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 Nitroketene 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.

1. Paterson DL. Tuberculosis. N Engl J Med. 2011;364:1551-1561.
2. World Health Organization. Global Tuberculosis Report 2019. World Health Organization; 2019.
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.

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...

| Comp No. | Structure of the ligand | Comp No. | Structure of the ligand | Comp No. | Structure of the ligand |
|----------|------------------------|----------|------------------------|----------|------------------------|
| 1        | ![Structure 1](image1)  | 14       | ![Structure 14](image14) | 27       | ![Structure 27](image27) |
| 2        | ![Structure 2](image2)  | 15       | ![Structure 15](image15) | 28       | ![Structure 28](image28) |
| 3        | ![Structure 3](image3)  | 16       | ![Structure 16](image16) | 29       | ![Structure 29](image29) |
| 4        | ![Structure 4](image4)  | 17       | ![Structure 17](image17) | 30       | ![Structure 30](image30) |
| 5        | ![Structure 5](image5)  | 18       | ![Structure 18](image18) | 31       | ![Structure 31](image31) |
| 6        | ![Structure 6](image6)  | 19       | ![Structure 19](image19) | 32       | ![Structure 32](image32) |
| 7        | ![Structure 7](image7)  | 20       | ![Structure 20](image20) | 33       | ![Structure 33](image33) |
| 8        | ![Structure 8](image8)  | 21       | ![Structure 21](image21) | 34       | ![Structure 34](image34) |
| 9        | ![Structure 9](image9)  | 22       | ![Structure 22](image22) | 35       | ![Structure 35](image35) |
| 10       | ![Structure 10](image10) | 23      | ![Structure 23](image23) | 36       | ![Structure 36](image36) |
| 11       | ![Structure 11](image11) | 24      | ![Structure 24](image24) | 37       | ![Structure 37](image37) |
| 12       | ![Structure 12](image12) | 25      | ![Structure 25](image25) | 38       | ![Structure 38](image38) |
| 13       | ![Structure 13](image13) | 26      | ![Structure 26](image26) | 39       | ![Structure 39](image39) |
| Comp No. | Structure of the ligand | Comp No. | Structure of the ligand | Comp. No. | Structure of the ligand |
|---------|------------------------|---------|------------------------|---------|------------------------|
| 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      |

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:
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).

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      |
| Rifampicin19  | 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.

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

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
Conclusion

Molecular docking of 4\',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 2,18 and 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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References

http://www.molsoft.com/mprop/mprop.cgi

Johnson, Rabia, et al. “Drug Resistance in Mycobacterium Tuberculosis.” Current Issues in Molecular Biology, vol. 8, no. 2, 2006, pp. 97-112.

“Lipinski Rule of Five.” Supercomputing Facility for Bioinformatics & Computational Biology, IIT Delhi, http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp

Morris, Richard J., et al. “Real Spherical Harmonic Expansion Coefficients as 3D Shape Descriptors for Protein Binding Pocket and Ligand Comparison.” Bioinformatics, vol. 21, no. 10, 2005.

Murakami, Katsuhiko S., et al. “Structural Basis of Transcription Initiation: RNA Polymerase Holoenzyme at 4 Å Resolution.” Science, vol. 296, 2002.

Protein Data Bank. www.rcsb.org

Rao, Surya Prakash, et al. “Nitrokene dithioacetal chemistry: Synthesis and characterization of some 1,1-dif(alkylsulfanyl)-2-nitroethylenes and 2-(nitromethylene)-1,3-dithia heterocycles.” Sulfur Letters, vol. 25, no. 5, 2002, pp. 207-218.

Rajamathé, S., et al. “Methyl (2RS,4aRS,8aRS)-2-(4-methylbenzyl)-3-oxoperhydrophthalalene-2-carboxylate.” Acta Crystallographica Section C, vol. 55, 1999.

Rajamathé, S. Diastereoselection in the Benzylation of Cyclic β-keto Ester Enolates: Remote Substituent Effects. Pondicherry University, 2003.

Sakhikumar, L., et al. “Synthesis, Characterization and Antibacterial Activity of Alkyl, Benzyl and Chloro substituted Benzyl Derivatives of Nitroketene Dithioacetals.” Der Pharma Chemica, vol. 6, no. 2, 2014, pp. 294-298.

Sakhikumar, L., and R. Mahalakshmi. “Phase Transfer Catalyst Assisted Synthesis
Antibacterial and CNS Depressant Activity Studies of Substituted Benzyl Products with Nitroketene Dithioacetal Motif.” *Indo American Journal of Pharmaceutical Research*, vol. 5, 2015.

Santosh Kumar, K, et al. “Development of Rifampicin Derivatives Sensitive to the rpoB Mutated Mycobacterium Tuberculosis: An Insilico Approach.” *Journal of Chemical and Pharmaceutical Research*, vol. 7, no. 5, 2015, pp. 153-159.

Sakthikumar, L., et al. “Synthesis, Spectral Characterization, and Single Crystal Structure Studies of (2-Nitro-Ethene-1,1-diyl)-bis-(4-isopropyl-benzyl)sulfane.” *Crystallography Reports*, vol. 60, 2015.

Shanmuga Sundara Raj, S., et al. “2-(Nitromethyl-ene)-1,3-dithietane.” *Acta Crystallographica Section C*, vol. 56, 2000.

Tangeti, Venkata Swamy, et al. “One-pot Multicomponent Diastereoselective Synthesis of Novel Dihydro-1H-furo[2,3-c]pyrazoles.” *Synthetic Communications*, vol. 46, 2016, pp. 878–884.

Virupakshaiah, DBM, et al. “Molecular Docking Studies of *Mycobacterium tuberculosis* RNA Polymerase β Subunit (rpoB) Receptor.” *International Journal of Biotechnology and Bioengineering*, vol. 7, no. 5, 2013.

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