine, Promethazine.

	buclizine			**cetirizine**			**loratadine**			**promethazine**		
Time (ns)	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**
0	55.13882	76.44319	133.2928	48.05029	12.76351	58.95379	46.20221	23.92347	68.33721	35.53099	23.13764	58.66862
10	55.13882	86.55434	143.4039	48.05029	40.75369	86.94398	46.20221	53.57831	97.99204	35.53099	44.61845	80.14944
20	55.13882	69.6348	126.4844	48.05029	42.35465	88.54494	46.20221	55.42177	99.83551	35.53099	47.19341	82.72439
30	55.13882	74.9578	131.8074	48.05029	39.08729	85.27758	46.20221	66.349	110.7627	35.53099	48.5721	84.10308
40	55.13882	67.17229	124.0219	48.05029	43.0767	89.26698	46.20221	59.18048	103.5942	35.53099	49.4858	85.01679
50	55.13882	63.76629	120.6159	48.05029	54.14947	100.3398	46.20221	65.23974	109.6535	35.53099	48.76277	84.29376
60	55.13882	70.95325	127.8028	48.05029	54.63144	100.8217	46.20221	64.86229	109.276	35.53099	54.46058	89.99156
70	55.13882	85.93291	142.7825	48.05029	48.93743	95.12772	46.20221	62.58527	106.999	35.53099	48.29001	83.821
80	55.13882	75.17027	132.0198	48.05029	43.87858	90.06886	46.20221	57.8489	102.2626	35.53099	48.31468	83.84567
90	55.13882	69.57344	126.423	48.05029	50.30035	96.49064	46.20221	61.51454	105.9283	35.53099	60.35855	95.88954
100	55.13882	68.39644	125.246	48.05029	49.31498	95.50526	46.20221	58.24169	102.6554	35.53099	56.53387	92.06486
110	55.13	76.17841	133.028	48.05	49.13529	95.32558	46.20	57.93292	102.3467	35.53	50.85418	86.38516

	882			029			221			099		
120	55.13882	71.94243	128.792	48.05029	60.351	106.5413	46.20221	63.73519	108.1489	35.53099	48.89562	84.42661
130	55.13882	69.65507	126.5047	48.05029	47.93116	94.12144	46.20221	68.72211	113.1358	35.53099	46.24254	81.77353
140	55.13882	69.33309	126.1827	48.05029	53.28756	99.47785	46.20221	71.29152	115.7053	35.53099	49.82669	85.35768
150	55.13882	68.03404	124.8836	48.05029	50.21171	96.402	46.20221	59.86965	104.2834	35.53099	51.48726	87.01825
160	55.13882	60.06784	116.9174	48.05029	46.55114	92.74142	46.20221	63.28325	107.697	35.53099	57.42328	92.95427
170	55.13882	65.50745	122.357	48.05029	54.76271	100.953	46.20221	68.20541	112.6191	35.53099	56.24476	91.77575
180	55.13882	64.6801	121.5297	48.05029	50.40135	96.59163	46.20221	64.93355	109.3473	35.53099	55.43012	90.96111
190	55.13882	76.84701	133.6966	48.05029	47.13169	93.32198	46.20221	63.76215	108.1759	35.53099	57.42021	92.9512
200	55.13882	63.37312	120.2227	48.05029	49.50619	95.69648	46.20221	65.54744	109.9612	35.53099	57.28459	92.81557
210	55.13882	68.37245	125.222	48.05029	50.86158	97.05186	46.20221	68.50458	112.9183	35.53099	56.55718	92.08817
220	55.13882	79.80619	136.6558	48.05029	59.3748	105.5651	46.20221	63.60272	108.0165	35.53099	51.25433	86.78532
230	55.13882	69.16465	126.0142	48.05029	59.32863	105.5189	46.20221	66.27471	110.6884	35.53099	54.54328	90.07427
240	55.13882	73.53521	130.3848	48.05029	53.48902	99.6793	46.20221	62.15969	106.5734	35.53099	58.67706	94.20805
250	55.13882	67.5633	124.4129	48.05029	54.42216	100.6124	46.20221	51.57894	95.99267	35.53099	60.47326	96.00424
260	55.13882	68.07793	124.9275	48.05029	55.0935	101.2838	46.20221	57.44198	101.8557	35.53099	53.80916	89.34015
270	55.13882	69.78106	126.6306	48.05029	60.58939	106.7797	46.20221	58.62438	103.0381	35.53099	55.33745	90.86843
280	55.13882	64.71869	121.5683	48.05029	54.61984	100.8101	46.20221	59.26611	103.6798	35.53099	52.03513	87.56612
290	55.13882	66.46936	123.3189	48.05029	66.56702	112.7573	46.20221	61.91418	106.3279	35.53099	51.04647	86.57746
300	55.13882	68.12381	124.9734	48.05029	59.56932	105.7596	46.20221	65.17648	109.5902	35.53099	53.65335	89.18434
310	55.13882	65.54501	122.3946	48.05029	58.46215	104.6524	46.20221	63.15499	107.5687	35.53099	53.63352	89.16451
320	55.13882	62.64518	119.4948	48.05029	59.19933	105.3896	46.20221	62.13243	106.5462	35.53099	58.81112	94.3421
330	55.13882	66.86438	123.714	48.05029	48.946	95.13629	46.20221	61.29694	105.7107	35.53099	56.25998	91.79096
340	55.13882	78.00045	134.85	48.05029	58.79386	104.9841	46.20221	58.43778	102.8515	35.53099	56.32103	91.85202
350	55.13882	82.14369	138.9933	48.05029	54.83352	101.0238	46.20221	67.01754	111.4313	35.53099	51.86167	87.39266
360	55.13882	82.20227	139.0518	48.05029	55.76435	101.9546	46.20221	64.43336	108.8471	35.53099	57.77529	93.30627
370	55.13882	70.3752	127.2248	48.05029	61.13802	107.3283	46.20221	59.54972	103.9635	35.53099	67.96583	103.4968
380	55.13882	69.84985	126.6994	48.05029	54.46627	100.6566	46.20221	64.46811	108.8818	35.53099	57.28945	92.82043
390	55.13882	69.51171	126.3613	48.05029	57.4144	103.6047	46.20221	61.68372	106.0975	35.53099	59.77072	95.30171
400	55.13882	79.53955	136.3891	48.05029	54.13849	100.3288	46.20221	75.6378	120.0515	35.53099	68.03431	103.5653
410	55.13882	72.95354	129.8031	48.05029	54.37174	100.562	46.20221	61.49047	105.9042	35.53099	63.41212	98.9431
420	55.13882	72.01398	128.8636	48.05029	57.27204	103.4623	46.20221	70.77946	115.1932	35.53099	63.90528	99.43627
430	55.13882	92.26991	149.1195	48.05029	58.35422	104.5445	46.20221	62.36253	106.7763	35.53099	56.89946	92.43045
440	55.13882	74.61095	131.4605	48.05029	62.35122	108.5415	46.20221	63.83786	108.2516	35.53099	57.44343	92.97441
450	55.13882	74.85436	131.7039	48.05029	56.59917	102.7894	46.20221	64.26033	108.6741	35.53099	54.64112	90.17211
460	55.13882	77.04447	133.894	48.05029	56.15652	102.3468	46.20221	62.6267	107.0404	35.53099	56.23207	91.76306
470	55.13882	73.57719	130.4268	48.05029	56.64878	102.8391	46.20221	64.64328	109.057	35.53099	51.23433	86.76531
480	55.13882	67.02561	123.8752	48.05029	55.61589	101.8062	46.20221	69.64415	114.0579	35.53099	53.35677	88.88775
490	55.13882	67.54003	124.3896	48.05029	59.49861	105.6889	46.20221	64.88159	109.2953	35.53099	52.66479	88.19578
500	55.13882	73.59829	130.4479	48.05029	61.97519	108.1655	46.20221	64.50391	108.9176	35.53099	53.98269	89.51368

Table 2. Comparison of Mont Carlo parameters (Energy: kcal/mol) at 310 K˚ in amber force field for Buclizine, Loratadine, Cetirizine, Promethazine.

	buclizine			cetirizine			loratadine			promethazine		
Time (ns)	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**	**EKIN**	**EPOT**	**ETOT**
0	59.13882	73.60378	132.7426	56.84958	61.98157	110.0319	44.43373	64.51615	110.7184	36.96177	53.99298	90.95475
10	59.13882	75.48274	134.6216	56.84958	53.6663	101.7166	44.43373	58.08411	104.2863	36.96177	49.64585	86.60762
20	59.13882	72.73796	131.8768	56.84958	56.28294	104.3332	44.43373	62.66463	108.8668	36.96177	53.06112	90.02289
30	59.13882	69.90088	129.0397	56.84958	56.17437	104.2247	44.43373	64.59626	110.7985	36.96177	59.59013	96.55189
40	59.13882	68.53002	127.6688	56.84958	61.43094	109.4812	44.43373	68.21158	114.4138	36.96177	50.10513	87.0669
50	59.13882	74.27886	133.4177	56.84958	63.65299	111.7033	44.43373	68.49643	114.6986	36.96177	52.56319	89.52495
60	59.13882	70.82911	129.9679	56.84958	55.52521	103.5755	44.43373	60.62135	106.8236	36.96177	52.77534	89.73711
70	59.13882	77.90476	137.0436	56.84958	52.65917	100.7095	44.43373	62.60499	108.8072	36.96177	53.52449	90.48626
80	59.13882	70.40487	129.5437	56.84958	53.98574	102.036	44.43373	57.86199	104.0642	36.96177	55.26085	92.22261
90	59.13882	75.64803	134.7869	56.84958	54.42971	102.48	44.43373	56.79516	102.9974	36.96177	57.48788	94.44965
100	59.13882	75.87751	135.0163	56.84958	54.01491	102.0652	44.43373	61.78428	107.9865	36.96177	55.11307	92.07484
110	59.13882	72.7329	131.8717	56.84958	59.14029	107.1906	44.43373	54.84092	101.0431	36.96177	59.85178	96.81355
120	59.13882	76.32639	135.4652	56.84958	56.61641	104.6667	44.43373	67.60594	113.8082	36.96177	61.43773	98.39949
130	59.13882	73.05263	132.1915	56.84958	61.60123	109.6515	44.43373	57.47725	103.6795	36.96177	54.27446	91.23623
140	59.13882	67.30032	126.4391	56.84958	48.33514	96.38544	44.43373	67.22281	113.425	36.96177	51.57563	88.5374
150	59.13882	77.5047	136.6435	56.84958	55.78603	103.8363	44.43373	70.94234	117.1445	36.96177	65.7588	102.7206
160	59.13882	76.32914	135.468	56.84958	65.64559	113.6959	44.43373	55.54511	101.7473	36.96177	59.80638	96.76815
170	59.13882	82.59798	141.7368	56.84958	64.32062	112.3709	44.43373	70.16907	116.3713	36.96177	55.65507	92.61684
180	59.13882	80.1983	139.3371	56.84958	54.91124	102.9615	44.43373	62.59504	108.7972	36.96177	57.77533	94.7371
190	59.13882	78.08083	137.2197	56.84958	44.36379	92.41408	44.43373	62.77926	108.9815	36.96177	59.08331	96.04507
200	59.13882	73.18838	132.3272	56.84958	49.81776	97.86806	44.43373	66.43705	112.6393	36.96177	49.55759	86.51936
210	59.13882	74.19798	133.3368	56.84958	55.20732	103.2576	44.43373	62.0479	108.2501	36.96177	56.16875	93.13051
220	59.13882	73.24	132.3788	56.84958	56.07842	104.1287	44.43373	60.26516	106.4674	36.96177	48.92421	85.88598
230	59.13882	83.28227	142.4211	56.84958	49.84169	97.89199	44.43373	59.00591	105.2081	36.96177	47.336	84.29776
240	59.13882	78.25899	137.3978	56.84958	46.53625	94.58655	44.43373	67.28082	113.483	36.96177	48.39843	85.36019
250	59.13882	82.16135	141.3002	56.84958	46.94055	94.99084	44.43373	66.83323	113.0354	36.96177	61.27165	98.23342
260	59.13882	77.86592	137.0047	56.84958	59.36088	107.4112	44.43373	54.34527	100.5475	36.96177	49.43761	86.39938
270	59.13882	74.41905	133.5579	56.84958	54.54706	102.5974	44.43373	62.56172	108.7639	36.96177	48.50623	85.468
280	59.13882	76.40466	135.5435	56.84958	57.11722	105.1675	44.43373	63.5354	109.7376	36.96177	50.06568	87.02744
290	59.13882	72.72917	131.868	56.84958	55.16626	103.2166	44.43373	68.52304	114.7252	36.96177	50.97755	87.93931
300	59.13882	69.49108	128.6299	56.84958	57.59057	105.6409	44.43373	71.36122	117.5634	36.96177	54.14748	91.10924
310	59.13882	80.78873	139.9276	56.84958	52.13329	100.1836	44.43373	69.094	115.2962	36.96177	49.96118	86.92295
320	59.13882	74.91938	134.0582	56.84958	63.03379	111.0841	44.43373	62.47858	108.6808	36.96177	53.95275	90.91452
330	59.13882	75.19598	134.3348	56.84958	53.58928	101.6396	44.43373	62.75635	108.9586	36.96177	55.50973	92.4715
340	59.13882	73.45872	132.5975	56.84958	59.17029	107.2206	44.43373	66.96243	113.1646	36.96177	53.86424	90.82601
350	59.13882	79.24037	138.3792	56.84958	48.73579	96.78608	44.43373	68.21632	114.4185	36.96177	55.6059	92.56766
360	59.13882	73.8871	133.0259	56.84958	46.74431	94.79461	44.43373	67.35888	113.5611	36.96177	65.22049	102.1823
370	59.13882	70.95161	130.0904	56.84958	52.10756	100.1579	44.43373	58.12382	104.326	36.96177	60.75175	97.71352

380	59.13882	72.34862	131.4874	56.84958	53.60683	101.6571	44.43373	70.76603	116.9682	36.96177	59.43871	96.40048
390	59.13882	69.8659	129.0047	56.84958	58.58673	106.637	44.43373	61.85793	108.0601	36.96177	61.04444	98.0062
400	59.13882	76.35409	135.4929	56.84958	59.59656	107.6469	44.43373	59.19862	105.4008	36.96177	62.18518	99.14695
410	59.13882	79.41693	138.5558	56.84958	56.16276	104.2131	44.43373	56.76923	102.9714	36.96177	58.26344	95.2252
420	59.13882	64.18236	123.3212	56.84958	56.0751	104.1254	44.43373	62.24528	108.4475	36.96177	58.68851	95.65028
430	59.13882	75.20761	134.3464	56.84958	54.81485	102.8651	44.43373	64.48346	110.6857	36.96177	60.45892	97.42068
440	59.13882	65.15075	124.2896	56.84958	54.28462	102.3349	44.43373	65.30573	111.5079	36.96177	64.26019	101.222
450	59.13882	69.78053	128.9194	56.84958	59.38183	107.4321	44.43373	65.58107	111.7833	36.96177	59.8053	96.76707
460	59.13882	78.57233	137.7112	56.84958	59.58578	107.6361	44.43373	62.08292	108.2851	36.96177	61.55907	98.52083
470	59.13882	80.6362	139.775	56.84958	62.84744	110.8977	44.43373	69.77733	115.9795	36.96177	59.22724	96.18901
480	59.13882	82.95557	142.0944	56.84958	58.32474	106.375	44.43373	66.03291	112.2351	36.96177	59.29392	96.25568
490	59.13882	77.908	137.0468	56.84958	58.33328	106.3836	44.43373	62.83161	109.0338	36.96177	54.96382	91.92558
500	59.13882	67.62117	126.76	56.84958	62.63112	110.6814	44.43373	64.53946	110.7417	36.96177	59.58944	96.55121

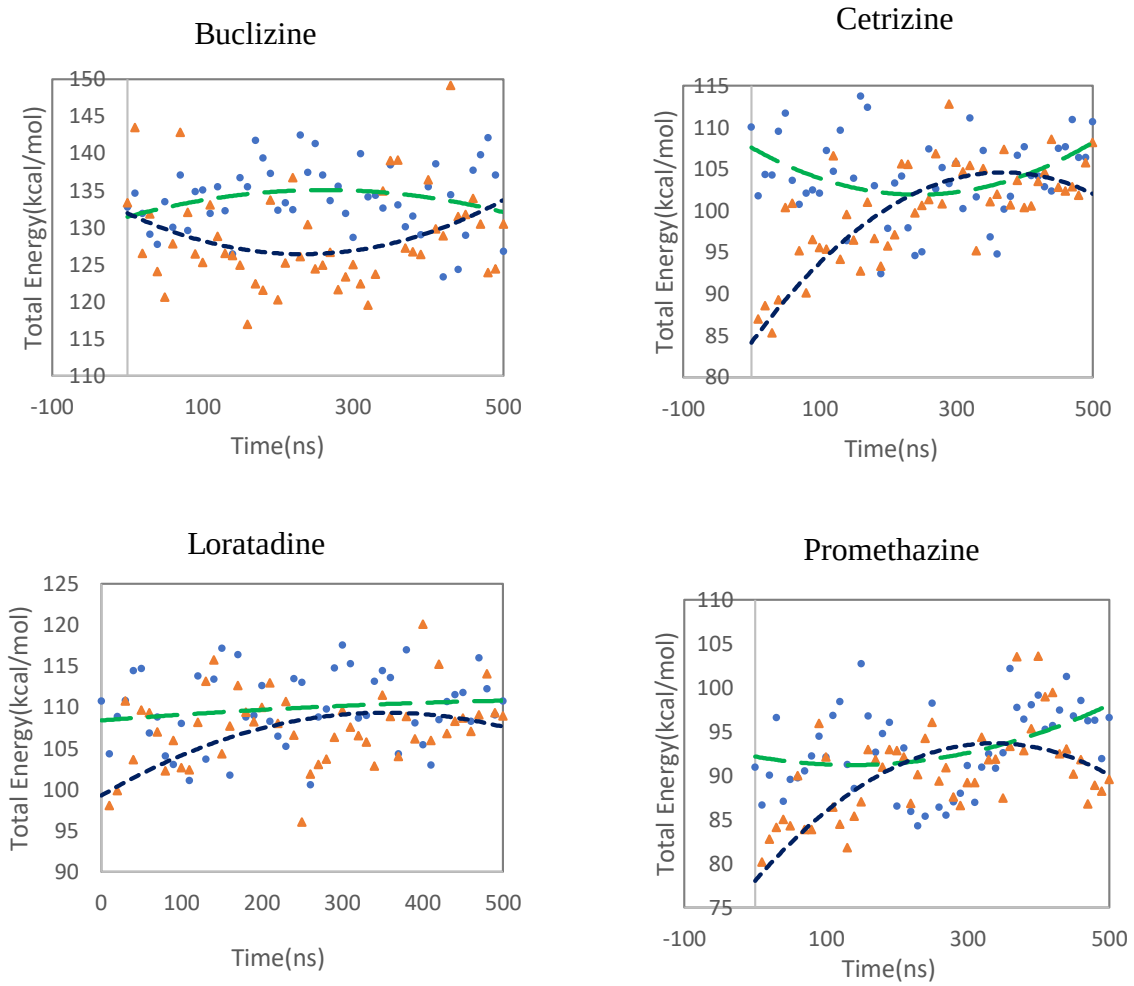

Figure 2. Analysis of total energy in monte carlo method for buclizine, loratadine, cetirizine and promethazine at 298 k˚(Δ, R^2: _ _ _)and 310 k˚(●, R^2: ----)

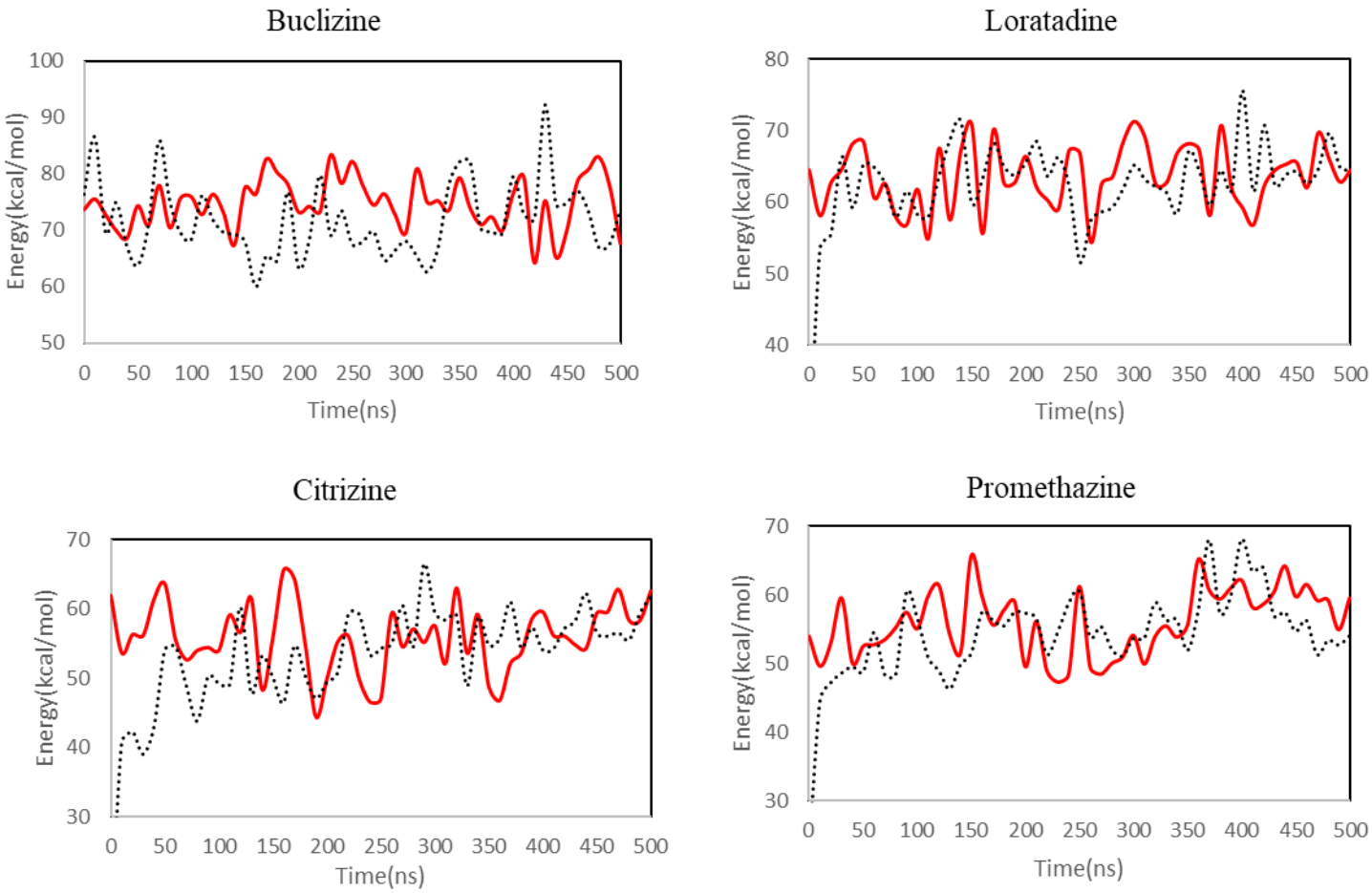

Figure 3. Analysis of potential energy in monte carlo method for buclizine, loratadine, cetirizine and promethazine at both 298 and 310 k˚

Table 3. Total, binding, isolated atomic, electronic energy, core- core interaction, heat of formation and gradient of Buclizine, Cetirizine, Loratadine, Promethazine in pm3 of semi empirical methods

	Buclizine	**Cetirizine**	**Loratadine**	**Promethazine**
Total Energy	-102925.2816331	-101300.1990195	-96552.7414636	-65270.2983316
Binding Energy	-6616.2730411	-5340.9796755	-5303.9158576	-4134.3881596
Isolated Atomic Energy	-96309.0085920	-95959.2193440	-441319.002	-327771.066
Electronic Energy	-963841.6836494	-815606.5668284	-810066.5239020	-61135.9101720
Core-Core Interaction	860916.4020163	714306.3678090	713513.7824384	446322.6214109
Heat of Formation	143.0029589	-16.0726755	28.1181424	105.1818404
Gradient of Reference Configuration	25.6894686	27.5162009	26.0649287	22.9593538

Table 4. Frequency energy parameters in Buclizine, Cetirizine, Loratadine and Promethazine

	Buclizine	**Cetirizine**	**Loratadine**	**Promethazine**
E_{ZPE}	0.590707	0.473325	0.444462	0.363307
E_{tot}	0.610763	0.490401	0.461409	0.376831
H_{corr}	0.611707	0.491345	0.462353	0.377775
G_{corr}	0.540425	0.426235	0.398148	0.322190
$E_0 = \varepsilon_0 + E_{ZPE}$	0.729036	0.595146	0.600527	0.482404
$E = \varepsilon_0 + E_{tot}$	0.749092	0.612222	0.617474	0.495928
$H = \varepsilon_0 + H_{corr}$	0.750036	0.613166	0.618418	0.496872
$G = \varepsilon_0 + G_{corr}$	0.678753	0.548056	0.554212	0.441287

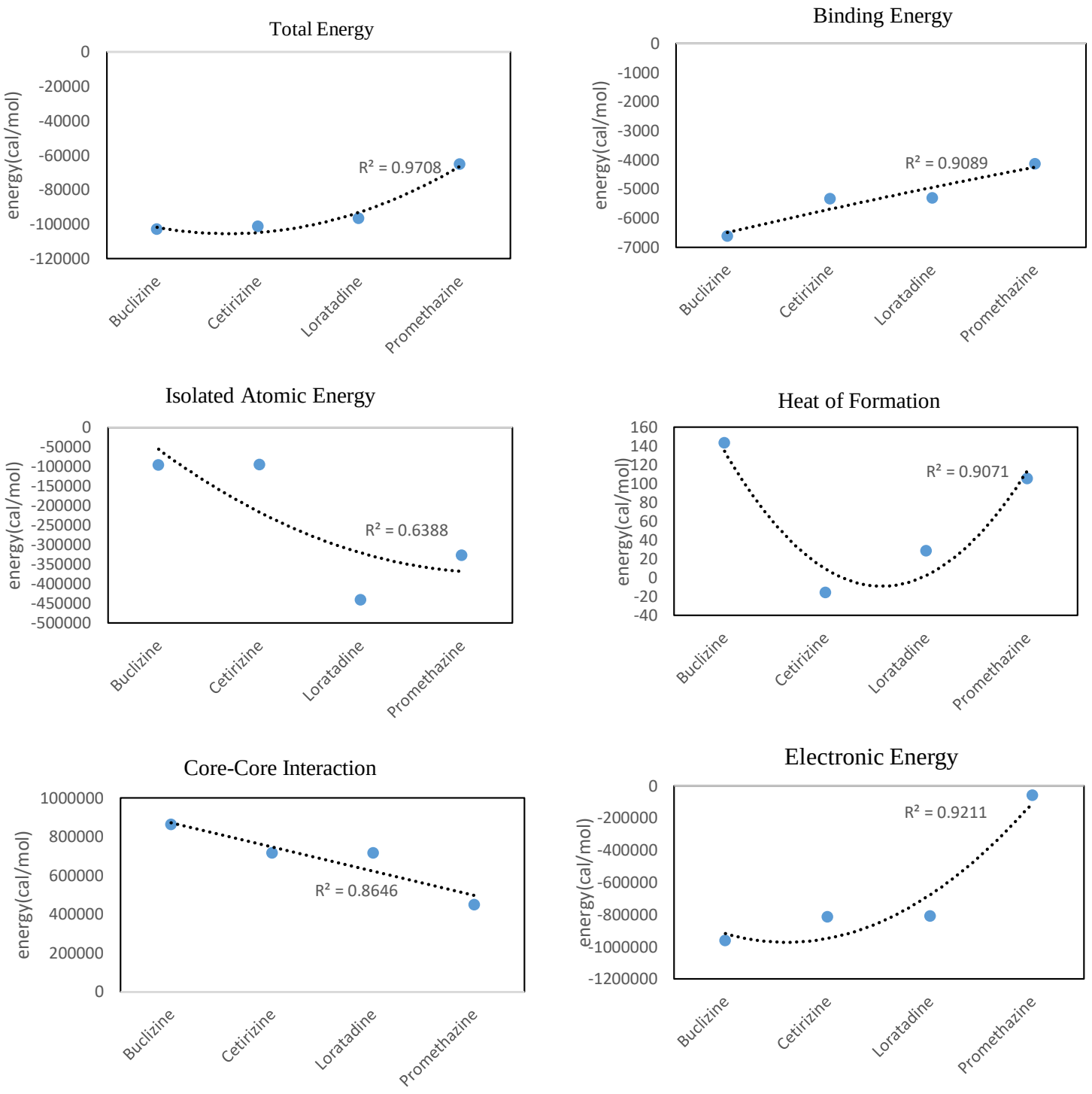

Figure 4. Optimized parameters of Total energy, Binding energy, isolated atomic energy, Electronic energy, Core–core interaction and Heat of formation (cal/mol) for buclizine, loratadine, cetirizine and promethazine

4. CONCLUSIONS

In this work we study theoretically the structure features of buclizine, cetirizine, loratadine and promethazine. Molecular mechanic and quantum mechanics data including potential, total and kinetic energy, geometrical optimization and vibrational analysis have been investigated by using Mont Carlo and Semi empirical methods. Free Gibbs energy, enthalpy and total energy investigated by frequency with BL3YP method and 6-31G (d) levels of theory. Following conclusions are obtained from the current study:

It is figured out in Mont Carlo study buclizine in both 298 and 310 k˚ at the end of process has the most potential energy and promethazine has the minimum value of potential energy in the both temperatures. Results came out from semi empirical obtained that binding energy is much more in promethazine as a result of more stable structure and the strongest connection of nuclear obtained in buclizine and breaking the buclizine bonds release more energy than others. According to the thermodynamic parameters, we find that the amount of Gibbs free energy (ΔG), standard enthalpies (ΔH) of buclizine is the most positive value.

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