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Research Article

Quantitative Structure Activity Relationship and Molecular Docking Studies on a Series of Thiourea and Thiazolidine-4-Carboxylic Acid Analogues as Potent Neuraminidase Inhibitors

Abha Shrivastava[1], Basheerulla Shaik[2], Manish Rao Ambedkar[3*], Vijay K Agrawal[1]

[1]Department of Chemistry, APS University, Rewa, India; [2]Department of Applied Sciences, National Institute of Technical Teachers Training and Research Institute, Bhopal, India; [3]Department of Chemistry, MMH (PG) College, Ghaziabad, India

ABSTRACT

Neuraminidase inhibitors are a type of medication that inhibits the neuraminidase enzyme. They are type of antiviral medication that is often used to treat influenza. In this paper we have taken 53 compounds which are derivatives of thiourea and thiazolidine-4-carboxylic acid derivatives. We modelled the pIC_{50} activity using RDF115p, E2s, R1i parameters. The excellent value of r^2=0.725 shows that following model is best suitable. We also performed docking study and the best docking score is -28.1891, and the best predicted activity is 8.36.

Keywords: QSAR studies; Docking; Neuraminidase inhibitors; Thiourea; pIC_{50} activity

INTRODUCTION

Neuraminidase (NA) is certainly considered one among glycoproteins on the floor of the influenza virus [1]. NA is accountable for viral launch from inflamed cells and viral shipping through the mucus with inside the breathing tract. Na has been identified as an ability goal for the manage influenza virus [2].

Neuraminidase Inhibitors (NIs) from key additives of pandemic preparedness plans as remedy and prophylaxis may want to lessen virus transmission [3]. The sialic acid analogs were the first NIs reported. Based on the structure of sialic acid, different NI series have been prepared, such as cyclohexenes, benzoic acids, pyrolidine derivatives etc. [4-7].

In the past decade, thiourea derivatives have been reported to be effective against HIV and have bactericidal effects [8]. Neuraminidase stays an appealing anti-influenza drug target, at the same time as the emergence of viruses proof against the presently to be had drug has offered a brand new challenge. Noticeably, the crystal shape of the organization-1 neuraminidase (H_1,N_4 and N_8) found out a unique hollow space adjoining to the lively web website online in organization 1 however now no longer in organization 2 proteins crystallography, suggesting new possibilities for drug layout that concentrate on this hollow space similarly to acknowledged lively web website online [9].

Earlier crystallographic and making sure SAR research have found out that the lively web page of NA can be divided into 4 important binding sites. Steindl and Lange defined the improvement of surprisingly selective pharmacophore fashions for inhibitors of viral NA inside the catalyst section possess sturdy structural resemblance in the ones parts, which correspond to the truth that the 4 wallet are important for interplay with the lively web page of NA [10].

However, few studies have evaluated substituted acyl (thio) urea and 2H-1,2,4-thiadiazolo (2,3-α) pyrimidines for their antiviral activities. In 2006, a brand new elegance of substituted acyl (thio) urea and 2H-1,2,4-thiadiazolo (2,3-α) pyrimidine derivatives with notably particular anti-influenza virus class have been organized with the aid of using Sun, et al. Their *in vitro* inhibitory class of opposition to influenza neuraminidase (H_1N_1) has been additionally investigated and located to correlate nicely with their antiviral efficacy in class of subculture.

Studied QSAR of forty thiourea analogs the use of spatial, topological, electronic, thermodynamic and E-state indices. Yu Liu, et al. have derived that thiazolidine-4-carboxylic acid could

Correspondence to: Manish Rao Ambedkar, Department of Chemistry, MMH (PG) College, Ghaziabad, India; E-mail: drmanish.2rao@gmail.com

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show potent NA inhibitory activity and his finding can be used to design novel influenza NA inhibitors that exhibit increased activity based on Thiazolidine ring [11]. Also, Thiazolidine-4-carboxylic acid was synthesized in good yields starting from commercially available L-cysteine hydrochloride using a suitable synthetic strategy.

MATERIALS AND METHODS

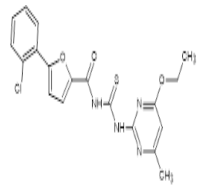
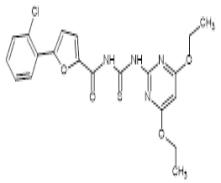
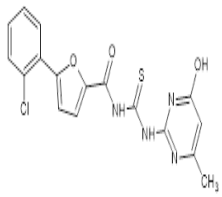
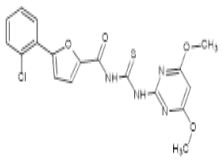
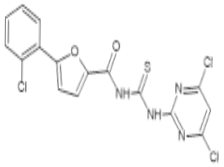
All the compounds for the study have been taken from Jiaying sun, et al. and Yu liu, et al. All the compounds are listed in Table 1 along with their inhibitory activity. For QSAR studies, out of 53 compounds, 75% of them (40 compounds) were selected for the training set by random selection, and the remaining 25% (13 compounds) were used for the test set for evaluating the predictability of the developed models.

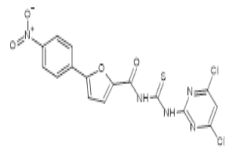
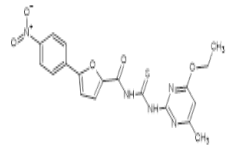
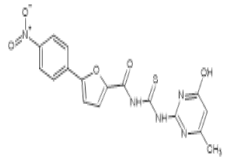
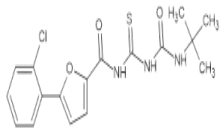
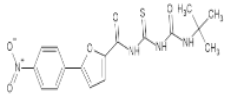
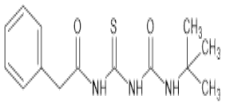
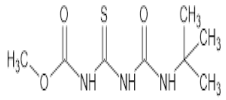
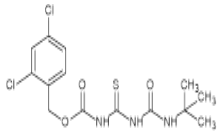
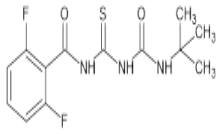
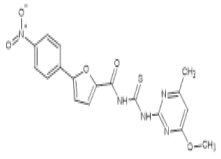
The chemical structure was drawn using ACD/Chemskecth software and the physiochemical/topological descriptors were calculated using Alva software [12]. Among all the calculated descriptors, descriptors listed in Table 2 are found to be correlated with the activity.

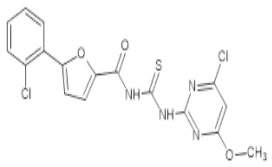
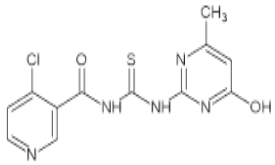
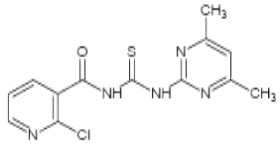
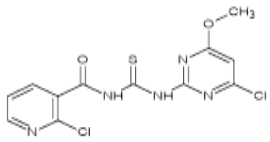
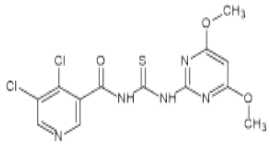
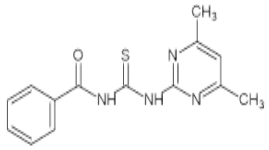
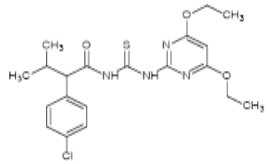
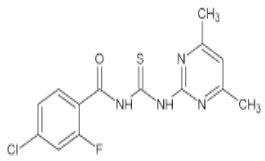
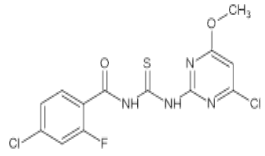
In the Table 1, the test set compounds are marked with superscript (*). The most significant structural descriptors that were found to govern the activity of the compounds were as follows.

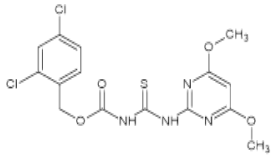
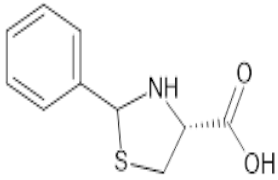
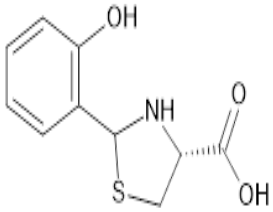
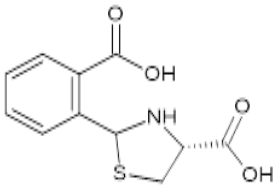
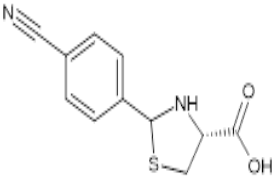
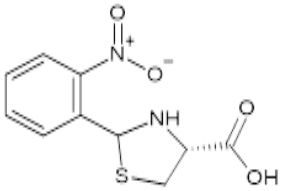
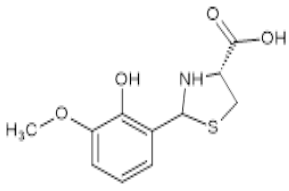
- RDF115p
- E2s
- R1i

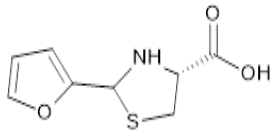
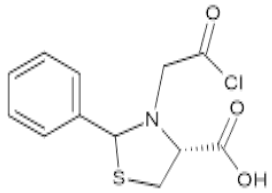
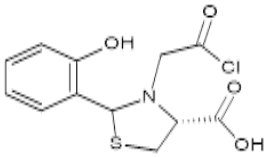
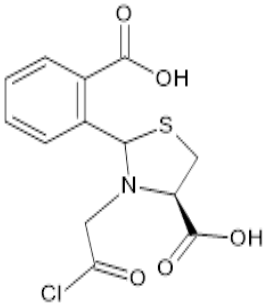
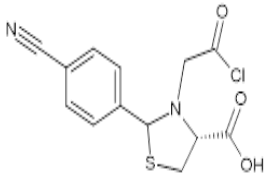
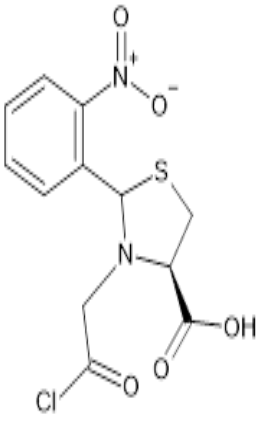
Table 1: A series thiourea analogs and thiazolidine-4-carboxylic acid derivatives as potent influenza neuraminidase inhibitors.

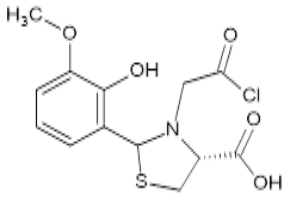
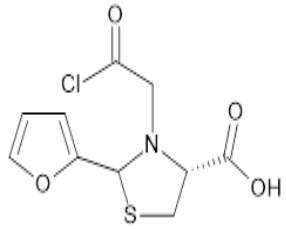
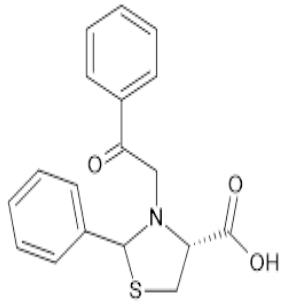
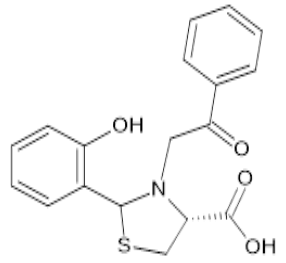
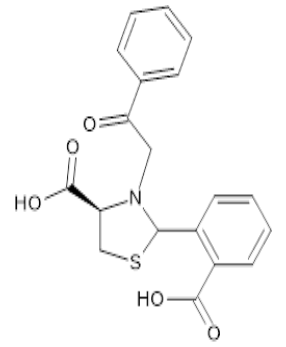
Compound no.	Molecular structure	RDF115p	E2s	R1i	pIC_{50} Obsd.	pIC_{50} Cald. From eq. 1	ΔpIC_{50}
1*		0.073	0.418	2.568	5.78	6.110	0.327
2		3.305	0.550	2.553	7.1	6.915	-0.182
3		0.000	0.482	2.575	6.49	6.205	-0.290
4		0.000	0.415	2.605	5.75	6.219	0.467
5		0.000	0.538	2.330	4.84	5.434	0.595

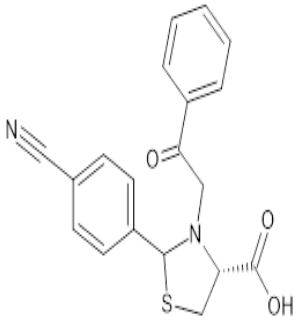
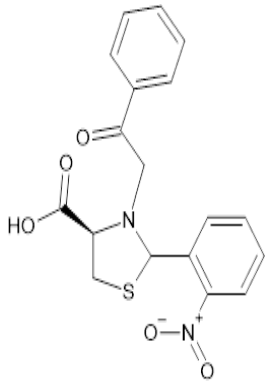
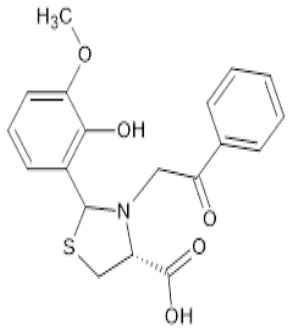
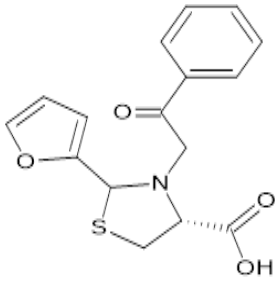
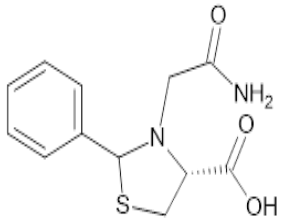
6		0.000	0.344	2.406	5.78	5.436	-0.344
7		0.187	0.324	2.640	5.64	6.257	0.619
8		0.000	0.388	2.653	6.44	6.348	-0.096
9		0.068	0.456	2.399	5.85	5.577	-0.271
10		0.000	0.374	2.537	5.89	5.929	0.043
11		0.000	0.584	2.384	5.75	5.683	-0.064
12*		0.528	0.552	2.171	5.74	5.015	-0.723
13		2.112	0.677	2.242	5.78	5.761	-0.016
14*		0.085	0.301	2.320	5.84	5.100	-0.745
15*		0.000	0.238	2.647	5.91	6.126	0.212

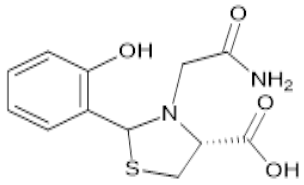
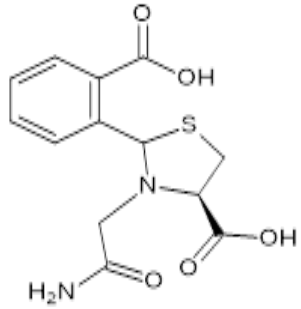
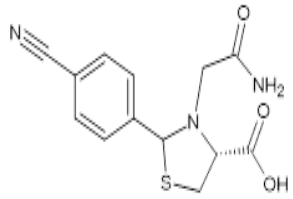
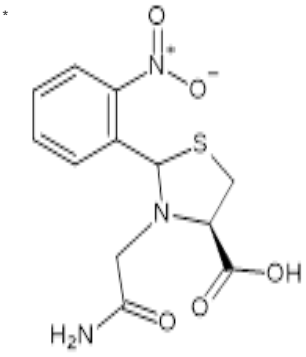
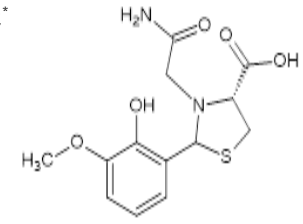
16		0.000	0.502	2.517	5.89	6.032	0.143
17		0.000	0.403	2.426	5.07	5.585	0.518
18		0.205	0.210	2.388	5.14	5.238	0.095
19		0.336	0.450	2.283	5.59	5.225	-0.362
20		0.668	0.428	2.362	4.73	5.538	0.805
21		0.223	0.477	2.403	5.68	5.651	-0.027
22*		0.472	0.323	2.491	6.51	5.801	-0.708
23		0.101	0.620	2.313	5.87	5.507	-0.359
24		0.000	0.425	2.251	5.29	5.010	-0.282

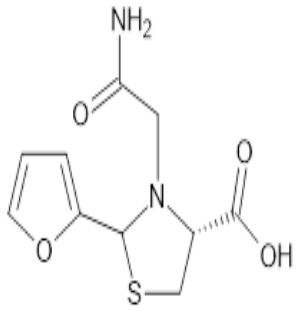
25		0.723	0.663	2.379	5.72	5.923	0.199
26		0.000	0.263	2.168	4.67	4.506	-0.166
27		0.000	0.295	2.233	4.69	4.774	0.079
28		0.000	0.352	2.286	4.74	5.033	0.291
29*		0.000	0.226	2.140	4.63	4.360	-0.271
30		0.000	0.386	2.216	4.65	4.837	0.189
31*		0.000	0.210	2.297	4.91	4.880	-0.030

32		0.000	0.300	2.179	4.37	4.594	0.228
33		0.000	0.708	2.160	5.12	5.076	-0.047
34		0.000	0.633	2.224	5.23	5.196	-0.038
35		0.000	0.805	2.282	4.97	5.627	0.656
36		0.000	0.575	2.133	5.06	4.804	-0.259
37		0.000	0.401	2.222	5.12	4.878	-0.238

38		0.000	0.635	2.298	5.10	5.454	0.353
39*		0.000	0.715	2.155	4.89	5.068	0.179
40*		0.000	0.414	2.407	5.92	5.534	-0.383
41*		0.000	0.301	2.451	6.19	5.534	-0.653
42		0.000	0.252	2.457	5.72	5.489	-0.228

43		0.000	0.292	2.391	5.61	5.315	-0.292
44*		0.000	0.243	2.448	5.73	5.446	-0.282
45		0.000	0.285	2.509	5.79	5.713	-0.077
46		0.000	0.304	2.401	5.54	5.366	-0.174
47		0.000	0.706	2.438	6.28	6.033	-0.243

48		0.000	0.614	2.507	6.68	6.147	-0.531
49		0.000	0.551	2.559	6.55	6.242	-0.311
50		0.000	0.542	2.414	6.09	5.730	-0.362
51*		0.000	0.478	2.484	5.99	5.886	-0.106
52*		0.000	0.558	2.580	6.85	6.324	-0.530

53		0.000	0.674	2.438	6.01	5.990	-0.019

RESULTS AND DISCUSSION

An Multiple Linear Regression (MLR) analysis was performed using statistical data miner on the training set compounds to establish a correlation between activity and various descriptors of the compounds. The most significant correlation obtained is shown by equation 1.

pIC_{50}=-3.3304+0.2102 (± 0.1842) RDF115p+1.3421 (± 0.7593) E2s+3.4518 (± 0.8113) R1i ..... (1)

n=40, r^2=0.7249, r^2_{cv}=0.655, r^2_{pred}=0.652, s=0.343, F=31.617

In equation 1, n refers to 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 Leave One Out (LOO) jackknife 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 equation 2 and 3, respectively, where obsd in equation 2 refers to the observed activity of compound in the training set and that in equation 3 to the compound obsd in test set. Similarly, pred in equation 2 refers to the predicted activity of compound pred in the training set obtained in LOO jackknife procedure and that in equation 3 to that predicted for the test test compounds by model obtained for the training set. However, av, obsd in both the equation refers to the average activity of the training set compound.

r^2_{cv}=1−(Σ (obsd−pred)^2/Σ (obsd−av, obsd)^2) ..... (2)

r^2_{pred}=1−(Σ(obsd−pred)^2/ Σ(obsd−av, obsd)^2) ..... (3)

The correlation is supposed to be valid and has the good internal predictive ability if r^2_{cv}>0.60. Similarly, the external predictive ability of the model is supposed to be good if its r^2_{pred}>0.5. From both the parameters, the correlation expressed by equation 1 is found to be quite valid. Among the remaining two statistical parameters, s and F, s is the standard deviation and F is the Fischer ratio between the variances of calculated and observed activities. The figure within the parentheses with (±) sign refers to the 95% confidence intervals.

The F-value given in parenthesis refers to the standard F value at the 99% level. A higher value of F indicates a good correlation. Also, all the descriptors used in this correlation are found to be quite significant if we remove them one by one, the significance of the correlation is appreciably dropped (equation 4 and 5).

PIC_{50}=-3.628+1.525(± 0.783) E2s+3.558 (± 0.851) R1i ..... (4)

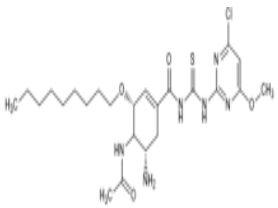
n=40, r^2=0.684, r^2_{cv}=0.575, r^2_{pred}=0.639, s=0.363, F=40.034

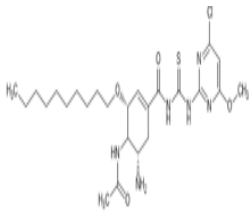
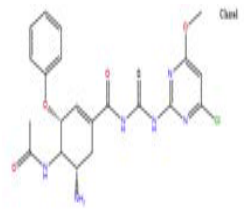
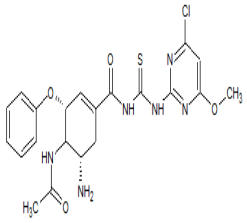
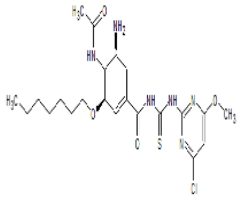
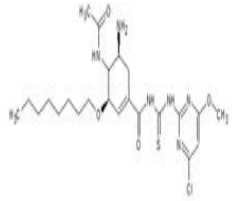
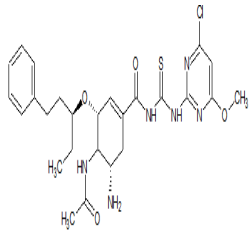
PIC_{50}=-2.406+3.347(± 0.992) R1i ..... (5)

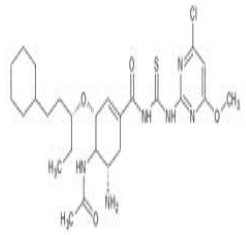
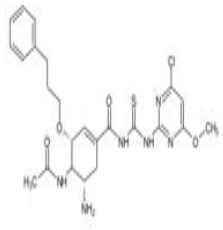
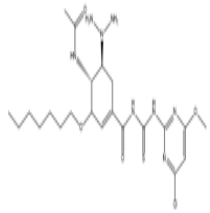
n=40, r^2=0.551, r^2_{cv}=0.497, r^2_{pred}=0.543, s=0.426, F=46.663

Thus, from the above results, it is clear that equation 1 has a noteworthy correlation between the inhibitory activity and the structural descriptors of the compounds. Although the correlation does not have any mechanistic aspects, but it has good predictive ability. A graph drawn between the predicated and observed activities for both the training and test sets further shows that the model has good predictive ability. Figure 1 shows that except 1 or 2 points, all other points lie near the straight line. Using this MLR model (equation 1), we have predicted some new compounds, as shown in Table 2, where each compound has a higher activity value than any compound in the existing series.

Table 2: Predicted compounds with proposed activity values.

Compound no.	Structure	RDF115p	E2s	R1i	pIC_{50}
1		7.376	0.667	2.678	8.36

2		8.126	0.467	2.619	8.04
3		4.979	0.547	2.701	7.77
4		2.883	0.6	2.63	7.16
5		4.856	0.514	2.629	7.45
6		5.964	0.487	2.627	7.64
7		3.262	0.536	2.674	7.3

8		3.531	0.554	2.706	7.5
9		6.25	0.469	2.636	7.71
10		3.957	0.606	2.761	7.85

Docking analysis

Molecular docking was performed on the predicted compounds in Table 2 using lead IT Flexx software to get the binding mode of these compounds. The potency of a molecule is determined by its ability to interact with an enzyme. For studying molecular docking, the crystal structure of the related enzyme is very important, which can now be retrieved from the RCSB protein data bank. We selected the enzyme with PDB entry code 1A4G.

The compounds listed in Table 2 were docked into this enzyme and their docking results are shown in Table 3. The molecular docking analysis was carried out on all of the compounds predicted to be present in the enzyme.

Here we cited only compound 1, this compound having the highest predicted activity and the compound 10 having the highest docking score just to illustrate the best possible interactions between the inhibitors and the enzyme (Figure 1). From Figures 2 and 3 it is clear that the predicted compounds have good interactions with the enzyme. They all undergo hydrogen bondings as well as steric interactions, in which several moieties of compounds are surrounded by the different active clefts of the enzyme (Table 4). The penetration of any moiety of any inhibitor in any cavity of the enzyme will depend on its flexibility. All these steric interactions might involve dispersion interactions, which is a set of electronic interactions.

Table 3: Molecular docking results of the predicted molecules.

Compound no.	No. of H-bonds	H-bonds	H-bonds length	Score
1	5	O(11)-LYS44	4.70	-27.3170
		O(27)-ASN150	4.61	
		H(38)-MET96	3.35	
		H(49)-GLY27	4.47	
		H(51)-THR23	4.38	
2	5	O(11)-LYS44	4.70	-27.9540
		O(27)-ASN150	4.60	

		H(39)-MET96	3.35	
		H(50)-GLY27	4.34	
		H(52)-THR23	4.36	
3	4	O(25)-ASP103	3.51	-27.1239
		H(52)-ASP103	8.16	
		H(52)-ASP103	3.36	
		H(53)-LEU21	4.43	
4	10	N(9)-ARG118	0.51	-20.5896
		O(11)-TYR406	2.51	
		O(14)-ARG292	2.85	
		O(14)-ARG292	3.96	
		O(14)-ARG371	4.70	
		O(25)-ASN294	2.61	
		O(25)-ARG292	0.32	
		H(35)-GLU119	4.70	
		H(46)-GLU276	0.21	
		H(57)-GLU276	0.43	
5	5	O(11)-ARG371	4.19	-19.5077
		O(11)-ARG118	4.7	
		O(14)-GLY348	4.28	
		O(25)-ARG152	4.38	
		H(48)-GLU152	8.3	
6	5	O(11)-ARG118	4.7	-18.6483
		O(11)-ARG371	4.21	
		O(14)-GLY348	4.28	
		O(25)-ARG152	4.37	
		H(49)-GLU119	8.3	
7	9	O(14)-ARG292	2.36	-23.0806
		O(14)-ARG292	3.17	
		O(14)-ARG371	4.7	
		O(25)-ARG152	4.7	
		O(27)-ARG156	3.03	
		H(39)-ASP151	2.73	
		H(51)-GLU119	8.3	
		H(53)-ASP178	1.25	
		H(72)-GLU119	0.13	
8	7	O(14)-ARG371	2.34	-24.5201
		O(14)-ARG118	4.7	
		O(25)-ARG152	4.7	
		O(27)-ARG156	3.21	

		H(39)-ASP151	1.28	
		H(51)-GLU119	8.3	
		H(53)-TRP178	1.88	
9	5	O(11)-ARG118	4.7	-21.3755
		O(11)-ARG371	2.97	
		O(14)-GLY348	3.41	
		O(25)-ARG152	0.26	
		H(50)-GLU119	8.3	
10	6	O(14)-ASP103	4.54	-28.1891
		N(29)-THR23	3.74	
		H(39)-ASP103	2.27	
		H(39)-ASP103	0.59	
		H(51)-GLU149	4.7	
		H(57)-THR23	4.24	

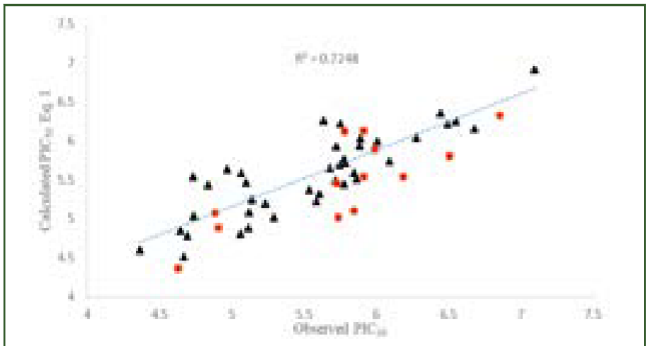


Figure 1: A plot between predicted and observed activities of compounds of Table 1.

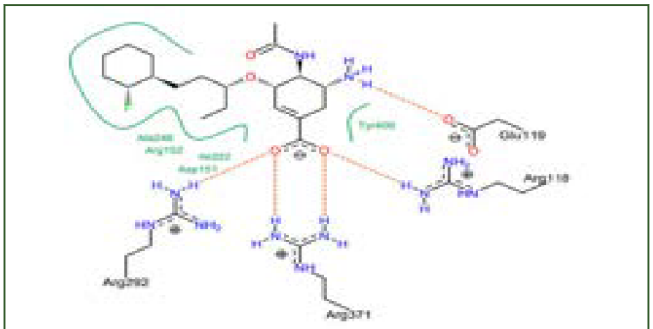


Figure 2: A representation of the binding of predicted compound 1 (Table 2) in 1A4G (PDBID: 1A4G).

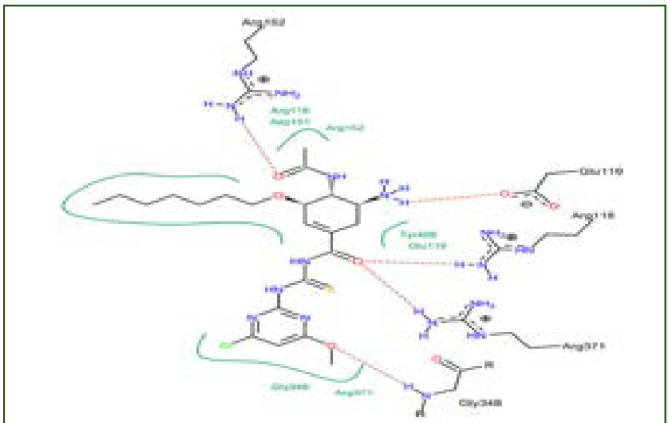


Figure 3: A representation of the binding of predicted compound 10 (Table 2) in 1A4G (PDBID: 1A4G).

Table 4: Pharmacokinetic properties of the predicted compounds of Table 2.

Total Mol weight	cLogP	cLogS	H-Acceptors	H-Donors
490.971	1.5781	-4.484	10	4
513.061	2.7389	-4.805	10	4
527.088	3.1933	-5.075	10	4

527.088	3.1933	-5.075	10	4
561.105	3.1769	-5.508	10	4
567.153	3.5335	-5.969	10	4
533.051	2.3632	-4.86	10	4
540.954	-0.4975	-4.065	12	5
521.001	-0.325	-4.084	12	5
529.064	0.3814	-4.135	12	5
591.135	1.2738	-5.108	12	5

Pharmacokinetic studies

The pharmacokinetic properties of the predicted compounds were obtained using data warriors software, and the results are shown in Table 3. These pharmacokinetic properties include Molecular Weight (MW), ClogP, number of H-bond Acceptors (HA), and number of H-bond Donors (HD). According to Lipinski's rule of five, compounds with MW<500 and ClogP<5 should have good absorption and penetration capacity.

CONCLUSION

The inhibition activity of a series of thiourea analogs compounds was found to be well correlated with various physicochemical properties. The correlation between activity and structure provided new information about which thiourea based compounds are more active. Through docking studies of the predicted compounds, it was found that all of them interact with the enzyme 1A4G in a number of ways, involving their bulky groups in significant steric interactions with some of the site's residues. Studies on the pharmacokinetic characteristics of the predicted compounds show that they have good pharmacokinetic properties.

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