The Development, And Synthesis of Some Derivatives of Triazole Schiff's Base as Feasible Antitubercular Drugs

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Abstract-Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), continues to be a major cause of death worldwide, especially in developing nations. To increase patient compliance and reduce treatment durations, new anti-TB medications that are efficient, reasonably priced, compatible with HIV treatment, and active against drug-resistant strains are desperately needed. The design and synthesis of TLM analogues as possible anti-TB medicines was the main goal of this investigation. Twelve triazole analogues were created in order to overcome the difficulties in creating chiral TLM analogues. These compounds were thoroughly described using a variety of spectroscopic methods.

Keywords: *Mycobacterium tuberculosis*, Thiolactomycin analogues, Anti-TB drugs, Triazole analogues, HIV-compatible treatment, Spectroscopic characterization, Chiral synthesis.

INTRODUCTION

The airborne infectious disease known as tuberculosis (TB), which is caused by the Mycobacterium tuberculosis, is preventive and curable, but it can also be dangerous if left undetected [1]. It is estimated that two billion individuals, or one-third of the world's population, are infected with M. tuberculosis, and one in ten of them will develop active TB at some point in their lives [2–4]. Individuals who have contracted HIV are significantly more vulnerable. The development of strains of Mycobacterium tuberculosis that are resistant to many drugs has complicated efforts to control the illness. The creation of new medications and the discovery of new therapeutic targets are necessary for the disease's effective control [5]. M. tuberculosis's cellular envelope is composed of a polypeptide layer, free lipids, and a peptidoglycan layer.

Apart from the cellular envelope, the primary components of the mycobacterial cell wall are mycolic acids, a complex structure of fatty acids [6] that may serve as an effective lipophilic barrier to prevent the diffusion of certain known antibiotics through the cell wall. The importance of mycolic acids for the growth of mycobacteria and the enzymes involved in their metabolism make them interesting targets for the development of new anti-mycobacterial drugs [5].

One crucial enzyme in the FAS-II system is mycobacterial β-ketoacyl ACP synthase I. Through a ping-pong mechanism, the enzyme catalyzes the condensation of malonyl-AcpM with the expanding acyl chain [7, 8]. Since conditional depletion of KasA causes cell lysis, it has been demonstrated that KasA is necessary in Mycobacteria. These findings highlight the significance of KasA in Mycobacteria and imply that this enzyme could be a desirable target for the creation of new medications to treat M. tuberculosis [8–13].

The unique thiolactone antibiotic (R)-(+)-Thiolactomycin (TLM, Fig. 1) was first isolated from a soil Nocardia species. It can inhibit the mycobacterial β-ketoacyl synthases KasA and KasB, but is particularly sensitive to KasA. TLM exhibits strong in vivo efficacy against a variety of harmful bacteria, such as M. tuberculosis and both Gram-positive and Gram-negative bacteria [7, 8]. TLM can bind to both the free enzyme and the acylated form of KasA, according to recent kinetic studies. Additionally, TLM has a slow rate of binding kinetics throughout the inhibitory reaction and preferentially binds to the acyl-enzyme intermediate, which is crucial for the compound's in vivo efficacy [12].

Several studies have synthesized and tested TLM analogues, which contain aliphatic and other substituents connected to the 5-position of a thiolactone intermediate. The activity of these analogues was markedly increased in comparison to the mycolate synthesis. Ten carbon isoprenoid-based side-chains produced good results [5]. However, the utilization of substituents with known chemical

stability and anticipated conformation may be helpful in obtaining possible medications and in comprehending their mode of action. TLM has been extensively studied over the past 25 years as a great lead molecule for TB medication development because of its ability to inhibit the fatty acid biosynthesis with enzymes KasA and KasB. However, the chirality of the C5 carbon atom of the thiolactone ring is the primary drawback of this chemical that restricts its application as a TB medication [14, 5, 8]. In contemporary drug discovery, single enantiomers are typically used to reduce the possibility of unfavourable pharmacokinetics and pharmacodynamics as well as unintended side effects when using a racemic mixture of any a chemical [5]. An investigation of the literature revealed a small number of achiral rings that have demonstrated intriguing properties as FabH inhibitors and that might be regarded as isosteric alternatives to the chiral thiolactone ring of TLM. Antimycobacterial action was observed in 1,2-dithiol-3-thione (2) and 1,2-dithiol-3-one (3) derivatives (Fig. 1), which were synthesized and biologically investigated as achiral analogues of TLM [15]. Similar 1,2,4-triazole derivatives have recently been synthesized and biologically assessed as anti-mycobacterium tuberculosis agents by numerous research groups. They discovered that the cytotoxicity and in vivo pharmacokinetic parameters have an acceptable safety index, in vivo stability, and bio-availability [16–18].

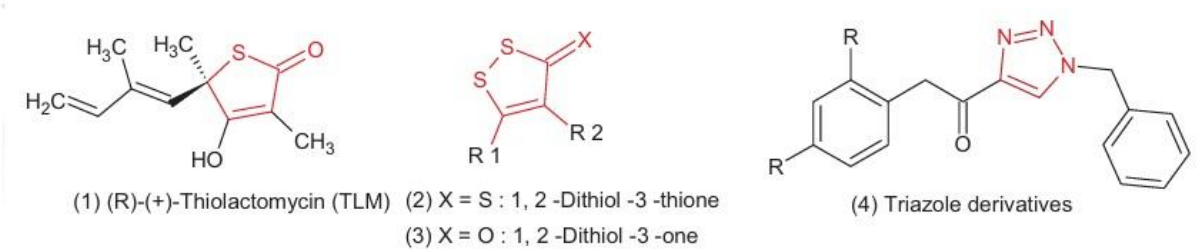


Figure:1

METHODS

1. Materials and Solvents

All of the chemical solvents and ingredients used in the synthesis of Schiff bases were of the highest purity and were acquired from Sigma Aldrich and Fluka Analytical without the need for additional purification. To achieve the necessary drug concentrations, standard isoniazid was dissolved in sterile millipore water after being acquired from Sigma-Aldrich.

2. Instruments

The compounds were synthesized using a microwave closed system. An Electrothermal SMP30 melting point device was used to measure melting points using open capillary tubes. The Varian FT-IR spectrophotometer 660 was used to record the infrared spectra of the produced compounds in the 4000–400 cm^{-1} range. Additionally, the UV spectrophotometer was used to record the UV-visible spectra in a 1 cm quartz cuvette. The NMR Spectrometer was used to determine the proton and carbon NMR spectra in DMSO, with tetramethylsilane serving as an internal standard.

3. Procedure for the Synthesis of Schiff's Base Derivatives Synthesis [19, 20]

The literature describes the microwave-synthesis method used to create Schiff's base derivatives [19, 20]. Equimolar amounts of the starting components (3-amino-1,2,4 triazole and aldehyde) should be weighed, combined, and placed in tiny vials before being microwaved. The microwave's power and time were changed, starting at 300 watts and one minute. TLC was used to track the reaction's development over time. Below are the ideal power and time requirements for each chemical produced using this process. After the proper workup, pure materials were obtained.

3.1 3-[(E)-(4H-1,2,4-Triazol-3-ylimino) Methyl] Naphthalen-2-ol (1)

Compound 1 was created in accordance with standard protocol by reacting 2-hydroxynaphthalene-1-carbaldehyde (3) (1.62 g, 11.89 mmol) with 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) at 350 Watts for two minutes. The reaction was seen with UV light at 254 nm and examined by TLC with hexane and ethyl acetate (6:4) as a mobile phase. Three recrystallization

processes of the crude product from ethanol produced pure crystals of component 1. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 97%. M. P = 270.6 – 270.8 ºC. FT-IR (cm-1): 1530 cm^{-1} (C=N), 2858 (C-H aromatic), 3286 (N-H str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.46 (s, 1H, HC=N), 8.22 - 7.15 (m, 6H, Ar-H), 6.44 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 157 (HC=N), 155 (C=C*-OH), 152 (N-CH=N), 149 ((N)2 -C=N), 140.2(1C, Ar), 126.15(1C, Ar), 124.05 (2C, Ar), 120.08 (2C, Ar), 114.90 (1C, Ar), 111.48 (2C, Ar).

3.2 N, N-Dimethyl-4-[(E)-(4H-1,2,4-triazol-3-ylimino) methyl] Aniline (2)

Compound 2 was created in accordance with standard protocol by reacting 4-dimethylaminobezaldehyde (0.887 g, 11.89 mmol) with 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) at 400 Watts for two minutes. Hexane and ethyl acetate (7:3) was used as a mobile phase in the TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used for detection. The crude result from ethanol underwent three recrystallization procedures to yield the pure crystals of compound 2.

Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 94%. M. P = 201.2 201.4 ºC. FT-IR (cm^{-1}): 1538 cm^{-1} (C=N), 2890 (C-H aromatic), 3094 (N-H str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 9.45 (s, 1H, HC=N), 7.65 - 6.88 (dd, 4H, Ar-H), 6.14 (s, 1H, N-CH=N), 3.18 (s, 6H, (CH_3)2-N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 156 (HC=N), 155 (N-CH=N), 152 ((N)2 -C=N), 125.04 (2C, Ar), 113.48 (2C, Ar), 42.23 (2C ,(CH_3)2-N).

3.3 1-(4-Nitrophenyl)-N-(4H-1,2,4-triazol-3-yl) Methanimine (3)

Compound 3 was created by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 4-nitrobenzaldehyde (0.89 g, 11.89 mmol) at 450 Watts for three minutes, in accordance with standard technique. UV light at a wavelength of 254 nm was used to identify the reaction after it was examined by TLC with hexane and ethyl acetate (8:2) as a mobile phase. Three recrystallization steps of the crude product from ethanol resulted in three pure crystals. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 97%. M. P = 266.7 - 268 ºC. FT-IR (cm^{-1}): 1514 cm^{-1} (C=N, str), 2918 (C-H aromatic, str), 3108 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 9.88 (s, 1H, HC=N), 8.97 - 8.44 (dd, 4H, Ar-H), 6.35 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 165.38 (HC=N), 155.88 (N-CH=N), 151.32 ($(N)_2$ -C=N), 154.72 (1C, Ar), 147.04 (1C, Ar), 128.63 (2C, Ar), 125.54 (2C, Ar).

3.4 2-(((4H-1,2,4-Triazol-3-yl)Imino) Methyl) Phenol (4)

Following the standard protocol, Compound 4 was created by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 2-hydroxybenzaldehyde (1.45 g, 11.89 mmol) for two minutes at 450 Watts. Hexane and ethyl acetate (5:5) was used as a mobile phase in the TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used to detect it. Three recrystallization steps of the crude product from ethanol resulted in four pure crystals. Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 96%. M. P = 262 .6 – 263.4 ºC. FT-IR (cm^{-1}): 1514 cm^{-1} (C=N), 2921 (C-H aromatic), 3196 (N-H str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.74 (s, 1H, HC=N), 7.84 - 7.11 (m, 4H, Ar-H), 6.22 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 158.62 (HC=N), 162.74 (C=C*-OH), 154.29 (N-CH=N), 151.60 ((N)2 -C=N), 134.14(2C, Ar), 122.11(2C, Ar), 116.05 (1C, Ar).

3.5 3-(((4H-1,2,4-Triazol-3-yl)Imino) Methyl) Benzene-1,2-diol (5)

Compound 5 was created by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 2,3-dihydroxybenzaldehyde (1.64 g, 11.89 mmol) at 400 Watts for two minutes, in accordance with the standard approach. UV light at a wavelength of 254 nm was used to identify the reaction after it was examined by TLC with hexane and ethyl acetate (7:3) as a mobile phase. Three recrystallization processes of the crude product from ethylacetate produced five pure crystals. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 93%. M. P = 281 .8 – 282.3 ºC. FT IR (cm^{-1}): 1620 cm^{-1} (C=N), 2874 (C-H aromatic), 3287 (N-H str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.97 (s, 1H, HC=N), 7.55 - 7.12 (m, 3H, Ar-H), 6.54 (s, 1H, N-CH=N), 3.26 (s, 2H, OH). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 159.77 (HC=N), 153.64 (C=C*-OH), 153.55 (N-CH=N), 150.16 ($(N)_2$ -

C=N), 148.52 (C=C*-OH), 128.78(1C, Ar), 128.43 (1C, Ar), 115.97 (2C, Ar).

3.6 2-Ethoxy-4-[(E)-(4H-1,2,4-Triazol-3-Ylimino) Methyl] phenol (6)

Compound 6 was developed by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 4-hydroxy-3-methoxybenzaldehyde (0.80 g, 11.89 mmol) at 350 Watts for two minutes, in accordance with the standard technique. Hexane and ethyl acetate (8:2) was used as a mobile phase in the TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used to detect it. Three recrystallization procedures of the crude product from ethanol produced the six pure crystals. Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 96%. M. P = 151.4 – 151.8 ºC. FT-IR (cm^{-1}): 1514 cm^{-1} (C=N, str), 2643 (C-H aromatic, str), 2982 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.56 (s, 1H, HC=N), 7.82 - 6.54 (m, 3H, Ar-H), 6.43 (s, 1H, N-CH=N), 4.17 (q, 2H, CH_2), 1.15 (t, 3H, CH_3). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 162.13 (HC=N), 152.89 (N-CH=N), 150.67 ((N)2 -C=N), 150.14 (1C, Ar), 148.05 (1C, Ar), 134.52 (1C, Ar), 126.02 (1C, Ar), 116.35 (1C, Ar), 111.46 (1C, Ar), 65.73 (1C, CH_2), 17.55 (1C, CH_3).

3.7 1-Phenyl-N-(4H-1,2,4-triazol-3-yl) Methanimine (7)

The typical approach for creating Compound 7 was reacting benzaldehyde (0.63 g, 11.89 mmol) with 4H-1, 2, 4-triazol-3-amine (0.5 g, 11.89 mmol) at 350 watts for two minutes. Using hexane and ethyl acetate (7:3) as a mobile phase, TLC was used to monitor the reaction. UV light at a wavelength of 254 nm was then used to detect it. Three recrystallization steps of the crude product from ethanol resulted in seven pure crystals. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 96%. M. P = 196.5 – 169.6 ºC. FT-IR (cm^{-1}): 1592 cm^{-1} (C=N, str), 3048 (C-H aromatic, str), 3245 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.26 (s, 1H, HC=N), 7.94 - 7.62 (m, 5H, Ar-H), 6.54 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 159.37 (HC=N), 154.83 (N-CH=N), 150.92 ((N)2 -C=N), 137.57 (1C, Ar), 132.52 (1C, Ar), 130.44 (2C, Ar), 127.36 (2C, Ar)

3.8 N-(Thiophen-2-Ylmethylene)-4H-1,2,4-Triazol-3-Amine (8)

Following the standard protocol, Compound 8 was created by reacting 0.5 g of 4H-1,2,4-triazol-3-amine with 1.33 g of thiophene-2-carbaldehyde at 350 Watts for three minutes. Hexane and ethyl acetate (8:2) was used as a mobile phase in TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used to detect it. Three recrystallization processes of the crude product from ethylacetate produced pure crystals of 8. Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 92%. M. P = 166.1 – 167.6 ºC. FT IR (cm^{-1}): 1675 cm^{-1} (C=N, str), 3138 (C-H aromatic, str), 3295 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 7.76 (s, 1H, HC=N), 7.47 - 7.32 (m, 3H, Ar-H), 6.28 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 156.65 (HC=N), 154.15 (N-CH=N), 150.67 ((N)2 -C=N), 139.18 (1C, Ar), 132.44 (1C, Ar), 128.35 (1C, Ar), 126.60 (1C, Ar).

3.9 1-(4-Chlorophenyl)-N-(4H-1,2,4-Triazol-3-yl) Methanimine (9)

Compound 9 was created by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 4-chlorobenzaldehyde (0.83 g, 11.89 mmol) at 350 Watts for one minute, in accordance with standard protocol. Using hexane and ethyl acetate (6:4) as a mobile phase, TLC was used to monitor the reaction. UV light with a wavelength of 254 nm was then used to detect it. Three recrystallization steps of the crude product from ethanol resulted in nine pure crystals. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 96%. M. P = 202.8 – 202.1 ºC. FT-IR (cm^{-1}): 1570 cm^{-1} (C=N, str), 2854 (C-H aromatic, str), 3146 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.75 (s, 1H, HC=N), 7.72 - 7.53 (dd, 4H, Ar-H), 6.28 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 161.34 (HC=N), 154.75 (N-CH=N), 153.20 ((N)2 -C=N), 139.45 (1C, Ar), 133.03 (1C, Ar), 129.40 (2C, Ar), 127.66 (2C, Ar).

3.10N-((E)-3-Phenylallylidene)-4H-1,2,4-Triazol-3-Amine (10)

The general approach was followed to create Compound 10 by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with cinnamaldehyde (1.56 g, 11.89 mmol) at 600 Watts for 2.5 minutes. Hexane and ethyl acetate (5:5) was used as a mobile phase in

the TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used to detect it. Three recrystallization processes of the crude product from ethanol produced ten pure crystals. Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 93%. M. P = 157.1 – 158.0 ºC. FT-IR (cm^{-1}): 1630 cm^{-1} (C=N, str), 3267 (C-H aromatic, str), 3348 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 7.76 (s, 1H, HC=N), 7.52 - 7.17 (m, 5H, Ar-H), 7.16 – 6.36 (m, 2H, CH=CH, olefinic) 6.56 (s, 1H, N-CH=N). 13C NMR (400 MHz, DMSO-d6): δ [ppm] 163.12 (HC=N), 152.45 (N-CH=N), 150.92 ($(N)_2$ -C=N), 138.18 (1C, Ar), 135.30 (1C, Ar-C*H=CH) 130.28 (2C, Ar), 129.64 (2C, Ar), 125.64 (1C, Ar), 117.70 (1C, Ar-CH=C*H).

3.11N-(Furan-2-ylmethylene)-4H-1,2,4-Triazol-3-Amine (11)

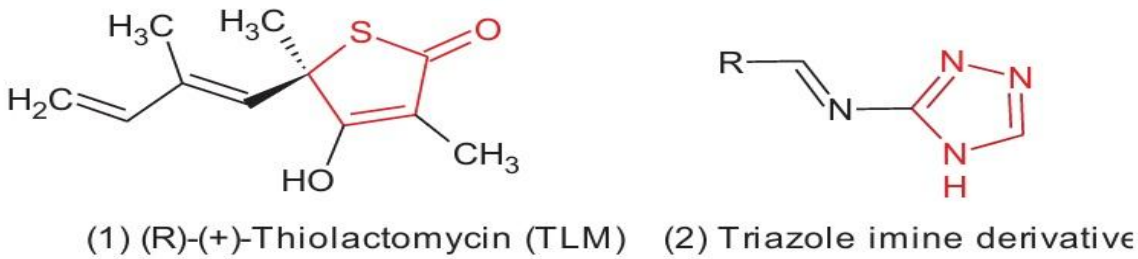
Following the standard protocol, Compound 11 was created by reacting furan-2-carbaldehyde (0.98 g, 11.89 mmol) with 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) at 450 Watts for 1.5 minutes. UV light at a wavelength of 254 nm was used to identify the reaction after it was tracked by TLC with hexane and ethyl acetate (6:4) as a mobile phase. Three recrystallization processes of the crude product from ethanol produced the pure crystals of 11. The same mobile phase was used in TLC to verify the purity of the obtained crystals. (Y = 91%. M. P = 163.8 – 164.6 ºC. FT-IR (cm^{-1}): 1610 cm^{-1} (C=N, str), 2758 (C-H aromatic, str), 3018 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 8.40 (s, 1H, HC=N), 7.42 - 7.00 (m, 3H, Ar-H), 6.74 (s, 1H, N-CH=N). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 156.15 (N-CH=N), 151.30 ($(N)_2$ -C=N), 149.89 (HC=N), 147.26 (1C, Ar), 130.17 (1C, Ar), 119.55 (1C, Ar), 112.98 (1C, Ar).

3.121-(4-Methoxyphenyl)-N-(4H-1, 2, 4-triazol-3-yl) Methanimine (12)

Compound 12 was created by reacting 4H-1,2,4-triazol-3-amine (0.5 g, 11.89 mmol) with 4-methoxybenzaldehyde (0.80 g, 11.89 mmol) at 350 Watts for two minutes, in accordance with standard technique. Hexane and ethyl acetate (8:2) was used as a mobile phase in the TLC to monitor the reaction, and UV light with a wavelength of 254 nm was used to detect it. By recrystallizing the crude product from ethanol in three processes, twelve pure crystals were produced. Using the same mobile phase, TLC verified the purity of the obtained crystals. (Y = 98%. M. P = 171.8 - 174 ºC. FT-IR (cm^{-1}): 1520 cm^{-1} (C=N, str), 2918 (C-H aromatic, str), 3145 (N-H, str). 1H-NMR (400 MHz, DMSO-d6): δ [ppm] 9.42 (s, 1H, HC=N), 7.52 - 7.22 (dd, 4H, Ar-H), 6.20 (s, 1H, N-CH=N), 4.10 (s, 3H, CH_3). 13C-NMR (400 MHz, DMSO-d6): δ [ppm] 165.40 (1C, Ar), 163.88 (HC=N), 154.75 (N-CH=N), 150.46 ($(N)_2$ -C=N), 135.60 (2C, Ar), 129.06 (1C, Ar), 118.96 (2C, Ar), 60.85 (1C, CH_3).

RESULTS AND DISCUSSION

To produce the test compound, the thiolactone ring was isosterically substituted in the TLM molecule, which had a smaller size and a ring shape that was simpler to synthesis. Additionally, this study has examined and chosen the triazole ring, which is the primary component of many medications. We decide to synthesize triazole derivatives with the imine (Schiff's base) functional group based on the ease of use and adaptability of the synthetic pathway. According to recent studies, imine functionality helps isoniazid and p-amino salicylic acid become more potent and less hazardous [21, 22]. Furthermore, Fig. (2) shows the structural similarities between TLM and the triazole imine derivatives. These changes may anticipate to exhibit comparable behaviour at the target enzyme's active region, which we can investigate using molecular modelling in future.



(1) (R)-(+)-Thiolactomycin (TLM) (2) Triazole imine derivative

Figure:2

CONCLUSION

A few achiral TLM analogues were designed and synthesized in order to substitute the chiral thiolactone ring of TLM. The triazole ring scaffold, which is therapeutically significant, was selected to accomplish the task. The availability of the chemicals and reagents needed for our synthetic technique, as well as their structural resemblance to the lead TLM, led to this approach.

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