QM Study on the Mechanism of Carbonic Anhydrase II Inhibition with Glycosylcoumarin as Non-Zinc Mediated Inhibitors from Thermodynamic View Point

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Abstract: Carbonic anhydrase is an enzyme which has the zinc as the metallic part of it. This enzyme catalyzes the reversible reaction of turning carbon dioxide into bicarbonate. In this research the mechanism of inhibition a new class of inhibitor of this enzyme, glycosyl coumarin has been modeled using the density functional theory (DFT). First, the most constant confirmer of this four coumarin sugar derivatives which includes galactose, mannose, ribose and glucose has been selected and then they had been interacted as inhibitor with CA (II) enzyme's active site. In further for showing the effect of sugar in these molecules, coumarin itself had been chosen as inhibitor and the inhibitory effect is surveyed. All calculations have been done by density functional theory in level of B3LYP with basic set 6-31G* and with Minnesota function M06 with basic set 6-31+G*. Thermodynamic functions like enthalpy of formation, entropy of formation and Gibbs free energy for CA-inhibitor have been computed. The results indicate that the reaction among these groups of inhibitors and Carbonic anhydrase is not of the type of direct and syndetic but the enzyme is deactivated with space effect and addition to this, the computed thermodynamic functions show that although this coumarin sugar derives have deterrence in the range of micro molar but, coumarin without sugar is a stronger deterrence for CA II. Finally, the interaction between the most constant confirmer (galactose coumarin) is surveyed as the best deterrence using the explicit solvent method.

Keywords: Carbonic Anhydrase**,** glycosylcoumarin, inhibition mechanism, Density functional theory, explicit solvent method.

1. INTRODUCTION

Carbonic anhydrase (CA) is a ubiquitous zinc enzyme that accelerates the reversible hydration of CO2 into bicarbonate. There are five groups (α, β, γ, δ, ε) of genetic distinct Carbonic anhydrase enzymes in the whole phylogenetic tree. The first genetic group is alpha Carbonic anhydrases (α CAs) which are found in vertebrates, single cells, alga, cytoplasm of green plants and some of the bacterias. All the Carbonic anhydrases are metalloenzymes. Alpha Carbonic anhydrases use zinc (Zn(II)) in their active site [1-11]. The active site of all these enzymes show a similar topology. The three remained histidine, a water molecule / hydroxide ion are tetrahedrally coordinated into zinc ion [12]. Carbonic anhydrase is inhibited by an extended numbers of different inhibitors and often using their anion [13], for instance: metal complexing anion, sulfonamides, sulfamides, phenols and polyamines that bind to the metal ion through the enzyme active center or are anchored to the water molecule coordinated to the metal ion[14,15]. These inhibitors function as CA I and II strong inhibitors [16-18].

In the recent years a new group of CA inhibitors (coumarin and its derivatives) have been reported[19-21] that inhibit CA isoforms IX, XII, and XIII, Figure **1**. The mechanism of coumarins is different from all the known inhibitors. In fact, many of the known inhibitors connect directly to zinc ion using the active site but coumarins occupy the entrance space of the enzyme's active site in which it does not make any connection with three remained histidine and water molecule [22-24]. Scheme **1** presents the proposed inhibition mechanism of CAII by galactose coumarin, leading to cis- or trans-2-hydroxy-cinamic acid. The main problem of classic carbonic anhydrase inhibitors is their lack of selectivity. Recently, some coumarin sugar derivatives with strong inhibition have been discovered which they are related to CA XII and CA IX isoforms that Prevent the growth of primary tumors and metastasis. These sugar derivatives have selectivity manner and they are stronger inhibitors for CA XII and CA IX [12]. This research is going to study the mechanism of the inhibition of the new group of the inhibitors (coumarin sugar derivatives) with active form of CA II. According to previous study the presence of the sugar moieties in glycosidic sulfonamide carbonic anhydrase II inhibitors show less effective inhibition [25]. Figure **2** shows the derivatives of coumarin.

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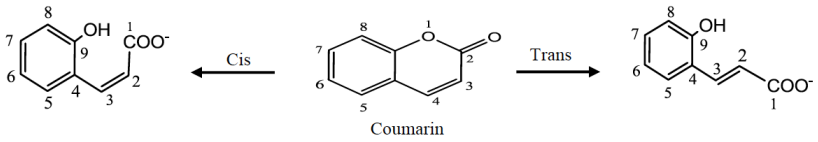
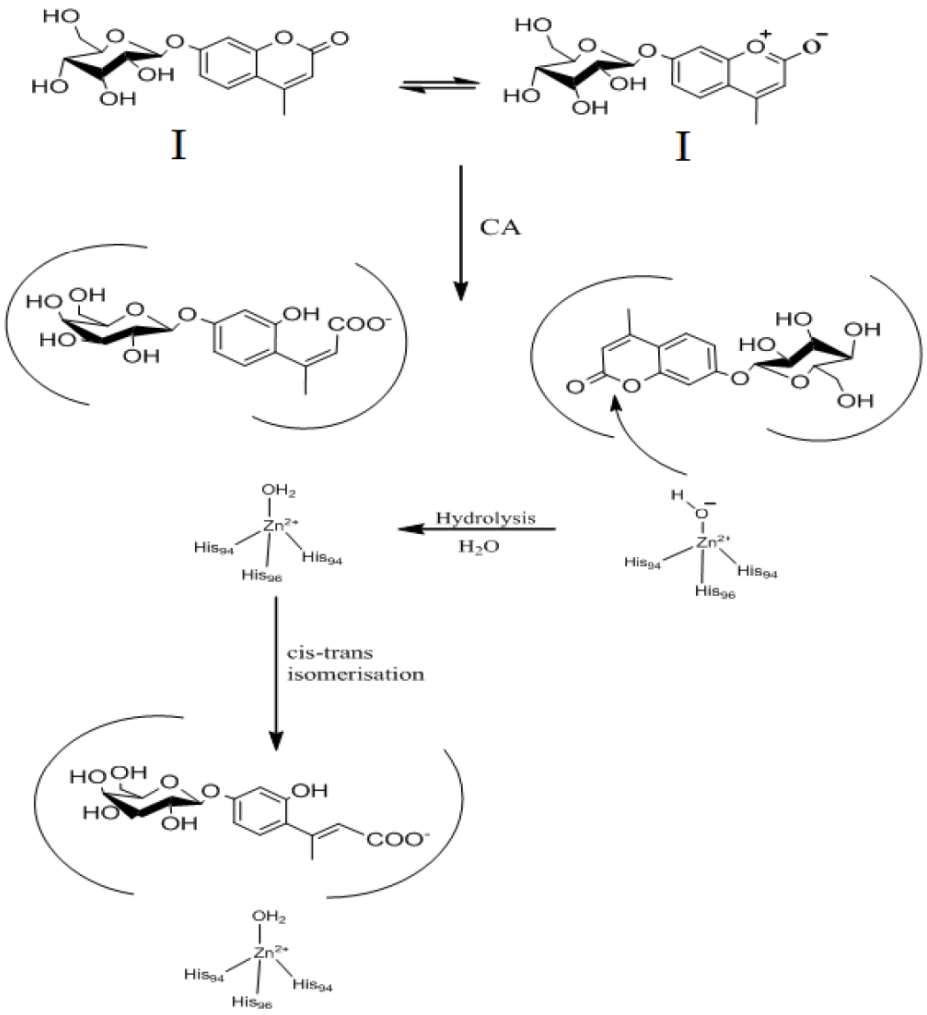


Figure 1: Presentation of coumarin molecule and its hydrolysis product, cis- and trans-2-hydroxycinnamic acid with numbering for key atoms.



Scheme 1: Proposed inhibition mechanism of CAII by galactose coumarin that leading to cis/trans-2-hydroxy cinnamic acid.

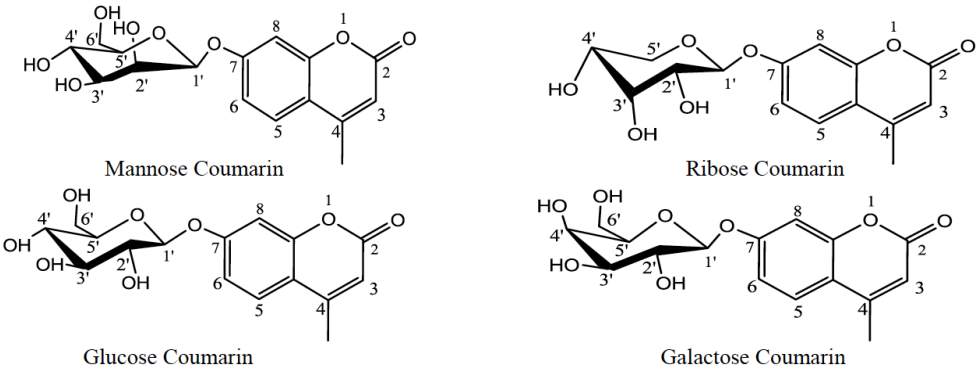


Figure 2: Presentation of 7-glycosyl-4-methyl coumarin with numbering for key atoms.

2. COMPUTATIONAL SCHEME

2.1. Ab Initio Calculations

All the calculations have been done via the software Gaussian 2009 [26] and guess view application [27]. The geometry of the active and inactive form of active site of Carbonic anhydrase, inhibitors and their hydrolyzed form (cis and trans) and the complex between inhibitors and Carbonic anhydrase is fully optimized by DFT methods [28]. All the calculations with no symmetry constrains have been carried out at two levels of DFT methods to compute the energy and geometrical parameters:

1. 6-31G* using the popular B3LYP level of theory that consists of hybrid Becke-Hartree–Fock exchange and Lee-Yang-Parr correlation functional with non-local correction [29].

2. 6-31+ G* basis set with M06 functional which has been introduced recently as hybrid meta-GGA (generalized gradient approximation) exchange functional correlation [30].

To verify the optimized geometry related to a local minimum and the absence of delusive frequencies, the harmonic vibrational frequencies has been computed. Moreover, the thermodynamic properties of all the substances is obtained by computing the frequency at 298.15 k and 1.0 atmosphere pressure. All the reported enthalpies were modified under consideration of Zero Point Energy (ZPE). Solvent effect is done by explicit solvent procedure to consider the water molecule. By defining the rotations angles as $O_5 – C_5 – C_6 – O_6$, $C_5 – C_6 – O_6 – H$ and $H_1 – C_1 – O – C$, the angles' scan has been done on the geometrical parameters with the step 5° and then the geometry has been optimized without any limitation around every potential minimum.

2.2. Calculation of Thermodynamic Functions

All the thermodynamic functions that are reported in this study, have been obtained by computing the frequency at 298.15 k and 1.0 atmosphere pressure. The total enthalpies of the studied species at the T temperature have been estimated usually by equation 1 [31-33].

$$H(x) = E_0 + ZPE + E_{trans} + E_{vib} + E_{rot} + RT \quad (1)$$

Which E_0 is the final electrical energy, ZPE is the abbreviation of zero point energy, E_{trans} , E_{vib} and E_{rot} are the representation of transition ,rotation and vibration in enthalpy and finally RT represent the term pv-work which is added to change the energy into enthalpy. The equation of changing the enthalpy of reaction goes like this:

$$\Delta H^{\circ}_r = [H^{\circ}_{product}] – [H^{\circ}_{reactant}] \quad (2)$$

And also changing the entropy of reaction is like what follows:

$$\Delta S^{\circ}_r = [S^{\circ}_{product}] – [S^{\circ}_{reactant}] \quad (3)$$

Base on the thermodynamic equation, $\Delta G = \Delta H - T\Delta S$, Gibbs free energy change of the reaction (ΔG°_r) can be computed which it is a measure of progress and Spontaneity of the reaction.

3. RESULTS AND DISCUSSION

3.1. Geometry Optimization of the Carbonic Anhydrase II Active Center in the Active and Inactive Forms, [EZn^{2+}- OH^-] and [EZn^{2+}- OH_2]

The model consists of a zinc cation which is located at the bottom of the conical active center which is bonded to H_2O (in inactive form) or OH^- (in active form) group, three imidazole rings belonging to the three remained histidine, His 94, His 96 and His 119 which they all can be seen in the Figure **3**. Structure of the active form of carbonic anhydrase II (ACA II) and the inactive form (ICA II) can be fully optimized at M06/6-31+G* and B3LYP/6-31G* without any Symmetric constraint.

Figure **3** shows the optimized structure and some structural details of ACA II in gas phase. The average distance between Zn^{2+} and the atom N in histidine in the both methods B3LYP and M06 is 2.04 Å.

3.2. Geometry Optimization and Conformational Search of Inhibitors

Since the most important angle in sugars is the dihedral angle in and around anomeric carbon and also the spot where glycosidic bond is made, Figure **4**. Therefore the structural search plays an important role in this study. For all the inhibitors which include galactose, mannose, glucose and ribose coumarin, to find the most stable conformers, the dihedral angles (ω = O5'–C5'–C6'–O6'), (θ = C5'–C6'–O6'–H) and (φ = H1'–C1'–O–C7) from 0° to 360° with the step of 5° were scanned. Assuming that only the structures with the energy difference of 5-10 kcal/mol can be present at the room temperature, for all the four inhibitors only

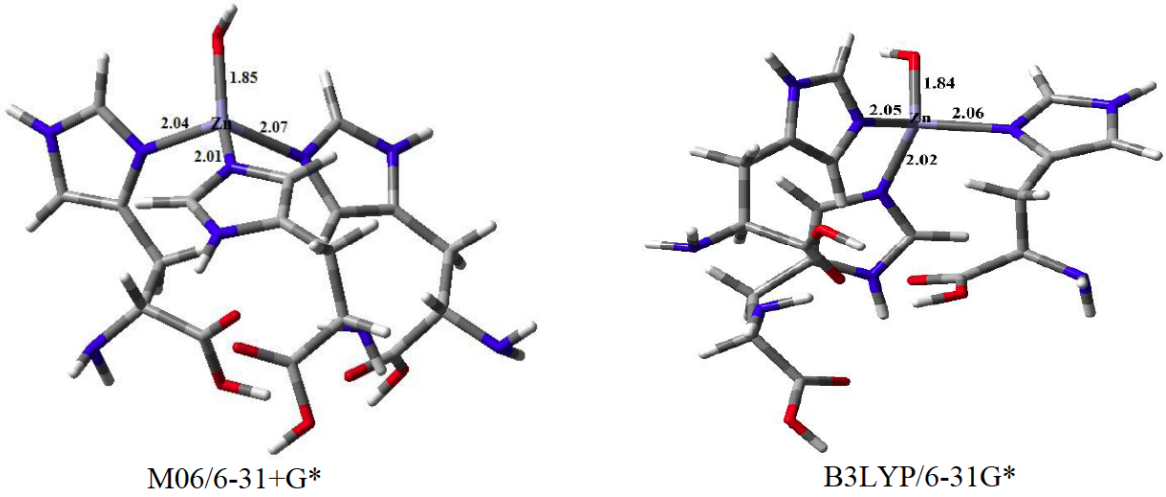


Figure 3: Optimized structure of the native CA II active site enzyme in the gas phase by using B3LYP/6-31G*and M06/6-31+G* methods. Distances are based on Å.

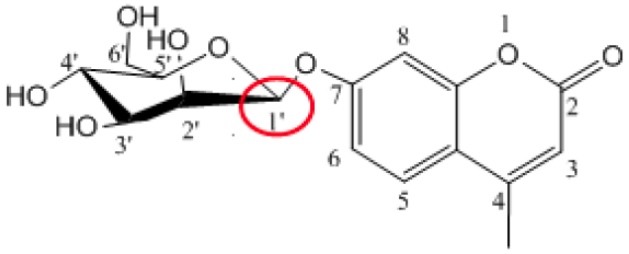


Figure 4: carbon anomeric's location.

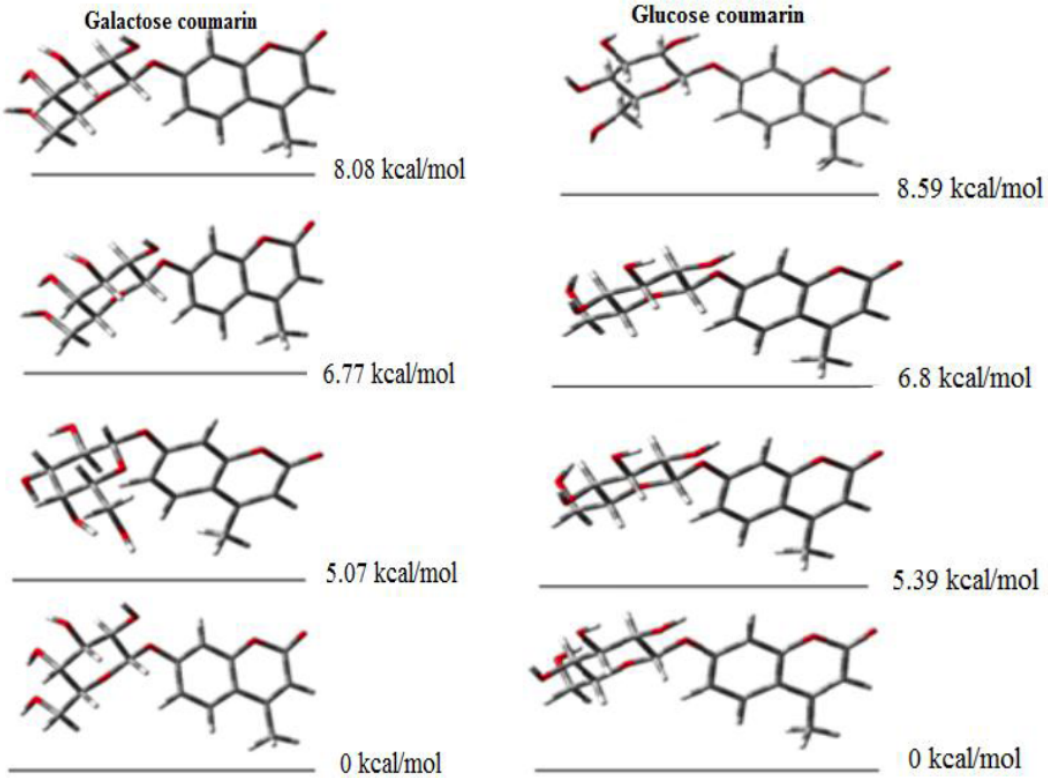


Figure 5: Energy difference of the conformers of the glycosyl coumarin derivatives.

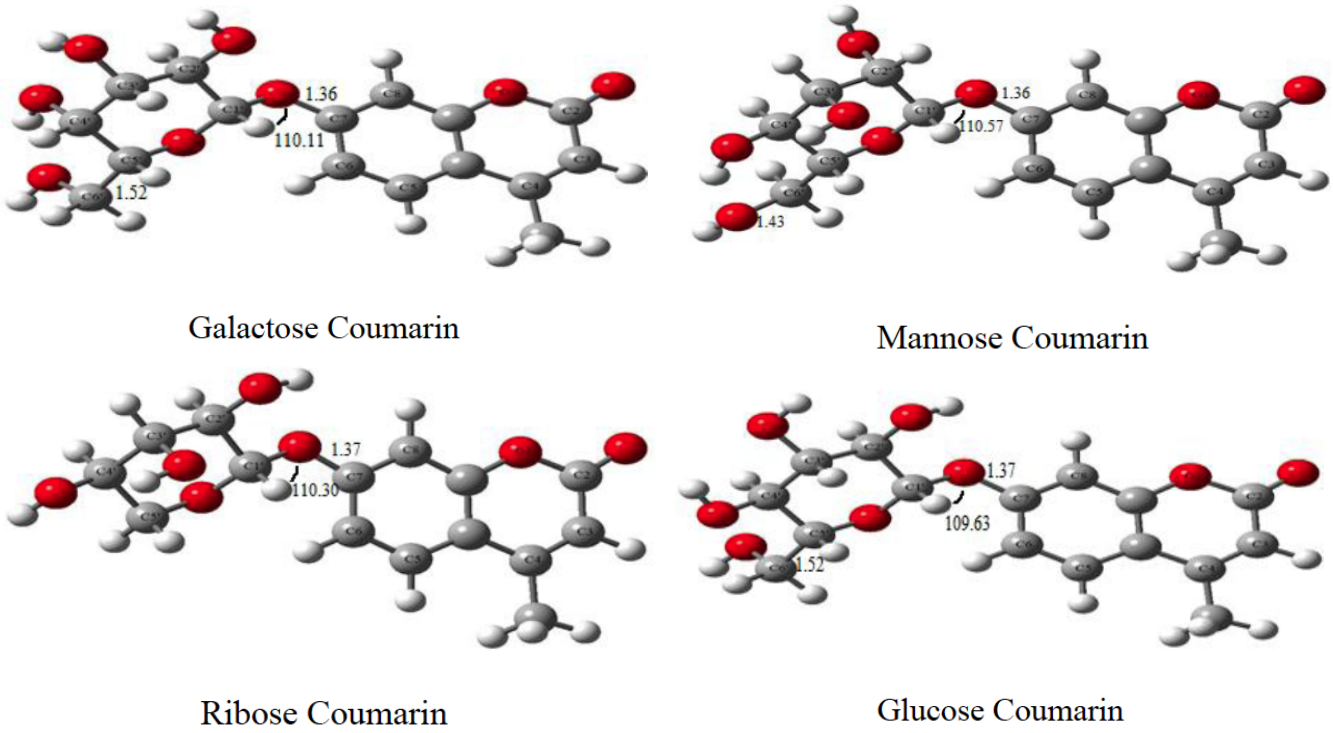


Figure 6: Presentation of optimized geometry of galactose, mannose, ribose and glucose coumarin derivatives at the B3lyp/6-31G* method in gas phase.

one conformer was found, Figure **5**. The most stable conformer of inhibitors is presented in Figure **6**.

3.3. Interaction between the Active Site of the Native CA II and Inhibitors

As we can see in the Scheme **1**, the inhibitor is placed in a space pocket close to the active form of the enzyme and unlike the other inhibitors, it doesn't make any interaction with zinc ion.

At the presence of the water molecule which hydrolyzes the enzyme and the inhibitor, the interaction goes on till the coumarin's inhibitor ring is opened and the both isomers, cis and trans are made, meanwhile hydroxyl enzyme group will turn to H_2O which it will inactive carbonic anhydrase enzyme. There's a notable point in this interaction which it is approaching the inhibitor to enzyme and its effect of inactivation on it only based on the space effect and in this interaction, the inhibitor does not make any connection with the active center of enzyme.

In order to study the interaction of coumarin and carbonic anhydrase enzyme, first the reactants such as inhibitor, the active form of the enzyme and water molecule were separately and independently optimized and then all three molecules approaches each other so they can have space interaction, again these three groups of molecules were optimized at an approximate distance of 2-3 A°. finally, the products including cis and trans isomers of inhibitors and the inactive form of enzyme has been optimized. The results indicate that cis isomer is more constant about 27.99, 4.4, 24.04 and 31.13 than trans isomer at galactose, mannose, ribose and glucose coumarin respectivly. This stability comes from the internal hydrogen bond between carbonyl oxygen atom and hydroxyl hydrogen atom in cis isomer. The optimized structures and also energy stability through the reaction's pathway of all four inhibitors displayed in the Figure **7**.

The energy barrier difference between reactions and products for the total reaction is calculated according to equation 4 and is about 132.54, 220.6, 137.85 and 130.45 kcal/mol for the cis isomer of galactose, mannose, ribose and glucose coumarin derivatives respectively in the B3LYP/6-31G* method.

$$\Delta E=(E_{int.}+E_{ICA}) - (E_{ACA} + E_{inh}) \quad (4)$$

E_{int}, E_{ICA}, E_{ACA} and E_{inh} in order refer to the total calculated energy of cis or trans intermediate isomer, inactive and active form of CA II and inhibitor molecule respectively. To survey the role of sugar moiety in inhibition mechanism, we chose coumarin without sugar and then repeated all the calculations for this inhibitor, Figure **8**. For all the five inhibitors, the energy

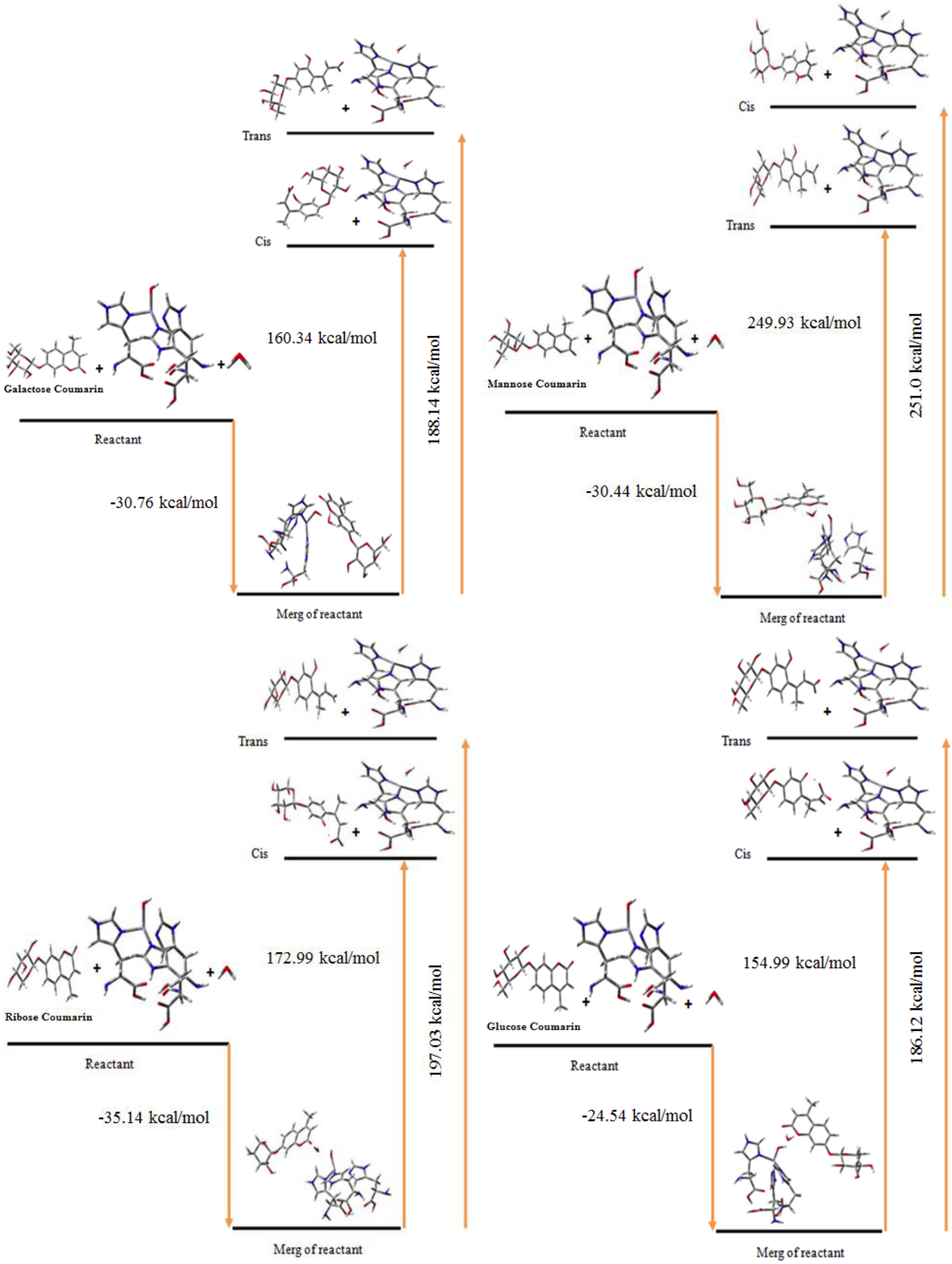


Figure 7: The optimized geometry and also energy stability through the reaction's pathway by galactose, mannose, ribose and glucose coumarin derivatives in the presence of one water molecule.

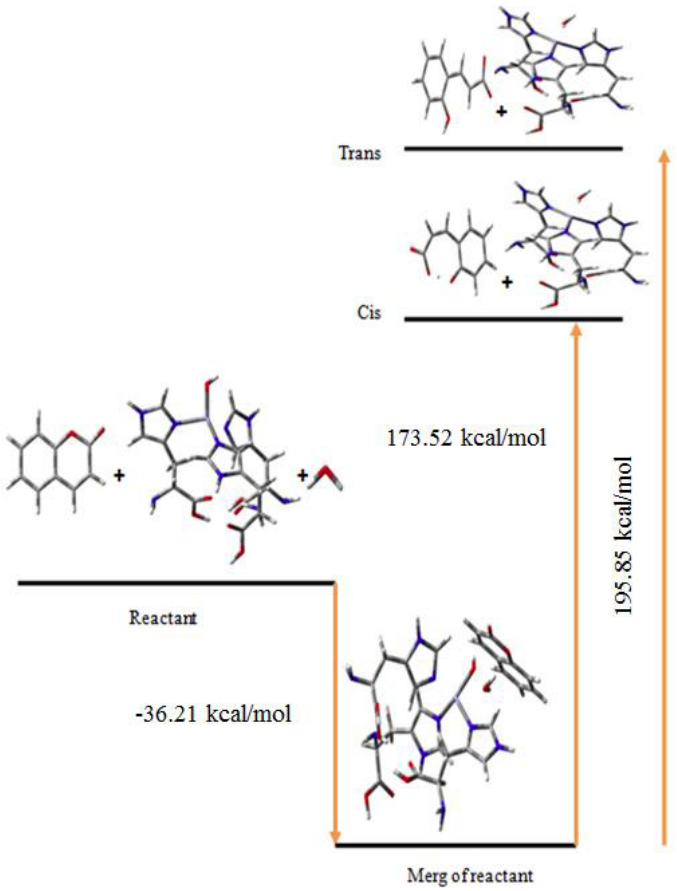


Figure 8: The optimized geometry of modeled systems in inhibition mechanism of CA II by coumarin in the presence of one water molecule.

Table 1: Thermochemistry of the reaction between five inhibitors and CA II calculated at B3LYP/6-31G* and M06/6-31+G* methods. ΔE_{tot} is the reaction energy with the zero point energies included. Note that the conversion energy change values are in kcal/mol and the entropy change values are in cal/mol

Inhibitor	Isomer	B3LYP/6-31G*				M06/6-31+G*		
		ΔE^{tot}_{rxn}	$\Delta H°_{rxn}$	$\Delta G°_{rxn}$	ΔS°rxn	ΔE^{tot}_{rxn}	$\Delta H°_{rxn}$	$\Delta G°_{rxn}$
Galactos Coumarin	Cis	132.54	131.96	144.75	-42.86	126.57	125.99	138.78
	Trans	160.53	159.95	168.85	-29.85	151.36	150.73	159.63
Glocose Coumarin	Cis	130.45	129.87	142.65	-42.86	128.45	127.87	140.65
	Trans	161.58	161.0	169.9	-29.85	154.24	153.66	162.56
Ribose Coumarin	Cis	137.85	137.27	150.05	-42.86	135.29	134.71	147.49
	Trans	161.89	161.31	170.21	-29.85	155.18	154.6	163.5
Mannose Coumarin	Cis	220.6	219.48	232.26	-42.86	229.23	228.65	241.43
	Trans	219.49	218.91	227.81	-29.85	231.55	230.97	239.87
Coumarin	Cis	137.31	136.73	146.75	-33.63	132.72	132.14	142.16
	Trans	159.64	159.06	167.62	-28.73	149.47	148.89	157.39

difference(ΔE_{rxn}) and all thermodynamic data for the reaction, including enthalpies ($\Delta H°_{rxn}$) and Gibbs free energies ($\Delta G°_{rxn}$) were computed at both levels M06/6-31+G* and B3LYP/6-31G*. The result can be seen in the Table **1**. ΔG°rxn values indicate that sugar moiety's existence does not enhance coumarin's inhibition

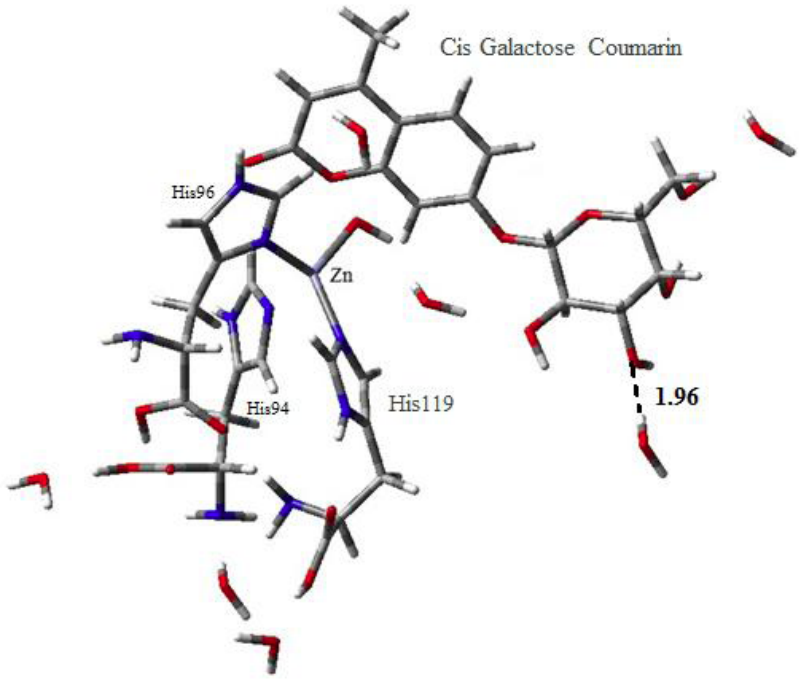


Figure 9: The optimized geometry of [ICA II/cis-galacto 2-hydroxy cinnamic acid] in the presence of six water molecules; Bond length is given in Å.

Table 2: Thermochemistry of the reaction between galactose coumarin as the most effectiove inhibitor and CA II active site calculated at B3LYP/6-31G* method in the presence of six water molecules. ΔE_{tot} is the reaction energy with the zero point energies included

/kcal.mol^{-1}	ΔE^{tot}_{rxn}	$\Delta H°_{rxn}$	$\Delta G°_{rxn}$
Cis isomer	-28.31	-28.89	-19.99

power for the four CA IIs inhibitor and even in some cases like mannose coumarin, it decreases its power dramatically which we noticed this point at the previous experiments [23]. Base on the reported results in the Table **1**, we can predict the inhibition power of these four sugar coumarins derivatives base on the ΔG values which it is: galactose coumarin > glucose coumarin > ribose coumarin > mannose coumarin, therefore the tendency of galactose coumarin toward the CA II is more than the other studied derivatives.

The computed enthalpy values of all the inhibitors indicate that the reaction between the inhibitors and the active site of CA II is endothermic and we should notice that these results are obtained for gas phase and for only one water molecule so probably by considering the water molecule, the results will dramatically change which we will investigate it later.

3.4. The Explicit Solvent Effect

To investigate the solvent effect and water molecule's role in this study, explicit solvent method has been used. In this method six water molecule have been optimized and then they were arranged around the optimized structure of the reactant's merge. Since galactose coumarin was the strongest derive, solvent effect was checked for inhibitor, Figure **9**. Table **2** shows the thermochemical functions of galactose coumarin's reaction with the active form of carbonic anhydrase II In the presence of six water molecule. Thermodynamic functions were computed only for the most stable isomer (cis isomer). The results of the calculations indicate that, by adding six water molecules, the reaction got more stable by 28.31 kcal/mol. The negative values of the thermodynamic functions for the interaction between active form of CA II and 7-galacto inhibitor shows that the reaction is exothermic and spontaneous.

4. CONCLUSION

In this research in order to make a theoretical study about the inhibition effect of a new group of inhibitors (coumarin and its sugar derivatives) on carbonic

anhydrase II enzyme, quantum Computing and two levels of DFT methods in gas phase and explicit solvent have been used. First coumarin molecule and its sugar derivatives were optimized in gas phase and then their effect was investigated on the optimized active form of carbonic anhydrase enzyme. The presence of one water molecule is necessary to do the hydrolysis in the reaction. By doing this reaction, carbonic anhydrase becomes inactive and the inhibitor molecule opens and leads to form the isomers cis or trans. Energy difference between reactants and intermediate and products level is mean that the reaction is endothermic. Due to the high absorption rate of energy in gas phase, solvent effect with explicit method has been done for the most powerful inhibitor, galactose, which led to decrease thermodynamics parameters so the reaction can be done at the body temperature Spontaneously and it is exothermic. It is notable to say that these inhibitors are solved in water which it is an advantage for clinical usage of these inhibitors.

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