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Regression Analysis and Docking Study of Hydroxyl Quinoline 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 thirty nine substituted hydroxyl quinoline 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 hydroxyl quinoline 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 hydroxyl quinoline 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, descriptors.*

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]

Hydroxyl quinolone is an important precursor for the synthesis of a wide variety of heterocyclic compounds. The variety of compounds synthesized reported to have various biological activities such as antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrhythmic and sedative. [8]

The distinctive structure and chemical properties of hydroxyl quinolone and its derivatives gave these compounds

therapeutic importance and hence have application in agricultural and medical fields. Hydroxyl quinolone and numerous of its derivatives exhibit potent activities against several strains of insects, fungi and bacteria which make them good candidates for the treatment of many parasitic and microbial infection diseases. In addition, other 8-HQ derivatives have showed antitumor and antioxidant activities. [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 hydroxyl quinoline inhibitory activity. The studied compounds are Tuberculosis inhibitors which inhibit Mycobacterium Tuberculosis. Interestingly, all these compounds were active and showed M. Tuberculosis inhibition with IC50 values ranged between 128 and 62 μM. [12] [13]

IIa. Descriptors generation

Firstly, the thirty nine 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 hydroxyl quinoline 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 (clog P), 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 2.1: 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	386.59	176.65	---	2.188	.032	33.801	739.39	---	---	---	---	---
TMW	.033	.271	.068	0.121	.904	-.509	.574	.300	.015	.009	.015	64.530
cLogP	-13.33	16.571	-.397	-.805	.424	-46.43	19.756	-.63	-.099	-.057	.021	48.681
cLogS	9.888	6.063	.213	1.631	.108	-2.22	21.996	.377	.198	.115	.294	3.406
TSA	-0.209	.145	-.320	-1.44	.155	-.499	.081	.191	-.176	-.102	.101	9.858
Drug likeness	-2.755	.735	-.313	-3.75	.000	-4.223	-1.288	-.55	-.422	-.265	.717	1.394
LEP	-481.5	234.61	-.640	-2.05	.044	-950.1	-12.97	-.25	-.247	-.145	.051	19.477
LELP	-.998	4.406	-.132	-.226	.822	-9.797	7.802	-.33	-.028	-.016	.015	67.825

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

Biological Activity = 386.597 + 0.033 x Total Mol. Wt. + (-13.338) x cLogP + 9.888 x cLogS + (-0.209) x Total Surface area + (-2.755) x Drug likeliness + (-481.54) x LE + (-0.998) x LELP.s

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 hydroxyl quinoline 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 hydroxyl quinoline given as:

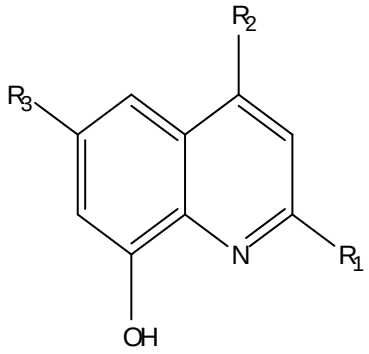

Figure 1:Substituted hydroxyl Quinoline

Table 3.1, 3.2 and 3.3 list the series of substituted hydroxyl quinoline derivatives designed in current project.

Table 3.1: Id, Abbreviations and name for Unknown compounds – Series 1.

ID	Compound	ID	Compound
UK A31	N,N'-(8-hydroxy-2-methoxyquinoline-4,6-diyl)diacetamide	UK A18	6-butoxy-2-methoxyquinolin-8-ol
UK A28	4,6-bis(2-aminoethyl)-2-methoxyquinolin-8-ol	UK A38	8-hydroxy-2-methoxyquinolin -4-yl acetate
UK A40	8-hydroxy-2-methoxyquinoline-4,6-diyl diacetate	UK A39	8-hydroxy-2-methoxyquinolin-6-yl acetate
UK A46	8-hydroxy-2-methoxyquinoline-4,6-diyl dibutyrate	UK A29	N-(8-hydroxy-2-methoxyquinolin-4-yl)acetamide
UK A34	N,N'-(8-hydroxy-2-methoxyquinoline-4,6-diyl)dipropionamide	UK A30	N-(8-hydroxy-2-methoxyquinolin-6-yl)acetamide
UK A25	4,6-bis(aminomethyl)-2-methoxyquinolin-8-ol	UK A32	N-(8-hydroxy-2-methoxyquinolin-4-yl)propionamide
UK A37	N,N'-(8-hydroxy-2-methoxyquinoline-4,6-diyl)dibutyramide	UK A33	N-(8-hydroxy-2-methoxyquinolin-6-yl)propionamide
UK A43	8-hydroxy-2-methoxyquinoline-4,6-diyl dipropionate	UK A41	8-hydroxy-2-methoxyquinolin-4-yl propionate
UK A19	4,6-dibutoxy-2-methoxyquinolin-8-ol	UK A42	8-hydroxy-2-methoxyquinolin-6-yl propionate
UK A13	4,6-diethoxy-2-methoxyquinolin-8-ol	UK A26	4-(2-aminoethyl)-2-methoxyquinolin-8-ol
UK A44	8-hydroxy-2-methoxyquinolin-4-yl butyrate	UK A27	6-(2-aminoethyl)-2-methoxyquinolin-8-ol
UK A45	8-hydroxy-2-methoxyquinolin-6-yl butyrate	UK A22	4,6-diamino-2-methoxyquinolin-8-ol
UK A16	2-methoxy-4,6-dipropoxyquinolin-8-ol	UK A49	2-methoxyquinoline-4,6,8-triol
UK A35	N-(8-hydroxy-2-methoxyquinolin-4-yl)butyramide	UK A23	4-(aminomethyl)-2-methoxyquinolin-8-ol
UK A36	N-(8-hydroxy-2-methoxyquinolin-6-yl)butyramide	UK A24	6-(aminomethyl)-2-methoxyquinolin-8-ol
UK A10	2,4,6-trimethoxyquinolin-8-ol	UK A14	2-methoxy-4-propoxyquinolin-8-ol
UK A17	4-butoxy-2-methoxyquinolin-8-ol	UK A15	2-methoxy-6-propoxyquinolin-8-ol

Table 3.2: Id, Abbreviations and name for Unknown compounds – Series 2.

ID	**Compound**	**ID**	**Compound**
UK G25	4,6-bis(aminomethyl)-2-phenylquinolin-8-ol	UK G35	N-(8-hydroxy-2-phenylquinolin-4-yl) butyramide
UK G28	4,6-bis(2-aminoethyl)-2-phenylquinolin-8-ol	UK G36	N-(8-hydroxy-2-phenylquinolin-6-yl) butyramide
UK G31	N,N'-(8-hydroxy-2-phenylquinoline-4,6-diyl)diacetamide	UK G17	4-butoxy-2-phenylquinolin-8-ol

UK G40	8-hydroxy-2-phenylquinoline-4,6-diyl diacetate	UK G18	6-butoxy-2-phenylquinolin-8-ol
UK G34	N,N'-(8-hydroxy-2-phenylquinoline-4,6-diyl)dipropionamide	UK G32	N-(8-hydroxy-2-phenylquinolin-4-yl) propionamide
UK G46	8-hydroxy-2-phenylquinoline-4,6-diyl dibutyrate	UK G33	N-(8-hydroxy-2-phenylquinolin-6-yl)propionamide
UK G43	8-hydroxy-2-phenylquinoline-4,6-diyl dipropionate	UK G41	8-hydroxy-2-phenylquinolin-4-yl propionate
UK G37	N,N'-(8-hydroxy-2-phenylquinoline-4,6-diyl)dibutyramide	UK G42	8-hydroxy-2-phenylquinolin-6-yl propionate
UK G22	4,6-diamino-2-phenylquinolin-8-ol	UK G19	4,6-dibutoxy-2-phenylquinolin-8-ol
UK G10	4,6-dimethoxy-2-phenylquinolin-8-ol	UK G16	2-phenyl-4,6-dipropoxyquinolin-8-ol
UK G13	4,6-diethoxy-2-phenylquinolin-8-ol	UK G11	4-ethoxy-2-phenylquinolin-8-ol
UK G44	8-hydroxy-2-phenylquinolin-4-yl butyrate	UK G12	6-ethoxy-2-phenylquinolin-8-ol
UK G45	8-hydroxy-2-phenylquinolin-6-yl butyrate	UK G14	2-phenyl-4-propoxyquinolin-8-ol
UK G49	2-phenylquinoline-4,6,8-triol	UK G15	2-phenyl-6-propoxyquinolin-8-ol
UK G26	4-(2-aminoethyl)-2-phenylquinolin-8-ol	UK G8	4-methoxy-2-phenylquinolin-8-ol
UK G27	6-(2-aminoethyl)-2-phenylquinolin-8-ol	UK G9	6-methoxy-2-phenylquinolin-8-ol
UK G38	8-hydroxy-2-phenylquinolin-4-yl acetate	UK G20	4-amino-2-phenylquinolin-8-ol
UK G39	8-hydroxy-2-phenylquinolin-6-yl acetate	UK G21	6-amino-2-phenylquinolin-8-ol
UK G23	4-(aminomethyl)-2-phenylquinolin-8-ol	UK G47	2-phenylquinoline-4,8-diol
UK G24	6-(aminomethyl)-2-phenylquinolin-8-ol	UK G48	2-phenylquinoline-6,8-diol
UK G29	N-(8-hydroxy-2-phenylquinolin-4-yl) acetamide	UK G56	4-(pent-1-en-1-yl)-2-phenylquinolin-8-ol
UK G30	N-(8-hydroxy-2-phenylquinolin-6-yl) acetamide	UK G59	4-(pent-1-en-1-yl)-2-phenylquinolin-8-ol

Table 3.3: Id, Abbreviations and name for Unknown compounds – Series 3.

ID	Compound	ID	Compound
UK J31	N,N'-(2-amino-8-hydroxyquinoline -4,6-diyl) diacetamide	UK J10	2-amino-4,6-dimethoxyquinolin-8-ol
UK J40	2-amino-8-hydroxyquinoline-4,6-diyl diacetate	UK J17	2-amino-4-butoxyquinolin-8-ol
UK J28	2-amino-4,6-bis(2-aminoethyl)quinolin-8-ol	UK J18	2-amino-6-butoxyquinolin-8-ol
UK J46	2-amino-8-hydroxyquinoline-4,6-diyl dibutyrate	UK J38	2-amino-8-hydroxyquinolin-4-yl acetate
UK J37	N,N'-(2-amino-8-hydroxyquinoline-4,6-diyl)dibutyramide	UK J39	2-amino-8-hydroxyquinolin-6-yl acetate
UK J34	N,N'-(2-amino-8-hydroxyquinoline-4,6-diyl)dipropionamide	UK J32	N-(2-amino-8-hydroxyquinolin-4-yl)propionamide
UK J43	2-amino-8-hydroxyquinoline-4,6-diyl dipropionate	UK J33	N-(2-amino-8-hydroxyquinolin -6-yl)propionamide
UK J25	2-amino-4,6-bis(aminomethyl)quinolin-8-ol	UK J41	2-amino-8-hydroxyquinolin-4-yl propionate
UK J19	2-amino-4,6-dibutoxyquinolin-8-ol	UK J42	2-amino-8-hydroxyquinolin-6-yl propionate
UK J13	2-amino-4,6-diethoxyquinolin-8-ol	UK J29	N-(2-amino-8-hydroxyquinolin -4-yl) acetamide
UK J44	2-amino-8-hydroxyquinolin-4-yl butyrate	UK J30	N-(2-amino-8-hydroxyquinolin -6-yl) acetamide
UK J45	2-amino-8-hydroxyquinolin-6-yl butyrate	UK J26	2-amino-4-(2-aminoethyl) quinolin-8-ol
UK J16	2-amino-4,6-dipropoxyquinolin-8-ol	UK J27	2-amino-6-(2-aminoethyl) quinolin-8-ol
UK J35	N-(2-amino-8-hydroxyquinolin-4-yl)butyramide	UK J52	2-amino-4,6-diphenylquinolin -8-ol
UK J36	N-(2-amino-8-hydroxyquinolin-6-yl)butyramide		

Table 3.4 shows the observed IC50 values of known molecules.

Table 3.4: 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 1	128	298.297	2.1613	-3.249	232.36	-2.11	0.40691	4.3641	5.3115
K 2	128	366.294	3.0096	-4.027	261.82	-9.3	0.3396	3.4266	8.8621
K 3	128	332.742	2.7673	-3.985	247.78	-2.0152	0.38639	3.7106	7.162
K 4	128	366.294	3.0636	-4.051	261.82	-9.3	0.3396	3.3726	9.0211
K 5	128	434.291	3.9119	-4.829	291.28	-9.3	0.29094	2.4503	13.446
K 6	128	434.291	3.9119	-4.829	291.28	-9.3	0.29094	2.4503	13.446
K 7	128	434.291	3.9119	-4.829	291.28	-9.3	0.29094	2.4503	13.446
K 8	128	434.291	3.9119	-4.829	291.28	-9.3	0.29094	2.4503	13.446
K 9	128	450.29	4.1626	-5.074	301.28	-12.84	0.28086	2.1839	14.821
K 10	128	400.739	3.6696	-4.787	277.24	-9.2052	0.32504	2.7275	11.29
K 11	128	384.284	3.1644	-4.365	268.17	-9.3	0.32597	3.2509	9.7078
K 12	128	464.317	3.8419	-4.847	313.54	-9.1628	0.27151	2.4913	14.15
K 13	128	502.288	4.7602	-5.607	320.74	-9.3	0.25416	1.5388	18.729
K 14	128	435.184	4.2756	-5.523	292.66	-9.2052	0.31168	2.0857	13.718
K 15	128	370.36	2.5346	-3.714	286.13	-2.11	0.32678	3.8968	7.7563
K 16	128	434.291	3.9119	-4.829	291.28	-9.3983	0.29094	2.4503	13.446
K 17	128	436.307	4.3546	-4.918	288.8	-9.0087	0.29085	2.0056	14.972
K 18	128	450.358	4.2777	-4.738	297.53	-8.3559	0.29022	2.0687	14.74
K 19	128	443.342	5.3936	-5.684	302.83	-12.505	0.28116	0.95966	19.183
K 20	118.5	433.303	4.6363	-5.39	292.52	-9.9832	0.29099	1.7269	15.933
K 21	100	338.449	5.3816	-6.34	291.98	-11.133	0.35507	1.0889	15.156
K 22	100	355.396	6.8606	-6.54	269.72	1.8018	0.32769	-0.41131	20.936
K 23	73	357.412	6.2113	-5.497	269.72	2.0472	0.32757	0.23553	18.962
K 24	64.9	418.292	3.9182	-5.342	281.28	-4.2869	0.30174	2.4603	12.985
K 25	62.5	597.635	4.9574	-6.913	437.46	-2.9277	0.20329	1.2662	24.386
K 26	62.5	597.635	4.9574	-6.913	437.46	-2.9277	0.20329	1.2662	24.386
K 27	62.5	663.641	5.9556	-7.622	470.57	-6.4917	0.18425	0.22247	32.323
K 28	62.5	625.67	4.4409	-6.321	459.72	-2.8734	0.19342	1.7628	22.959
K 29	62.5	695.658	5.6706	-8.053	489.42	-9.6823	0.17599	0.487	32.221
K 30	62.5	580.633	3.8557	-5.804	429.87	-2.9277	0.20866	2.3804	18.478
K 31	62.5	664.57	5.7605	-7.5	445.68	-5.8765	0.2067	0.41696	27.869
K 32	62.5	615.763	6.6752	-7.357	479.93	-19.825	0.19814	-0.46461	33.689
K 33	62.5	547.628	4.2099	-6.449	414.35	2.9223	0.22026	2.0516	19.114
K 34	62.5	547.628	4.2099	-6.449	414.35	2.9223	0.22026	2.0516	19.114
K 35	62.5	613.634	5.2081	-7.158	447.46	-3.7617	0.19819	1.004	26.278
K 36	62.5	575.663	3.6934	-5.857	436.61	2.9766	0.20879	2.5464	17.69
K 37	62.5	645.651	4.9231	-7.589	466.31	-7.2523	0.18871	1.2669	26.088
K 38	62.5	530.626	3.1082	-5.34	406.76	2.9223	0.22655	3.167	13.72
K 39	62.5	565.756	5.9277	-6.893	456.82	-13.975	0.21427	0.31967	27.665

Table 3.5 shows the calculated IC50 values by SPSS of known molecules.

Table 3.5: Descriptor values with calculated biological activity for Known set of molecules.

ID	Cal. 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 75	123.0414	363.221	2.5872	-3.664	234.91	-7.902	0.35339	3.8526	7.3212

K76	118.4833	434.291	3.9095	-4.441	291.28	-10.163	0.29094	2.4527	13.437
K 77	118.3242	360.452	4.8062	-5.241	297.15	-27.471	0.33997	1.637	14.137
K 78	117.2494	366.294	3.0096	-4.027	261.82	-9.3	0.3396	3.4266	8.8621
K 79	117.012	402.274	3.2652	-4.679	274.52	-9.3	0.31335	3.1303	10.42
K 80	117.012	402.274	3.2652	-4.679	274.52	-9.3	0.31335	3.1303	10.42
K 81	112.483	444.33	4.5007	-4.937	301.59	-12.505	0.28112	1.8516	16.01
K 82	107.5385	332.399	3.8974	-4.701	269.63	-19.461	0.37031	2.5809	10.525
K 83	99.85001	318.372	3.443	-4.431	255.87	-15.041	0.38753	3.0541	8.8845
K 84	94.63223	304.345	2.9886	-4.161	242.11	-11.841	0.40637	3.528	7.3545
K 85	92.95876	330.47	5.0505	-4.857	282	-22.425	0.37046	1.4304	13.633
K 86	90.82	321.423	2.4831	-5.42	234.32	-5.3365	0.37115	4.0098	6.6904
K 87	89.76056	316.356	2.8872	-4.625	242.61	-7.9097	0.38769	3.6126	7.4471
K 88	89.67291	316.443	4.5961	-4.587	268.24	-19.555	0.38769	1.9036	11.855
K 89	85.42117	290.318	2.4391	-3.999	225.59	-7.19	0.42705	4.098	5.7114
K 90	84.13612	290.318	2.5342	-3.891	228.35	-7.0864	0.42705	4.0029	5.9341
K 91	80.29692	286.33	3.1208	-4.567	220.35	-10.965	0.42745	3.4223	7.301
K 92	79.48568	269.347	2.4896	-4.479	212.15	-10.29	0.45064	4.0801	5.5246
K 93	79.24235	302.416	4.1417	-4.317	254.48	-14.415	0.40654	2.3777	10.188
K 94	78.06661	297.397	4.4838	-4.519	241.95	-15.858	0.40699	2.0429	11.017
K 95	76.52752	613.634	4.6117	-6.617	443.81	-2.9167	0.19819	1.6004	23.269
K 96	75.60999	563.627	3.8642	-6.153	420.7	2.9333	0.21432	2.3848	18.03
K 97	73.07683	272.303	2.7788	-4.297	206.59	-8.4316	0.45032	3.7861	6.1708
K 98	72.31325	591.721	4.5524	-6.382	442.38	-2.3954	0.2136	1.6755	21.313
K 99	72.21249	283.37	4.1418	-4.249	228.19	-13.376	0.42774	2.4058	9.6829
K 100	71.08276	609.671	4.7866	-6.617	453.37	-2.8911	0.19828	1.4283	24.14
K 101	70.95119	255.32	2.1476	-4.209	198.39	-7.7641	0.47604	4.4453	4.5114
K 102	70.21947	559.664	4.0391	-6.153	430.26	2.9589	0.21443	2.213	18.837
K 103	69.83652	541.714	3.8049	-5.918	419.27	3.4546	0.23234	2.4613	16.377
K 104	68.85012	412.488	4.3683	-7.614	297.77	-5.7753	0.28254	2.0163	15.461
K 105	67.64578	323.439	3.9424	-5.706	252.43	-7.7641	0.37099	2.5478	10.627
K 106	67.64578	323.439	3.9424	-5.706	252.43	-7.7641	0.37099	2.5478	10.627
K 107	67.12879	627.661	4.8874	-6.931	459.72	-2.8911	0.19338	1.3149	25.273
K 108	67.03975	283.37	4.0775	-4.219	228.19	-11.025	0.42774	2.4701	9.5326
K 109	67.02199	351.492	4.6264	-6.246	279.95	-10.29	0.34055	1.8277	13.585
K 110	67.02199	351.492	4.6264	-6.246	279.95	-10.29	0.34055	1.8277	13.585
K 111	66.78265	577.654	4.1399	-6.467	436.61	2.9589	0.20874	2.0984	19.833
K 112	63.41776	288.346	3.412	-4.566	226.59	-6.9069	0.42725	3.1281	7.986
K 113	63.41776	288.346	3.412	-4.566	226.59	-6.9069	0.42725	3.1281	7.986
K 114	63.41209	340.422	4.6276	-5.818	260.63	-8.4316	0.35493	1.8404	13.038
K 115	62.56439	274.363	3.2329	-3.777	226.96	-6.795	0.45009	3.3288	7.1828
K 116	62.03273	246.265	2.171	-3.671	189.57	-6.9069	0.50368	4.4376	4.3103
K 117	61.40076	368.475	5.3116	-6.358	288.15	-10.965	0.32689	1.122	16.249
K 118	60.96818	246.265	2.225	-3.695	189.57	-6.9069	0.50368	4.3836	4.4175
K 119	60.91223	306.408	3.2472	-5.143	222.86	-0.13635	0.38852	3.2665	8.3578
K 120	60.24441	404.596	6.277	-6.709	320.62	-14.364	0.29235	0.11598	21.471

Table 3.6: Descriptor values with calculated biological activity and docking score for Unknown set of molecules of Series 1.

ID	Cal. 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.	For 1QPQ		
										Total Energy	VDW	H-bond
UK A31	90.58317	289.29	1.318	-3.253	218.1	0.5200	0.4271	5.22	3.0872	-83.88	-55.30	-28.58
UK A28	89.29562	261.32	0.781	-2.713	207.3	-1.877	0.4753	5.801	1.6438	-72.99	-54.98	-18.01
UK A40	88.95952	291.25	1.884	-3.169	215.2	-1.53	0.4269	4.651	4.4142	-24.93	-3.36	-21.57
UK A46	81.53532	347.36	3.702	-4.249	270.2	-4.525	0.3544	2.756	10.445	-3.77	10.79	-14.57
UK A34	81.21326	317.34	2.227	-3.793	245.6	1.7809	0.3876	4.27	5.7467	-92.21	-64.39	-27.82

UK A25	80.3121	233.27	-0.079	-2.489	179.7	-1.716	0.5352	6.71	-0.147	-86.15	-67.30	-18.85
UK A37	80.10017	345.39	3.136	-4.333	273.2	-1.255	0.3545	3.325	8.845	-92.49	-65.16	-27.32
UK A43	76.70276	319.31	2.793	-3.709	242.7	0.7223	0.3874	3.702	7.2099	95.33	97.43	-2.10
UK A19	61.95097	319.4	4.401	-4.285	262.3	-6.76	0.3874	2.094	11.36	-68.08	-52.59	-15.49
UK A13	60.22137	263.29	2.583	-3.205	207.2	-3.122	0.4750	3.995	5.439	-83.54	-66.52	-17.03
UK A44	59.39001	261.27	2.806	-3.409	202.7	-4.525	0.4753	3.776	5.9052	-97.20	-79.79	-17.42
UK A45	59.39001	261.27	2.806	-3.409	202.7	-4.525	0.4753	3.776	5.9052	-78.60	-65.78	-12.82
UK A16	55.17206	291.34	3.492	-3.745	234.7	-1.962	0.4269	3.042	8.1805	-71.58	-55.21	-16.36
UK A35	53.94156	260.29	2.523	-3.451	204.2	-1.255	0.4754	4.060	5.3084	-82.45	-69.96	-12.49
UK A36	53.94156	260.29	2.523	-3.451	204.2	-1.255	0.4754	4.060	5.3084	-73.68	-48.01	-25.67
UK A10	51.17419	235.23	1.771	-2.605	179.7	-1.688	0.5349	4.857	3.3114	-78.37	-60.69	-17.68
UK A17	47.12179	247.29	3.156	-3.427	198.7	-6.76	0.5035	3.450	6.2684	-74.33	-61.12	-13.21
UK A18	47.12179	247.23	3.156	-3.427	198.7	-6.76	0.5035	3.450	6.2684	-77.07	-70.14	-6.93
UK A38	46.93499	233.22	1.898	-2.869	175.2	-1.53	0.5352	4.734	3.5462	-87.25	-63.69	-23.56
UK A39	46.93499	233.22	1.898	-2.869	175.2	-1.53	0.5352	4.734	3.5462	-76.71	-56.97	-19.73
UK A29	44.76506	232.23	1.615	-2.911	176.7	0.5200	0.5353	5.019	3.0167	-80.84	-63.15	-17.69
UK A30	44.76506	232.23	1.615	-2.911	176.7	0.5200	0.5353	5.019	3.0167	-72.88	-60.80	-12.07
UK A32	44.31339	246.26	2.069	-3.181	190.4	1.7809	0.5036	4.539	4.1086	-80.06	-57.75	-22.31
UK A33	44.31339	246.26	2.069	-3.181	190.4	1.7809	0.5036	4.539	4.1086	-74.61	-58.25	-16.36
UK A41	43.70849	247.24	2.352	-3.139	189	0.7223	0.5035	4.254	4.6717	-92.18	-74.36	-17.81
UK A42	43.70849	247.24	2.352	-3.139	189	0.7223	0.5035	4.254	4.6717	-79.50	-65.47	-14.03
UK A26	41.72954	218.25	1.346	-2.641	171.2	-1.877	0.5711	5.314	2.3572	-77.35	-64.98	-12.38
UK A27	41.72954	218.25	1.346	-2.641	171.2	-1.877	0.5711	5.314	2.3572	-72.95	-63.56	-9.39
UK A22	36.36161	205.21	0.556	-2.721	152.2	-1.667	0.6116	6.131	0.91015	-82.22	-59.87	-22.35
UK A49	35.00089	207.18	1.219	-1.977	147.9	-1.688	0.6112	5.463	1.9957	-84.13	-61.26	-22.87
UK A23	31.79531	204.22	0.916	-2.529	157.5	-1.716	0.6118	5.773	1.4974	-78.74	-67.30	-11.44
UK A24	31.79531	204.22	0.916	-2.529	157.5	-1.716	0.6118	5.773	1.4974	-76.28	-65.78	-10.50
UK A14	31.01416	233.26	2.702	-3.157	185.0	-1.962	0.5352	3.930	5.0485	-72.90	-59.55	-13.35
UK A15	31.01416	233.26	2.702	-3.157	185.0	-1.962	0.5352	3.930	5.0485	-74.41	-67.42	-6.99

Table 3.7: Descriptor values with calculated biological activity and docking score for Unknown set of molecules of Series 2.

ID	Cal. 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.	For 1QPQ		
										Total Energy	VDW	H-bond
UK G25	91.05096	279.34	1.3899	-3.724	217.29	-1.968	0.4281	5.164	3.2463	-95.27	-78.67	-16.61
UK G28	89.66707	307.39	2.2501	-3.948	244.81	-2.167	0.3884	4.2622	5.7927	-79.61	-62.93	-16.68
UK G31	82.39182	335.36	2.7875	-4.488	255.67	0.495	0.3552	3.687	7.8457	-82.12	-56.24	-25.88
UK G40	80.68257	337.33	3.3535	-4.404	252.75	-1.632	0.3551	3.1184	9.4425	-108.1	-80.98	-27.16
UK G34	66.7098	363.41	3.6963	-5.028	283.19	1.7571	0.3272	2.7433	11.297	-88.46	-76.55	-11.91
UK G46	62.1851	393.43	5.1711	-5.484	307.79	-4.743	0.303	1.234	17.066	-121.2	-94.11	-27.12
UK G43	62.16415	365.38	4.2623	-4.944	280.27	0.6062	0.3270	2.175	13.031	14.42	28.85	-14.43

UK G37	60.77733	391.47	4.6051	-5.568	310.71	-1.379	0.3031	1.8022	15.193	-91.10	-80.89	-10.21
UK G22	60.24396	251.28	2.0255	-3.956	189.77	-1.765	0.4765	4.5743	4.2505	-84.94	-67.42	-17.52
UK G10	60.01812	281.31	3.2401	-3.84	217.25	-1.582	0.4279	3.3107	7.5712	-91.24	-77.43	-13.81
UK G13	59.2261	309.36	4.0527	-4.44	244.77	-3.237	0.3882	2.4568	10.438	-81.21	-66.92	-14.29
UK G44	58.6121	307.34	4.2756	-4.644	240.26	-4.743	0.3884	2.2368	11.007	-104.3	-81.09	-23.26
UK G45	58.6121	307.34	4.2756	-4.644	240.26	-4.743	0.3884	2.2368	11.007	-82.36	-69.05	-13.31
UK G49	58.4717	253.25	2.6887	-3.212	185.43	-1.771	0.4762	3.9077	5.6451	-85.96	-68.78	-17.17
UK G26	58.28716	264.32	2.8151	-3.876	208.77	-2.167	0.4512	3.7628	6.2391	-81.03	-65.58	-15.46
UK G27	58.28716	264.32	2.8151	-3.876	208.77	-2.167	0.4512	3.7628	6.2391	-79.28	-70.50	-8.79
UK G38	56.3419	279.29	3.3668	-4.104	212.74	-1.632	0.4281	3.1871	7.8635	-94.88	-71.62	-23.26
UK G39	56.3419	279.29	3.3668	-4.104	212.74	-1.632	0.4281	3.1871	7.8635	-77.98	-63.50	-14.49
UK G23	55.96764	250.3	2.385	-3.764	195.01	-1.968	0.4766	4.2165	5.0036	-83.24	-69.67	-13.57
UK G24	55.96764	250.3	2.385	-3.764	195.01	-1.968	0.4766	4.2165	5.0036	-83.91	-73.20	-10.71
UK G29	54.11633	278.31	3.0838	-4.146	214.2	0.495	0.4282	3.4717	7.2009	-74.33	-61.97	-12.36
UK G30	54.11633	278.31	3.0838	-4.146	214.2	0.495	0.4282	3.4717	7.2009	-78.18	-62.68	-15.50
UK G35	53.05251	306.36	3.9926	-4.686	241.72	-1.379	0.3885	2.5212	10.276	-72.25	-55.81	-16.44
UK G36	53.05251	306.36	3.9926	-4.686	241.72	-1.379	0.3885	2.5212	10.276	-84.81	-69.36	-15.45
UK G17	50.95586	293.36	4.6252	-4.662	236.27	-7.019	0.4073	1.9074	11.354	-73.18	-58.53	-14.65
UK G18	50.95586	293.36	4.6252	-4.662	236.27	-7.019	0.4073	1.9074	11.354	-76.99	-63.51	-13.48
UK G32	48.02723	292.33	3.5382	-4.416	227.96	1.7571	0.4074	2.9959	8.6836	-71.75	-61.22	-10.53
UK G33	48.02723	292.33	3.5382	-4.416	227.96	1.7571	0.4074	2.9959	8.6836	-81.12	-65.62	-15.50
UK G41	47.52892	293.32	3.8212	-4.374	226.5	0.6062	0.4073	2.7115	9.3803	-99.21	-76.07	-23.14
UK G42	47.52892	293.32	3.8212	-4.374	226.5	0.6062	0.4073	2.7115	9.3803	-83.85	-72.32	-11.53
UK G19	47.04649	365.47	5.8703	-5.52	299.81	-7.019	0.3270	0.5668	17.948	-76.48	-66.93	-9.55
UK G16	46.54647	337.41	4.9615	-4.98	272.29	-2.213	0.3551	1.5103	13.97	-77.94	-62.01	-15.93
UK G11	44.87505	265.31	3.7164	-4.122	208.75	-3.237	0.4510	2.8598	8.2387	-75.15	-64.45	-10.70
UK G12	44.87505	265.31	3.7164	-4.122	208.75	-3.237	0.4510	2.8598	8.2387	-80.54	-72.02	-8.52
UK G14	40.45716	279.33	4.1708	-4.392	222.51	-2.213	0.4281	2.3831	9.7415	-71.98	-55.70	-16.28
UK G15	40.45716	279.33	4.1708	-4.392	222.51	-2.213	0.4281	2.3831	9.7415	-75.44	-68.44	-7.00
UK G8	40.14965	251.28	3.3101	-3.822	194.99	-1.582	0.4765	3.2897	6.9462	-77.81	-67.06	-10.75
UK G9	40.14965	251.28	3.3101	-3.822	194.99	-1.582	0.4765	3.2897	6.9462	-78.16	-68.61	-9.55
UK G20	38.4192	236.27	2.7028	-3.88	181.25	-1.765	0.5050	3.9238	5.3516	-80.61	-69.90	-10.71
UK G21	38.4192	236.27	2.7028	-3.88	181.25	-1.765	0.5050	3.9238	5.3516	-78.77	-71.40	-7.37
UK G47	37.58745	237.25	3.0344	-3.508	179.08	-1.771	0.5049	3.5904	6.0098	-80.69	-69.65	-11.04
UK G48	37.5874	237.25	3.0344	-3.508	179.08	-1.771	0.5049	3.5904	6.0098	-79.29	-66.57	-12.72
UK G56	30.6626	289.37	5.3795	-5.252	239.01	-6.409	0.4077	1.159	13.194	-65.55	-50.53	-15.02
UK G59	30.6626	289.37	5.3795	-5.252	239.01	-6.409	0.4077	1.159	13.194	-81.42	-76.86	-4.56

Table 3.8: Descriptor values with calculated biological activity and docking score for Unknown set of molecules of Series 3

ID	Cal. 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.	For 1QPQ		
										Total Energy	VDW	H-bond

UK J31	91.1776	274.279	0.711	-3.311	204.43	0.435	0.4501	5.8504	1.5805	-86.33	-64.08	-22.25
UK J40	89.84479	276.247	1.277	-3.227	201.51	-1.6942	0.4498	5.2813	2.8394	-102.8	-71.60	-31.29
UK J28	87.63818	246.313	0.174	-2.771	193.57	-2.1675	0.5036	6.4345	0.3454	-77.61	-61.14	-16.47
UK J46	86.29867	332.355	3.095	-4.307	256.55	-4.6775	0.3703	3.3834	8.3577	27.43	39.19	-11.77
UK J37	84.68704	330.387	2.529	-4.391	259.47	-1.3687	0.3704	3.952	6.8266	-88.74	-69.91	-18.82
UK J34	83.89203	302.333	1.620	-3.851	231.95	1.7307	0.4065	4.8993	3.9853	-88.59	-67.58	-21.00
UK J43	79.61216	304.301	2.186	-3.767	229.03	0.61685	0.4063	4.3305	5.3798	84.98	83.15	1.83
UK J25	74.66189	218.259	-0.68	-2.547	166.05	-1.968	0.5711	7.3472	-1.201	-84.33	-72.87	-11.46
UK J19	65.27361	304.389	3.794	-4.343	248.57	-6.9439	0.4063	2.7224	9.337	-71.82	-53.37	-18.45
UK J13	58.52318	248.281	1.976	-3.263	193.53	-3.3175	0.5034	4.6285	3.9264	-83.65	-63.93	-19.72
UK J44	57.58622	246.265	2.199	-3.467	189.02	-4.6775	0.5036	4.4091	4.3669	-105.2	-80.78	-24.42
UK J45	57.58622	246.265	2.199	-3.467	189.02	-4.6775	0.5036	4.4091	4.3669	-91.99	-62.29	-29.70
UK J16	56.30983	276.335	2.885	-3.803	221.05	-2.1484	0.4498	3.6732	6.4137	-78.57	-59.93	-18.64
UK J35	51.99139	245.281	1.916	-3.509	190.48	-1.3687	0.5038	4.6938	3.804	-77.70	-70.73	-6.97
UK J36	51.99139	245.281	1.916	-3.509	190.48	-1.3687	0.5038	4.6938	3.804	-84.46	-62.40	-22.06
UK J10	45.00758	220.227	1.164	-2.663	166.01	-1.6677	0.5708	5.4931	2.0392	-88.35	-72.51	-15.84
UK J17	43.71749	232.282	2.549	-3.485	185.03	-6.9439	0.5353	4.0849	4.7615	-78.52	-62.89	-15.63
UK J18	43.71749	232.282	2.549	-3.485	185.03	-6.9439	0.5353	4.0849	4.7615	-73.78	-55.45	-18.34
UK J38	41.27232	218.211	1.290	-2.927	161.5	-1.6942	0.5711	5.3704	2.2599	-93.34	-68.75	-24.59
UK J39	41.27232	218.211	1.290	-2.927	161.5	-1.6942	0.5711	5.3704	2.2599	-84.93	-55.24	-29.69
UK J32	40.40278	231.254	1.462	-3.239	176.72	1.7307	0.5355	5.1738	2.7303	-78.61	-60.29	-18.32
UK J33	40.40278	231.254	1.462	-3.239	176.72	1.7307	0.5355	5.1738	2.7303	-81.69	-59.13	-22.55
UK J41	39.99358	232.238	1.745	-3.197	175.26	0.61685	0.5353	4.889	3.2597	-98.55	-74.06	-24.49
UK J42	39.99358	232.238	1.745	-3.197	175.26	0.61685	0.5353	4.889	3.2597	-88.25	-58.53	-29.72
UK J29	38.84136	217.227	1.007	-2.969	162.96	0.435	0.5713	5.6554	1.7638	-76.28	-59.32	-16.96
UK J30	38.84136	217.227	1.007	-2.969	162.96	0.435	0.5713	5.6554	1.7638	-78.87	-62.46	-16.41
UK J26	33.88052	203.244	0.739	-2.699	157.53	-2.1675	0.6120	5.953	1.2074	-75.99	-64.78	-11.22
UK J27	33.88052	203.244	0.739	-2.699	157.53	-2.1675	0.6120	5.953	1.2074	-77.37	-60.44	-16.93
UK J52	31.04497	312.371	4.622	-6.799	241.01	-1.7657	0.3718	1.8829	12.431	-83.94	-68.04	-15.90

Table 3.9: Summary statistics for the QSAR Model.

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	0.822[a]	0.675	0.640	31.028162	0.675	19.285	7	65	.000	1.172
a. Predictors: (Constant), LELP01, Druglikeness01, TSA01, cLogS01, LE01, cLogP01, TMW01										
b. Dependent Variable: IC50										

The values of fraction variance may vary between 0 and 1. QSAR model having $r^2 > 0.675$ will only be considered for validation. For example, the value r = 0.848 and r2 = 0.719 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 = 386.597 + 0.033 x Total Mol. Wt. + (-13.338) x cLogP + 9.888 x cLogS + (-0.209) x Total Surface area + (-2.755) x Drug likeliness + (-481.54) x LE + (-0.998) x LELP"

can be useful for predicting the activity of new substituted hydroxyl quinoline 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 UKA34, UKA37, UKA43, UKA44, UKA41, UKG40, UKG46, UKG44, UKJ40, UKJ44 are found to be excellent drug candidate based on the molecular docking studies and its ADME properties.

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

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