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Theoretical Study to Predict the Ability to Use Different Organic Substituents as Carrier Linkages for Diclofenac

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The research includes unrestricted (UDFT) and (UPM3) quantum mechanical calculations for studying the reaction path of bonds rupture energies of (O-R) and (C-OAr) in twelve diclofenac derivatives containing different substituted organic groups. All the calculations were performed at the optimize geometries in vacuum phase by using Gaussian 09 program. Comparison was done between the studied diclofenac derivatives and the standard ionic diclofenac of sodium and potassium included geometrical structures, physical properties, total energies of the reactants and products, activation energies and transition states. The results showed that some substituted organic groups could be used to form good carrier bonds for the acidic drug diclofenac, while others were less efficient depending on the nature of the substituted carrier, and that there is a preference for carriers of the type (–R) over the carriers of the type (–Ar).

Keywords: Diclofenac ester derivatives, Bonds rupture, Physical properties.

INTRODUCTION

The main aim of the medicinal research in the recent times has been to develop drugs with enhanced efficacy, reduced toxicity and side effects. Over the years, innovations in new drug therapy has become, more complex, time consuming, costly and the practicing medicinal chemists have been bombarded with surplus new methods and technologies to make the job of drug discovery more efficient. These include quantitative structure-activity relationship (QSAR) analysis, rational drug design, molecular modeling and structure based design [1]. The term 'Prodrug' signifies a pharmacologically inactive chemical derivative that could be used to alter the physicochemical properties of drugs in a temporary manner to increase their usefulness and/or to decrease associated toxicity [2,3]. The chemical modification of a biologically active compound forms a new compound that upon *in vivo* enzymatic attack will liberate the parent compound. Prodrug can be defined as pharmacologically inert chemical derivatives which can be enzymatically or non-enzymatically converted *in vivo* to the active drug molecule to exert a therapeutic effect. Prodrug is defined as any compound that undergoes biotransformation before exhibiting its pharmacological effects. Depending upon the constitution, lipophilicity, method of deactivation and the catalyst involved in bioactivation, prodrugs are classified into two categories-carrier linked prodrug and bio-precursor [4,5].

In recent years, numerous prodrugs have developed to overcome barriers to drug utilization such as low oral absorption properties, lack of site specificity, chemical instability, toxicity, bad taste, bad odour and pain at the application site [6,7]. Most of the reported prodrugs and codrugs have shown to undergo biotransformation by enzymatic catalysis. The latter has many disadvantages because prodrug-activating enzymes can vary from person to person due to age or drug and food interaction, which can cause variation in clinical effects. Therefore, it is necessary to make prodrugs that have the ability to undergo inter- or intra-conversion to their parent drugs without the involvement of metabolic enzymes such as esterases and amidases. The computational approach, which has been utilized by Karaman's group [8,9] considered linking a non-toxic linker to an active drug, such as NSAIDs, which has poor bioavailability or suffers from gastrointestinal adverse effects. In Karaman's approach, the prodrug undergoes an intramolecular cleavage to furnish the active parent drug without the need to enzyme

catalysis. Different linkers can be attached to the drug and the rate of the active drug's release can be determined upon the structural features of the linker attached to the drug. By this approach, the release of the parent drug from its prodrug can be controlled and the variation of clinical effects that might be caused by the enzyme catalysis will be prevented.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), which has a strong anti-inflammatory and analgesic effects, tablets and suppositories of diclofenac are prescribed for fever, pain relief and chronic inflammatory diseases such as osteoarthritis [3]. Most of the diclofenac prodrugs and codrugs prepared in the past twenty years and a comprehensive description of the different approaches to decrease diclofenac gastrointestinal side effects [10].

The aim of this work is to calculate and study the reaction path curves for the rupture energies of O-R and C-OAr bonds in some synthesized esters and amides of diclofenac derivatives [11-15], and others proposed as carriers for this drug, (Pro.D(1-12), Fig. 1), in an attempt to find alternative carriers of the sodium and potassium salts that are avoided for people with high blood pressure. This is done by using unrestricted density functional theory (UDFT) and unrestricted semi-emp-erical method (UPM3) [16]. The calculations included energy of the reactants, activation energies and transition states, in addition to the nature and stability of the breakage end products. Based on reported studies [17-19], it is expected that theoretical calculations can be adopted in order to obtain useful primary informants about the chemical nature of the prodrugs of diclofenac, as they can provide a useful and prior explanation of the primary drug data, in general.

COMPUTATIONAL METHODS

All the quantum chemical calculations were performed with complete geometry optimizations using Gaussian 09 software package [20]. The optimization structures of the studied diclofenac prodrugs were carried out first by using unrestricted density functional theory (UDFT) at the UB3LYP/6-311 level of the theory (Fig. 2) then unrestricted semi-empirical method UPM3 was used for analyzing the characteristics of the reactions path of rupture energies of O-R and C-OAr bonds in the studied

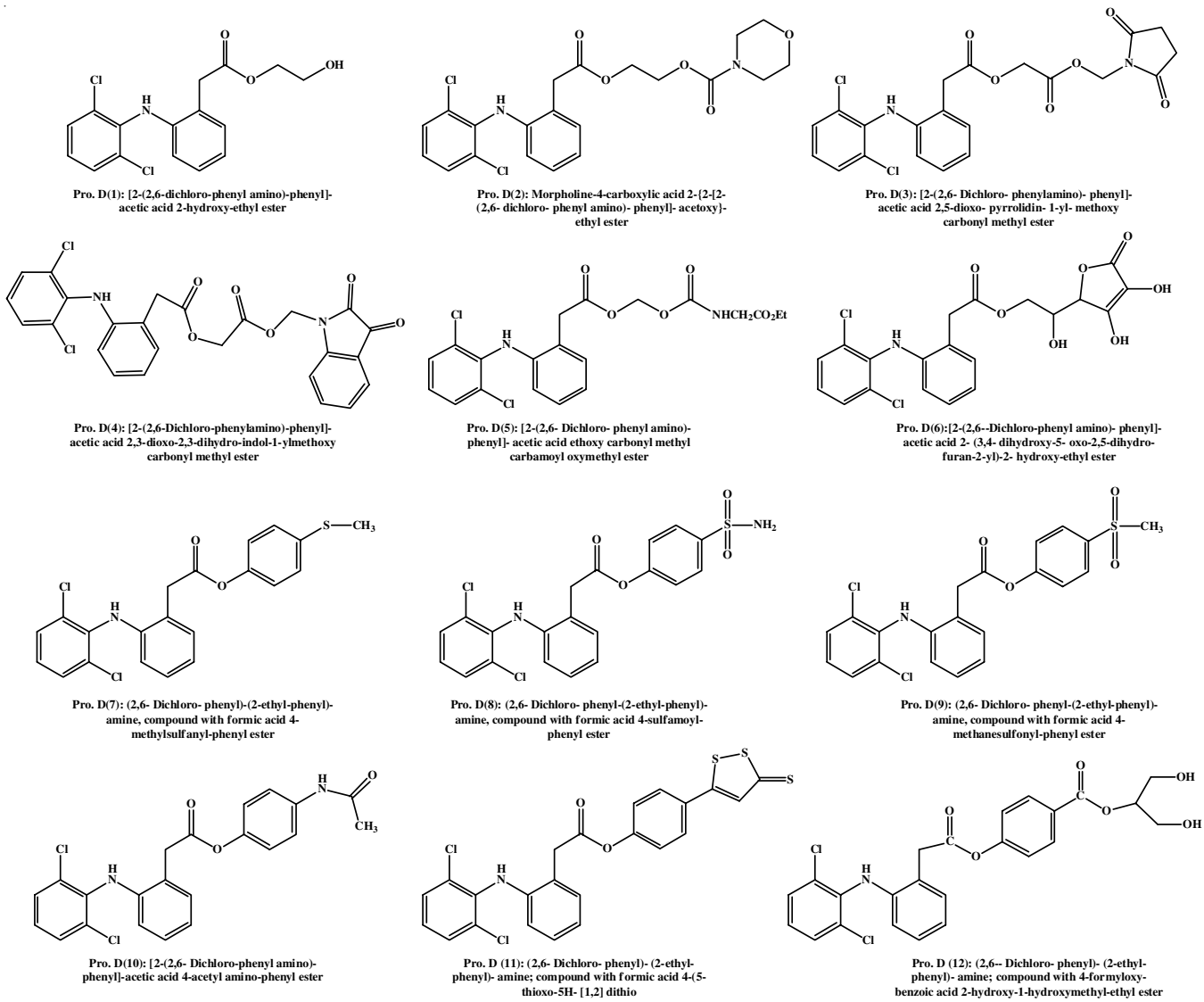


Fig. 1. Two dimensions structures of the calculated diclofenac ester derivatives (Pro. D(1–12)) as applied in the present work

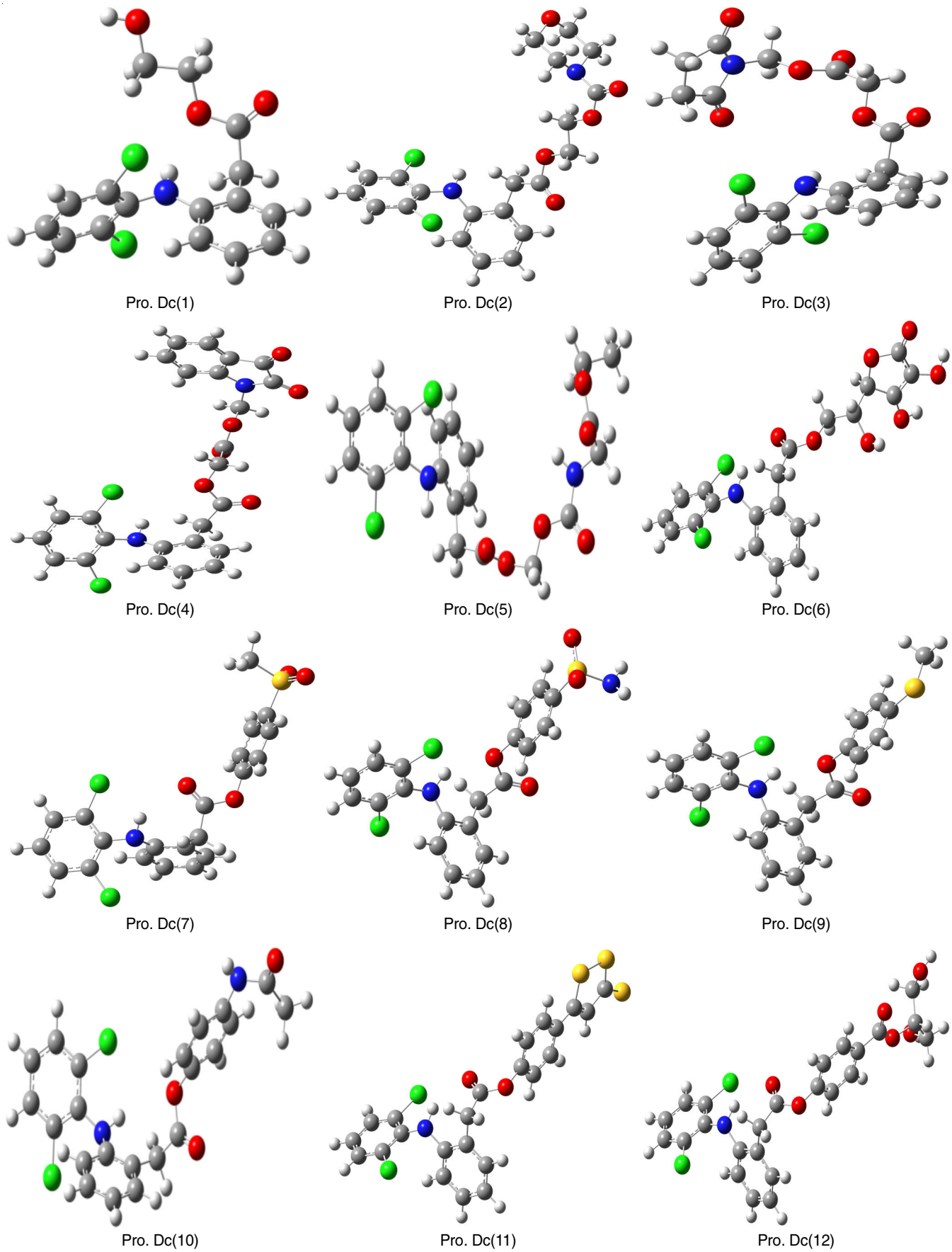


Fig. 2. Three dimension optimized structures of the calculated diclofenac ester derivatives (Pro. Dc(1–12)), as calculated using UDFT (UB3LYP/6-311) method

diclofenac derivatives and to describe the structural nature of the reactants, transition states and end products of the reactions path. The theoretical calculations were performed in the vacuum medium only for expecting intramolecular proton transfer reaction (IPT) to be almost the same as in solution [8,21]. The optimized energies (for reactants or products) have no negative vibrational frequencies [6,15].

RESULTS AND DISCUSSION

Optimized geometrical structures of Pro.Dc(1-12): The research aims to study the potential energy curves of UDFT and UPM3 methods which were used to calculate the lengths of the links. Those bonds which bind the drug to the carrier [length of O-R bonds in Pro.Dc(1-6) and C-OAr bonds in Pro.Dc(7-12)] were calculated at their optimized geometry. The longer bond length was related to the O-R of the primary carriers (1º) of Pro.Dc(1-6). These were in the range of (1.4161-1.4814 Å) by using UDFT, and in the range of (1.4028-1.4277 Å) upon using UPM3 methods. The shorter bonds length belonged to (C-OAr) of the secondary aromatic carriers (2º) of (Pro.Dc(7-12)). These were in the range of (1.3746-1.3991 Å) on using UDFT, and in the range of (1.3746-1.3990) on using UPM3 methods. The difference in the bonds lengths of O-R and C-OAr in Pro.Dc(1-12) is due to the difference in the force constant because of the inductive and electronegativity effects of the organic groups present in the drug. It is normal for the lengths of the covalent bonds involved in the studied prodrugs to be shorter than the length of ionic bonds (O^-Na^+ and O^-K^+) of the standards diclofenac sodium and potassium which were 2.0324 and 2.0698 Å for O^- Na^+, 2.5796 and 2.2002 Å for O^- K^+ on using UDFT and UPM3, respectively (Tables 1 and 2).

Tables 1 and 2 listed the calculation structures (bond lengths Å) and some physical properties such as total energy (E_{tot}), heat of formation (ΔH_f), energy of high occupied molecular orbital (E_{HOMO}), energy of low unoccupied molecular orbital (E_{LUMO}), the energy different between them (E_{Gap}= E_{LUMO}-E_{HOMO}), dipole moment (μ) for diclofenac sodium & potassium, and for Pro.Dc(1–12) at their equilibrium geometries using UDFT and UPM3 methods (Table-3).

Comparison of the physical properties and energies for Pro.Dc(1-12): For comparison, the calculated values of the primary derivatives (1º) of Pro.Dc(1-6) and secondary derivatives (2º) of Pro.Dc(7-12) with the standard prodrugs of Pro.Dc(1&2) were studied. Theoretically, the expected physical characteristics for favourites carriers are of high dipole moment (μ), high E_{HOMO}, low E_{tot}, low ΔH_f, low E_{LUMO}, low E_{gap} and long bond length [16-18]. According to Tables 1 and 2, there is an agreement in the relationships between the physical properties obtained from the two calculation methods (UDFT and UPM3) with very slight differences. However, with the expectation that the calculated numerical values according to UDFT will be more accurate and close to the experimentally results compared to the numerical, values which were calculated using the approximate UPM3 method. On checking the physical values of the standard carriers, it is noticed that the potassium values are better than sodium, as it has higher dipole moment, higher E_{HOMO}, longer bond length, lower $E_{tot.}$ and lower E_{Gap}. Possessing higher dipole moment makes prodrug more soluble, higher E_{HOMO} makes it more ability for interaction, longer bond

TABLE-1
UDFT CALCULATIONS OF STRUCTURES (BOND LENGTHS Å) AND PHYSICAL PROPERTIES FOR THE IONIC SODIUM AND POTASSIUM DICLOFENAC PRODRUG AND FOR THE STUDIED DICLOFENAC DERIVATIVES

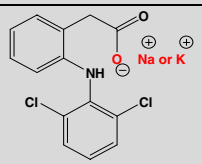
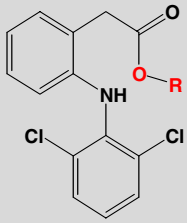
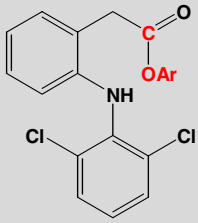
Pro. Dc.	Subt. No.	Bond length (Å)	$E_{tot.}$ (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{Gap} (eV)	μ (Debye)
			O^- Na^+ or K^+				
	01	2.0324	-49729.912	-5.316	-2,097	3.219	8.946
	02	2.5796	-61638.159	-4.862	-2.076	2.784	13.250
			O-R				
	1	1.4814	-49513.137	-5.984	-1.186	4.798	5.815
	2	1.4722	-60395.156	-6.112	-1.172	4.940	5.598
	3	1.4394	-62377.549	-6.133	-1.242	4.891	6.150
	4	1.4290	-66523.966	-6.024	-3.317	3.317	9.018
	5	1.4161	-61372.716	-6.063	-1.120	4.943	6.856
	6	1.4598	-61880.134	-5.910	-1.593	4.317	3.385
			C-OAr				
	7	1.3991	-63519.237	-6.016	-1.029	4.987	3.087
	8	1.3867	-68043.682	-6.216	-1.794	4.422	3.725
	9	1.3746	-67606.331	-6.243	-1.647	4.597	7.396
	10	1.3876	-59450.813	-6.060	-1.157	4.903	4.487
	11	1.4022	-87230.864	-6.185	-3.034	3.151	6.147
	12	1.3880	-64046.761	-6.028	-1.487	4.541	5.588

TABLE-2
UPM3 CALCULATION OF SOME PHYSICAL PROPERTIES OF ORGANIC CARRIER'S FOR DICLOFENAC PRODRUGS

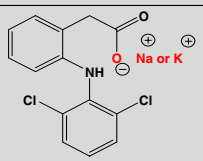
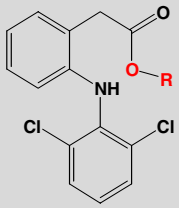
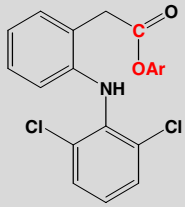
Pro. Dc.	Subt. No.	Bond length (Å)	ΔH_f (kcal/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{Gap} (eV)	μ (Debye)
			$O^- Na^+$ or K^+				
	01	2.0698	-81.220	-8.656	-0.413	8.243	8.543
	02	2.2002	-76.790	-7.573	-0.464	7.109	10.843
			O-R				
	1	1.4277	-89.129	-8.780	-0.407	8.373	4.525
	2	1.4273	-161.967	-8.862	-0.394	8.468	6.196
	3	1.4235	-201.518	-8.729	-0.333	8.396	5.552
	4	1.4122	-151.008	-8.829	-1.126	7.703	6.964
	5	1.4028	-213.598	-8.960	-0.504	8.456	6.351
	6	1.4284	-226.925	-8.738	-0.573	8.165	4.879
			C-OAr				
	7	1.3990	-10.051	-8.541	-0.392	8.149	1.369
	8	1.3768	-76.523	-8.907	-0.797	8.110	4.078
	9	1.3746	-75.157	-8.656	-0.811	8.245	5.996
	10	1.3875	-55.068	-8.879	-0.464	8.415	4.171
	11	1.3751	60.398	-8.836	-2.669	6.167	7.271
	12	1.3741	-180.941	-8.762	-0.598	8.164	5.442

TABLE-3
CORRELATION OF PHYSICAL PROPERTIES of IONIC DICLOFENAC DERIVATIVES AND OF DIFFERENT SUBSTITUTED ORGANIC GROUPS

Correlation of physical properties for Pro. Dc(01 & 02)								
μ (Debye)		E_{Gap} (eV)		E_{HOMO} (eV)		E_{LUMO} (eV)	E_{total} (eV)	Bond length (Å)
02> 01		02< 01		02> 01		02< 01	02< 01	02> 01
Correlation of physical properties for Pro. Dc(1-6) with Pro. Dc(01 & 02)								
μ (Debye)	02>	4>	01>	5>	3>	1>	2>	6
E_{Gap} (eV)	02<	01<	4<	6<	1<	3<	2<	5
E_{HOMO} (eV)	02>	01>	6>	1>	4>	5	2>	3
E_{LUMO} (eV)	02<	01<	4<	6<	1<	3<	2<	5
E_{total} (eV)	4<	3<	6≅	02≅	5≅	2	01<	1
Bond length (Å)	02>	01>	1>	2>	6>	3>	4>	5
Correlation of physical properties for Pro. Dc(7-12) with Pro. Dc(01 & 02)								
μ (Debye)	02>	01>	11>	9>	12>	10>	8>	7
E_{Gap} (eV)	02<	11<	01<	8≅	7≅	12≅	9<	10
E_{HOMO} (eV)	02>	01>	7>	12>	10>	11>	8>	9
E_{LUMO} (eV)	11<	01<	02<	8<	9<	12<	1<	7
E_{total} (eV)	11<	8<	9<	12<	7<	10<	02<	01
Bond length (Å)	02>	01>	11>	7>	12>	10>	8>	9

length makes easier bond rupture, lower E_{tot} meaning increase in stability and lower E_{Gap} makes prodrug more effective and has a faster effect. These results are fully consistent with the experimental results of the difference in the characteristics of the sodium and potassium carriers. Moreover, diclofenac sodium was a delayed release while diclofenac potassium was a quick release. So diclofenac potassium was preferred since it is more soluble in water than diclofenac sodium and relieves the pain of the patient in a faster time [22].

For the calculated results of the primary derivatives (1°) of Pro.Dc(1-6) and secondary derivatives (2°) of Pro.Dc(7-12), the results for diclofenac sodium and diclofenac potassium [Pro. Dc(01&02)] were considered as a reference. The studied ester derivatives of diclofenac showed the good physical properties as a primary test with respect to all the parameters related to the physical properties, the best of which are close in their physical properties to those of the standard Pro. Dc(01&02) UDFT and UPM3 calculations (Tables 1&2).

It was observed that there was a match in the order of preference in many parameters, especially E_{Gap} and E_{LUMO} in both UDFT and UPM3 methods (Table-3). The expected net result for the best drug carriers is according to the following sequence:

For group of Pro.Dc(1-6)

Pro.Dc(2) > Pro.Dc(4) > Pro.Dc(1) > Pro.Dc(6) > Pro.Dc(5) > Pro.Dc(3)

For group of Pro.Dc(7-12)

Pro.Dc(2) > Pro.Dc (11) > Pro.Dc(1) > Pro.Dc(9) > Pro.Dc(12) > Pro.Dc(8) Pro.Dc(10) > Pro.Dc(7)

On taking into consideration the most influencing factors such has μ, E_{Gap}, E_{HOMO} and E_{LUMO}, the sequence is Pro.Dc(4) (diclofenac isatin), Pro.Dc(6) (ascorbic acid diclofenac and then Pro.Dc(5) are the best among the first group. Pro.Dc(9), Pro.Dc(11) and Pro.Dc(12) are the best among the second group. As a whole, the primary derivatives (1º) of Pro.Dc(1-6) has an advantage over the second derivatives (2º) of Pro.Dc(7-12) in terms of better numerical values of physical properties. It has also been experimentally proven that the Pro.Dc(6) is a potential candidate for enhancing the short half-life of diclofenac *in vivo* [14].

The O-R and C-OAr bond rupture energies: After the calculation of the equilibrium geometries of the studied ester derivatives of diclofenac using UDFT method, the potential energy curves for cracking (ΔH_f) with the increase of the length of O-R or C-OAr) were calculated and studied from the equilibrium geometry to the transition states down to the stable products of the cracking process. This was done by using the approximate calculation method UPM3 for reducing the time required for calculating the reaction path. In these calculations, only O-R or C-OAr bond lengths are frozen at the appropriate degree of freedom, while all other bond lengths are freely optimized. From these curves, one could obtained the energy for the reactants, the energy of the transition state and the energy of the products of the cracking process, as well as the activation energy required to cracking each bond ($E_a^{\#} = \Delta H_f$ (transition state) – ΔH_f (reactant)). No negative frequencies were found in the reactant or products, but only two negative frequencies were found in the geometries of the transition state structures. The calculations for the cracking energies using UPM3 for the standards (Pro. Dc(01) and Pro. Dc(02)) and for Pro.Dc(1-12) were doesn't included any solvent [18]. In previous studies, it was found that the results of calculations of the rupture of O-R bond give a reaction path in which a sudden decline in the total molecular energy occurs immediately after the transition state [15-17]. There was also obvious increase in the dipole moment (μ), E_{HOMO}, total energy (E_{total}) and (ΔH_f), and decrease in the E_{LUMO} of the molecule with increasing the bond distance of (O-R or C-OAr) towards transition state. It was important to inspect the shape of the reaction curve and extend the treatment to different prodrugs. The change in molecular energy along the reaction path and the structures of the transition states as well as the reaction products. The calculated reaction path of cracking processes for some of the calculating Prodrugs by UPM3 are shown in Fig. 3. By studying the potential energy

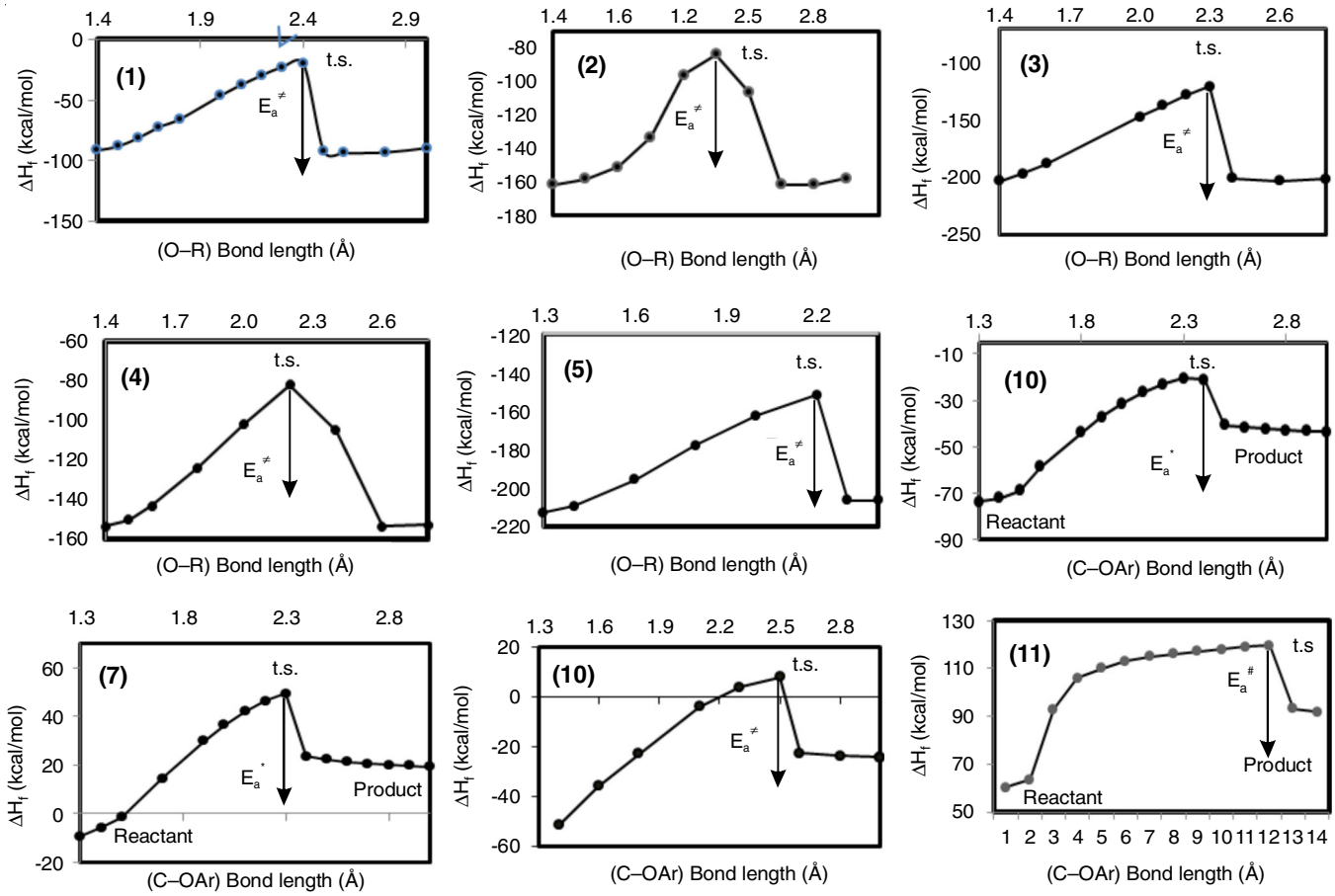


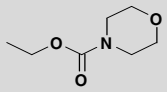
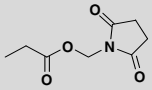
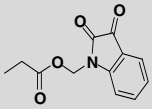
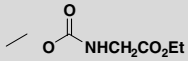
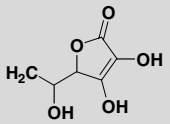
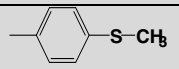
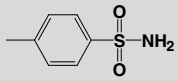
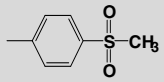
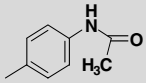
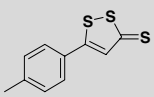
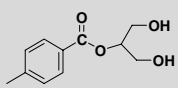
Fig. 3. Reaction path of the O-R or C-OAr bonds rupture energies in some of the studied diclofenac prodrugs as calculated using UPM3 method

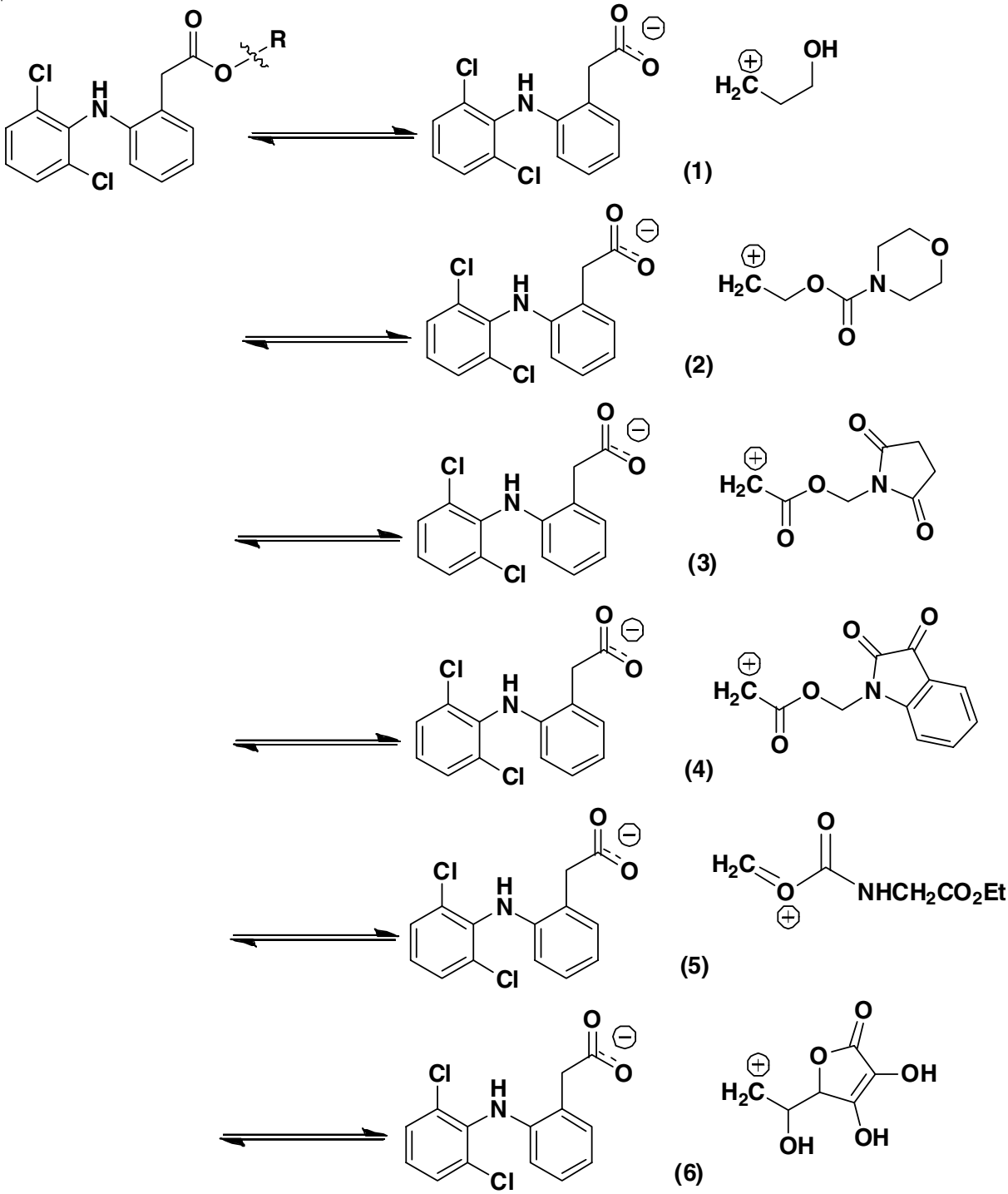
curves, it was shown that the O-R bond ruptures reactions of diclofenac ester prodrugs (Pro.D(1–6) are reversible, of high energy barrier, high activation energy ($E_a^{\#}$), very low heat of cracking (ΔHc) ranging from -1.987 to 1.940 kJ/mol. The ΔHc increases with decreases in O-R bond lengths, exothermic for Pro.D(1–3) and endothermic for Pro.D(4–6) (Table-4).

The optimized structures for Pro.D(1-6) were at O-R bond length of 1.4277, 1.4273, 1.4235, 1.4112, 1.4028, 1.4274 Å respectively. The primary cracking structures were at O-R bond length of 1.5277, 1.5273, 1.5235, 1.6112, 1.6028, 1.5274 Å, beyond the transition state produces ó radical structure then giving cation and anion fractions at the transition state. The transition states were at O-R bond length of (2.3277, 2.3273, 2.3273, 2.3112, 2.7967, 2.4274 Å), converted to cation and anion fragments. The end reversible products were at O-R bond length of (2.4279, 2.6279, 2.4235, 2.4112, 2.8967, 2.5274 Å) at which they returned to their origin structures in absence of hydrolysis process (**Scheme-I**) and diclofenac is obtained by hydrolysis the prodrug in acidic medium (**Scheme-II**).

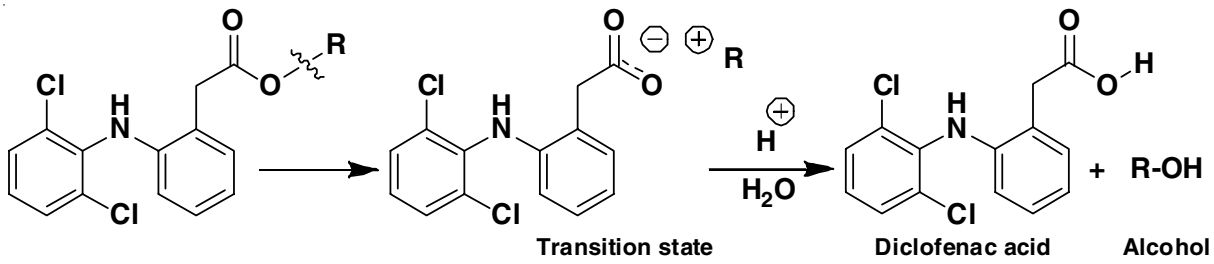
Experimentally, it was proven that the ester prodrugs like Pro.Dc(1-6) are known to have a very good anti-inflammatory and analgesic activities with less gastrointestinal irritation than their active parent drug, diclofenac, and underwent a rapid enzymatic hydrolysis [14]. These results were confirmed by

TABLE-4
UPM3 CALCULATIONS ENERGIES FOR THE (O-R AND C-OAr) BONDS RUPTURE REACTIONS IN DICLOFENAC ESTER DERIVATIVES

Declo. Deri. No.	Carrier linkage	Bond length (Å)	ΔH_f (kcal/mol) (Reactant)	ΔH_f (kcal/mol) (Product)	ΔH_c (kcal/mol)	$E_{t.s}$ (kcal/mol)	Ea^* (kcal/mol)
			O^- cation				
Stand. (01)	Na^+	2.0698	-81.220	-81.838	-0.615	-77.314	03.909
(02)	K^+	2.2002	-76.790	-110.500	-33.720	-68.980	07.802
			O-R				
(1)		1.4277	-89.013	-90.996	-1.983	-20.555	68.458
(2)		1.4273	-159.682	-160.168	-0.486	-87.120	72.563
(3)		1.4235	-201.519	-201.566	-0.048	-121.804	79.715
(4)		1.4112	-151.009	-150.364	0.645	-72.717	78.292
(5)		1.4028	-213.598	-212.672	0.926	-151.711	61.887
(6)		1.4274	-230.827	-228.030	2.797	-149.795	81.032
			C-OAr				
(7)		1.3990	-10.051	13.473	23.524	48.805	58.856
(8)		1.3768	-76.523	-55.294	21.229	-22.805	53.718
(9)		1.3746	-75.157	-91.247	-16.091	-17.645	57.512
(10)		1.3875	-55.068	-32.965	22.103	3.862	58.930
(11)		1.3751	60.398	91.343	31.045	119.608	59.210
(12)		1.3741	-180.941	-148.649	32.292	-117.167	63.774



Scheme-I: Reversible reactions of the O-R bond rupture of the diclofenac prodrugs (**1-6**), as calculated using UPM3 method



Scheme-II: Hydrolysis process of the Pro. Dc(1-6) after O-R bond rupture in presence of an acid medium

the very low cracking energy of (O-R) bonds of these carriers in the range of -1.983 to 2.797 kJ/mol. These values are close to the values of the breakage energy of the ionic bond in the two standard diclofenac prodrugs of Dc(01&02). Figs. 4 and 5 show the 3D geometrical structures for the reversible O-R breakage bond of prodrugs Dc(3&5). On the other hand, Pro.D(7-12) gives irreversible C-OAr rupturing reaction. The optimized geometrical structures were at C-OAr bond length of 1.3990, 1.3768, 1.3746, 1.3875, 1.3751, 1.3742 Å, respectively. The primary cracking structures were at C-OAr length of 1.5990, 1.5768, 1.5764, 1.5875, 1.5751, 1.5742 Å give two free radical species. The transition states were at C-OAr length of 2.3990, 2.4768, 2.4746, 2.6875, 2.8751, 2.6742 Å show the proton transfer [23,24]. The end products for cracking were at C-OAr length of 2.3990, 2.6768, 2.6746, 2.8875, 2.9751, 2.7742 Å, then all end products of Pro.D(7-12) give diclofenac acid drug when the process of hydrolysis in acidic environment occurs. **Scheme-I** shows the reversible reactions of the O-R bond rupture of the diclofenac prodrugs (1-6), as calculated using UPM3 method. Table-4 listed UPM3 calculations energies for the O-R and C-OAr bonds rupture reactions in diclofenac ester derivatives.

According to the relationships in Table-5, the expected net result for the best drug carriers is according to the following sequence:

For primary derivatives (1^0) of Pro. Dc(1-6): Pro. Dc(02)> Pro. Dc(4)> Pro. Dc(01)> Pro. Dc(6)> Pro. Dc(5)> Pro. Dc(3)> Pro. Dc(1) Pro. Dc(2)

For secondary derivatives (2^0) of Pro. Dc(7-12): Pro. Dc(02)> Pro. Dc(11)> Pro. Dc(01)> Pro. Dc(9)> Pro. Dc(12)> Pro. Dc(8) Pro. Dc(10)> Pro. Dc(7)

As a whole, primary derivatives (1º) of Pro.Dc(1-6) has an advantage over the second derivatives (2º) of Pro.Dc(7-12) in terms of better numerical values of the physical properties.

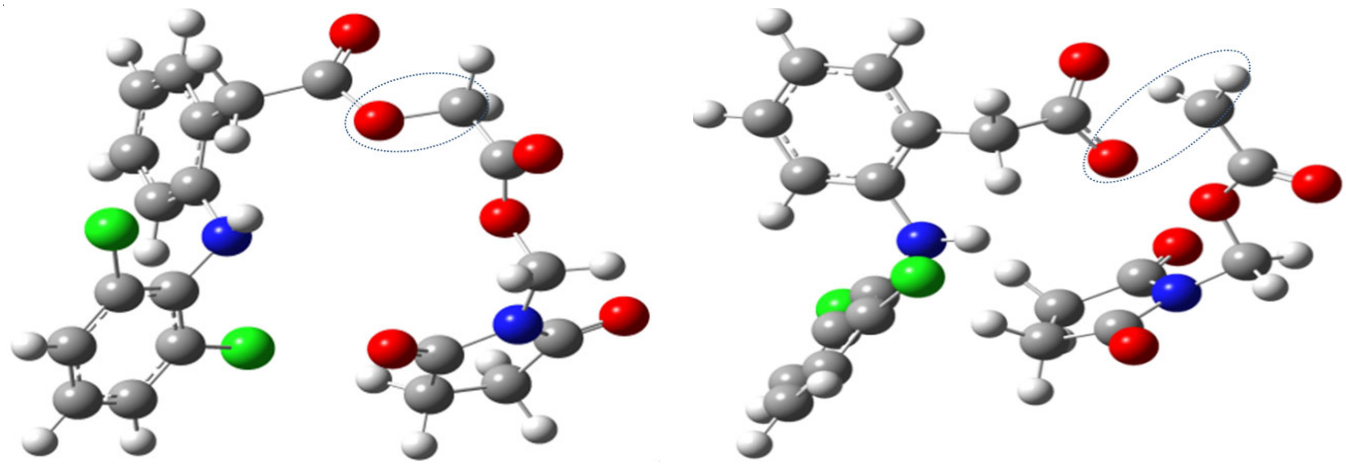


Fig. 4. Three dimensions geometrical structures for the reversible O-R breakage bond of diclofenac ester prodrug (Pro. Dc(3)) at; (a) Optimized structure (O-R= 1.4235 Å), and (b) Transition state (O-R= 2.4235 Å)

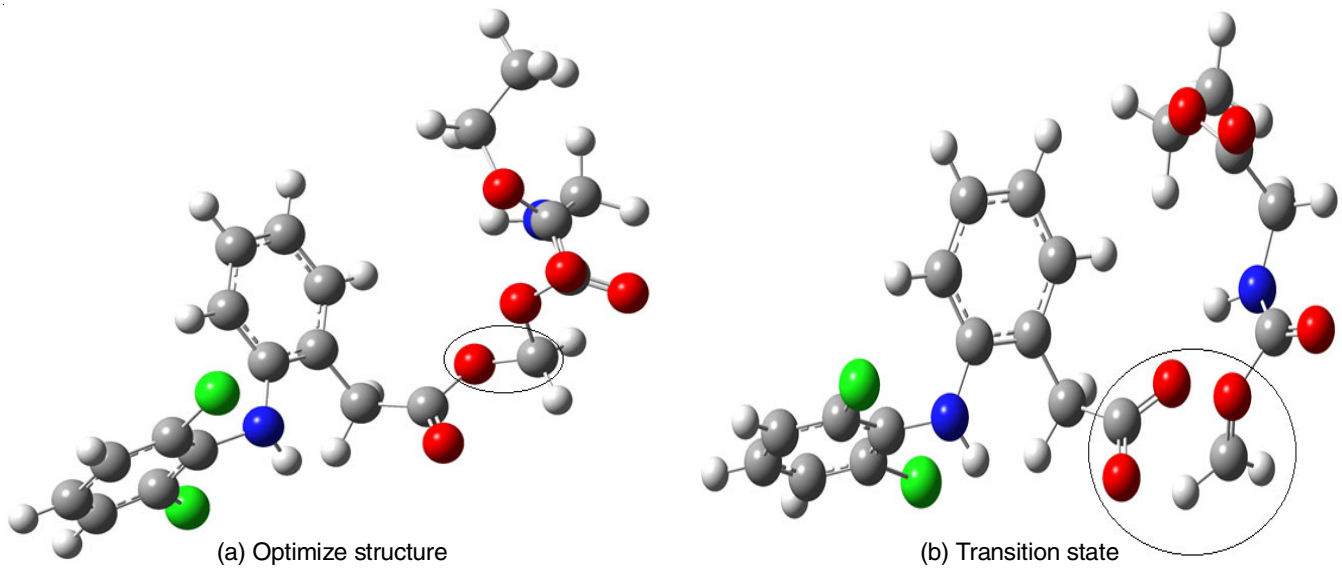


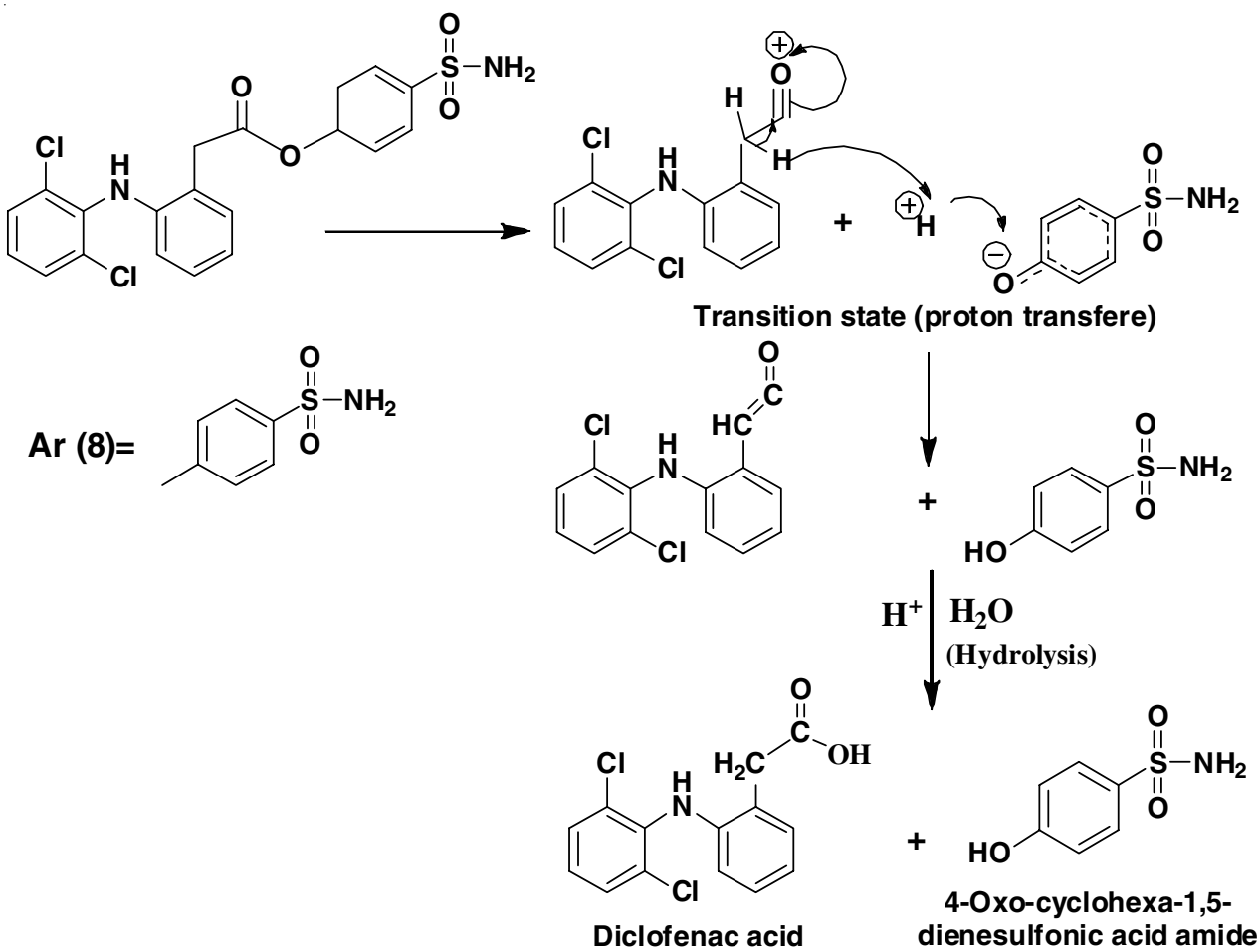
Fig. 5. Geometrical structures for the reversible O-R breakage bond of diclofenac ester prodrug (Pro. Dc(5)) at; (a) Optimize structure (O-R= 1.4028 Å), and (b) Transition state (O-R= 2.4028 Å)

The lower ΔH_f value indicated the stability of the prodrug, whereas lower E_a value indicates that prodrug is more effective and has a quick release for the origin drug. A relationship was performed for the breakage energies of ionic, O-R and C-OAr bonds in diclofenac derivatives of ionic and different substituted organic groups (Table-5).

For Pro.Dc(7-9), it is very important to pay attention and take caution that although these prodrugs give good results as carriers of diclofenac and despite their good physical properties as carriers of diclofenac acid, they are not suitable because their breakage products give along with the drug acid a product known for its toxic side effects [4], so it is not preferable to

TABLE-5
RELATIONSHIPS FOR THE BREAKAGE ENERGIES OF IONIC, O-R AND C-OAr BONDS IN DICLOFENAC DERIVATIVES OF IONIC AND DIFFERENT SUBSTITUTED ORGANIC GROUPS

Relationships for the breakage energies of (O^-Na^+ & O^-K^+) bond in Pro. Dc(01-02)								
ΔH_f (kcal/mol) (Product)	ΔH_c (kcal/mol)		Ea^* (kcal/mol)		$E_{t.s}$ (kcal/mol)		Bond length (Å)	
02 < 01	02 < 01		02 > 01		02 > 01		02 > 01	
Relationships between the breakage energies of (O-R) bond in Pro. Dc(1-6) and with the two standard compounds (01 and 02)								
ΔH_f (kcal/mol) (Product))	6<	5<	3<	2<	4<	02<	1<	01
ΔH_c (kcal/mol)	02<	1<	01<	2<	3<	4<	5<	6
E_a^* (kcal/mol)	6>	3>	4>	2>	1>	5>	02>	01
$E_{t.s}$ (kcal/mol)	1>	02>	4>	01>	2>	3>	6>	5
O-R bond length (Å)	02>	01>	1>	2>	6>	3>	4>	5
Relationships between the breakage energies of (**C**-OAr) bond in Pro. Dc(7-12) and with the two standard compounds Pro. Dc(01 and 02)								
ΔH_f (kcal/mol (Product))	12<	02<	01<	8<	9<	10<	7<	11
ΔHc (kcal/mol)	02<	9<	01<	7<	10<	8<	11<	12
E_a^* (kcal/mol)	7>	8>	10>	12>	11>	9>	01>	02
$E_{t.s}$ (kcal/mol)	11>	7>	10>	9>	6>	02>	01>	12
C-OAr bond length (Å)	02>	01>	11>	7>	12>	10>	8>	9



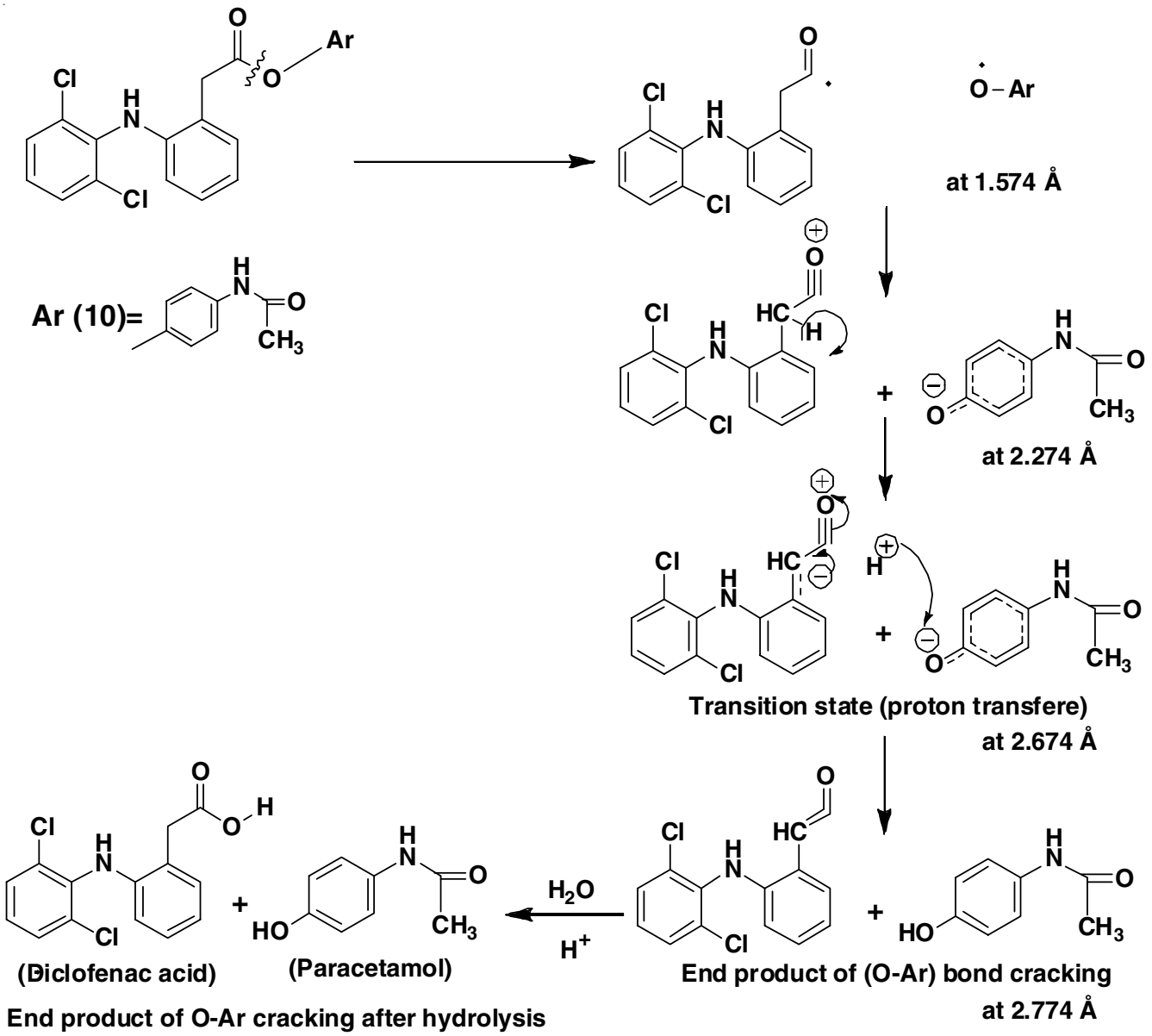
Scheme-III: Mechanism of the C-OAr bond rupture reaction in diclofenac prodrug (**7**), as calculated using UPM3 method

use these prodrugs. Hence, it is necessary to study the theoretical properties of the primary drug to acquire adequate knowledge and familiarity with the safe properties of prodrugs carrier experimentally, in order to ensure that the primary drug is not given toxic products on thermodynamically cracking. **Scheme-I** shows the reversible reactions of O-R bond rupture energies of the diclofenac prodrugs (1-6) as carriers using UPM3 method. All these prodrugs gave positive primary carbonium ion at the fragment of the carrier and negative carbanion ion in the transition state, except Pro.Dc(5), which gave oxygen anion instead of primary carbonium ion. All these prodrugs in the presence of an acidic aqueous medium are converted immediately into diclofenac acid and the corresponding alcohol (**Scheme-II**).

Figs. 4 and 5 illustrate the steps of the reversible cracking reaction between equilibrium geometry and transition state for O-R bond in Pro.Dc(3&5) within three dimensions as calculated using UPM3 method. All transition states in Pro.Dc(7-12) involved the proton transfer from the methyl group in diclofenac fraction to the oxygen carrier, forming the hydroxyl group as shown in **Schemes III & IV**. Figs. 6 and 7 show the steps of cracking diclofenac ester prodrugs [Pro.Dc(9&10)] including the geometrical structures at equilibrium, at bond breakage, at the transition state (showing the proton transfer) and at the end products of C-OAr bond cracking when hydrolysis in the acidic medium at three dimensions using the UPM3 method.

Conclusion

In this work, quantum mechanical methods of UPM3 and UDFT have used to explore the possibility of using new carrier linkages for declofenac drug. The ability of using these carriers were done by examining the reaction path for O-R ( ) bond breakage energies in (Pro.Dc(1-6)) and for C-OAr ( ) bond breakage energies in (Pro.Dc(7-12)), in comparison with the declofenac sodium and potassium prodrugs as



Scheme-IV: Mechanism of the C-OAr bond rupture reaction in diclofenac prodrug (**10**), as calculated using UPM3 method

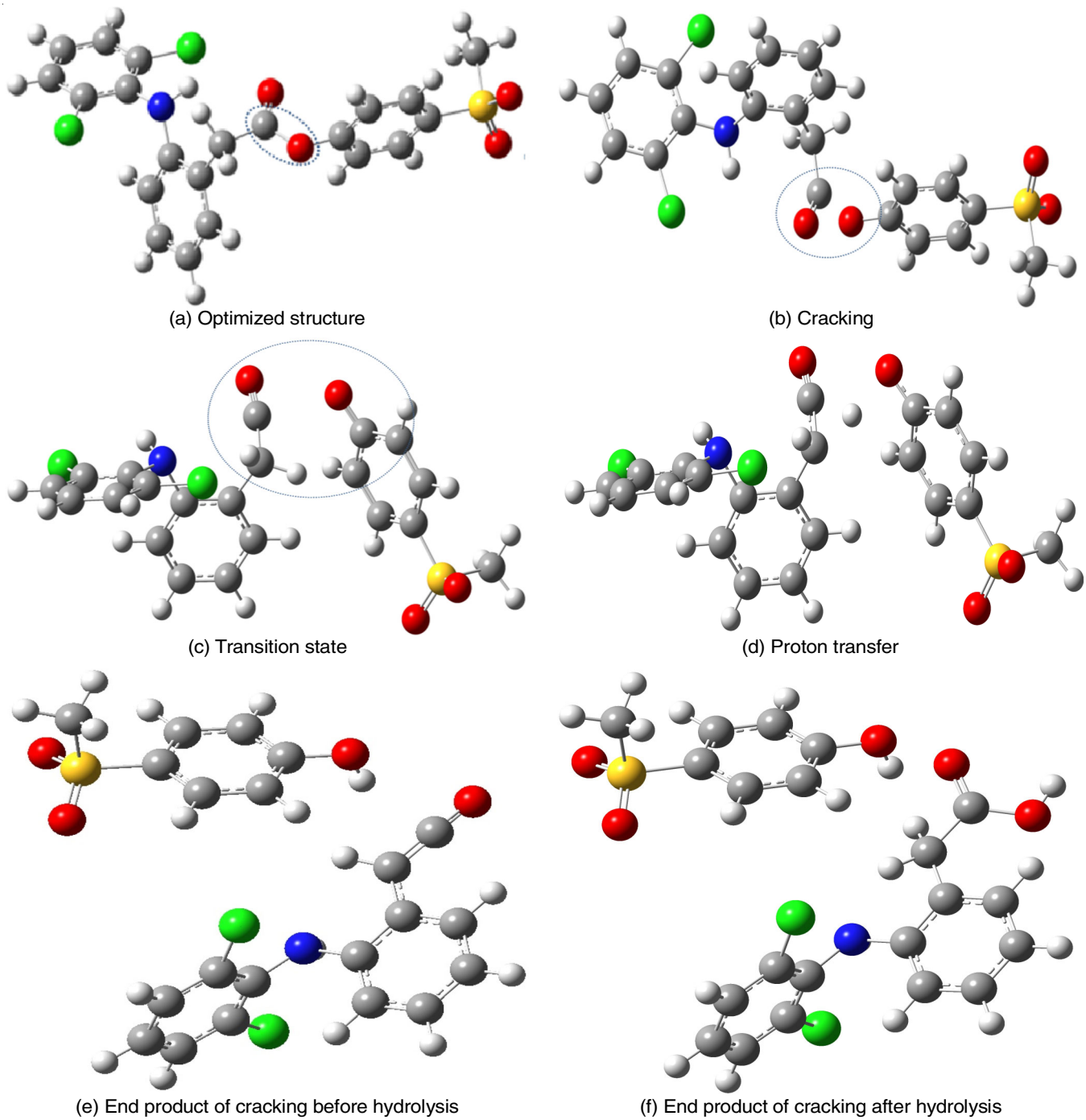


Fig. 6. Geometrical structures for diclofenac ester prodrug (Pro. Dc(9)) at; (a) Equilibrium geometry (C-OAr = 1.3875 Å), (b) breakage bond (C-OAr = 1.5875 Å), (c) transition state (C-OAr = 2.4875 Å), (d) the proton transfer (C-OAr = 2.6875 Å), (e) the end products for cracking (C-OAr = 3.0875 Å), (f) the end products for C-OAr bond cracking after hydrolysis in acidic medium

standards. The 1º ester derivatives of prodrugs (1-6) giving the reversible cracking reactions for O-R bonds with a high activation energy and very low exothermic or endothermic heat of cracking, whereas 2º ester derivatives of prodrugs (7-12) gave an irreversible moderate endothermic or exothermic heat of cracking. The cracking reactions occur for C-OAr bonds not for O-Ar bonds, because of the aromaticity of (-Ar carriers). All these compound gave two neutralize fractions at the end of cracking and on hydrolysis in acidic medium yield diclofenac drug and alcohol. Moreover, Pro.Dc(7-9) were ignored as carriers of diclofenac acid, and found not suitable since the final product contains a substance that has toxic side effects. The final results predicted that Pro.Dc(1-6) have an advantage over Pro.Dc (10-12) when compared with standards of declofenac sodium and potassium, as they can release the drug faster in acidic environment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

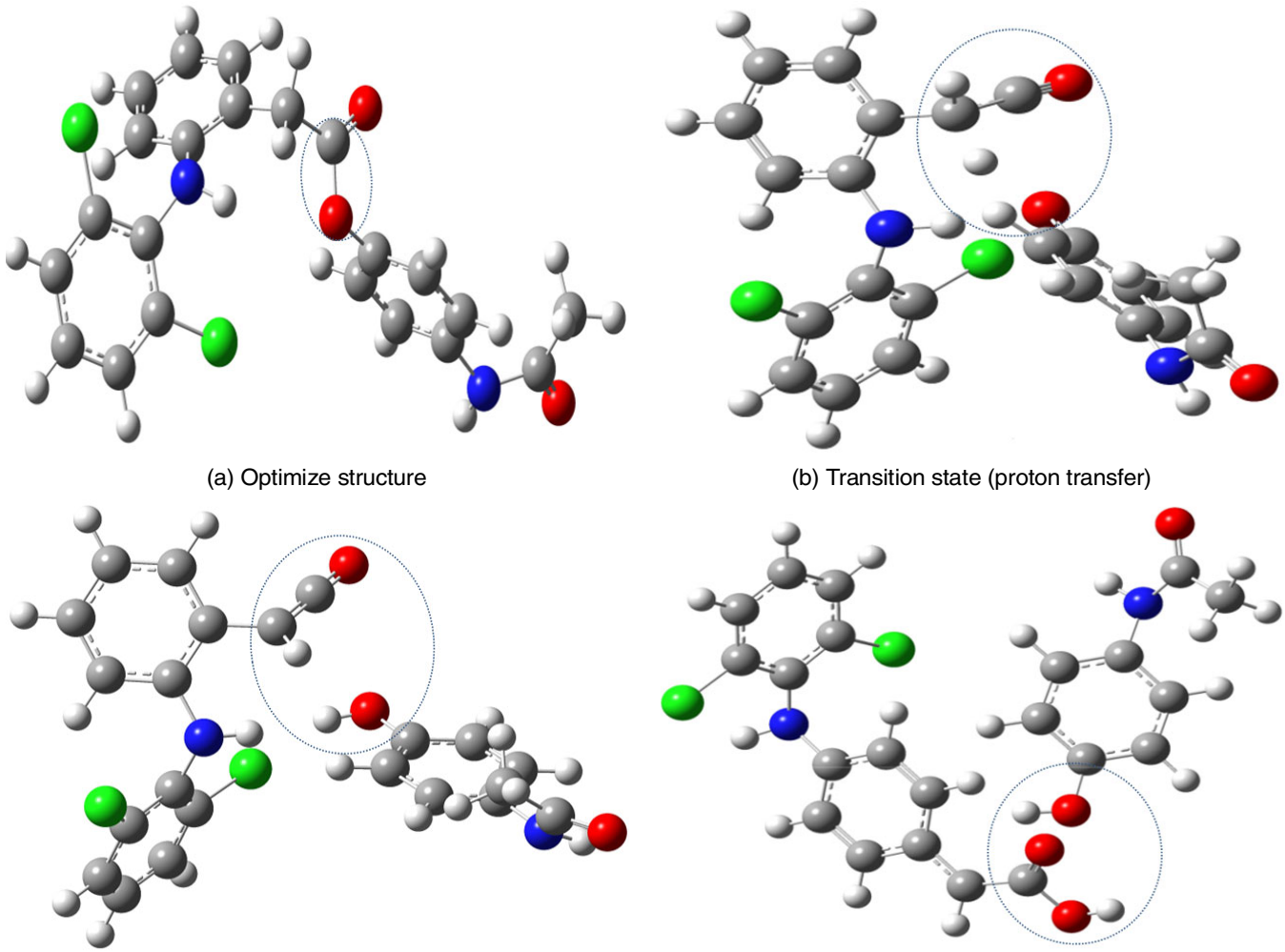


Fig. 7. Geometrical structures for diclofenac ester prodrug (**Pro. Dc(10)**) at; (a) Equilibrium geometry (C-OAr = 1.374 Å), (b) Transition state (proton transfer) (C-OAr = 2.674 Å), (c) End products for cracking (C-OAr = 2.874 Å), (d) End products for C-OAr bond cracking after hydrolysis in acidic medium

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