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IN-SILICO STUDY ON SOME VIRAL NEURAMINIDASE INHIBITORS (NAIS)

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ABSTRACT

The drug of first choice in treatment of epidemic disease specially - todays that is COVID19 is Emergency, so this study concerned on study the interaction of some antiviral, antimalarial and antibiotics with neuraminidase enzyme that is responsible on viral reproduction by budding from the host cell and spreading viral disease. A simulation study was done in this research using molecular operating environment (MOE) software for mimic the biological activity of the studied drugs and viral neuraminidase enzyme and computational analysis was done. Quantitative structure activity relationship QSAR study for the interaction of the studied ligands with the mentioned enzyme was carried out, evaluated and validated. QSAR revealed the most effective factors in the interaction of the enzyme and the studied drugs that include the molecular descriptors; topological polar surface area TPSA and number of H- bond acceptor atoms (a-acc). The QSAR was Evaluated and validated using MOE. This study showed the probability of using the studied drugs as Anti- COVID19 remedies.

KEYWORDS: Anti-COVID19, chloroquine, hydroxychloroquine, zanamivir, viral neuraminidase inhibitors.

1. INTRODUCTION

Corona virus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness.[1] Some western, traditional or home remedies may provide comfort and alleviate

symptoms of COVID-19, there is no evidence that current medicine can prevent or cure the disease. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. However, there are several ongoing clinical trials that include both western and traditional medicines. WHO will continue to provide updated information as soon as clinical findings are available.[2] The main difference between bacteria and virus is that bacteria are living cells, reproducing independently and viruses are nonliving particles, requiring a host cell for their replication.[3] Elecctron micrographs of negative stained COVID19 were generally spherical with some pleomorphism. Diameter varied from about 60-140nm and distinctive spikes about 9-12nm and gave virions the appearance of a solar corona[4] and can be prevented from breathing by masks. There is a potential need for testing several antiviral, antibiotics and antimalarial drugs for clinical treatment of this serious disease either by simulation or by clinical trials. This simulation research was done for guess the pharmacological action of some antiviral, antimalarial and antibacterial drugs against this diseases by simulation of these drugs interaction with viral neuraminidase enzyme (inhibiting NA enzyme that is responsible on reproduction of the virus by budding from the host cell and inhibition of spreading viral disease[5]) and testing the probability of using these drugs in treatment of COVID19 disease. The studied drugs (see Fig.1 and Fig. 2) were: antiviral drugs; oseltamivir ((1E) – N -[(1R,2R,6S) – 6 – Amino – 4 -(ethoxycarbonyl) -2- (3-pentanyloxy) -3-cyclohexen-1-yl]ethanimidic acid), peramivir ((1S,2S,3R,4R) -3- (1-Acetamido-2-ethylbutyl) -4-carbamimidamido-2-hydroxycyclopentanecarboxylic acid), Zanamivir ((6R) -5-Acetamido-2,6-anhydro-4-carbamimidamido-3,4,5-trideoxy-6- [(1R,2R)-1,2,3-trihydroxypropyl] -L-threo- hex-2- enonic acid; neuraminidase inhibitors), Antimalarial drugs: chloroquine (N^4-(7-Chloro-4-quinolinyl)-N^1, N^1-diethyl-1,4-pentanediamine) and hydroxychloroquine (2-[{4-[(7-Chloro-4-quinolinyl)amino] pentyl} (ethyl)amino] ethanol; antagonists of certain preformed prostaglandins and accumulate in lysosomes) and the antibiotic: azithromycin ((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R) – 2 - Ethyl-3,4,10 - trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-11- {[3,4,6-trideoxy-3- (dimethylamino) -β-D-xylo-hexopyranosyl] oxy}-1-oxa-6- azacyclopentadecan-13-yl 2,6-dideoxy-3- C-methyl-3- O-methyl -α-L-ribo-hexopyranoside; inhibition of bacteria by interfering with programmed ribosomal protein biosynthesis.[6] Neuraminidase inhibitors like; Oseltamivir, peramivir and zanamivir prevent the role played by the surface glycoproteins hemagglutinin, an enzyme that is important for viral binding to host cell receptors via a terminal sialic acid residue and also inhibit neuraminidase NA (an enzyme that is involved in various aspects of activation of influenza

viruses and is found in both influenza A and B viruses ,also it is thought to be involved in catalytically cleaving glycosidic bonds between terminal sialic acid residues and adjacent sugars on hemagglutinin). The cleavage of sialic acid bonds facilitates the spread of viruses by Enhancing Adsorption to cell surface receptors and, thus increases the infective level of the virus. Since neuraminidase also appears to play a role in preventing viral inactivation by respiratory mucus and responsible on viral reproduction by budding from the host cell, so the neuroaminidase inhibitors NAIs prevent viral activation and block the function of viral neuraminidase of the influenza virus.[5,6]

2. METHOD

Modeling and Docking studies were carried out on Dell Precision™ T3600 Workstation [Intel Xeon E5-1660 3.3 GHz, 16 GB 1600 MHz DDR3, ECC RDIMM 1 TB (7200 RPM), 1 GB NVIDIA Quadro 2000, Windows 7 Professional (64 bit)]. Molecular Operating Environment (2011) package version 2011.10 was used for performing studies.

2.1. Docking procedure

Preparing the receptor (viral neuraminidase enzyme[7]) for docking after selecting it's structure (crystal structure) from the saved database (line mode of the structure). Protonate the 3D structure of the receptor. Then selecting the ligand (each drug) for docking process (ball and stick mode of structure). After that energy minimizing of the drug. Finally carrying out simulated docking (bee ensure that ligand inside the receptor structure). Click OK to start docking (see Fig.3). When the docking is finished, the docked poses and scores will be written to the 'dock.mdb' output database. The docking results will appear in a DBV window (dock.mdb). See in the S field that the docking poses are ranked by the MM/GBVI binding free energy calculation which is identical to the E_refine score.

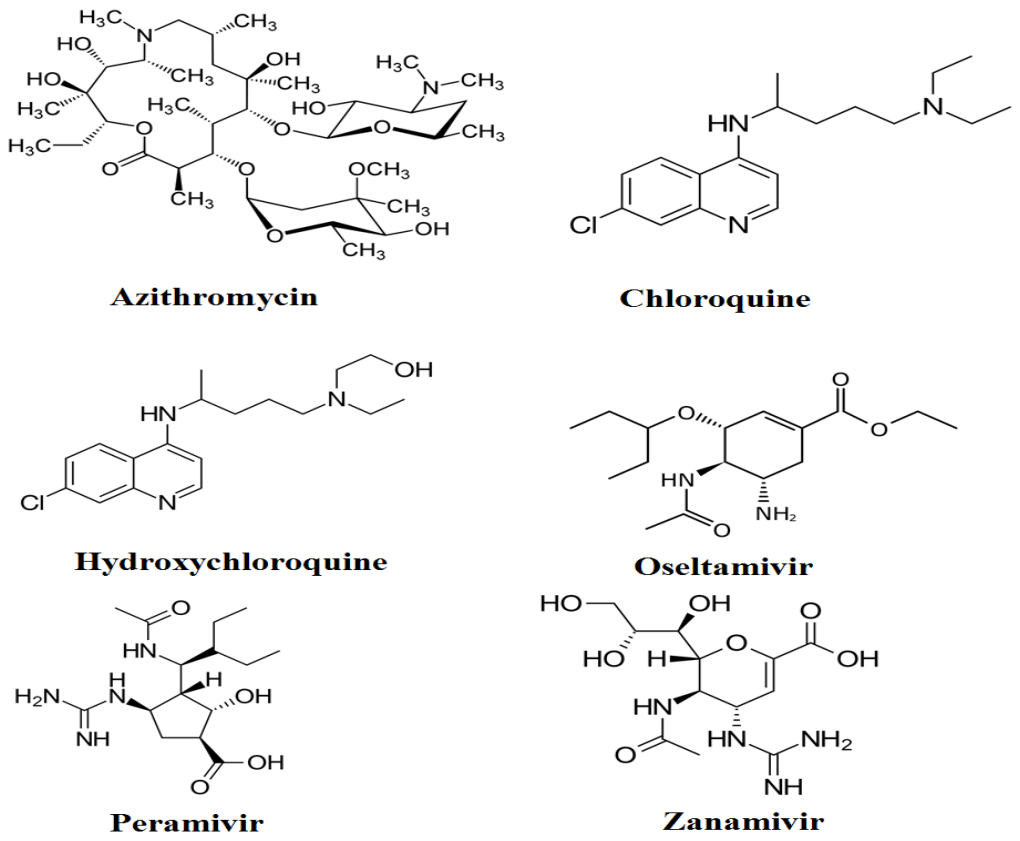

Figure 1: 2D Chemical structures of the studied drugs.

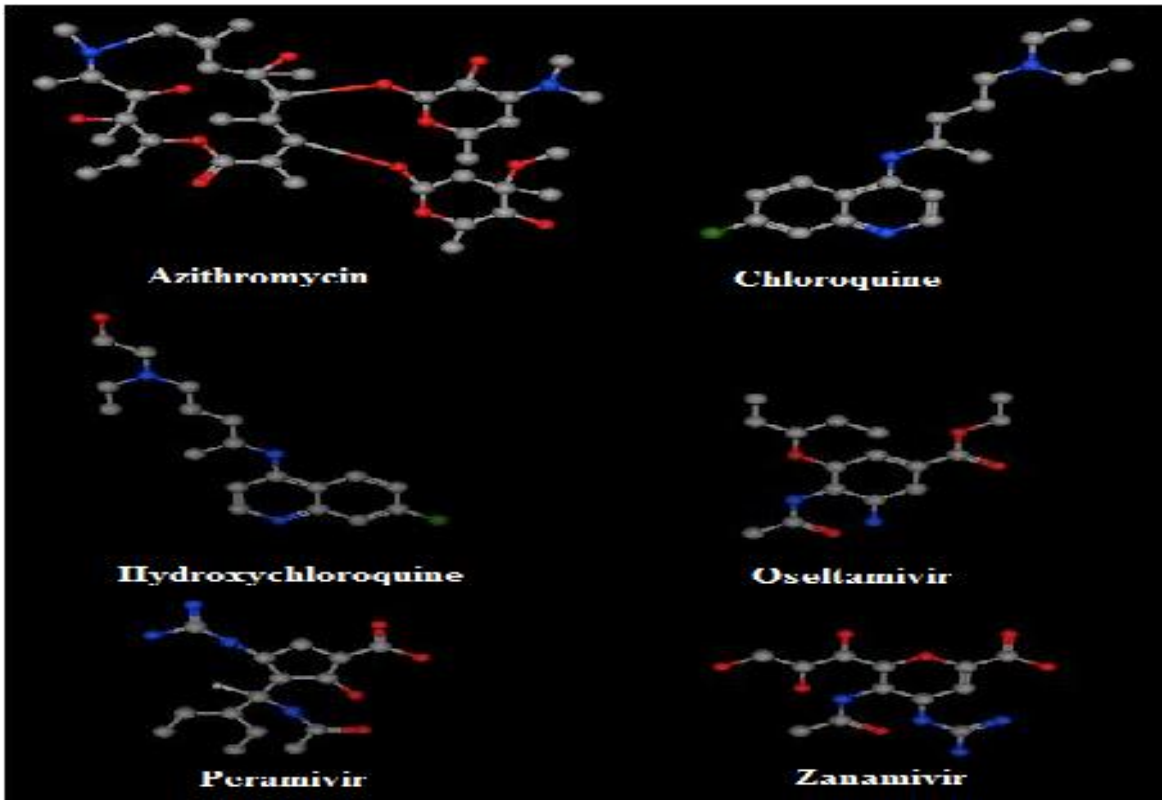

Figure 2: 3D structures of the studied drugs obtained by molecular operating environment (MOE) software.

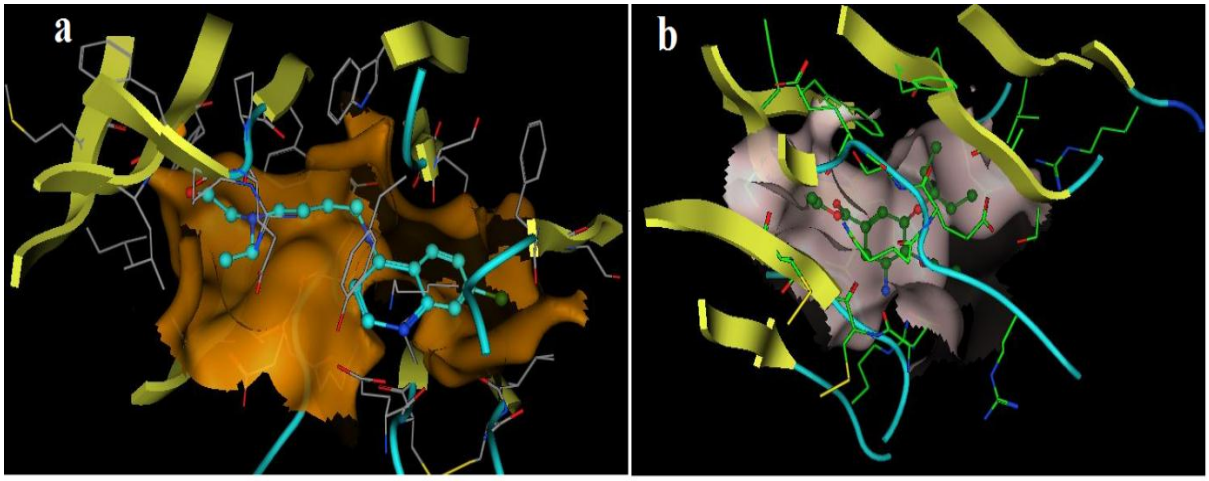

Figure 3: 3D graphs for docking of (a) hydroxychloroquine and (b) oseltamivir with viral neuraminidase (receptor) using MOE.

2.2. LigX procedure

LigX Method is a suite of MOE features for exploring protein-ligand interactions and for manually constructing novel compounds in protein binding sites. Novel compounds can be energy minimized inside the binding site and evaluated by for binding free energy and affinity calculations. It was used for prediction the interaction of the studied drugs with the studied receptor. This method was taken place by preparing the enzyme and the ligands and study the interaction between them. First the enzyme prepared as line form and the ligand as ball and stick, then choose ligX, After that the interacted substances, 3D protonated and tethered and energy minimized. Finally interaction between the ligand and the receptor was carried out.

3. RESULTS

The simulation study was done using molecular operating environment software MOE. After preparation of ligands (studied drugs) and the receptor (the mentioned enzyme) and using two methods; ligand -receptor docking and ligX method. The results of the interaction; the sites of binding ,type of the binding and the percentage of binding (S), as shown in Table 1. In order to understand the mechanism of the interaction between the ligands and the mentioned enzyme some 2D descriptors; octanol–water partition coefficient [logP(o/w)], number of H-bond donor atoms (a-don), number of H- bond acceptor atoms (a-acc), molar refractivity (Mr) ,topological polar surface area (TPSA) and number of rings and 3D descriptor was Van der Waals energy (E-vdw) were investigated for this purpose and calculated by MOE software and the results were obtained as in Table 2.

Table 1: Type of interaction sites of the studied drugs with the studied receptor and their scores S% using MOE software.

Drug	Type	Residue[c]	S%
Azithromycin	H-don[a]	SER	67.6
	H-don	VAL	34.8
	H-don	GLY	23.7
	H-don	TYR	13.5
	H-don	TRP	37.8
	H-acc[b]	SER	67.6
	H-acc	GLU	31.5
	H-acc	ARG	18.3
	H-acc	LYS	33.9
	H-acc	GLY	26.0
	H-acc	GLY	19.2
	H-acc	SER	20.5
	H-acc	SER	18.6
	H-acc	GLU	55.8
Chloroquine	H-don	PRO	16.5
	H-acc	LYS	11.0
Hydroxychloroquine	H-don	THR	86.5
	H-don	LEU	37.9
Oseltamivir	H-don	THR	13.0
	H-don	GLU	13.6
	H-acc	GLY	24.7
Peramivir	H-don	GLN	28.4
	H-don	GLU	32.4
	H-don	SER	66.8
	H-don	SER	64.6
	H-don	CYS	13.9
	H-don	LYS	22.2
	H-don	LYS	21.7
	H-acc	SER	66.8
Zanamivir	H-don	ALA	40.8
	H-don	GLN	27.6
	H-don	GLN	14.4
	H-don	SER	10.2
	H-don	GLU	10.8
	H-don	GLU	14.4
	H-don	SER	71.7
	H-don	VAL	14.3\
	H-don	GLY	13.0
	H-acc	GLN	55.0
	H-acc	GLU	23.1
	H-acc	SER	38.6
	H-acc	LYS	30.3
	H-acc	LYS	25.5
	H-acc	SER	80.6

[a] H-don is hydrogen bond donor atoms, [b] H-acc hydrogen bond acceptor atoms, [c] Residue of the enzyme amino acid interacted with ligand.

Table 2: Some 2D and 3D molecular descriptors for the studied drugs docked with viral neuraminidase receptor calculated using MOE software.

Drug	S[a]	a-acc[b]	a-don[c]	E-vdw[d]	TPSA[e]	log P(o/w)[f]	Mr[g]	rings
Azithromycin	-10.75	11.0	5.0	13868.8	182.5	3.4	19.5	3.0
Chloroquine	-14.38	1.0	1.0	54.6	29.4	4.3	9.5	2.0
Hydroxychlo-roquine	-17.21	1.0	1.0	546.8	52.4	3.7	9.7	2.0
Oseltamivir	-16.24	3.0	1.0	1317.7	92.3	1.3	8.6	1.0
Peramivir	-11.79	2.0	2.0	290.1	153.1	0.5	8.6	1.0
Zanamivir	-12.40	8.0	9.0	66.3	198.2	-2.8	7.6	1.0

[a] S Interaction score, [b] a-acc is number of H- bond acceptor atoms, [c] a-don is number of H-bond donor atoms, [d] E-vdw is Van der Waals energy, [e] TPSA is the topological polar surface area, [f] log P(o/w) is octanol–water partition coefficient and [g] Mr Molar refractivity.

3.1. QSAR analysis

The QSAR analysis was derived by means of regression using the interaction score as the dependent variable and structural parameters (descriptors) as independent variables. Computational analysis was used for relating molecular descriptors to the interaction scores between the studied receptor and the studied ligands. The calculation of the molecular descriptors was performed using MOE software after ionization and energy minimization. Correlation matrix between the molecular descriptors and interaction score were calculated as shown in Table 3. After that the three dimension relationship between the most effective molecular descriptors (a-acc and TPSA) and the interaction score was plotted and the relationship modeled, evaluated and validated, the results as revealed in Table 4 and Fig.4.

4. DISCUSSION

The results in Table 1 showing the number of hydrogen bond acceptor atoms H-acc and the number of hydrogen bond donor H-don atoms, zanamivir (9 H-don & 6 H acc), azithromycin (9 H-acc and 5 H-don) have the most hydrogen bond forming atoms, then peramivir (1 H-acc & 7-don), after that oseltamivir (2H-don&1H-acc), finally chloroquine (1H-don and 1 H-acc) and hydroxychloroquine (2H don). So azithromycin and zanamivir have many interaction sites with the receptor, peramivir and oseltamivir have in between H-acc & H-don atoms. Hydroxychloroquine and chloroquine have the least binding sites. The results in Table 2 revealed that all the studied drugs having antiviral activity via interaction with the receptor but varied in the degree of the interaction. The strongest interaction between ligands and the

studied receptor was with hydroxychloroqune and oseltamivir, followed with chloroquine and zanamivir (in-between), finally peramivir and azithromycin. The correlation matrix between interaction scores and the molecular descriptors revealed some interesting correlations (see Table 3). The highest correlation coefficient (r = 0.79) was obtained between the interaction score and TPSA, significant correlations were also obtained between S interaction score and a-acc and a-don. Evaluation of the QSAR model showed that the residual values between the interaction score S (obtained value) and the predicted values (calculated by the software) are ≤1.91, see Table 4, which confirms that the model is good for evaluating the relationship;

S = -17.10791+0.08966 * a-acc+0.02478 * TPSA

Root mean square error (RMSE): 1.42080

Correlation coefficient (R^2): 0.63559

The model also was validated regarding $Z-SCORE values (the absolute difference between the predicted values and the obtained S value, divided by the square root of the mean square error of the dataset) which were ≤ 1.34 (Table 4 and Fig.4), indicating that there were no outliers in the data sets (Molecular Operating Environment, 2011).[7]

Table 3: Correlation matrix of interaction score and calculated molecular descriptors using MOE software.

	S	rings	E-vdw	Mr	a-acc	a-don	TPSA	log P(o/w)
S	1.00	0.20	0.53	0.48	**0.69**	0.60	**0.79**	-0.33
rings		1.00	0.78	0.88	0.39	-0.5	-0.09	0.73
E-vdw			1.00	**0.98**	0.77	0.24	0.43	0.32
Mr				1.00	0.67	0.14	0.30	0.46
a-acc					1.00	0.79	0.81	-0.30
a-don						1.00	0.82	-0.71
TPSA							1.00	-0.69
log P(o/w)								1.00

Table 4: Database of the tested compounds showing the interaction score S of the investigated drugs with the receptor, (QSAR) model evaluation and validation.

Drug	S[a]	$PRED[b]	$RES[c]	$Z SCORE[d]
Azithromycin	-10.75	-11.60	0.85	0.60
Chloroquine	-14.38	-16.29	1.91	1.34
Hydroxychloroquine	-17.21	-15.72	-1.49	1.05
Oseltamivir	-16.24	-14.55	-1.69	1.19
Peramivir	-11.79	-13.13	1.34	0.95
Zanamivir	-12.40	-11.48	-0.92	0.65

[a] S Interaction score, [b] $PRED Predicted values, [c] RES Residual values , [d] $Z SCORE is (the absolute difference between the predicted values and the obtained S value, divided by the square root of the mean square error of the dataset).

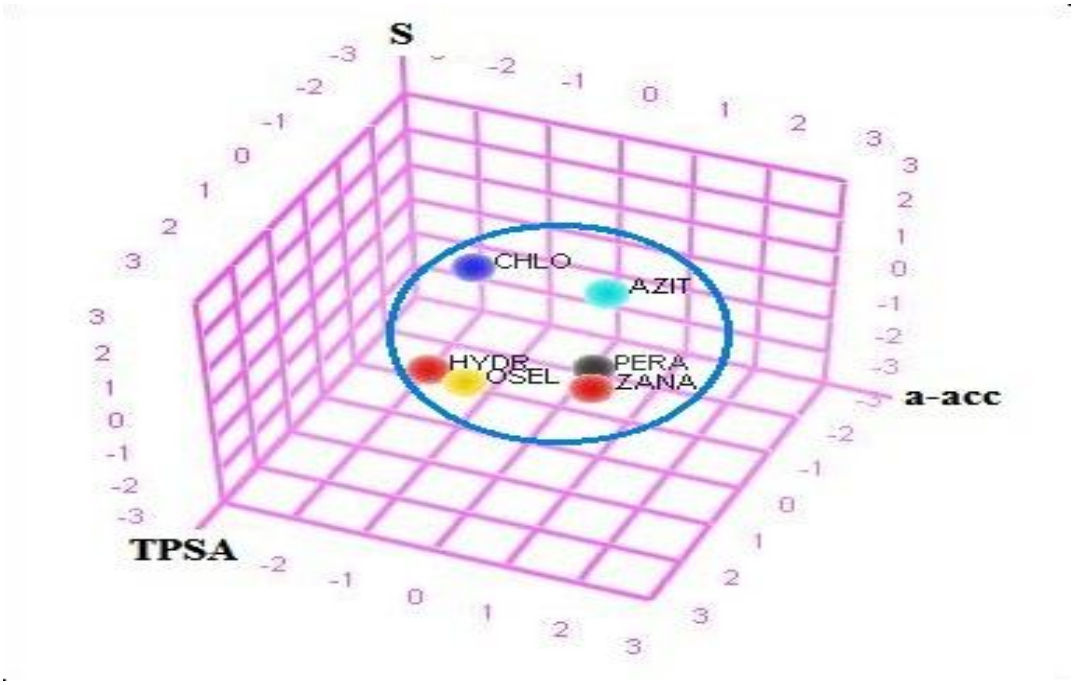

Figure 4: 3D Plot illustrating the relationship between number of H-bond acceptor atoms a-acc, topological polar surface area TPSA and S interaction score of the investigated compounds interaction with the studied receptor obtained by MOE software.

5. CONCLUSION

This In-silico study represents an indication and prediction of using the studied drugs as anti-COVID 19 remedies, since it revealed good therapeutic activity against the studied neuraminidase enzyme that plays a serious role in spreading of Corona virus and other viral diseases and causing acute severe respiratory tract symptoms, so they act as neuraminidase inhibitors (NAIs). The study also represents a very simple procedure for simulation process

of the studied drugs as antiviral. The mechanism of simulated interactions of the ligands with the studied enzyme was confirmed by QSAR analysis. The factors that affect simulation process were determined, especially the topological polar surface area TPSA and the number of H-bond acceptor atoms a-acc. QSAR modeling for the simulation process of the investigated drugs was carried out, evaluated and validated. In addition, the computational analysis revealed that the investigated compounds are grouped in a very good agreement with their chemical structures and interactions with the specified receptor.

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The author declares that there are no conflicts of interest.

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