Molecular Docking Studies of a Few of Derivatives of Nitro Ketene Dithiols , Decalin-β-keto Ester Enolate and Furo Pyrazole Derivatives for Mycobacterium Tuberculosis

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Abstract
Tuberculosis (TB) is a common and often mortal bacterial infectious disease caused by constrains pathogens (Mycobacterium). The present study is about the in silico drug screening of 75 (Nitrogen, sulfur, and oxygen-containing) derivatives of Nitroketen dithiol, decalin-β- keto ester enolate, and Furo pyrazole to control the viral growth by blocking the active site of Tuberculosis protein 1L9U. After docking 75 ligand molecules, three hits were selected based on the binding affinities. Lipinski's rule, the hydrogen bonding, and drug-likeness were also investigated for their potentiality as suitable drug candidates. The present analysis identifies three derivatives of nitro ketene dithiol, which can be used as a potentially better drug candidate to the commercial drug Rifampicin, which is used for the treatment of Tuberculosis. These three compounds have better binding and drug properties with a simple structure; it is of interest to consider them for further in-vitro and in vivo evaluation to declare them as better drug candidates for TB.

Keywords: Tuberculosis, Mycobacterium, Nitorketene dithiol, Decalin-β- keto ester enolate, Furo pyrazole derivatives, PyRx, PyMol.

Introduction

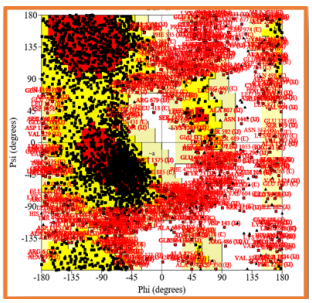
Tuberculosis is an airborne, infectious disease usually caused by constrains human pathogen, Mycobacterium tuberculosis Bacteria which predominantly attack the lungs but can also infect other organs of the body. MTB has always been a persistent challenge throughout human history because of its acute social implications. It has been speculated that the genus Mycobacterium emerged more than 150 million years ago. Symptoms of TB are weight loss, Fever, Sweating at night, No appetite.[1]

The treatment for TB was limited until the discovery of antibiotics. In the middle Ages, Cod liver oil, vinegar massages, and inhaling hemlock or turpentine were all treatments for TB. Nowadays, Isoniazid (1951), Pyrazinamide (1952), Ethambutol (1961), and Rifampicin (1966) are four drugs that are used to treat TB disease. This 4-drug combination is still the most usual treatment for drug-susceptible TB. Treatment for latent TB infection can take 6 to 9 months[2]. Antibiotic resistance in Mycobacterium tuberculosis occurs by arbitrary, single step, spontaneous mutation at a low rate but predictable frequency in large bacterial populations.

The main aim of our study is to perform in silico drug screening of 75 (Nitrogen, sulfur, and oxygen-containing) recorded derivatives3-11 of decalin-β-keto ester enolate, Nitro ketene dithiol, and Furo pyrazole to mitigate the viral growth by blocking the active sites of Tuberculosis protein RNA polymerase. An Attempt was made, to identify the derivatives with higher binding energies and drug property against the commercial drug Rifampicin.

Materials and Methods

In our investigation, we used biological repositories like PDB (Protein Data Bank) and free softwares like PyRx 0.8, PyMol 2.3.2, and big plus 1.4. The structural data of Biological macromolecules were extracted from the PDB (Protein Data Bank), which is the usual worldwide account, established in Brookhaven National Laboratories (BNL) in 1971(The Protein Data Bank, 2000)12. It uses NMR and X-ray crystallographic methods to determine the structural data of Biological macromolecules. RNA polymerase protein of Ramachandran plot, illustrated in Figure 1, is generated using Pro Check 2.3 to obtain stable conformations13. The circles and squares represent amino acid protein, where the brown, red, and yellow regions illustrate the allowed, favoured, and generously allowed regions, respectively 14.



Plot statistics

Residues in most favoured regions [A,B,L]	2274	42.1%
Residues in additional allowed regions [a,b,l,p]	2167	40.1%
Residues in generously allowed regions [~a,~b,~l,~p]	651	12.1%
Residues in disallowed regions	308	5.7%
Number of non-glycine and non-proline residues	5400	100.0%
Number of end-residues (excl. Gly and Pro)	52	
Number of glycine residues (shown as triangles)	464	
Number of proline residues	334	
Total number of residues	6250	

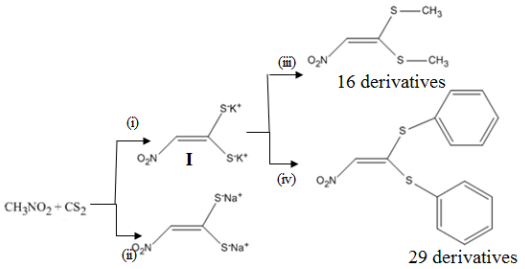
Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Figure 1: Ramachandran Plot of RNA POLYMERASE Protein(1L9U) Generated using Pro Check 2.3

Synthesis of Lead Compounds

Out of 75 derivatives, 3-11 docked for, in silico screening, the Nitro ketene dithiol lineages were the best drug candidates. The general procedure for synthesising the lineages, of the Nitro ketene dithiol is described below as presented in Scheme 13-8.

The aryl or non-aryl derivatives of nitro ketene dithiol can be prepared readily in a two-step procedure using nitromethane, carbon disulfide and an aryl / non-aryl halide as presented in the model Scheme 1. In the initial step (Scheme 1), the condensation of nitromethane and carbon disulfide in the presence of potassium hydroxide results in the dipotassium salt of 2-nitro-1,1-ethylenedithiol I. This is followed by alkylation of the salt I with suitable Aryl or non-aryl dihalides in 50% aqueous CH3OH. The dipotassium salt I can be prepared conveniently in dry methanol as solvent and potassium hydroxide as a base, the potassium salt is best suited for subsequent alkylation compared to sodium salt.



Reagents and Conditions

(i) MeOH/KOH (ii) MeOH/NaOH
(iii) 50% aq.MeOH/CH3I (iv) 50% aq.MeOH/ C6H5CH2Cl

Scheme 1: Synthesis of Aryl-non-Aryl Derivatives of Nitroketene Dithiol

Preparation of Ligand Structure

The chemical structure of derivatives was prepared by ChemDraw Ultra 12.0. Minimise the optimisation energy of the total 75 molecules using Gaussian 3 and Gauss view 5.0. Download the structure of ligands and this derivative of molecules in the MOL SDF format and convert to PDBQT file using PyRx tool to generate atomic coordinates. Nitro ketene dithiol SMILES was obtained from SDF files. View the structure of the drug-ligand interaction through Ligplot. Different analogues of nitro ketene

dithiol derivatives medication were generated by using the SMILES of the original medication and then reforming it. To obtain the 3D structures of the analogs, PyMol 2.3.2 is used. The docking analysis of Nitro ketene dithiol lineages with RNA polymerase inhibitor was performed using PyRx 0.8 docking software.

Preparation of Protein Structure

Download the Protein targets from the database Protein Data Bank (PDB). 1L9U is the PDB ID of the target protein (PubMed: 12016306). The resolution of the protein is 4.00Å. View the target protein through PyMol. Figure 2 shows the 3 –D structure of the receptor, and Figure 3 shows the 2-D Crystal Structure of RNA polymerase.

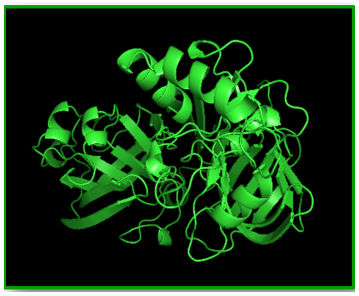


Figure 2: PyMOL View of the Protein 1L9U - TB

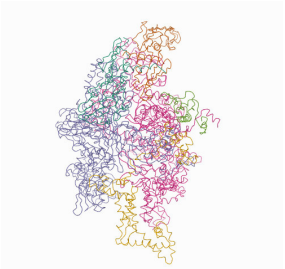


Figure 3: Crystal Structure of RNA Polymerase 15

Download the X-ray crystal of protein structure from Protein Data Bank based on a literature survey. PDB ID: 1L9U for protein structure and resolution structure of core RNA polymerase (RNAP) from Thermus aquatics (Taq) revealed a crab claw-shaped molecule with a 27 Å wide internal channel (3, 10). The enzyme active site is located on the back wall of the channel, where an essential Mg21 ion is chelated15. Remove all the hetero atoms from PDB ID: 1L9U, making the complex receptor-free of any ligand before docking. Run the Graphical User Interface Program "PyRx" and analyse the docking simulations.

Ligand Docking

The docking of analogues to the protein was performed by using AutoDock Vina software. Docking was performed to obtain the possible conformations and orientations for the ligand at the binding site. Non-polar hydrogen atoms were merged by using the software. All bonds of ligands were set to be rotatable. The best conformation was chosen with the lowest docked energy. An illustration of the screenshot of the docked structure of ligand 2 with the virus protein 1L9U is given in Figure 4.

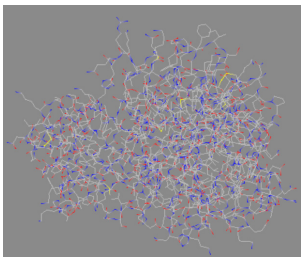


Figure 4: PyRx view for Ligand 53 -1L9U Complex

PyRx explores the path to dock the two molecules, namely drugs and an enzyme RNA polymerase receptor, fit together. The molecules binding to a receptor inhibit its function and thus act as a drug. The collection of Nitro ketene dithiol, its lineage and receptor complexes was identified via docking and their relative stabilities.

Results and Discussion

Our present investigation of virtual screening of the drug candidates for the medication of Tuberculosis by using the free molecular docking software PyRx 0.8, Structures of screened 75 organic molecules (Ligands / Analogs) are presented in Table 1 2. Screened ligands were subjected to molecular docking with the choose proteins of the bacterium causing, Tuberculosis (protein-1L9U). The structure and character of the peptide bond chains of the protein is verified by 'Ramachandran plots'

The analogues scoring criterion such as binding energies, Lipinski parameters 16, ADME / BBB parameters 17, and drug-likeness scores 18 are

presented in Table 3 and Figure 4. Most of the ligands 80%, pass the ADME test by having good GI absorption, and 65% of the ligands have positive Blood-Brain barrier (BBB) diffusion, as given in Table 3. All the 75 ligand molecules progress the four rules of the Lipinski and 75% of them progress all the five rules. 25% of the ligands log P values range from 5 to 8 given in Table 3. The positive value for BBB is seen in most of the ligands, which can also consider for possible CNS drugs.

Table 1: Derivatives of Nitroketene Dithiol (Compound No. 1 to 39) contd...

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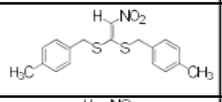
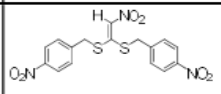
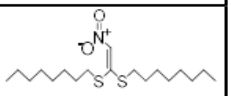
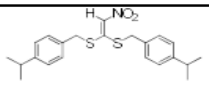
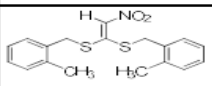
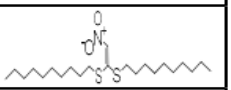
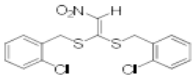
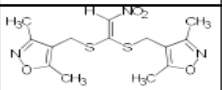
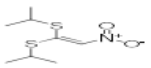
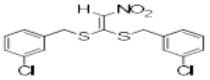
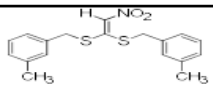
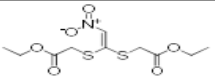
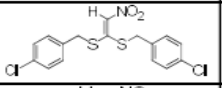
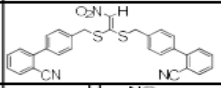
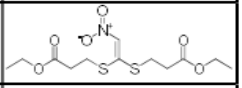
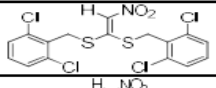
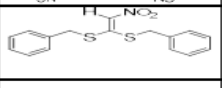
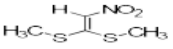
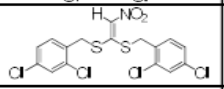
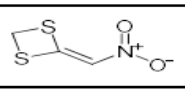
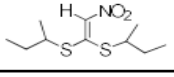
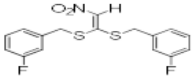
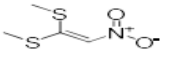
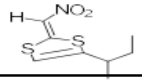
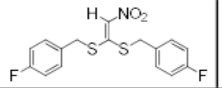
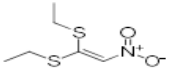
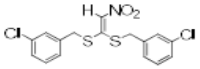
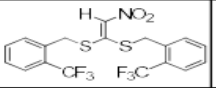
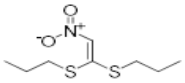
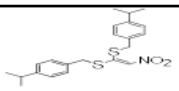
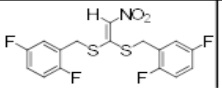
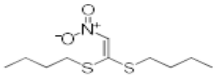
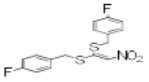
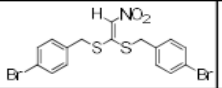
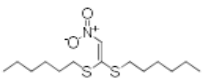
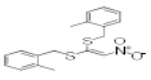
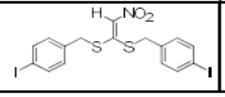
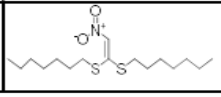
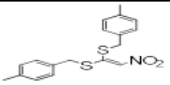
1		14		27	
2		15		28	
3		16		29	
4		17		30	
5		18		31	
6		19		32	
7		20		33	
8		21		34	
9		22		35	
10		23		36	
11		24		37	
12		25		38	
13		26		39	

Table 2: Derivatives of Nitroketene Dithiol (Compound No. 40 to 75)

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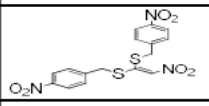
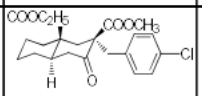
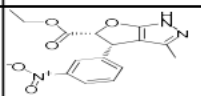
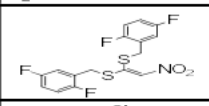
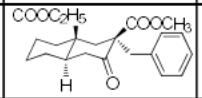
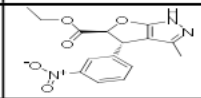
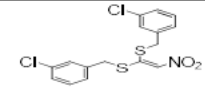
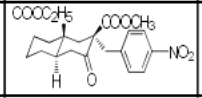
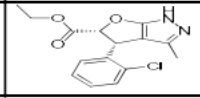
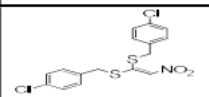
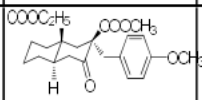
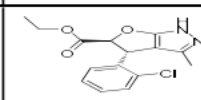
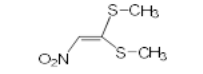
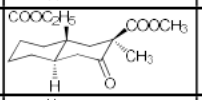
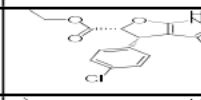
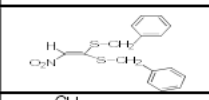
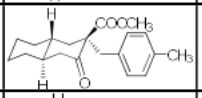
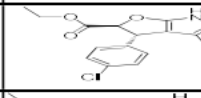
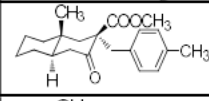
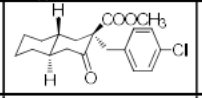
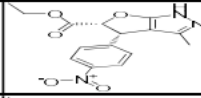
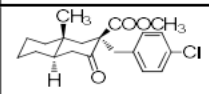
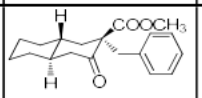
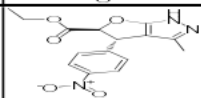
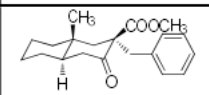
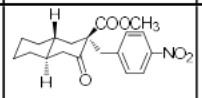
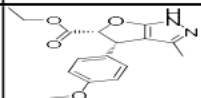
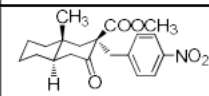
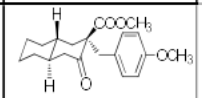
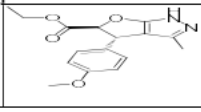
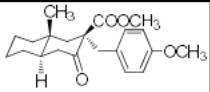
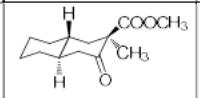
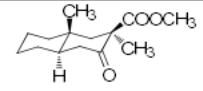
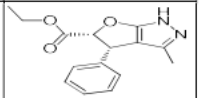
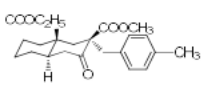
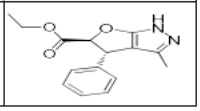
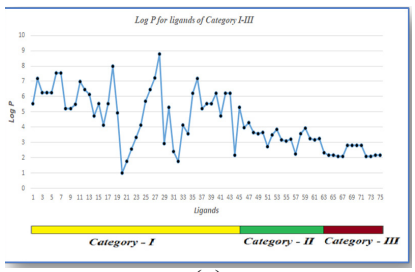
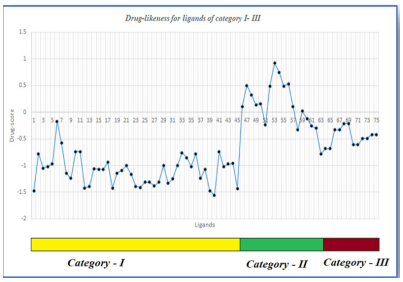
40		53		66	
41		54		67	
42		55		68	
43		56		69	
44		57		70	
45		58		71	
46		59		72	
47		60		73	
48		61		74	
49		62		75	
50		63			
51		64			
52		65			

Table 3: Log p & Drug Likeness Scores for the Ligands (1-75)

Ligands	Log P	Drug score	Ligands	Log P	Drug score	Ligands	Log P	Drug score
1	5.54	-1.47	26	6.46	-1.31	51	2.72	-0.24
2	7.17	-0.78	27	7.24	-1.38	52	3.5	0.49
3	6.24	-1.05	28	8.8	-1.31	53	3.85	0.92
4	6.24	-1.02	29	2.95	-1	54	3.19	0.75
5	6.24	-0.97	30	5.3	-1.33	55	3.1	0.49
6	7.54	-0.17	31	2.43	-1.25	56	3.2	0.53
7	7.54	-0.58	32	1.78	-1	57	2.26	0.1
8	5.2	-1.14	33	4.12	-0.76	58	3.57	-0.33
9	5.2	-1.24	34	3.59	-0.85	59	3.92	0.02
10	5.48	-0.74	35	6.23	-1.02	60	3.26	-0.12
11	6.96	-0.74	36	7.17	-0.78	61	3.17	-0.26
12	6.45	-1.42	37	5.2	-1.24	62	3.27	-0.3
13	6.13	-1.39	38	5.54	-1.07	63	2.33	-0.78
14	4.74	-1.06	39	5.54	-1.47	64	2.17	-0.68
15	5.54	-1.07	40	6.23	-1.56	65	2.17	-0.68
16	4.14	-1.07	41	4.74	-0.74	66	2.08	-0.33
17	5.54	-0.94	42	6.23	-1.02	67	2.08	-0.33
18	8	-1.42	43	6.23	-0.97	68	2.82	-0.21
19	4.93	-1.14	44	2.17	-0.96	69	2.82	-0.21
20	1	-1.09	45	5.31	-1.43	70	2.82	-0.61
21	1.78	-1	46	3.96	0.11	71	2.82	-0.61
22	2.56	-1.16	47	4.31	0.5	72	2.08	-0.49
23	3.34	-1.39	48	3.65	0.32	73	2.08	-0.49
24	4.12	-1.41	49	3.56	0.14	74	2.18	-0.42
25	5.68	-1.31	50	3.66	0.16	75	2.18	-0.42



(a)



(b)

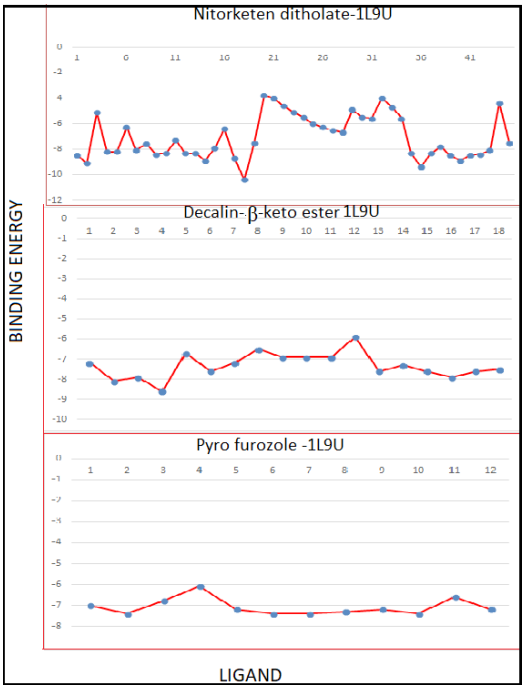
Dervatives of Nitroketene dithols
Dervatives of decalin-β-keto ester enolate
Dervatives of Furo pyrazole

Graph 1: Graphical Representation of (a) Log P & (b) Drug-Likeness Score Calculate by the Molsoft Software for the Ligand 1-75

Table 4: Values of the Binding Energy (Criteria (i)) for the Protein 1L9U of Tuberculosis

Ligand No.	Binding Affinity	Ligand No.	Binding Affinity	Ligand No.	Binding Affinity
1	-8.5	26	-6.3	51	-7.6
2	-9.1	27	-6.5	52	-7.2
3	-5.1	28	-6.7	53	-6.5
4	-8.2	29	-4.9	54	-6.9
5	-8.2	30	-5.5	55	-6.9
6	-6.3	31	-5.6	56	-6.9
7	-8.1	32	-4	57	-5.9
8	-7.6	33	-4.7	58	-7.6
9	-8.4	34	-5.6	59	-7.3
10	-8.3	35	-8.3	60	-7.6
11	-7.3	36	-9.4	61	-7.9
12	-8.3	37	-8.3	62	-7.6
13	-8.3	38	-7.8	63	-7.5
14	-8.9	39	-8.5	64	-7
15	-7.9	40	-8.9	65	-7.4
16	-6.4	41	-8.5	66	-6.8
17	-8.7	42	-8.4	67	-6.1
18	-10.4	43	-8.1	68	-7.2
19	-7.5	44	-4.4	69	-7.4
20	-3.8	45	-7.5	70	-7.4
21	-4	46	-7.2	71	-7.3
22	-4.6	47	-8.1	72	-7.2
23	-5.1	48	-7.9	73	-7.4
24	-5.5	49	-8.6	74	-6.6
25	-6	50	-6.7	75	-7.2

Protein-ligand energy of binding affinities results are presented in Table 4 is vitalising. For the 1L9U protein of the Tuberculosis, the binding energies of the analogues range from -10.4 to -3.8 kcal/mol for the 75 ligands. Generally, in Molecular docking studies, the best drug candidates are marked based on the drug result of the ligands. The drug results for the 75 ligands are transpired by considering the four criteria: (i) The binding energies, (ii) Their Drug likeliness score, (iii) Their Lipinski parameters, and (iv) Their ADME parameters. The three best drug scores of the ligands and structural nature of the Protein-ligand complexes for 1L9U type of protein under each category are discussed below:



Graph 2: Binding energy Vs Derivatives (Analogs)

Compound 18

From the Lig-Plot figure, the hydrogen bonding interaction of compound 18 with Alanine 22 (A) and Serine94 (A) of the protein is detected. Both the Hydrogen of the amino group of Alanine 22 (A) and Serine94 (A) makes hydrogen (2.93Å and 2.83Å) respectively bond with one of the oxygen atoms of the nitro group present in compound 18.

There is also a strong hydrophobic interaction of six amino acids lining the protein cavity, apart from hydrogen bonding interaction with the compound 18. The hydrophobic interaction of amino acid involved with the compound 18 are Aspartic Acid 64 (A); Glycine14 (A)/ 96N (A); Isoleucine21 (A) / 16 (A)/ 122 (A)/ 95 (A); Phenylalanine 41 (A) / 97 (A); Serine 20 (A) and Valine 65 (A).

Compound 36

From the Lig-Plot figure, it is evident that the hydrogen bonding interaction of compound 36 with Isoleucine 194 (A) of the protein is detected. The hydrogen of the amino group of Isoleucine 194 (A) makes a hydrogen (3.21Å) bond with one of the oxygen atoms of the nitro group present in compound 36.

There is also a strong hydrophobic interaction of seven amino acids lining the protein cavity, apart from hydrogen bonding with the compound 36. The hydrophobic interaction of amino acid involved with the compound 36 are Alanine191 (A); Glycine192 (A); Isoleucine 21 (A); Methionine 147 (A) / 161 (A) / 199 (A); Phenylalanine149 (A); Proline193 (A) and Tyrosine 158 (A). 3.

Compound 2

From the Lig-Plot figure, it is evident that the hydrogen bonding interaction of compound 2 with Alanine22 (A) and Isoleucine 21 (A) of the protein is detected. The hydrogen of the terminal amino group of Alanine22 (A) and Isoleucine 21 (A) makes a hydrogen bond (3.17Å and 3.20 Å) with each one of the oxygen atoms of the nitro group present in compound 2.

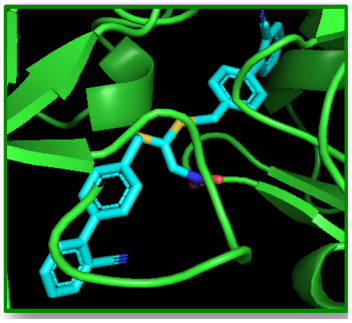
There is also a strong hydrophobic interaction of seven amino acids lining the protein cavity, apart from hydrogen bonding interaction with compound 2. The hydrophobic interaction of amino acid involved with the compound 2 are Alanine 191 (A); Glycine14 (A) / 192 (A)/ 96 (A); Isoleucine 194 (A) / 95 (A) / 122 (A); Leucine 63 (A); Phenylalanine 41 (A)/ 149 (A) Serine20 (A)/ 94 (A) and Valine65 (A)

Docking results of the drug candidate through PyRx software impart that the e-value of Analog 18 is -10.4 Kcal/mol is better Binding affinity compared to other derivatives of Nitro ketene dithiol lineages. The important assumption of our study is that the three lineages of Nitro ketene dithiol (18, 36 and 2) have better binding energies than the reference compound Rifampicin as presented in Table 5.

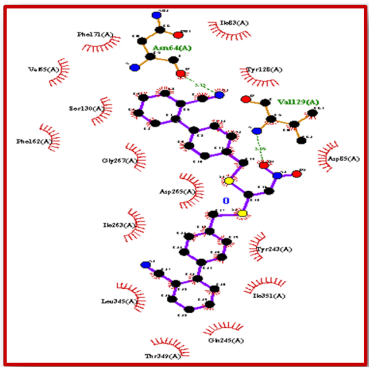
Table 5: The Best Three Drug Candidates Based on Criteria (i), (ii), (iii) & (iv) for the Treatment of Tuberculosis

Lig. No / Name	Mol. Formula	Mass	H-Bond Donor	H-Bond acceptor	B.E. (k.cal/ mol)	Log P	Drug score
18	C28H21N3O2S2	519	0	4	-10.4	8	-1.42
36	C22H27NO2S2	401	0	2	-9.4	7.17	-0.78
2	C22H27NO2S2	401	0	2	-9.1	7.17	-0.78
Rifamipicn19	C43H58N4O12	823	6	5	-7.2	-0.053	-0.20

Schematic representation of PyMol view and Ligplus view of protein-ligand complexes 18,36 and 2 are represented in Figures 4, 5 and 6.



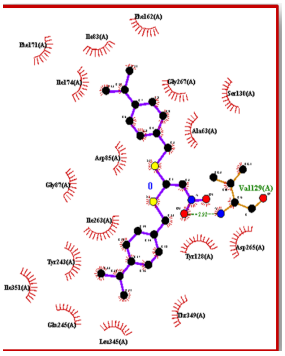
(a)



(b)

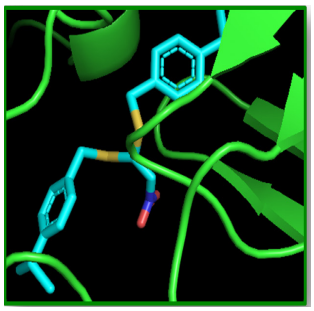
Figure 4: (a) PyMol view of the Protein-Ligand -18 (b) LigPlot View of the Protein- Ligand-18 Complex 1L9U of TB

(a)

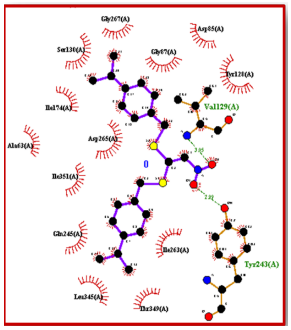


(b)

Figure 5: (a) PyMol view of the Protein-Ligand-36 the protein 1L9Uof TB (b) LigPlot View of the Protein-Ligand-36 Complex 1L9U of TB



(a)



(b)

Figure 6: (a) PyMol view of the Protein-Ligand-2 the Protein 1L9Uof TB (b) LigPlot View of the Protein- Ligand-2 Complex 1L9U of TB

Conclusion

Molecular docking of 4',4'''-(((2-nitroketene-1, 1-diyl)bis(sulfanediyl))bis(methylene))bis (([1,1'-biphenyl]-2-carbonitrile,1-((1-(4-isopropylbenzylthio) -2-nitrovinylthio)methyl)-4-iso propylbenzene and (2-nitroketene-1,1-diyl)bis((4-isopropylbenzyl) sulfane) - (a derivative of nitro ketene dithiol -) with Tuberculosis (TB) protein of 1L9U shows stronger binding energy compared to reference compounds Rifampicin. Compared to the recently approved Pretomanid Tablets in combination with bedaquiline and linezolid to treat a specific type of highly drug-resistant tuberculosis (TB) of the lungs, the compounds 2,18and 36 have a simple structure and good drug scores. Therefore, it has certain significance to pursue those three analogues of nitro ketene dithiol as compounds of interest for further in vitro and in vivo studies to treat Tuberculosis.

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