Research Article

"Design and Synthesis of Novel Schiff Base Derivatives Based on Benzotriazole".

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ABSTRACT

This work's objective is to design and synthesis of novel Schiff base derivatives based on benzotriazole. Pharmaceutical companies have recently shifted their focus away from investing heavily in chemistry, believing that synthetic chemistry is a well-established technology with limited potential for innovation in drug discovery. There is need to quantify or develop efficient and yield oriented process for the preparation of such derivatives. Finding novel, effective, and non-toxic anti-TB medication options is imperative, particularly in light of the COVID-19 pandemic's lingering effects.

KEYWORDS: - Benzotriazole, Almar blue assay, ^{13}C NMR, TLC, anti-TB, Schiff's base.

INTRODUCTION

❖ Synthetic Chemistry

Pharmaceutical companies have recently shifted their focus away from investing heavily in chemistry, believing that synthetic chemistry is a well-established technology with limited potential for innovation in drug discovery. However, we maintain that excellence and creativity in synthetic chemistry are fundamental for success across all stages of drug development. [1]

❖ Medicinal chemistry

Chemists play a pivotal role in formulating hypotheses for new drug projects by utilizing their expertise in crafting novel compounds and understanding target diseases and competitive therapies. They are instrumental in selecting compounds for screening as lead candidates and resynthesizing hits for further evaluation. The responsibilities of chemists also encompass the purification and characterization of newly developed chemicals.[2] In the past, drug discovery

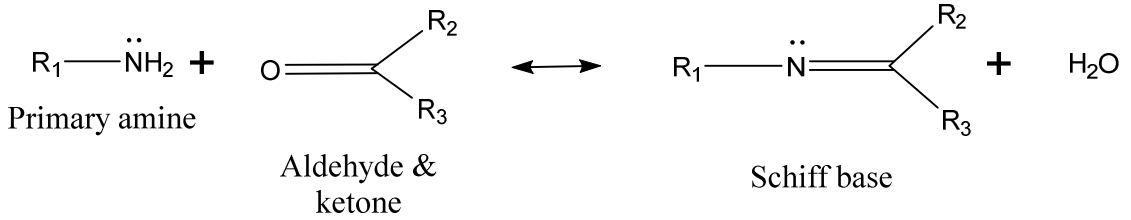
processes operated at a slower pace with limited knowledge resources. Many challenges hindered progress, including limited information about diseases, the scarcity of compounds for screening, the absence of advanced computer technologies, manual literature searches, the manual preparation of new compounds for testing, and a lack of integration of insights from other disciplines.

❖ **Schiff Base**

Hugo Schiff employed ketone, aldehyde, or primary amine, and azeotropic distillation was used for the first time in 1864 to produce Schiff's base. These compounds are referred to as "Schiff bases" when they are used as ligands to create complexes for coordination with ions of metal. Although corrin combinations occur normally, most man-made Schiff bases are utilized to create a variety of significant catalysts, including Jacobsen's catalyst.[3] Schiff bases are imines that have a group of alkyl or aryl at R3, as opposed to a hydrogen atom. R1 and R2 may represent atoms of hydrogen. Numerous biological characteristics, including antiviral, anticancer, and antibacterial ones, are present in Schiff bases. Schiff bases also inhibit the aggregation of amyloid-β. These are common enzymatic stages created when a lysine residue's terminal group interacts reversibly with an intermediate's or substrate's carbonyl or ketone. An aldehyde or ketone of a cofactor or reagent reversibly bonds with the terminal group of a lysine residue. The most common uses for these are catalysts, polymer stabilizers, pigments, dyes, and intermediates in organic synthesis.[4]

❖ **Synthesis of Schiff bases**

In 1864, Hugo Schiff produced the earliest imines of the nineteenth century. Numerous techniques have now been devised for the production of imines. According to Schiff, the traditional synthesis involves condensing an amine and a carbonyl molecule using azeotropic distillation.[5] Using a molecular sieve, all of the water that had developed within the system was eliminated. In the 1990s, An in-situ technique for extracting water was developed using dehydrating liquids such as trimethyl orthoformate.[6]

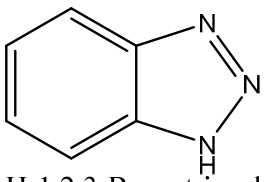


❖ Importance of Heterocycle in drug design

Heterocyclic compounds are quite intriguing in everyday life. Several structural components of heterocyclic compounds include heteroatoms. They might be non-cyclical or cyclical in nature. Heterocyclic compounds possess a broad range of uses.[7] Their primary uses are in veterinary products, agrochemicals, and pharmaceuticals. Rings with up to six members with heteroatoms of nitrogen, oxygen, or sulfur are the most common types of heterocycles. Functional groups can be added to heterocyclic compounds as part of the ring or as substituents, which is a significant structural characteristic.[8] Basic nitrogen atoms, for example, can be substituents in amino acids or contained in rings.

❖ Chemistry of 1H-1,2,3-Benzotriazole

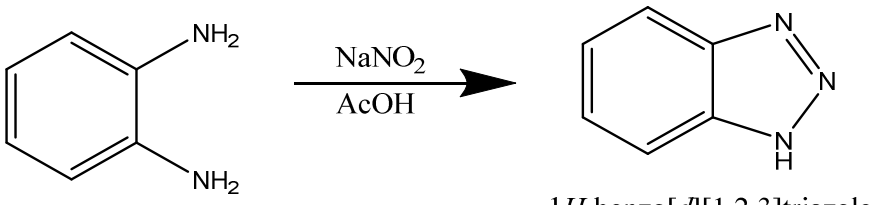
For instance, basic nitrogen atoms might be included in rings or as amino substituents. This indicates that the structures can provide or simulate a functional group in a very flexible way. The difficulties in finding new heterocyclic systems and comprehending their characteristics also keep the field's research active.[9] Important nitrogen-containing heterocyclic compounds with intriguing biological characteristics and potential medicinal uses are benzotriazole and its derivatives.[10] The moiety of benzotriazole exhibits unique properties in biological systems. The benzene and triazole rings of benzotriazole are fused to form a fused heterocycle. In medicinal chemistry, benzotriazole and its derivatives are extremely important. Many chemists employ the derivatives to treat various medical ailments.[11] Artificial substances with the following properties: anticonvulsant, antimicrobial, antibacterial, antifungal, antiviral, antitubercular, anticancer, and anti-inflammatory.[12]



1H-1,2,3-Benzotriazole

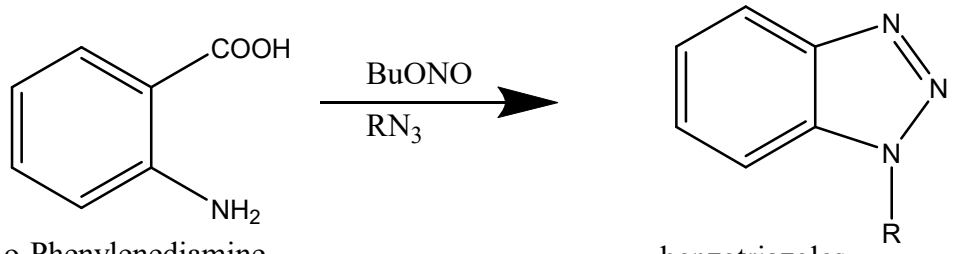
❖ Synthesis of Benzotriazole

Benzotriazoles are produced when O-phenylenediamine is treated using acetic acid and NaNO2. and proceeds through cyclization within molecules. [13]



o-Phenylenediamine 1*H*-benzo[*d*][1,2,3]triazole

Benzyne (dehydrobenzene) is produced in situ with the gradual benzotriazoles are produced by an alkyl nitrite is mixed with anthranilic acid, It is then supplemented with acyl, sulfonyl, and Alkyl azide.[14]



o-Phenylenediamine benzotriazoles

❖ **Biological Activity**

Heterocycles have been recognized as a crucial structural element in pharmaceutical chemistry. Additionally, they are frequently found in sizable concentrations in biomolecules, such as nutrients, enzymes, organic goods, and substances that have biological activity. [15] such as enzyme inhibitors, antifungal, anti-HIV, antidiabetic, antibacterial, antioxidant, anticonvulsant, and insecticidal agents.[16]

❖ **Tuberculosis**

Robert Koch discovered Mycobacterium tuberculosis for the first time in 1882, and in 1905 For this finding, he received the Nobel Prize Since tuberculosis (TB) is one of the first infectious illnesses to impact humans, its history is intertwined with human history.[17] Bone TB was found to be the cause of death in bones from the Middle East and Europe that were 4000 years old, indicating that the illness was already a common health issue at the time. Hippocrates describes people who were withering away, had chest discomfort, and coughed up blood in their sputum in historical records. Hippocrates was able to diagnose tuberculosis (TB), also known as consumption, based on these symptoms.[18] The recurrent accounts of individuals exhibiting similar symptoms suggested that the illness was well-established even in prehistoric times.[19]

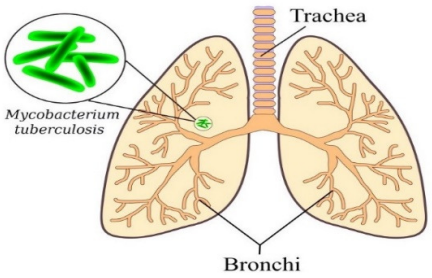


Figure 01: Tuberculosis

A tuberculin skin test or an interferon-gamma-releasing assay can detect a latent infection. The interferon-gamma release assay and tuberculin skin test are recommended as screening tools for latent infection with tuberculosis in different age and risk groups by particular guidelines to the Agency for the Control of Disease and Prevention in the US, the National Institute over Clinical and Health Excellence in the UK, and the European Centre for Prevention and Control of Diseases.[20]

❖ **Classification of Antitubercular Drugs**

First line, second line, and third line antitubercular medications are categorized according to Their availability, cost, toxicity, adverse effects, and efficacy. [21,22] The main antitubercular medications are:

Streptomycin

Rifampicin

Ethambutol

Isoniazid

Pyrazinamide

❖ **Tuberculosis Types**

Primary tuberculosis (TB): This is the first stage of the illness. At this stage, you could not show any symptoms of TB, or you might have a few flu-like symptoms. The immune system of the body might be able to get rid of the infections, but occasionally it leaves some behind, which allows them to keep growing. [24]

Latent TB: Your immune system keeps the germs in your body from spreading, despite their presence. You're not contagious because you don't exhibit any symptoms The virus is still there,

though and it might activate at any time. In cases when you are highly susceptible to reactivation, your physician may recommend medication to prevent active TB. This frequently happens to people who are HIV positive, have been infected within the last 24 months, have an abnormal chest X-ray, or have weakened immune systems.[25]

Active TB: As the bacterium proliferates, you get sick. You might spread your infection to other people. Approximately 90% of current cases of TB in adults are caused by latent infections. [26]

Active TB external to the lungs: Extrapulmonary TB is a kind of a TB infection that disseminates to several bodily regions from the lungs. Your symptoms could be different depending on whatever part of your body is afflicted.[27]

❖ **Tuberculosis Symptoms:**

Latent tuberculosis is symptomless. You can find out whether you have active TB in your lungs by taking a skin or blood test:

a) A cough lasting longer than three weeks,
b) Chest pain
c) Sputuming out blood
d) Constantly feeling fatigued
e) Night sweats
f) Chills
g) Fever
h) Appetite loss
i) Loss of weight

❖ **Treatment of Tuberculosis**

The first medication used to treat TB was streptomycin.13–15 Selman Abraham Waksman isolated it in 1944, and in 1952, he was granted the Nobel Prize in recognition of this discovery. Jorgen Lehmann found para-aminosalicylic acid (PAS) to be an efficient tuberculosis medication two years later, in 1946. [28-30] For six to eight months, a multi-drug regimen is used to treat TB. Ethambutol, pyrazinamide, rifampicin, or isoniazid are the recommended first-line medications.[26] Second-line medications are utilized when the strain of bacteria develops resistance to one or more of these treatments.[31-33] Among these are fluoroquinolones, kanamycin, streptomycin, ethionamide, and P-amino salicylic acid. Second-line medications

are typically more hazardous and less effective than first-line medications. The main focus of this investigation will be the metabolism and related toxicities of primary antituberculosis medications.[34]

MATERIALS AND METHODS

The capillary tube method was used to determine the melting points. Compounds are separated using thin-layer chromatography on a TLC plate that has been pre-coated with GF 250 silica gel. The IR spectra of synthetic substances are studied using ATR-IR spectroscopy. ^{13}C NMR spectra are usually used as supporting information to confirm the structure of a compound. A method to precisely determine a compound's molecular mass is mass spectroscopy.

Materials

3-Chlorobenzaldehyde, 3-Nitrobenzaldehyde ,4-Bromobenzaldehyde,4-chlorobenzaldehyde, P-nitro benzaldehyde, Glacial acetic acid, Benzotriazole, Acetone, Ethyl chloroacetate, Urea, Guanidine, Thiourea.

Synthesis and characterization

Step:1 Synthesis of 1H-benzo[d][1,2,3]triazole.

Dissolve 2.9 g of benzene-1,2-diamine in mixture of 3 ml of GAA and 10 ml water in beaker. Slight warming may be necessary. Cool the solution at 15 ℃, stir magnetically and add solution of 4 gm sodium nitrite in 4 ml water in one portion. The mixture gets warm and reaches a temperature about 85 ℃ within 2-3 min and continue stirring for 15 min. The temperature will be dropped 35 ℃ and then thoroughly chill in ice-water bath for 30 min. Collect the product by vacuum filtration of the pale brown solid which separated.

Step:2 Synthesis of Ethyl 2-(1H-benzo[d][1,2,3]triazole-1-yl)acetate.

Benzotriazole (2.3 g) was dissolved in dry acetone (60 ml) and then anhydrous potassium carbonate (5g) and ethyl chloro acetate (2.15 ml) was added. The contents of the flask were mixed magnetically at 45°C, and then refluxed for 8 hours. The resulting hot solution after filtration was poured into a beaker containing crushed ice. The separated solid was filtered and then recrystallized from ethanol.

Step:3 Synthesis of 2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-carbamoyl[R1-Substituted].

Ethyl2-(1H-benzo[d][1,2,3]triazole-1-yl)acetate (4.1 g) in ethanol, Urea/Thiourea/Guanidine (5.1g) was added. The solution was then refluxed for 5 hours and poured into cold water. The separated solid product was filtered and recrystallized from ethanol.

Step:4 Synthesis of final derivatives(K1,K2,K3,K4) [R2-Substituted].

The equimolar amount of compound step-3 and substituted aldehyde was mixed with 10 ml ethanol. Add 2-3 drops of GAA and Refluxed for five hrs. The resulting mixture was chilled to 4°C. Schiff base product was formed. The product was derided and recrystallized with ethanol.

Derivative K1, m.p. of 90°C. IR (KBr) ν, cm^{-1}: 1706 cm^{-1} (C=O), 3327 cm^{-1} (N-H), 1282 cm^{-1} (C-N), 2968 cm^{-1} (C-H), 1621 cm^{-1} (C=N), 730 cm^{-1} (C-Cl). Mass (Varian 1200 L,ESI,MS)341.11.C^{13}NMR(400MHz,$CDCl_3$)d,ppm:136.38,119.50,110.29,145.07,132.64,131.52,130.35,128.41,126.36 ppm (Aromatic Carbon), 170.21,164.38 ppm (Amide Carbon), 60.7 ppm (Aliphatic Carbon), 163.52 ppm(Imine Carbon).

Derivative K2, m.p. of 80°C. IR (KBr) ν, cm^{-1}: 1740 cm^{-1} (C=O), 3374 cm^{-1} (N-H), 1304 cm^{-1} (C-N), 2921 cm^{-1} (C-H), 1580 cm^{-1} (C=N), 1370 cm^{-1} (N-O). Mass (Varian 1200 L,ESI,MS) 352.03.C^{13}NMR(400MHz,$CDCl_3$)d,ppm:145.07,132.64,119.50,110.29,139.38,124.36,127.35, 126.41ppm (Aromatic Carbon), 164.50, 170.21ppm (Amide Carbon), 60.7ppm (Aliphatic Carbon), 163.41ppm(Imine Carbon).

Derivative K3, m.p. of 75°C. IR (KBr) ν, cm^{-1}: 1725 cm^{-1} (C=O), 3396 cm^{-1} (N-H), 1295 cm^{-1} (C-N), 2925 cm^{-1} (C-H), 1643 cm^{-1} (C=N), 659 cm^{-1} (C-Cl). Mass (Varian 1200 L,ESI,MS) 340.16.C^{13}NMR(400MHz,$CDCl_3$)d,ppm:130.28,145.24,132.52,136.28,119.10,110.18,131.43, 128.45, 126.86ppm (Aromatic Carbon), 171.11 ppm (Amide Carbon), 61.8ppm (Aliphatic Carbon), 163.15 ppm(Imine Carbon).

Derivative K4, m.p. of 80°C. IR (KBr) ν, cm^{-1}: 1724 cm^{-1} (C=O), 3328 cm^{-1} (N-H), 1341 cm^{-1} (C-N), 2925 cm^{-1} (C-H), 1645 cm^{-1} (C=N), 658 cm^{-1} (C-Br). Mass (Varian 1200 L,ESI,MS) 385.09.C^{13}NMR(400MHz,$CDCl_3$)d,ppm:145.13,132.23,125.76,131.12,128.07,119.72,110.29, 126.21 ppm (Aromatic Carbon), 171.54 ppm (Amide Carbon), 61.2 ppm (Aliphatic Carbon), 163.29 ppm(Imine Carbon).

Activity study against P388 leukemia murine cells

An activity in-vitro anti-TB was analyzed by Almar blue assay, on the basis of colour observation and percentage inhibition with the help of rifampicin as a positive control (standard).

RESULTS AND DISCUSSION

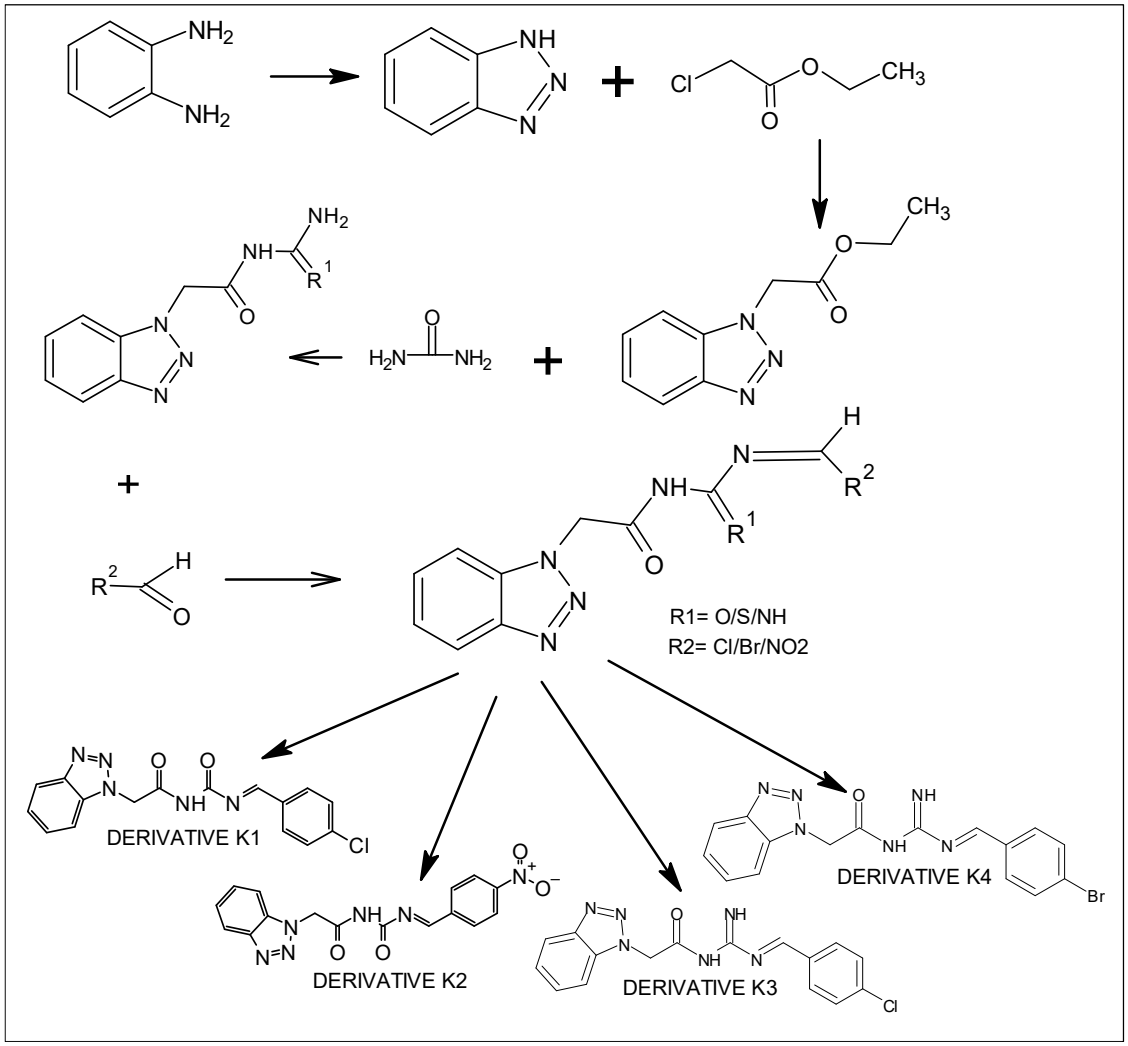


Figure 02: Synthesis pathway

The IR spectroscopy finger print area (500 cm-1 to 1450 cm-1) and functional group region (1450 cm-1 to 4000 cm-1) are effective ranges for confirming functional groups.

^{13}C NMR spectra are usually used as supporting information to confirm the structure of a compound. A method to precisely determine a compound's molecular mass is mass spectroscopy. Mass spectroscopy is the technique in which a compound under investigation is bombarded with a beam of molecule or ionic fragments of the original species. and then resulting assortment of charged particles is separated according to their masses.

Infrared spectroscopy:

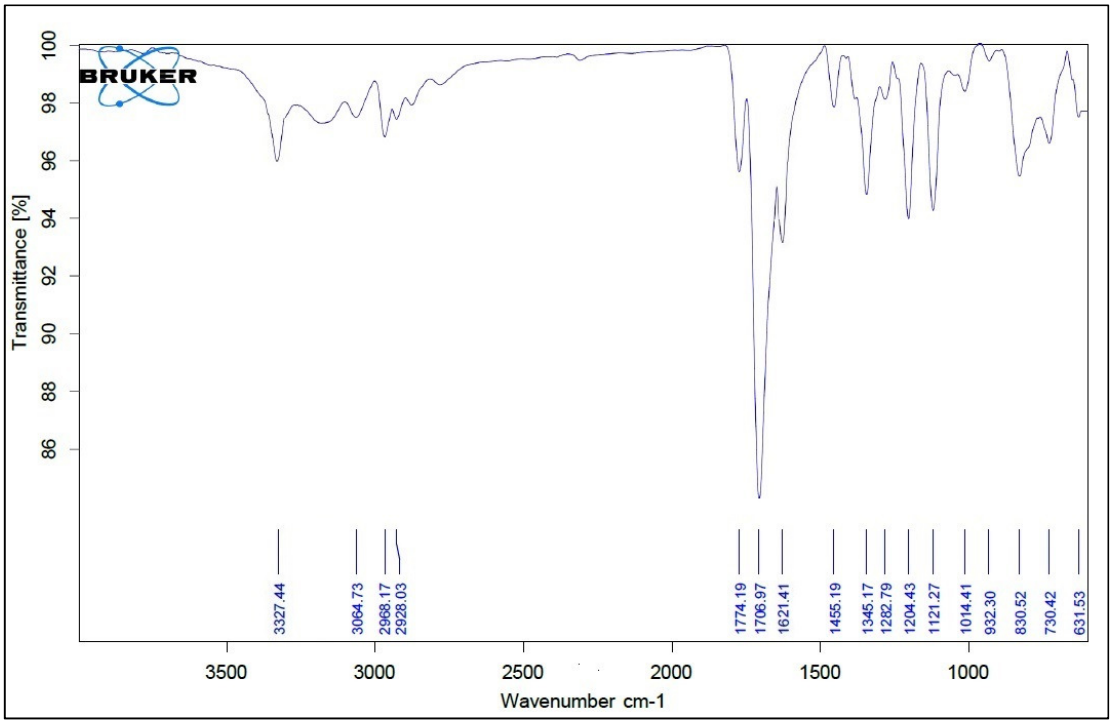


Figure 03: IR spectra of compound K1

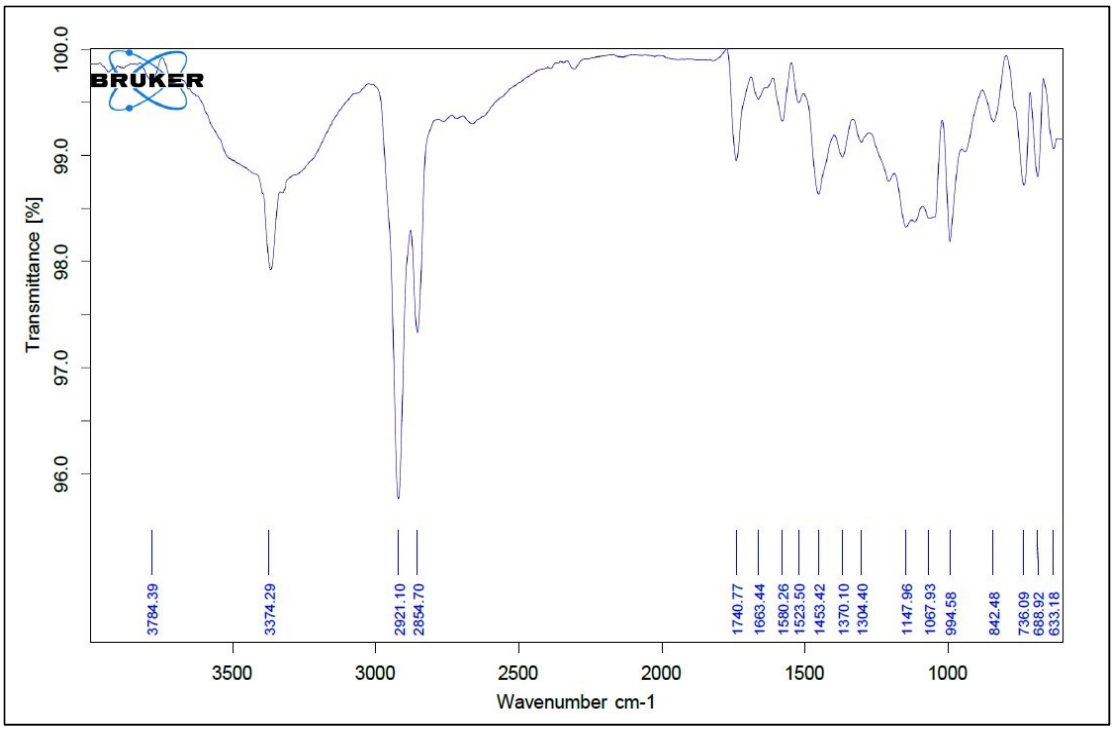


Figure 04: IR spectra of compound K2

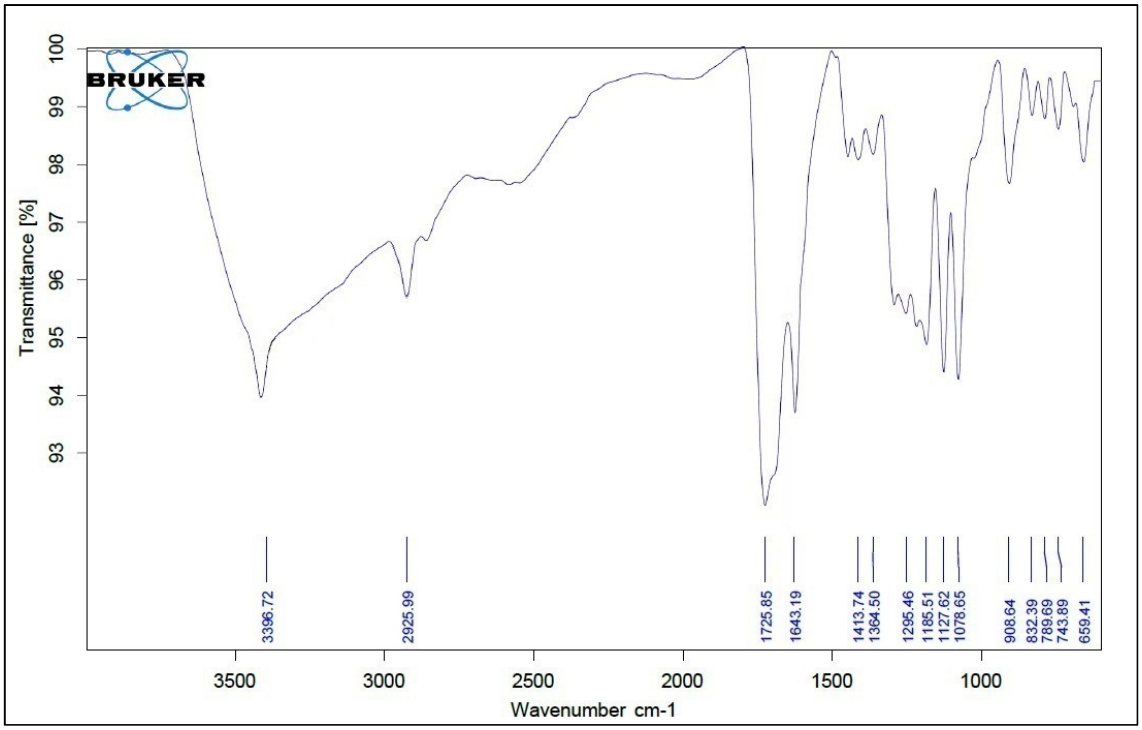


Figure 05: IR spectra of compound K3

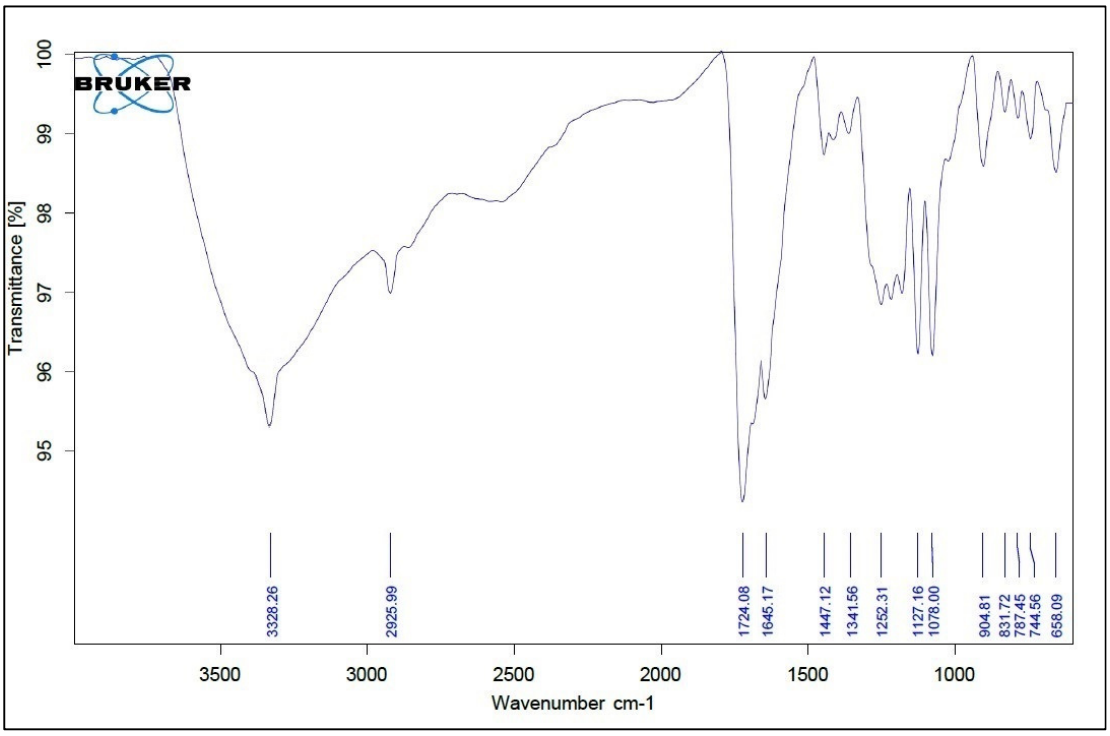


Figure 06: IR spectra of compound K4

MASS SPECTROSCOPY:

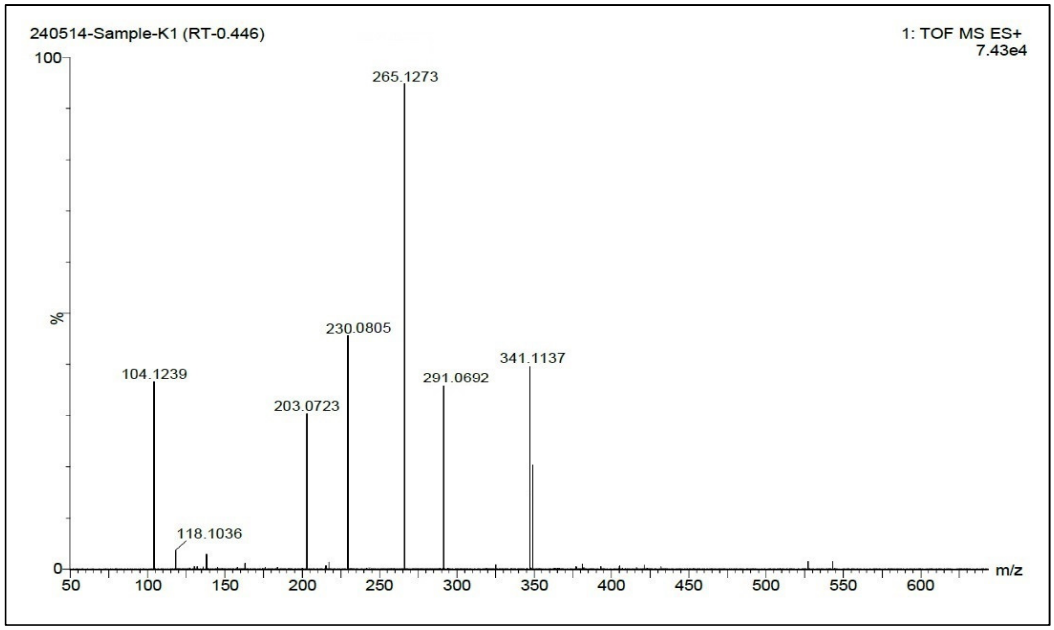


Figure 07: Mass spectra of compound K1

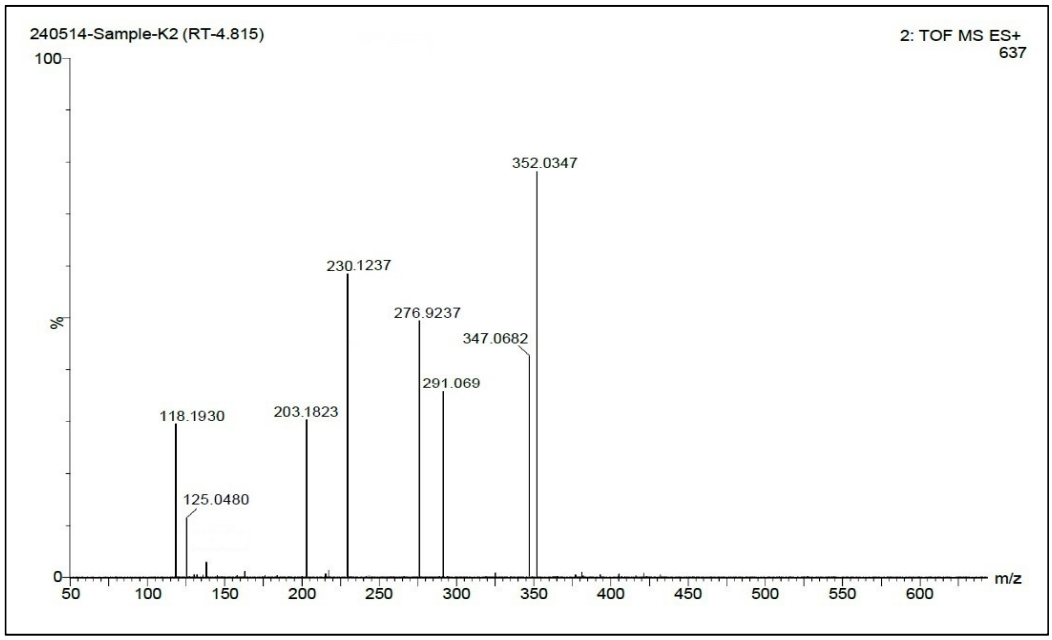


Figure 08: Mass spectra of compound K2

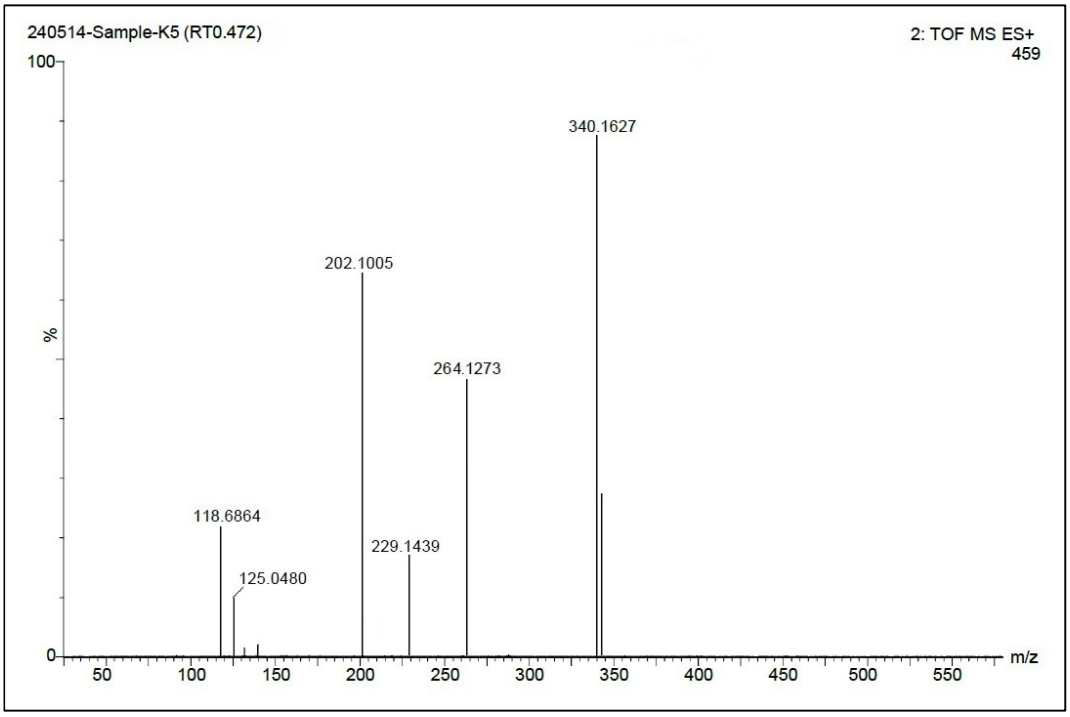


Figure 09: Mass spectra of compound K5

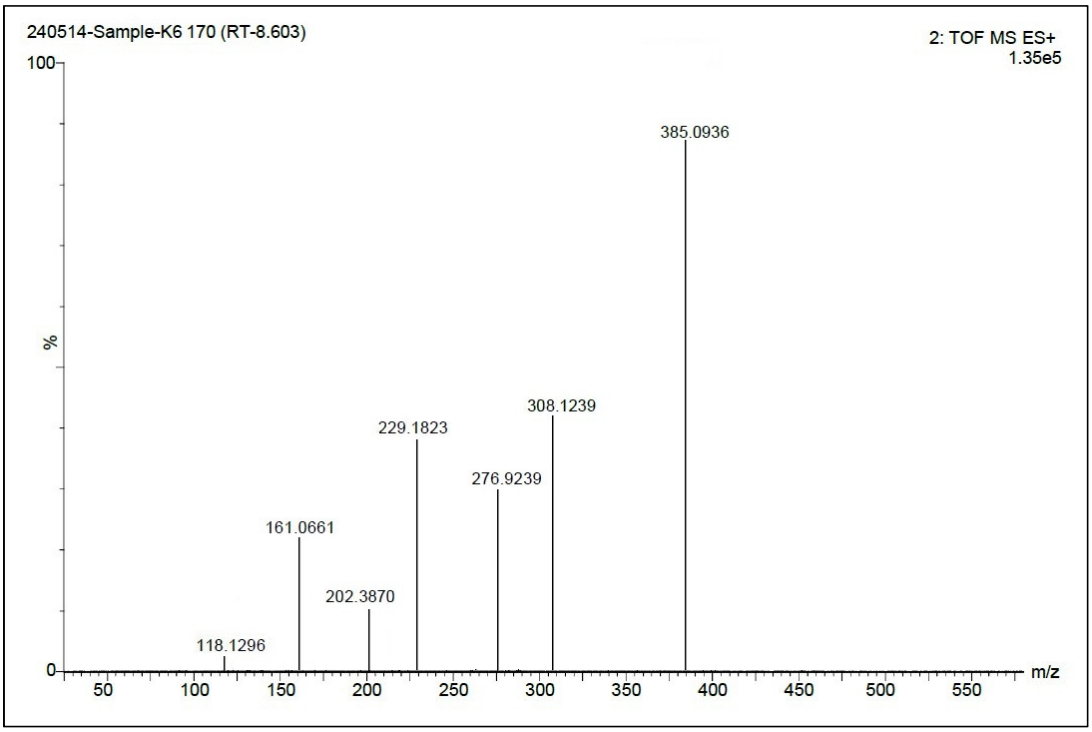


Figure 10: Mass spectra of compound K6

Anti-TB activity of the sample K1, K2, K5, K6.

Table 1. The in-vitro anti-TB activity values of synthesized compounds

Sr No	Sample Code	Concentration(µg/ml)	Absorbance at 600nm			Mean	% Of Growth Inhibition
			Test 1	Test 2	Test 3		
1	Growth C		1.603	1.603	1.603	1.603	-
2	Standard	7.8	1.593	1.594	1.594	NE	NE
	(Rifampicin)	15.6	1.538	1.538	1.538	NE	NE
		31.2	1.421	1.421	1.421	1.421	11.35%
		62.5	1.397	1.398	1.397	1.397	12.85%
		125	0.834	0.834	0.834	0.834	47.97%
		250	0.611	0.611	0.611	0.611	61.88%
		500	0.531	0.531	0.531	0.531	66.87%
		1000	0.422	0.422	0.422	0.422	73.67%
3	**K1**	7.8	NE	NE	NE	NE	NE
		15.6	NE	NE	NE	NE	NE
		31.2	NE	NE	NE	NE	NE
		62.5	1.541	1.542	1.542	1.541	3.86%
		125	1.289	1.262	1.257	1.269	20.83%

		250	1.032	1.025	1.025	1.027	35.93%
		500	0.956	0.956	0.956	0.956	40.36%
		1000	0.732	0.732	0.732	0.732	54.33%
4	**K2**	7.8	1.474	1.474	1.474	1.474	8.04
		15.6	1.460	1.460	1.460	1.460	8.92
		31.2	1.420	1.420	1.420	1.420	11.41
		62.5	1.235	1.235	1.235	1.235	22.95
		125	1.574	1.574	1.574	1.574	1.80
		250	0.943	0.943	0.943	0.943	41.17
		500	0.730	0.730	0.730	0.730	54.46
		1000	0.648	0.648	0.648	0.648	59.57
5	**K3**	7.8	1.485	1.485	1.485	1.485	7.36
		15.6	1.470	1.470	1.470	1.470	8.29
		31.2	1.436	1.436	1.436	1.436	10.41
		62.5	1.231	1.231	1.231	1.231	23.20
		125	1.579	1.579	1.579	1.579	1.49
		250	0.940	0.940	0.940	0.940	41.35
		500	0.730	0.730	0.730	0.730	54.46
		1000	0.642	0.642	0.642	0.642	59.95

6	**K4**	7.8	1.480	1.480	1.480	1.480	7.67
		15.6	1.475	1.475	1.475	1.475	7.98
		31.2	1.315	1.315	1.315	1.315	17.96
		62.5	1.105	1.105	1.105	1.105	31.06
		125	1.554	1.554	1.554	1.554	3.05
		250	0.942	0.942	0.942	0.942	41.23
		500	0.725	0.725	0.725	0.725	54.77
		1000	0.639	0.639	0.639	0.639	60.13

Graph representing percent inhibition of Compound:

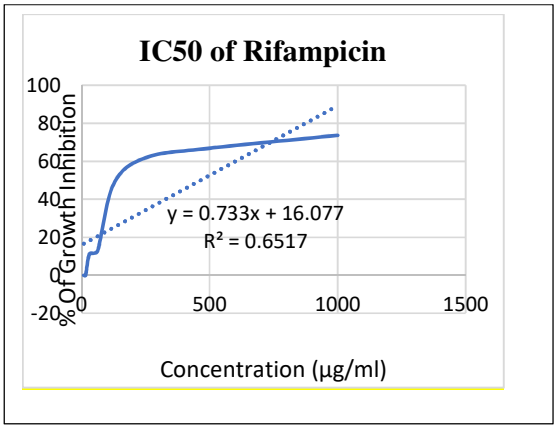


Figure 11: Percent inhibition of Standard Rifampicin

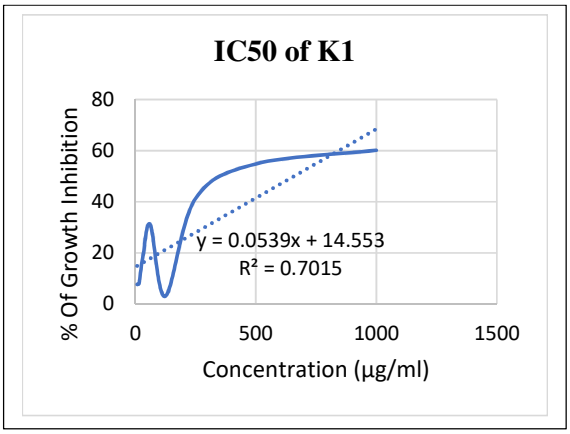


Figure 12: Percent inhibition of Compound K1.

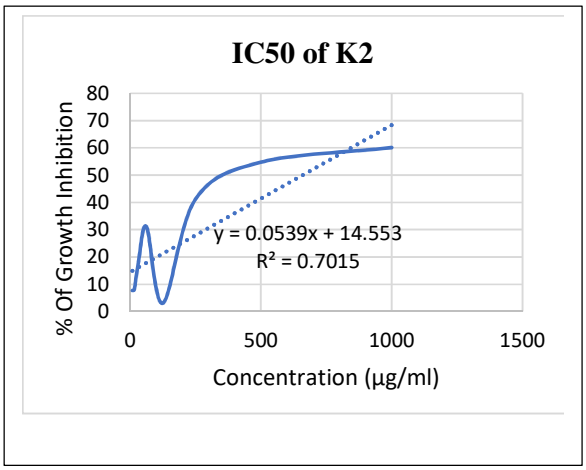


Figure 13: Percent inhibition of Compound K2.

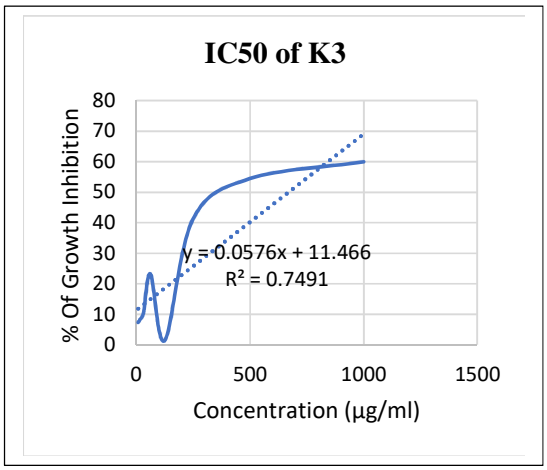


Figure 14: Percent inhibition of Compound K3.

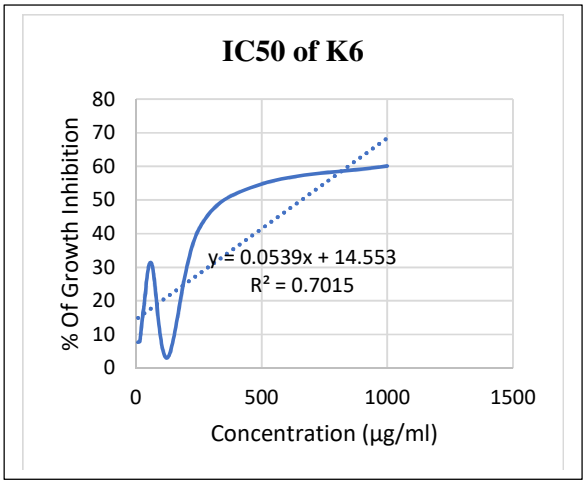


Figure 15: Percent inhibition of Compound K4.

CONCLUSION

A heterocyclic lead molecule with a variety of pharmacological properties was created and produced. The innovative, simple Schiff base synthesis described in this work yields benzotriazole analogs with a yield ranging from 70% to 84. The melting point is utilized to validate the preliminary analysis, and TLC is used to identify the completion of the reaction for synthesized lead compounds. The evaluation of the synthetic compounds' structures was ascertained by a variety of spectroscopic methods, including ^{13}C NMR, MASS, and IR. pharmacological analysis with the Alamar Blue Microplate Assay The outcomes showed that every synthetic chemical had strong antitubercular activity. A prominent infectious illness that has a detrimental impact on both global health and the global economy is tuberculosis (TB). The obtained results demonstrated that all the synthesized compounds have good anti-TB activity. Before the COVID-19 pandemic, tuberculosis (TB) was the most common infectious disease-related cause of death worldwide. Therefore, it is necessary to find or create novel anti-tubercular chemicals that are both strong and less harmful. Several novel benzotriazole compounds were created and synthesized, and MASS, 13C NMR, and IR were used to evaluate their structural integrity. The Microplate Alamar Blue Assay for Antitubercular Activity was used to determine pharmacological or biological activity. By comparison with the reference medicine, the anti-TB activity of sample codes K1, K2, K5, and K6 is good.

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