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A Theoretical Study of the Docking of Medicines with some Proteins

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Abstract:

A set of ten drug compounds containing an amino group in the structure were determined theoretically. The parameters were entered into a model to forecast the optimal values of practical (log P) medicinal molecules. The drugs were evaluated theoretically using different types of calculations which are AM1, PM3, and Hartree Fock at the basis set (HF/STO-3G). The Physico-chemical data like (entropy, total energy, Gibbs Free Energy,…etc were computed and played an important role in the predictions of the practical lipophilicity values. Besides, Eigenvalues named HOMO and LUMO were determined. Linearity was shown when correlated between the experimental data with the evaluated physical properties. The statistical analysis was used to analyze the descriptors like multiple linear regression analysis performed to derive quantitative structure-activity relationship models which were further evaluated for the values of the prediction. The correlation coefficient gives an excellent relationship of more than (0.980, 0.980, and 0.978) for AM1, PM3, and HF/STO-3G respectively. A docking study was applied for the interaction of medicines with protein. All the drugs were connected with the protein to give the best energy stability for the docking mixtures. Nepafenac (compound No. 8) had the most stable energy with the protein compared with the 4-Aminosalicylic acid (compound No. 2) which had less energy stability.

Keywords: Amino drugs, Computational, HOMO, Lipophilicity, LUMO.

Introduction:

Lipophilicity term is obtained by the partition and distribution between an aqueous solvent (water) and an immiscible organic solvent like octanol-water membrane which is used widely as a measurement in the drug compound activity[1]. The discovery of pharmaceutical actions and biological activity depends on lipophilicity[2]. The theoretical quantum chemistry[3] especially quantitative structure-activity relationships analysis (QSAR) and (QSPR) [4] were applied to predict these values in the drugs[5,6]. Besides, many derivatives of chalcone and flavones have been predicted experimentally and theoretically to calculate the logP[7]. The chromatographic technique[8] was applied to calculate the logP and for different kinds of profen medicines[9]. The statistical methods of a simple linear regression did not give an excellent correlation compared to the multiple linear regression which found an excellent relationship between the experimental and the calculated descriptors[10].

Quantum method calculations were carried out using Hartree-Fock (HF) at 6-31G as a basis set for aryl-thiazole derivatives. Dipole moment, HOMO, LUMO heat of formation, and logP have been determined theoretically. There is a relationship between the predicted lipophilicity with their activity[11]. Furthermore, quantitative structural relationships for modeling the lipophilicity of platinum complexes and predicting their Log P values have been developed [12]. There are many methods to calculate and measure the lipophilicity of the HPLC[13], the extraction of liquid-liquid[14], and chromatographic technique[15]. A theoretical study of docking for (6YHU) was determined with the coumarin group as a treatment for the COVID-19 [16].

In a previous study, many drug compounds containing amino groups were calculated at semi-empirical and ab initio levels [17]. Finally, theoretical calculations were applied widely in chemistry like corrosion protection[18, 19]. The docking study [20-22] of (twenty-three) molecules with QRF3a SARS-CoV2 was studied using molecular docking. Using in

silico modeling, researchers were able to discover leading compounds with potential inhibitory and virucidal properties[23]. Utilizing DockThor and Molegro docking scores, bioinformatics analysis was conducted using docking techniques and molecular dynamics to predict the binding and disruption caused by the ivermectin in proteins linked with SARS-CoV-2 [24]. It was investigated how human serum albumin (HSA) interacts with two physiologically active derivatives (FNP and FNP4Br). Hydrogen bonding and electrostatic interactions (dipole-dipole) are the predominant binding factors for the associations between HSA: FNP and HSA:FNP4Br, according to thermodynamic characteristics and molecular docking data [25]. The most promising two ligand-pocket complexes from docking experiments (alacepril and lisinopril) also had molecular dynamics (MD) simulations followed by binding free energy calculations to clarify some information on their thermodynamic and dynamic features and corroborate the docking results. These findings most likely presented a good lead candidate for the development of COVID-19 medicinal medicines [26].

Chem Bio Office (version 11.0.1) software was applied for the descriptor's computational parameters. The MM2 force field method was used first to convert the structures to more stability and less steric energy. Later, (Gaussian 03W) [27] package is used to evaluate the Physico-chemical properties. Many data of thermodynamic values were calculated depending on the output file .

The goal of molecular docking is to use computational methods to anticipate the structure of the ligand-receptor complex. Docking is accomplished in two steps: first, sampling ligand conformations in the active site of the protein, and then rating these conformations using a scoring function.

The package of (MOE) [28] software (ver. 2015) was used for studying the docking between the medicines with (6YHU) protein. They were imported into MOE, and the MOE structure preparation wizard was used to fix all the problems with the protein structures. All solvent molecules were removed from the structures before the hydrogen atoms were added, and the structures were subsequently subjected to energy minimization. In the working directory, the final optimized structures were stored.

The aim of this study is the medications were theoretically assessed using several forms of computations. Thermodynamic parameters were calculated and had a significant impact in predicting realistic lipophilicity values. For the interaction of medications with proteins, docking research was used. All of the pharmaceuticals were attached to the protein to provide the best energy stability for the docking mixes.

Results and Discussion:

Ten drug compounds were applied in this study as shown in their name and log P data in Table. 1. Semi-empirical (AM1 and PM3) and ab initio methods (HF/STO-3G) were chosen to calculate the physical properties of these drugs. These parameters were analyzed using statistical equations depending on the simple and multiple linear regression. The last regression was used to find the correlation and relationship between the evaluated physical properties with the practical lipophilicity. Many models of the correlation were analyzed to choose the best equation to depend on the coefficient (R) and values of Fisher (F) to predict the values and compare with the experimental parameters .

Set of Data :

Table. 1 shows the values of the physical properties of the ten drugs using three methods of calculation. Also, we can notice the practical parameters of (logP) [29] for all the drug compounds. The steric energy effect was shown clearly for the drugs, the steric effect had little for the small configuration compared to the bulk compound which has a big value. The thiazole derivatives had more steric compared to the others .

Table 1. Set Three, the experimental* and the theoretical data are for Set three using methods AM1, (PM3), and [HF/STO-3G].

Drugs	Steric Energy	Log P*	HOMO	LUMO	Zero-point Energies	Thermal Energies	Enthalpies	Free Energies
			Hartree	Hartree	Hartree	Hartree	Hartree	Hartree
Aminoglutethimide	4.61	1.41	-0.32009 (-0.32430) [-0.24183]	0.00724 (-0.00124) [0.26214]	0.28173 (0.27226) [0.32167]	0.29697 (0.28810) [0.33611]	0.29792 (0.28904) [0.33706]	0.23883 (0.22888) [0.27925]
4-Aminosalicylic acid	1.10	0.32	-0.32308 (-0.32872) [-0.24228]	-0.00382 (-0.00555) [0.22357]	0.13948 (0.13741) [0.15587]	0.14898 (0.14762) [0.16495]	0.14992 (0.14856) [0.16590]	0.10397 (0.10091) [0.12079]
Dapsone	180.14	0.94	-0.32658 (-0.33172) [-0.25438]	-0.00935 (-0.01448) [0.23552]	0.22910 (0.22139) [0.25254]	0.24430 (0.23707) [0.26778]	0.24524 (0.23802) [0.26873]	0.18495 (0.17591) [0.20781]
Felbamate	-9.02	1.2	-0.35387 (-0.36005) [-0.28002]	0.01055 (0.00350) [0.25963]	0.25335 (0.24356) [0.28755]	0.27074 (0.26101) [0.30339]	0.27169 (0.26196) [0.30433]	0.20332 (0.19408) [0.24027]
Hydroflumethiazide	377.08	0.54	-0.36394 (-0.36569) [-0.28679]	-0.04956 (-0.05866) [0.18368]	0.18640 (0.17675) [0.19775]	0.20469 (0.19596) [0.21775]	0.20563 (0.19690) [0.21869]	0.13911 (0.12872) [0.14846]
Methazolamide	197.91	0.13	-0.34894 (-0.34688) [-0.25108]	-0.04055 (-0.04549) [0.21910]	0.15327 (0.14599) [0.16988]	0.16812 (0.16223) [0.18599]	0.16906 (0.16317) [0.18693]	0.10923 (0.09954) [0.12401]
Modafinil	0.44	1.4	-0.34618 (-0.34653) [-0.25077]	-0.00619 (-0.02229) [0.22672]	0.27531 (0.26539) [0.31228]	0.29237 (0.28316) [0.32775]	0.29331 (0.28410) [0.32870]	0.22814 (0.21732) [0.26565]
Nepafenac	23.97	1.17	-0.31604 (-0.33024) [-0.25202]	-0.01704 (-0.01823) [0.20424]	0.27065 (0.26229) [0.30325]	0.28732 (0.27925) [0.31877]	0.28827 (0.28019) [0.31971]	0.22397 (0.21427) [0.25769]
Oxcarbazepine	8.91	1.25	-0.33894 (-0.34508) [-0.25308]	-0.02299 (-0.02344) [0.20753]	0.24982 (0.24017) [0.27864]	0.26450 (0.25548) [0.29216]	0.26545 (0.25642) [0.29310]	0.20703 (0.19671) [0.23753]
Trichlormethiazide	374.47	0.57	-0.36487 (-0.36263) [-0.29343]	-0.04367 (-0.04799) [0.17684]	0.18102 (0.16956) [0.19266]	0.20016 (0.19030) [0.21381]	0.20111 (0.19124) [0.21476]	0.13132 (0.11744) [0.14050]

Table 1. Continue …

Drugs	E Thermal	CV	S	HF	Molar Refractivity#	Partition Coefficient#
	KCal/Mol	Cal/ Mol-K	Cal/ Mol-K	Hartree		
Aminoglutethimide	186.35 (180.78) [210.91]	58.93 (61.41) [54.57]	124.37 (126.61) [121.66]	-0.10579 (-0.11584) [-750.77]	6.5666	0.7660
4-Aminosalicylic acid	93.48 (92.63) [103.50]	35.36 (37.81) [34.32]	96.71 (100.30) [94.93]	-0.17888 (-0.17888) [-541.14]	3.8630	1.0562
Dapsone	153.30 (148.77) [168.03]	58.82 (60.46) [56.74]	126.89 (130.72) [128.20]	-0.02763 (-0.02046) [-1103.87]	6.8097	0.8860
Felbamate	169.89 (163.79) [190.37]	61.35 (62.75) [55.74]	143.89 (142.85) [134.84]	-0.24218 (-0.23191) [-822.46]	6.1226	0.4970
Hydroflumethiazide	128.44 (122.96) [136.63]	68.22 (72.17) [70.94]	140.01 (143.50) [147.81]	-0.38921 (-0.38905) [-1840.38]	6.3364	-0.2100
Methazolamide	105.50 (101.80) [116.71]	52.23 (55.88) [53.36]	125.93 (133.93) [132.44]	-0.03882 (-0.05983) [-1414.20]	5.4165	0.0880
Modafinil	183.46 (177.69) [205.66]	65.01 (67.54) [57.65]	137.16 (140.57) [132.70]	-0.03551 (-0.01820) [-1164.26]	7.8350	0.9370
Nepafenac	180.30 (175.23) [200.02]	63.38 (64.54) [58.07]	135.32 (138.74) [130.54]	-0.04597 (-0.04703) [-824.34]	7.4000	1.3850
Oxcarbazepine	165.98 (160.32) [183.33]	57.88 (60.30) [53.12]	122.96 (125.68) [116.96]	0.00642 (-0.02398) [-823.20]	7.2226	1.2061
Trichlormethiazide	125.61 (119.41) [134.17]	70.46 (75.56) [73.33]	146.89 (155.32) [156.30]	-0.18639 (-0.18244) [-2909.99]	7.7641	0.8803

*** = Experimental**
 # = Used for all Compounds

Depending on the calculated values, Tables. 2-4, show the binary correlation between all the data. for the (AM1, PM3, and HF/STO-3G) methods, the best relationship happened between the logP with (Z.P.E, T.E, Enth., F.E and E) values.

Table 2. Binary correlations between parameters using (AM1)

	S.E	LogP	M.R.	P.C	HOMO	LUMO	Z.P.E	T.E	$E_{nth.}$	F.E	E	CV	S	HF
S.E	1													
LogP	-0.58	1												
M.R	0.143	0.61	1											
P.C	-0.57	0.48	0.28	1										
HOMO	-0.65	0.31	-0.19	0.63	1									
LUMO	-0.84	0.61	-0.14	0.43	0.58	1								
Z.P.E	-0.53	0.97	0.65	0.41	0.327	0.551	1							
T.E	-0.5	0.97	0.68	0.38	0.29	0.523	0.99	1						
Enth.	-0.5	0.97	0.68	0.38	0.29	0.523	0.99	1	1					
F.E	-0.58	0.98	0.61	0.44	0.386	0.585	0.99	0.99	0.99	1				
E	-0.5	0.97	0.68	0.38	0.29	0.523	0.99	1	1	0.99	1			
CV	0.449	0.39	0.86	-0.16	-0.506	-0.33	0.46	0.50	0.50	0.40	0.50	1		
S	0.423	0.28	0.73	-0.27	-0.621	-0.282	0.36	0.40	0.40	0.29	0.40	0.93	1	
HF	-0.48	0.32	0.27	0.61	0.542	0.239	0.35	0.33	0.33	0.38	0.33	-0.18	-0.257	1

S.E: Steric Energy, M.R.= Molar Refractivity, P.C.= Partition coefficient, Z.P.E.= Zero Point Energy, T.E.= Thermal Energy
Enth.= Enthalpy, F.E. = Free Energy, E= Energy, S= Entropy, H.F= heat of formation

Table 3. Binary correlations between parameters using (PM3)

	S.E	LogP	M.R	P.C	HOMO	LUMO	Z.P.E	T.E	Enth.	F.E	E	CV	S	HF
S.E	1													
LogP	-0.58	1												
M.R	0.143	0.61	1											
P.C	-0.57	0.48	0.28	1										
HOMO	-0.59	0.23	-0.23	0.57	1									
LUMO	-0.85	0.55	-0.21	0.52	0.61	1								
Z.P.E	-0.56	0.97	0.63	0.42	0.27	0.514	1							
T.E	-0.52	0.97	0.66	0.40	0.23	0.477	0.99	1						
Enth.	-0.52	0.97	0.66	0.40	0.23	0.477	0.99	1	1					
F.E	-0.61	0.98	0.57	0.45	0.33	0.559	0.99	0.99	0.99	1				
E	-0.52	0.97	0.66	0.40	0.23	0.477	0.99	1	1	0.99	1			
CV	0.526	0.30	0.83	-0.21	-0.60	-0.50	0.34	0.38	0.38	0.27	0.38	1		
S	0.532	0.15	0.72	-0.28	-0.69	-0.49	0.21	0.26	0.26	0.13	0.26	0.93	1	
HF	-0.49	0.35	0.30	0.64	0.59	0.312	0.39	0.37	0.37	0.41	0.37	-0.19	-0.19	1

Table 4. Binary correlations between parameters using (HF/STO-3G)

	S.E	LogP	M.R	P.C	HOMO	LUMO	Z.P.E	T.E	Enth.	F.E	E	CV	S	HF
S.E	1													
LogP	-0.58	1												
M.R	0.143	0.61	1											
P.C	-0.57	0.48	0.28	1										
HOMO	-0.70	0.20	-0.28	0.44	1									
LUMO	-0.69	0.45	-0.25	0.07	0.49	1								
Z.P.E	-0.58	0.97	0.61	0.42	0.25	0.49	1							
T.E	-0.54	0.97	0.64	0.39	0.21	0.46	0.99	1						
Enth.	-0.54	0.97	0.64	0.39	0.21	0.46	0.99	1	1					
F.E	-0.63	0.97	0.56	0.45	0.31	0.52	0.99	0.99	0.99	1				
E	-0.54	0.97	0.64	0.39	0.21	0.46	0.99	1	1	0.99	1			
CV	0.725	0.07	0.70	-0.35	-0.77	-0.52	0.08	0.13	0.13	0.01	0.13	1		
S	0.718	-0.03	0.61	-0.44	-0.80	-0.45	0.00	0.05	0.05	-0.06	0.05	0.95	1	
HF	-0.88	0.39	-0.39	0.34	0.76	0.69	0.41	0.37	0.37	0.47	0.37	-0.8	-0.82	1

The SPSS software was used to analyse the physic-chemical values. Multiple linear regression was applied for the theoretical methods (PM3 and AM1) and Hartree-Fock method (HF/STO-3G):

logP = -3.758 + 0.001(S.E) – 11.158(HOMO) + 2.530(LUMO) + 29.468(F.E) – 0.028 (E) + 0.005 (C.V) – 0.094(M.R.) + 0.267(Part.Coeff.) ------ (AM1)
(No. 10, R= 1.00, St. Error =0.016, F=954.00)

logP = -1.305 - 0.001(S.E) – 4.834(HOMO) + 8.254(LUMO) + 3.701(F.E) + 0.028 (C.V) – 0.018(S) + 0.148(M.R.) – 0.083(Part.Coeff.) ------ (PM3)
(No. 10 , R= 1.00, St. Error = 0.006, F= 5951.61)

logP = -2.017 – 0.001(S.E) – 7.648(HOMO) + 2.949(LUMO) + 4.436(F.E) + 0.018 (C.V) – 0.021(S) + 0.171(M.R.) – 0.068(Part.Coeff.) ------ (HF/STO-3G)
(No. 10 , R= 0.998, St. Error = 0.088, F= 31.165)

While at using (stepwise) method, the equations were shown at the following:

logP = -0.685 + 8.916 (FreeEne) ------ (AM1)
(No. 10, R= 0.980, St. Error = 0.097, F= 197.98)

logP = -0.618 + 9.027 (FreeEne) ------ (PM3)
(No.10, R= 980, St. Error = 0.099, F= 189.58)

logP = -0.584 + 7.304(FreeEne) ------ (HF/STO-3G)
(No.10, R= 0.978, St. Error = 0.103, F= 174.16)

So, the relationship between the practical and the predicted shows an excellent correlation expected for the ten medicines found (R=0.9802) to all. Table. 5 and Fig. 1 show the predicted values of (logP) for the ten medicine mistreatment stepwise equation.

Table 5. Experimental and predicted logP using all methods.

No	Drugs		AM1		PM3		HF/STO-3G	
		Log P (Pract.)	Log P (Predicted)	Residuals	Log P (Predicted)	Residuals	Log P (Predicted)	Residuals
1	Amino-glutethimide	1.41	1.44	0.03	1.45	0.04	1.46	0.05
2	4-Amino-salicylic acid	0.32	0.24	-0.08	0.29	-0.03	0.30	-0.02
3	Dapsone	0.94	0.96	0.02	0.97	0.03	0.93	-0.01
4	Felbamate	1.2	1.13	-0.07	1.13	-0.07	1.17	-0.03
5	Hydro-flumethiazide	0.54	0.56	0.02	0.54	0.00	0.50	-0.04
6	Methazolamide	0.13	0.29	0.16	0.28	0.15	0.32	0.19
7	Modafinil	1.4	1.35	-0.05	1.34	-0.06	1.36	-0.04
8	Nepafenac	1.17	1.31	0.14	1.32	0.15	1.30	0.13
9	Oxcarbazepine	1.25	1.16	-0.09	1.16	-0.09	1.15	-0.10
10	Trichlor-methiazide	0.57	0.49	-0.08	0.44	-0.13	0.44	-0.13
	R		0.9806		0.9789		0.9776	
	Fisher Value		201.0		183.95		172.6	

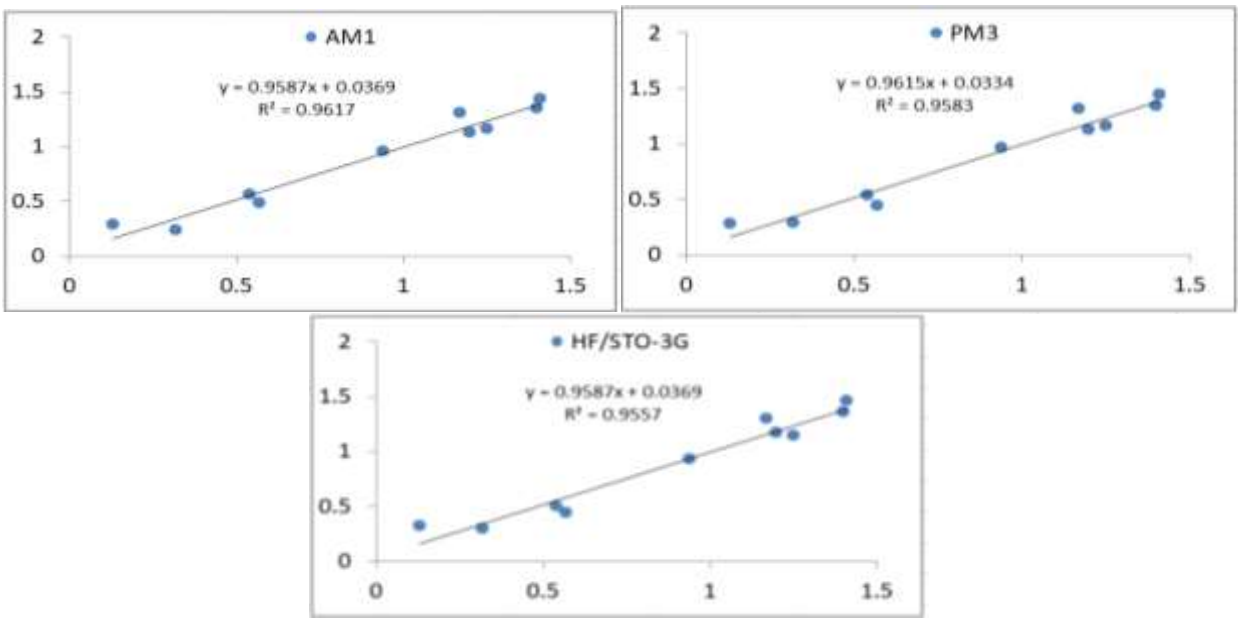

Figure 1. The relationship between the practical and the experimental values at AM1, PM3, and HF/STO-3G.

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Docking Drugs with protein (6YHU):

All the drugs were docking with the protein named (6YHU). There is a difference in the stability between the medicines and the protein. Drug number (8) is more stable compared to drug number (2) having less stability with the protein as shown in Fig. 2 and table. 6.

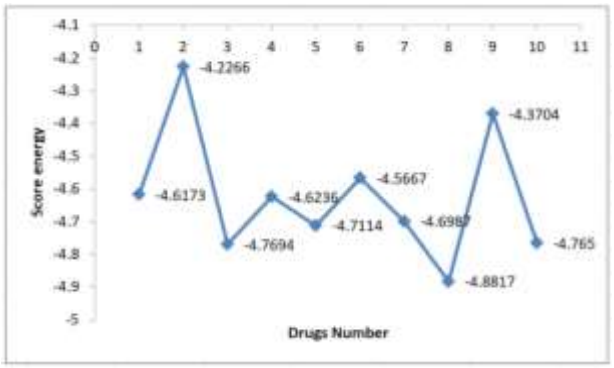


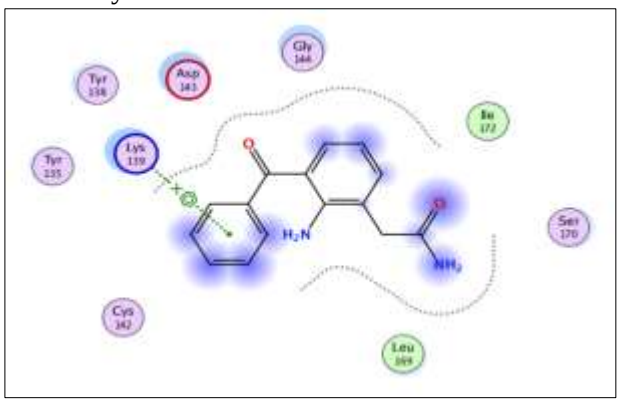
Figure 2. Comparison between the medicines with their stability.

The following Table explains the energy of the docking between all medicines with the protein (6YHU).

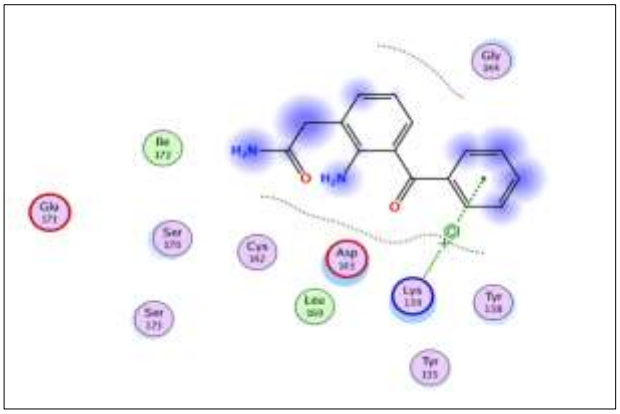
Table 6. The E-Score and E-conformation of the docking.

Drug	E-Score	E-Conformation
1	-4.6173	-38.7766
2	-4.2266	-45.1731
3	-4.6236	36.6248
4	-4.6236	-146.6781
5	-4.7114	-142.4855
6	-4.5667	19.2492
7	-4.6987	-16.1746
8	-4.8817	-11.6307
9	-4.3704	-49.6365
10	-4.7650	-129.0901

Also, Figs. 3, 4, 5, and 6 show the docking of the medicine with the protein which has the docking with many amino acids in different directions.



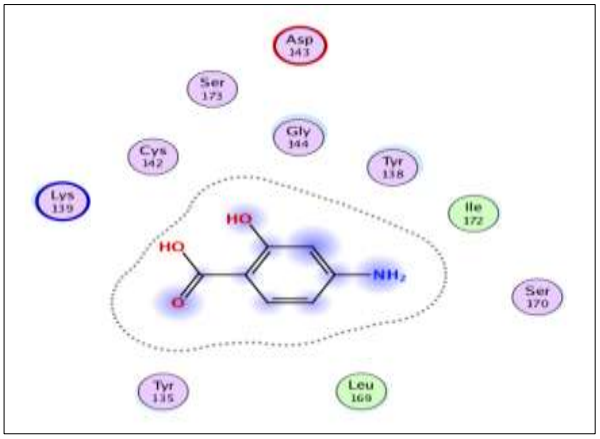
[More stable]



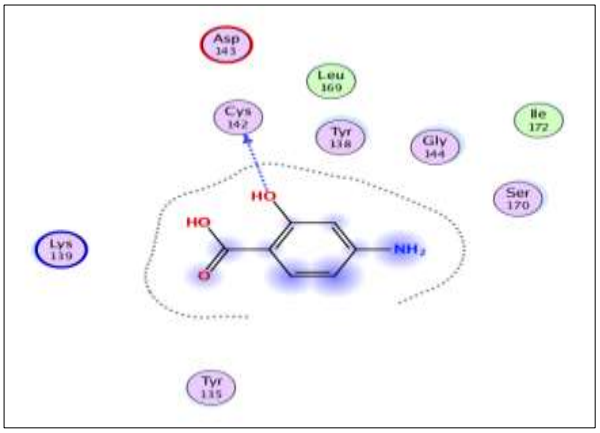
[Less stable]

Figure 3. More and less stable for medicine (8) with protein (6YHU)

It was shown that the medicine in the benzene ring was attached with (Lys139) having this amino acid with different active groups like (-NH2), (-OH), and (-C=O). These groups were docking with medicine and had more stability. While a less stable state, the configuration was different compared with its configuration at more stable.



[More stable]



[Less stable]

Figure 4. More and less stable for medicine (2) with protein (6YHU)

Also, it was shown that the medicine for the (-OH) group in the benzene ring was attached with (Cys 142) having this amino acid with different active groups. These groups were docking with medicine and were very close to the medicine and the steric effect is compared to the more stable.

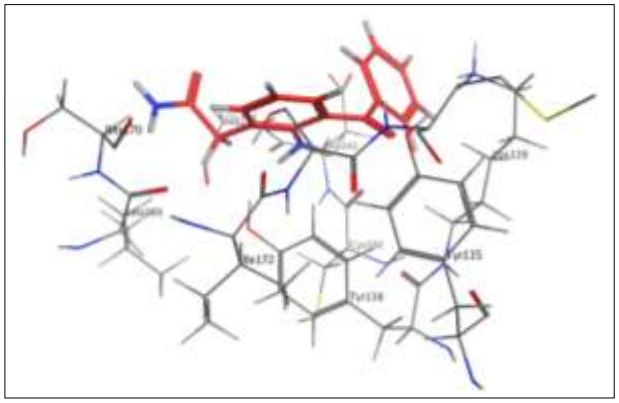


Figure 5. The 3D structure of more stable for medicine (8) with protein (6YHU)

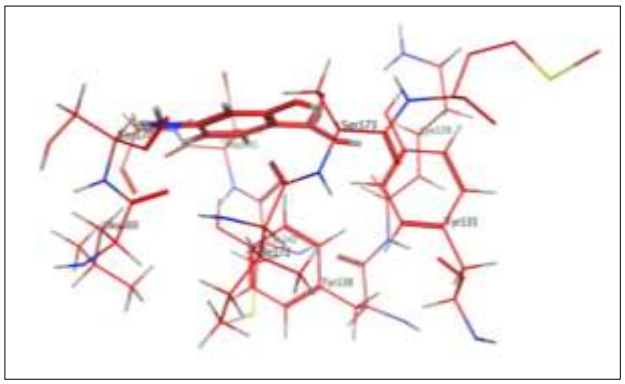


Figure 6. The 3D structure of more stable for medicine (2) with protein (6YHU)

Conclusion:

Computational quantum and statistical approaches calculate docking in greater depth using various descriptors, resulting in a broad interpretation of medical effects. The prediction of the log P values is determined by three different methods of calculation. These methods give an excellent correlation between the practical values with the experimental. But (AM1) method gives the best relationship compared with (PM3) and (HF/STO-3G) depending on the Fisher values.

Some drugs have been explored using a theoretical technique and molecular docking calculations due to their high efficacy in the treatment of the COVID-19 pandemic. These medications and protein molecular structures have been optimized.

The docking analysis has found that the medicine number (8) has more stability with the protein (6YHU) compared with the medicine (2). The reason may depend on the fact that the medicine contains (8) two amino groups (-NH2) and two carbonyls (C=O) compared to the medicine (2) which has two hydroxyl groups (-OH) and one amino group (-NH2) and one carbonyl (C=O). So, the ion pair is more effective in medicine (8) rather than in medicine (2). This means that the interaction between the amino group (-NH2) with the amino acid in the surrounding is more stable compared with the hydroxyl group (-OH) [30].

Author's declaration:

- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine, 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 Mosul.

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دراسة نظرية لترابط الادوية مع عدد من البروتينات

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قسم الكيمياء، كلية العلوم، جامعة الموصل، الموصل، العراق.

الخلاصة:

دراسة نظرية لمجموعة مكونة من عشرة مركبات عقاقير تحتوي في التركيب الكيميائي على مجموعة أمينية. تم إدخال البيانات كنموذج للتنبؤ بأفضل قيم عملية محسوبة سابقا (log P). تم حساب قيم هذه الأدوية نظريًا باستخدام أنواع مختلفة من الحسابات وهي AM1 و PM3 و Hartree Fock بالاعتماد على قاعدة الاساس (HF / STO-3G). تم حساب البيانات الفيزيائية والكيميائية مثل (الانتروبي ، الطاقة الكلية ، طاقة جيبس الحرة ، ... إلخ) والتي تلعب دورًا مهمًا في تنبؤ القيم العملية. إلى جانب ذلك ، تم ايجاد القيم HOMO و LUMO. تم ايجاد العلاقة الخطية ومعامل الارتباط بينهما من خلال استخدام البيانات التجريبية مع الخصائص الفيزيائية المحسوبة نظريا، واستخدم التحليل الإحصائي لتحليل البيانات مثل تحليل الانحدار الخطي المتعدد لاشتقاق نماذج العلاقة الكمية بينهم والتي تم تقييمها بشكل أكبر لحساب القيم . وجد انه هناك علاقة خطية ومعامل ارتباط أكثر من (0.980 ، 0.980 ، 0.978) لـ AM1، PM3، HF / STO-3G على التوالي. تم تطبيق دراسة التداخل لتفاعل الأدوية مع البروتين ، تم ربط جميع الأدوية بالبروتين لإعطاء أفضل طاقة لاستقرارهما. كان نيبافيناك (المركب رقم 8) يمتلك الطاقة الأكثر استقرارًا مع البروتين مقارنة بـ 4. حمض أمينوساليسيليك (المركب رقم 2) الذي يتمتع باستقرار أقل للطاقة.

الكلمات المفتاحية: ادوية الحاوية على مركب الامين، اعلى اوربيتال جزيئي مشغول، اللايبوفيليسيتي، اوطا اوربيتال جزيئي غير مشغول.