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Research Article

SYNTHESIS, REGRESSION ANALYSIS, DOCKING STUDIES OF ISONIAZID-BASED COMPOUNDS AS ANTI-TUBERCULOSIS THERAPEUTIC AGENTS

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ABSTRACT. In the drug-design process, a structure-activity relationship is a method for the estimation of the biological activity of the newly designed unknown molecules by using regression analysis. This method aims to develop a mathematical relationship between the structural features of molecules (descriptors) and the property of interest, i.e. biological activity based on reference molecules. Based on this relationship, biological activity can be predicted for newly designed molecules. Initially, the molecules with known biological activities were considered as a Training set for regression analysis model-building purposes. The properties module from Datawarrior is used to calculate descriptors related to the molecule's structural features. Employing the structure-activity relationship method a significant relationship is developed between these descriptors with observed biological activity in the form of a mathematical equation. This mathematical equation calculates the newly designed molecules' biological activity. In the present study, the new substituted Isoniazid molecules are designed and optimized and their descriptors were calculated using Datawarrior modules. Then by using the Regression analysis model, their biological activities are calculated. The molecules with good biological activity are subjected to inhibition studies for the protein 1QPQ by the molecular docking method to confirm the inhibition activity of these molecules against Mycobacterium tuberculosis. Thus, based on regression analysis study and docking studies of substituted isoniazid derivatives, we can conclude that the Isoniazid derivatives reported here can be a good therapeutic agent against tuberculosis.

Keywords: *Structure-activity, biological activity, tuberculosis, descriptors.*

INTRODUCTION

In the drug-design process, the quantitative structure-activity relationship (QSAR) has come to play a major role. In this process, the objective is the 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 mathematically 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 structural representation and then identified in the modeling process. In this manner, the synthesis of new candidates may be guided towards the desired goal.

A structure-based approach is a coherent approach to the Quantitative structure-activity relationship (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) [1].

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 how 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].

Isoniazid (INH), a first-line anti-TB drug is one of the most effective agents used for the treatment of Mycobacterium tuberculosis infection since 1952 [8]. Isoniazid (INH) is known to inhibit InhA, a 2-trans-enoyl-acyl carrier protein reductase enzyme responsible for the maintenance of cell walls in Mycobacterium tuberculosis but as new drug-resistant strains of the bacterium appear, next-generation therapeutics will be essential to combat the rise of the disease [9]. In the last decade, the number of INH-resistant Mycobacterium tuberculosis strains isolated from TB patients had been increasing at an alarming rate. One of the intrinsic factors contributing to INH resistance in Mycobacterium tuberculosis is the underlying architecture of the bacterial cell envelope [10].

In the drug-design process, regression analysis has come to play a major role. In this process, the objective is the development of a relationship between structural features and the property of interest, so that property values can be predicted for new candidate structures [2]. Two approaches have been taken to the design of computer systems to predict biological activity based on chemical structure. Traditional regression analysis aims to detect trends in data associated with compounds having particular patterns of activity, and thus develop models that can predict the properties of new compounds [11].

MATERIALS AND METHODS

In the current study, the experimental work consists initially of the building of an equation (model) by using regression analysis for a known set of molecules i.e. molecules with known biological activities. This equation represents the relationship between biological activity and molecular descriptors of known 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 the Quinolinic acid phosphoribosyltransferase (QAPRTase) enzyme (PDB code: 1QPQ), an important target protein for designing novel potential inhibitors for tuberculosis as it plays important role in the metabolism of Mycobacterium Tuberculosis [12].

The biological activity parameter used in this study is substituted Isoniazid inhibitory activity. The considered known compounds are Tuberculosis inhibitors which inhibit

Mycobacterium Tuberculosis. Interestingly, all these compounds were active and showed M. Tuberculosis inhibition with biological activity values ranging between 374 and 16 μM [13, 14].

Table 1 and Table 2 list the series of substituted isoniazid derivatives designed in the current project.

Table 1. *Id and name for Unknown compounds – Series 1.*

Sr. No.	ID	Compound	Sr. No.	ID	Compound
1	UK INH 1	2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide	6	UK INH 6	2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)-N-propylacetamide
2	UK INH2	2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)-N-methyl acetamide	7	UK INH 7	2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)-N-propoxyacetamide
3	UK INH 3	N-ethyl-2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide	8	UK INH 8	N-butoxy-2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide
4	UK INH 4	2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)-N-methoxyacetamide	9	UK INH 9	N-(aminomethyl)-2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide
5	UK INH 5	N-ethoxy-2-(4-((2-isonicotinoylhydrazono)methyl) phenoxy)acetamide	10	UK INH 10	N-(2-aminoethyl)-2-(4-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide

Table 2. *Id and name for Unknown compounds – Series 2.*

Sr No.	ID	Compound	Sr No.	ID	Compound
1	UK INH A1	N'-(3,4-dimethoxybenzylidene) isonicotinohydrazide	12	UK INH A12	N'-(2-hydroxybenzylidene) isonicotinohydrazide
2	UK INH A2	N'-(3-methoxybenzylidene) isonicotinohydrazide	13	UK INH A13	N'-(3-hydroxybenzylidene) isonicotinohydrazide
3	UK INH A3	Sodium 2-((2-isonicotinoyl hydrazono) methyl) benzenesulfonate	14	UK INH A14	N'-(4-hydroxybenzylidene) isonicotinohydrazide
4	UK INH A4	N'-(2-chlorobenzylidene) isonicotinohydrazide	15	UK INH A15	N'-(2-nitrobenzylidene) isonicotinohydrazide

Table 2. *(Continues)*

Sr No.	ID	Compound	Sr No.	ID	Compound
5	UK INH A5	N'-(3-chlorobenzylidene) isonicotinohydrazide	16	UK INH A16	N'-(3-nitrobenzylidene) isonicotinohydrazide
6	UK INH A6	N'-(4-chlorobenzylidene) isonicotinohydrazide	17	UK INH A17	N'-(4-nitrobenzylidene) isonicotinohydrazide
7	UK INH A7	N'-(4-methoxybenzylidene) isonicotinohydrazide	18	UK INH A18	N'-(3,4,5-trimethoxybenzylidene) isonicotinohydrazide
8	UK INH A8	N'-(4-hydroxy-3,5-dimethoxybenzylidene) isonicotinohydrazide	19	UK INH A19	2-(2-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide
9	UK INH A9	N'-(4-(dimethylamino) benzylidene) isonicotinohydrazide	20	UK INU A20	2-(3-((2-isonicotinoylhydrazono) methyl)phenoxy)acetamide
10	UK INH A10	N'-(3-ethoxy-4-hydroxybenzylidene) isonicotinohydrazide	21	UK INH A21	2-(4-((2-isonicotinoylhydrazono)met hyl) phenoxy)acetamide
11	UK INH A11	N'-(4-fluorobenzylidene) isonicotinohydrazide	22	UK INH A22	N'-(2-aminobenzylidene) isonicotinohydrazide

Descriptors generation

Initially, the newly designed molecules were pre-optimized by employing Molecular Mechanics. After that, the resulting minimized structures were further refined using semi-empirical techniques. Then, these substituted Isoniazid molecules were re-optimized by using the Gaussian program package.

The QSAR properties module from Datawarrior version 4.6.1 package was used to calculate the descriptors for these molecules e.g. 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).

Regression analysis

Multiple linear regression analysis of molecular descriptors with their known biological activities was carried out using the stepwise strategy in SPSS version 19 for Windows for building regression equations [15].

Table 3 shows the parameters for the regression model built up for the known molecules set.

Table 3. *The coefficient values for the regression model of substituted Isoniazid molecules develop by using SPSS.*

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-29.114	19.773		-1.472	.163
	TMW01	-.009	.005	-.301	-1.927	.074
	cLogP01	-8.586	2.102	-7.079	-4.086	.001
	cLogS01	-2.334	.429	-1.652	-5.435	.000
	TSA01	.003	.027	.040	.094	.926
	Druglikeness01	-.156	.064	-.325	-2.452	.028
	LE01	81.634	41.419	1.305	1.971	.069
	LELP01	2.207	.620	6.574	3.559	.003

a. Dependent Variable: Biological activity

The equation for determination of biological activity generated by regression analysis: Biological Activity = (-29.114) + (-0.009) x Total Mol. Wt. + (-8.586) x cLogP + (-2.334) x cLogS + (0.003) x Total Surface area + (-1.156) x Drug likeliness + (81.634) x LE + (2.207) x LELP.

The above equation is used to determine the biological activity of newly designed molecules i.e. for molecules of the unknown set.

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 phosphoribosyltransferase (QAPRTase) enzyme (PDB code: 1QPQ) can stop the FAS I pathway as it will make it deficient in NAD.[16] Therefore the Quinolinic acid phosphoribosyltransferase (QAPRTase) enzyme provides an attractive target for designing novel potential inhibitors for tuberculosis [17].

iGEMDOCK is an integrated tool that creates a 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 [18]. The selected set of three ligands was subjected to accurate docking (very slow docking) by setting a population size of 700 sets with 70 generations and 10 solutions. After the completion of the docking, the post docking analysis was performed to find the docking pose and its energy values.

Synthesis & Characterization

Selected molecules that show good values for biological activity and also give good docking interactions are synthesized to verify the synthetic accessibility of newly designed molecules.

Synthesis of N'-(4-methoxybenzylidene) isonicotinohydrazide

Step 1: Preparation of isonicotinohydrazide form 4-cyanopyridine. (Precursor)

a) 1milimoles of 4-cyanopyridine in 30 ml of water were reacted with 1milimoles of hydrazine hydrate (H2NNH2.H2O) in the presence of 0.01 gm of NaOH at 1000 C under reflux on a heating mantel for 7- 8 hours at a stretch.
b) Reaction mixture is filtered in the Buchner funnel under the suction pump and the clear filtrate was evaporated to dryness in an electric water bath carefully.
c) The yield of the crude product with melting point 170 ℃ to 171℃.

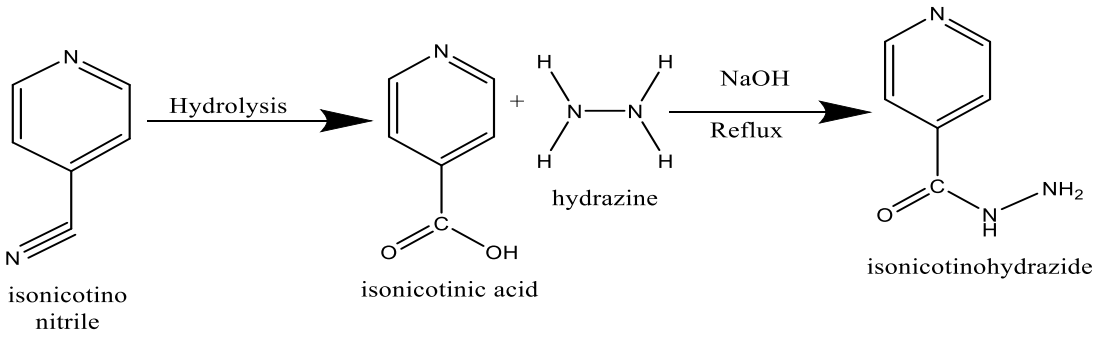

Fig. 1. *Preparation of isonicotinohydrazide form 4-cyanopyridine.*

Step 2: Preparation of substituted isoniazid derivatives from isonicotinohydrazide.

Isonicotinohydrazide (1milimoles), Ethanol (14 ml), and Substituted Benzaldehyde (1milimoles) are refluxed for 6 to 7 hours. After refluxing cool it in a water bath then filter it and wash it with water. Dry it and take its melting point (138 ℃ to 150 ℃).

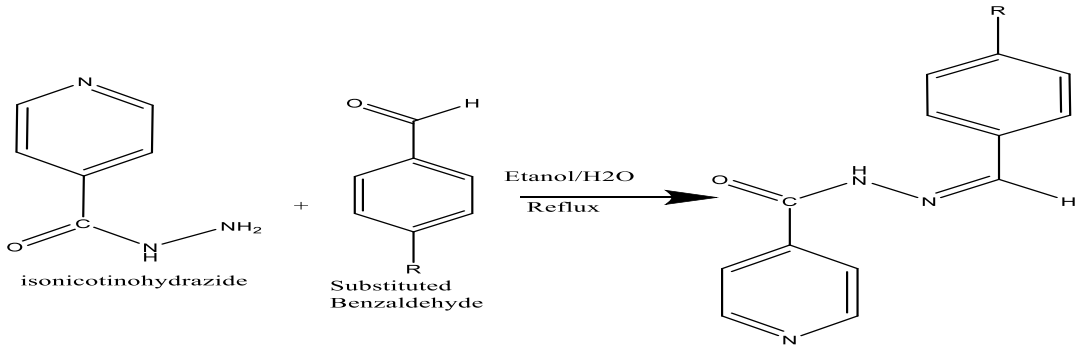

Fig. 2. *Preparation of substituted isoniazid derivatives from isonicotinohydrazide.*

RESULTS AND DISCUSSION

Structure-activity relationships (SAR)

We have studied eight physiochemical proprieties of a series of substituted isoniazid derivatives in which various degrees of substituents on the aromatic ring have been introduced, these substituents include electron-donating groups such as methoxy and electron-withdrawing groups like nitro, using Hyperchem software. The structure for substituted isoniazid is given as Figure 3.

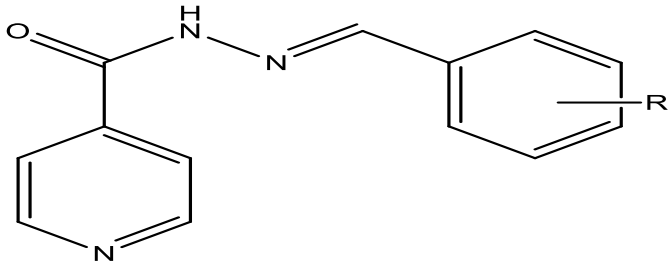

Fig. 3. *Structure of Substituted isoniazid derivative.*

Table 4 shows the observed biological activity values of known molecules along with descriptor values.

Table 4. *Descriptor values with biological activity for a Known set of molecules.*

ID	Observed Biological Activity (µM)	Total Mol. Wt.	cLogP	cLogS	Total Surface Area	Drug like-ness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
K INH 1	0.78	360.372	3.6251	-4.912	284.72	-4.2694	0.32738	2.8181	11.073
K INH2	0.39	374.399	3.969	-5.256	296.98	-4.338	0.31488	2.4577	12.605
K INH 3	0.78	388.426	4.3846	-5.415	310.74	-4.5358	0.30327	2.0261	14.458
K INH 4	0.78	402.453	4.8121	-5.783	321.74	-4.582	0.29245	1.5832	16.454
K INH 5	0.78	378.362	3.7259	-5.226	291.07	-5.6094	0.31466	2.6962	11.841
K INH 6	0.78	378.362	3.7259	-5.226	291.07	-5.6094	0.31466	2.6962	11.841
K INH 7	0.78	378.362	3.7259	-5.226	291.07	-5.6094	0.31466	2.6962	11.841
K INH 8	0.78	394.817	4.2311	-5.648	300.14	-4.2378	0.31375	2.1725	13.486
K INH 9	0.78	394.817	4.2311	-5.648	300.14	-4.2378	0.31375	2.1725	13.486
K INH 10	0.78	394.817	4.2311	-5.648	300.14	-4.2378	0.31375	2.1725	13.486
K INH 11	0.78	439.268	4.3503	-5.746	303.35	-6.0594	0.31148	2.007	13.967
K INH 12	0.78	439.268	4.3503	-5.746	303.35	-6.0594	0.31148	2.007	13.967
K INH 13	0.78	439.268	4.3503	-5.746	303.35	-6.0594	0.31148	2.007	13.967
K INH 14	0.39	390.398	3.5551	-4.93	306.98	-4.2629	0.30316	2.8534	11.727
K INH 15	3.125	405.369	2.7035	-5.372	308.39	-9.3911	0.29231	3.6886	9.2488
K INH 16	0.78	361.36	2.9756	-4.642	283.48	-4.2694	0.32732	3.4665	9.0907
K INH 17	0.39	361.36	2.6242	-4.117	283.48	-4.2694	0.32732	3.8179	8.0171
K INH 18	0.39	388.426	3.6784	-5.072	310.74	-7.2796	0.30327	2.7323	12.129
K INH 19	0.39	404.425	3.2645	-4.746	320.74	-7.2039	0.29236	3.1287	11.166
K INH 20	0.78	374.399	3.3345	-4.728	298.48	-7.2192	0.31488	3.0922	10.59
K INH 21	0.78	388.426	3.7646	-4.84	312.24	-8.4508	0.30327	2.6461	12.414
K INH 22	3.125	410.432	4.8195	-6.518	319.32	-4.2694	0.28264	1.5673	17.052

Table 5 and Table 6 show the calculated biological activity values by SPSS for unknown molecules of Series I and Series II.

Table 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 like-ness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
UK INH 1	11.9982	298.301	0.8629	-2.795	235.78	4.5364	0.40691	5.6624	2.1206
UK INH 2	9.73872	312.328	1.2144	-2.711	250.98	5.1571	0.38803	5.291	3.1297
UK INH 3	8.48458	326.355	1.6207	-3.011	264.74	5.3856	0.37077	4.8656	4.3712
UK INH 4	10.0861	328.327	0.9496	-2.998	260.98	4.5396	0.37062	5.5341	2.5622
UK INH 5	8.67085	342.354	1.3559	-3.298	274.74	2.7286	0.3548	5.1096	3.8216
UK INH 6	7.31480	340.382	2.0751	-3.281	278.5	5.2017	0.35493	4.3929	5.8464
UK INH 7	7.88296	356.381	1.8103	-3.568	288.5	3.9886	0.34023	4.6378	5.3208
UK INH 8	6.66301	370.408	2.2647	-3.838	302.26	0.33098	0.32678	4.1666	6.9304
UK INH 9	12.0241	327.343	0.3156	-3.109	261	4.6313	0.37069	6.1694	0.85138
UK INH 10	9.43092	341.37	0.2962	-2.58	274.76	2.296	0.35487	6.1706	0.83468

Table 6. *Calculated biological activity values by SPSS of unknown molecules Series II.*

ID	Calculated Biological Activity	Total Mol. Wt.	cLogP	cLogS	Total Surface Area	Drug like-ness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
UK INH A1	9.5819	285.302	2.0607	-2.96	230.27	4.3419	0.42755	4.484	4.8198
UK INH A2	11.8013	255.276	2.1307	-2.94	208.01	4.3419	0.47604	4.4623	4.4759
UK INH A3	16.0276	327.295	-1.2762	-1.53	221.86	-6.0165	0.42365	7.7613	-3.0124
UK INH A4	12.2881	259.695	2.8067	-3.66	201.17	4.4715	0.50192	3.7788	5.5919
UK INH A5	12.2881	259.695	2.8067	-3.66	201.17	4.4715	0.50192	3.7788	5.5919
UK INH A6	12.2881	259.695	2.8067	-3.66	201.17	4.4715	0.50192	3.7788	5.5919
UK INH A7	11.8013	255.276	2.1307	-2.94	208.01	4.3419	0.47604	4.4623	4.4759
UK INH A8	8.98175	301.301	1.715	-2.67	236.62	4.3145	0.40664	4.806	4.2175
UK INH A9	10.7413	268.319	2.0971	-2.96	220.57	5.1665	0.45076	4.4742	4.6524
UK INH A10	8.85213	285.302	2.1913	-2.95	228.12	2.7806	0.42755	4.3534	5.1253
UK INH A11	13.1684	243.24	2.3015	-3.24	192.1	3.1287	0.50409	4.3125	4.5657
UK INH A12	13.8245	241.249	1.855	-2.63	192.1	4.4204	0.50436	4.7625	3.6779
UK INH A13	13.8245	241.249	1.855	-2.63	192.1	4.4204	0.50436	4.7625	3.6779
UK INH A14	13.8245	241.249	1.855	-2.63	192.1	4.4204	0.50436	4.7625	3.6779
UK INH A15	13.7946	270.247	1.2791	-3.39	209.42	-0.75305	0.45054	5.2891	2.839
UK INH A16	13.7946	270.247	1.2791	-3.39	209.42	-0.75305	0.45054	5.2891	2.839
UK INH A17	13.7946	270.247	1.2791	-3.39	209.42	-0.75305	0.45054	5.2891	2.839
UK INH A18	8.00793	315.328	1.9907	-2.98	252.53	4.3419	0.38778	4.5105	5.1336

Table 6. *(Continues).*

ID	Calculated Biological Activity	Total Mol. Wt.	cLogP	cLogS	Total Surface Area	Drug like-ness	LE from Total Mol. Wt.	LLE from Total Mol. Wt.	LELP from Total Mol. Wt.
UK INH A19	11.9982	298.301	0.8629	-2.8	235.78	4.5364	0.40691	5.6624	2.1206
UK INU A20	11.9982	298.301	0.8629	-2.8	235.78	4.5364	0.40691	5.6624	2.1206
UK INH A21	11.9982	298.301	0.8629	-2.8	235.78	4.5364	0.40691	5.6624	2.1206
UK INH A22	16.0908	240.265	1.5234	-3	194.27	4.3905	0.50449	5.0959	3.0197

Table 7 shows docking parameters with protein 1QPQ for unknown Isoniazid molecules (Series I and II).

Table 7. *Docking parameters with protein 1QPQ for unknown (newly designed molecules) Isoniazid molecules (Series I).*

Sr. No.	ID	Total Energy	VDW	H Bond	AverConPair
1	UK INH 1	-83.1436	-64.2508	-18.8927	23.9091
2	UK INH2	-80.7082	-63.7054	-17.0028	22.2174
3	UK INH 3	-86.2025	-62.4137	-23.7888	22.9583
4	UK INH 4	-86.4953	-67.0514	-19.4439	21.4583
5	UK INH 5	-87.2538	-67.6025	-19.6513	20.88
6	UK INH 6	-81.8323	-64.7419	-17.0904	20.6
7	UK INH 7	-87.4378	-67.758	-19.6798	20.0769
8	UK INH 8	-87.4834	-67.8015	-19.6819	19.3704
9	UK INH 9	-82.859	-63.5803	-19.2788	22.125
10	UK INH 10	-81.4261	-64.4916	-16.9345	20.64

Table 8 shows summary statistics for the QSAR Model.

Table 8. *Summary statistics for the QSAR Model.*

Model Summary[b]				
Model	**R**	**R Square**	**Adjusted R Square**	**Std. Error of the Estimate**
Isoniazid	0.955[a]	0.912	0.869	.26719

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

[b] *Dependent Variable: Biological activity*

The values of fraction variance may vary between 0 and 1. QSAR model having r^2>0.912 will only be considered for validation. For example, the value r=0.955 and r^2=0.912 allowed us to indicate firmly the correlation between different parameters (independent variables) with the biological activity of the compounds. In the 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 biological activity.

Docking Studies

Table 9 shows the docking results for the unknown Isoniazid molecules against the Quinolinic Acid Phosphoribosyltransferase (1QPQ) enzyme which plays an important role in the metabolism of Mycobacterium tuberculosis. Characterization of synthesized molecules are given in Figures 4, 5 and 6.

Table 9. *Docking parameters with protein 1QPQ for unknown Isoniazid molecules (Series II).*

Sr. No.	ID	Total energy	VDW	H Bond	Aver Con Pair
1	UK INH A1	-76.2543	-65.8414	-10.4129	25.1053
2	UK INH A2	-85.9381	-73.883	-12.0551	24.8947
3	UK INH A3	-91.2293	-70.5148	-20.7144	23.6818
4	UK INH A4	-76.7354	-67.2356	-9.49982	26.5556
5	UK INH A5	-76.664	-67.5578	-9.10613	23.2222
6	UK INH A6	-74.8622	-64.421	-10.4411	25.1111
7	UK INH A7	-82.2368	-68.2811	-13.9558	23.7619
8	UK INH A8	-95.6221	-72.9328	-22.6893	25.9545
9	UK INH A9	-77.4251	-67.0459	-10.3792	24
10	UK INH A10	-84.3578	-69.1722	-15.1856	25.2857
11	UK INH A11	-74.9831	-64.5751	-10.408	25.0556
12	UK INH A12	-78.0453	-64.4252	-13.6201	25.3889
13	UK INH A13	-80.8007	-64.1657	-16.6351	24.5556
14	UK INH A14	-81.2886	-61.0684	-20.2202	25.7778
15	UK INH A15	46.4783	47.3872	-2.0848	17.65
16	UK INH A16	-90.7175	-67.1754	-24.9669	24.25
17	UK INH A17	-87.8607	-61.0908	-25.2939	24.35
18	UK INH A18	-84.9575	-65.1876	-19.7699	23.4348
19	UK INH A19	-93.9945	-78.6949	-15.2996	25.4545
20	UK INU A20	-82.8821	-62.591	-20.2911	24.5455
21	UK INH A21	-89.5626	-67.1797	-22.3828	24.5
22	UK INH A22	-77.5611	-61.1447	-16.4164	21.8333

Characterization of synthesized molecules

N'-(4-methoxybenzylidene) isonicotinohydrazide

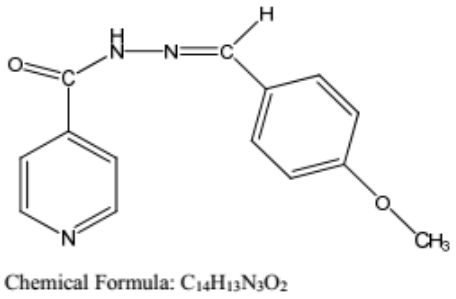

Fig. 4. *N'-(4-methoxybenzylidene) isonicotinohydrazide*

Exact Mass: 255.10
Molecular Weight: 255.27
m/z: 255.10 (100.0%), 256.10 (16.3%), 257.11 (1.5%)
Elemental Analysis: C, 65.87; H, 5.13; N, 16.46; O, 12.54

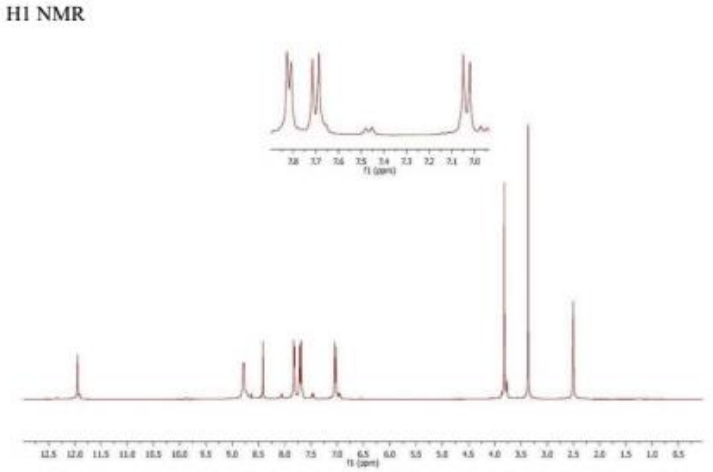

Fig. 5*. NMR spectra of N'-(4-methoxybenzylidene) isonicotinohydrazide*

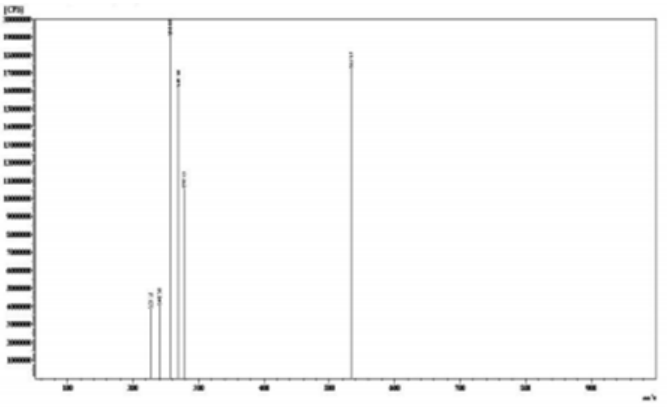

Fig. 6. *Mass spectra of N'-(4-methoxybenzylidene) isonicotinohydrazide*

CONCLUSION

Based on the present investigation it can be concluded that the equation can be useful for predicting the activity of new substituted isoniazid derivatives before their synthesis.

Biological Activity = (-29.114) + (-0.009) x Total Mol. Wt. + (-8.586) x cLogP +(-2.334) x cLogS + (0.003) x Total Surface area + (-1.156) x Drug likeliness + (81.634) x LE + (2.207) x LELP.

The validity of calculated biological activities based on regression equation is verified using the Reliability test and Correlations Statistics using SPSS software. The results are given in Table 10.

Table 10. *Result of Reliability test and Correlations Statistics.*

Regression	Reliability test (r)	Correlations Statistics (α)
Isoniazid	0.579	0.569

Once the equation is available, it is possible to enhance the biological activity by replacing the functional groups at various substitution positions on the lead molecule. The present study attempted the same by designing the number of a new set of molecules for Isoniazid. These molecules are designed virtually and tested for their valid 3D structure.

The docking studies of the substituted Isoniazid compounds have been carried out with Quinolinic Acid Phosphoribosyltransferase (1QPQ.pdb) specifies that N-butoxy-2-(4-((2-isonicotinoylhydrazono)methyl) phenoxy) acetamide (UK INH 8) binds with the amino acid residue LEU-165, LEU-170, GLU-604 and ARG-605 through hydrogen bonding. It also exhibited a large number of Vander Waal's bonding with a wide range of residues. Some of the residues involved in this type of interaction are ARG-139, ARG-162, LEU-165, LYS-172, GLU-604, and ARG-605.

The docking studies verify the results obtained by regression analysis and give insight into the interaction of biologically active molecules with proteins which helps in designing target-based therapeutic agents for tuberculosis.

Also, the synthetic accessibility of these molecules was validated as selected molecules are synthesized and are reported in the current project.

Thus, based on the regression analysis study and docking study of substituted isoniazid derivatives, it can be concluded that the newly designed molecules reported in this study can act as therapeutic agents against Mycobacterium tuberculosis.

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Conflict of Interest. The author declared that there is no conflict of interest.

Authorship Contributions. Concept: M.P.: A.P., Data Collection or Processing: A.P., Analysis or Interpretation: M.P., L.K., Literature Search: R.P., Writing: G.B. & M.P.

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