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Regression Analysis and Docking Study of Pyrimidine Based Compounds as anti-Tuberculosis Therapeutic Agents

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Abstract- In the drug-design process, structure activity relationship is an important tool for estimation of biological activity of the unknown compounds. In this process, the objective is development of a relationship between structural features of molecules and the property of interest i. e. biological activity. On the basis of this relationship, the biological activity can be predicted for new candidate structures. Initially, the forty two substituted pyrimidine molecules with known biological activities were considered as known set for regression analysis model building purpose. The properties module from Datawarrior used to calculate descriptors. Structure activity model indicates that these descriptors have significant relationships with observed bioactivity. We have observed a high relationship between experimental and predicted activity values, indicating the validation and the excellent quality of the derived model. In the present study, the new substituted pyrimidine molecules are designed, optimized and their descriptors were calculated using Datawarrior modules. Then by using the Regression analysis model, their biological activities are studied as well as inhibition studies for the 1QPQ by molecular docking method are also carried out. Thus on the basis of regression analysis study and docking study of substituted pyrimidine derivatives, we can conclude that these compounds on further studies may prove to be therapeutic agent against tuberculosis.

Keywords: *Structure activity, biological activity, docking, tuberculosis, descriptor, pyrimidine..*

I. INTRODUCTION

In the drug-design process, quantitative structure activity relationship (QSAR) has come to play a major role. In this process, the objective is development of a relationship between structural features and the property of interest, so that property values can be predicted for new candidate structures. [1] The goal of QSAR modeling is to establish a trend in the descriptor values, which parallels the trend in biological activity. [2]

As per the techniques developed in the recent period, the experimental property values have been related directly to structure information. The structure of the molecule is represented in a mathematical manner so that necessary information can be encoded and extracted in a form that lends itself to modeling. In this process, it is expected that the significant structural features are encoded in the structure representation and then identified in the modeling process. In this manner, the synthesis of new candidates may be guided towards the desired goal.

The structure-based approach is a coherent approach to the QSAR problem that has been developed over the past 25 years, and is part of a broader approach, the so-called Quantitative Information Analysis (QIA) [3].

In the QIA approach, emphasis is placed on the two aspects of the data that are known directly, the measured activity and/or property values on the one hand, and the molecular structures in the data set on the other. The required information is related to the manner in which molecules present themselves to each other in non-covalent interactions. It now appears clear that this approach can be accomplished without the need for explicit three-dimensional (3D) structure information. The necessary information is implicit in the encoded descriptors. It should be pointed out that topological structure descriptors are used to produce good predictive models for logP. [4] [5] [6] [7]

Pyrimidine is an important precursor for the synthesis of a wide variety of heterocyclic compounds. The variety of compounds synthesized reported to have various biological anticancer, antiviral, antibacterial, antioxidant, antituberculosis and antidepressant. [8]

Compounds with heteroatom are exist in nature and have significance as their structure exist in many natural products

such as vitamins, hormones, and antibiotics and hence they are used in the design of biologically active molecules. Some substituted pyrimidine derivatives were also found to show antibacterial and antifungal activity. [9] [10]

Datawarrior version 4.6.1 package [11] is able to calculate certain physico-chemical properties, lead- or drug-likeness related parameters, ligand efficiencies, various atom and ring counts, molecular shape, flexibility and complexity as well as indications for potential structure activity.

In current study, the experimental work consist initially the equation (model) building for regression analysis by using known set of molecules. By using this equation, the biological activities for newly designed (unknown) molecules are determined. These newly designed molecules are also subjected to inhibition studies against Quinolinic acid phosphoribosyl transferase (QAPRTase) enzyme (PDB code: 1QPQ), an important target for designing novel potential inhibitor for tuberculosis.

II. EXPERIMENTAL

The activity parameter used in this study is substituted pyrimidine inhibitory activity. The studied compounds are Tuberculosis inhibitors which inhibit Mycobacterium Tuberculosis. Interestingly, all these compounds were active and showed M. Tuberculosis inhibition with biological activities values ranged between 374 and 16 μM. [12] [13]

IIa. Descriptors generation

Firstly, the forty two investigated molecules were pre-optimized by means of the Molecular Mechanics. After that, the resulted minimized structures were further refined using the semi-empirical techniques. Then, these substituted pyrimidines were re-optimized by using Gaussian program package.

The QSAR properties module from Datawarrior version 4.6.1 package was used to calculate: Total Molecular Weight, partition coefficient octanol/water (clogP), Aqueous Solubility (cLogS), Polar Surface Area, Fragment-based Drug-Likeness Prediction (LE), Ligand Efficiency (LE), lipophilic ligand Efficiency (LLE), Ligand Efficiency lipophilic price (LELP).

IIb. Regression analysis

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows.

Table 1.1: Parameters of regression analysis by SPSS

Model	Unstandardized Coefficients /Standardized Coefficients			t	Sig.	95.0% Confidence Interval for B		Correlations			Collinearity Statistics	
	B	Std. Error	Beta			Lower Bound	Upper Bound	Zero order	Partial	Part	Tolerance	VIF
Constant	-320.28	996.680		-.321	.750	-2345.782	1705.21					
TMW	-.447	1.286	-.210	-.348	.730	-3.061	2.167	-.128	-.060	-.054	.066	15.069
cLogP	-92.618	72.833	-1.073	-1.272	.212	-240.633	55.397	-.160	-.213	-.198	.034	29.303
cLogS	-18.068	44.693	-.154	-.404	.689	-108.895	72.759	.135	-.069	-.063	.167	5.994
TSA	.566	2.872	.178	.197	.845	-5.271	6.403	-.141	.034	.031	.030	33.695
Drug-likeness	-2.948	7.699	-.089	-.383	.704	-18.595	12.699	-.105	-.066	-.060	.452	2.214
LE	1171.113	887.873	.729	1.319	.196	-633.263	2975.48	.233	.221	.206	.080	12.553
LELP	30.258	28.549	1.353	1.060	.297	-27.761	88.277	-.117	.179	.165	.015	67.064

The equation for determination of biological activity generated by regression analysis:

Biological Activity = (-320.284) + (-.447) x Total Mol. Wt. + (-92.618) x cLogP + (-18.068) x cLogS + (.566) x Total Surface area + (-2.948) x Drug likeliness + (1171.11) x LE + (30.258) x LELP.

IIc. Docking Studies

Quinolinic acid Phosphoribosyltransferase (QAPRTase) having PDB code 1QPQ was selected as the target enzyme. Its 3D electronic structure having natural inhibitor was procured from protein repository databank. Quinolinic acid phosphoribosyl transferase (QAPRTase) enzyme (PDB code: 1QPQ) can stop the FAS I pathway as it will make it deficient of NAD.[14] Therefore the Quinolinic acid phosphoribosyl transferase (QAPRTase) enzyme provides an attractive target for designing novel potential inhibitor for tuberculosis. [15].

iGEMDOCK is an integrated tool that creates virtual screening environment from preparations through post-screening analysis with pharmacological interactions. First, iGEMDOCK provides interactive interfaces to prepare both

the binding site of the target protein and the screening compound library. Then, each compound in the library is docked into the binding site by using the docking tool iGEMDOCK. Subsequently, iGEMDOCK generates protein-compound interaction profiles of electrostatic, hydrogen-bonding, and van der Waals interactions. Finally, iGEMDOCK ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of iGEMDOCK. [16] The selected set of three ligands were subjected to accurate docking (very slow docking) by setting population size of 700 is set with 70 generation and 10 solutions. After the completion of the docking, the post docking analysis was performed to find the docking pose and its energy values.

III. RESULTS AND DISCUSSION

IIIa. Structure activity relationships (SAR)

We have studied eight physical chemical proprieties of series of substituted pyrimidine derivatives in which various degrees of substituents on aromatic ring have been introduced, these substituents include electron donating group such as methoxy and electron withdrawing group like nitro, using HyperChem software. The structure for substituted pyrimidine given as:

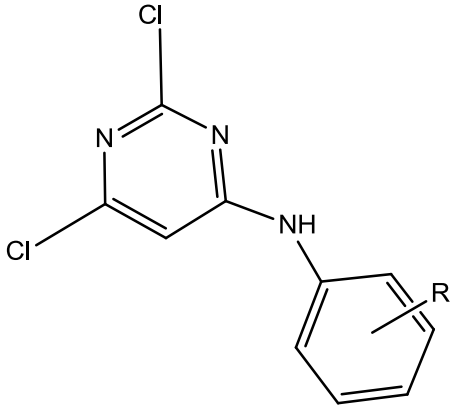

Table 1.2 and 1.3 list the series of substituted pyrimidine derivatives designed in current project.

Table 1.2: Id and name for Unknown compounds – Series 1.

Sr No.	ID	Compound	Sr No.	ID	Compound
1	UK pyr 1	N-phenylpyrimidin-4-amine	29	UK pyr 29	2-(2-aminoethyl)-N-phenylpyrimidin-4-amine
2	UK pyr 2	2-methyl-N-phenylpyrimidin-4-amine	30	UK pyr 30	6-(2-aminoethyl)-N-phenylpyrimidin-4-amine
3	UK pyr 3	2,6-dimethyl-N-phenylpyrimidin-4-amine	31	UK pyr 31	2,2'-(6-(phenylamino)pyrimidine-2,4-diyl)diethanamine
4	UK pyr 4	6-methyl-N-phenylpyrimidin-4-amine	32	UK pyr 32	N-(4-(phenylamino)pyrimidin-2-yl)acetamide
5	UK pyr 5	2-ethyl-N-phenylpyrimidin-4-amine	33	UK pyr 33	N-(6-(phenylamino)pyrimidin-4-yl)acetamide
6	UK pyr 6	6-ethyl-N-phenylpyrimidin-4-amine	34	UK pyr 34	N,N'-(6-(phenylamino)pyrimidine-2,4-diyl)diacetamide
7	UK pyr 7	2,6-diethyl-N-phenylpyrimidin-4-amine	35	UK pyr 35	N-(4-(phenylamino)pyrimidin-2-yl)propionamide
8	UK pyr 8	2-methoxy-N-phenylpyrimidin-4-amine	36	UK pyr 36	N-(6-(phenylamino)pyrimidin-4-yl)propionamide
9	UK pyr 9	6-methoxy-N-phenylpyrimidin-4-amine	37	UK pyr 37	N,N'-(6-(phenylamino)pyrimidine-2,4-diyl)dipropionamide
10	UK pyr 10	2,6-dimethoxy-N-phenylpyrimidin-4-amine	38	UK pyr 38	N-(4-(phenylamino)pyrimidin-2-yl)butyramide
11	UK pyr 11	2-ethoxy-N-phenylpyrimidin-4-amine	39	UK pyr 39	N-(6-(phenylamino)pyrimidin-4-yl)butyramide
12	UK pyr 12	6-ethoxy-N-phenylpyrimidin-4-amine	40	UK pyr 40	N,N'-(6-(phenylamino)pyrimidine-2,4-diyl)dibutyramide
13	UK pyr 13	2,6-diethoxy-N-phenylpyrimidin-4-amine	41	UK pyr 41	4-(phenylamino)pyrimidin-2-yl acetate
14	UK pyr 14	N-phenyl-2-propylpyrimidin-4-amine	42	UK pyr 42	6-(phenylamino)pyrimidin-4-yl acetate
15	UK pyr 15	N-phenyl-6-propylpyrimidin-4-amine	43	UK pyr 43	6-(phenylamino)pyrimidine-2,4-diyl

					diacetate
16	UK pyr 16	N-phenyl-2,6-dipropylpyrimidin-4-amine	44	UK pyr 44	4-(phenylamino)pyrimidin-2-yl propionate
17	UK pyr 17	N-phenyl-2-propoxypyrimidin-4-amine	45	UK pyr 45	6-(phenylamino)pyrimidin-4-yl propionate
18	UK pyr 18	N-phenyl-6-propoxypyrimidin-4-amine	46	UK pyr 46	6-(phenylamino)pyrimidine-2,4-diyl dipropionate
19	UK pyr 19	N-phenyl-2,6-dipropoxypyrimidin-4-amine	47	UK pyr 47	4-(phenylamino)pyrimidin-2-yl butyrate
20	UK pyr 20	2-butoxy-N-phenylpyrimidin-4-amine	48	UK pyr 48	6-(phenylamino)pyrimidin-4-yl butyrate
21	UK pyr 21	6-butoxy-N-phenylpyrimidin-4-amine	49	UK pyr 49	6-(phenylamino)pyrimidine-2,4-diyl dibutyrate
22	UK pyr 22	2,6-dibutoxy-N-phenylpyrimidin-4-amine	50	UK pyr 50	4-(phenylamino)pyrimidin-2-ol
23	UK pyr 23	N4-phenylpyrimidine-2,4-diamine	51	UK pyr 51	6-(phenylamino)pyrimidin-4-ol
24	UK pyr 24	N4-phenylpyrimidine-4,6-diamine	52	UK pyr 52	6-(phenylamino)pyrimidine-2,4-diol
25	UK pyr 25	N4-phenylpyrimidine-2,4,6-triamine	53	UK pyr 53	N,2-diphenylpyrimidin-4-amine
26	UK pyr 26	2-(aminomethyl)-N-phenylpyrimidin-4-amine	54	UK pyr 54	N,6-diphenylpyrimidin-4-amine
27	UK pyr 27	6-(aminomethyl)-N-phenylpyrimidin-4-amine	55	UK pyr 55	N,2,6-triphenylpyrimidin-4-amine
28	UK pyr 28	(6-(phenylamino)pyrimidine-2,4-diyl)dimethanamine			

Table 1.3: Id and name for Unknown compounds – Series 2.

Sr. No.	Molecule	Molecule name	Sr. No.	Molecule	Molecule name
1	UK pyrs1	2,6-dichloro-N-(2-nitrophenyl)pyrimidin-4-amine	12	UK pyrs12	1-(4-((2,6-dichloropyrimidin-4-yl)amino)phenyl)ethanone
2	UK pyrs2	2,6-dichloro-N-(4-nitrophenyl)pyrimidin-4-amine	13	UK pyrs13	2,6-dichloro-N-(o-tolyl)pyrimidin-4-amine
3	UK pyrs3	2-((2,6-dichloropyrimidin-4-yl)amino)benzenesulfonic acid	14	UK pyrs14	2,6-dichloro-N-(p-tolyl)pyrimidin-4-amine
4	UKpyrs4	4-((2,6-dichloropyrimidin-4-yl)amino)benzenesulfonic acid	15	UK pyrs15	2-((2,6-dichloropyrimidin-4-yl)amino)phenol
5	UKpyrs5	2,6-dichloro-N-(2-chlorophenyl)pyrimidin-4-amine	16	UK pyrs16	4-((2,6-dichloropyrimidin-4-yl)amino)phenol
6	UK pyrs6	2,6-dichloro-N-(4-chlorophenyl)pyrimidin-4-amine	17	UK pyrs17	N1-(2,6-dichloropyrimidin-4-yl)benzene-1,2-diamine
7	UK pyrs7	N-(2-bromophenyl)-2,6-dichloropyrimidin-4-amine	18	UK pyrs18	N1-(2,6-dichloropyrimidin-4-yl)benzene-1,4-diamine
8	UK pyrs8	N-(4-bromophenyl)-2,6-dichloropyrimidin-4-amine	19	UK pyrs19	2,6-dichloro-N-(2,4,6-trichlorophenyl)pyrimidin-4-amine
9	UK pyrs9	2,6-dichloro-N-(2-iodophenyl)pyrimidin-4-amine	20	UK pyrs20	2,6-dichloro-N-(2,4,6-triiodophenyl)pyrimidin-4-amine
10	UK pyrs10	2,6-dichloro-N-(4-iodophenyl)pyrimidin-4-amine	21	UK pyrs21	2,6-dichloro-N-(naphthalen-1-yl)pyrimidin-4-amine
11	UK pyrs11	1-(2-((2,6-dichloropyrimidin-4-yl)amino)phenyl)ethanone			

Table 1.4 shows the observed biological activity values of known molecules.

Table 1.4: Descriptor values with biological activity for Known set of molecules.

ID	Observed Biological Activity	Total Mol. Wt.	cLogP	cLogS	Total Surface Area	Drug likeness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
K PYR 1	331	219.674	3.2242	-3.588	169.68	-0.90842	0.60895	3.434	5.2947
K PYR 2	165.5	256.352	3.4546	-3.99	216.6	1.9941	0.47591	3.1366	7.2589
K PYR 3	331	270.379	2.4796	-4.468	227.7	2.7554	0.45053	4.0884	5.5038
K PYR 4	82.75	296.417	4.2271	-4.776	244.62	4.4193	0.40708	2.301	10.384
K PYR 5	82.75	310.443	3.2521	-5.254	255.72	5.0045	0.38818	3.2559	8.3777
K PYR 6	20.65	352.524	4.2838	-6.286	292.5	5.0045	0.34048	2.169	12.582
K PYR 7	374.5	220.299	2.6847	-4.099	162.84	-6.8696	0.60884	3.9723	4.4095
K PYR 8	75.9	308.408	5.9035	-5.838	238.84	-1.3412	0.40601	0.60738	14.54
K PYR 9	250	322.435	6.2474	-6.182	251.1	-1.4387	0.3872	0.24416	16.135
K PYR 10	250	336.462	6.663	-6.341	264.86	-1.6789	0.37001	-0.18993	18.008
K PYR 11	72.1	324.407	5.5578	-5.542	245.19	-1.4453	0.38704	0.93111	14.36
K PYR 12	71.2	338.434	5.8335	-5.856	261.1	-1.4875	0.36987	0.63703	15.772
K PYR 13	119.4	338.434	5.8335	-5.856	261.1	-1.4875	0.36987	0.63703	15.772
K PYR 14	250	352.417	6.0149	-6.549	259.1	-1.5895	0.35411	0.43804	16.986
K PYR 15	250	368.46	5.7635	-5.874	283.36	-1.4875	0.33947	0.67011	16.978
K PYR 16	250	398.486	5.6935	-5.892	305.62	-1.4875	0.31355	0.70609	18.158
K PYR 17	250	354.433	5.4878	-5.56	267.45	-1.4988	0.35397	0.96267	15.504
K PYR 18	250	384.459	5.4178	-5.578	289.71	-1.4988	0.32596	0.99735	16.621
K PYR 19	200	499.432	7.8391	-7.726	354.07	-8.9071	0.27887	-1.5376	28.11
K PYR 20	250	353.405	4.9819	-6.298	262.51	-6.5934	0.35404	1.4698	14.072
K PYR 21	250	353.405	4.9819	-6.298	262.51	-6.5934	0.35404	1.4698	14.072
K PYR 22	16.2	376.405	6.7518	-6.616	268.3	-8.5312	0.33898	-0.32745	19.918
K PYR 23	15.7	376.405	6.7518	-6.616	268.3	-8.5312	0.33898	-0.32745	19.918
K PYR 24	71.1	326.398	6.0043	-6.152	245.19	-2.6812	0.38689	0.48195	15.52
K PYR 25	300	326.398	6.0043	-6.152	245.19	-2.6812	0.38689	0.48195	15.52
K PYR 26	250	342.853	6.5095	-6.574	254.26	-1.3257	0.38561	-0.04461	16.881
K PYR 27	124.3	342.853	6.5095	-6.574	254.26	-1.3257	0.38561	-0.04461	16.881
K PYR 28	250	387.304	6.6287	-6.672	257.47	-3.1312	0.38245	-0.21675	17.332
K PYR 29	24.3	387.304	6.6287	-6.672	257.47	-3.1312	0.38245	-0.21675	17.332
K PYR 30	300	333.418	5.7391	-6.611	260.55	-5.6212	0.37024	0.73791	15.501
K PYR 31	250	372.495	6.7851	-7.331	287.2	-1.3412	0.32665	-0.35622	20.772
K PYR 32	250	372.495	6.7851	-7.331	287.2	-1.3412	0.32665	-0.35622	20.772
K PYR 33	35	362.5	6.8306	-6.67	292.86	-5.6302	0.33984	-0.38991	20.099
K PYR 34	39.9	312.396	4.7794	-5.407	242.29	-1.67	0.40566	1.7259	11.782
K PYR 35	20.8	311.412	4.3672	-4.773	242.17	-0.47093	0.40574	2.1395	10.763
K PYR 36	300	400.509	5.1165	-5.284	308.62	-1.3412	0.30264	1.2809	16.906
K PYR 37	145.1	323.423	4.5898	-4.93	251.36	-1.3412	0.38712	1.9004	11.856
K PYR 38	299.2	302.445	5.8417	-5.467	240.03	-4.8911	0.42589	0.67765	13.716
K PYR 39	239.7	274.391	4.8215	-5.02	216.1	-1.7595	0.47378	1.7401	10.177
K PYR 40	72.6	336.462	6.0182	-6.093	263.6	-1.3447	0.37001	0.45487	16.265
K PYR 41	160.2	302.445	5.7303	-5.56	243.62	-1.4275	0.42589	0.78905	13.455
K PYR 42	250	398.533	7.1183	-6.874	311.1	-1.3412	0.30274	-0.71876	23.513

Table 1.5 and 1.6 shows the calculated biological activity values by SPSS of unknown molecules Series I and Series II.

Table 1.5: Calculated biological activity values by SPSS of unknown molecules Series I

ID	Calculated Biological Activity	Total Mol. Wt.	cLogP	cLogS	Total Surface Area	Drug likeness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
UK pyr 1	624.2156	171.202	1.9782	-2.715	142	-0.825	0.71406	4.7883	2.7703
UK pyr 2	563.568	185.229	2.2116	-2.343	154.26	-1.0024	0.65971	4.5207	3.3524
UK pyr 3	519.0692	199.256	2.6095	-2.711	166.52	-1.0024	0.61283	4.0911	4.2581
UK pyr 4	569.247	185.229	2.3761	-3.083	154.26	-1.0024	0.65971	4.3562	3.6018
UK pyr 5	516.3739	199.256	2.6272	-2.502	168.02	-1.3406	0.61283	4.0734	4.287
UK pyr 6	522.6277	199.256	2.7917	-3.242	168.02	-1.3406	0.61283	3.9089	4.5554
UK pyr 7	452.4304	227.31	3.4407	-3.029	194.04	-1.3406	0.53611	3.2027	6.4179
UK pyr 8	537.7487	201.228	2.2777	-3.004	164.26	-0.93934	0.61244	4.4186	3.7191
UK pyr 9	543.119	201.228	2.2596	-3.258	164.26	-0.93934	0.61244	4.4367	3.6895
UK pyr 10	489.4799	231.254	2.5591	-3.547	186.52	-0.93934	0.53551	4.0768	4.7788
UK pyr 11	506.3404	215.255	2.684	-3.304	178.02	-2.6308	0.57165	3.983	4.6952
UK pyr 12	511.6471	215.255	2.6659	-3.558	178.02	-2.6308	0.57165	4.0011	4.6635
UK pyr 13	457.8591	259.308	3.3717	-4.147	214.04	-2.6308	0.47555	3.2145	7.0901
UK pyr 14	484.8035	213.283	3.0816	-2.772	181.78	-3.4155	0.57199	3.5894	5.3875
UK pyr 15	491.6381	213.283	3.2461	-3.512	181.78	-3.4155	0.57199	3.4249	5.6751
UK pyr 16	424.1414	255.364	4.3495	-3.569	221.56	-3.4155	0.47603	2.2433	9.137
UK pyr 17	473.1969	229.282	3.1384	-3.574	191.78	-1.5537	0.53581	3.5012	5.8573
UK pyr 18	478.4401	229.282	3.1203	-3.828	191.78	-1.5537	0.53581	3.5193	5.8235
UK pyr 19	440.4466	287.362	4.2805	-4.687	241.56	-1.5537	0.42735	2.2611	10.016
UK pyr 20	465.6343	243.309	3.5928	-3.844	205.54	-6.412	0.50408	3.021	7.1275
UK pyr 21	470.814	243.309	3.5747	-4.098	205.54	-6.412	0.50408	3.0391	7.0916
UK pyr 22	463.9392	315.415	5.1893	-5.227	269.08	-6.412	0.38777	1.3118	13.382
UK pyr 23	599.7515	186.217	1.6704	-3.062	150.52	-0.9353	0.65948	5.0596	2.5329
UK pyr 24	605.1883	186.217	1.6523	-3.316	150.52	-0.9353	0.65948	5.0777	2.5055
UK pyr 25	587.0271	201.232	1.3445	-3.663	159.04	-0.9353	0.61244	5.3518	2.1953
UK pyr 26	580.063	200.244	0.8726	-1.959	164.28	-1.1705	0.61263	5.8258	1.4243
UK pyr 27	586.3228	200.244	1.0371	-2.699	164.28	-1.1705	0.61263	5.6613	1.6929
UK pyr 28	555.6118	229.286	-0.0685	-1.943	186.56	-1.1705	0.53581	6.7081	-0.12784
UK pyr 29	535.213	214.271	1.3027	-2.071	178.04	-1.4642	0.57182	5.3663	2.2782
UK pyr 30	542.0475	214.271	1.4672	-2.811	178.04	-1.4642	0.57182	5.2018	2.5658
UK pyr 31	492.8843	257.34	0.7917	-2.167	214.08	-1.4642	0.47579	5.7978	1.664
UK pyr 32	497.1944	228.254	2.0514	-3.328	183.47	0.43291	0.53597	4.5902	3.8275
UK pyr 33	502.4376	228.254	2.0333	-3.582	183.47	0.43291	0.53597	4.6083	3.7937
UK pyr 34	463.0151	285.306	2.1065	-4.195	224.94	0.43291	0.42755	4.4382	4.9269
UK pyr 35	467.5092	242.281	2.5058	-3.598	197.23	1.7575	0.50422	4.1099	4.9697
UK pyr 36	472.6889	242.281	2.4877	-3.852	197.23	1.7575	0.50422	4.128	4.9338
UK pyr 37	452.5068	313.36	3.0153	-4.735	252.46	1.7575	0.38794	3.4887	7.7726

UK pyr 38	458.4033	256.308	2.9602	-3.868	210.99	-1.4189	0.47592	3.631	6.22
UK pyr 39	463.5194	256.308	2.9421	-4.122	210.99	-1.4189	0.47592	3.6491	6.182
UK pyr 40	476.2157	341.414	3.9241	-5.275	279.98	-1.4189	0.35486	2.5426	11.058
UK pyr 41	490.3734	229.238	2.3344	-3.286	182.01	-1.1623	0.53582	4.3053	4.3567
UK pyr 42	495.6166	229.238	2.3163	-3.54	182.01	-1.1623	0.53582	4.3234	4.3229
UK pyr 43	452.9037	287.274	2.6725	-4.111	222.02	-1.1623	0.42735	3.8692	6.2536
UK pyr 44	459.0787	243.265	2.7888	-3.556	195.77	1.056	0.50408	3.8251	5.5324
UK pyr 45	464.2583	243.265	2.7707	-3.81	195.77	1.056	0.50408	3.8432	5.4965
UK pyr 46	443.9246	315.328	3.5813	-4.651	249.54	1.056	0.38778	2.9199	9.2354
UK pyr 47	457.3393	257.292	3.2432	-3.826	209.53	-4.2655	0.4758	3.3464	6.8164
UK pyr 48	462.4525	257.292	3.2251	-4.08	209.53	-4.2655	0.4758	3.3645	6.7783
UK pyr 49	478.1427	343.382	4.4901	-5.191	277.06	-4.2655	0.35473	1.9741	12.658
UK pyr 50	576.6043	187.201	2.002	-2.69	148.35	-0.96557	0.65926	4.7257	3.0368
UK pyr 51	582.0381	187.201	1.9839	-2.944	148.35	-0.96557	0.65926	4.7438	3.0093
UK pyr 52	543.0372	203.2	2.0077	-2.919	154.7	-0.96557	0.61205	4.6844	3.2803
UK pyr 53	446.8978	247.3	3.6212	-4.86	201.76	-0.82797	0.47704	2.9856	7.591
UK pyr 54	437.1354	247.3	3.7284	-4.493	201.76	-0.82797	0.47704	2.8784	7.8157
UK pyr 55	469.7895	323.398	5.3714	-6.638	261.52	-0.82797	0.35615	1.1189	15.082

Table 1.6: Calculated biological activity values by SPSS of unknown molecules Series II

ID	Calculated Biological Activity	Total Molweight	cLogP	cLogS	Total Surface Area	Drug likeness	LE from Total Molweight	LLE from Total Molweight	LELP from Total Molweight
UK pyrs1	206.215	285.09	1.2693	-2.05	105.95	-4.7645	0.49883	5.2757	2.5445
UK pyrs2	194.8372	285.09	1.2693	-2.05	105.95	-0.905	0.49883	5.2757	2.5445
UK pyrs3	222.9136	320.156	-1.03	-1.895	115.5	-3.1459	0.46894	7.5247	-2.1967
UK pyrs4	211.3626	320.156	-1.03	-1.895	115.5	0.77236	0.46894	7.5247	-2.1967
UK pyrs5	210.1046	274.538	3.4123	-3.256	98.37	-4.4182	0.56259	3.1491	6.0653
UK pyrs6	198.7395	274.538	3.4123	-3.256	98.37	-0.563	0.56259	3.1491	6.0653
UK pyrs7	209.1565	318.989	3.5433	-3.398	101.58	-12.648	0.557	2.9529	6.3614
UK pyrs8	197.7923	318.989	3.5433	-3.398	101.58	-8.7931	0.557	2.9529	6.3614
UK pyrs9	145.011	365.985	3.7957	-2.979	109.23	-3.78	0.55188	2.6408	6.8777
UK pyrs10	133.5541	365.985	3.7957	-2.979	109.23	0.10633	0.55188	2.6408	6.8777
UK pyrs11	175.3621	282.129	2.8292	-2.96	105.22	-5.2336	0.49918	3.7204	5.6677
UK pyrs12	163.8772	282.129	2.8292	-2.96	105.22	-1.3378	0.49918	3.7204	5.6677
UK pyrs13	216.2544	254.119	3.3966	-3.089	95.21	-4.0024	0.56547	3.1984	6.0067
UK pyrs14	205.7908	254.119	3.3966	-3.089	95.21	-0.453	0.56547	3.1984	6.0067
UK pyrs15	244.8595	256.092	2.2752	-2.53	89.3	-3.7779	0.56518	4.3164	4.0256
UK pyrs16	233.1713	256.092	2.2752	-2.53	89.3	0.1869	0.56518	4.3164	4.0256
UK pyrs17	277.0168	255.108	1.8774	-2.606	91.47	-8.3321	0.56532	4.7159	3.3209

UK pyrs18	259.6003	255.108	1.8774	-2.606	91.47	-2.4242	0.56532	4.7159	3.3209
UK pyrs19	117.0722	343.428	3.9823	-3.91	125.03	0.84182	0.49267	2.4819	8.0831
UK pyrs20	-49.72	617.769	5.1325	-3.079	157.61	1.48	0.47324	1.0767	10.846
UK pyrs21	120.5357	290.152	4.0567	-3.875	90.36	-4.4182	0.47203	2.4807	8.5942

Table 1.7 and 1.8 shows docking parameters with protein 1QPQ for unknown pyrimidine molecules (Series I and II).

Table 1.7: Docking parameters with protein 1QPQ for unknown pyrimidine molecules (Series I).

Sr. No.	ID	Total Energy	VDW	HBond	AverConPair
1	UK pyr 1	-62.7223	-52.5308	-10.1914	25.0769
2	UK pyr 2	-64.1028	-59.6373	-4.46552	27.2143
3	UK pyr 3	-67.2325	-63.4215	-3.81099	27.2667
4	UK pyr 4	-65.7642	-55.0006	-10.7636	25
5	UK pyr 5	-66.0143	-54.7455	-11.2688	22.2667
6	UK pyr 6	-66.7223	-57.8275	-8.89477	24.1333
7	UK pyr 7	-68.3495	-65.0294	-3.3201	25.6471
8	UK pyr 8	-71.7606	-58.1153	-13.6452	25.3333
9	UK pyr 9	-67.6386	-55.2021	-12.4365	24.3333
10	UK pyr 10	-74.6419	-60.9366	-13.7053	22.3529
11	UK pyr 11	-75.2882	-61.3725	-13.9156	23.375
12	UK pyr 12	-70.2454	-56.2063	-14.0391	25.5625
13	UK pyr 13	-77.8719	-64.1059	-13.766	21.2105
14	UK pyr 14	-68.5268	-56.6233	-11.9035	24.1875
15	UK pyr 15	-66.453	-54.5694	-11.8836	21.5
16	UK pyr 16	-70.9854	-60.5987	-10.3867	20.8421
17	UK pyr 17	-76.8034	-62.9324	-13.871	22.5294
18	UK pyr 18	-70.5127	-60.5674	-9.94523	23.1176
19	UK pyr 19	-83.3051	-71.2047	-12.1005	22.2857
20	UK pyr 20	-77.9492	-63.9783	-13.9708	21.6667
21	UK pyr 21	-71.3992	-60.8992	-10.5	25.7222
22	UK pyr 22	-84.2857	-72.1334	-12.1523	20.8696
23	UK pyr 23	-69.3133	-49.1249	-20.1885	25.7143
24	UK pyr 24	-67.7868	-52.7665	-15.0202	25.3571
25	UK pyr 25	-71.9818	-58.6872	-13.2945	29.7333
26	UK pyr 26	-70.7695	-64.7762	-5.99332	27.6
27	UK pyr 27	-67.9195	-50.4531	-17.4664	28.2667
28	UK pyr 28	-75.6705	-55.5765	-20.094	28.4706
29	UK pyr 29	-69.2823	-62.2823	-7	24.375
30	UK pyr 30	-66.98	-55.9935	-10.9865	25.5625
31	UK pyr 31	-71.5394	-58.7941	-12.7453	21.2105

32	UK pyr 32	-81.9606	-66.3836	-15.5769	26.2941
33	UK pyr 33	-81.1744	-63.7252	-17.4491	25.3529
34	UK pyr 34	-86.5691	-66.6472	-19.9219	24.0952
35	UK pyr 35	-85.2654	-69.7298	-15.5356	25.9444
36	UK pyr 36	-84.4913	-66.8354	-17.6559	24.2222
37	UK pyr 37	-91.1798	-71.1819	-19.9978	23.4348
38	UK pyr 38	-82.2284	-67.5288	-14.6997	25.1053
39	UK pyr 39	-86.0416	-69.066	-16.9756	23.4737
40	UK pyr 40	-86.5393	-70.8854	-15.654	18.2
41	UK pyr 41	-78.0141	-69.1096	-8.90456	26.1765
42	UK pyr 42	-80.7482	-59.8732	-20.875	23.8824
43	UK pyr 43	-80.5343	-62.904	-17.6303	19.7619
44	UK pyr 44	-85.3536	-65.1234	-20.2302	23.2222
45	UK pyr 45	-86.3866	-65.3825	-21.0041	24.3333
46	UK pyr 46	-96.8059	-76.4032	-20.4028	23.5217
47	UK pyr 47	-83.5746	-62.6332	-20.9414	22
48	UK pyr 48	-86.9215	-67.6668	-19.2548	22.8947
49	UK pyr 49	-91.2584	-68.5932	-22.6652	18.8
50	UK pyr 50	-69.116	-55.3228	-13.7932	25.5714
51	UK pyr 51	-68.5876	-58.0876	-10.5	26.0714
52	UK pyr 52	-74.7601	-59.6527	-15.1074	25.8667
53	UK pyr 53	-73.3889	-64.4239	-8.96498	21.2105
54	UK pyr 54	-71.3509	-60.8764	-10.4745	27.9474
55	UK pyr 55	-74.7236	-64.9488	-9.77476	17.76

Table 1.8: Docking parameters with protein 1QPQ for unknown pyrimidine molecules (Series II).

Sr. No.	ID	Binding Energy	VDW	HBond	AverConPair
1	UK pyrs1	17.377	17.0682	0	20.5556
2	UK pyrs2	-78.989	-57.3475	-23.7755	24.5
3	UK pyrs3	-82.1703	-58.4182	-15.492	25.7368
4	UK pyrs4	-97.84	-62.8341	-29.1804	24.7895
5	UK pyrs5	-67.0732	-60.0732	-7	23.5
6	UK pyrs6	-65.5205	-58.5205	-7	22.8125
7	UK pyrs7	-66.9514	-59.9514	-7	23.5
8	UK pyrs8	-65.3454	-57.2472	-8.09817	22.9375
9	UK pyrs9	-66.7527	-59.0042	-7.74843	23.75
10	UK pyrs10	-65.2178	-56.4706	-8.74717	22.75
11	UK pyrs11	-43.452	-37.9882	-5.46376	16.3889
12	UK pyrs12	-82.6416	-63.853	-18.7886	24.6111
13	UK pyrs13	-67.1661	-60.1661	-7	23.625
14	UK pyrs14	-66.0166	-59.0384	-6.97812	27.3125

15	UK pyrs15	-67.1567	-57.6567	-9.5	21.125
16	UK pyrs16	-67.5031	-47.797	-19.7061	21.875
17	UK pyrs17	-68.83	-58.33	-10.5	21.125
18	UK pyrs18	-67.1823	-60.2069	-6.97541	28
19	UK pyrs19	-69.289	-62.3609	-6.92813	23.2778
20	UK pyrs20	-66.7187	-59.0242	-7.69455	23.1667
21	UK pyrs21	-78.1383	-71.1502	-6.98812	23

Table 1.9 shows summary statistics for the QSAR Model.

Table 1.9: Summary statistics for the QSAR Model.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics					Durbin-Watson
					R Square Change	F Change	df1	df2	Sig. F Change	
1	0.416[a]	0.173	0.003	106.687082	0.173	1.017	7	34	0.437	1.746

a. Predictors: (Constant), LELP01, Druglikeness01, TSA01, cLogS01, LE01, cLogP01, TMW01

b. Dependent Variable: Biological activity

The values of fraction variance may vary between 0 and 1. QSAR model having $r^2 > 0.173$ will only be considered for validation. For example, the value r = 0.416 and $r^2 = 0.173$ allowed us to indicate firmly the correlation between different parameters (independent variables) with biological activity of the compounds. In equation of biological activity, the negative coefficients of molecular volume (MV) and molecular weight (MW) explain that any increase in molecular volume or molecular weight of the compounds causes a decrease in the biological activity.

IV CONCLUSIONS

Based on the present investigation it can be concluded that the equation

"Biological Activity = (-320.284) + (-.447) x Total Mol. Wt. + (-92.618) x cLogP + (-18.068) x cLogS + (.566) x Total Surface area + (-2.948) x Drug likeliness + (1171.11) x LE + (30.258) x LELP."

can be useful for predicting the activity of new substituted pyrimidine derivatives prior to their synthesis.

Structure activity model indicates that these descriptors have significant relationships with observed bioactivity. We have observed a high relationship between experimental and predicted activity values, indicating the validation and the excellent quality of the derived model.

In equation of biological activity, the negative coefficients of surface area that any increase in surface area of the molecules causes a decrease in the biological activity.

As well as, the inhibition of Quinolinic acid Phosphoribosyltransferase (QAPRTase) having PDB code 1QPQ proteins can be an effective drug in the prevention and treatment of tuberculosis. In the present study, the ligands were generated and were studied for its ability to inhibit the 1QPQ by molecular docking method. The ligands with good inhibitory properties were generated among which UK pyr 46, UK pyr 49, UK pyr 37, UK pyrs3 and UK pyrs4 are found to be excellent drug candidate based on the molecular docking studies and its regression studies.

Thus on the basis of regression analysis study and docking study of substituted pyrimidine derivatives, it can be concluded that these compounds on further studies may prove to be therapeutic agent against mycobacterium tuberculosis.

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