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Study of In Silico on Schiff Base Ligand Against Mycobacterium Tuberculosis

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Abstract: Here, we have synthesized the hetero-atoms containing; 3, 4, 6–Triazabicyclo [6, 3, 1] dodeca–1 (12), 2, 6, 8, 10–pentene–5–thione (TBD) macrocyclic Schiff base ligand for the application in antituberculosis (anti-TB). This TBD ligand moiety has high donor ability due to the presence of three nitrogen donor atoms, which are also the reason for the interaction between the ligand and protein molecule. The TBD Schiff base ligand is characterized by various spectroscopic techniques such as; Fourier-Transform Infrared (FT-IR), Proton Nuclear Magnetic Resonance (1HNMR), and Ultraviolet-Visible (UV-Vis) and Electron Spray Ionization (ESI) Mass spectroscopy, to understand the bond stretching, the electronic environment of protons, electronic transitions (π–π* and n–π*), and M/Z values, respectively. The computational study was carried out to calculate the molecular docking score using AutoDock Vina software against the glutamine protein enzyme (PDB ID-3ZXR). The molecular docking score was –6.3 kcal mol^{-1} for the TBD Schiff base ligand, whereas –4.6 kcal mol^{-1} is reported for the standard drug (Pyrazinamide). The product formation yield of TBD Schiff base ligand is found to be ~78 % during synthesis.

Keywords: Schiff base; Non-conjugated moiety; Molecular docking; Antituberculosis.

1. Introduction

Tuberculosis (TB) treatment is now an emerging area for medicinal research. The synthesis of bio-molecule biomarkers and host-based diagnostics is emerging and needs to be shaped for impact [1–3]. In the first-line treatment, Isoniazid, Pyrazinamide, Rifampin, and Streptomycin type drugs have proven effective in treating TB [4–6]. Still, with the emergence of drug-resistant bacteria, this first-line therapy often fails to cure TB [7]. Therefore, it is essential to utilize second-line drugs to treat multidrug-resistant TB (MDR-TB), which is resistant to Isoniazid and Rifampicin. However, the second-line drugs are challenging to synthesize and are either less effective or toxic [8–10]. In addition, Mycobacterium TB developed drug-resistant and drug-resistant strains extensively after MDR-TB resistance emerged [11,12]. Therefore, the development of new antitubercular agents which are safe and cost-effective is an essential strategy for detecting and treating drug-resistant TB and XDR-TB [13-15].

Currently, methods for the controlled release of antibiotics, drugs, bioactive agents, and cells are being developed that change the surface by saturation with bioactive compounds, particularly supramolecular compounds [16]. There are several advantages to using supramolecular compounds, such as liposomes, micelles, carbon nanotubes, hydrogels, and dendrimers, which have limited stability and are not controlled by drug release rates [17–19]. Supramolecular compounds can deliver drugs and protect them from degradation at the desired target [20,21]. As chemistry and molecular biology intersect, studies on the interaction of small molecules with nucleic acids have become increasingly important in recent decades [22,23]. Because heterocyclic core systems can form various bonds within the active sites of their targets, they are intriguing scaffolds for drug discovery and development [24]. Since nitrogen is highly electronegative and forms polar bonds quickly, it is of greater importance among heteroatoms [25]. Furthermore, nitrogen can accept and donate hydrogen bonds, making it an essential element in lead discovery [26,27].

Schiff base moieties are used in various areas like organic multi-responsive molecules whose optical properties can be regulated by multiple chemical stimuli due to their ability to have different types of interactions [28–32]. Schiff bases are common organic structures that can easily be synthesized through a one-step synthetic procedure [33,34]. Schiff base ligands have received attention from researchers because of

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their ease of synthesis and ability to form complexes with almost all metals [35–37].

Schiff base-based macrocyclic conjugated compounds behave as chelating ligands and form complexes with metal ions [38-40]. They combined with Dynamic Covalent Chemistry (DCC) of imine covalent bonds in metal-organic molecules [41,42]. Although successful implantation of sulfur atoms into macrocyclic Schiff bases has been achieved by preparing certain thionolate-containing di-aldehydes [43,44], selectivity and center specificity are the main issues that must be considered when designing such ligands. [45,46]. Schiff base constitutes one of the most widely studied classes of ligands in this context due to their ability to coordinate with a wide range of metal ions in their various oxidation states [47–49].

Schiff bases have also been investigated for chemo-sensor applications [50]. The coordination bonds between Schiff bases and metal ions are suitable for generating sensing signals [51,52]. The change in their electronic properties via different Ligand to Metal (L-M) and Metal to Ligand (M-L) (i.e., π–π*, n–π*) charge transfer processes produces the sensing signal [53–55]. Origen of signal from these sensors emerges a strong metal ion interaction with sample molecule [56,57]. Non-conjugated Schiff-based materials that exhibit better solubility, lower cost, lower cytotoxicity, and better biological interaction [58,59] and occur in nature are generally known as non-emissive compounds. [60,61].

This work describes the synthesis, characterization, and computational study of macrocyclic Schiff base ligands 3,4,6-Triaza-bicyclo[6.3.1] dodeca-1(12),2,6,8,10-pentaene-5-thione (TBD), for application in tuberculosis (anti-TB) control.. The synthesis procedure of TBD Schiff base ligand involves nucleophilic addition followed by elimination reactions. The product formation yields of TBD Schiff base ligand is found to be ~78 % during synthesis. In addition, the computational study was carried out on TBD Schiff base ligand in interaction with protein, and the molecular docking score was calculated.

2. Experimental Section

2.1. Materials

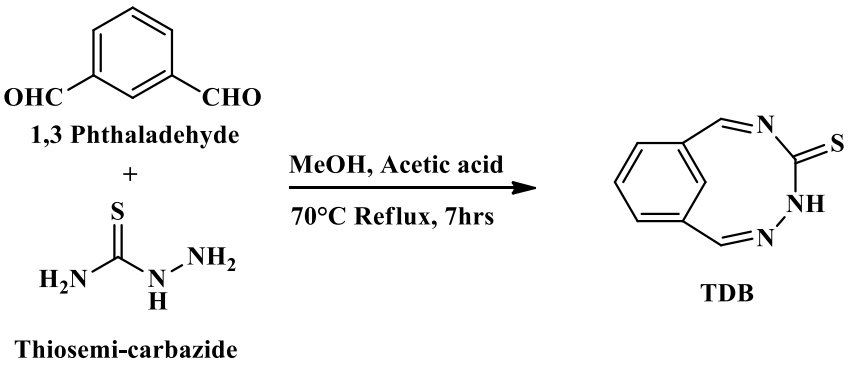
1, 3- Phthaladehyde (C_6H_4-1, 3-$(CHO)_2$) assay 97%, thiosemi-carbazide (CH_5N_3S) assay 99%, and Merck TLC Silica Plates 20x20 cm^2 were purchased from Sigma-Aldrich. TLC paper, Acetic acid (CH_3COOH), Methanol (CH_3OH), and ethanol (CH_3CH_2OH) were purchased from HiMedia Laboratories Pvt. Ltd. All the chemicals used were of analytical grade and utilized as received without any further purification.

2.2. Instrumentation

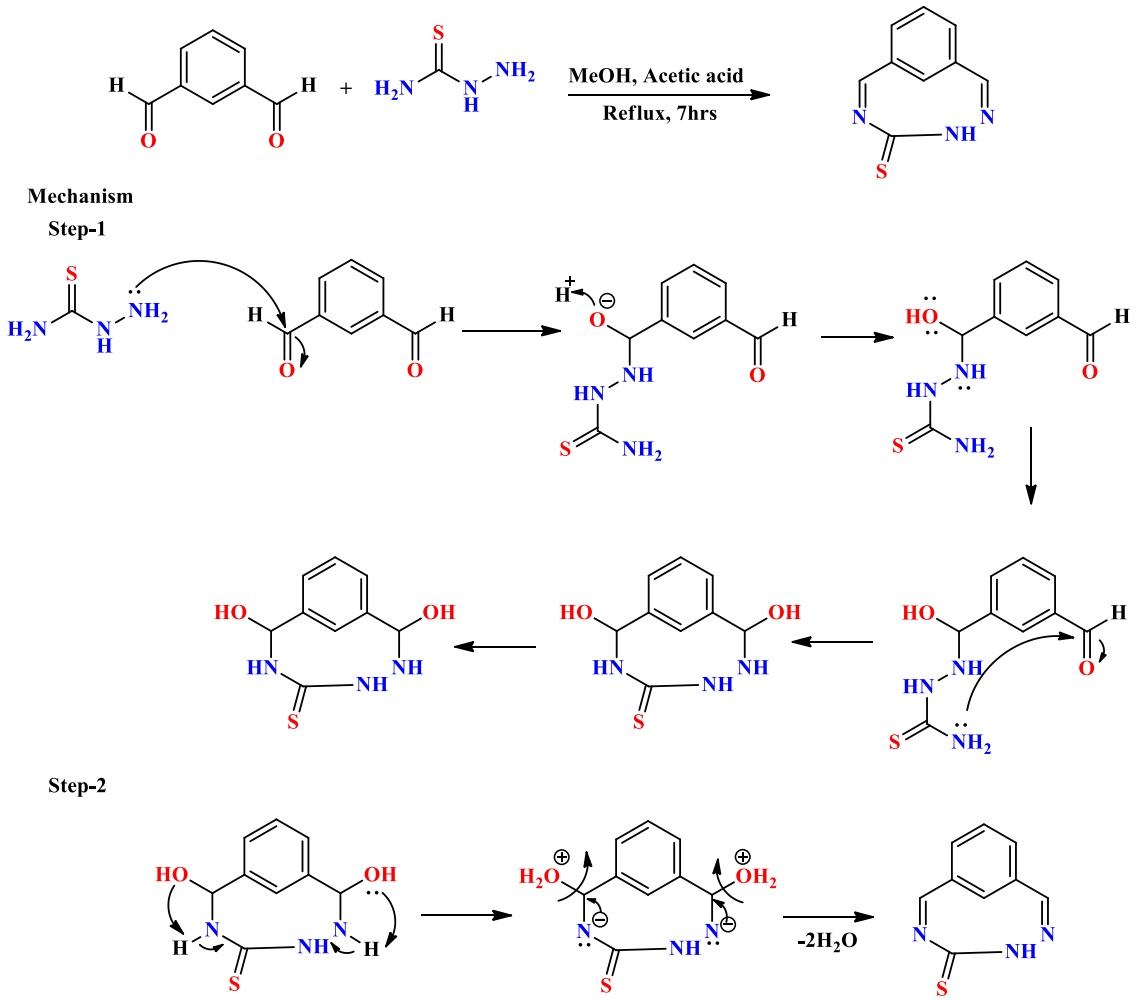
The UV-visible study was performed using the UV3092 UV-visible spectrophotometer from Labindia Analytical, and the FT-IR-8300 spectrophotometer was used to analyze the FT-IR spectrum. The 1HNMR study was carried out using a JEOL RESONANCE spectrometer in DMSO-d6 at 400MHz, and M/Z values were calculated by Electrospray Ionization Mass Spectrometer (ESI-MS), using Xevo® G2-XS QTof Instrument.

2.3. Synthesis of TBD Schiff base ligand

TBD Schiff base ligand was prepared by dissolving 1, 3-Phthalaldehyde (0.1341 mg) and thiosemicarbazide (0.0911 mg) in a 1:1 mole ratio in a round bottom flask containing the 5 mL of methanol. Then, 2~3 drops of glacial acetic acid were added to the above mixture for protonation. The reaction mixture was refluxed at 70°C for 7 hrs on a heating magnetic stirrer. The yellowish residue was obtained, which was washed with methanol several times to remove impurities. Then the resultant was dried at room temperature. The final yield obtained was ~78 %. The synthesis process is shown by schematic representation in Scheme 1.



Scheme 1. Schematic representation of the synthesis process of TBD



Proposed Mechanism of the reaction (Scheme 1)

3. Results and discussion

3.1. UV-Vis. Spectroscopy

In absorption spectra, band positions were recorded at room temperature (Fig. 1). A UV-visible spectrophotometer (UV3092 UV-visible spectrophotometer) was used to measure the UV-visible spectra of the compounds in methanol (at 2 x 10^{-5} M concentration). The electronic spectra of TBD Schiff base ligand exhibited two strong intensity absorption bands at λmax 245 nm and λmax 351 nm, respectively, were assigned to intraligand, which are due to π-π* and n-π*transitions respectively characteristic of the azomethine group. As reported in the literature, the peak at 245 nm is associated with -C-N, and the peak at 351 nm is associated with -C-N=S [62,63].

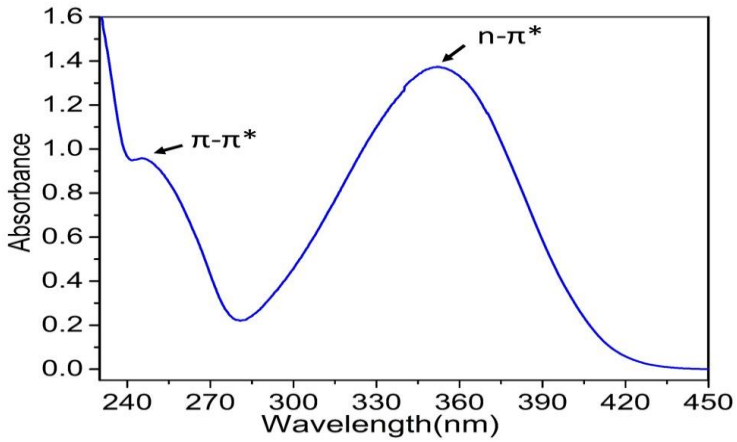


Figure 1. UV-Vis absorption spectrum TBD Schiff base ligand

3.2. FT-IR spectral studies

A study of the primary binding mode in the TBD Schiff base ligand is presented in Figure 2. The IR spectra of the TBD Schiff base ligand show characteristic bands in the region of 3017 cm-1, 2051 cm-1, and 1607 cm-1, attributed to the ν(N-H), ν(C=S), and ν(C=N) vibrations of the TBD Schiff base ligand, respectively [64,65], as shown in Figure 2. This indicates the presence of a symmetric and asymmetric stretching frequency in the TBD Schiff base ligand, which is confirmed by the literature [66]. Furthermore, the -C=N stretching frequency is reduced to 1607 cm^{-1} due to a highly conjugated system in the TBD [67]. Similarly, the –C=S stretching frequency has also been reduced due to conjugation among lone pair electrons of the nitrogen atom and the sulfur-carbon bond present in TBD, confirmed by the literature [68]. In comparison, no reduction in stretching frequency was found in the case of the N-H bond.

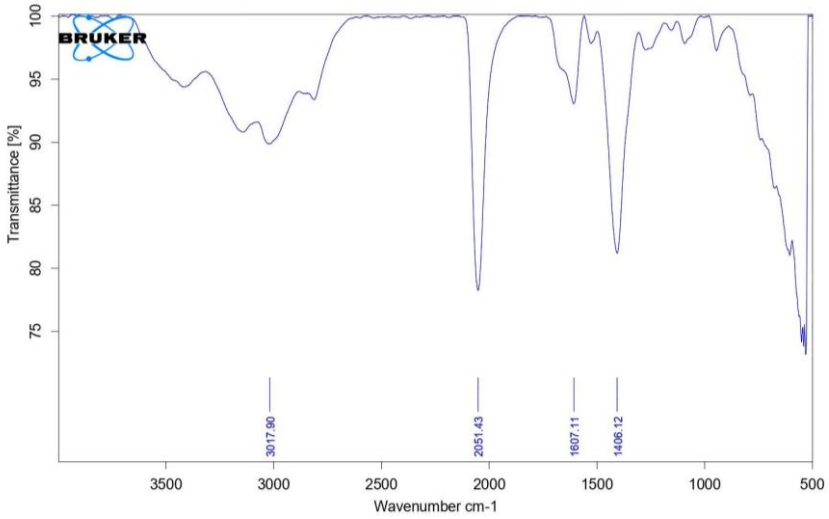


Figure 2. FT-IR Spectra of TBD Schiff base ligand

3.3. Mass Spectral studies

ESI-MS, study shows the Mass over charge ratio, and the values were as follow; m/z: 190.03 (100%), 189.03 (9.7%), 191.03 (4.5%), and 190.03 (1.1%). The different types of peaks are divided into two parts, one is a molecular peak, and the other one is an isotopic peak. (Figure 3).

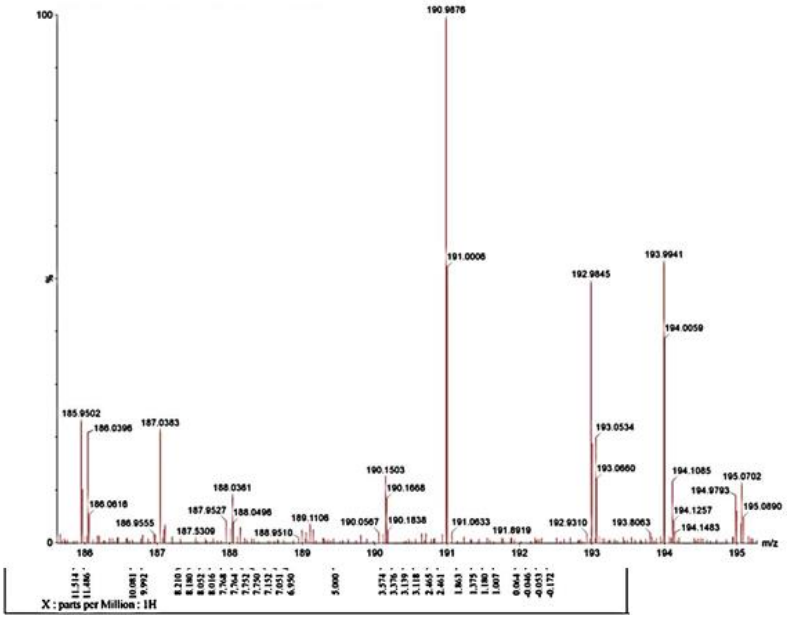


Figure 3. M/Z calculated by mass spectroscopy TBD Schiff base ligand

3.4. 1HNMR spectrum

The 1NMR spectrum of the Schiff base ligand TBD was recorded by dissolving a few amounts of TBD in a deuterated solvent, dimethylsulfoxide (DMSO), where tetramethylsilane (TMS) was used as a standard. The TBD moiety contains seven types of proton signals. Four singlets were observed at 10.00, 5.00, 5.00, and 1.96 ppm. The signals at 10 ppm are

highly shielded due to the aromatic region, whereas two singlet peaks at 5.00 ppm and 1.96 ppm are due to CH=N and N-H protons, respectively. The two doublet peaks appeared at 8.15, 8.21, 8.05, and 8.01 ppm, and one triplet at 6.95, 7.05, and 7.15 ppm due to the aromatic region.

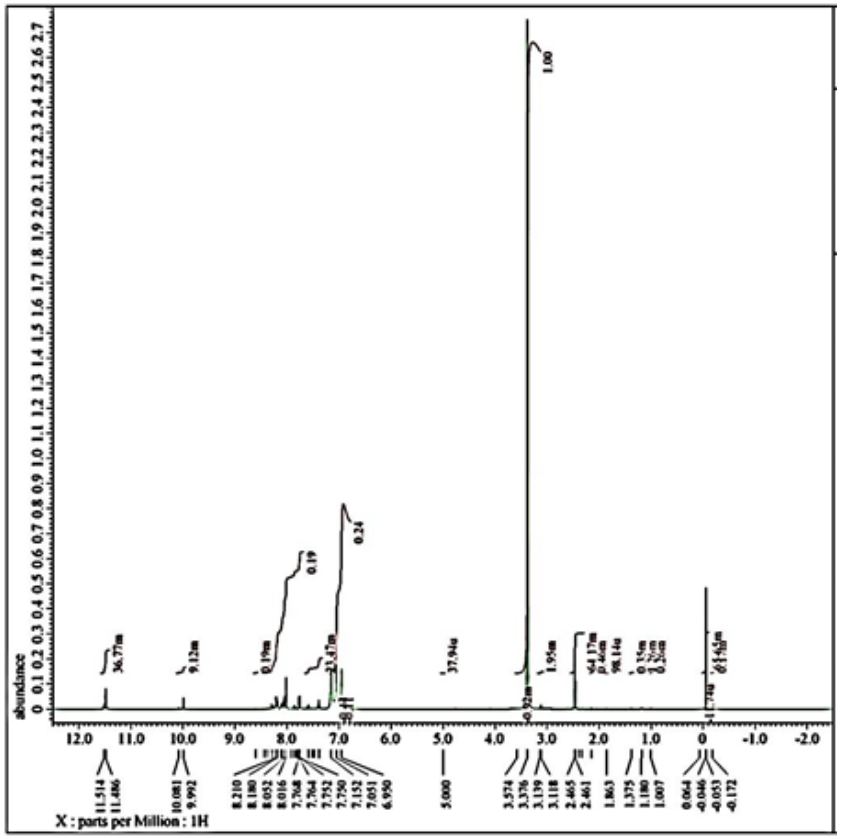


Figure 4. The 1HNMR spectrum of the different signals of the TBD Schiff base ligand

3.5. Adsorption Distribution Metabolism Excretion (ADME) prediction

The ADME prediction of TBD Schiff base ligand of physically significant and pharmaceutically relevant properties of the synthesized moiety was performed using SwissDock online service. An important factor in the drug development process is the ADME properties of the ligand. To eliminate false positive predictions, different online algorithms were used in the initial stage of screening. The molecular weight of the TBD Schiff base ligand is 189.24 g/mol. However, the reference compound, isoniazid, showed decreased molecular weight of 137.14 g/mol. The predicted data are presented in Table 1.

Table 1. *In silico* predicted physicochemical and pharmacokinetic parameters of the TBD Schiff base ligand.

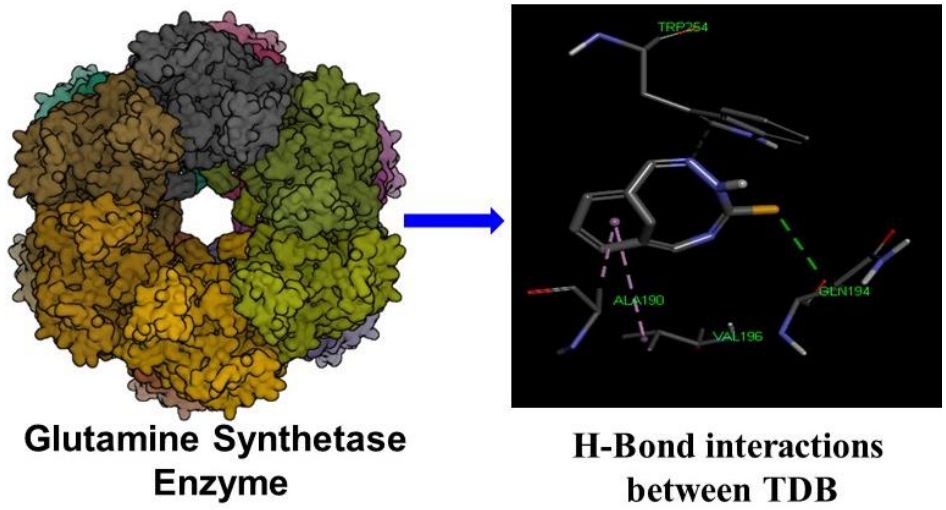
Compounds	Mol. Wt.	*TPSA (Å^2)	Rotatable bonds	Donor #HB	Acceptor #HB	WLog P o/w	metab	Rule of five	% Human intestinal absorption
TBD	189.24	73.66	0	1	2	2.25	5	0	94
Isoniazid	137.14	68.01	1	2	3	-0.31	3	0	99.61
Recommended values	130 - 725	>140 is poor	<10	0-6	2-20	2-6.5	1-8	Max 4	>80% is high <25% is poor

*TPSA = Topological Polar Surface Area (Angstroms squared (Å^2)), #HB = Hydrogen Bond,

3.6. Molecular Docking Studies

Docking is a molecular modeling technique to predict how microbes interact with ligands. Binding free energy and affinity can be calculated using this technique. When the binding free energy is lower, the enzyme/protein is more likely to be able to bind the molecule. TBD Schiff base ligand using molecular docking as a significant potential [69]. This molecule synthesis of a new variety of the compound and use, such as drug discovery, involves designing new

chemical agents that exhibit enhanced therapeutic potential [70,71]. Computer-Aided drug design utilizes computational software and tools that help identify the biological potential active site in the compound [72,73]. The designed molecules were docked against the target protein Glutamine synthetase-1 using AutoDock Vina software. It is an automated procedure for predicting the interaction of ligands with bio-macromolecular targets [74–76]. Various biosynthetic enzymes can be considered potential drug targets as they are crucial for Mycobacterium [77]. One of the critical enzymes essential for mycobacterium survival is Glutamine synthetase-1, mainly responsible for the growth of Mycobacterium TB bacteria [78,79]. The inhibition of Glutamine Synthetase secreted by M. tuberculosis is sufficient to inhibit the development of the bacterium [80]. Therefore, we selected Glutamine synthetase as the target of interest [81].



Scheme 2. Schematic diagram of the Glutamine synthetase-1 enzyme (PDB ID- 3ZXR.The pose obtained from molecular docking analysis shows that TDB interacts with the selective target molecule. The hydrogen bond interactions can be observed in the molecular docked pose of TBD interaction between the availability of the donor hetero-atom containing macrocyclic moiety of Schiff base ligand.

The enzyme was downloaded from (https://www.rcsb.org/structure/3ZXR) the Protein Data Bank ID 3ZXR in the PDB format and used in a silico molecular docking study. The results showed that ligand (TBD) has a high binding affinity (-6.3kcal/mol) compared to the standard drug Pyrazinamide (Z) (-4.6kcal/mol) [82], which suggests that the ligand could be a potential antibacterial agent against Mycobacterium TB bacteria. In addition, we have compared the docking score of our synthesized compound with a standard drug used to treat TB. The docking score of the synthesized ligand shows that they are highly effective drugs against Mycobacterium tuberculosis.

Table 2. Table representation of the standard drug v/s Docking Score in Kcal/mole.

Compounds	Docking Score in Kcal/mole	References
Pyrazinamide (sdt.)	-4.6	83
Wild	-5.21	83
F94L	-4.69	83
F94S	-4.73	83
G97C	-4.14	83
G97D	-3.22	83
G97S	-4.94	83
K96N	-3.97	83
K96R	-4.26	83
1g	-6.2	84
Ciprofloxacin (Sdt.)	-4.80	85

Moxifloxacin (Sdt.)	-3.60	[85]
Ofloxacin (Sdt.)	-3.58	[85]
Nitrofural	-5.6	[86]
NGX267	-6.0	[86]
Gamolenic acid	-6.1	[86]
Co-crystal ligand (FG-2)	-4.96	[87]
Isoniazid (Sdt.)	-5.83	[88]
1b to 30b	-4 to -6.2	[88]
5b	-6.1	[89]
6e	-6.1	[89]
5e	-6.3	[89]
3, 4, 6-Triaza-bicyclo [6.3.1] dodeca-1(12), 2, 6, 8, 10-pentaene-5-thione	**-6.30**	**This work**

Where sdt. = standard drugs used for antituberculosis.

4. Conclusion

An affordable chemical approach was employed to synthesize the TBD Schiff base ligand from 1, 3-Phthalaldehyde, and thiosemicarbazide with ~78 % yield. The synthesized ligand is a highly conjugated system containing –C=N, -C=S, and N-H bonds. Various spectroscopic techniques characterize the TBD Schiff base ligand. UV-Visible spectra confirm the absorption peaks at 245 nm and 351 nm due to π-π * and n-π *transitions, respectively. FT-IR analysis shows–C=N, -C=S, and N-H bonds stretching at 1607, 2051, and 3017 $cm^{-1,}$ respectively. 1HNMR shows the presence of seven types of protons signals; four singlets were observed at 10.00, 5.00, 5.00, and 1.96 ppm, whereas two singlet peaks at 5.00 ppm and 1.96 ppm are due to CH=N and N-H protons respectively. ESI-MS, study shows the Mass over charge ratio, and the values were as follow; m/z: 190.03 (100%), 189.03 (9.7%), 191.03 (4.5%), and 190.03 (1.1%). The computational study shows the molecular docking score against the glutamine protein enzyme (PDB ID-3ZXR). The molecular docking score was– 6.3 kcal mol^{-1} for the TBD Schiff base ligand, whereas – 4.6 kcal mol^{-1} is reported for the standard drug (Pyrazinamide). The results show that compounds have potential drug molecules concerning the assessment of their ecological applicability for the discriminating molecule against anti-TB. The approach described here involves the productive utilization of TBD Schiff base ligand using the drug design, which could benefit our society economically.

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Credit authorship contribution
Author Kaushal Kumar thanks Dr. Satyesh Raj Anand for his help in analyzing the UV-Visible data and correcting the manuscript. Mr. Himanshu Pandey is thanked for his help in the computer study. Mr. Mithun Kori contributed to the characterization of the IR spectrum data. Dr. Neha Mishra assisted in the analysis of the mass spectra. Finally, we thank Professor Satya Prakash Shrivastava for all the valuable suggestions and discussions during this study. Finally, we thank Professor Satya Prakash Shrivastava for all the practical advice and discussions during this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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