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Regression Analysis and Docking Study of 4-Quinolylhydrazone Based Compounds as Antituberculosis Agents

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Asian Journal of Organic & Medicinal Chemistry

Volume: 4 Year: 2019
Issue: 4 Month: October–December
pp: 248–255
DOI: https://doi.org/10.14233/ajomc.2019.AJOMC-P237

Received: 18 October 2019
Accepted: 5 December 2019
Published: 31 December 2019

ABSTRACT

In present study, at the beginning, the molecules whose biological properties are known are well-thought-out as a known set for regression analysis model building purpose. Using the Datawarrior software the descriptors were calculated for known set. Novel substituted 4-hydrazinylqunoline molecules were designed, improved and their descriptors were calculated. Morever, the regression analysis model was used to determine the biological activities of these new molecules. Along with this, the inhibition studies for 1QPQ and 1KNC by molecular docking method were also carried out to validate the therapeutic nature of these molecules. Accordingly, it can be concluded that these moieties on further studies may evident to be therapeutic representative against *Mycobacterium tuberculosis*.

KEYWORDS

Structure activity, Biological activity, Docking, Tuberculosis, Descriptor, Quinolines.

INTRODUCTION

In the present scenario, the drug design process get immense importance due to the applicability of the tool to the actual synthesis of the drug molecules. In this process the quantitative structure activity relationship (QSAR) plays a key role. The unique purposes of this process are development of relationship between structural features of molecules and the property of interest mainly biological activity. Using the SAR study data, the biological activity can be defined for novel entrant structures [1]. The target of QSAR modeling is to create a trend in the descriptor values, which matches the trends in biological activity [2,3]. As per the techniques developed in the current period, the experimental values of various properties have been related directly to structure information. The structure of the molecule is characterized in a mathematical way so that essential information can be programmed and take out in a form that lends itself to modeling. In this process, it is expected that the significant structural descriptions are encoded in the structure representation and then recognized in the modeling process. In this manner, the synthesis of new agents may be guided towards the expected goal. The structure-based methodology is a rational approach to the QSAR problem that has been developed over the preceding 25 years; this is the part of very huge approach, the so-called quantitative information

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analysis (QIA) [4]. The QIA method mainly focused on the two features of the data that are known directly, firstly on the measured activity and/or property values and secondly on the molecular structures in the data set. The essential data is related to the manner in which molecules present themselves to each other in non-covalent interactions. It is now looks clear that this approach can be achieved without the need for unambiguous three-dimensional (3D) structure information. The essential data implicits in the encoded descriptors. It should be pointed out that the topological structure descriptors are used to produce good predictive models for log P [5-8]. 4-Quinolylhydrazone is a pompous precursor for the synthesis of a wide range of heterocyclic compounds. Various hydrazine moieties synthesized, has been reported to have various biological activities such as antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic and antiarrhythmic [9,10]. The peculiar structure and chemical properties of 4-quinolylhydrazone and its derivatives gave these compounds therapeutic importance so as to give an agricultural and medicinal importance. 4-Quinolylhydrazone and the related derivatives of the same revel potent activities against the numerous stains of insects, fungi and bacteria which make them good candidates for the treatment of several parasitic and microbial diseases. The 8-hydroxyquinoline derivatives shows antitumor and antioxidant activities [11,12]. Datawarrior version 4.6.1 package [13] is capable to calculate certain physico-chemical properties, drug-likeness related parameters, ligand efficiencies, various atom and ring counts, molecular shape, flexibility and complexity as well as clues for potential structure activity. In present study, the experimental efforts 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 molecules are determined. These molecules are also subjected to inhibition studies against quinolinic acid phosphoribosyl transferase (QAPRTase) (PDB code: 1QPQ) and Enoyl-ACP Reductase (PDB code: 1KNC) enzymes, an important target for designing novel potential inhibitor for tuberculosis.

EXPERIMENTAL

Under the experimental phase the inhibitor activity of 4-quinolylhydrazone moiety, taken into account as an activity parameter. The various considered molecules played a role of inhibitor, which inhibits *Mycobacterium tuberculosis*. A series of substituted 4-qunolylhydrazone derivatives designed in present study are listed with their ID and compounds name (Table-1). All these compounds were active against the *Mycobacterium tuberculosis* [14,15].

Descriptor generation: In the process of descriptor generation, in the first step 41 unknown molecules were pre-optimized by means of molecular mechanics. In second step, the resulted minimized structures were further improved using the semi-empirical techniques. Finally, these substituted 4-quinolylhydrazone were re-optimized by using Gaussian program package.

TABLE-1
ID AND NAME OF UNKNOWN COMPOUNDS (SERIES-I)

ID	Name and structure of 4-quinolylhydrazone compound	ID	Name and structure of 4-quinolylhydrazone compound
U 1	Z-2-benzylidene-1-(quinoline-4-yl)hydrazine	U 22	(Z)-2-(2-(trifluoromethyl)benzylidene)-1-(quinolin-4-yl)hydrazine
U 2	(Z)-2-(4-chlorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 23	(Z)-2-(3-(trifluoromethyl)benzylidene)-1-(quinolin-4-yl)hydrazine
U 3	(Z)-2-(2-nitrobenzylidene)-1-(quinolin-4-yl)hydrazine	U 24	(Z)-2-(4-(trifluoromethyl)benzylidene)-1-(quinolin-4-yl)hydrazine
U 4	(Z)-2-(3-methoxybenzylidene)-1-(quinolin-4-yl)hydrazine	U 25	(Z)-2-(4-methanaminebenzylidene)-1-(quinolin-4-yl)hydrazine
U 5	(Z)-2-(4-methoxybenzylidene)-1-(quinolin-4-yl)hydrazine	U 26	(Z)-2-(2-ethoxybenzylidene)-1-(quinolin-4-yl)hydrazine
U 6	(Z)-2-(3-nitrobenzylidene)-1-(quinolin-4-yl)hydrazine	U 27	(Z)-2-(3-ethoxybenzylidene)-1-(quinolin-4-yl)hydrazine
U 7	(Z)-2-(4-hydroxybenzylidene)-1-(quinolone-4yl)hydrazine	U 28	(Z)-2-(4-ethoxybenzylidene)-1-(quinolin-4-yl)hydrazine
U 8	(Z)-2-(4-formylbenzylidene)-1-(quinolone-4yl)hydrazine	U 29	(Z)-2-(2-butylbenzylidene)-1-(quinolin-4-yl)hydrazine
U 9	(Z)-2-(2-chlorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 30	(Z)-2-(3-butylbenzylidene)-1-(quinolin-4-yl)hydrazine
U 10	(Z)-2-(3-chlorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 31	(Z)-2-(4-butylbenzylidene)-1-(quinolin-4-yl)hydrazine
U 11	(Z)-2-(4-N,N-diethylbenzeneamine)-1-(quinolin-4-yl)hydrazine	U 32	(Z)-2-(2-(propionamide)benzylidene)-1-(quinoline-4-yl)hydrazine
U 12	(Z)-2-(4-(acetamide)benzylidene)-1-(quinoline-4-yl)hydrazine	U 33	(Z)-2-(3-(propionamide)benzylidene)-1-(quinoline-4-yl)hydrazine
U 13	(Z)-2-(2-methoxybenzylidene)-1-(quinolin-4-yl)hydrazine	U 34	(Z)-2-(4-(propionamide)benzylidene)-1-(quinoline-4-yl)hydrazine
U 14	(Z)-2-(2-(naphthalen-1-yl)benzylidene)-1-(quinolin-4-yl)hydrazine	U 35	(Z)-2-(2-(propionamide)benzylidene)-1-(quinoline-4-yl)hydrazine
U 15	(Z)-2-(2-(quinolin-4-yl)benzylidene)-1-(quinolin-4-yl)hydrazine	U 36	(Z)-2-(3-(acetate)benzylidene)-1-(quinoline-4-yl)hydrazine
U 16	(Z)-2-(4-(quinolin-4-yl)benzylidene)-1-(quinolin-4-yl)hydrazine	U 37	(Z)-2-(4-(acetate)benzylidene)-1-(quinoline-4-yl)hydrazine
U 17	(Z)-2-(2-fluorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 38	(Z)-2-(2-N,N-dimethylbenzeneamine)-1-(quinolin-4-yl)hydrazine
U 18	(Z)-2-(3-fluorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 39	(Z)-2-(3-N,N-dimethylbenzeneamine)-1-(quinolin-4-yl)hydrazine
U 19	(Z)-2-(4-fluorobenzylidene)-1-(quinolin-4-yl)hydrazine	U 40	(Z)-2-(3-nitrobenzylidene)-1-(quinolin-4-yl)hydrazine
U 20	(Z)-2-(2-cynobenzylidene)-1-(quinolin-4-yl)hydrazine	U 41	(Z)-2-(4-N,N-dimethylbenzeneamine)-1-(quinolin-4-yl)hydrazine
U 21	(Z)-2-(4-cynobenzylidene)-1-(quinolin-4-yl)hydrazine		

The QSAR properties module from Datawarrior version 4.6.1 package was used to calculate the various properties like: partition coefficient octanol/water (clog P), aqueous solubility (clog S), total molecular weight, polar surface area, fragment-based drug-likeness prediction, ligand efficiency (LE), lipophilic ligand efficiency (LLE), ligand efficiency lipophilic price (LELP), hydrogen donor, hydrogen acceptor, *etc*.

Regression analysis: Linear regression analysis of molecular descriptors is carried out using the stepwise strategy in SPSS version 24 for Windows [16]. Linear regression analysis performed for all compounds *i.e.* for 4-qunolylhydrazone, molecular series.

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

Biological activity = 266.421 + 0.034 × Monoisotopic mass + 9.888 × clog S + (-0.004) × H-Acceptors + 0.001 × H-Donors + 0.209 × Total surface area + 0.021 × Relative PSA + -2.754 × Drug likeness + -481.381 × LE from Structure No + 13.326 × LLE from Structure No + (-1.004) × LELP from Structure No + 0.009 × Drug score

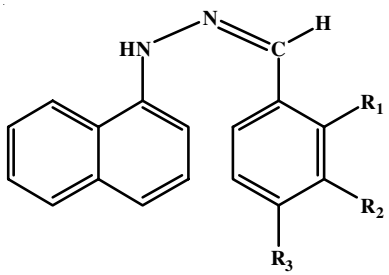
The computer based model system provides number of additional information about the regression (Table-2).

Docking studies: Quinolinic acid phosphoribosyltransferase (QAPRTase) having PDB code 1QPQ and enoyl-ACP reductase (PDB code: 1KNC) was selected as the target enzyme. Their 3D electronic structure having natural inhibitor was obtained 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 [17]. Due to this reason the quinolinic acid phosphoribosyl transferase (QAPRTase) enzyme offers an attractive target for designing novel potential inhibitor for *Mycobacterium tuberculosis* [18].

In docking study, the pharmacological interactions are very important to identify lead compounds and understanding the ligand binding mechanisms for therapeutic target. iGEMDOCK [19] software provides docking, virtual screening and post screening analysis. It provides the biological insights by giving the pharmacological interactions from screening compounds. Initially, iGEMDOCK provides interactive interfaces to prepare 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 [20]. The selected set of ligands was 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.

RESULTS AND DISCUSSION

Structure activity relationships (SAR): In present study, the structure activity relationships of known and unknown molecules have been performed by using the aforementioned combinatorial tools and various physico-chemical properties of various substituted 4-qunolylhydrazone were determined (Tables 3-6). In this process, carboxyaldehyde aromatic ring in 4-qunolylhydrazone molecule was substituted with different groups containing either electron withdrawing and/or electron donating groups using the HyperChem software. The general structure with various possible substitution in 4-qunolylhydrazone is given as follows:



Structure of substituted 4-qunolylhydrazone

Table-7 shows docking parameters of unknown series of 4-qunolylhydrazone compounds (Series-I) with proteins 1QPQ and 1KNC binding sites.

TABLE-2
REGRESSION ANALYSIS DATA

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.	95.0 % Confidence interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
(Constant)	266.421	0.31		8533.807	0.000	266.357	266.485
Mono isotopic mass	0.034	0.000	0.040	716.830	0.000	0.033	0.034
clog S	9.888	0.002	0.241	6469.069	0.000	9.885	9.891
H-Acceptors	-0.004	0.002	0.000	-1.867	0.073	-0.008	0.000
H-Donors	0.001	0.002	0.000	0.287	0.776	-0.004	0.005
Total surface area	0.209	0.000	0.196	2137.253	0.000	0.209	0.209
Relative PSA	0.021	0.19	0.000	1.090	0.285	-0.019	0.061
Polar surface area	0.00008	0.000	0.000	0.330	0.744	0.000	0.001
Drug likeness	-2.754	0.008	-0.246	-8650.126	0.000	-2.755	-2.754
LE from total m.w.	-481.38	0.028	-1.250	-17062.393	0.000	-418.439	-481.323
LLE from total m.w.	13.326	0.003	0.403	4411.513	0.000	13.319	13.332
LELP from total m.w.	-1.004	0.002	0.078	-655.097	0.000	-1.008	-1.001
Drug score	0.009	0.012	0.000	0.718	0.479	-1.016	0.034

Dependent variable: Calculated biological activity.

TABLE-3
DESCRIPTOR VALUES AND BIOLOGICAL ACTIVITY VALUES FOR KNOWN SET OF MOLECULES OF SERIES-I

m.f.	Dataset name	Total m.w.	m.w.	Monoisotopic mass	clog P	clog S	H-Acceptors	H-Donors	Total surface area	Relative PSA	Polar surface area
$C_{21}H_{24}N_4O$	N1	348.449	348.449	348.195	5.7959	-4.509	5	1	287.2	0.16536	49.75
$C_{22}H_{26}N_4O$	N2	362.475	362.475	362.2107	6.2022	-4.809	5	1	300.96	0.1578	49.75
$C_{20}H_{21}N_4Cl$	N3	352.868	352.868	352.1455	6.4719	-5.227	4	1	280.36	0.13372	40.52
$C_{23}H_{25}N_3$	N4	343.473	343.473	343.2048	7.6916	-5.99	3	1	282.66	0.12007	37.28
$C_{21}H_{17}N_3O$	N5	327.386	327.386	327.1372	6.2813	-5.479	4	1	259.46	0.16935	46.51
$C_{22}H_{19}N_3O_2$	N6	357.412	357.412	357.1477	6.2113	-5.497	5	1	281.72	0.19147	55.74
$C_{23}H_{21}N_3O_2$	N7	371.439	371.439	371.1634	6.6092	-5.865	5	1	293.98	0.18348	55.74
$C_{23}H_{21}N_3O_2$	N8	371.439	371.439	371.1634	6.6092	-5.865	5	1	293.98	0.18348	55.74
$C_{18}H_{17}N_3O_2$	N9	307.352	307.352	307.1321	5.0169	-3.891	5	1	247.12	0.21827	55.74
$C_{17}H_{15}N_3O_2$	N10	293.325	293.325	293.1164	4.7412	-3.577	5	2	231.21	0.2467	66.74
$C_{19}H_{20}N_4O$	N11	320.395	320.395	320.1637	4.9833	-3.909	5	1	259.68	0.18288	49.75
$C_{17}H_{19}N_3O_2$	N12	297.357	297.357	297.1477	4.8577	-4.644	5	1	230.9	0.23361	55.74
$C_{18}H_{15}N_3O_3$	N13	321.335	321.335	321.1113	5.1983	-4.584	6	1	245.12	0.26085	64.97
$C_{18}H_{15}N_3O_2$	N14	305.336	305.336	305.1164	5.6662	-4.934	5	1	235.12	0.22941	55.74
$C_{17}H_{21}N_3O$	N15	283.374	283.374	283.1685	4.6763	-3.951	4	1	232.9	0.18866	46.51
$C_{17}H_{13}N_3O_2$	N16	291.309	291.309	291.1008	5.2683	-4.566	5	1	222.86	0.24204	55.74
$C_{18}H_{22}N$	N17	251.372	251.372	251.1674	5.2791	-5.144	1	0	199.44	0.055004	12.89
$C_{22}H_{25}N$	N18	279.426	279.426	279.1987	5.9631	-5.684	1	0	226.96	0.048335	12.89
$C_{16}H_{21}N$	N19	227.35	227.35	227.1674	4.8013	-4.236	1	0	198.44	0.055281	12.89
$C_{16}H_{11}N_3Cl_2$	N20	316.19	316.19	315.033	6.3689	-5.327	3	1	233.44	0.14539	37.28
$C_{16}H_{11}N_3BrCl$	N21	360.641	360.641	358.9825	6.4881	-5.425	3	1	236.65	0.14342	37.28
$C_{16}H_{11}N_3BrCl$	N22	360.641	360.641	358.9825	6.4881	-5.425	3	1	236.65	0.14342	37.28
$C_{16}H_{11}N_3ClF$	N23	299.735	299.735	299.0626	5.8637	-4.905	3	1	224.37	0.15127	37.28
$C_{16}H_{11}N_3ClF$	N24	299.735	299.735	299.0626	5.8637	-4.905	3	1	224.37	0.15127	37.28
$C_{16}H_{12}N_3OCl$	N25	297.744	297.744	297.0669	5.4172	-4.295	4	2	224.37	0.20965	57.51
$C_{19}H_{11}N_4OBr$	N26	391.227	391.227	390.0116	5.9011	-7.85	5	1	248.55	0.21493	63.3
$C_{19}H_{19}N_3O_2$	N27	321.379	321.379	321.1477	5.4148	-4.259	5	1	259.38	0.20796	55.74
$C_{21}H_{17}N_4O$	N28	342.401	342.401	342.1481	5.8548	-4.971	5	1	270.48	0.20301	59.4
$C_{21}H_{18}N_4O$	N29	342.401	342.401	342.1481	5.8008	-4.947	5	1	270.48	0.20301	59.4
$C_{20}H_{21}N_3O_2$	N30	335.406	335.406	335.1634	5.8211	-4.559	5	1	273.14	0.19748	55.74
$C_{18}H_{20}N_4O$	N31	308.384	308.384	308.1637	3.6855	-3.808	5	2	254.58	0.21761	58.54
$C_{10}H_{11}N_3O$	N32	189.217	189.217	189.0902	1.8681	-2.134	4	2	148.86	0.32044	60.17
$C_{11}H_{13}N_3O$	N33	203.244	203.244	203.1059	2.2744	-2.434	4	2	162.62	0.29332	60.17
$C_{13}H_{17}N_3$	N34	215.299	215.299	215.1422	3.6064	-3.159	3	2	180.14	0.20928	50.94
$C_{13}H_{17}N_3O$	N35	231.298	231.298	231.1372	3.6053	-3.883	4	2	162.26	0.12215	61.68
$C_{20}H_{25}N_3O$	N36	323.439	323.439	323.1998	3.9424	-5.706	4	2	252.43	0.20101	68.01
$C_{11}H_{10}O_2Cl_2$	N37	241.12	241.12	240.0221	2.8642	-3.819	2	1	176.44	0.12713	24.92
$C_{19}H_{28}N_3Cl$	N38	333.905	333.905	333.1972	4.9456	-5.147	3	2	279.62	0.13483	50.94
$C_{17}H_{16}N_2O_3$	N39	296.325	296.325	296.1161	2.674	-3.574	5	0	237.36	0.23614	57.38
$C_{22}H_{24}N_3O_3Cl$	N40	413.904	413.904	413.1506	4.6844	-5.687	6	2	323.53	0.20687	72.48

TABLE-4
DESCRIPTORS VALUE AND BIOLOGICAL ACTIVITY VALUES FOR KNOWN SET OF MOLECULES

m.f.	Dataset name	Drug likeness	LE from structure No	LLE from structure No	LELP from structure No	Mutagenic	Tumo-rigenic	Repro-ductive effective	Irritant	Drugs core	Biological activity
$C_{21}H_{24}N_4O$	N1	3.962	0.47488	3.2041	12.205	High	Low	None	None	0.2348	84.4603
$C_{22}H_{26}N_4O$	N2	2.4855	0.45729	2.7978	13.563	High	Low	None	None	0.2021	90.59613
$C_{20}H_{21}N_4Cl$	N3	4.2027	0.49388	2.5281	13.104	High	Low	None	None	0.1891	56.3509
$C_{23}H_{25}N_3$	N4	-2.6625	0.47488	1.3084	16.197	High	None	None	None	0.1008	57.68473
$C_{21}H_{17}N_3O$	N5	2.0472	0.49388	2.7187	12.718	High	High	None	None	0.1348	57.51597
$C_{22}H_{19}N_3O_2$	N6	2.0472	0.45729	2.7887	13.583	High	High	None	None	0.1327	80.67112
$C_{23}H_{21}N_3O_2$	N7	1.9335	0.44096	2.3908	14.988	High	High	None	None	0.1162	81.52498
$C_{23}H_{21}N_3O_2$	N8	1.9335	0.44096	2.3908	14.988	High	High	None	None	0.1162	81.52498
$C_{18}H_{17}N_3O_2$	N9	2.0472	0.53682	3.9831	9.3455	High	None	None	None	0.3539	69.53093
$C_{17}H_{15}N_3O_2$	N10	2.0084	0.56122	4.2588	8.448	High	None	None	None	0.3832	61.77799
$C_{19}H_{20}N_4O$	N11	2.9478	0.51446	4.0167	9.6866	High	High	None	None	0.2188	80.80222
$C_{17}H_{19}N_3O_2$	N12	-2.8491	0.56122	4.1423	8.6556	High	None	None	None	0.1851	62.91711
$C_{18}H_{15}N_3O_3$	N13	1.8925	0.51446	3.8017	10.104	High	None	None	None	0.3087	70.73892
$C_{18}H_{15}N_3O_2$	N14	1.8018	0.53682	3.3338	10.555	High	None	None	None	0.2706	47.45185

$C_{17}H_{21}N_3O$	N15	-2.7321	0.58795	4.3237	7.9536	High	None	None	None	0.2113	59.65226
$C_{17}H_{13}N_3O_2$	N16	1.9109	0.56122	3.7317	9.3872	High	None	None	None	0.3109	42.48791
$C_{18}H_{22}N$	N17	-1.7206	0.64984	3.7209	8.1237	None	High	None	None	0.1765	-0.99243
$C_{22}H_{25}N$	N18	-3.3675	0.58795	3.0369	10.142	None	High	None	None	0.1277	23.54778
$C_{16}H_{21}N$	N19	-4.3136	0.72629	4.1987	6.6107	None	High	None	None	0.1944	-14.803
$C_{16}H_{11}N_3Cl_2$	N20	2.3845	0.58795	2.6311	10.832	High	None	None	None	0.2330	7.697389
$C_{16}H_{11}N_3BrCl$	N21	0.59454	0.58795	2.5119	11.035	High	None	None	None	0.1876	12.00499
$C_{16}H_{11}N_3BrCl$	N22	0.59454	0.58795	2.5119	11.035	High	None	None	None	0.1876	12.00499
$C_{16}H_{11}N_3ClF$	N23	1.0445	0.58795	3.1363	9.9731	High	None	None	None	0.2470	20.71872
$C_{16}H_{11}N_3ClF$	N24	1.0445	0.58795	3.1363	9.9731	High	None	None	None	0.2470	20.71872
$C_{16}H_{12}N_3OCl$	N25	2.170	0.58795	3.5828	9.2137	High	None	None	None	0.3184	30.29614
$C_{19}H_{11}N_4OBr$	N26	-0.497	0.49388	3.0989	11.949	None	None	None	None	0.2091	46.7473
$C_{19}H_{19}N_3O_2$	N27	1.933	0.51446	3.5852	10.525	High	None	None	None	0.3121	73.51352
$C_{21}H_{17}N_4O$	N28	1.933	0.47488	3.1452	12.329	High	None	None	None	0.2569	80.87713
$C_{21}H_{18}N_4O$	N29	1.933	0.47488	3.1992	12.215	High	None	None	None	0.2602	81.94847
$C_{20}H_{21}N_3O_2$	N30	0.4157	0.49388	3.1789	11.787	High	None	None	None	0.2370	81.29872
$C_{18}H_{20}N_4O$	N31	1.3035	0.53682	5.3145	6.8654	High	None	None	None	0.4040	94.22707
$C_{10}H_{11}N_3O$	N32	-4.4026	0.88192	7.1319	2.1182	High	High	None	None	0.1715	-36.7294
$C_{11}H_{13}N_3O$	N33	-6.1137	0.82313	6.7256	2.7631	High	High	None	None	0.1662	-9.39606
$C_{13}H_{17}N_3$	N34	-10.184	0.77168	5.3936	4.6734	High	High	None	None	0.1486	3.810851
$C_{13}H_{17}N_3O$	N35	-7.295	0.72629	5.3947	4.964	None	None	None	High	0.2325	7.065545
$C_{20}H_{25}N_3O$	N36	-7.7641	0.51446	5.0576	7.6633	None	High	None	None	0.1645	107.0328
$C_{11}H_{10}O_2Cl_2$	N37	0.11723	0.82313	6.1358	3.4797	High	High	High	None	0.1351	-44.7008
$C_{19}H_{28}N_3Cl$	N38	-9.5325	0.53682	4.0544	9.2127	High	None	None	None	0.1561	97.76596
$C_{17}H_{16}N_2O_3$	N39	-5.8775	0.56122	6.326	4.7646	None	None	None	None	0.4154	116.166
$C_{22}H_{24}N_3O_3Cl$	N40	-4.8141	0.42576	4.3156	11.003	None	None	None	High	0.1383	146.4214

TABLE-5
DESCRIPTOR VALUES WITH CALCULATED BIOLOGICAL ACTIVITY FOR UNKNOWN SET OF MOLECULES OF SERIES 1

m.f.	Dataset name	Total m.w.	Monoisotopic mass	clog P	clog S	H-Acceptors	H-Donors	Total surface area	Relative PSA	Polar surface area
$C_{16}H_{13}N_3$	U1	247.3	247.1109	5.1569	-3.855	3	1	202.6	0.16752	37.28
$C_{16}H_{12}N_3Cl$	U2	281.745	281.072	5.7629	-4.591	3	1	218.02	0.15567	37.28
$C_{16}H_{12}N_4O_2$	U3	292.297	292.096	4.0649	-4.315	6	1	226.27	0.28444	83.1
$C_{17}H_{15}N_3O$	U4	277.326	277.1215	5.0869	-3.873	4	1	224.86	0.19541	46.51
$C_{17}H_{15}N_3O$	U5	277.326	277.1215	5.0869	-3.873	4	1	224.86	0.19541	46.51
$C_{16}H_{12}N_4O_2$	U6	292.297	292.096	2.9572	-4.845	6	1	203.3	0.20359	72.68
$C_{16}H_{13}N_3O$	U7	263.299	263.1059	4.8112	-3.559	4	2	208.95	0.22513	57.51
$C_{17}H_{13}N_3O_2$	U8	291.309	291.1008	4.4716	-3.868	5	2	226.7	0.26502	74.58
$C_{16}H_{12}N_3Cl$	U9	281.745	281.072	5.7629	-4.591	3	1	218.02	0.15567	37.28
$C_{16}H_{12}N_3Cl$	U10	281.745	281.072	5.7629	-4.591	3	1	218.02	0.15567	37.28
$C_{20}H_{22}N_4$	U11	318.423	318.1844	5.8659	-4.491	4	1	264.94	0.1415	40.52
$C_{18}H_{16}N_4O$	U12	304.352	304.1324	4.8606	-4.197	5	2	244.07	0.23944	66.38
$C_{17}H_{15}N_3O$	U13	277.326	277.1215	5.0869	-3.873	4	1	224.86	0.19541	46.51
$C_{26}H_{19}N_3$	U14	373.458	373.1579	8.0105	-7.547	3	1	296.96	0.11429	37.28
$C_{25}H_{18}N_4$	U15	374.446	374.1531	7.2231	-6.339	4	1	295.72	0.15187	50.17
$C_{25}H_{18}N_4$	U16	374.446	374.1531	7.1321	-6.647	4	1	295.72	0.15187	50.17
$C_{16}H_{12}N_3F$	U17	265.29	265.1015	5.2577	-4.169	3	1	208.95	0.16243	37.28
$C_{16}H_{12}N_3F$	U18	265.29	265.1015	5.2577	-4.169	3	1	208.95	0.16243	37.28
$C_{16}H_{12}N_3F$	U19	265.29	265.1015	5.2577	-4.169	3	1	208.95	0.16243	37.28
$C_{17}H_{12}N_4$	U20	272.31	272.1062	4.9925	-4.628	4	1	224.31	0.21176	61.07
$C_{17}H_{12}N_4$	U21	272.31	272.1062	4.9925	-4.628	4	1	224.31	0.21176	61.07
$C_{17}H_{12}N_3F_3$	U22	315.297	315.0983	6.0052	-4.633	3	1	232.06	0.14626	37.28
$C_{17}H_{12}N_3F_3$	U23	315.297	315.0983	6.0052	-4.633	3	1	232.06	0.14626	37.28
$C_{17}H_{12}N_3F_3$	U24	315.297	315.0983	6.0052	-4.633	3	1	232.06	0.14626	37.28
$C_{17}H_{16}N_4$	U25	276.342	276.1375	4.1618	-3.815	4	2	224.88	0.21883	63.3
$C_{18}H_{17}N_3O$	U26	291.353	291.1372	5.4932	-4.173	4	1	238.62	0.18414	46.51
$C_{18}H_{17}N_3O$	U27	291.353	291.1372	5.4932	-4.173	4	1	238.62	0.18414	46.51
$C_{18}H_{17}N_3O$	U28	291.353	291.1372	5.4932	-4.173	4	1	238.62	0.18414	46.51
$C_{20}H_{21}N_3$	U29	303.408	303.1735	6.8252	-4.898	3	1	256.14	0.13251	37.28
$C_{20}H_{21}N_3$	U30	303.408	303.1735	6.8252	-4.898	3	1	256.14	0.13251	37.28
$C_{20}H_{21}N_3$	U31	303.408	303.1735	6.8252	-4.898	3	1	256.14	0.13251	37.28
$C_{19}H_{18}N_4O$	U32	318.379	318.1481	5.315	-4.467	5	2	257.83	0.22666	66.38
$C_{19}H_{18}N_4O$	U33	318.379	318.1481	5.315	-4.467	5	2	257.83	0.22666	66.38
$C_{19}H_{18}N_4O$	U34	318.379	318.1481	5.315	-4.467	5	2	257.83	0.22666	66.38

$C_{18}H_{15}N_3O_2$	U35	305.336	305.1164	5.1436	-4.155	5	1	242.61	0.23486	63.58
$C_{18}H_{15}N_3O_2$	U36	305.336	305.1164	5.1436	-4.155	5	1	242.61	0.23486	63.58
$C_{18}H_{15}N_3O_2$	U37	305.336	305.1164	5.1436	-4.155	5	1	242.61	0.23486	63.58
$C_{18}H_{18}N_4$	U38	290.369	290.1531	5.0533	-3.891	4	1	237.42	0.15791	40.52
$C_{18}H_{18}N_4$	U39	290.369	290.1531	5.0533	-3.891	4	1	237.42	0.15791	40.52
$C_{16}H_{12}N_4O_2$	U40	292.297	292.096	2.9572	-4.845	6	1	203.3	0.20359	72.68
$C_{18}H_{18}N_4$	U41	290.369	290.1531	5.0533	-3.891	4	1	237.42	0.15791	40.52

TABLE-6
DESCRIPTORS VALUE AND CALCULATED BIOLOGICAL ACTIVITY VALUES FOR UNKNOWN MOLECULES (SERIES-I)

m.f.	Dataset name	Drug likeness	Muta-genic	Tumo-rigenic	Repro-ductive effective	Irritant	LE from total m.w.	LLE from total m.w.	LELP from total m.w.	Drugs core	Bio. activity calculated
$C_{16}H_{13}N_3$	U1	2.4225	High	None	None	None	0.47704	1.4499	10.81	0.361161	51.202
$C_{16}H_{12}N_3Cl$	U2	2.3845	High	None	None	None	0.4493	0.78724	12.826	0.292847	50.904
$C_{16}H_{12}N_4O_2$	U3	-3.1321	High	None	None	None	0.40746	2.4693	9.9762	0.214961	116.332
$C_{17}H_{15}N_3O$	U4	2.0472	High	None	None	None	0.42835	1.4701	11.875	0.355111	80.365
$C_{17}H_{15}N_3O$	U5	2.0472	High	None	None	None	0.42835	1.4701	11.875	0.355111	80.365
$C_{16}H_{12}N_4O_2$	U6	-7.0604	None	None	None	None	0.40746	3.577	7.2577	0.349042	134.600
$C_{16}H_{13}N_3O$	U7	2.1702	High	None	None	None	0.45132	1.7684	10.66	0.387217	73.469
$C_{17}H_{13}N_3O_2$	U8	1.861	High	None	None	None	0.40755	2.064	10.972	0.385157	100.619
$C_{16}H_{12}N_3Cl$	U9	2.3845	High	None	None	None	0.4493	0.78724	12.826	0.292847	50.904
$C_{16}H_{12}N_3Cl$	U10	2.3845	High	None	None	None	0.4493	0.78724	12.826	0.292847	50.904
$C_{20}H_{22}N_4$	U11	4.2135	High	Low	None	None	0.37138	0.6311	15.795	0.238083	90.367
$C_{18}H_{16}N_4O$	U12	3.035	High	None	None	None	0.3887	1.656	12.505	0.363697	100.304
$C_{17}H_{15}N_3O$	U13	2.0472	High	None	None	None	0.42835	1.4701	11.875	0.355111	80.365
$C_{26}H_{19}N_3$	U14	2.4225	High	High	None	None	0.30407	-1.5827	26.344	0.088242	65.954
$C_{25}H_{18}N_4$	U15	2.4225	High	None	None	None	0.30402	-0.79649	23.759	0.173444	90.768
$C_{25}H_{18}N_4$	U16	2.4225	High	None	None	None	0.30402	-0.70549	23.459	0.168079	89.236
$C_{16}H_{12}N_3F$	U17	1.0825	High	None	None	None	0.45109	1.3186	11.655	0.310183	63.619
$C_{16}H_{12}N_3F$	U18	1.0825	High	None	None	None	0.45109	1.3186	11.655	0.310183	63.619
$C_{16}H_{12}N_3F$	U19	1.0825	High	None	None	None	0.45109	1.3186	11.655	0.310183	63.619
$C_{17}H_{12}N_4$	U20	-1.8575	High	None	None	None	0.42887	1.5724	11.641	0.197307	84.714
$C_{17}H_{12}N_4$	U21	-1.8575	High	None	None	None	0.42887	1.5724	11.641	0.197307	84.714
$C_{17}H_{12}N_3F_3$	U22	-4.7675	High	None	None	None	0.38778	0.49608	15.486	0.145048	97.339
$C_{17}H_{12}N_3F_3$	U23	-4.7675	High	None	None	None	0.38778	0.49608	15.486	0.145048	97.339
$C_{17}H_{12}N_3F_3$	U24	-4.7675	High	None	None	None	0.38778	0.49608	15.486	0.145048	97.339
$C_{17}H_{16}N_4$	U25	1.9768	High	None	None	None	0.42845	2.3968	9.7135	0.40892	95.576
$C_{18}H_{17}N_3O$	U26	0.40076	High	None	None	None	0.40755	1.0424	13.479	0.269838	87.987
$C_{18}H_{17}N_3O$	U27	0.40076	High	None	High	None	0.40755	1.0424	13.479	0.161903	87.986
$C_{18}H_{17}N_3O$	U28	0.40076	High	None	None	None	0.40755	1.0424	13.479	0.269838	87.987
$C_{20}H_{21}N_3$	U29	-3.5643	High	None	None	None	0.38878	-0.30723	17.556	0.1281	82.768
$C_{20}H_{21}N_3$	U30	-3.5643	High	None	None	None	0.38878	-0.30723	17.556	0.1281	82.768
$C_{20}H_{21}N_3$	U31	-3.5643	High	None	None	None	0.38878	-0.30723	17.556	0.1281	82.768
$C_{19}H_{18}N_4O$	U32	4.0521	High	None	None	None	0.37138	1.1821	14.311	0.327208	98.394
$C_{19}H_{18}N_4O$	U33	4.0521	High	None	None	None	0.37138	1.1821	14.311	0.327208	98.394
$C_{19}H_{18}N_4O$	U34	4.0521	High	None	None	None	0.37138	1.1821	14.311	0.327208	98.394
$C_{18}H_{15}N_3O_2$	U35	1.4944	High	None	None	None	0.38861	1.3716	13.236	0.324103	100.208
$C_{18}H_{15}N_3O_2$	U36	1.4944	High	None	None	High	0.38861	1.3716	13.236	0.194462	100.207
$C_{18}H_{15}N_3O_2$	U37	1.4944	High	None	High	None	0.38861	1.3716	13.236	0.194462	100.207
$C_{18}H_{18}N_4$	U38	3.2365	High	None	None	None	0.40764	1.4837	12.397	0.368969	89.606
$C_{18}H_{18}N_4$	U39	3.2365	High	None	None	None	0.40764	1.4838	12.397	0.368969	89.606
$C_{16}H_{12}N_4O_2$	U40	-11.868	None	None	None	None	0.40746	3.577	7.2577	0.348745	147.840
$C_{18}H_{18}N_4$	U41	3.2365	High	High	None	None	0.40764	1.4838	12.397	0.221381	89.606

The values of fraction variance may vary between 0 and 1. In the QSAR model having $r^2 > 0.218$ will only be considered for validation. In equation of biological activity, the negative coefficients of molecular volume (MV) and molecular weight (MW) explains that any increase in molecular volume or molecular weight of the compounds causes a decrease in the biological activity.

The docking studies verified the results obtained by regression analysis (Table-8) and gives insight toward the interaction of biological active molecules with proteins which helps in designing of target based therapeutic agent for tuberculosis.

TABLE-8
PARAMETERS FOR VERIFICATION OF REGRESSION EQUATION

Regression model	Reliability test (r)	Correlations statistics (α)
Quinoline	0.119	0.092

TABLE-7
DOCKING RESULTS OF PROTEINS 1QPQ AND 1KNC WITH UNKNOWN SUBSTITUTED 4-QUNOLYLHYDRAZONE COMPOUNDS (SERIES-I)

Molecules	1QPQ				1KNC			
	Total energy (kcal/mol)	VDW (kcal/mol)	H Bond (kcal/mol)	Aver con pair (kcal/mol)	Total energy (kcal/mol)	VDW (kcal/mol)	H Bond (kcal/mol)	Aver con pair (kcal/mol)
U1	-78.8315	-65.5201	-13.3114	24.9474	-82.3718	-69.8423	-12.5295	25.8421
U10	-78.6182	-66.2937	-12.3245	24.35	-80.3062	-65.8519	-14.4543	25.8
U11	-69.6923	-61.3427	-8.34962	19.0833	-86.7379	-76.6062	-10.1316	22.1667
U12	-72.7079	-49.6819	-23.026	22.8261	-86.6232	-67.6519	-18.9713	20.4348
U13	-79.0202	-68.5202	-10.5	22.6667	-82.5753	-74.3221	-8.25316	24.619
U14	-70.3813	-66.8999	-3.48144	14.5172	-100.723	-100.723	0	24.4138
U15	-66.5616	-53.509	-13.0526	14.3103	-103.079	-91.8015	-11.2775	20.3793
U16	-61.5129	-58.1513	-3.36158	14.2414	-101.364	-80.5745	-20.789	19.7241
U17	-71.4391	-64.8192	-6.61994	21.4	-84.209	-70.5245	-13.6844	23.9
U18	-72.2056	-68.0009	-4.2047	22.25	-82.1182	-74.9443	-7.17393	25.85
U19	-78.1837	-67.6837	-10.5	24.95	-85.7662	-77.7903	-7.97592	26.35
U2	-69.9317	-66.4358	-3.49595	22	-81.7571	-76.8387	-4.91834	26.8
U20	-76.3312	-73.9388	-2.39245	21.5238	-81.6523	-67.6731	-13.9792	23.1905
U21	-74.6334	-59.358	-15.2754	22.3333	-83.5107	-55.919	-27.5917	20
U22	-69.9265	-59.3433	-10.5832	24.2609	-83.9352	-73.2769	-10.6583	21.3478
U23	-68.3118	-58.0107	-10.3011	15.1739	-83.3341	-68.4114	-14.9227	21.913
U24	-79.5565	-68.5301	-11.0264	22	-82.3047	-78.8047	-3.5	21.5652
U25	-83.709	-73.209	-10.5	22.6667	-84.8049	-79.3659	-5.43904	29.0952
U26	-64.0795	-57.0795	-7	27.5	-78.87	-63.945	-14.925	21
U27	-71.5655	-65.5655	-6	22.7727	-96.4013	-75.5114	-20.89	27.7273
U28	-62.2143	-35.5533	-26.661	22.7727	-87.0602	-66.1969	-20.8633	20.7727
U29	-64.3451	-35.5631	-28.782	16.5652	-86.4478	-69.5291	-16.9187	23.4348
U3	-89.1335	-68.2266	-21.5827	24.6818	-78.5171	-56.3796	-23.103	21.0455
U30	-66.6544	-57.5629	-9.09153	15	-89.3562	-80.3067	-9.04956	23.7391
U31	-62.4802	-38.9668	-23.5134	14.1304	-82.5567	-69.7517	-12.805	21.5217
U32	-58.3157	-38.9267	-19.389	14.25	-87.8646	-73.4392	-14.4254	25.0833
U33	-66.2711	-53.3648	-12.9063	29.1667	-86.6998	-69.3515	-17.3483	19.125
U34	-76.4395	-61.5218	-14.9177	21.4583	-87.5749	-72.083	-15.4919	22.625
U35	-77.11	-55.3701	-21.7399	22.087	-84.197	-70.5409	-13.6561	22.6522
U36	-61.7498	-38.2755	-23.4743	14.2609	-87.8796	-69.2856	-18.5939	23.4348
U37	-71.869	-64.8756	-6.99344	21.8696	-91.9977	-66.8033	-25.1944	21.8261
U38	-86.0727	-80.3894	-5.68331	23.0909	-77.9898	-74.4898	-3.5	22
U39	-84.6142	-72.7176	-11.8966	24.3182	-87.6698	-83.1749	-4.49492	28.7273
U40	-83.1784	-72.935	-11.7178	24.7727	-100.677	-76.8012	-22.5181	26.4545
U4	-70.704	-65.6474	-5.05663	24.0476	-84.2561	-70.2583	-13.9978	25.0476
U41	-71.8843	-59.743	-12.1413	28.5909	-89.4471	-72.169	-17.2781	22.6818
U5	-76.8515	-69.0082	-7.84334	21.6667	-81.6164	-68.0876	-13.5287	22.2857
U6	-84.7433	-72.8484	-8.80125	21.5455	-91.9171	-80.7305	-12.7093	27.9091
U7	-61.3249	-45.4678	-15.8571	26.75	-82.2171	-62.6866	-19.5305	24.1
U8	-72.9381	-33.9778	-32.6102	22.1364	-87.558	-58.4735	-27.4966	20.2727
U9	-64.7317	-57.7317	-7	18.9	-76.8667	-62.2495	-14.6172	20.35

Conclusion

In present work, two leading enzymes which plays an important role in inhibition activity of *Mycobacterium tuberculosis* were selected for docking study against derivatives of 4-quinolyl hydrazone as well as the biological activities of derivatives of 4-quinolyl hydrazone were also calculated by means of regression analysis. The molecules were filtered on the basis of their calculated biological activity and docking study parameters. Substituted 4-quinolylhydrazone based molecules shows the hydrogen bond interaction with HIS-161, THR-138, ARG-139, LYS-140, HIS-161, LYS-172, LEU-220, ARG-605. ASP- 137, SER-248 amino acids of binding site of quinolinic acid phosphoribosyltransferase protein which plays an important role in de novo pathway of NAD metabolism of mycobacterium. Similarly, different atoms of substituent groups of substituted quinolines, substituted pyrimidines and substituted isoniazide molecules shows the hydrogen bond interaction with ARG-103, GLU-12, ASP-16, HIS-137, ASP-16, CYS-130, ARG-103, PRO-110, GLU-12, GLU-118, TYR-13, LYS-15, amino acids of binding site of enoyl ACP reductase protein, which plays an important role in mechanism of alkylhydroperoxidase activity in which CYS-130 was deprotonated by a distant glutamic acid (118 GLU) *via* the relay action of HIS-137 and a water molecule. Thus it provides an antioxidant defence for the mycobacterium. The comprehensive study of docking interaction and binding energies of both the enzymes quinolinic acid phosphoribosyltransferase and enoyl ACP reductase unveiled that the newly designed compounds were in good conformity with the concept of *in silico* drug design.

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