Research Article

Investigation and Synthesis of Benzothiazole-Derived Schiff Base Ligand Against Mycobacterium tuberculosis

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Tuberculosis (TB) is a critical issue for medical purposes. The synthesis of the hetero-atoms holding in the compound, Benzhydrylidene-(6-methyl-benzothiazol-2-yl)-amine (MTA) Schiff base ligand for the versatile application in anti-tuberculosis (anti-TB). Synthesis of the aliphatic or aromatic amine reacts with an active carbonyl compound (aldehyde or ketone) by nucleophilic addition, giving a hemiaminal solution followed by elimination of water to form a C=N double bond (an imine) during reflux of seven hr. at the 65oC. Reaction in ethanol, equimolar amounts of 6-methyl-benzothiazol-2-ylamine and Diphenyl-methanone were combined to form the Schiff base ligand. The MTA Schiff base ligand is characterized by several spectroscopic techniques like Fourier-Transform Infrared (FT-IR), Proton Nuclear Magnetic Resonance (1H-NMR), and Ultraviolet-Visible (UV-Vis) and Electron Spray Ionization (ESI) Mass spectroscopy. The computational study checked the biological activity to calculate the molecular docking against the glutamine protein enzyme (PDB ID-3ZXR). The molecular docking score was − 8.1 kcal mol-1 for the MTA Schiff base ligand, whereas − 4.6 kcal mol-1 is reported for the standard drug (Pyrazinamide). The MTA Schiff base ligand's product formation yield has significant potential. The synthesized compound is obtained, yielding 86%.

Satyesh Raj Anand and Kaushal Kumar equally contributed to this work.

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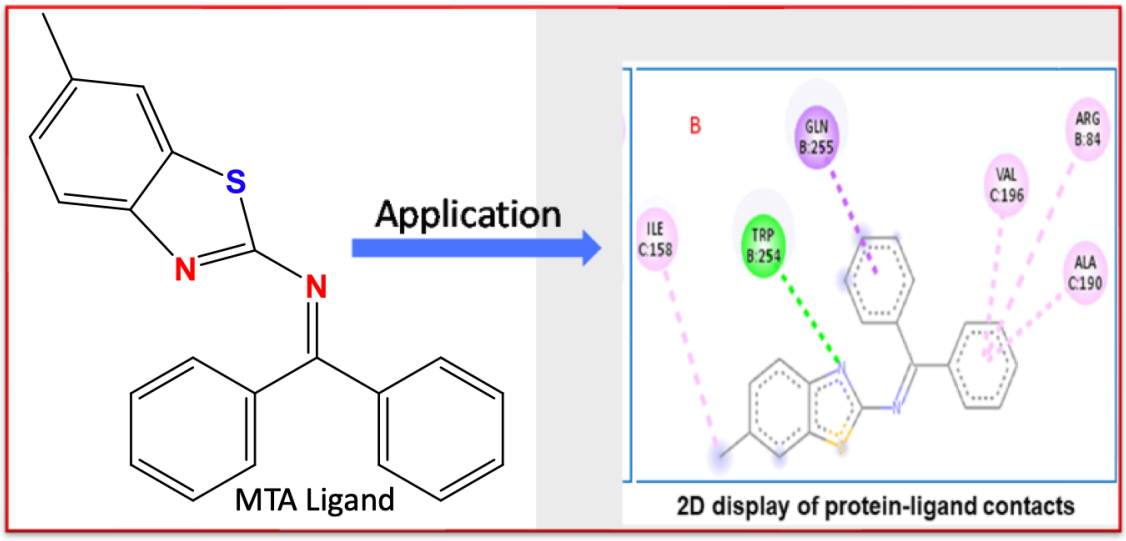


Introduction

In 2020, approximately 10 million people will be infected with tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb). But about 1.4 million people die every year, so this is now a big problem. The World Health Organization developed DOTS (direct observation, short-term intervention). The treatment success rate has been proven to be over 90%. Control of pathogenic bacteria using these drugs has become difficult due to the length of the DOTS approach (approximately 6-9 months) and the negative change in pathogen genes. WHO Report 2020[1]. Due to this situation, there has been a growth in cases of multi-drug resistance (MDR) and extensive drug resistance (XDR) in current years[2]. The strategies required for treating and controlling the disease are to solve the problems related to this disease as soon as possible. In concept, targeting enzymes involved in Mtb survival and growth in the host cell may be possible[3][4]. New antibiotics can be discovered by levelling enzymes in the biosynthetic pathway[5]. Over the past few years, the interaction between azomethylene and proteases has become increasingly popular due to its many uses. The heterocyclic moiety of benzothiazole has two types of heteroatoms: nitrogen and sulfur. Therefore, it is essential for biological and medicinal purposes[6].Due to the long-range conjugation and mesoscopic effects in Schiff base crystal molecules and their derivatives, they have been widely studied as promising linear and second-order organic nonlinear optical (NLO) materials[7]. A one-step strengthening reaction among an amino and aldehyde group yields a Schiff base. It was discovered in 1864 by German chemist and Nobel Prize winner Hugo Schiff[8]. Azo functional group association displaces the system amid acceptor and donor. The reverse reaction of an amino group

with an aldehyde group can form Schiff bases with conjugated carbon-nitrogen double bonds[9][10]. A less toxic, cheaper, and more potent method of protein-enzyme interaction is urgently needed to solve the problem of treating diseases. Our aim in this study is to create a new benzothiazole Schiff base ligand[11][12]. Additionally, Schiff bases have been studied mainly in medicinal chemistry for their antibacterial[13], antituberculosis[14], anti-inflammatory[15], antioxidant[16], and anticancer effects[17]. Schiff bases are used as catalysts, dyes, organic synthesis intermediates, and polymer stabilizers[18][19]. Moreover, benzothiazole compounds are heterocyclic compounds with various biological activities, including anti-inflammatory, anti-HIV, anti-tumor, anti-inflammatory, anti-malarial and disease prevention[20][21][22]. Additionally, Schiff bases derived from benzothiazoles have many applications in medicine, biology, chemistry, and medicine[23][24][25][26][27]. An important aspect of chemistry is the formation and synthesis of organic complexes[28][29][30]. It has been determined that the effectiveness of the treatment increases when organic compounds form complexes with the help of transition metals. Inorganic chemistry has also become one of the most promising and developing areas of medical research[31][32][33]. Due to the variety of Schiff base complexes and their metal complexes, there is an excellent opportunity to investigate the therapeutic potential of Schiff base compounds[34][35][36]. Schiff bases derived from benzothiazoles also have many applications in chemical, biological, inorganic, medical, and pharmaceutical fields[37][38]. Several unique biological properties of benzothiazole[24].The Schiff Foundation contributes to drug research on antioxidant, antibacterial[39][40], antiviral, antibacterial, antifungal, and cytotoxic properties. Several unique biological properties of benzothiazole[41][42][43][44][45].

The study presented here is intended to be a synthesis of the compounds used in the identification and studies of diphenylidene-(6-methyl-benzothiazol-2-yl)-amine (MTA) Schiff base ligands for anti-tuberculosis (anti-tuberculosis). Using the MTA Schiff base ligand synthesis method, An elimination reaction follows nucleophilic addition. The production rate during MTA Schiff base ligands synthesis is 86%. The remainder will be the conversion of reactant molecules or byproducts. For this reason, he is not recognized in the department. The synthetic material used in computational studies was based on the interaction of the MTA Schiff base ligand with the protein, and molecular docking scores were calculated. Thus, the most crucial observation is that the MTA Schiff base ligand consumption is 8.1 kcal mol-1, while the consumption of the standard drug (pyrazinamide) is 4.6 kcal mol^{-1}.

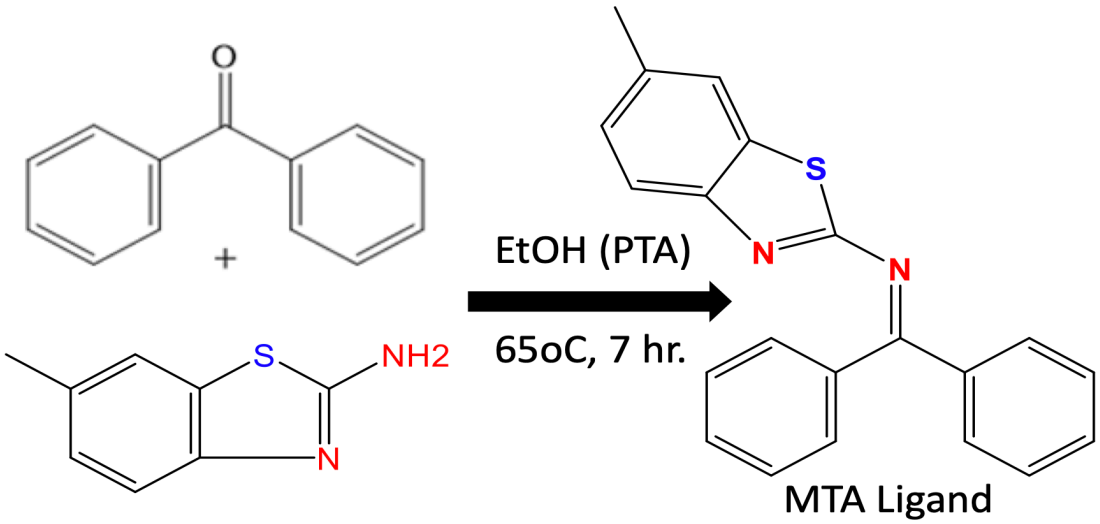
Materials and Methods

General methods

The chemicals (6-methyl-benzothiazol-2-ylamine and Diphenyl-methanone) used throughout the reactions were purchased from Sigma Aldrich. Some basic chemicals needed, such as solvents, ethanol, and methanol, were purchased from Himedia Ltd. Pvt. India. To characterize the molecular structure of MTA Schiff base ligand, the FT-IR transmittance spectrum was recorded on a Shimadzu FT-IR spectrophotometer in the wavenumber range of 4000-400 cm^{-1} and 1H-NMR spectra were done at room temperature by employing a JEOL RESONANCE 400 MHz instrument in deuterated DMSO solvent. The UV-Visible studies of MTA Schiff base ligand were performed using lab India analytical-UV3092 UV-Visible spectrophotometer and Electron-Spray Ionization Mass Spectrum (ESI-MS) was recorded on XEVO G2S QPOF mass spectrometer.

Experimental Methods

Schiff bases (named after Hugo Schiff) combine an aliphatic or aromatic amine with an active carbonyl compound (aldehyde or ketone) by nucleophilic addition to form a hemiaminal solution, followed by removal of water to create a C=N double bond (Immigration)[8]. Seven hours at 65°C temperature while refluxing. In the reaction in ethanol, equimolar amounts of 6-methylbenzothiazol-2-ylamine and diphenylmethane were combined to form the Schiff base ligand. The light-yellow amorphous powder formed from the reaction mixture after cooling was collected. After separation with Whatman filter paper and drying at room temperature, the yield was about 86%. To purify the yellow compound, it was recrystallized twice with ethanol. The schematic representation shows that Scheme 1 describes the synthetic procedure of the primary Schiff ligand MTA.



Scheme-1. Schematic representation shows in the synthesized MTA Schiff base ligand.

In silico studies

For medicinal chemistry or quantitative research on drug design and drug structure, the three-dimensional (3D) structure of glutamine synthetase1 protein (PDB ID 3ZXR) from Mycobacterium tuberculosis is selected as the best candidate for docking with synthetic Schiff base ligands[45]. Best targeting protein among commercially available drugs, isoniazid, and pyrazinamide (PZA), are often used as standard drugs[46]. Check the structure for missing atoms and broken chains. Crystalline water molecules have nothing to do with structure. Fascinating computer simulation studies are essential to pharmacology and modern medical science. The foremost focus of structure analysis is bioactivity, toxicity, metabolism, and other properties.

The structure of the glutamine synthetase1 molecule was downloaded as two-dimensional (2D) structure information from the Protein Data Bank (PDB) ID 3ZXR and used in silico molecular docking studies to reduce the structure. Use spherical energy to fix the structure of the glutamine synthetase1 molecule[47]. A docking gradient algorithm was used on the binding envelope of the enzyme glutamine synthetase 1 for optimization purposes using AutoDock Vina software[48].

Results and Discussion

FT-IR and UV-Vis spectroscopy Characterization

The MTA Shiff base ligand was analysed using FTIR spectroscopic performances. These performances showed a different type of peak at 1635 cm -1 due to the C=N stretching, and this frequency peak reported in the literature[49]. The C=C stretch absorptions are found at 1523, 1488 and 1444 cm-1. The peak detected around 746 cm-1 is attributed to the out-of-plane bending of ring C-S bonds. The wave number at 2911 cm -1 is allocated for CH_3 stretching vibrations. Demonstrations another peak at 3600 cm-1 approximately. N-H Peak demonstrations as a bifurcated Figure 1(a). The electronic absorption bands were considered by UV-vis Spectroscopic of MTA Schiff base ligand in methanol, demonstrating three different absorption bands at 264 nm, 233 nm, and 210 nm. The MTA Schiff base ligand are three absorption bands allocated to the π-π/ π-π* transitions of the aromatic rings in a Schiff base ligand Figure 1(b).

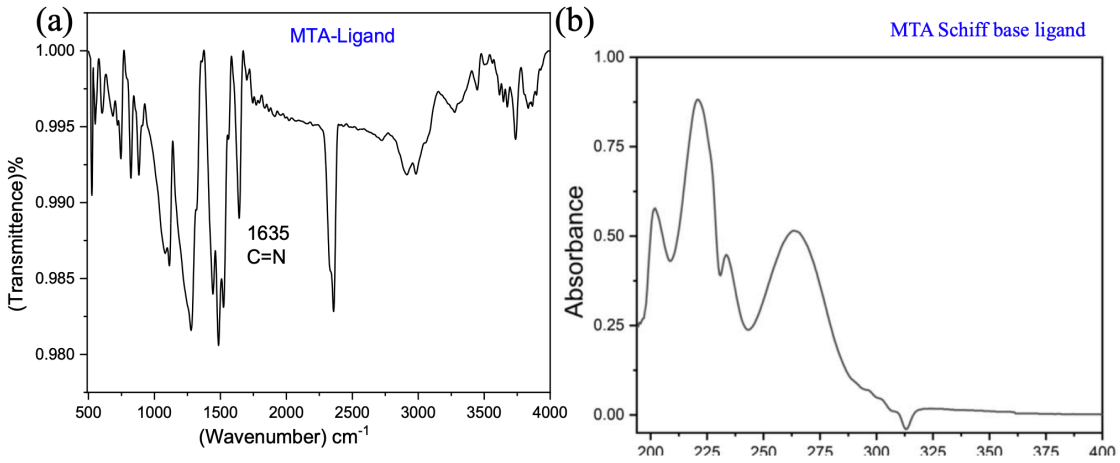


Figure 1. (a) The Characterization of FT-IR Schiff base ligand and; **(b)** UV-Vis. Spectrum of MTA Schiff base ligand

1H-NMR spectrum analysis

The1HNMR spectra of MTA Schiff base ligands were recorded by liquefying a small amount of MTA in deuterated dimethyl sulfoxide (DMSO) solvent using tetramethyl silane (TMS) as the standard. There are eight types of proton signals in the MTA segment. Three signals were observed for the benzothiazole

moiety at 8.6, 8.2, and 8.0 ppm. The signals at 7.6, 7.5, 7.4, and 7.3 ppm are from the aromatic region of the biphenyl ring, and the signal at 2.4 ppm is from the CH3 group. As shown in Figure 2.

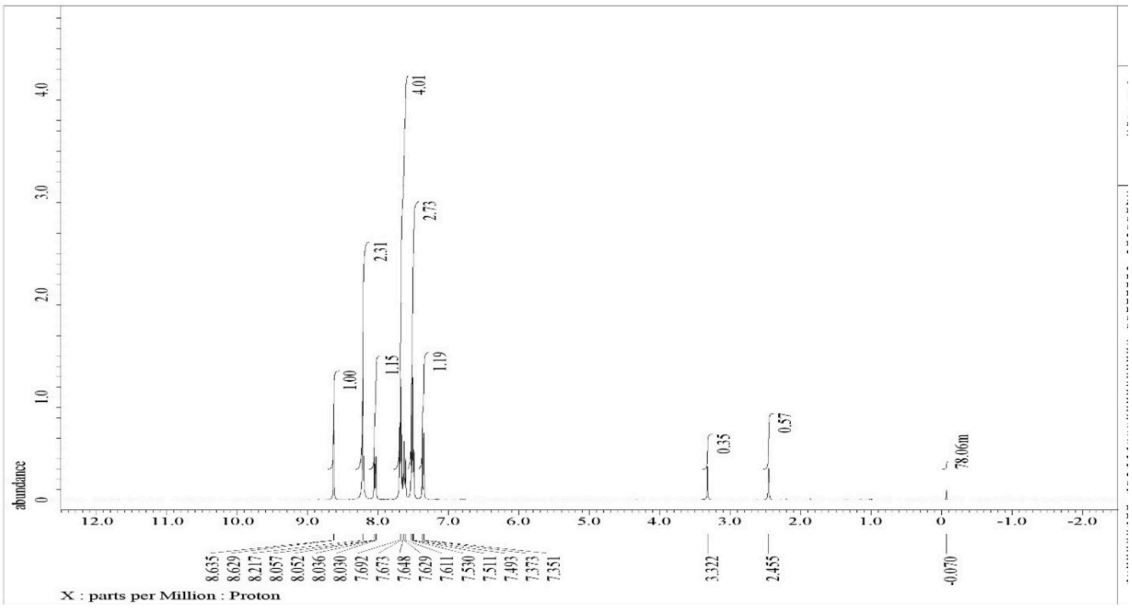


Figure 2. Characterization of ^{1}H-NMR spectrum of MTA Schiff base ligand

ESI mass spectral studies

ESI-MS studies showed a mass-to-charge ratio with the following values: m/z: 329.1 (100%), 330.0 (15.6%), and 331.1 (15.1%). The various peaks are divided into two parts: one is the molecular peak, and the other is the isotope peak. The 100% peak is called the molecular peak and is shown in Figure 3.

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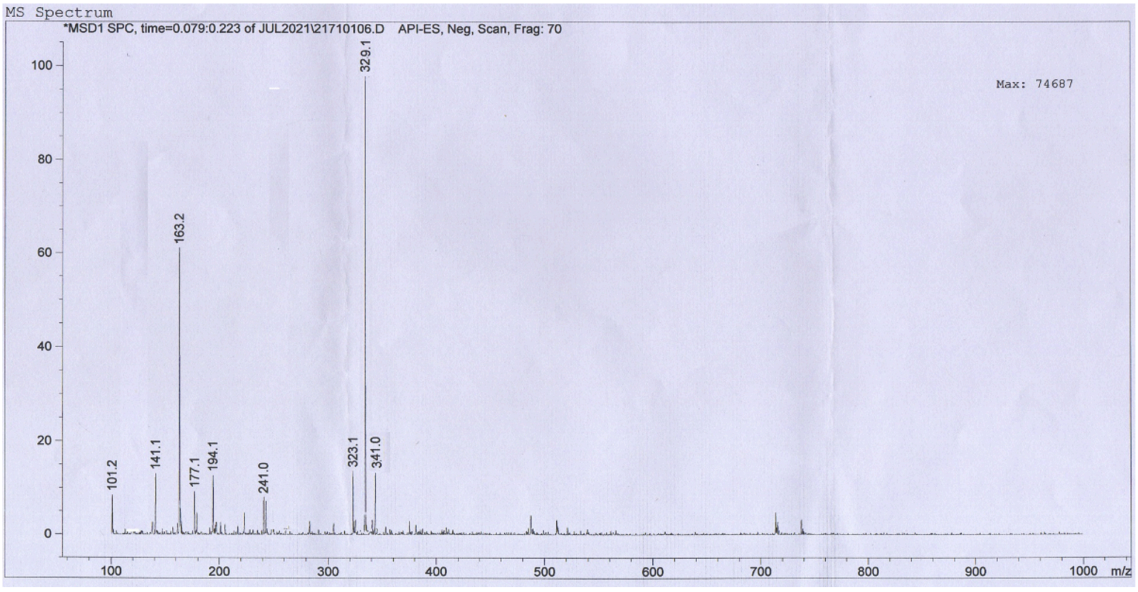

Figure 3. Characterization M/Z Mass spectrum of MTA Schiff base ligand.

ADME prediction and Molecular docking study of MTA ligand

Adsorption Distribution Metabolism Excretion (ADME) prediction

ADME prediction of MTA Schiff base ligands with significant potential and helpful chemical properties as compounds using the Swiss Dock online service for body composition analysis models[50]. The most critical factor in drug development is the ADME properties of the ligand. In the preliminary screening phase, chemical chemistry eliminates incorrect predictions in different online algorithms such as distribution, biological activity, metabolism, and behaviours. The molecular weight of the MTA Schiff base ligand is 328.10 g/mol. However, the molecular weight of the isoniazid material decreases by 137.14 g/mol. Estimated data are shown in Table 1.

Comps	Mol. Wt.	*TPSA (Å^2)	Rotatable bonds	Donor #HB	Acceptor #HB	WLogP o/w	Metab	Rule of five	% Human intestinal absorption
MTA	328.10	53.49	3	0	2	5.48	5	0	90
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

Table 1. Insilico fascinating predicted physicochemical and pharmacokinetic parameters of the TBD Schiff base ligand.

**TPSA = Topological Polar Surface Area, #HB = Hydrogen Bond*

Molecular Docking Studies

MTA Schiff base ligands have significant potential for use in molecular docking[51]. Molecular synthesis of new complexes and their applications, such as drug sighting, involves forming new drugs with therapeutic potential[51][52][53]. Computer-aided design uses computational software and tools to help identify potential recreation areas within compounds[49][54]. The designed molecule was docked with the target protein glutamine synthetase 1 using AutoDock Vina software[55][56]. It is an automated program for predicting the interactions of ligands with macromolecular biological targets[57]. Many biosynthetic enzymes can be considered drug targets because they are essential for mycobacterial function[58][21]. One of the critical enzymes required for the survival of mycobacteria is glutamine synthetase1, which is responsible for the growth of Mycobacterium tuberculosis[59]. Therefore, inhibition of glutamine synthetase secreted by M. tuberculosis is sufficient to prevent disease progression. We chose glutamine synthetase as the target of interest, as shown in Figure 4.

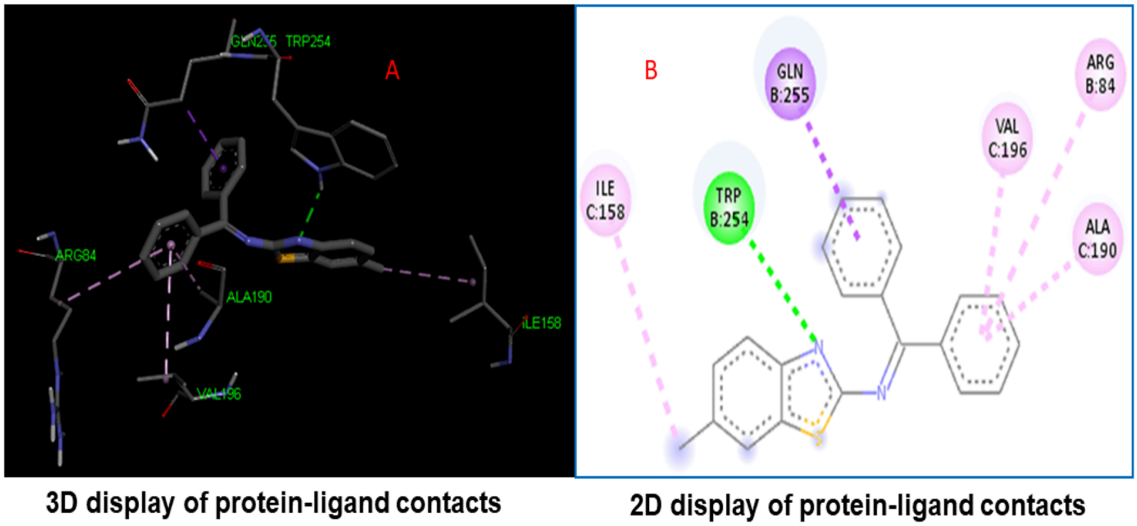

Figure 4. Molecular docking study of MTA Schiff base ligand with targeted protein

Conclusion

Using an inexpensive chemical formula, MTA Schiff base ligands were synthesized in 86% yield from 6-methyl-benzothiazol-2-ylamine and diphenylmethanone. Characterization of MTA Schiff base ligands using various spectroscopic techniques. MTA ligand is present in the nitrogen and sulfur atoms that the moiety contains. Which is the main reason for interaction between the ligand and protein molecule as well as necessary from the biological point of view. The UV-visible spectrum confirmed three absorption peaks at 264 nm, 233 nm, and 210 nm caused by π-π* f the aromatic ring. FT-IR analysis showed that -C=N, C=S, and OH bonds were stretched at 1635, 2320, and 3600 cm-1, respectively. 1H NMR shows that the MTA component has an eight-proton signal. Three signals were observed for the benzothiazole moiety at 8.6, 8.2, and 8.0 ppm. The signals at 7.6, 7.5, 7.4, and 7.3 ppm originate from the aromatic region of the biphenyl ring. ESI-MS studies showed a mass-to-charge ratio with the following values: m/z: 329.1 (100%), 330.0 (15.6%), and 331.1 (15.1%). The various peaks are divided into two parts: one is the molecular peak, and the other is the isotope peak. Search results show the molecular docking score for glutamate protease (PDB ID-3ZXR). While the molecular docking score for the MTA Schiff base ligand is 8.1 kcal mol^{-1}, the molecular docking score for the standard drug (pyrazinamide) is 4.6 kcal mol^{-1}. The results show that the compounds can utilize drug molecules, essential for assessing their ecological suitability as known antituberculosis molecules. The approach described here involves the production of MTA Schiff base ligands using synthetic drugs, which can provide economic benefits to our society.

Statements and Declarations

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Conflict of Interest: None.

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