Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: April 2021 **2021, 18(4): 1249-1260** **E-ISSN: 2411-7986**

DOI: http://dx.doi.org/10.21123/bsj.2021.18.4.1249

Reactivity of O-Drug Bond in some Suggested Voltarine Carriers: Semiempirical and ab Initio Methods

***Rehab M. Kubba*[1]** ***Mustafa M. Kadhim*[2*]**

[1]Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.
[2]Department of Dentistry, Kut College University, Kut, Wasit, Iraq.
[*]Corresponding author: Rehab_mmr_kb@yahoo.com, mustafa_kut88@yahoo.com[*]
[*]ORCID ID: https://orcid.org/0000-0001-5272-1801, https://orcid.org/0000-0003-4855-7871[*]

Received 13/1/2020, Accepted 5/1/2020, Published Online First 30/4/2021, Published 1/12/2021

Abstract:

In this work, the possibility to use new suggested carriers (D= Aspirin, Ibuprofen, Paracetamol, Tramal) is discussed for diclofenac drug (voltarine) by using quantum mechanics calculations. The calculation methods (PM3) and (DFT) have been used for determination the reaction path of (O-D) bond rupture energies. Different groups of drugs as a carrier for diclofenac prodrugs (in a vacuum) have been used; at their optimized geometries. The calculations included the geometrical structure and some of the physical properties, in addition to the toxicity, biological activity, and NLO properties of the prodrugs, investigated using HF method. The calculations were done by Gaussian 09 program. The comparison was made for total energies of reactants, activation energies, and transition states to final products. The suggested prodrugs aim to improve the diclofenac carrier's properties and obtain new alternatives for the approved carriers theoretically.

Keywords: Biological activity, DFT, Diclofenac, PM3, Toxicity.

Introduction:

Ab initio, quantum chemistry has long been used as an essential tool for investigating the structure, stability, kinetics of reactions, and mechanisms of various molecular systems. Ab initio, calculations based on the Schrödinger equation have the advantage of being based only on the fundamental laws of physics and universal constants. Therefore, the calculations do not need any empirical constants. The use of ab initio calculations has become an essential method in recent years to understand the chemical properties of corrosion, prodrugs, and other applications (1,2). The semi-empirical theory (PM3) developed by Dewar and coworkers (3-6) considered the success of molecular cloning, the repetition of molecular structures, and the analysis of chemical reactions. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the world's most widely used classes of medicines used to treat pain, fever, and inflammation (7). Nowadays, one of the significant challenges facing the pharmaceutical industry is to discover new drugs to treat chronic inflammation without adverse effects. Diclofenac and its various salts are well-known non-steroidal anti-inflammatory drugs (NSAIDs), often used orally, topically and parenterally to treat a wide range of inflammatory conditions (8). Prodrugs have many advantages over their parent products, are designed to improve the physicochemical and pharmacokinetic properties of their parent active drugs, and thus to boost their oral absorption, water solubility, bioavailability; reduce their toxicity and/or bitter sensation (9-10). Kubba et al. have theoretically studied the rupturing of O-R bond in some ampicillin, cefuroxime and cefpodoxime derivatives containing various substitute organic groups, using quantum mechanical calculations of semiempirical PM3 and (UHF) methods, in an attempt to show which of these groups could be used as a good carrier link for them (11-13). The main side effect of NSAID's is their gastric acidity, due to released free H^+. On the other hand, all NSAIDs have free –COOH (carboxylic acid) group which works by competitive cyclooxygenase enzyme inhibition (COX1/COX2). The purpose of this project is to transform the free (COOH) of diclofenac into a prodrug of ester (of drugs carrier (COOD)) with sensitive drugs as a carrier (14).

Computational methods

In this study, the calculations were based on Parameterization Model 3 (PM3), Density Functional Theory (DFT), and Harte-Fock methods, using Gaussian-09 software package. Geometry optimization for diclofenac drug was performed with the suggested carriers, Fig. 1, using Unrestricted DFT of (STO-3G) level ab initio open-shell theory (15). U-PM3 and U-DFT/ STO-3 G methods were used to calculate the reaction path of (O-D) bond rupture. Toxic calculations were done with HF/6-31+G level. The lowest energy conformations of the compounds were obtained using DFT method (16). Nonlinear optical (NLO) properties were calculated by HF/321 in a vacuum. The biological activity was calculated in water as a solvent. The calculated quantum chemical descriptors included; the highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), ionization energy (IE), electron affinity (EA), energy gap (E_{GAP}), absolute hardness (η), absolute softness (S), optical softness (So), absolute electronegativity (χ), chemical potential (CP), electrophilicity index (ω), nucleophilicity index (N), additional electronic charges (N_{Max}), polarizability (α), the first hyperpolarizability (β_o) and dipole moment (μ), Equations (1-13). Urea was used as a standard in determination of NLO properties (17-19).

IE (Ionization potential)= $-E_{HOMO}$ (1)

EA (Electron affinity)= $-E_{LUMO}$ (2)

$E_{gap}= E_{LUMO}-E_{HOMO}$ (3)

η (Hardness)= $(\partial^2E/\partial N^2)\nu(r)$ η= (IE-EA)/ (4)

S (global softness)= 1/ η (5)

$S_o= 1/ E_{gap}$ (6)

χ (Electronegativity)= $-\mu= -(\partial E/\partial\Lambda)\nu(\rho)=$ (IE+EA)/2 (7)

CP= -χ (8)

Global electrophilicity index (ω)= $(-x)^2/2\eta= \mu^2/2\eta$ (9)

$N_{Max}=$ - CP/ η (10)

N= 1/ ω (11)

α (Polarizability)= $1/3(\alpha_{xx}+\alpha_{yy}+\alpha_{zz})$ (12)

β_o (hyperpolarizability)= $[(\beta_{xxx}+\beta_{xyy}+\beta_{xzz})^2+(\beta_{yyy}+\beta_{yzz}+\beta_{yxx})^2+(\beta_{zzz}+\beta_{zxx}+\beta_{zyy})^2$ (13)

Where the α_{xx}= polarizability in the x-axis direction, α_{yy}= polarizability in the y-axis direction, α_{zz}= polarizability in the z-axis direction. The β_{xxx}, β_{yyy}, β_{zzz}= hyperpolarizability in x, y, and z-axes, respectively. Figure 1 shows the two dimensions structures of the suggested drug carriers with the label of atoms.

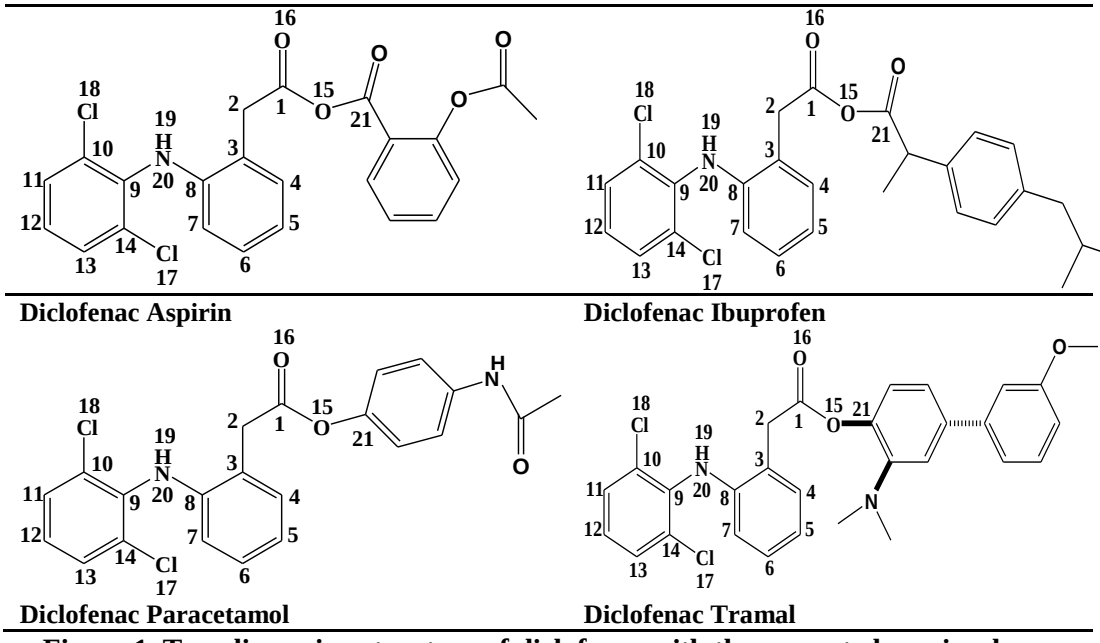


Figure 1. Two dimension structure of diclofenac with the suggested carrier drugs.

Results and Discussion:

Ground state of the molecular structure:

The results calculated from PM3 and U-DFT for the (bond lengths Å) of the studied diclofenac prodrugs to drugs as carries (Aspirin, Ibuprofen, Paracetamol, and Tramadol) at the equilibrium geometry are shown in **Table 1.** The tabulated results showed that the difference for (O-D) (D= Asp, Ibu, Prm, and Trm.) bond was slightly shorter or slightly longer. The extensive studies focused on the bond length of (O-D), where (D represents C21). The bonds length of OD of the Pro.Dc (1-4) calculated by PM3 and U-DFT/STO-3G were in the range of (1.369 to 1.437 Å). The O-D bond length with (Ibu) carriers is shorter than O-D bond length of Pro.Dc (Asp, Prm, Trm). This difference in the length of the bonds is due to the spatial arrangement and the number of different atoms in these molecules (20). The shortest bond length of OIbu (1.369 Å) for the Pro.Dc (Ibu) leads to expect that it has the most significant rupture

energies for cracking purposes and vice versa for the other carriers.

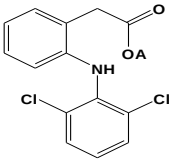
Table 1. PM3 and U-DFT calculations of bonds lengths (A°) for the studied diclofenac prodrugs at their equilibrium geometries.

Bond description	Bond length Dc.Asp		Bond length Dc.Ibu		Bond length Dc.Prm		Bond length Dc.Trm	
	PM3	U-DFT	PM3	U-DFT	PM3	U-DFT	PM3	U-DFT
O15-C21	1.38743	1.38743	1.36976	1.36976	1.39511	1.39511	1.43782	1.43782
O16=C1	1.21330	1.21330	1.39127	1.39127	1.21095	1.21095	1.36713	1.36713
C1-C2	1.51612	1.51612	1.20632	1.20632	1.51534	1.51534	1.21431	1.21431
C2-C3	1.49542	1.49542	1.51029	1.51029	1.49513	1.49513	1.51238	1.51238
C8-N20	1.44790	1.44790	1.44083	1.44083	1.44959	1.44959	1.45062	1.45062
N20-H19	0.99913	0.99913	1.00233	1.00233	0.99752	0.99752	0.99779	0.99779
N20-C9	1.44319	1.44319	1.44885	1.44885	1.45464	1.45464	1.45496	1.45496
C14-Cl 17	1.67945	1.67945	1.68521	1.68521	1.68166	1.68166	1.68502	1.68502
C10-Cl 18	1.68841	1.68841	1.68236	1.68236	1.68244	1.68244	1.68181	1.68181

Examination of geometrical optimization structures:

Pro. Dc (D) of the studied Drugs with carriers (of Aspirin, Ibuprofen, Paracetamol, and Tramadol) showed a decrease in total energy in the order of (Ibu< Trm< Prm< Asp). At the same time, Pro. Dc.(D) of (Asp, Ibu, Prm, Trm) compounds showed an increase in dipole moment (μ) in the order of (Prm> Ibu> Trm> Asp) see (**Tables 2**,**3**) directly proportional to the size of the molecular and the different in geometrical of the studied compounds (21). In addition, there is a decrease in E_{LUMO} and E_{Gap} with an increase in dipole moment (μ). Therefore, they are probably more stable and more viable to use as a carrier linkage for diclofenac drug. Further, there is a decrease in E_{tot} with the increasing in the length of the bond of the Ibu, Par, and Trm respectively.

Table 2. U-DFT calculations of some physical properties for carrier drugs prodrugs of diclofenac.

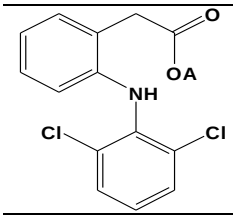
Dc. Pro.	A	OA Bond Length (Å)	E_{tol} (kcal/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{Gap} (eV)	μ (Debye)
	**Asp**	1.38743	-1387625	-5.134	-1.676	3.458	3.243
	Ibu	1.36976	-1392812	-5.116	-1.885	3.231	7.449
	Prm	1.39511	-1305022	-4.718	-1.825	2.893	8.093
	Trm	1.43782	-1500211	-5.355	-1.918	3.437	6.925

O-D bond rupture energies calculations:

The coordinate reaction method (where O-D bond was controlled to an applicable degree of freedom and other bonds lengths were freely optimized) (22) was used to calculate O-D bond rupture energy for (Asp, Ibu, Pra and Trm). In this method, one bond length is constrained for the appropriate degree of freedom, while the other internal coordinates are freely optimized. The activation energy values of O-D bond rupture calculated the difference in energy for global minimum structure and derived transition state (t.s). Eenergies of reactants, products, and transition states were calculated and studied using PM3 and U-DFT methods. All calculations done without using solvents. It was essential to reinsert the shape of the reaction curve and extend the treatment to ester and anhydride derivatives of diclofenac drug. The treatment showed a change in curve energy with the reaction path, activation energy, and structures of transition states as well as the reaction products. The results of O-D bond rupture energies of diclofenac esters prodrugs are shown in **Tables 3,4. Figures 2 - 5** shows the reaction paths of O-D bond rupture energies for the calculated carrier drugs prodrugs.

Baghdad Science Journal
2021, 18(4): 1249-1260
P-ISSN: 2078-8665
E-ISSN: 2411-7986

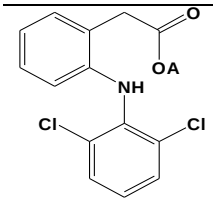
Table 3. PM3 calculated energies values for the O-D bond rupture reactions in diclofenac drug with suggested drugs as carriers.

Dc.Pro.no.	A	ΔH_f (kcal/mol) reactant	ΔH_f (kcal/mol) Product	ΔHc (kcal/mol)	Ea* (kcal/mol)	$E_{t.s}$ (kcal/mol)
	Asp	-129.200	-116.025	13.1992	38.2116	-91.0130
	Ibu	-85.140	-69.004	16.1379	54.9805	-30.1614
	Prm	-50.616	-40.611	1.35116	72.3503	21.7341
	Trm	-62.485	-61.381	3.80049	52.1072	-58.6845

ΔH_f **(cracking)=** ΔH_f **(**product) − ΔH_f **(**reactant) (14)

$Ea^{\#}$**=** ΔH_f **(**transition state) − ΔH_f **(**reactant) (15)

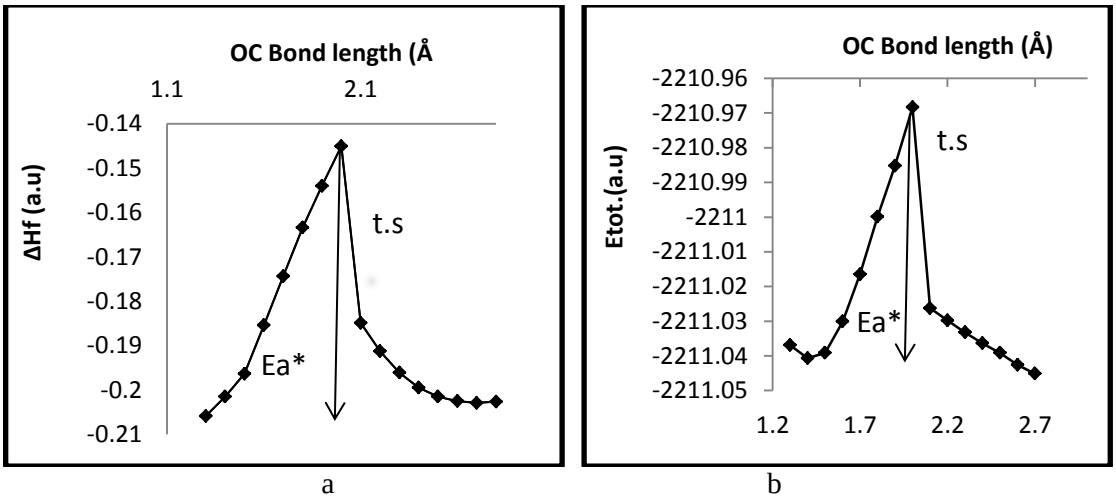
Table 4. U-DFT calculated energies values for the O-D bond rupture reactions in diclofenac drug and suggested carrier drugs.

Dc.Pro.no.	A	$E_{tot.}$ (kcal/mol) reactant	$E_{tot.}$ (kcal/mol) product	ΔEc (kcal/mol)	Ea* (kcal/mol)	$E_{t.s}$ (kcal/mol)
	Asp	-1387625	-1387618	6.693191	43.04244	-1387582
	Ibu	-1392812	-1392766	46.73344	84.38579	-1392728
	Prm	-1305022	-1305011	10.89492	73.83159	-1304948
	Trm	-1500211	-1500199	11.7236	60.48958	-1500200

E_{total} **(cracking)=** E_{total} (product)− E_{total} (reactant) (16)

$Ea^{\#}$**=** E_{total}(transition state)−E_{total} (reactant) (17)

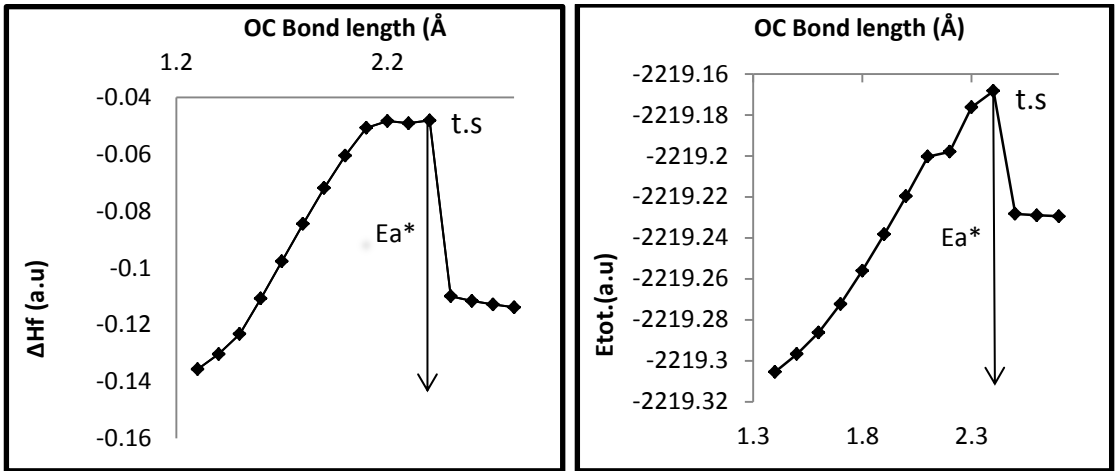
E_{total}= total molecular energy.



a b

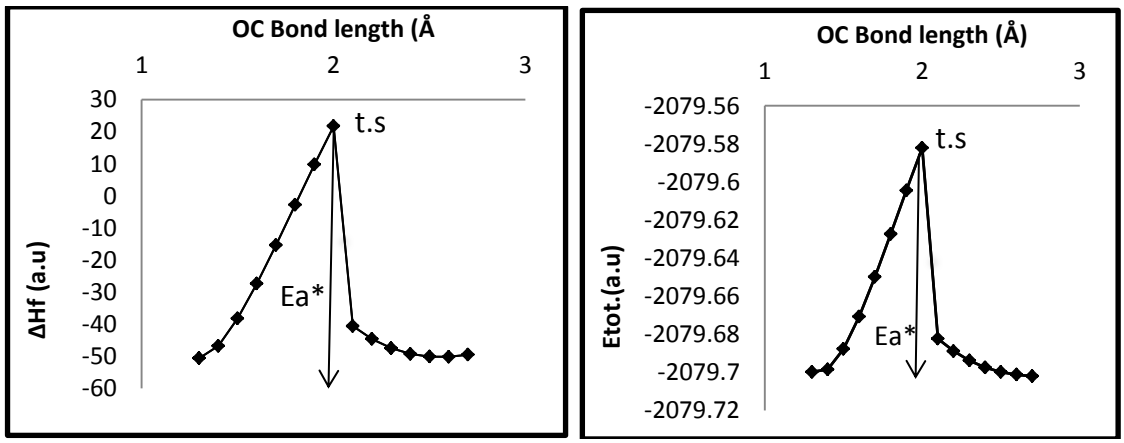
Figure 2. Potential energy curve for O-D energy bond rupture in Dc.Asp (D= -Asp) using (a): PM3 semiempirical method and (b): ab initio U-DFT method.

Baghdad Science Journal
2021, 18(4): 1249-1260
P-ISSN: 2078-8665
E-ISSN: 2411-7986



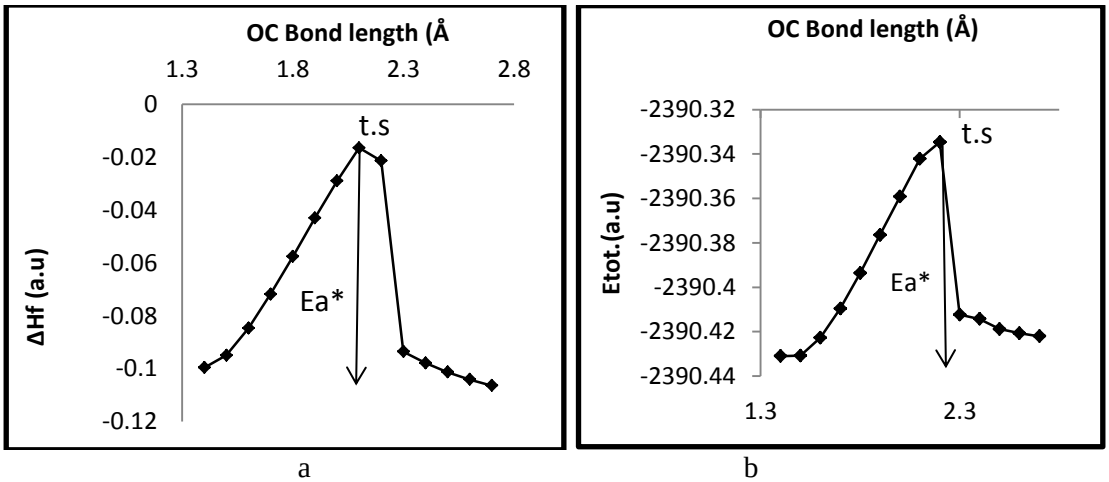
a b

Figure 3. Potential energy curve for O-D energy bond rupture in Dc.Ibu (D= -Ibu) using (a): PM3 semiempirical method and (b): ab initio U-DFT method.



a b

Figure 4. Potential energy curve for O-D energy bond rupture in Dc.Prm (D= -Prm) using (a): PM3 semiempirical method and (b): ab initio U-DFT method.



a b

Figure 5. Potential energy curve for O-D energy bond rupture in Dc.Trm D= -Trm) using (a): PM3 semiempirical method and (b): ab initio U-DFT method.

The suggested carriers (Dc.Asp, Dc.Prm) did not produce the acid drug as a final product of O-D bond rupturing, but produced, instead two free radical molecules in the intermediate step in reversible rupture reaction, **Fig. 6**. The rupture bond calculation for (Dc.Asp, Dc.Prm) shows low heat of cracking ΔHc (1.351163, 16.13793 kcal/mol) and (10.89492, 46.73344 kcal/mol) for

PM3 and U-DFT/STO-3G respectively Equations 14, 15. The activation energy (72.3503, 54.98051 kcal/mol) and (73.83159, 84.38579 kcal/mol) for PM3 and U-DFT/STO-3G are shown in **Figs. 1** and **8 - 11.** The reaction leads to O15—C21 bond breaking at length about 2.1, 2.5 Å with proton transfer, and the results in the final product fragment. The transition state was at the O15—C21 length of 2, 2.4 Å, **Figs. 3** and **8 - 11**.

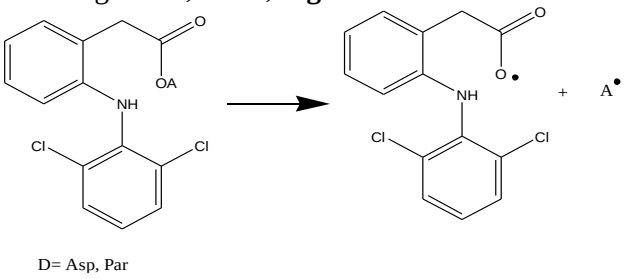


Figure 6. Calculated O-D bond rupture reaction products in diclofenac ester prodrugs (Dc.Asp, Dc.Prm).

The suggested prodrugs of drugs carriers (Dc.Ibu, Dc.Trm) adopt irreversible reaction for O-D bond rupture **Fig. 7,** and produced acidic product. The ΔHc and ΔE are a positive value (endothermic reaction) ranging from (16.13793 to 3.800498 kcal/mol) for PM3 and from (46.73344 to 11.7236 kcal/mol) for DFT **Tables (3,4)**. In comparison with common diclofenac prodrug, (Dc.Na, Dc.K) showed ΔHc range (-0.614 to -33.723 kcal/mol), and ΔE (-5.153 to -5.624 kcal/mol) with activation energy $Ea^{\#}$ (3.909, 7.802 kcal/mol) respectively by PM3 and (15.513, 17.012 kcal/mol) by DFT. These results were obtained for all the derivatives, which were given the acid drug. The derivative Dc.Trm, was found in a good prodrug due to low values of ΔHc, ΔE (3.800498, 11.7236 kcal/mol), respectively, middle activation energy $Ea^{\#}$ (52.10722, 60.48958 kcal/mol) by PM3 and DFT **Fig. 5**. The breakage of O15—C21 bond was at a bond length of 1.4 Å, leading to form cation and anion fragment. The activation energy range is (54.98051 to 52.10722) kcal/mol. The transition state was at the bond length 2.2 Å product fragment at 2.3 Å, **Fig. 11**. Proportion to the activation and cracking energies of O-D bond (D= Ibu, Trm) of these carriers, would hopefully be present for these drugs to be good link carriers.

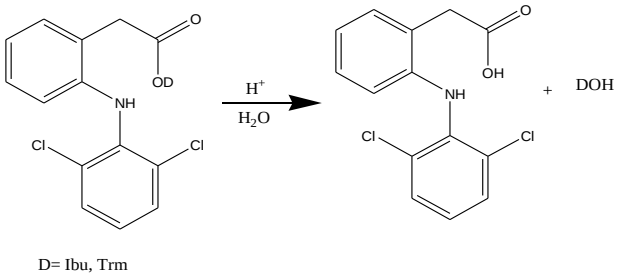


Figure 7. The result of cracking the diclofenac prodrugs (Dc.Ibu, Dc.Trm).

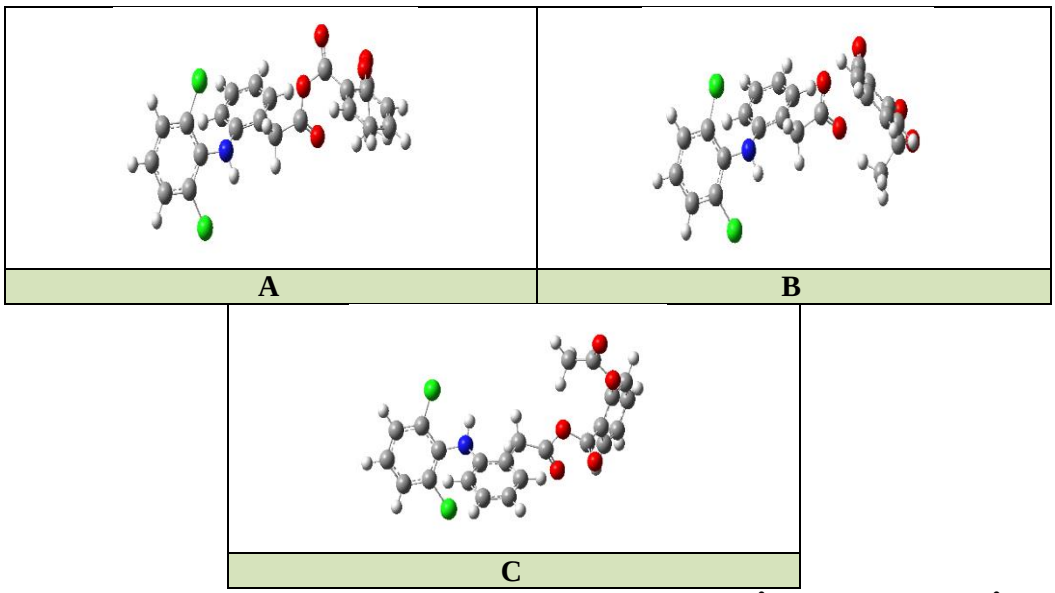


Figure 8. The optimize structures of Dc.Asp a- reactant, r (OD) = 1.3 Å, b- t.s, r(OD)= 2 Å, c- product, r(OD)= 2.1 Å.

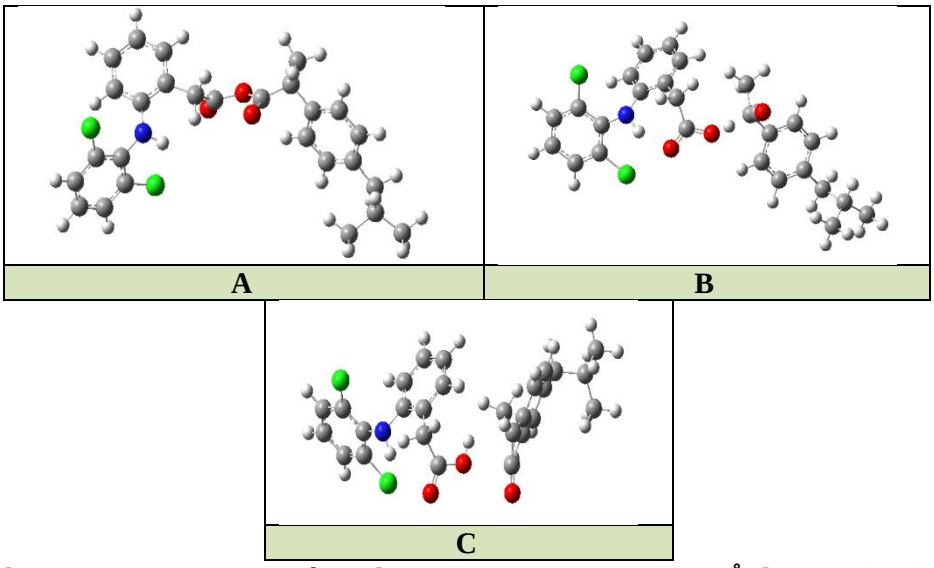


Figure 9. The optimize structures of Dc.Ibu a- reactant, r (OD) = 1.3 Å, b- t.s, r (OD) = 2.4 Å, c- product, r (OD) = 2.5 Å.

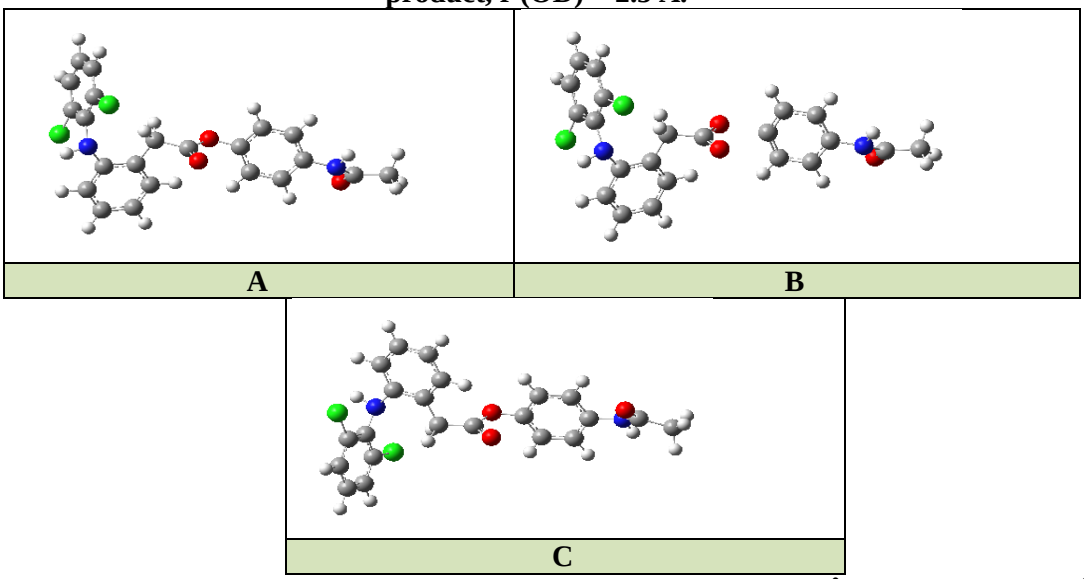


Figure 10. The optimize structures of Dc.Prm a- reactant, r (OD) = 1.3 Å, b- t.s, r (OD) = 2 Å, c- product, r (OD)= 2.1 Å.

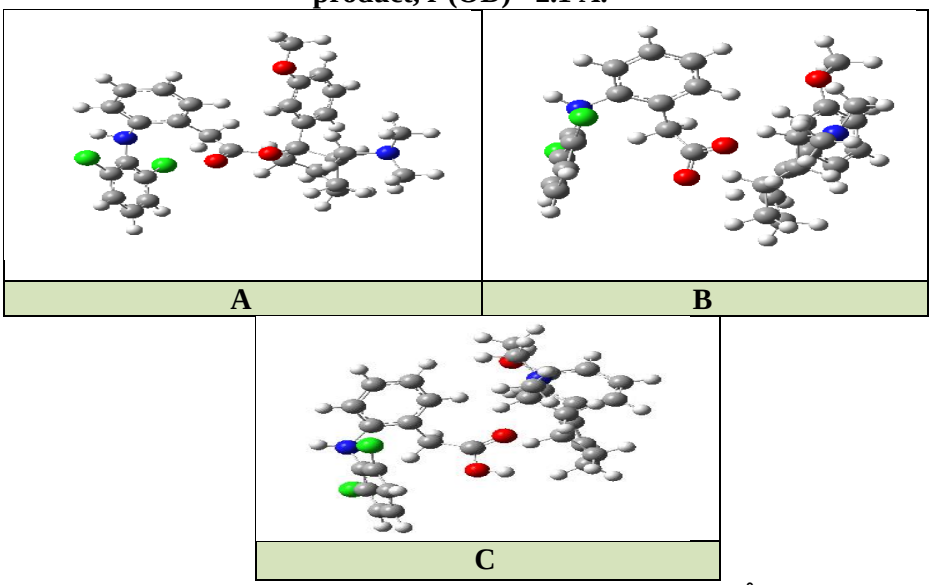


Figure 11. The optimize structures of Dc.Trm a- reactant, r (OD) = 1.4 Å, b- t.s, r (OD) = 2.2 Å, c- product, r (OD) = 2.3 Å.

Lethal concentration method:

LC50 (mg/L), aquatic toxicity to Pimephales promelas expressed as a chemical concentration at which 50 percent lethality is observed in a test batch of fish within 96 hours of exposure for Dc.Asp, Dc.Ibu, Dc.Prm and Dc.Trm. The acute toxicity values of LC50 compounds were correlated with the commonly prodrugs Dc.Na and Dc.K values $2.72*10^{-6}$ and $1.89*10^{-6}$ mol/L. The calculations of drug carrier's toxicity were done by HF method with a (631G+) basis set. The values of the suggested (Asp, Ibu, Prm, Trm) carriers are ($1.35*10^{-7}$, $7.36*10^{-8}$, $2.10*10^{-7}$, $6.18*10^{-6}$ M), respectively see Equation 18, **Table 5**. The predicted results give a possibility of using the suggested carriers as a non-toxic with diclofenac prodrug at the maximum of these concentrations (23). For HF descriptors, several equations were generated, and by using all the variables, the statistically best model is the four-parameter formula, as shown below:

$$HF\text{-}LogLC50=38.00 - 1.13Str + 1.38x10^{-3}\ \omega H - 2.22x10\text{-}3\ \omega L - 0.36IA \quad (18)$$

S_{tr}= Translational entropy, ω= vibrational wavenumber, I_A= principal moment of inertia.

Table 5. Predicted toxic concentration of the studied prodrugs.

Prodrugs	Str	IA	ωH	ωL	LC50 Mol./L
Asp	44.248	0.99990	3784.15	-121.43	$1.35*10^{-7}$
Ibu	44.413	0.99991	3754.00	-104.98	$7.36*10^{-8}$
Prm	44.053	1.00000	3815.92	-089.02	$2.10*10^{-7}$
Trm	43.304	0.99998	4102.81	-190.49	$6.18*10^{-6}$

Predicted biological activity of prodrugs (19):

Quantum chemical calculations were used to investigate the biological activity of the calculated compounds by using HF method. The biological processes usually take place in an aqueous medium. Depending on quantum chemical calculations, the time and material costs involved in practical experiments can be reduced. The calculated quantum chemical descriptors were compared with each other. These parameters are listed in **Table 6**.

Table 6. Quantum chemical descriptors of the biological reactivity calculated in aqueous solution.

Prodrug	E_{HOMO}[a]	E_{LUMO}[a]	IE[a]	EA[a]	E_{gap}[a]	η[a]	S[b]	So[b]
Dc.Asp	-8.6324	2.6749	8.6324	-2.6749	11.3074	5.6537	0.1768	0.0884
Dc.Ibu	-8.6379	2.9353	8.6379	-2.9353	11.573	5.7866	0.1728	0.0864
Dc.Prm	-8.7938	2.9018	8.7938	-2.9018	11.6957	5.8478	0.1710	0.0855
Dc.Trm	-8.7968	2.9157	8.7968	-2.9157	11.7125	5.8562	0.1707	0.0853
Dc.Asp	χ[a] 2.9787	CP[a] -2.9787	ω 0.7847		N_{Max} 0.5268	ΔN 0.3556	μ[c] 10.7628	
Dc.Ibu	2.8512	-2.8512	0.7024		0.4927	0.3584	1.0667	
Dc.Prm	2.9459	-2.9459	0.7420		0.5037	0.3466	5.0119	
Dc.Trm	2.9405	-2.9405	0.7382		0.5021	0.34659	4.2226	

a: in eV, b: in eV^{-1} c: in Debye

HOMO energy is the first parameter. If the energy of this molecular orbital is high, it is easy to donate electron to the biological material suggested prodrugs. It means that when rising the biological reactivity (E_{HOMO}) increases. The second parameter is the energy of LUMO. This value is small, the molecule can easily accept electrons, and these tests have shown that with decreasing (E_{LUMO}), the biological activity increases. The small values of ionization energy (IE) lead to high biological activity. The high values of affinity to electrons (EA) give rise to low biological activity. An essential parameter is the energy difference ($E_{HOMO-LUMO}$). For the other parameters, such as global electronegativity, low values of global electronegativity mean that the electron is delocalized on the molecule and thus, the molecule can easily give electrons. The decline in the index of nucleophilicity (almost) means high biological reactivity. N_{max} and N are linked with compound charges; the biological activity of compounds decreases with increasing values of N_{max} and N. For the last parameters, global softness (S_o) and dipole moment (μ); increasing the values of these

parameters, leads to increase the biological activity of the prodrugs. The rankings of the parameters could be described as follows:

E_{HOMO} Dc.Asp > Dc.Ibu > Dc.Par > Dc.Trm
E_{LUMO} Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm
EA Dc.Asp > Dc.Ibu > Dc.Trm > Dc.Prm
ω Dc.Ibu > Dc.Trm > Dc.Prm > Dc.Asp
N Dc.Ibu > Dc.Asp > Dc.Trm > Dc.Prm
N_{max} Dc.Asp > Dc.Prm > Dc.Trm > Dc.Ibu
IE, E_{GAP}, η, S_o Dc.Asp > Dc.Ibu > Dc.Par > Dc.Trm
χ Dc.Asp > Dc.Prm > Dc.Trm > Dc.Ibu
S Dc.Asp > Dc.Ibu > Dc.Trm > Dc.Par
μ Dc.Asp > Dc.Prm > Dc.Trm > Dc.Ibu

According to the high ranking, there is no general ranking but Dc.Asp seems to be the most reactive prodrug. The Dc.Ibu is the second. Dc.Prm and Dc.Trm is approximately of the same biological activity region. These parameters show the biological activity and changing according to the target cell, medium, and structure of biological material or interaction region **Fig. 12.** Dc.Asp, Dc.Ibu, Dc.Prm and Dc.Trm showed heaving in electron density that leads to high the biological activity. Moreover, these results give excellent initial suggestions.

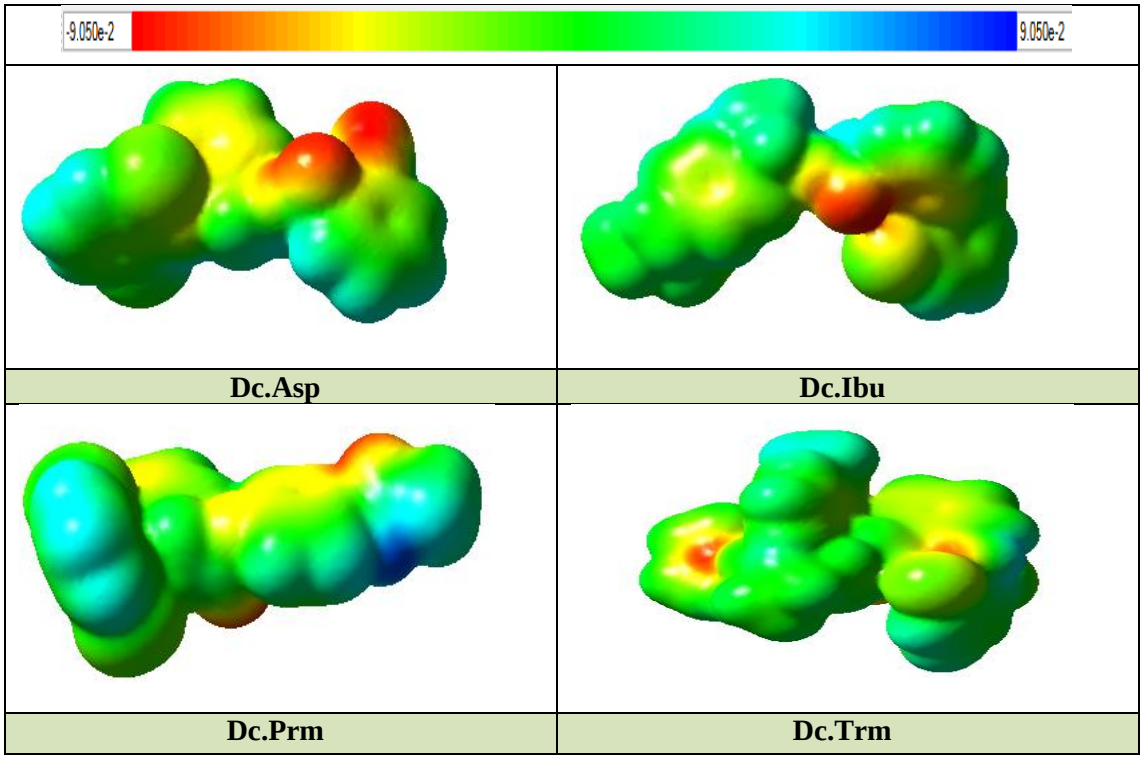


Figure 12. MEP maps of the investigated prodrugs (in aqueous solution).

The color line in **Fig. 12** with range (-9.050 to 9.050) represents the electron density regions, whereas the red color indicates the region of high electronic density, and the blue color represents the region of low electronic density. The region of donating and accepting electrons is the green region, and the nearer region to a red color is the region of low electron density.

Investigations of non-linear optical (NLO) properties:

Vacuum medium was used to calculate NLO properties. The urea was considered as a reference in these investigations (19,24). The determination of activity of a molecule based on some parameters, nonlinear optical properties are relevant.

Table 7. Quantum chemical descriptors of NLO properties for the studied prodrugs (calculated in vacuum).

Prodrug	E_{HOMO} [a]	E_{LUMO} [a]	IE [a]	EA [a]	E_{gap} [a]	η [a]	S [b]	So [b]
Asp	-8.5342	2.7217	8.5342	-2.7217	11.2559	5.6279	0.1776	0.0888
Ep	-8.3641	2.9867	8.3641	-2.9867	11.3509	5.6754	0.1761	0.0880
Prm	-8.4670	2.8686	8.4670	-2.8686	11.3357	5.6678	0.1764	0.0882
Trm	-8.4572	3.0959	8.4572	-3.0959	11.5531	5.7765	0.1731	0.0865
Urea	-6.7270	1.5590	9.5220	-1.5590	8.2860	2.633	0.3800	0.1210
Prodrug	**χ [a]**	**CP [a]**	**ω**		**N_{Max}**	**α [c]**	**β_o [d]**	**μ (Debye)**
Asp	2.9062	-2.9062	0.7503		0.5163	9.96355	$-26.805*10^{-35}$	0.8263
Ep	2.6886	-2.6886	0.6368		0.4737	8.61852	$-21.000*10^{-35}$	8.3564
Prm	2.7991	-2.7991	0.6912		0.4938	9.15573	$9.9008*10^{-33}$	3.8332
Trm	2.6806	-2.6806	0.6219		0.4640	8.59460	$28.7397*10^{-35}$	3.0094
Urea	6.8890	-6.8890	0.8050		2.6160	2.15300	$3.1300*10^{-28}$	6.8890

a in eV, b in eV^{-1}, c in $Å^3$, d in cm^5/esu

The parameters related to NLO properties are listed in **Table 7**. They are ordered as follows;

- (E_{HOMO}), increased energy HOMO values increase molecular NLO properties by the following order:

Urea> Dc.Ibu> Dc.Trm>Dc.Prm>Dc.Asp

- Energy LUMO (E_{LUMO}), increase the energy value of LUMO, decrease the molecules of NLO products in the following order:

Urea> Dc.Asp> Dc.Prm> Dc.Trm> Dc.Ibu

- Low value ionization energy (IE) suits with a high NLO property:

Dc.Ibu> Dc.Trm> Dc.Prm> Dc.Asp> Urea

- Electron affinity (EA), high (EA) values, meaning NLO property is increasing:

Urea> Dc.Asp> Dc.Prm >Dc.Ibu> Dc.Trm

- HOMO's energy difference with LUMO (Eg). The reduction in energy gap values indicates that the NLO property is growing:

Urea> Dc.Asp> Dc.Prm> Dc.Trm> Dc.Ibu

- Absolute chemical hardness, low hardness values, means increasing NLO properties in the following order:

Urea > Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm

- Softness (S) and optical softness (So) are other important parameters, and higher values mean increasing NLO properties:

Urea > Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm

Urea > Dc.Trm > Dc.Asp > Dc.Ibu > Dc.Prm

- Absolute electronegativity (χ). Decreasing energy gap values indicate an increase in NLO property according to the following order:

Urea > Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm

- Chemical potential (CP) and nucleophilic indexes (ω). The properties of the NLO decrease with decreasing them:

Urea > Dc.Asp >Dc.Prm > Dc.Ibu > Dc.Trm

Dc.Trm > Dc.Ibu > Dc.Prm > Dc.Asp > Urea

- Electronic charge (NMAX), the higher the value, the more active in NLO applications:

Dc.Trm > Dc.Ibu > Dc.Prm > Dc.Asp > Urea

- Polarizability (α) and hyperpolarizability (βo); the NLO properties increase by increasing them.

Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm > Urea

Urea > Dc.Prm > Dc.Ibu > Dc.Asp > Dc.Thr

- The increase in dipole moment □□) increases the NLO activity:

Dc.Ibu > Dc.Prm > Dc.Trm > Urea > Dc.Asp

The net order for activity of the studied prodrugs with NLO properties are:

Dc.Asp > Dc.Prm > Dc.Ibu > Dc.Trm

Conclusion:

The proposed carriers (Asp, Ibu, Prm, and Trm) are compared to the standard ion carrier link (Na^+, K^+). Biological activity is discussed theoretically to determine the efficacy of prodrugs. Dc.Asp seems to be the most reactive prodrug, Dc.Ibu is the second, Dc.Prm and Dc.Trm are

approximately in the same biological activity region. The suggested drug carriers show a positive LC50 result as non-toxic compared with Dc.Na and Dc.K values. The outcomes of this study confirm the superiority of Ibu as a drug carrier of diclofenac, followed by Trm, whereas Dc.Asp and Dc.Prm are not good as carriers. The study confirm the possibility of adopting theoretical quantum mechanical calculations for the determination of some compounds as pharmacological acid carriers by calculating the O-D bond rupture reaction pathway.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

References:

1.Eva A, Rana A, Majid H, Ivan H , Mustafa M. Aminotriazole derivative as anti-corrosion material for iraqi kerosene tanks: electrochemical, computational and the surface study. Chem. Sel. 2019; 4: 9883 -9892.

2.Al-Yassiri M ,Shanshal M J. Reaction pathways and transition states of the C-C and C-H bond cleavage in the aromatic pyrene molecule A Density Functional study. Eur. J. of Chem. 2015; 6(3), 261-269.

3.Dewar M ,Thiel W. The MNDO method. Approximations and parameters. J. of Amr. Chem. Society. 1977; 99: 4899-4907.

4.Santoro F, Jacqueline D. Vibrationally resolved absorption and emission spectra of di thiophene in the Gas Phase and in Solution by First-Principle Quantum Mechanical calculations. Comput. Mol. Sci. 2016; 6: 460–486.

5. Lichtenberger L, Phan T, Fang D, Dial E. Chemoprevention with phosphatidylcholine non-steroidal anti-inflammatory drugs in vivo and in vitro, Onc. Lett. 2018;15(5):6688–6694.

6.Rauk A. Orbital interaction Theory of Organic Chemistry 2th Edition Chapter 14 John Wiley & Sons: New York; 2001. 196-208.

7.Khawaja y , Karaman R. A Novel Mathematical Equation for Calculating the Number of ATP Molecules Generated From Sugars in Cells. Worl. J. of Pharma. Res. 2015; 4(4): 303-312.

8.Maier T.J, Janssen A, Schmidt R, Geisslinger G, Grösch S. Targeting the beta-catenin/APC pathway: A novel mechanism to explain the cyclooxygenase-2-independent anticarcinogenic effects of celecoxib in human colon carcinoma cells. FASEB J. 2005; 19; 1353–1355.

9.Karaman, R. Computationally Designed Prodrugs Based on Enzyme Models. Aperito J. of Drug Desi. and Pharm. 2015; 2: 111.

10.Abu-Jaish A, Mecca G, Jumaa S, Thawabteh A, Karaman R. Mefenamic acid Prodrugs and Codrugs-Two Decades of Development. Worl. J. of Pharma. Res. 2015; 4(6): 2408-2429.

11.Kubba R ,Abdullah H. Theoretical study of the vibration Frequencies and IR absorption intensities for tricyclobutabenzene compound with its heating energy cracking. Nat. J. of Chem. 2005; 18: 235-260.

12.Kubba R. Quantum Mechanical Calculations for Reaction Path of O-R Bond Breakage in Some of Cefpodoxime Prodrugs. Asia. J. of Chem. Sci. 2018; 30: 1291-1298.

13.Kubba R , Sallam A. Quantum mechanical investigations of R-O thermal bond rupture energies in some ampicilin prodrugs. Iq. J. of Sci. 2013; 54: 291-129.

14.Shirke S, Shewale S , Satpute M. Prodrug design: an overview. Intern. J. of Pharma. Chem. and Bio. Sci. 2015; 5(1): 232-241.

15.Karelson M , Lobanov V. Quantum chemical descriptors in QSAR/QSPR studies. Chem. Rev. 1996; 96: 1027–1043.

16.Kohn W , Sham L. Self-Consistent equations including exchange and correlation effects. Phys. Rev. 1965; 140: A1133.

17.Lewars E. Computational chemistry (Introduction to the theory and applications of molecular and quantum mechanics), 2th Edition, Canada; Chemistry Department Trent University Peterborough, Ontario 111. 2004.

18.Ericka C, George A, John A, Michael J , Jan M. Unrestricted coupled cluster and brueckner doubles variations of W1 theory. J. of Chem. Theo. and Compute. 2009;5(10):2687-2693.

19.Sayin K, Erkan S, Tastan M, ALagoz ST , Karakas D. Investigations of structural, spectral, electronic and biological properties of N-heterocyclic carbene Ag (I) and Pd (II) complexes. J. Mole. Struc. 2018; 18: 0022-2860.

20.Jean P, Antonio M, Olivier P, Claude G. Study of the difference between HF and DFT intermolecular interaction energy values: The importance of the charge transfer contribution. J. of Chem. Edu. 2005; 26: 1052–1062.

21.Shanshal M, Yusuf Q.A. C- C and C- H bond cleavage reactions in the chrysene and perylene aromatic molecules: An ab- initio density functional theory study, Eur. J. of Chem. 2017; 8 (3): 288-292.

22.Binkly J, Whiteside R, Krishnan R, Seeger R, Defrees D, Schlegel S et al. Quantum Chemistry Program Exchange Ind. Uni. Bloom. 1980. 406.

23.Pavan M, Worth A , Netzeva T. Comparative QSTR study using Semi-Empirical and first principle methods based descriptors for acute toxicity of diverse organic compounds to the fathead minnow

joint. Res. Cent. Intern. J. of Mole. Sci. 2007; 8: 1265-1283.
24. Fatemeh M , Yasaman A. Synthesis and investigation of nonlinear optical properties of Para Red: Z-scan technique and quantum mechanical calculations. Mater. Sci.-Pol. 2018; 36(3): 445-451.

فعالية الاصرة بين الاوكسجين والدواء المقترح كحامل للفولتارين: استخدام الطرق التقريبية والطرق الدقيقة

رحاب ماجد كبه[1] **مصطفى محمد كاظم[2]**

[1]قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق
[2]قسم طب الاسنان، كلية الكوت الجامعة، كوت، واسط، عراق

الخلاصة:
تمت مناقشة إمكانية استخدام مادة حاملة مقترحة جديدة (D) لعقار ديكلوفيناك (فولتارين) باستخدام حسابات ميكانيكا الكم. تم استخدام طرق الحساب (PM3) و (DFT) لتحديد مسار التفاعل لطاقات كسر الرابطة (O-Drug). تم استخدام مجموعات مختلفة الأدوية كحاملات لعقاقير أولية من ديكلوفيناك (في الفراغ كوسط تفاعل) عند الشكل الهندسي التوازني. تضمنت الحسابات التركيب الهندسي وبعض الخواص الفيزيائية، بالإضافة إلى السمية والنشاط البيولوجي وخصائص NLO للدواء مع حوامله، والتي درست باستخدام طريقة HF. تم إجراء العمليات الحسابية بواسطة برنامج Gaussian 09. تم إجراء المقارنة بين الطاقات الكلية للمواد المتفاعلة وطاقات التنشيط والحالات الانتقالية إلى الحالة النهائية. تهدف العقاقير الأولية المقترحة إلى تحسين خصائص حوامل الديكلوفيناك والحصول على بدائل جديدة للناقلات المعتمدة نظريا.

الكلمات المفتاحية: فعالية بيولوجية، دكلوفيناك، سمية، PM3، DFT