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Density Functional Theory Study on Chemical Reactivity of Aspirin: Substituent Effect

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Abstract

There is strong evidence that thrombotic and inflammatory mechanisms play a role in COVID-19 severity. COVID-19 morality may be reduced by common drugs that block these pathways, such as Aspirin. New Aspirin derivatives were suggested by functionalizing the benzene ring with acetate, amine, amide, and ribose at 2, 3, 4, and 5 positions. Through density functional theory (DFT) B3LYP / (6–31G), their energetic characteristics and chemical reactivity were estimated. The band gap of Aspirin is 0.199 eV, while 3-acetate Aspirin, 3-amine Aspirin, 4-amide Aspirin, and 5-ribose Aspirin have the least band gap equal to 0.187, 0.144, 0.177, and 0.162 eV, respectively. Electronegativity (χ), chemical potential (μ), hardness (η), electrophilicity index (ω), ionization potential (I), and electron affinity (A) of Aspirin are -0.166, 0.166, 0.098, -0.14, 0.265, and 0.068 eV, while for 3-amine Aspirin they are -0.130, 0.130, 0.072, -0.117, 0.202, and 0.058, respectively. On the other hand, the energy barriers of Aspirin and 3-amine Aspirin reactions with Serine are -39.286 and -152.559 Hartree, respectively. These results indicate that 3-amine Aspirin is more active than Aspirin. However, these results open the way for the development of new effective drugs for anti-inflammatory and cardiovascular diseases.

Keywords: Aspirin, Chemical reactivity, DFT, Global index, Serine.

Introduction

Aspirin is the most commonly prescribed and used drug on the planet. Aspirin's origins can be traced back thousands of years to the use of plant extracts containing salicylate. In 1874, salicin was produced from white willow and successfully used to reduce the fever, pain, and inflammation of rheumatic fever [1]. Aspirin is a nonsteroidal anti-inflammatory medicine available over-the-counter that has analgesic, anti-inflammatory, and antipyretic actions on some body cells. Studies have shown that taking Aspirin daily can help people in their 50s live longer since it lessens the risk of several diseases connected with aging [2]. Because of Aspirin's irreversible anti-thrombotic impact on platelets, which manifests as a prolonged bleeding period, it is often used for primary and secondary cardiovascular disease (CVD) prophylaxis [3]. In patients with a history of CVD, secondary prevention involves preventing a

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recurrent cardiovascular attack. Primary prevention is the prevention of a cardiovascular incident in those who have never had one before [4].

The oxidoreductase enzyme cyclooxygenase (COX) converts arachidonic acid to biological modulators such as prostaglandins (PGs), prostacyclins, and thromboxane. COX isoenzymes are divided into three categories: COX-1, COX-2, and COX-3 [5]. COX-1 and COX-2 have a molecular weight equal to 70 and 72 kDa. COX-1 is responsible for manufacturing thromboxane A2, which aggregates platelets, and Aspirin is an irreversible COX-1 inhibitor. Platelet aggregation is prevented in the absence of thromboxane A2, which inhibits the synthesis of a thrombus at a damaged atherosclerotic plaque. The risk of arterial occlusion is reduced without thrombus formation, avoiding a cardiovascular event such as myocardial infarction (MI) or stroke [6].

To decrease the cost and time of drug development, computational programs are employed to perform molecular simulations. It is important for the formation and discovery of new drugs. Quantum mechanics is a high-calculation method that yields precise geometries and relative energy for various molecule conformations. DFT is the most famous and commonly used quantum theory for examining the electronic structures of molecules. DFT is used to analyze the precise electronic characteristics of isolated drug molecules and drug delivery devices in drug modeling research. DFT is particularly effective for explaining reaction processes when medicinal compounds act at enzyme active sites because it provides chemical precision. As a result, DFT is useful for describing pharmacological characteristics as well as their inhibitory effects on therapeutic targets [7, 8].

Chemists often keep one component of a structural unit constant and optimize the structures of compounds, as well as examine the structure-activity relationship by adding or changing various types of functional groups, to create candidate medications with good pharmacological properties. Drug properties are heavily influenced by functional classes. The different functional groups were used to modify drugs such as $–NH_2$, $–NO_2$, $–CONH_2$, –COOH, and –ribose [9, 10].

The objective of this work is to design new Aspirin derivatives for cardiovascular disease treatment. Theoretical chemical parameters such as the energies of the highest occupied molecular orbital (HOMO) and the least unoccupied molecular orbital (LUMO), the energy gap (E_{gap}), the electronegativity (χ), chemical potential (μ), hardness (η), electrophilicity (ω), ionization potential (I), electron affinity (A), and the total energy were calculated.

Materials and Methods

Theoretical computations are done using Gaussian 09 [11]. The geometries of all the molecular structures have been completely optimized using density functional theory B3LYP at basis sets 6–31G. The calculations were performed in the gaseous state. In order to confirm that the structures produced are minima, vibration frequency calculations at the same level of theory are performed after the optimization of the molecular geometries. The global parameters have been determined by the relations below Eq. 1,2,3,4, and 5. [12, 13]:

$$\mu = -\chi = \frac{1}{2}(E_{LUMO} + E_{HOMO}) = -\frac{1}{2}(I + A) \dots\dots.1$$

$$\eta = \frac{1}{2}(I - A) = \frac{1}{2}(E_{LUMO} - E_{HOMO}) \dots\dots 2$$

$$\omega = \frac{\mu^2}{2\eta} \dots\dots\dots\dots 3$$

$$I = -E_{HOMO} \dots\dots.4$$

$$A = -E_{LUMO} \dots\dots.5$$

The internal energy contributions that occur between the product and the reactant have been used to compute the reaction's thermodynamic parameters as follows Eq. 6:

$$\Delta X_r = \sum \Delta X(\text{product}) - \sum \Delta X(\text{reactant}) \quad \dots\dots 6$$

Where X: enthalpy H, Gibbs free energy G, and entropy S.

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Results and Discussion

Optimizing the Structure of Aspirin

As illustrated in Fig. 1, the molecular structural characteristics of Aspirin were approximated using density functional theory (B3LYP) at basis sets 6–31G [14]. The total energy released by Aspirin is -609.037 Hartree. The oriented bound atoms are identified by a number that represents the numerical order in the geometry-optimized structure [15, 16]. Table 1 shows the energetic properties of Aspirin.

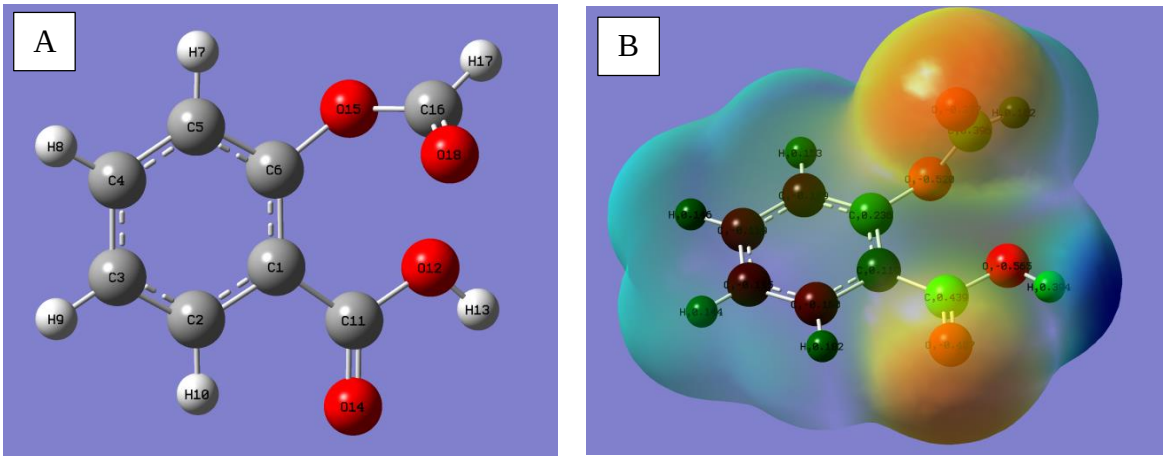

Figure1. The optimized structure of Aspirin: A- labeling scheme B- Mullikan charge.

Table1. Energetic properties of Aspirin

Total Energy (Hartree)	-609.037
The Heat of Formation (Hartree)	-609.036
ΔS^o (Cal/mol/deg)	99.804
ΔG^o (Hartree)	-609.084
Zero Point Energy (Hartree)	-609.047
Dipole Moment (D)	2.938
LUMO (eV)	-0.068
HOMO (eV)	-0.267
E_{gap} (eV)	0.199

The Mullikan charge distribution on atoms of Aspirin was also shown in Fig. 1. The positive charge of atoms indicates that it is acceptor atoms, while the negative charge indicates that they are donor atoms. The negative charges are highlighted by the red color and dispersed on the oxygen atoms due to the high electronegativity. The positive charges are represented by the green colour [17]. The Mullikan atomic charges of Aspirin are listed in Table 2.

Table 2. Mullikan atomic charge distribution of Aspirin

Atoms	Charges	Atoms	Charges
1 C	0.119	11 C	0.438
2 C	0.236	12 O	-0.565
3 C	-0.108	13 H	0.393
4 C	-0.118	14 O	-0.406
5 C	-0.114	15 O	-0.520
6 C	-0.159	16 C	0.396
7 H	0.153	17 H	0.162
8 H	0.146	18 O	-0.377
9 H	0.143		
10 H	0.182		

The bond lengths and angles of optimized Aspirin have been estimated. Table 3 shows the bond lengths and angles of the main chemical bonds of Aspirin. The bond lengths of Aspirin range from 0.98 to 1.476 A°. The bond angles of the Aspirin ranged from 109.235° to 127.031°.

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Table 3. Bond lengths and angles of Aspirin

Chemical bond	Bond length Aº	Bond angles	Degree	Bond angles	Degree
C1—C2	1.409	C2—C=C6	117.904	C4=C5—H15	121.548
C1=C6	1.410	C2—C1—C7	120.153	C6—C5—H15	118.630
C1—C7	1.476	C6=C1—C7	121.931	C1=C6—C5	121.273
C2=C3	1.394	C1—C2=C3	121.111	C1=C6—O10	122.075
C2—H18	1.081	C1—C2—H18	118.390	C5—C6—O10	116.535
C3—C4	1.400	C3=C2—H18	120.598	C1—C7=O8	127.031
C3—H14	1.084	C2=C3—C4	119.896	C1—C7—O9	112.448
C4=C5	1.397	C2=C3—H17	119.848	C7—C9—H13	109.235
C4—H16	1.084	C4—C3—H17	120.254	C6—O10—C11	120.925
C5—C6	1.393	C3—C4=C5	119.996	O10—C11—O12	125.421
C5—H15	1.083	C3—C4—H16	120.314	O10—C11—H14	107.784
C6—O10	1.413	C5—C4—H16	119.695	O12—C11—H14	126.757
C7=O8	1.238	C4=C5—C6	119.820		
C7—O9	1.383				
O9—H13	0.980				
O10—C11	1.393				
C11=O12	1.219				
C11—H14	1.089				

The molecular orbital HOMO and LUMO in three dimensions were investigated, as shown in Fig. 2. The positive section of the wave function that would be attacked by a nucleophile is shown in green, while the negative section of the wave function that would be attacked by an electrophile is indicated by red [18]. A high HOMO value indicates a significant preference for donating electrons to an acceptor molecule with a low empty molecular orbital energy. A low LUMO value, on the other hand, indicates a significant predisposition for receiving electrons from the metal surface.

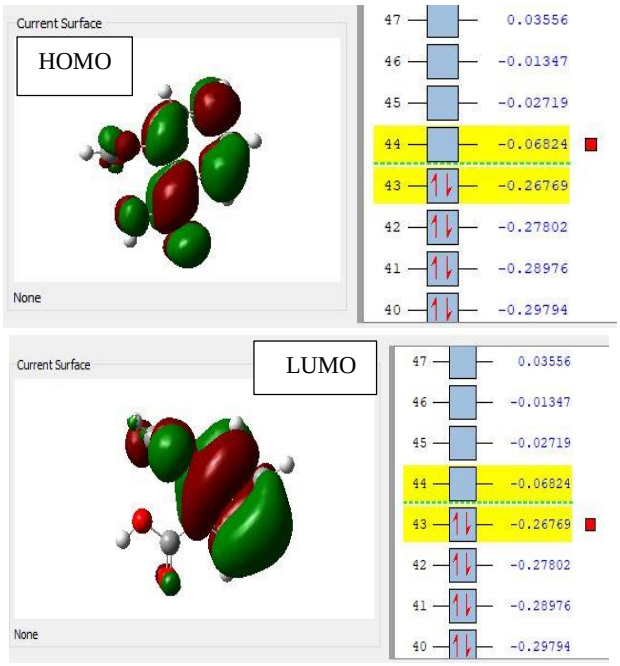

Figure2. HOMO and LUMO orbitals of Aspirin.

The molecular electrical transport properties depend on the band gap energy. Changes in band gap energy and dipole moment are used to evaluate the chemical reactivity and biological activity of chemical substances [19, 20]. The energy values of the HOMO and LUMO orbitals are equal to -0.267 and -0.068 eV,

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respectively. The energy gap of Aspirin is equal to 0.199 eV.

Modulation of New Suggested Derivatives

To suggest new Aspirin derivatives, relevant functional groups must be inserted into the Aspirin molecular structure. The reorientation of electronic density around the Aspirin molecular structure is the main impact of the added functional groups. The acetate, amine, amide, and ribose groups were substituted at 2, 3, 4, and 5 positions to alter the electronic density of Aspirin. The energetic properties of Aspirin derivatives are listed in Table 4.

Table4. Energetic properties of Aspirin derivatives

Group type	**2- acetate**	**3- acetate**	**4- acetate**	**5- acetate**
Total Energy (Hartree)	-836.777	-836.774	-836.775	-836.783
The Heat of Formation (Hartree)	-836.776	-836.773	-836.774	-836.782
ΔSº (Cal/mol/deg)	128.016	126.107	125.108	128.328
ΔGº (Hartree)	-836.837	-836.833	-836.833	-836.843
Zero Point Energy (Hartree)	-836.792	-836.789	-836.790	-836.798
Dipole Moment (D)	3.814	5.945	3.187	1.468
LUMO (eV)	-0.078	-0.087	-0.085	-0.070
HOMO (eV)	-0.268	-0.274	-0.279	-0.259
E_{gap} (eV)	0.190	0.187	0.194	0.189
Group type	2- amine	3- amine	4- amine	5- amine
Total Energy (Hartree)	-664.244	-551.091	-664.361	-551.071
The Heat of Formation (Hartree)	-664.243	-551.090	-664.360	-551.070
ΔSº (Cal/mol/deg)	117.300	97.361	105.898	96.230
ΔGº (Hartree)	-664.299	-551.136	-664.410	-551.115
Zero Point Energy (Hartree)	-664.257	-551.100	-664.372	-551.080
Dipole Moment (D)	4.617	4.852	6.945	9.060
LUMO (eV)	-0.081	-0.058	-0.063	-0.030
HOMO (eV)	-0.227	-0.202	-0.226	-0.217
E_{gap} (eV)	0.146	0.144	0.163	0.187
Group type	2- amide	3- amide	4- amide	5- amide
Total Energy (Hartree)	-778.172	-777.653	-777.654	-777.655
The Heat of Formation (Hartree)	-778.171	-777.652	-777.653	-777.654
ΔSº (Cal/mol/deg)	118.898	117.196	117.113	114.054
ΔGº (Hartree)	-778.228	-777.708	-777.709	-777.708
Zero Point Energy (Hartree)	-778.186	-777.667	-777.667	-777.668
Dipole Moment (D)	2.750	5.991	4.189	3.671
LUMO (eV)	-0.054	-0.077	-0.087	-0.077
HOMO (eV)	-0.256	-0.260	-0.264	-0.261
E_{gap} (eV)	0.202	0.183	0.177	0.184
Group type	2- ribose	3- ribose	4- ribose	5- ribose
Total Energy (Hartree)	-1104.95	-1104.941	-1104.942	-1104.926
The Heat of Formation (Hartree)	-1104.949	-1104.940	-1104.941	-1104.926
ΔSº (Cal/mol/deg)	139.914	150.810	146.564	159.747
ΔGº (Hartree)	-1105.015	-1105.012	-1105.011	-1105.001
Zero Point Energy (Hartree)	-1104.968	-1104.961	-1104.962	-1104.947
Dipole Moment (D)	3.266	3.028	4.336	3.690
LUMO (eV)	-0.086	-0.059	-0.078	-0.070
HOMO (eV)	-0.254	-0.250	-0.264	-0.232
E_{gap} (eV)	0.168	0.191	0.186	0.162

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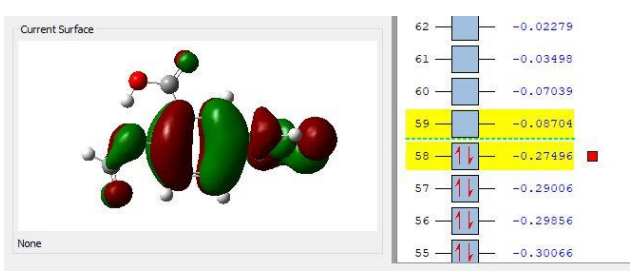
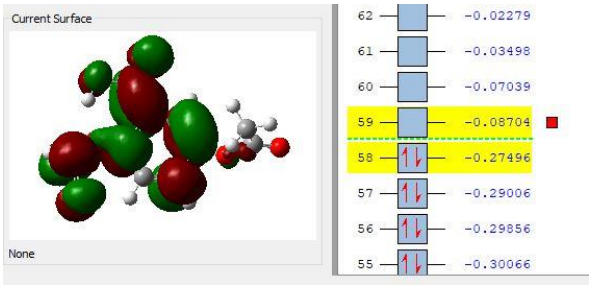
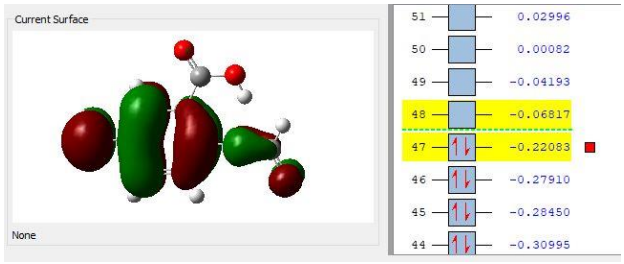
The results indicate that the band gap energy was reduced at the entire derivative with different position substitutions. The best functional group is the amine group at position 3, with an energy gap equal to 0.144 eV. These results are fitted with the effect of donor substituents, which increases the energy of the HOMO orbital and decreases the energy of the LUMO orbital compared with the bare molecule [21, 22]. For the same reason, dipole momentum is higher than other derivatives [23]. The 3-amine Aspirin derivative has the lowest heat of formation, equal to -551.090 Hartree. The molecular orbital HOMO and LUMO in three dimensions of the best derivatives at the different functional groups were investigated, as shown in Fig. 3



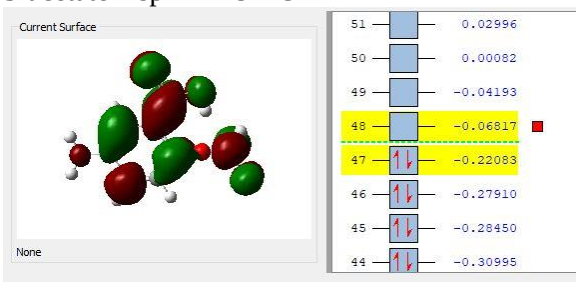
3-acetate Aspirin HOMO



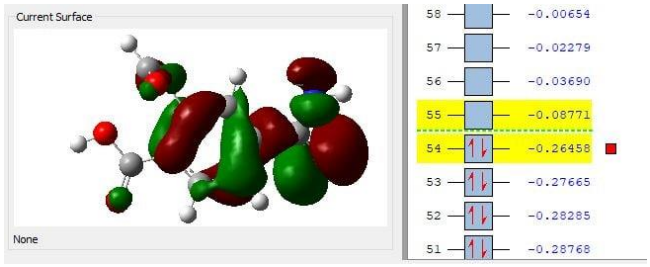
3-acetate Aspirin LUMO



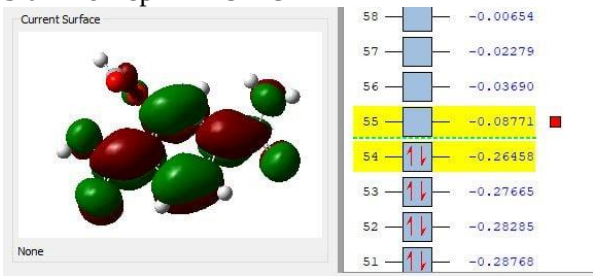
3-amine Aspirin HOMO



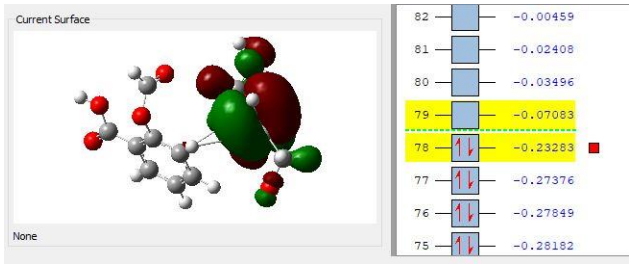
3-amine Aspirin LUMO



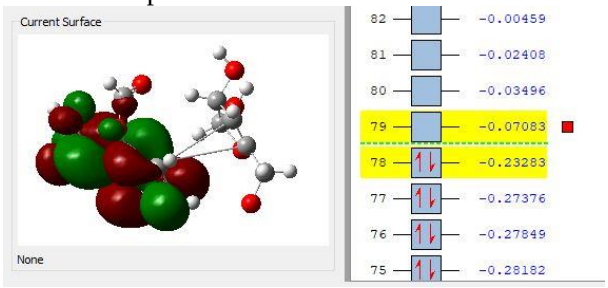
4- amide Aspirin HOMO



4- amide Aspirin LUMO



5-ribose Aspirin HOMO



5-ribose Aspirin LUMO

Figure 3. HOMO and LUMO orbitals of Aspirin derivatives.

The global index of 3-amine Aspirin was calculated to improve the enhancement in chemical reactivity. Due to lower E_{gap} values, 3-amine Aspirin derivatives have lesser stability, higher reactivity, and softer molecules than other derivatives [24]. Table.5 shows the global index of Aspirin derivatives. Due to low values of chemical hardness, which evaluate an atom's resistance to charge transfer, 3-amine Aspirin is more reactive than other derivatives [25]. Low electrophilicity levels indicate a

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good nucleophile, while higher values indicate a good electrophile [26].

Table 5. Global index values of Aspirin and derivatives

Index	Aspirin	3-acetate Aspirin	3-amine Aspirin	4-amide Aspirin	5-ribose Aspirin
χ	-0.166	-0.180	-0.130	-0.175	-0.151
μ	0.166	0.180	0.130	0.175	0.151
η	0.098	0.093	0.072	0.088	0.081
ω	-0.140	-0.174	-0.117	-0.174	-0.140
I	0.265	0.274	0.202	0.264	0.232
A	0.068	0.087	0.058	0.087	0.070

Binding with COX

Theoretical calculations of the reaction of Aspirin and 3-amine Aspirin with COX were performed. The active site of COX, Serine 516, has been acetylated using Aspirin and 3-amine Aspirin [27]. Fig. 4 shows the reaction of Aspirin and 3-amine Aspirin with serine. The energetic properties of these two reactions are shown in Table.6. The reaction with 3-amine Aspirin has the lowest energy barrier, equal to -152.559 Hartree. Thermodynamic parameters indicate that the reaction is spontaneous and exothermic [28].

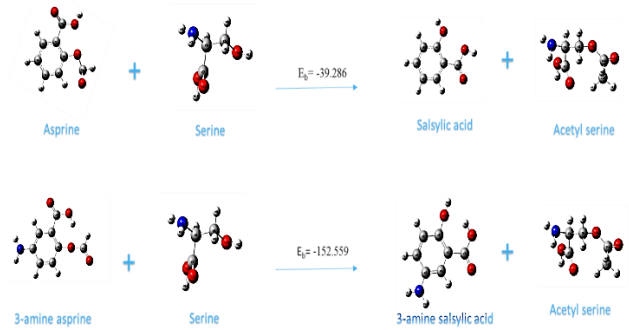

Figure 4. Reaction of Aspirin and 3-amine Aspirin with Serine.

Table 6. Thermodynamic parameters for the reaction of Aspirin and 3-amine Aspirin with Serine

Parameters	Aspirin	3-amine Aspirin
ΔH° (Hartree)	-39.287	-152.559
ΔS° (Cal/mol/deg)	5.844	13.364
ΔG° (Hartree)	-39.289	-152.566

Conclusion

In this paper, the chemical reactivity of Aspirin was enhanced by modifying the chemical structure with acetate, amine, amide, and ribose functional groups. These functional groups were substituted in four positions on the benzene ring. The band gap energy of Aspirin is 0.199 eV while for 3-acetate Aspirin, 3-amine Aspirin, 4-amide Aspirin and 5-ribose Aspirin are 0.187, 0.144, 0.177, and 0.162 eV, respectively. These results were shown that the order of enhancement follows 3-amine Aspirin > 5-ribose Aspirin > 4-amide Aspirin > 3-acetate Aspirin. The energy barrier of the reaction of 3-amine Aspirin with Serine is -152.559 Hartree. The thermodynamic parameters of this reaction indicate that it is spontaneous and exothermic. The results have shown that the best Aspirin derivative is 3-amine Aspirin.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript. No human studies are present in the manuscript. No potentially identified images or data are present in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

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Authors' Contribution Statement

H.T. M. wrote a part of the manuscript and ran a section of the work on her computer. A. M. K wrote another part of the manuscript and publishing the research. H. M. A. worked on performing a section of the calculations on his computer. A.A. D. worked to explain some of the results. W. K. A. worked on interpreting some of the results.

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دراسة الفعالية الكيميائية للأسبرين باستخدام نظرية الدالة الوظيفية للكثافة: تاثير المجاميع المعوضة

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الخلاصة

يوجد دليل قوي على أن عمليات التخثر والالتهابات لها دورا في شدة الإصابة بفيروس كورونا. يمكن تخفيف تأثير الفيروس عن طريق استخدام بعض الأدوية الشائعة (مثل الأسبرين) التي تعمل على كبح هذه العمليات الضارة. تم اقتراح مشتقات جديدة للأسبرين بواسطة تعويض مجاميع الخلات والأمين والأميد والريبوز في المواقع 2 و 3 و 4 و 5 في حلقة البنزين. استخدمت نظرية الدالة الوظيفية للكثافة (DFT) B3LYP / (6–31G) لتقدير خصائصها النشطة وفعاليتها الكيميائية. أظهرت النتائج بان فجوة الطاقة للأسبرين تساوي 0.199 إلكترون فولت، بينما لمشتقات 3- خلات الأسبرين و 3- أمين الأسبرين و 4- أميد الأسبرين و 5- ريبوز الأسبرين لها فجوات طاقة اقل وكانت تساوي 0.187 و 0.144 و0.177 و 0.162 إلكترون فولت على التوالي. تم حساب المعاملات العالمية مثل الكهروسلبية (χ) والجهد الكيميائي (μ) والصلابة (η) ومؤشر الالفة للالكترونات (ω) و جهد التأين (I) والألفة الالكترونية (A) للأسبرين وكانت تساوي 0.166- و 0.166 و 0.098 و 0.140- و 0.265 و 0.068 بينما للأسبرين 3- أمين يساوي 0.130- و 0.130 و 0.072 و 0.117- و 0.202 و 0.058 على التوالي. من ناحية أخرى ، فإن حواجز الطاقة لتفاعلات الأسبرين و 3- أمين الأسبرين مع السيرين هي 39.286- و 152.559- هاتري. تشير هذه النتائج إلى أن 3- أمين الأسبرين أكثر نشاطًا من الأسبرين. أن هذه النتائج تفتح الطريق لتطوير دواء فعال جديد لمضادات الالتهابات وأمراض القلب والأوعية الدموية.

الكلمات المفتاحية: الاسبرين, الفعالية الكيميائية, نظرية الدالة الوظيفية للكثافة, المعاملات العالمية, سيرين.