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Antituberculosis: Synthesis and theoretical study of New Schiff base ligand; 2,2'-{(5-amino-1,3-phenylene) bis[nitrilo(E)methylylidene]}dibenzene-1,4-diol

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ABSTRACT

The ability to breathe and generate adenosine triphosphate is necessary to the persistence, physiology and pathogenesis of *Mycobacterium tuberculosis* that causes TuB. By doing a theoretical study of a chemical compound, Schiff Base 2,2'-{(5-amino-1,3-phenylene) bis[nitrilo(E)methylylidene]}dibenzene-1,4-diol, where almost all biological activities have been studied theoretically exploiting a computer software PASS (Prediction of Activity Spectra for Substance) for enhancing Computer Aided Drug Designing, as well as studying the class of toxicity in the human body by GUSAR software, which showed biological activity against the tuberculosis epidemic that killed many people, and a protocol was proposed for prepared and study of the properties of this compound.

Keywords: GUSAR software, Synthesis, Schiff base, Tuberculosis, Toxicity, PASS prediction.

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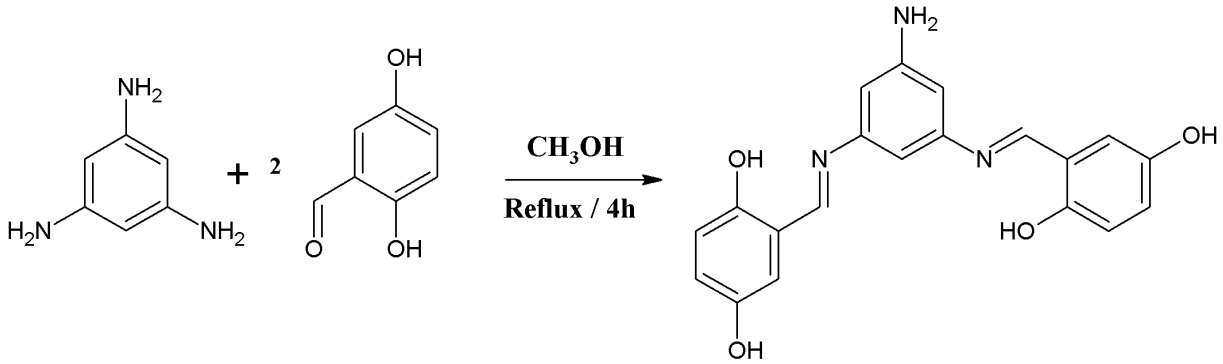
I. INTRODUCTION

Among the deadliest infectious diseases is tuberculosis. [1] In 2018, according to the census of the world organization approximation of 10.5 million people are contaminated by tuberculosis (TuB) worldwide. Including 5.7 million Men, 3.2 million Women and 1.1 million Children, whereas 1.5 million deaths due to this disease worldwide [2]. (TuB) is classified as an infectious epidemic caused by various types of mycobacteria, collectively called tubercle bacilli [3], including M. bovis, Mycobacterium tuberculosis, M. caprae, M. africanum, M. canettii, M. microti, and M. pinnipedii. It usually affects the lung (called pulmonary TuB) and has the ability to affect other organs (called extrapulmonary TuB) [4]. The disease has witnessed a spread widely in the last half century, followed by many and varied changes in economic, medical and even social factors, in addition to disease resistance to the same existing drugs. Although in recent years the research that explored effective drug doses and combinations for tuberculosis (TuB) treatment has expanded greatly, this led to a decrease in the death rate for (tub) by 22% last twenty years, yet the inevitable threats arising from resistant and persistent (TuB) are a serious concern [2, 5]. With the limited availability of anti-TuB drugs, whether natural or synthetic, the global burden of this epidemic remains looming on the horizon, with great losses in the rates of patients and deaths [6]. Therefore, the desired goal of treatment for tuberculosis is to develop and to create new drugs that are more effective, more affordable, and more easily produced [7, 8]. Now one of the most serious public health concerns around the world is the resurgence of (TuB). Despite its global risks to health, tuberculos is a non-priority disease, and no new TB treatments have been discovered on the market over the past 50 years, since the discovery of the drug with a new mechanism of action (rifampicin) in 1963 [9]. The complexity of the structure and characteristics of the mycobacterial cell wall, the lengthy treatment duration, multi-resistance and extensive drug resistance developed by the pathogen favors the recurrence of the infection and thus making difficult to treat the disease clinically [10]. About 50

years ago, a significant decrease in desease cases was observed worldwide due to the introduction of fist-line drugs such as adenosine triphosphate (ATP) and promises to breathe through the electron transport chain (ETC) and (Schiff bases) as compounds of new importance to the drug. Because it has many interesting properties and wide applications in the pharmaceutical, medical, material and agricultural sciences, Schiff base are given great interest [11-14]. It choosed because of the imine function in its structure which is highly effective in biological activities [15,16]. the Schiff base was first prepared by the researcher Hugo Schiff in 1864 [17]. They can be considered a sub-class of imines The term is often synonymous with azomethine, synthesized by reaction between aliphatic or aromatic amine and a carbonyl compound by nucleophilic addition to generate an imine group18. The compounds of Schiff bases have been classified for their active biological activities such as antioxidant [19], antimicrobial [20], antifungal [21], antibacterial [22], anticonvulsant [23], anticancer [24], antineoplastic [25], antiinflammatory [26], antiproliferative [27] and antituberculosic and so on [28]. Since the discovery of the Schiff bases, they have been manufactured on a large scale for industrial use and pharmacological properties and this is due to the importance of their medical assays as antioxidant, antitumor and bacterial purposes. However, the biological activity of these compounds mainly the antituberculosic activity deserves further research. This paper reviews a theoretical study of Schiff bases on antituberculosic activity and its toxicity level, and highlights the most effective activity of this compound, especially as an anti-TuB bacterium.

II. EXPERIMENTAL

Scheme.1 shows the preparation procedures of the 2,2'-{(5-amino-1,3-phenylene)bis[nitrilo (E)methylylidene]}dibenzene-1,4-diol. By reaction of the benzene-1,3,5-triamine and 2,5-dihydroxybenzaldehyde in refluxing methanol the Schiff base ligand was prepared. After evaporating the solvents, the precipitates were filtered off and dried in air [29].



Scheme 1: Reaction of benzene-1,3,5-triamine with 2,5-dihydroxybenzaldehyde to produce the Schiff base.

Table 1: Predicted activity of synthesized compound 2,2'-{(5-amino-1,3-phenylene)bis [nitrilo(E)methylylidene]}dibenzene-1,4-diol by PASS:

Predicted Activity	Synthesized compound		Predicted Activity	Synthesized compound	
	P_a	P_i		P_a	P_i
Antituberculosic	0,737	0,004	Antihypoxic	0,315	0,143
Laccase inhibitor	0,808	0,004	Antifibrinolytic	0,233	0,065
Phosphatidylserine decarboxylase inhibitor	0,722	0,010	Antiviral (Herpes)	0,277	0,108
Antimycobacterial	0,707	0,005	Antispirochetal	0,185	0,029
Peroxidase inhibitor	0,711	0,011	Antihypotensive	0,202	0,055
Antiinfective	0,627	0,011	Antiviral (Trachoma)	0,155	0,017
Antiseborrheic	0,648	0,047	Antioxidant	0,194	0,058
Antiseptic	0,583	0,008	Antibiotic	0,170	0,038
Antineoplastic (breast cancer)	0,545	0,015	Antidote	0,217	0,089
Antiprotozoal (Coccidial)	0,523	0,005	Antineoplastic (melanoma)	0,185	0,064
Antiparasitic	0,520	0,014	Antipsoriatic	0,235	0,113
Antiviral (Picornavirus)	0,540	0,035	Antihemorrhagic	0,155	0,047
Antineoplastic (colorectal cancer)	0,465	0,015	Antiinflammatory, ophthalmic	0,259	0,155
Antineoplastic (colon cancer)	0,457	0,015	Antitoxic	0,220	0,117
Antidyskinetic	0,495	0,065	Antitreponemal	0,137	0,036

Antihelmintic	0,434	0,013	Antidiarrheal	0,196	0,098
Antifungal	0,455	0,038	Antiprotozoal (Plasmodium)	0,176	0,082
Antibacterial	0,437	0,023	Antiprotozoal (Babesia)	0,140	0,060
Antiprotozoal (Amoeba)	0,424	0,021	Anticarcinogenic	0,199	0,121
Antineoplastic	0,477	0,079	Antiprotozoal (Histomonas)	0,095	0,021
Antiviral (Adenovirus)	0,407	0,027	Antiuremic	0,163	0,106
Antinociceptive	0,447	0,073	Antithyroid	0,127	0,072
Antiprotozoal (Trypanosoma)	0,376	0,048	Antineoplastic (uterine cancer)	0,125	0,075
Antiprotozoal (Trichomonas)	0,331	0,016	Antiperistaltic	0,181	0,132
Antineoplastic (lung cancer)	0,322	0,036	Antifungal (Pneumocystis)	0,060	0,023
Antiprotozoal	0,323	0,038	Antidote, heavy metal	0,084	0,050
Antipyretic	0,306	0,043	Antiviral (Influenza A)	0,213	0,185
Antiprotozoal (Toxoplasma)	0,283	0,020	Antineoplastic (sarcoma)	0,155	0,143
Antischistosomal	0,274	0,020	Antibacterial, ophthalmic	0,125	0,114
Antiviral (Poxvirus)	0,304	0,057	Antidote, organophosphates	0,022	0,022
Antileprosy	0,262	0,018	Antiviral (Hepatitis B)	0,159	0,159
Antineoplastic (liver cancer)	0,269	0,032	Antihypoxic	0,315	0,143
Antimyopathies	0,333	0,105	Antifibrinolytic	0,233	0,065
Antihematotoxic	0,236	0,029	Antiviral (Herpes)	0,277	0,108
Astringent	0,219	0,013	Antispirochetal	0,185	0,029
Antirickettsial	0,229	0,026	Antihypotensive	0,202	0,055
Antineoplastic antimetabolite	0,225	0,029	Antiviral (Trachoma)	0,155	0,017
Antineoplastic antimetabolite	0,225	0,029	Antioxidant	0,194	0,058
Antinephritic	0,288	0,106	Antibiotic	0,170	0,038
Antiviral (CMV)	0,251	0,075	Antidote	0,217	0,089
Antineoplastic (melanoma)	0,185	0,064			

III. RESULTS

Acute rat toxicity prediction of Schiff base

The theoretical study of the acute toxicity and the classification of the toxicity of the schiff base studied by computer approaches allow to give important information before its preparation. In addition, due to the time consuming and high cost of animal models and even the ethical side, theoretical predictions have been used as a surrogate in in vivo toxicological studies. The values of (Intraperitoneal route of administration IP, Intravenous route of administration IV, Oral route of administration and Subcutaneous route of administration SC) and the predicted toxicity class for 2,2 '- {(5-amino-1,3 phenylene) bis [nitrilo (E) methylylidene]} dibenzene-1,4-diol were predicted by GUSAR software in rodents. The results show that the compound was classified in the fifth class for subcutaneous administration with a high LD_{50} value of 1571,000 mg/kg. the same thing noted for the Intraperitoneal and Oral administration routes were classified in the fifth class with LD_{50} values of 1032,000 and 3681,000 mg/kg, respectively, on the other hand the Intravenous route was classified in the fourth class with an LD_{50} value of 105,000 mg/kg (table 2), and that indicates our Schiff base is classified in the non-toxic class.

Table 2: Acute rat toxicity prediction of 2,2'-{(5-amino-1,3 phenylene)bis[nitrilo (E) methylylidene]}dibenzene-1,4-diol.

Administration route	LD50 log10(mmol/kg)	LD50 (mg/kg)	Predicted toxicity class
Intraperitoneal (IP)	0.453	1032.000	Class 5
Intravenous (IV)	-0.539	105.000	Class 4
Oral administration	1.006	3681.000	Class 5
Subcutaneous (SC)	0.636	1571.000	Class 5

CONCLUSION

in this study we have proposed synthesis of novel 2,2'-{(5-amino-1,3-phenylene)bis[nitrilo(E)methylylidene]}dibenzene-1,4-diol. By method is maintaining environmental friendly approach for the synthesis of Schiff base, along with their prediction of biological activities using a computer software PASS, which gave a good antituberculosis property against M. tuberculosis and their toxicity by GUSAR software which showed weak toxicity. Nevertheless, the anti-TuB activity of this compound requires further research and development, and there is ample scope to explore new promising leads for designing more effective antimycobacterial drugs to counter the classic example of poverty-TuB.

Conflict of Interest: No conflict of interest was declared by the authors in this research article.

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