Investigating the effectiveness of Benzamide Derivatives as Anti-TB Agents: A Comparative Analysis with Existing Drugs

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Abstract **- This research investigates the potential of benzamide derivatives as anti-TB agents. A total of 72 molecules were designed by substituting some Quinazoline derivatives, which have previously shown good anti-tubercular activities. These molecules were then subjected to pharmacokinetic studies using Swiss ADME software. To further evaluate their effectiveness, the designed molecules were docked using Molegro Virtual Docker to study their amino-acid interactions with target proteins. The results showed that some of the designed molecules had promising amino-acid interactions and could potentially be effective anti-TB agents. This study provides valuable insights into the development of new drugs to combat TB.**

Keywords- **Benzamide derivatives, anti-TB agents, Quinazoline derivatives, pharmacokinetic studies using Swiss ADME software, Molegro Virtual Docker docking, amino-acid interactions with target proteins, 4U0K,4U0J, tuberculosis.**

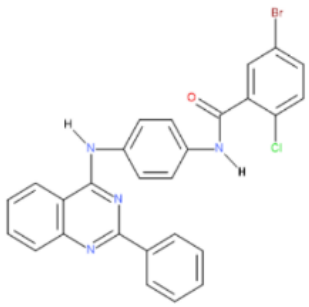
1. INTRODUCTION

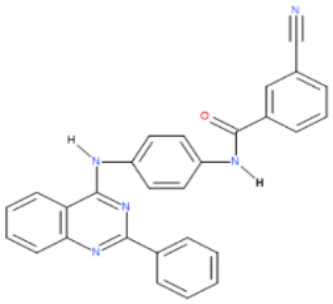
Tuberculosis (TB) is a significant cause of death worldwide, caused by Mycobacterium tuberculosis. The infection can either remain dormant or progress into active disease, resulting in tissue damage and death if not treated correctly. While TB rates are declining in the United States due to public health initiatives, it remains prevalent and out of control in many developing countries, with one-third of the global population currently infected. In India, approximately one person dies of TB every minute. With increasing drug resistance, urgent action is necessary to control TB before the most effective treatments become permanently ineffective.

Mycobacterium tuberculosis is known to primarily infect humans, while M.bovis is a closely related species that can cause a similar disease in cattle and other livestock. In the past, TB was commonly spread to humans through contaminated milk from infected cattle, leading to pasteurization. Today, the main threat of TB to humans is through the airborne transmission of M. tuberculosis. Evidence of TB has been found in ancient human remains and was referred to by various names such as "consumption," "wasting disease," and the "white plague." TB significantly impacted human history, particularly in Europe during the Middle Ages and the Industrial Revolution, where it was responsible for approximately 25% of all deaths. The threat of TB led to the rise of public health departments and healthcare practices such as the isolation of infected patients. Unfortunately, TB remains a significant issue in developing nations where healthcare practices may not be widely available.[i]

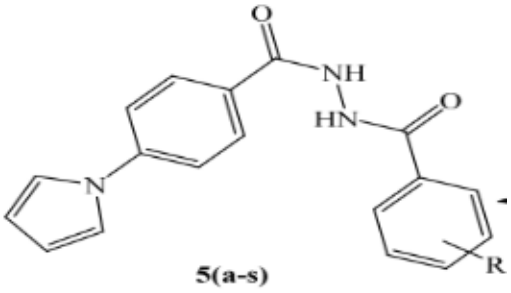
2. LITERATURE REVIEW

Satyaveni Malasala, et.al (2020) synthesized and screened 25 New 2-arylquinazoline benzamide derivatives against the H37RV strain, compounds that displayed specific and potent anti-mycobacterial activity against Mycobacterium tuberculosis. Among these 9 molecules exhibited selective and good inhibitory activity against Mycobacterium tuberculosis with the MIC values range of 4–32 µg/mL. The results of molecular modeling studies suggest that the active molecules have a good fit in the binding pocket of GlmU, with strong ligand-protein interactions, high binding energies, and favorable ADMET properties, including compliance with the Lipinski rule of 5. Overall, these studies indicate that the new quinazoline derivatives have the potential to be developed into promising leads for anti-mycobacterial therapies.[ii]



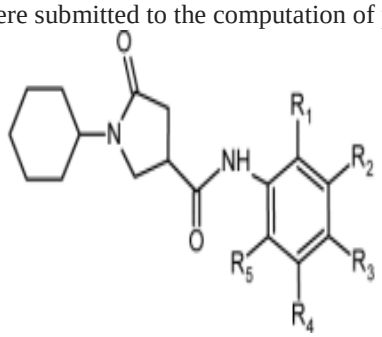


Shrinivas D. Joshi, et.al (2017) synthesized and screened a novel series of 19 pyrrolyl benzo hydrazides for their ability to target the enoyl-ACP reductase enzyme, which plays a crucial role in the type II fatty acid biosynthetic pathway of Mycobacterium tuberculosis. Several representative compounds were also evaluated for toxicity to mammalian cells using a human lung cancer cell line (A549) and were found to be non-toxic. These compounds demonstrated moderate levels of inhibition activity against InhA.[iii]

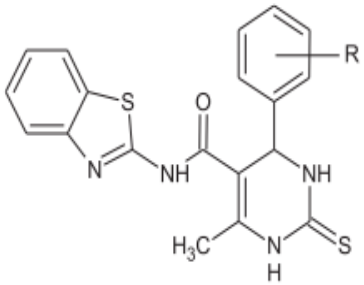


5(a-s)

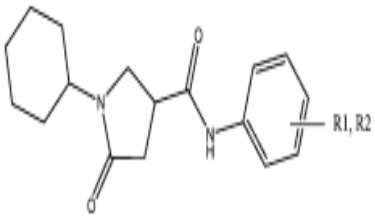
Affiba Florance Kouassi, et.al (2015) carried out a computer-aided design to develop orally bioavailable pyrrolidine carboxamide inhibitors of enoyl-acyl carrier protein reductase, an enzyme in Mycobacterium tuberculosis. In the endeavor to create a diverse virtual combinatorial library of novel pyrrolidine carboxamide (PCAM) analogs featuring various substitutions on the benzene ring was utilized in the analysis of the interactions that occur between InhA and PCAMs within the enzyme's active site. About 115 most promising virtual hits targeting InhA were submitted to the computation of predicted InhA inhibitory potencies.[iv]



Rupesh Chikhale, et.al (2015) used a Structure-based drug discovery approach to yield 20 novel derivatives of benzothiazolylpyrimidine-5-carboxamides (7a–t) which were synthesized by a three-component one-pot reaction involving benzothiazolyl oxobutanamide, thiourea, and substituted aromatic benzaldehydes. These derivatives were evaluated for the antitubercular activity to determine MIC and compounds 7a, 7e, ,7f and 7o were found to be potentially active against Mycobacterium tuberculosis (H37Rv).[v]



Xin He, et.al (2006) discovered a novel class of InhA inhibitors, pyrrolidine carboxamides, using high-throughput screening and microarray parallel synthesis methods. More potent inhibitors were discovered through subsequent in situ screening without purification. An iterative structure-based library approach was applied to rapidly optimize the initial leads, resulting in highly focused and optimized inhibitors with low nanomolar inhibitory activity against InhA, with the best inhibitor exhibiting an IC50 of 62 nM. A 160-fold gain in potency was thus realized through library optimization. The resolution of racemic mixtures and biological evaluation of the pure enantiomer revealed that only one stereoisomer was responsible for the inhibition.[vi]



3. EXPERIMENTAL WORK

3.1. Materials

3.1.1. ***2-arylquinazoline benzamide derivatives****:* Quinazolines are a class of heterocyclic compounds that exhibit a wide range of biological activities, including but not limited to antibacterial, antifungal, antiviral (e.g. anti-HIV), anticancer, anti-inflammatory, and analgesic effects. Therefore, they are considered one of the most important heterocyclic compounds with diverse pharmacological potentials.[vii]

3.1.2. ***Molecular Designing:*** The designing of molecules is an essential part of any study with their pharmacokinetic parameters and also the selection of target protein. The software used for studies is as follows:

3.1.3. Drawing of designed molecules: **Biovia draw** is used to perform computations of chemical, biological, and materials properties; to simulate, visualize and analyze chemical and biological systems.

3.1.4. Pharmacokinetics parameters of Designed molecules: **Swiss** ADME is used to calculate physicochemical descriptors and forecast ADME parameters, pharmacokinetic properties, drug-likeness, and medicinal chemistry suitability of single or multiple small molecules, with the aim of facilitating drug discovery efforts.[viii]

3.1.5. Selection of Protein Target: **RCSB PDB** is a global Protein Data Bank that archives 3D structure data for large biological molecules (proteins, DNA, and RNA) essential for research and education in fundamental biology, health, energy, and biotechnology.[ix]

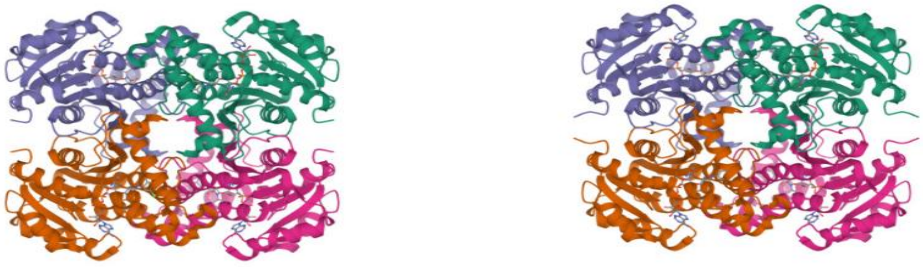
3.2. *Molecular Docking:*

This is a computational tool utilized to simulate and investigate the interaction between a small molecule and a protein at the atomic level. This approach enables the characterization of the behavior of small molecules in the binding site of target proteins and facilitates the elucidation of fundamental biochemical processes underlying the interaction.[x]

3.2.1. ***Molegro Virtual Docker (MVD):*** This is a comprehensive platform that integrates various functionalities to predict protein-ligand interactions. The software is specifically designed to manage the entire docking process, from preparing molecules to identifying potential binding sites of the target protein and predicting the binding modes of the ligands. The software boasts a user-friendly experience, thanks to its novel optimization technique, which yields high docking accuracy.[xi]

3.2.2. ***Ligand Preparation:*** It is a crucial step in the process of identifying the optimal binding between a small molecule (ligand) and a protein. This method is commonly employed in drug discovery and development efforts to identify potential drug candidates. The aim of ligand preparation is to optimize the chemical and structural properties of the ligand, ensuring its compatibility with the target protein and enhancing its binding affinity.

3.2.3. ***Target Protein Selection:*** The Target proteins are selected on the basis of their active site and the literature available on the same. The proteins are downloaded using RCSB PDB namely 4U0J and 4U0K shown below.

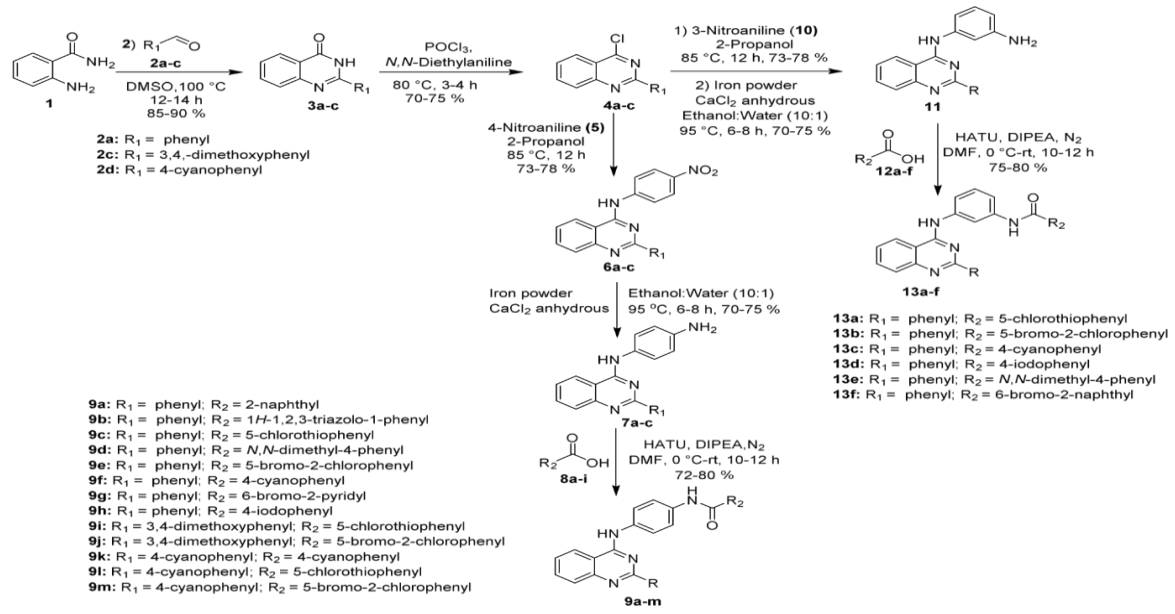


4U0J **4U0K**

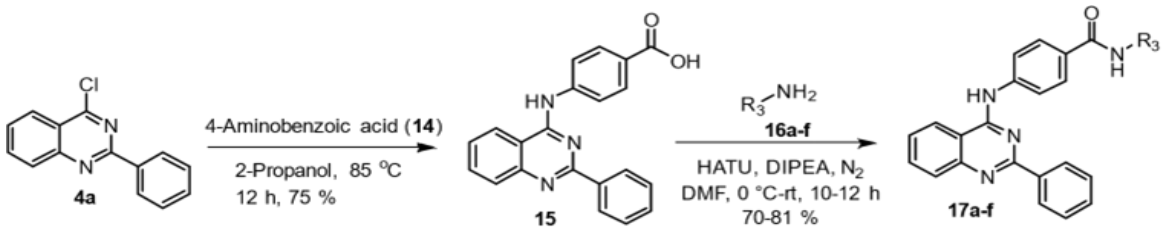
Fig.1. Protein Structures of PDB ID[xii]

3.3. Methods

3.3.1. ***Designing:*** The designing of molecules is based on the already available literature which includes the possible scheme for the preparation of the molecules.



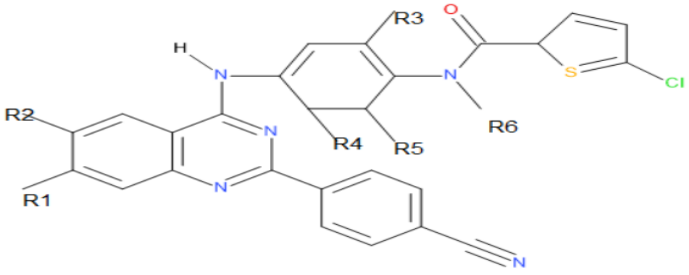
Scheme 1. Synthesis of N-(4-((2-phenylquinazolin-4/3-yl) amino) phenyl) benzamide derivatives.



17a: R_3 = 3,5-dimethoxyphenyl
17b: R_3 = 3,4,5-trimethoxyphenyl
17c: R_3 = 3-chloro-4-fluorophenyl
17d: R_3 =ethyl alanate
17e: R_3 = ethyl leucinate
17f: R_3 = 4-chlorobenzyloxy

Scheme 2. Synthesis of N-phenyl-4-((2-phenylquinazolin-4-yl) amino) benzamide derivatives.

Table 2: Designing of the molecules using Biovia Draw based on propose the scheme.



S.No.	Molecule ID	Substitutions
At R1 Position		
1.	C1	OH
2.	C2	CH_3
3.	C3	Cl
4.	C4	F
5.	C5	Br
6.	C6	NH_2
At R2 Position		
7.	D1	OH
8.	D2	CH_3
9.	D3	Cl
10.	D4	F
11.	D5	Br
12.	D6	NH_2
At R3 Position		
13.	E1	OH
14.	E2	CH_3
15.	E3	Cl
16.	E4	F
17.	E5	Br
18.	E6	NH_2
At R4 Position		
19.	F1	OH
20.	F2	CH_3
21.	F3	Cl
22.	F4	F
23.	F5	Br
24.	F6	NH_2
At R5 Position		
25.	G1	OH
26.	G2	CH_3
27.	G3	Cl
28.	G4	F
29.	G5	Br
30.	G6	NH_2
At R6 Position		
31.	H1	OH
32.	H2	CH_3
33.	H3	Cl
34.	H4	F
35.	H5	Br
36.	H6	NH_2

Substitution in Only R1 and R2 positions

S.No	Substitution in the R1 position	Molecule ID
R2- OH		
37.	OH	I1
38.	CH_3	I2
39.	Cl	I3
40.	F	I4
41.	Br	I5
42.	NH_2	I6
R2-CH_3		
43.	OH	J1
44.	CH_3	J2
45.	Cl	J3
46.	F	J4

47.	Br	J5
48.	NH_2	J6
R2-Cl		
49.	OH	K1
50.	CH_3	K2
51.	Cl	K3
52.	F	K4
53.	Br	K5
54.	NH_2	K6
R2-F		
55.	OH	L1
56.	CH_3	L2
57.	Cl	L3
58.	F	L4
59.	Br	L5
60.	NH_2	L6
R2-Br		
61.	OH	M1
62.	CH_3	M2
63.	Cl	M3
64.	F	M4
65.	Br	M5
66.	NH_2	M6
R2-NH_2		
67.	OH	N1
68.	CH_3	N2
69.	Cl	N3
70.	F	N4
71.	Br	N5
72.	NH_2	N6

3.3.2. ***Pharmacokinetic Parameters*:** The Swiss ADME was used for the study of Pharmacokinetics parameters including Lipinski's Rule, log P, and molecular weight.

Table 3. Representation of Pharmacokinetics parameters of designed molecules by substituting at R1,R2,R3,R4,R5 AND R6 position using Swiss ADME.

S.No.	**Molecule ID**	**Mol. Wt.**	**Consensus Log P**	**Num. of Rotable Bonds**	**Num. of H bond acceptors**	**Num. of H bond donors**	**Molar Refractivity**
1	C1	498.96 g/mol	3.17	6	5	3	141.05
2	C2	496.99 g/mol	3.81	6	4	2	143.99
3	C3	517.41 g/mol	4.01	6	4	2	144.03
4	C4	500.95 g/mol	3.82	6	5	2	138.98
5	C5	561.86 g/mol	4.07	6	4	2	146.72
6	C6	497.98 g/mol	3.03	6	4	3	143.43
7	D1	500.98 g/mol	2.91	6	5	3	140.08
8	D2	499.01 g/mol	3.57	6	4	2	143.03
9	D3	519.43 g/mol	3.17	6	4	2	143.07
10	D4	502.97 g/mol	3.53	6	5	2	138.02
11	D5	563.88 g/mol	3.78	6	4	2	145.76
12	D6	499.99 g/mol	2.77	6	4	3	142.46
13	E1	500.98 g/mol	2.88	6	5	3	139.63
14	E2	499.01 g/mol	3.49	6	4	2	142.87
15	E3	519.43 g/mol	3.64	6	4	2	142.86

16	E4	502.97 g/mol	3.5	6	5	2	138.11
17	E5	563.88 g/mol	3.71	6	4	2	145.93
18	E6	499.99 g/mol	2.65	6	4	3	140.77
19	F1	500.98 g/mol	2.52	6	5	3	139.22
20	F2	541.09 g/mol	4.2	7	4	2	157.03
21	F3	519.43 g/mol	3.45	6	4	2	142.86
22	F4	502.97 g/mol	3.37	6	5	2	138.11
23	F5	563.88 g/mol	3.54	6	4	2	145.93
24	F6	499.99 g/mol	2.42	6	5	3	140.77
25	G1	500.98 g/mol	2.52	6	5	3	139.22
26	G2	499.01 g/mol	3.47	6	4	2	142.87
27	G3	519.43 g/mol	3.45	6	4	2	142.86
28	G4	502.97 g/mol	3.37	6	5	2	138.11
29	G5	563.88 g/mol	3.54	6	4	2	145.93
30	G6	499.99 g/mol	2.42	6	5	3	140.77
31	H1	500.98 g/mol	3.04	6	5	2	138.88
32	H2	499.01 g/mol	3.43	6	4	1	142.96
33	H3	519.43 g/mol	3.68	6	4	1	142.95
34	H4	502.97 g/mol	3.59	6	5	1	138.21
35	H5	563.88 g/mol	3.77	6	4	1	146.02
36	H6	499.99 g/mol	2.84	6	5	2	140.86

Table 4. Representation of Pharmacokinetics parameters of designed molecules by substituting at R1 and R2 position using Swiss ADME.

S.no	**Mol. ID**	**Mol. wt.**	**Consensus log P**	**No. of Rotable bond**	**No. of H bond acceptors**	**No. of H bond donors**	**Molar Refractivity**
1	I1	516.98 g/mol	2.5	6	6	4	142.11
2	I2	515.01 g/mol	3.19	6	5	3	145.05
3	I3	535.42 g/mol	3.38	6	5	3	145.09
4	I4	518.97 g/mol	3.2	6	6	3	140.04
5	I5	579.88 g/mol	3.44	6	5	3	147.78
6	I6	515.99 g/mol	2.44	6	5	4	144.49
7	J1	515.01 g/mol	3.11	6	5	3	145.05
8	J2	513.03 g/mol	3.85	6	4	2	147.99
9	J3	533.45 g/mol	4	6	4	2	148.04
10	J4	517.00 g/mol	3.81	6	5	2	142.98
11	J5	577.90 g/mol	4.06	6	4	2	150.73
12	J6	514.02 g/mol	2.97	6	4	3	147.43
13	K1	535.42 g/mol	3.3	6	5	3	145.09
14	K2	533.45 g/mol	4	6	4	2	148.04
15	K3	553.87 g/mol	4.19	6	4	2	148.08
16	K4	537.42 g/mol	4	6	5	2	143.03
17	K5	598.32 g/mol	4.25	6	4	2	150.77
18	K6	534.44 g/mol	3.17	6	4	3	147.47
19	L1	518.97 g/mol	3.11	6	6	3	140.04
20	L2	517.00 g/mol	3.81	6	5	2	142.98

21	L3	537.42 g/mol	4	6	5	2	143.03
22	L4	520.96 g/mol	3.82	6	6	2	137.98
23	L5	581.87 g/mol	4.07	6	5	2	145.72
24	L6	517.99 g/mol	2.98	6	5	3	142.42
25	M1	579.88 g/mol	3.36	6	5	3	147.78
26	M2	577.90 g/mol	4.06	6	4	2	150.73
27	M3	598.32 g/mol	4.25	6	4	2	150.77
28	M4	581.87 g/mol	4.07	6	5	2	145.72
29	M5	642.77 g/mol	4.32	6	4	2	153.46
30	M6	578.89 g/mol	3.23	6	4	3	150.16
31	N1	515.99 g/mol	2.36	6	5	4	144.49
32	N2	514.02 g/mol	3.05	6	4	3	147.43
33	N3	534.44 g/mol	3.25	6	4	3	147.47
34	N4	517.99 g/mol	3.06	6	5	3	142.42
35	N5	578.89 g/mol	3.31	6	4	3	150.16
36	N6	515.01 g/mol	2.22	6	4	4	146.87

3.3.3. ***Molecular Docking:*** Molecular docking is performed on target proteins with all 40 designed molecules utilizing two software Biovia Discovery Studio and Molegro Virtual Docker.

3.3.3.1. Molegro Virtual Docking 6.0

Molegro Virtual Docker is a comprehensive platform that predicts protein-ligand interactions by handling all stages of the docking process, including molecule preparation, identification of potential binding sites, and prediction of ligand binding modes. MVD employs a novel optimization technique and offers a user-friendly interface that enhances productivity and ease of use. Notably, Molegro Virtual Docker has demonstrated superior docking accuracy compared to other state-of-the-art products, with an accuracy of 87%, while Glide achieved 82%, Surflex achieved 75%, and FlexX achieved 58%.[xiii]

a) PDB ID **4U0J**

Fig.2. 566 Ligand Summary[xiv]

Identifier	Ranking for goodness of fit	Ranking for geometry	Real space R factor	Real space correlation coefficient	RMSZ-bond-length	RMSZ-bond-angle	Outliers of bond length	Outliers of bond angle	Atomic clashes	Stereochemical errors	Model completeness	Average occupancy
4U0J_566_A_401	68%	15%	0.094	0.907	2.73	1.24	8	3	2	0	100%	1

Table 5: Docking result (Mol Dock Score) of the target protein (4U0J) and Molecules C1-H6 using Molegro Virtual Docker.

Name	**MolDock Score**	**HBond**	**Mol. Wt.**	**Rerank Score**
[00]566_401 [A]	-105.547	-2.21453	286.369	-88.6355
C1	949.371	-2.5	500.979	188.235
C2	949.983	-2.5	499.007	187.107
C3	947.922	-2.5	518.417	186.294
C4	-44.076	-3.53337	502.97	62.6158
C5	948.135	-2.5	562.868	186.604
C6	948.974	-2.5	499.995	194.436
D1	-46.9493	-3.46866	500.979	107.408
D2	-48.9753	-3.22046	499.007	123.03
D3	-51.0645	-3.22175	518.417	122.365
D4	-48.9697	-3.23508	502.97	122.16

D5	-50.9451	-3.24938	562.868	133.738
D6	-47.3408	-3.14304	499.995	118.281
E1	969.095	-5.76597	498.963	176.639
E2	-37.4305	-3.14765	495.983	177.015
E3	950.328	-3.22213	521.441	128.588
E4	975.311	-0.42074	501.962	212.567
E5	-63.535	-3.1495	565.892	77.733
E6	-45.9564	-5.05471	496.971	100.021
F1	-68.0229	-2.5	498.963	181.707
F2	-74.2992	-2.5	531.007	176.68
F3	-68.4878	-2.5	518.417	182.738
F4	-68.4791	-2.5	501.962	182.994
F5	-72.9554	-2.5	563.876	181.238
F6	-68.0167	-2.5	496.971	182.716
G1	-34.0992	-2.5	497.956	201.037
G2	-34.461	-2.5	494.975	204.563
G3	-101.509	-2.05361	521.441	49.5994
G4	-34.5045	-2.5	500.955	194.235
G5	-101.527	-2.09682	565.892	49.7338
G6	-34.1492	-2.5	495.963	197.677
H1	972.679	-2.5	501.987	208.078
H2	972.468	-1.74597	500.014	209.731
H3	964.374	-2.17074	521.441	216.85
H4	-34.0709	0	503.978	145.235
H5	-42.3956	-3.1924	565.892	120.888
H6	-38.2397	0	501.003	146.41

Table 6: Docking result (Mol Dock Score) of the target protein (4U0J) and Molecules I2-N6 using Molegro Virtual Docker.

Name	**MolDock Score**	**HBond**	**Rerank Score**	**MW**
[00]566_401 [A]	-105.547	-2.21453	-88.6355	286.369
I2	-72.7728	-4.62466	68.7841	515.006
I3	928.266	-4.7574	100.043	536.432
I4	-72.8284	-4.54339	27.0866	518.97
I5	924.851	-6.02651	39.9629	580.883
I6	-76.4502	-4.87731	39.9724	515.994
J1	-78.5738	-5.36191	34.5528	515.006
J2	931.878	-4.50649	67.8567	513.033
J4	-81.9499	-3.54245	30.165	578.911
J4	950.331	-0.554632	76.841	516.997
J6	-77.5787	-3.76312	39.3793	514.021
J6	924.087	-4.50863	43.9932	534.46
K1	-86.1953	-6.2058	28.2095	536.432
K2	923.901	-4.49794	56.9649	534.46
K3	921.957	-4.52228	44.3159	553.87
K4	-68.3828	-2.5	28.9726	538.423
K5	921.833	-4.50321	45.0633	598.321
K6	918.635	-6.4458	50.8616	535.448
L1	-78.5468	-5.4354	29.4915	518.97

L2	-74.1516	-3.59108	48.7272	516.997
L3	923.877	-4.50207	45.224	538.423
L4	931.872	-4.51447	45.569	520.961
L5	923.88	-4.49989	45.2274	582.874
L6	948.436	-5.01179	66.2264	517.985
M1	-86.3509	-5.49003	27.7489	580.883
M2	923.911	-4.50201	57.0469	578.911
M3	-84.0793	-3.49859	27.8774	598.321
M4	923.939	-4.49264	45.2528	582.874
M5	921.764	-4.50045	44.8594	642.772
M6	-86.4747	-4.24257	28.0151	579.899
N1	928.153	-7.80324	47.8076	515.994
N2	-61.9255	-2.41287	47.6071	514.021
N3	925.415	-4.54613	40.5144	535.448
N4	-68.5546	-4.40737	189.948	517.985
N5	925.405	-4.54362	40.444	579.899
N6	-76.8043	-4.43295	41.0375	515.009

b) PBD ID **4U0K**

Identifier	Ranking for goodness of fit	Ranking for geometry	Real space R factor	Real space correlation coefficient	RMSZ-bond-length	RMSZ-bond-angle	Outliers of bond length	Outliers of bond angle	Atomic clashes	Stereochemical errors	Model completeness	Average occupancy
4U0K_744_A_501	6%	41%	0.318	0.761	1.08	1.28	1	4	4	0	100%	0.64

Fig. 3. 744 Ligand Summary[xv]

Table 7: Docking result (Mol Dock Score) of the target protein (4U0K) and Molecules C1-H6 using Molegro Virtual Docker.

Name	**MolDock Score**	**Rerank Score**	**HBond**	**MW**
[00]744_501 [A]	-114.136	-78.7938	-1.06043	334.84
C1	930.766	47.2643	-6.44126	500.979
C2	936.995	56.2291	-4.1344	499.007
C3	935.435	50.3071	-2.49275	518.417
C4	-64.6963	45.2405	-3.30017	502.97
C5	934.952	51.9738	-4.07204	562.868
C6	933.193	50.7901	-4.63377	499.995
D1	-79.9976	30.3272	-5.46914	500.979
D2	-77.832	29.7505	-3.59026	499.007
D3	-80	34.7713	-3.18927	518.417
D4	-77.8495	30.3038	-3.57944	502.97
D5	-80.2596	31.4278	-3.35069	562.868
D6	-80.1338	27.4648	-5.08412	499.995
E1	939.36	54.0447	0	498.963
E2	-60.355	55.7271	0	495.983
E3	918.67	36.5073	0	521.441
E4	941.522	65.3028	0	501.962
E5	-80.0593	21.7882	0	565.892

E6	-60.3545	52.6246	0	496.971
F1	-91.8535	16.6422	-4.27333	498.963
F2	-89.3522	29.6455	-4.36038	531.007
F3	-92.1724	17.5524	-4.27354	518.417
F4	-92.1053	17.5449	-4.15494	501.962
F5	-96.5987	15.0773	-4.15547	563.876
F6	-79.4914	50.6394	-0.69366	496.971
G1	-59.6594	49.7043	-4.13548	497.956
G2	-55.2993	62.1418	-4.3604	494.975
G3	-89.4551	66.6654	-4.07671	521.441
G4	-55.3061	53.6159	-4.35771	500.955
G5	-95.083	14.902	-0.1104	565.892
G6	-48.6141	71.0392	0	495.963
H1	952.709	60.1939	-3.88722	501.987
H2	948.336	69.4254	-3.85755	500.014
H3	948.403	71.8251	-2.13367	521.441
H4	-62.6582	39.0781	-3.74505	503.978
H5	-55.4461	63.1445	0	565.892
H6	-51.4763	207.27	-5.40548	501.003

Table 8: Docking result (Mol Dock Score) of the target protein (4U0K) and Molecules I2-N6 using Molegro Virtual Docker.

Name	**MolDock Score**	**Rerank Score**	**HBond**	**MW**
[00]744_501 [A]	-110.868	-66.3848	-2.5	334.84
I2	-65.8158	56.5452	-5.56155	515.006
I3	926.675	44.045	-6.91461	536.432
I4	-65.7891	36.1328	-5.58216	518.97
I5	926.676	44.0347	-6.90613	580.883
I6	-69.0886	203.396	-9.91905	515.994
J1	-72.7018	36.2481	-5.70286	515.006
J2	947.634	107.849	0	513.033
J3	939.85	96.0534	0	534.46
J4	935.827	47.2733	-4.25475	516.997
J5	-73.7674	38.685	-3.74972	578.911
J6	-70.195	43.4787	-3.81402	514.021
K1	-80.5321	32.683	-5.93033	536.432
K2	934.79	54.3852	-5.75119	534.46
K3	925.908	45.4676	-4.25731	553.87
K4	-66.1388	39.7404	-6.15497	538.423
K5	925.938	45.3576	-4.25634	598.321
K6	935.714	54.2182	-5.76454	535.448
L1	-72.7195	33.6059	-5.76729	518.97
L2	-66.0375	55.8206	-3.25397	516.997
L3	928.138	46.2192	-4.264	538.423
L4	935.949	47.8461	-4.26055	520.961
L5	934.788	54.2991	-5.75084	582.874
L6	931.919	46.8518	-5.13865	517.985
M1	-80.4933	31.9952	-5.51164	580.883
M2	928.065	53.5863	-4.25845	578.911

M3	-75.9537	37.5824	-3.28852	598.321
M4	928.148	45.8877	-4.2667	582.874
M5	925.882	45.6021	-4.25572	642.772
M6	-79.3501	36.8837	-5.40434	579.899
N1	928.636	43.868	-8.44247	515.994
N2	-66.0897	57.4671	-5.01272	514.021
N3	929.305	46.6666	-4.30043	535.448
N4	-66.1127	36.1502	-4.89213	517.985
N5	935.304	50.9306	-2.49931	579.899
N6	-70.3022	39.9283	-5.88474	515.009

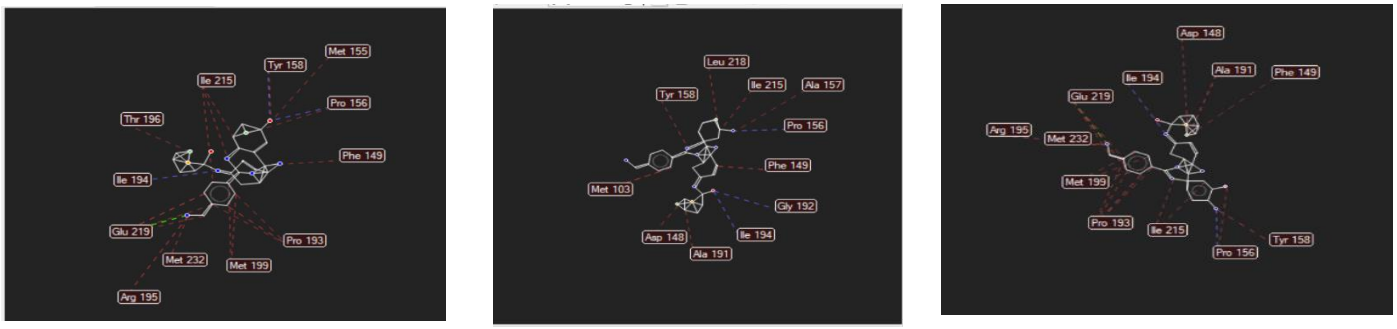
Table 9: Docking result (Amino Acid Interactions) of the target protein using Molegro Virtual Docker.

S. No	**Mol. ID**	**Amino Acid Sequencing at target site**	
		At 4U0J	**At 4U0K**
1	C1	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103, Gly 192, Ile 194, Asp 148, Ala 191, Phe 149, Pro 156, Ale 157, Tyr 158
2	C2	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103, Ile 194, Gly 192, Ile 21, Asp 148, Ala 191, Phe 149, Ala 157, Pro 156, Ile 215,Leu 218, Tyr 158
3	C3	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Ile 16, Ser 20, Gly 14, Asp 64, Ile 95, Phe 97
4	C4	Met 98, Phe 97, Gly 96, Thr 17, Ile 16	Met 199, Tyr 158, Gly 192, Ile 194, Ile 21, Asp 148, Phe 149, Ala 157, Pro 156, Ile 215, Leu 218
5	C5	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103,Phe 149, Leu 218, Pro 156, Ala 157, Asp 148, Ile 215, Ala 191, Ile 21, Gly 192, Ile 194, Tyr 158
6	C6	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103, Gly 192, Ile, 194, Ile 21, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218, Tyr 158
7	D1	Gly 96, Ala 198, Thr 196, Thr 17, Leu 197, Tyr 158	Ile 194, Asp 148, Phe 149, Pro 156, Met 199, Tyr 158
8	D2	Tyr 158, Gly 98, Phe 97, Ala 198, Thr 17, Leu 197	Met 199, Pro 156, Tyr 158, Ile 194, Asp 148, Leu 218
9	D3	Met 199, Tyr 158, Ile 194,Asp 148, Pro 156, Leu 218	Met 199, Pro 156, Ile 215, Tyr 158, Phe 149, Gly 192, Ile 194, Asp 148
10	D4	Gly 96, Phe 97, Ala 198, Thr 196, Thr 17, Leu 197, Thy 158	Ile 194, Asp 148, Pro 156,Leu 218, Tyr 158,Met 199
11	D5	Thy 158, Thr 17, Leu 195, Thr 196, Ala 198, Phe 97, Gly 98	Tyr 158, Pro 156, Met 199, Ile 194,Asp 148
12	D6	Gly 96, Phe 97, Ala 198, Thr 196, Thr 17, Leu 197, Tyr 158	Ile 194, Asp 148, Pro 156,Leu 218, Tyr 158,Met 199
13	E1	Phe 97, Gly 96, Thr 17, Ala 198, Thr 196	Phe 149, Met 103, Ile 215, Tyr 158
14	E2	Gly 96,Thr 196, Ala 19, Leu 197, Thr 17	Phe 149, Ala 157, Ile 215, Met 103
15	E3	Gly 96, Phe 97, Leu 197, Thr 196, Ala 198	Met 103, Tyr 158, Phe 149, Ile 215
16	E4	Leu 197, Thr 196, Met 199, Ile 16, Gly 96	Ala 191, Phe 149, Ile 215, Ala 157, Met 103

17	E5	Gly 104, Ala 157, Met 103, Ile 215	Met 103, Met 161, Ala 191, Phe 149, Tyr 158, Ile 215
18	E6	Gly 96, Phe 97, Thr 17,Leu 197, Thr 196, Ala 198	Ala 157, Ile 215, Met 103, Phe 149
19	F1	Gly 192, Phe 149, Ile 215, Ala 157, Gly 104, Met 103	Phe 149, Asp 148, Ala 191, Gly 192, Ile 194, Met 103, Tyr 158
20	F2	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Asp 148, Ala 191, Met 199, Pro 193, Tyr 158, Met 103
21	F3	Tyr 158, Gly 96, Ala 198, Phe 97, Thr 196	Ile 194, Gly 192, Tyr158, Phe 149, Met 103,Ala 191, Asp 148
22	F4	Phe 97, Gly 96, Tyr 158, Ala 198, Thr 196	Tyr 158, Met 103, Ile 194, Gly 192, Asp 148, Ala 191, Phe 149
23	F5	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Ala 191, Asp 148, Phe 149, Tyr 158, Met 103, Gly 192, Ile 194
24	F6	Phe 149, Pro 156, Ile 215, Met 103, Gly 192, Ile 194, Pro 196, Asp 148	Met 161, Phe 149, Pro 193, Gly 192, Ala 191, Met 147, Met 199, Leu 218, Tyr 158
25	G1	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103, Tyr 158, Phe 149, Gly 192, Ile 194, Asp148, Ala 191
26	G2	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Asp 148, Ala 191, Met 199, Pro 193, Tyr 158, Met 103
27	G3	Met 199, Tyr 158, Met 161, Gly 96, Ala 198	Met 147, Ile 95, Lys 165, Tyr 158, Gly 192, Ile 194, The 149, Met 199
28	G4	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Met 103, Tyr 158, Met 199, Pro 193, Ala 191, Asp 148
29	G5	Met 161, Met 98, Gly 96, Ala 198, Met 199, Tyr 158	Phe 149, Gly 192, Ala 191, Met 103
30	G6	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Tyr 158, Met 103, Ile 215, Ala 157, Leu 207, Pro 193
31	H1	Phe 97, Gly 96, Tyr 158, Ala 198, Thr 196	Pro 193, Met 199, Phe 149, Tyr 158, Met 103, Asp 148, Ala 191
32	H2	Met 98, Met 103, Ala 198, Thr 196, Tyr 158	Met 103, Gly 192, Ile 194, Ala 191, Asp 148, Phe 149, Tyr 158
33	H3	Tyr 158, Phe 97, Gly 96, Ala 198, Thr 196	Se 94, Gly 14, Ile 95, Phe 97
34	H4	Gly 96, Phe 97, Thr 17, Leo 197, Ser 19, Ala 198, Thr 196	Ile 194, Asp 148, Leu 218, Met 199, Tyr 158
35	H5	Leu 197, Thr 17, Thr 196, Ala 198, Gly 96	Met 161, Tyr 158, Ala 191, Phe 149, Met 103, Ile 215
36	H6	Gly 96, Thr 17, Leu 197, Ser 19, Ala 198, Thr 196	Leu 218, Pro 156, Ala 157, Met 103, Ile 202, Leu 207, Ile 215, Ala 211, Gly 212, Met 199, Phe 149
37	I2	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Met 199, Tyr 158, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Ile 215, Pro 156
38	I3	Ile 194, Thr 196, Glu 219, Met 232, Arg 195, Pro 193, Met 199, Ile 215, Pro 156, Met 155, Tyr 158, Phe 149	Ser 20, Gly 14, Asp 64, Val 65, Leu 63, Ser 94, Gly 96, Phe 97
39	I4	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Tyr 158, Met 199, Gly 192, Ile 194, Asp 148, Phe 149, Ale 157, Ili 215, Pro 156

40	I5	Ile 194, Gly 192, Phe 149, Ala 157, Pro 156, Met 103	Leu 63, Val 65, Asp 64, Ser 94, Phe 97, Gly 96, Ser 20, Gly 14
41	I6	Met 199, Tyr 158, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Pro 156, Ile 215,Leu 218	Ile 21, Gly 192, Ile 194, Glu 219, Met 232, Arg 195, Pro 193, Met 199, Ile 215, Leu 218, Pro 156, Tyr 158
42	J1	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Met 199, Tyr 158, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218
43	J2	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Tyr 158, Met 103, Ile 215, Ley 207, Ala 191
44	J3	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Tyr 158,Met 103, Ile 215, Leu 207, Ala 191
45	J4	Gly 192, Pro 193, Met 103, Pro 156, Ala 157, Leu 218, Tyr 158, Gly 96	Met 103, Gly 192, Ile 194, Asp 148, Ala 191, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218, Tyr 158
46	J5	Leu 218, Pro 156, Ala 157, Ile 215, Phe 149, Met 199, Gly 192, Ile 194, Asp 148, Tyr 158	Met 199, Tyr 158, Phe 149, Ile 194, Asp 148, Gly 192, Leu 218, Ala 157, Ile 215
47	J6	Met 199, Tyr 158, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Pro 156, Ile 215,Leu 218	Met 199, Tyr 158, Phe 149, Ile 194, Asp 148, Gly 192, Leu 218, Ala 157, Ile 215, Pro 156
48	K1	Met 199,Phe 149, Leu 218, Ala 157, Pro 156, Ile 194, Gly 192, Asp 148, Tyr 158	Tyr 158, Met 199, Gly 192, Ile 194,Asp 148, Pro 156,Phe 149, Leu 218, Ile 215,Ala 157
49	K2	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 147, Ile 95, Gly 96, Ser 94, Ile 16, Ile 15, Phe 41, Ser 19, Thr 17, Thr 196
50	K3	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Pro 156, Ala 157, Ile 215, Leu 218 Ile 194, Gly 192, Ala 191, Asp 148, Phe 149
51	K4	Gly 192, Pro 193, Met 103	Ser 20, Ser 19, Thr 17, Ile 16, Ile 15, Phe 41, Ser 94,Gly 96, Ile 95, Met 147
52	K5	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Pro 156, Ala 157, Ile 215, Leu 218, Ile 194, Gly 192, Ala 191, Asp 148, Phe 149
53	K6	Ala 191, Asp 148, Ile 194, Gly 192, Phe 149, Leu 218, Ala 157, Pro 156, Ile 215, Tyr 158, Met 103	Thr 196, Thr 17, Ser 19, Phe 41, Ile 15, Ile 26, Ser 94, Gly 96, Ile 95, Met 147
54	L1	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218
55	L2	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218
56	L3	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Gly 192, Phe 149, Met 103, Ala191, Asp 148, Tyr 158, Pro 156, Ala 157, Ile 215, Leu 218, Ile 194

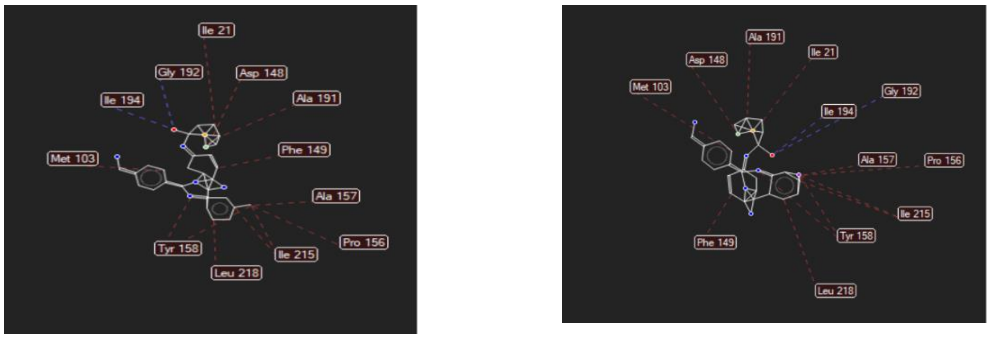
57	L4	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Leu 218, Ile 215, Pro 156, Ala 157, Phe 149, Asp 148, Ile 194, Gly 192
58	L5	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Se 19, Thr 17, Thr 196, Ile 16, Phe 41, Ile 15, Met 147, Ile 95, Gly 96, Ser 94
59	L6	Ser 19, Thr 17, Thr 196, Ile 16, Phe 41, Ser 94, Ile 95, Gly96, Met 147	Met 103, Gly 192, Ile 194, Asp 148, Ala 191, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218, Tyr 158
60	M1	Met 199,Phe 149, Leu 218, Ile 215, Ala 157, Pro 156, Ile 194, Gly 192, Asp 148, Tyr 158	Pro 156, Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Leu 218, Ile 215, Ala 157
61	M2	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Ile 215, Pro 156, Leu 218, Ala 157, Asp 148, Ala 191, Ile 194, Gly 192, Phe 149
62	M3	Phe 149, Tyr 158, Gly 192, Ile 194,Met 199,Asp 148, Ala 157, Pro 156, Ile 215,Leu 218	Pro 156, Ala 157, Ile 215, Leu 218, Asp 148, Ile 194, Gly 192, Phe 149, Tyr 158, Met 199
63	M4	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Ile 215, Pro 156, Leu 218, Ala 157, Asp 148, Ala 191, Ile 194, Gly 192, Phe 149
64	M5	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Tyr 158, Ala 157, Pro 156, Ili 215, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149, Met 103
65	M6	Ile 194,Asp 148,Ala 157, Pro 156, Leu 218, Ile 215,Tyr 158, Met 199	Ala 157, Pro 156, Phe 149, Ile 194, Gly 192,Asp 148, Tyr 158, Met 199, Leu 218, Ile 215
66	N1	Met 103, Tyr 158, Ala 157, Pro 156, Leu 218, Asp 148, Ala 191, Gly 192, Ile 194, Phe 149	Met 103, Tyr 158, Ile 215, Ala 157, Asp 148, Ala 191, Ile 194, Gly 192, Phe 149
67	N2	Gly 192, Met 161, Met 103, Leu 218, Ala 157, Pro 156	Tyr 158 Met 199, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Ile 215, Pro 156
68	N3	Met 103, Ile 194, Gly 192, Phe 149, Ala 157, Pro 156	Met 103, Tyr 158, Ala 157, Phe 149, Gly 192, Ile 194, Asp 148
69	N4	Phe 149, Ala 191, Asp 148, Ile 194, Glu 219, Arg 195, Met 232, Met 199, Pro 193, Ile 215, Pro 156, Tyr 158	Tyr 158, Met 199, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Ile 215, Pro 156
70	N5	Met 103, Ile 194, Gly 192, Phe 149, Ala 157, Pro 156	Phe 97, Gly 96, Ser 20, Gly 14, Asp 64, Val 65, Gly 96
71	N6	Tyr 158, Met 199, Ile 194, Gly 192, Asp 148, Phe 149, Pro 156, Ala 157, Ile 215, Leu 218	Met 199, Tyr 158, Gly 192, Ile 194, Asp 148, Phe 149, Ala 157, Ile 215, Pro 156



(A)Molecule I3 (B) Molecule K6 (C) Molecule N4

Fig. 4. Amino Acid Interactions on PDB(4U0J)

(A) Molecule I6 (B) Molecule M4



(C) Molecule C2 (D) Molecule C5

Fig. 5. Amino Acid Interactions on PDB (4U0K)

4. RESULT & DISCUSSION

Benzamide derivatives were designed considering the antitubercular potential of the substituent referring the literature and In-silico molecular parameters were calculated for proposed derivatives. And considering therapeutic potential of 2-aryl quinazoline benzamide derivatives, 40 compounds have been designed using literature about substitution which may enhance the antitubercular activity (Table 2).

SWISS ADME was used to study the log P values, violation of Lipinski's rule of five and drug likeness properties Maximum compounds obeys the parameters and results were reported (Table 3 and Table 4). The molecules showing good parameters were further considered for docking studies

The designed compounds are subjected for molecular docking studies in order to get binding possibilities of designed molecules on selected target of Mycobacterium tuberculosis by utilizing software (Molegro Virtual Docker). The docking results obtained according to amino acid sequencing (Table 9) and the docking results obtained according to MolDock score (Table 5, Table 6, Table 7 and Table 8).

The best molecules according to Molegro Virtual Docker on target protein 4U0J and 4U0K are D2, D6 and F6.

D2 with MolDock score of -48.9753 and -77.832; Rerank score of 123.03 and 29.7505; Hbond -3.46866 and -3.59026 and interactions Tyr 158, Gly 98, Phe 97, Ala 198, Thr 17, Leu 197 and Met 199, Pro 156, Tyr 158, Ile 194, Asp 148, Leu 218 at 4U0J and 4U0K respectively.

D6 with MolDock score of -47.3408 and -80.1338; Rerank score of 118.281 and 27.4648; Hbond -3.14304 and -5.08412 and interactions Gly 96, Phe 97, Ala 198, Thr 196, Thr 17, Leu 197, Tyr 158 and Ile 194, Asp 148, Pro 156,Leu 218, Tyr 158,Met 199 at 4U0J and 4U0K respectively.
F6 with MolDock score of -68.0167 and -79.4914; Rerank score of 182.716 and 50.6394; Hbond -2.5 and -0.69366 and interactions Phe 149, Pro 156, Ile 215, Met 103, Gly 192, Ile 194, Pro 196, Asp 148 and Met 161, Phe 149, Pro 193, Gly 192, Ala 191, Met 147, Met 199, Leu 218, Tyr 158 at 4U0J and 4U0K respectively.

5. CONCLUSION

The immune-compromised host suffering from Tuberculosis became Drug Resistant in past years. Quinazoline derivatives have various biological activities including the anti-tubercular activity. The Benzamide derivatives also shows good antitubercular activity. When both Quinazoline and Benzamide derivatives were taken together resembles better antitubercular activity. All the designed compounds with maximum binding interactions on Molegro Virtual Docker Software on target protein 4U0J are I3, K6, and N4.

All the designed compounds with maximum binding interactions on Molegro Virtual Docker Software on target protein 4U0K are I6, M4, C2 and C5. It was found that above mentioned compounds have good binding affinities with the target proteins for antitubercular activity. The concluded result of docking study of the molecules with good Amino acid interaction can be synthesized and used for further antitubercular studies.

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