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QSAR and molecular docking studies on pyrimidine and pyrrolidine derivatives as potent inhibitors of influenza virus neuraminidase

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Neuraminidase inhibitors(NAIs) are crucial to fight against influenza, targeting the neuraminidase enzyme to prevent the virus from spreading. Therefore, exploring novel NAIs is essential for developing effective treatments and strategies to combat influenza outbreak and thepandemic. In the present study a quantitative structure-activity relationship (QSAR) study has been carried out on a series of pyrimidine and pyrrolidine derivatives as potent inhibitors of influenza virus neuraminidase. The present study aimed to develop a robust QSAR model for predicting the inhibitory activity of the pyrimidone and pyrrolidine derivatives for understanding the molecular features of these compounds, which are essential for their inhibitory activity. The multiple regression analysis (MLR) revealed a significant correlation between the inhibitory activity values and the structural descriptors of the compounds. Using the MLR model expressed by this study, we predicted some new pyrimidine and pyrrolidine compounds. Each predicted compound has a very high potency than the any in the present series. A molecular docking study was performed on each predicted compound with the enzyme (PDB id: 2HU0), suggesting that the predicted compounds were found to form various significant hydrogen bonds with the enzyme.

Keywords: Quantitative structure-activity relationship (QSAR) study, Pyrimidines & pyrrolidine derivatives, Molecular docking, Neuraminidase inhibitors

Neuraminidase inhibitors (NAIs) are a crucial class of drugs that inhibit the enzyme neuraminidase of the influenza virus, preventing the virus from reproducing and acting as anti-influenza drugs. Some of the essential anti-influenza drugs, such as Tamiflu (Oseltamivir), Relenza (zanamivir), Inavir (laninamivir), and peramivir, belong to this class. Influenza viruses are of two types, A and B, and while some anti-influenza drugs act only against the A-type of the virus, neuraminidase inhibitors are effective against both types[1,2].

Neuraminidase inhibitors (NAIs) effectively treat and prevent influenza by reducing symptoms and complications. By blocking the neuraminidase enzyme that helps the virus spread, neuraminidase inhibitors play an important role in combating influenza. These NAIs can help to treat and prevent influenza, as they are especially good at lowering the signs and complications of the infection. Recent studies have shown their benefit in easing the seriousness of influenza, though more independent trials are needed to grasp their effect on complications and transmission fully[3,4].

In particular, the avian influenza A virus (H5N1) is a significant threat to human health, causing potentially severe public health and economic problems[3]. Person-to-person transmission is sporadic. However, genetic re assortment resulting in the new virulent subtype of avian influenza virus has made the prospect of a new pandemic, particularly alarming[4-7]. Influenza viruses contain two major membrane glycoproteins, hemagglutinin (HA) and neuraminidase (NA). NA. is one of the surface glycoproteins of the influenza virus, catalysing the release of newly formed virions from infected cells and is considered an essential target for designing anti-influenza drugs[8–10]. Zanamivir (I), Oseltamivir (II), and Peramivir (III) asshown in (Fig. 1) are the three NA inhibitors that have been now approved to treat Influenza infections[10]. However, Zanamivir and

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Peramivir are rarely used because of their low bioavailability and rapid elimination. Thus, currently, Oseltamivir is the only drug to be used against the influenza virus worldwide[11-14]. It is orally available and quite effective against the virus. However, the generation and circulation of oseltamivir-resistant seasonal influenza mutants, such as H5N1, require the development of new NAIs to fight against the potential human influenza pandemic.

The Influenza A virus is a Matrix-2 (M2) protein, which is a proton-selective viroporin. The neuraminidase inhibitors (NAIs) and M2 inhibitors constitute the two significant classes antivirals available for the treatment and prevention of Influenza. The M2 inhibitors are inexpensive but only active against Influenza A viruses, but the resistance arises rapidly. The Influenza A H3N2 and epidemic A/(H1N1)pdm09 viruses repelled by the M2 inhibitors, as are numerous H5N1 viruses[15].

Pyrimidine and pyrrolidine derivatives, which are heterocyclic compounds, are essential and valuable in various fields, such as pharmaceuticals, agriculture, and material science. These derivatives have possible applications in antiviral therapy, combination therapy, prevention and prophylaxis, antiviral resistance management, and the development of novel therapeutics.

Pyrrolidines and pyrimidines are heterocyclic compounds that exhibit a wide range of pharmacologic properties, *e.g*., they may have anti-HCV (anti-hepatitis C virus), anti-bacterial, and anti-cancer properties. Recently Singh *et al*. performed QSAR and docking studies on a series of indole-based pyridone analogues acting as HCV NS5B polymerase inhibitors[16]. Acyl(thio)urea and thiadiazol[2, 3-α] pyrimidine derivatives were found to act as potent neuraminidase inhibitors on which a QSAR study was performed by Gupta *et al*.[17]. Now we report here QSAR and molecular docking studies on a series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives (Fig. 2) possessing neuraminidase inhibition activity. The developed QSAR model may help to find the critical structural features and their relationship with the inhibitory activity.

Quantitative Structure-Activity Relationship (QSAR) and molecular docking are powerful drug discovery and design computational tools. Recent advances in these areas have been reported. These studies highlight the potential of QSAR and molecular docking in developing novel therapeutics[18-27].

Materials and Methods

A series of 43 compounds of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidine-5-carboxylate and pyrrolidine core derivatives (Fig. 2) were taken from the literature[28-29]. All the compounds are listed in Table 1, along with their physicochemical properties and

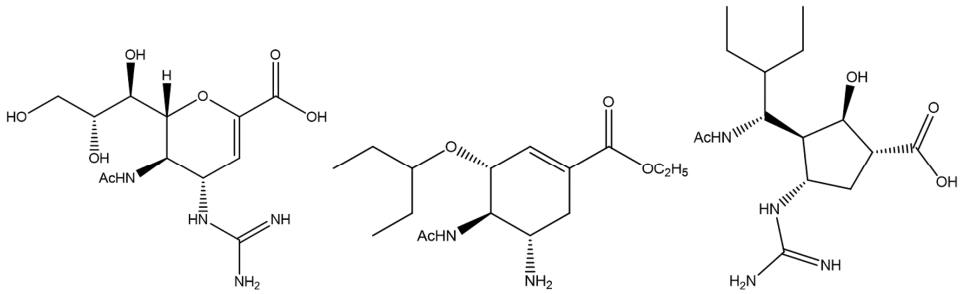


Fig. 1 — Approved neuraminidase inhibitors for the treatment of Influenza

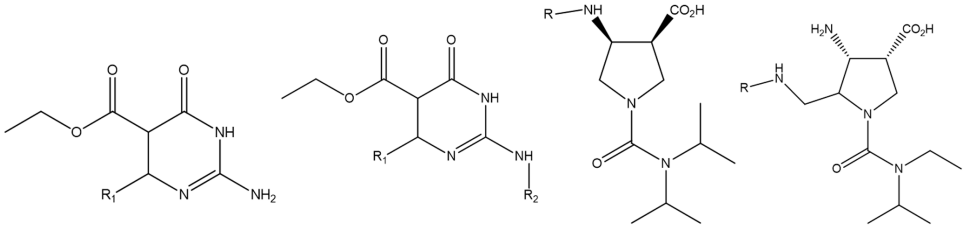
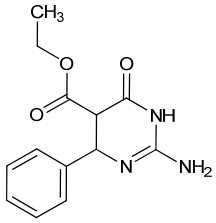
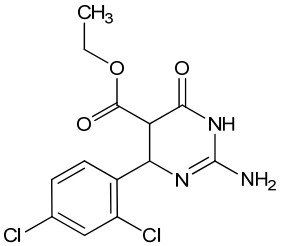
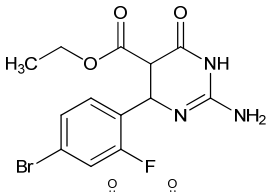
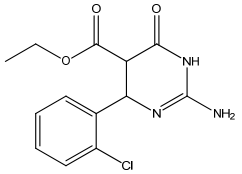
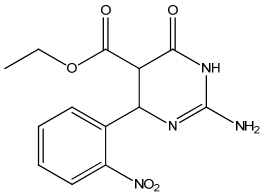
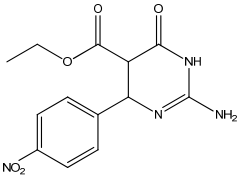


Fig. 2 — Structures of tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives possessing neuraminidase inhibition activity

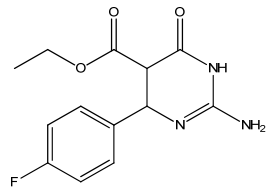
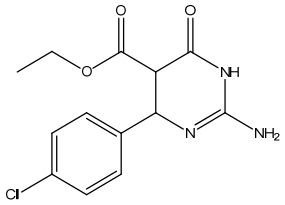
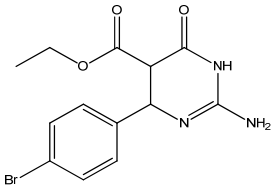
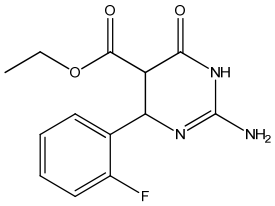
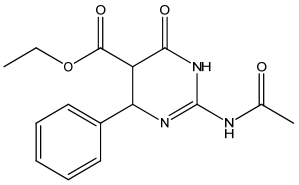
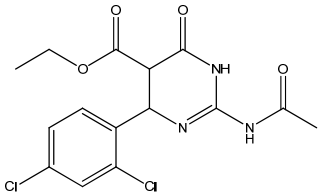
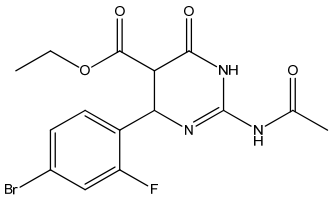
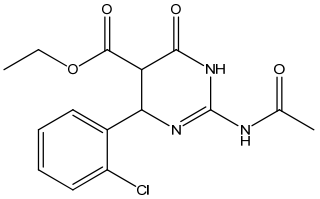
neuraminidase inhibition activity. For QSAR studies, out of 43 compounds, 33 compounds (75%) were selected for the training set by random selection, using Statistica Dataminer software, for the generation of the model, and the remaining 13 compounds (25%) were used for the test set to evaluate the predictability of the developed model. ACD/ChemSketch software[30]has been used to draw all the chemical structures of the compounds listed in (Table 1). A total of 4888 descriptors, including 2D and 3D, were calculated using DRAGON software[31]. Among all the calculated physicochemical and topological descriptors, only three descriptors, as listed in (Table 1), were found to be correlated with the activity. In this Table, test set compounds are marked with a superscript 'b', and the compounds marked with the superscript 'c' are those that acted as outliers and thus were removed in the model development. The most significant structural descriptors that were found to govern the activity of the compounds were as follows:

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50} Obsd.[a]	pIC_{50} Cald. From eq. 1	Pred. LOO	ΔpIC_{50}
1		0.80	1.34	0.57	3.89	3.50	3.41	-0.39
2		1.00	0.94	1.87	3.92	4.20	4.22	0.28
3		1.00	0.84	3.69	3.92	3.99	4.01	0.07
4[b]		0.80	0.97	1.17	4.06	3.84	-	-0.22
5		0.80	1.13	1.76	4.12	3.53	3.44	-0.59
6		0.83	1.05	2.14	3.72	3.63	3.62	-0.09

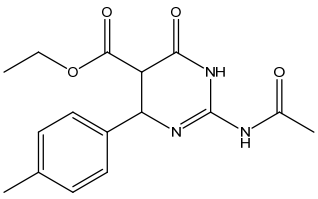
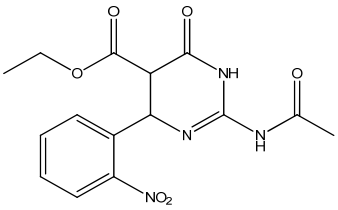
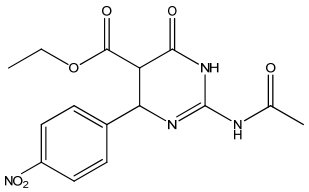
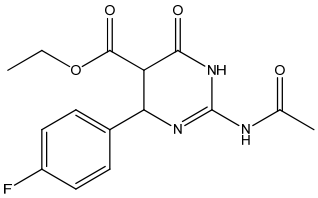
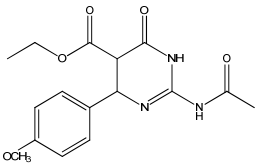
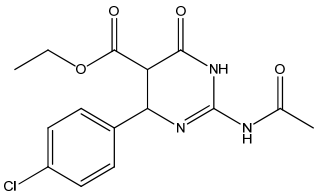
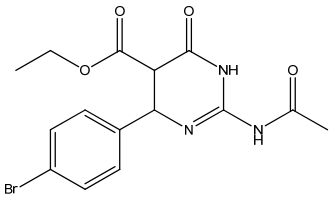
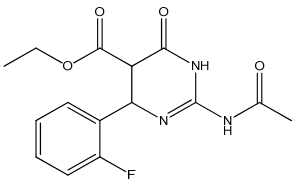
(*Contd.*)

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values (*Contd.*)

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50} Obsd.[a]	pIC_{50} Cald. From eq. 1	Pred. LOO	ΔpIC_{50}
7		1.00	1.13	2.64	3.84	3.82	3.81	-0.02
8[b]		1.00	1.25	1.55	3.96	3.86	-	-0.10
9		1.00	1.30	1.02	3.90	3.90	3.90	0.00
10[b]		0.80	0.84	3.55	4.05	3.57	-	-0.48
11		1.00	1.19	0.43	4.24	4.14	4.13	-0.10
12		1.00	0.89	0.94	4.55	4.42	4.41	-0.13
13		1.00	0.81	1.63	4.53	4.40	4.38	-0.13
14		1.00	0.91	0.54	4.44	4.46	4.46	0.02

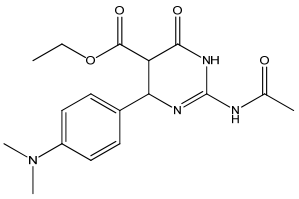
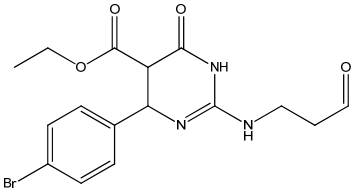
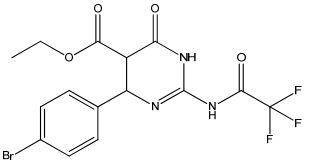
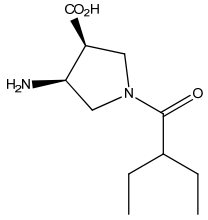
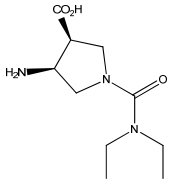
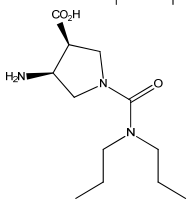
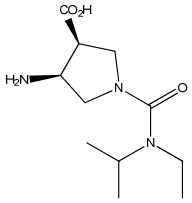
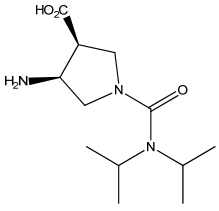
(*Contd.*)

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values (*Contd.*)

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50}		Pred. LOO	ΔpIC_{50}
					Obsd.[a]	Cald. From eq. 1		
15		1.00	1.21	0.07	3.78	4.18	4.23	0.40
16		1.00	1.06	0.42	4.75	4.31	4.28	-0.44
17[b]		0.83	0.99	1.08	3.84	3.91	-	0.07
18		1.00	1.05	1.16	4.02	4.19	4.20	0.17
19		0.83	1.07	0.24	3.78	3.96	3.97	0.18
20		1.00	1.14	0.60	4.05	4.18	4.19	0.13
21		1.00	1.17	0.57	4.15	4.14	4.14	-0.01
22[b]		1.00	0.81	2.10	4.33	4.31	-	-0.02

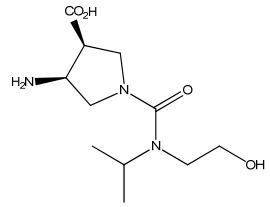
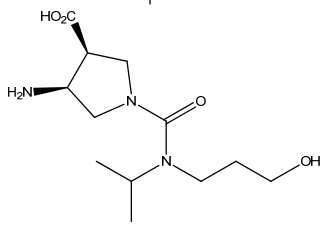
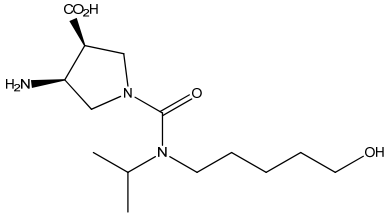
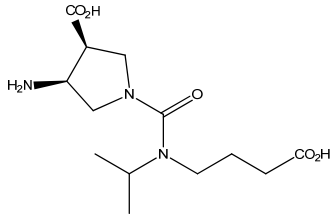
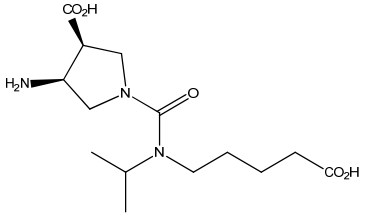
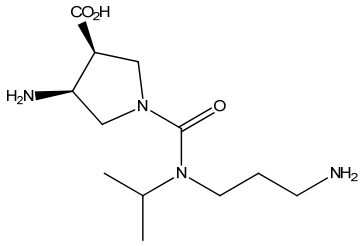
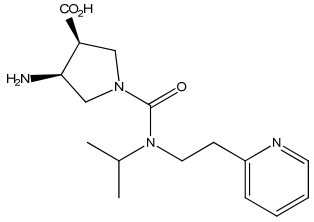
(*Contd.*)

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values (*Contd*.)

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50}		Pred. LOO	ΔpIC_{50}
					Obsd.[a]	Cald. From eq. 1		
23		0.83	1.10	-0.55	3.86	4.06	4.08	0.20
24		1.00	1.17	-0.48	3.97	4.33	4.38	0.36
25		0.83	1.04	-0.72	4.16	4.16	4.16	0.00
26		1.00	0.36	-1.81	4.66	5.58	5.72	0.92
27[b]		1.00	0.29	-2.29	4.60	5.74	-	1.14
28		0.80	0.70	-1.65	4.49	4.68	4.70	0.19
29		1.00	0.27	-0.96	5.80	5.53	5.46	-0.27
30[b]		1.00	0.24	-1.40	5.40	5.65	-	0.25

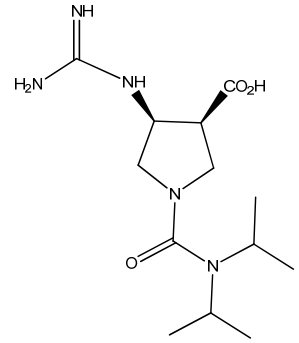
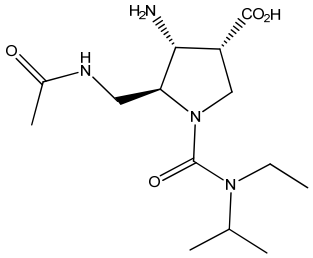
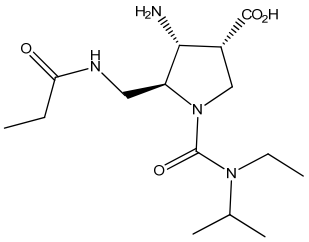
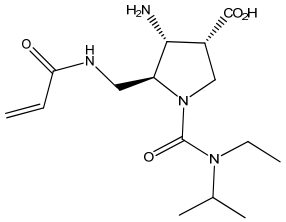
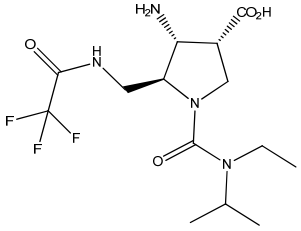
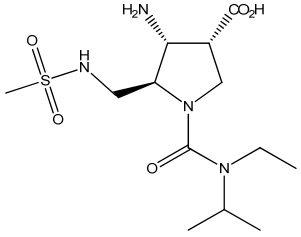
(*Contd*.)

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values (*Contd*.)

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50}		Pred. LOO	ΔpIC_{50}
					Obsd.[a]	Cald. From eq. 1		
31		0.80	0.66	-1.54	4.68	4.71	4.71	0.03
32		1.00	0.47	-1.82	5.68	5.44	5.41	-0.24
33		1.00	0.51	-3.27	5.70	5.65	5.64	-0.05
34		0.83	0.46	0.56	4.72	4.65	4.63	-0.07
35		1.00	0.51	-1.53	5.89	5.34	5.29	-0.55
36[b]		1.00	0.45	-1.34	4.34	5.38	-	1.04
37		1.00	0.40	-2.28	5.89	5.61	5.57	-0.28

(*Contd*.)

Table 1 — A Series of 6-oxo-1, 4, 5, 6-tetrahydro pyrimidone-5- carboxylate and pyrrolidine core derivatives with their structural parameters and na inhibitory activity values (*Contd*.)

Compd. No.	Structure	PJI2	GATS6e	Mor21s	pIC_{50}		Pred. LOO	ΔpIC_{50}
					Obsd.[a]	Cald. From eq. 1		
38[b]		0.80	0.33	-2.27	4.89	5.25	-	0.36
39		0.80	0.65	-3.11	5.12	5.00	4.98	-0.12
40[b]		1.00	0.64	-1.17	4.80	5.11	-	0.31
41[c]		1.00	0.63	-1.96	4.02	-	-	-
42		1.00	0.57	-7.83	6.55	6.40	6.24	-0.15
43		0.80	0.67	-0.91	3.89	4.58	4.68	0.69

[a]Taken from ref [28-29], [b]Test set, [c]Outliers

PJI2 = 2D Petitjean shape index
GATS6e = Geary autocorrelation of lag six weighted by Sanderson electronegativity
Mor21s = signal 21 / weighted by I-state
The above parameters characterize the molecules' bulk or electronic characteristics[32–34].

Results and Discussion

A multiple linear regression (MLR) analysis was performed using Statistica Dataminer[35] on the training set compounds to establish a correlation between observed activity and various calculated descriptors of the compounds. The most significant correlation achieved was as shown by Eq. (1).

pIC_{50} = 2.2084 (±1.3827) PJI2 – 1.2339 (±0.4838)GATS6e – 0.1804 (±0.0695)Mor21s + 3.4803 …(1)

n =32, r^2 = 0.8302, r^2_{cv} = 0.7763, r^2_{pred} = 0.6803, s = 0.3356, $F_{3,\ 28}$ = 45.62(2.92)

In Eq. (1), n denotes the number of data points used in the correlation, r^2 is the square of the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by the leave-one-out (LOO) jack knife procedure, and r^2_{pred} is the square of correlation coefficient obtained for test set compounds to judge the external validity of the correlation. Values of r^2_{cv} and r^2_{pred} are calculated according to Eqs. (2) and (3), respectively, where $y_{i,\ obsd}$ in Eq. (2) refers to the observed activity of compound i in the training set and that in Eq. (3) to the compound i in the test set. Similarly, $y_{i,\ pred}$ in Eq. (2) refers to the predicted activity of compound $i$in the training set obtained in leave-one-out jack knife procedure and that in Eq. (3) to that predicted for the test set compounds by the model obtained in the training set. However, $y_{av,\ obsd}$ in the equations refers to the average activity of the training set compounds. Now eq. 1 indicates that the positive value of descriptor PJI2 refers to an increase in the measure of the molecule's shape, and the negative values of the descriptors GATS6e and Mor21s decrease in the distribution of electronegativity and electron topological states in the molecule will enhance the inhibitory activity of the compounds.

$$r^2_{cv} = 1 - [\Sigma_i(y_{i,\ obsd} - y_{i,\ pred})^2 / \Sigma_i(y_{i,\ obsd} - y_{av,\ obsd})^2] \quad \ldots(2)$$

$$r^2_{pred} = 1 - [\Sigma_i(y_{i,\ obsd} - y_{i,\ pred})^2 / \Sigma_i(y_{i,\ obsd} - y_{av,\ obsd})^2] \quad \ldots(3)$$

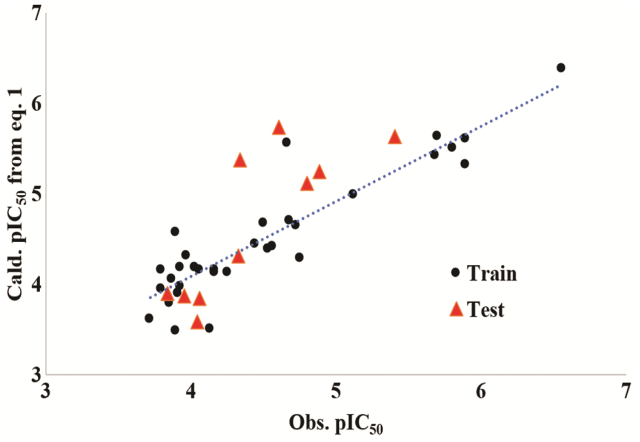


Fig. 3 — A graph between predicted and observed activities of compounds of Table 1

The correlation is supposed to be valid and have a good internal predictive ability if r^2_{cv}> 0.60. Similarly, the external predictive ability of the model is supposed to be good if it's r^2_{pred}> 0.5. From both parameters, the correlation expressed by Eq. (1) is quite valid. Among the remaining two statistical parameters, s, and F, s is the standard deviation, and F is the Fischerratio between the variances of the calculated and observed activities. The figures within the parentheses with ± sign refer to the 95% confidence intervals. The F-value given in parentheses refers to the standard F-value at the 99% level. A higher value of F than this indicates a good correlation. Thus, all descriptors used in this correlation are found to be quite significant and if we remove them one by one, the significance of the correlation is appreciably dropped (Eqs. 4-5).

pIC_{50}= –1.3117(±0.5552)GATS6e – 0.17094 (±0.07985)Mor21s + 5.56180 …(4)

n =32, r^2 = 0.7652, r^2_{cv} = 0.7086, r^2_{pred} = 0.6795, s = 0.3877, $F_{2,\ 29}$ = 47.26(3.33)

pIC_{50} = – 1.9666(±0.5864)GATS6e+ 6.2668

n = 32, r^2 = 0.6100, r^2_{cv} = 0.5524, r^2_{pred} = 0.6972, s = 0.4913, $F_{1,\ 30}$ = 46.92(4.17) …(5)

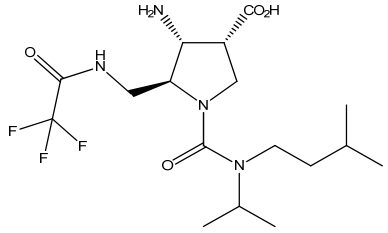
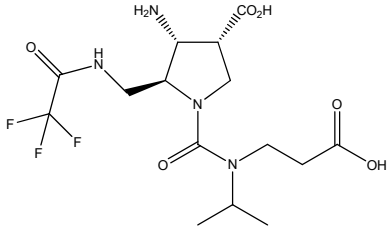
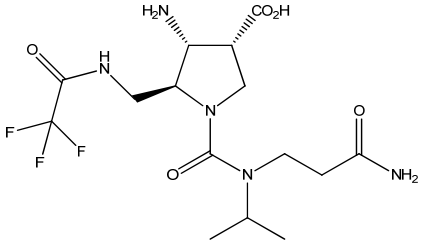
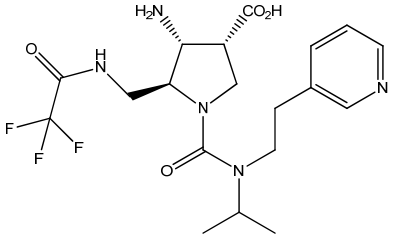
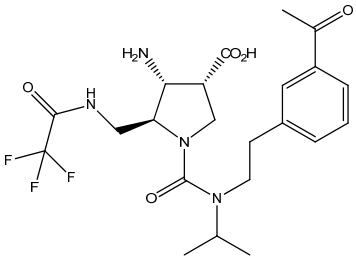
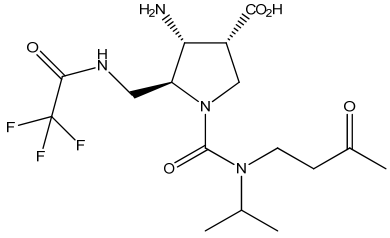
Thus, from the above results, Eq. (1) has a significant correlation between the inhibitory activity values and the structural descriptors of the compounds. Although the correlation does not have any mechanistic aspects, it has a good predictive ability. A graph is drawn between the predicted and observed activities for both the training and test sets (Fig. 3), showing that the model has a good predictive ability. Figure 3 shows that almost all the points, except a few, lie near the straight line. Thus, using

Eq. 1, we predicted some new compounds, as reported in (Table 2), where each compound has a higher activity value than any compound in the existing series (Table 1).

Docking analysis

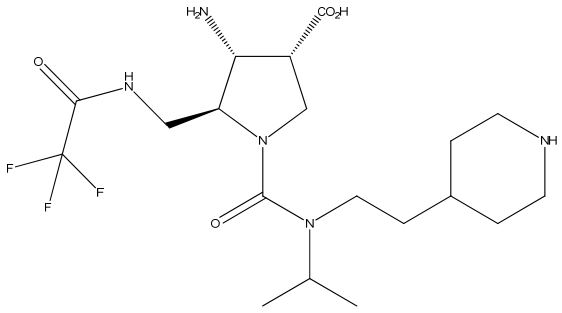
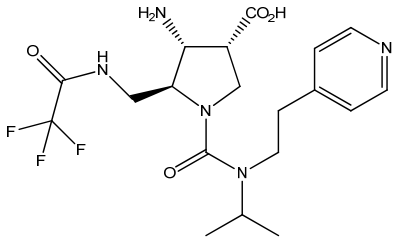
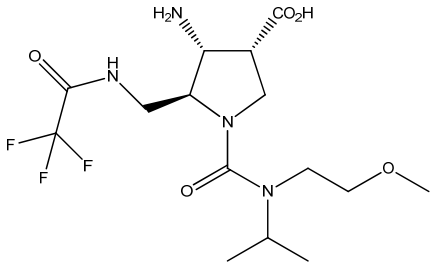
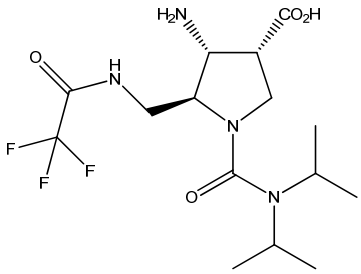
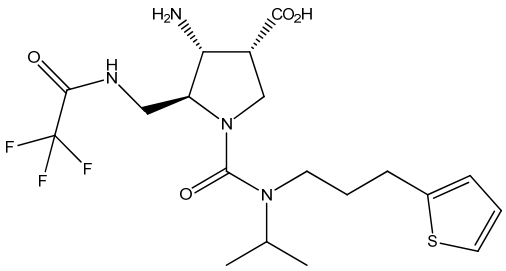
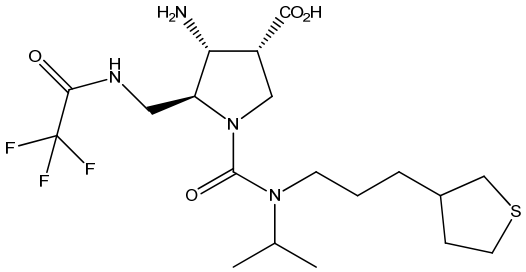
Molecular docking analysis was performed on the predicted compounds (Table 2) using LeadIT FlexX software to get the binding mode of these compounds.

Table 2 — Some proposed compounds belonging to the series of Table 1 and their predicted activity

Compd. No	Structure	PJI2	GATS6e	Mor21s	Pred.
1		1.00	0.62	-10.26	6.78
2		1.00	0.59	-9.54	6.68
3		1.00	0.59	-9.79	6.73
4		1.00	0.61	-9.99	6.74
5		0.88	0.63	-10.85	6.60
6		1.00	0.59	-10.64	6.87

(*Contd*.)

Table 2 — Some proposed compounds belonging to the series of Table 1 and their predicted activity (*Contd*.)

Compd. No	Structure	PJI2	GATS6e	Mor21s	Pred.
7		1.00	0.63	-10.48	6.80
8		1.00	0.62	-9.90	6.72
9		1.00	0.70	-10.20	6.67
10		1.00	0.51	-10.50	6.95
11		1.00	0.63	-11.32	6.95
12		1.00	0.64	-9.43	6.60

The ability of a molecule to interact with an enzyme decides its potency. For the study of molecular docking, the crystal structure of the related enzyme is vital, which can now be retrieved from the RCSB protein data bank. We selected the enzyme with PDB entry code 2HU0 (http://www.pdb.org)[36]. All predicted compounds listed in (Table 2) were docked in this enzyme, and the docking results are reported in (Table 3).

The molecular docking analysis was carried out on all predicted compounds in the enzyme. Here, we cited only compounds 10 and 2 (Figs. 4A and B), the first compound 10 being the compound having the highest predicted activity and the second having the highest docking score (Table 3), just to illustrate the best possible interactions between the inhibitors and the BACE-1 enzyme. From these Figures 4A and B, it is clear that the predicted compounds have good interactions with the enzyme. We have also docked the two FDA-approved drugs, *i.e.*, Zanamivir and Perivimir, into the enzyme 2HU0 to compare with our predicted compounds. The docking results of these two are cited in (Figs 5A and B), respectively. They all undergo hydrogen bonding and steric interactions, in which other active clefts of the enzyme surround several moieties of compounds. The penetration of any moiety of any inhibitor in any enzyme cavity will depend on its flexibility. All these steric interactions might involve dispersion interactions, which is a sort of electronic interaction.

Pharmacokinetic studies

The pharmacokinetic profiles of the predicted compounds have been obtained using Data Warrior software[37] and the results are listed in (Table 4). These pharmacokinetic profiles include molecular weight (M.W.), ClogP, number of hydrogen bond acceptors (H.A.s), number of hydrogen bond donors (H.D.s), and number of rotatable bonds (NRBs)[38-39]. For any drug to be active, it should follow Lipinski's rule of five, which states that any drug to be active should follow at least three of the following 4 conditions:

(i) Its logP value should not be greater than 5.
(ii) Number of its hydrogen bond acceptors should not be more than 10.
(iii) Number of its hydrogen bond donors (the total number of N-H and O-H bonds) should not be more than 5.
(iv) Its molecular weight should not be more than 500.

Note that it is called the rule of five as all numbers are multiples of five. Compounds having M.W.< 500 and ClogP< 5 are supposed to have good absorption and permeation abilities. Similarly, according to Viber's rule, compounds having NRB < 10 are considered to have good oral bioavailability[40–42]. Thus, all predicted compounds have excellent pharmacokinetic profiles.

Table 3 — Docking results of predicted molecules

Compd. No.	No. of Hydrogen bonds	H-bonds	H-bonds Length (Å)	Score
1	7	O(9) –Arg152	3.39	–36.5584
		O(18) –Arg152	4.33	
		O(27) –Arg 292	7.06	
		O(27) –Arg 292	4.82	
		O(27) –Arg371	8.30	
		O(27) –Arg371	7.12	
		H(57) –Glu27	8.18	
2	10	O(9) –Tyr 406	1.37	–47.8008
		O(18) –Arg 156	2.57	
		O(18) –Arg 156	4.20	
		O(24) –Arg 371	8.30	
		O(25) –Arg 292	7.28	
		O(25) –Arg 292	3.18	
		O(25) –Arg 371	8.30	
		O(28) –Arg 152	8.30	
		H(34) –Trp 178	0.52	
		H(50) –Glu 227	7.65	

(*Contd.*)

Table 3 — Docking results of predicted molecules (*Contd.*)

Compd. No.	No. of Hydrogen bonds	H-bonds	H-bonds Length (Å)	Score
3	9	O(9) –Tyr 406	2.30	–38.5799
		O(27) –Arg 371	7.04	
		O(28) –Arg 292	2.90	
		O(28) –Arg 371	8.30	
		O(18) –Arg 156	3.60	
		H(49) –Asp 151	3.72	
		H(52) –Asp 151	8.12	
		H(51) –Glu 276	1.59	
		H(51) –Glu 276	4.61	
4	10	O(9) –Tyr 406	4.55	–33.3826
		O(18) –Arg 156	4.70	
		O(30) –Arg 118	0.78	
		O(30) –Arg 118	8.24	
		O(30) –Arg 371	3.68	
		O(30) –Arg 371	3.30	
		O(30) –Arg 371	6.02	
		O(30) –Arg 292	1.02	
		N(27) –Asn 294	1.15	
		H (57) –Asp 151	4.91	
5	8	O(9) –Tyr 406	4.47	–31.3504
		O(33) –Arg 371	8.30	
		O(18) –Arg 156	0.84	
		O(18) –Arg 156	2.31	
		O(34) –Arg 292	1.15	
		O(34) –Arg 292	2.25	
		O(34) –Arg 371	8.30	
		H (63) –Asp 151	2.06	
6	8	O(34) –Arg 292	2.88	–32.3661
		O(34) –Arg 292	3.95	
		O(34) –Arg 371	2.67	
		H(34) –Glu227	8.30	
		H(53) –Glu227	8.16	
		O(28) –Arg 156	6.45	
		O(28) –Arg 156	3.59	
		O(18) –Arg 152	0.72	
7	9	O(34) –Arg 371	8.13	–42.6096
		O(34) –Arg 371	0.75	
		H(58) –Glu227	8.30	
		O(31) –Arg 371	7.28	
		O(31) –Arg 118	1.98	
		O(31) –Arg 118	6.39	
		H(63) –Glu227	8.30	
		O(9) –Tyr 347	2.05	
		O(9) –Arg 292	3.21	

(*Contd.*)

Table 3 — Docking results of predicted molecules (*Contd.*)

Compd. No.	No. of Hydrogen bonds	H-bonds	H-bonds Length (Å)	Score
8	7	O(9) –Tyr 406	4.70	–32.9399
		O(31) – Arg 371	8.30	
		O(31) – Arg 292	8.30	
		O(31) – Tyr 347	1.28	
		O(18) – Arg 156	2.40	
		H(52) –Asp 151	3.27	
		H(57) –Asp 151	4.36	
9	8	O(26) –Arg 118	7.86	–32.8390
		O(27) –Arg 118	7.34	
		O(31) –Arg 371	8.30	
		O(9) –Tyr 406	4.70	
		H(48) –Asp 151	2.30	
		H(52) –Asp 151	8.30	
		O(23) –Arg 156	4.66	
		O(18) –Arg 156	0.61	
10	7	O(25) –Arg 292	7.97	–38.7231
		O(25) –Arg 292	4.29	
		O(25) –Arg 371	8.30	
		O(26) –Arg 371	8.30	
		H (51) –Glu 277	8.09	
		O(9) –Arg 152	1.77	
		O(18) –Arg 152	3.74	
11	9	O(21) –Arg 371	4.13	–29.6435
		O(21) –Arg 371	6.53	
		O(22) –Arg 371	5.51	
		O(21) –Arg 118	4.95	
		O(21) –Arg 118	6.51	
		O(9) – Tyr 347	4.40	
		O(9) – Arg 292	4.24	
		S(31) – Tyr 406	1.72	
		H(38) – Asp 151	4.48	
12	7	O(15) –Ser 179	0.25	–30.1258
		O(21) –Arg 156	8.30	
		O(21) –Arg 156	8.30	
		H(63) –Glu 227	8.30	
		H(37) –Glu 227	7.02	
		S(29) –Asn 294	2.71	
		O(21) –Arg 152	2.35	
Zanamavir	7	O(3) –Arg 156	4.70	–32.9179
		O(6) –Arg 371	8.30	
		O(7) –Arg 371	4.17	
		O(7) –Arg 118	2.82	
		H(34) –Trp 178	4.02	
		H(37) – Trp 178	4.70	
		H(43) –Glu 227	4.99	

(*Contd.*)

Table 3 — Docking results of predicted molecules (*Contd.*)

Compd. No.	No. of Hydrogen bonds	H-bonds	H-bonds Length (Å)	Score
Peramivir	9	O(3) –Arg 292	5.42	–41.7601
		O(3) –Arg 292	6.21	
		O(3) –Arg 371	8.30	
		O(2) –Arg 371	8.30	
		O(4) –Tyr 406	4.61	
		H(49) –Glu 276	7.01	
		H(51) –Glu 276	4.96	
		H(49) –Glu 276	3.90	
		H(48) –Glu 277	3.70	

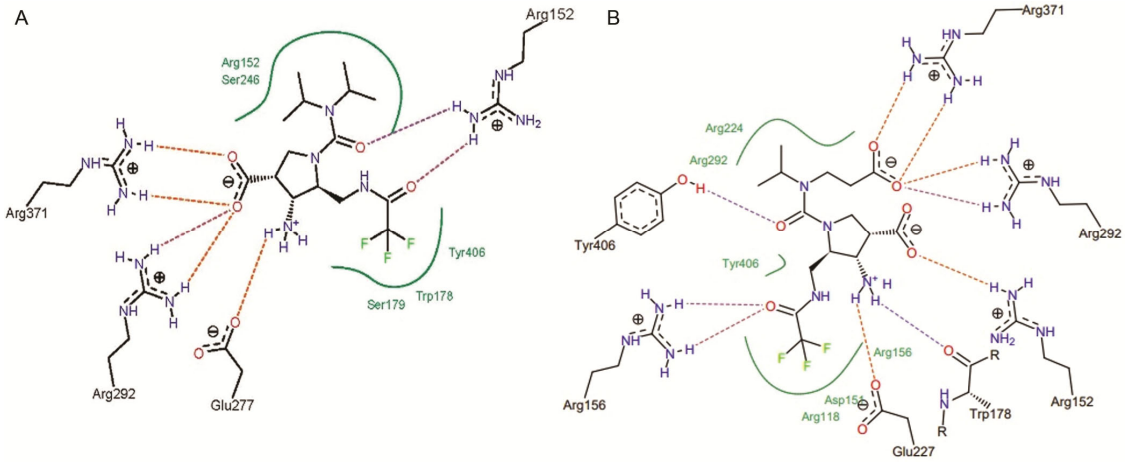


Fig. 4 — A representation of the binding of predicted (A) compound 10; and (B) compound 2 (Table 3) with the enzyme (PDB entry Code 2HU0)

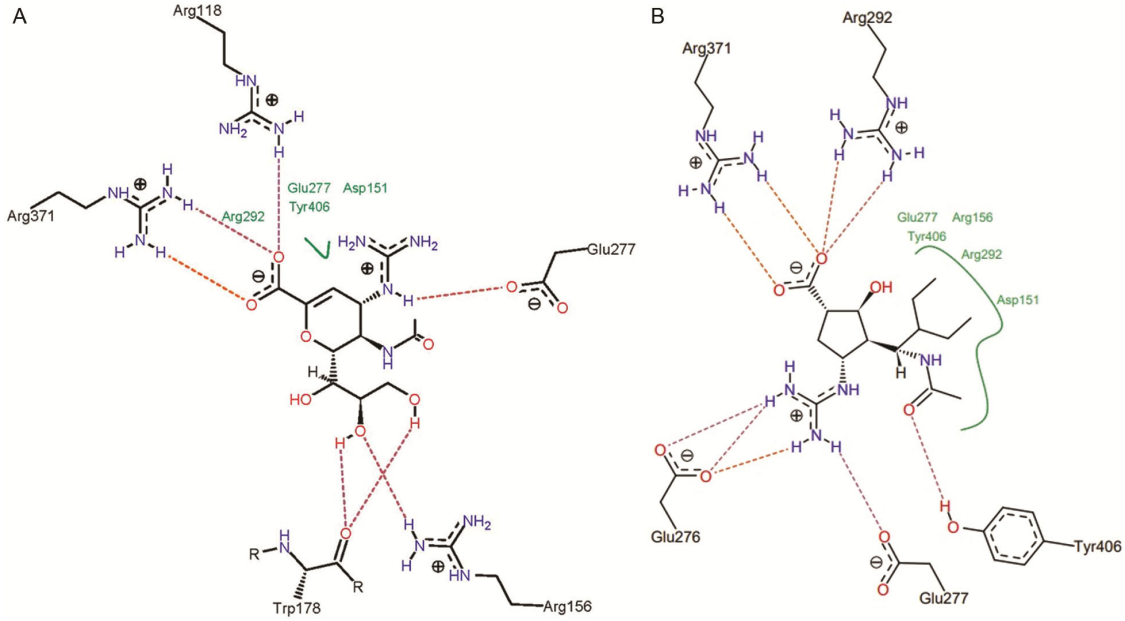


Fig. 5 — A representation of the binding of FDA-approved drug (A) (Zanamivir); and (B) (Peramivir) with the enzyme. (PDB entry Code 2HU0)

Table 4 — Pharmacokinetics properties of the proposed compounds (Table 2)

Compd No	M.W.	ClogP	NRB	HA	HD
1	410.44	-1.08	8	8	3
2	412.36	-3.03	8	10	4
3	411.38	-3.43	8	10	4
4	445.44	-1.77	8	9	3
5	486.49	-0.90	9	9	3
6	410.39	-2.36	8	9	3
7	451.49	-3.78	8	9	4
8	445.44	-1.77	8	9	3
9	398.38	-2.71	8	9	3
10	382.38	-1.85	6	8	3
11	464.51	-0.45	9	8	3
12	468.54	-1.06	9	8	3

Conclusion

The inhibitory activity of a series of pyrimidone and pyrrolidine derivatives has been correlated well with various physicochemical properties. Some new compounds possessing better activity have been proposed with the help of the MLR model [Eq. 1]. The docking study of the predicted compounds shows how the compounds interact with the enzyme. All predicted molecules were found to have several hydrogen bonds with the receptor and involve their bulky groups in significant steric interactions with some sites of the enzyme, which are better than the FDA-approved molecules. The study of the pharmacokinetic profiles of the proposed molecules has shown that they have good pharmacokinetic properties. Future research aims to find new chemical structures, logical drug design methods, and fast screening techniques to select potential candidates for influenza therapy and improve their effectiveness as antiviral therapeutics by studying their pharmacokinetic properties, potency, and safety profiles.

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Conflict of interest

All authors declare no conflict of interest.

References

1 Smith BJ, McKimm-Breshkin JL, McDonald M, Fernley RT, Varghese JN & Colman PM, Structural studies of the resistance of influenza virus neuramindase to inhibitors. *J Med Chem*, 45 (2002) 2207.

2 Gubareva LV, Molecular mechanisms of influenza virus resistance to neuraminidase inhibitors. *Virus Res*, 103 (2004) 199.

3 Zhang J, Wang Q, Fang H, Xu W, Liu A & Du G, Design, synthesis, inhibitory activity, and SAR studies of hydrophobic p-aminosalicylic acid derivatives as neuraminidase inhibitors. *Bioorg Med Chem*, 16 (2008) 3839.

4 Xie Y, Huang B, Yu K, Shi F, Liu T & Xu W, Caffeic acid derivatives: A new type of influenza neuraminidase inhibitors. *Bioorg Med Chem Lett*, 23 (2013) 3556.

5 Li W, Xia L, Hu A, Liu A, Peng J & Tan W, Design and synthesis of 4-alkyl-2-amino(acetamino)-6-aryl-1, 3-thiazine derivatives as influenza neuraminidase inhibitors. *Arch Pharm*, 346(2013)635.

6 Kongkamnerd J, Cappelletti L, Prandi A, Seneci P, Rungrotmongkol T, Jongaroonngamsang N, Rojsitthisak P, Frecer V, Milani A, Cattoli G, Terregino C, Capua I, Beneduce L, Gallotta A, Pengo P, Fassina G, Miertus S & De-Eknamkul W, Synthesis and *in vitro* study of novel neuraminidase inhibitors against avian influenza virus. *Bioorg Med Chem*, 15 (2012) 2152.

7 Chand P, Kotian PL, Morris PE, Bantia S, Walsh DA & Babu YS, Synthesis and inhibitoryactivity of benzoic acid and pyridine derivatives on influenza neuraminidase. *Bioorg Med Chem*, 13 (2005) 2665.

8 Zhang J, Wang Q, Fang H, Xu W, Liu A & Du G, Design, synthesis, inhibitory activity, and SAR studies of pyrrolidine derivatives as neuraminidase inhibitors. *Bioorg Med Chem*, 15 (2007) 2749.

9 Kim CU, Lew W, Williams MA, Liu H, Zhang L, Swaminathan S, Bischofberger N, Chen MS, Mendel DB, Tai CY, Laver WG & Stevens RC, Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J Am Chem Soc*, 119 (1997) 681.

10 Magesh S, Sriwilaijaroen N, Savita V, Ando H, Miyagi T, Suzuki Y, Ishida H & Kiso M, Investigation of 2-fluoro benzoic acid derivatives as Influenza a viral sialidase selective inhibitors. *Antiinfect Agents Med Chem*, 9 (2010) 198.

11 Meeprasert A, Khuntawee W, Kamlungsua K, Nunthaboot N, Rungrotmongkol T & Hannongbua S, Binding pattern of the long acting neuraminidase inhibitor laninamivir towards Influenza A subtypes H5N1 and pandemic H1N1. *J Mol Graph Model*, 38 (2012) 148.

12 Dao TT, Nguyen PH, Lee HS, Kim E, Park J, Lim S Il & Oh WK, Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from Glycyrrhiza inflata. *Bioorg Med Chem Lett*, 21 (2011) 294.

13 Feng E, Shin W-J, Zhu X, Li J, Ye D, Wang J, Zheng M, Zuo JP, No KT, Liu X, Zhu W, Tang W, Seong BL, Jiang H & Liu H, Structure-based design and synthesis of C-1- and C- 4-modified analogs of zanamivir as neuraminidase inhibitors. *J Med Chem*, 56 (2013) 671.

14 Woodhall T, Williams G, Berry A & Nelson A, Synthesis of screening substrates for the directed evolution of sialic acid aldolase: towards tailored enzymes for the preparation of Influenza A sialidase inhibitor analogues. *Org Biomol Chem,* 3 (2005) 1795.

15 McKimm-Breschkin JL, Influenza neuraminidase inhibitors: antiviral action and mechanisms of resistance. *Influenza Other Respi Viruses*, 7 (2013) 5.

16 Singh N, Shaik B, Agrawal N, KA, Agrawal VK & Gupta SP, QSAR and molecular modeling studies on a series of indole-based pyridone analogues as HCV NS5B polymerase inhibitors. *Lett Drug Des Discov,* 13 (2016) 757.

17 Gupta S, Quantitative structure activity relationship and docking studies on a series of substituted acyl(thio)ureas and thiadiazolo[2, 3 -α] - pyrimidine derivatives as potent inhibitors of influenza virus neuraminidase. *J Appl Biopharm Pharmacokinet,* 3 (2016) 4.

18 Bharti DV, Gupta SP & Kumar H, A quantitative structure-activity relationship (QSAR) study on a few series of potent, highly selective inhibitors of nitric oxide synthase. *Indian J Biochem Biophys,* 51 (2014) 29.

19 Kumar V & Gupta SP, A QSAR and molecular modeling study on a series of 3, 4-dihydro-1-isoquinolinamines and thienopyridines acting as nitric oxide synthase inhibitors. *Indian J Biochem Biophys,* 50 (2013) 72.

20 Sharma A, Gupta SP & Ahmed SA, A QSAR study on a series of thiourea derivatives acting as anti-hepatitis C virus agents. *Indian J Biochem Biophys,* 50 (2013) 278.

21 Zuo Yan-Qiu, Yi Zhong-Sheng, Xu Jie, Rui Yue-Fan, Wei Yu-Cheng & Liu Hong-Yan, Molecular simulation and spectroscopic studies on the interaction between perfluorohexadecanoic acid and human serum albumin. *Indian J Biochem Biophys,* 56 (2019) 185.

22 Saila MH & Thakur S, Molecular docking analysis of phytoconstituents of *Illicium verum* fruit against Caspase 3, MMP-9, and TNF-α. *Indian J Biochem Biophys,* 58 (2021) 510.

23 Kar S & Roy K, Development and validation of a robust QSAR model for prediction of carcinogenicity of drugs. *Indian J Biochem Biophys,* 48 (2011) 111.

24 Sharma A, *In silico*-based studies on phytochemicals from native Indian plants as potential inhibitors of SARS-CoV-2. *Indian J Biochem Biophys*, 59 (2022) 653.

25 Chakraborty S, Sengupta C & Roy K, Comparative QSAR modeling of COX-2 inhibitor 1, 2-diarylimidazoles using E-state and physicochemical parameters. *Indian J Biochem Biophys*, 59 (2022) 653.

26 Kaushik S, Gupta SP, Sharma PK & Anwer Z,A QSAR study on a series of N-methyl pyrimidones acting as HIV integrase inhibitors. *Indian J Biochem Biophys*, 48 (2011) 427.

27 Bajpai, A, Agarwal N & Gupta SP, A comparative 2D QSAR study on a series of hydroxamic acid-based histone deacetylase inhibitors *vis-à-vis* comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). *Indian J Biochem Biophys*, 51 (2014) 244.

28 Lou J, Yang X, Rao Z, Qi W, Li J, Wang H, Li Y, Li J, Wang Z, Hu X, Liu P & Hong X, Design and synthesis of 6-oxo-1, 4, 5, 6-tetrahydropyrimidine-5-carboxylate derivatives as neuraminidase inhibitors. *Eur J Med Chem,* 83 (2014) 466.

29 Wang GT, Chen Y, Wang S, Gentles R, Sowin T, Kati W, Muchmore S, Giranda V, Stewart K, Sham H, Kempf D & Laver WG, Design, synthesis, and structural analysis of influenza neuraminidase inhibitors containing pyrrolidine cores. *J Med Chem*, 44 (2001) 1192.

30 Advanced Chemistry Development, Inc. Chemsketch. Toronto, Canada; 2019. Available from: www.acdlabs.com

31 Todeschini R & Consonni V, Molecular Descriptors for Chemoinformatics (2 volumes) in the Series "*Methods and Principles in Medicinal Chemistry*." Mannhojd R, Kubinyi H, editor. Wiley-Vch: Wiley-VCH; 2009.

32 Petitjean M, Applications of the radius-diameter diagram to the classification of topological and geometrical shapes of chemical compounds. *J Chem Inf Comput Sci*, 32 (1992) 331.

33 Schuur JH, Selzer P & Gasteiger J, The coding of the three-dimensional structure of molecules by molecular transforms and its application to structure-spectra correlations and studies of biological activity. *J Chem Inf Comput Sci*, 36 (1996) 334.

34 Geary RC, The contiguity ratio and statistical mapping. *Inc Stat*, 5 (1954) 115.

35 StatSoft Inc. STATISTICA (data analysis software system), version 10, 2010.

36 RCSB. Protein Data Bank. 2020. Available from: www.rcsb.org.

37 Sander T, Freyss J, von Korff M & Rufener C, DataWarrior: An open-source program for chemistry aware data visualization and analysis. *J Chem Inf Model*, 55 (2015) 460.

38 Ghose AK, Viswanadhan VN & Wendoloski JJ, Prediction of hydrophobic (lipophilic) properties of small organic molecules using fragmental methods: An analysis of ALOGP and CLOGP Methods. *J Phys Chem A*, 102 (1998) 3762.

39 Ghose AK & Crippen GM, Atomic physicochemical parameters for three-dimensional-structure-directed quantitative structure-activity relationships. 2. Modeling dispersive and hydrophobic interactions. *J Chem Inf Comput Sci*, 27 (1987) 21.

40 Lipinski CA, Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov Today Technol*, 4 (2004) 337.

41 Lipinski CA, Lombardo F, Dominy BW & Feeney PJ, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*, 46 (2001) 3.

42 Abe K, Tani K & Fujiyoshi Y, Conformational rearrangement of gastric H+, K+-ATPase induced by an acid suppressant. *Nat Commun*, 2 (2011) 155.