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Antimicrobial Evaluation of 3-(4-Isobutyl 1 –Piperazinyl) Rifamycin, for the Treatment of Mycobacterium Tuberculosis

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Background: Mycobacterium tuberculosis (M. tb), the primary cause of tuberculosis, is a recalcitrant disease that is widespread across the world, formerly impacting almost a quarter of the global population.[1] In order to prevent the bacteria from spreading further and developing resistant strains, early detection and effective treatment of TB is crucial [2].Immunological, radiographic, microscopical, bacterial culture, and clinical approaches are among the frequently used diagnostic techniques. The primary function of immunological tests, such as the QuantiFERON-TB Gold (QFT) and the Tuberculin skin test (Mantoux test), aims to screen for and check out infections caused by tuberculosis [2].Current clinical trials are exploring new combinations of TB medications in patients with drug-susceptible pulmonary TB so as to facilitate rapidly evaluation of new TB drugs.[3].Four antibiotics—isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB)—that were all discovered around 60 years ago are now recommended for the treatment of DS-TB [3].
Methodology: 3-(4-ISOBUTYL-1-PIPERAZINYL) RIFAMYCIN, a chemical having the molecular formula C45H63N3O12 and a molecular weight of 838.0 g/mole, is studied in this work for its antibacterial Peculiarities. The compound was synthesized and tested against Mycobacterium tuberculosis using the HEXA DISC DIFFUSION METHOD. The pathogen was put into sterilized agar plates, and various quantities of the chemical were administered. The inhibitory zones' thicknesses around the wells have been determined and tested against a positive control.[4]

Keywords: Antitubercular application, 3-(4-Isobuty-1-piperazinyl) rifamycin, Tuberculin skin test (Mantoux test), Mycobacterium tuberculosis, QuantiFERON-TB Gold (QFT).

1. Introduction

Tuberculosis [TB] is a chronic bacterial infectious disease caused by mycobacterium TB. It remains a major health concern worldwide.[5]. Although the disease primarily effects the lungs referred to as pulmonary TB, It can also spread to other parts of the body (known as extra pulmonary TB [6]. Mycobacterium tuberculosis can lay latent for years and persist in

the body without any indication of illness, in which many people become asymptomatic carriers inactive TB [7]. Mortality due to TB is put at approximately 2 million annually. Approximately one-third of the world's population harboring tubercle bacilli in an asymptomatic latent state are at high risk of disease reactivation during their lifespan [8]. A major clinical problem in treating TB is that the number of drugs available is limited. This issue becomes considerably more severe in the treatment of MDR/XDR – TB. This worrying condition is due, in part, to an almost 50years long drought in anti-TB drug development. Overall, recent developments have not been sufficient and have not yet addressed the primary short comings of long, Toxic therapy and the rise of drug resistance. The WHO's recommendation's for patients infected with drug susceptible strains of TB have been set out in guidelines that were published in 2010 and updated in 2017 and 2022 [9] Rifamycin 1, an Ansamycin Antobiotic, was originally discovered from the metabolite of amycolatopsis rifamycinica in 1957 by an Italian pharmaceutical company gruppo lepetit SPA and demonstrates a significant antibacterial activity against gram positive bacteria and mycobacterium spp. [10] rifampicin 2 [11] Rifapentine 3 [12] an rifabutin 4 [13] are semisynthetic derivatives of rifamycin. Rifamycins, have been used as essential drugs for current TB treatment in combination therapy, as with isoniazid, for all treatment stages. These medications block bacterial DNA-Dependent RNA polymerase by binding to the site adjacent to the active center in RNA polymerase β subunit. [14,15] TB/HIV co-infection further exacerbates the problem. There are over 36.7 million HIV positive people worldwide; of the 1.1 million who die of HIV each year, 0.4 million [36%] suffered from TB/HIV coinfection. First line 1. Rifampin 2. isoniazid 3. Pyranizamide 4. Ethambutol. Second line 1. Kanamycin [discontinued used in USA] 2. Streptomycin 3. Capreomycin 4. Amikacin 5. livofloxacin 6. Moxifloxacin 7. Gatifloxacin 8. MDR-TB 9. Bedaquliline 10. Delamanid 11. Linezolid 12. Pretomanid anti TB drugs are generally well tolerated, but toxicities may occur in up to 80% of patients with TB [16] on of the most prevalent toxicities of anti TB drugs is hepatotoxicity related with isoniazid, rifamycin and pyrazinamide, [17] with occurs in 3% to 40% of TB patients [18-21].[22,23] impotently, neuropathy among HIV-infected patients may have alternative causes including HIV infection itself, particularly patients may have alternative causes including HIV itself, particularly with low CD 4 cell counts, and ART, especially nucleoside reverse transcriptase inhibitors [24]The high burden of toxicities among co infected patients with TB/HIV[22,23,25,26] can cause treatment interruption and related morbidity and mortality.[27] Isoniazid neuropathy is thought to be concentration-dependent and is more common in slow metabolizers of the drug.[28] the other common hepatotoxic agents are thought to have dose-related toxicity including rifampicin. historically, medicinal herbs were used to cure TB like smoke from burning the leaves of artemisia afra, the whole plant of myrothamnus flabellifolius, leaves of carica papaya, zanthoxylum capense (roots) and seeds of combretum hereroense, which was inhaled 3-4 times daily. Hot water leaf infusions of artemisia afra and lippia javanica into sink and patients inhaled the stream with a blanket wrapped over their head. Crushed citrus lemon, artemisia afra, and mentha sp. Leaves were burnt in a sheet wrapper 2 or 3 times daily. Such ayurvedic therapies are provided for a period ranging from two weeks to a month, susceptible to the Patients reaction to the formulation, as well as their tolerance to the medicine and its delivery [29,30]. Several diagnostic techniques are widely used, including immunological, radiographic, microscopical, bacterial, culture, and clinical procedures. Immunological tests, such as quantiferon-TB (qft) and tuberculin skin test

(Mantoux test), are primarily used to screen for and rule out tuberculosis infection [31] Sputum smear microscopy. Which uses Ziehl-neelsen strain to identify TB germs, has limitation such as low sensitivity an difficulty distinguishing M.Tuberculosis from other acid - fast bacilli[31]. Bactericidal medication immediately eliminates the majority of rapidly growing bacilli, reducing infectiousness and preventing disease progression. The sterilizing medications attack the dormant and semi-dormant bacillus populations, allowing cure and preventing relapse[32,33] the medication with the best sterilizing activity are those that can shorten the period of treatment. The two partner medication are no longer required bacteriological conversion [33,34].[35] thus, Tuberculosis is the leading cause of death among HIV- infected people. Combination therapy is the most often used chemotherapy for TB/HIV co-infection. However, there are certain issues with such combination therapy, such as overlapping side effects profiles of antituberculosis and antiretroviral medication, immunological reconstitution inflammatory syndrome, and drug drug interaction. For example between the antibiotic rifamycin and four kind of antiretroviral medicines pose significant challenges for these treatments. Rifamycin activate drug metabolizing enzymes such as cytochrome P450 enzymes, which are known to lower the serum half-life and concentration of antiretroviral medicines. The efficacy of rifamycin to simulate cytochrome P450 enzymes varies, with rifabutin, rifapentain, and rifapicin being the most potent examples. Thus, overcoming major drug-drug interactions is an important challenge for the treatment of TB/HIV co-infection [36,37,38]. The discovery of effective anti tuberculous agents such as streptomycin, isoniazide and para aminosalicylic acid in 1940s and early 1950s and their use in combinations regimens to prevent drug resistance arising the mycobacterium tuberculosis transform the lives of tuberculosis sufferers. The introduction of rifamycin class antibiotics in 1960s again revolutionized the treatment of tuberculosis and, as component of three or four drug regimen also including isoniazid pyrazinamide, it was crucial factor in reducing the duration of treatment from upto 18 to 6 months rising rates of cure at 6 months to more than 90%, and reducing relapse to less than 5%[32].

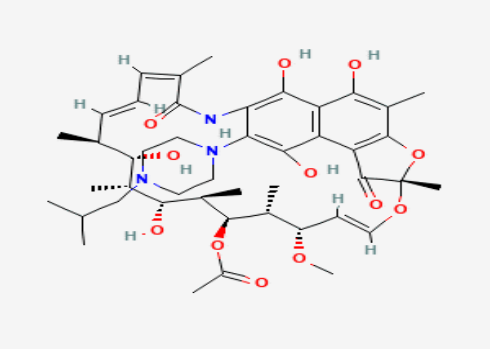
Compounds Used for the study [39]:

Compound Name: 3(-4-isobutyl-1-piperazinyl) rifamycin

Molecular formula: C45H63N3O12

Molecular Weight: 838.0g/mole

Chemical structure:



IUPAC Name :[(7S,9E,11S,12R,13S,14R,15R,16R,17S,18S,19E,21Z) 2,15,17,27,29-pentahydroxy-11-methoxy-3,7,12,14,16,18,22-heptamethyl-26-[4 (2-methylpropyl)piperazin-1-yl]-6,23-dioxo-8,30-dioxa-24 azatetracyclo[23.3.1.14,7.05,28]triaconta-1(28),2,4,9,19,21,25(29),26-octaen-13-yl] acetate

CAS: 57184-22-2

Gene: OPG125

Gene ID: 72551520

2. MATERIALS AND METHODS

Chemical Compound: [4]

The 3-(4-Isobutyl-1-piperazinyl) rifamycin chemical in solid powder form were procured from GMPL, Hyderabad.

Preparation of Antibiotic: 3-(4-Isobutyl-1-piperazinyl) rifamycin.[4]

For 45 minutes, POCl3 (15 ml) and the proper hydroxyl-1,8-naphthyridine (2) or (3) (10 mmole) were heated to 90 °C. Following cooling, concentrated NH4OH was used to alkalize the resultant solution, which was then treated with ice and water. The resulting solid (compound 4 or 5) was refined by crystallization after being rinsed with water.

Test organisms: [4]

Test organisms used for the screening of 3-(4-Isobutyl-1-piperazinyl) rifamycin against cell lines of Mycobacterium tuberculosis (MTB) bacteria such was procured from GMPL, Hyderabad.

Screening of extract of medicinal plant for antitubercular potency [40]

Considering The fruit of Acacia farnesiana, which is part of the flavanone and paraben class, is extracted in methanolic form and employed as an anti-TB drug because it has active pharmaceutical ingredients like galloyl glucopyranoside, which MABA observed to be efficient against multidrug-resistant M. tuberculosis G122 with a minimum inhibitory concentration (MIC) of 50µg/ml [6]. This plant was kept for its antitubercular properties. Based on the research on the microbial zone of inhibition, we have chosen a concentration of 80µg/ml of 3-(4-Isobutyl-1-piperazinyl)rifamycin.

ANTIBIOTIC SENSITIVITY TESTING USING DISC DIFFUSION METHOD.

Determination of anti-tubercular activity by Hexa Disc Diffusion Method [KIRBY-BAUER METHOD] [41].

Mueller-Hinton agar is used to cultivate the pathogen while different antimicrobial-impregnated filter paper discs are present. The presence or absence of growth around the discs is an indirect indicator of the compound's effectiveness to inhibit the organism. For routine testing of non-fastidious bacteria's susceptibility, MH agar is thought to be the ideal medium.

Preparation of inoculum: To ensure that the inoculum is distributed evenly, streak the swab

over the entire agar surface three times on a dried MH agar plate. Rotate the plate by around 60 degrees each time.[41]

Preparation of Antibiotic Disc: Place the disks that have been impregnated with the appropriate antibiotic on the agar surface. The rifamycin antibiotic was administered to each plate. To dispense the disks at different concentrations ranging from 20 mg/ml to 40, 60, 80, and 100 mg/ml, place the dispenser over the agar plates and firmly press the plunger once.[41]

Incubation: For 16 to 18 hours, keep them in an air incubator adjusted at 35°C. The temperature range for petri plate incubation is 35°C ± 2°C. After incubation, the diameter of the inhibitory zones produced around each well was measured in millimetres. Upon solidification, the MH agar's PH ought to vary from 7.2 to 7.4 at room temperature.[41]

Interpretation: The depth of the agar influences the size of the zone of inhibition of growth, as the antimicrobial diffuses in three dimensions, so a shallow layer of agar produces a greater zone of inhibition than a deeper layer [41].

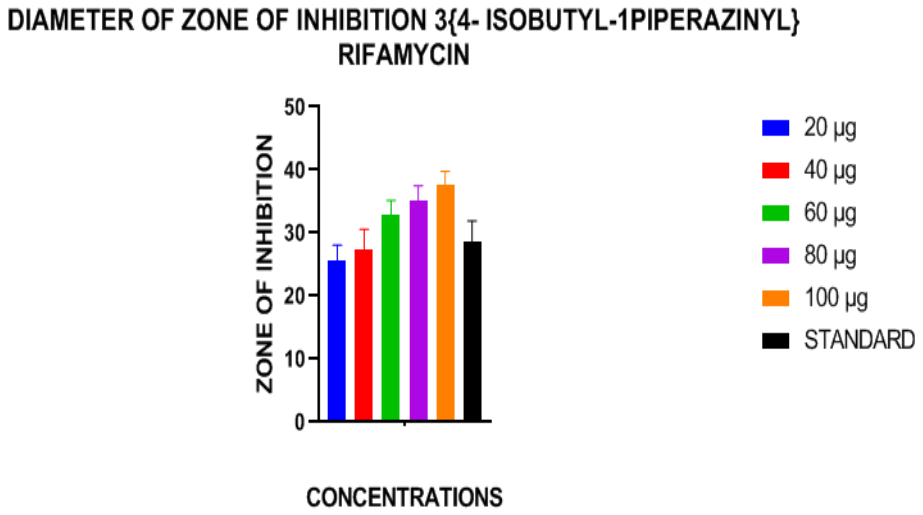
Note the reading in the tabular column [4]

Test	Diameter of Zone of inhibition (in mm)					
	20µg	40µg	60µg	80µg	100µg	Positive control
3-(4-Isobutyl-1piperazinyl) rifamycin	25.6±2.45	27.4±3.18	32.8±2.36	35.2±2.26	37.6±2.19	28.7±3.18
Mean ± SEM	19.3±2. 2	21.5±3.17	25.3±2.37	26.9±2.24	27.4±3.55	27.4±3.55

3. RESULTS:

According to the current study, the compounds 3-(4-Isobutyl-1 piperazinyl) rifamycin were chosen for the purpose of research due to their strong antitubercular characteristics, which can be very important in therapeutic interventions. The test doses of rifamycin have shown the variable zone of inhibition when administered to the tuberculosis causing agent which indicate its effective.

When compared to a positive placebo, the metabolites play an important role in the pharmaceutical compounds' effectiveness. This study promotes more research into and advancements in antitubercular applications to fight drug resistant TB.



4. DISCUSSION:

There are very few anti-Tubercular drugs joining the global tuberculosis medication development program. Further more, the present long-term therapy choices for tuberculosis ,as well as the evolution of medication resistance, have rekindled interest in the development of novel and effective anti-tubular medicines[42]. The study found that 26.0% of TB patients did not adhere to their anti-TB treatment [43]. The main purpose of this study was to assess the level of anti-TB drug acting on the mycobacterium tuberculosis. Similarly the second line drug like streptomycin, bedaquiline, delamanide shows anti-Tubercular property Among which the present study investigated the anti TB potential of (3,4isobutail Piperzinyl) Rifamycin which shows its effectiveness through the zone of inhibition. Results of MIC determination indicates values ranging from 19.32 27.4 micro gram/ml against mycobacterium tuberculii. The risk of major side events, such as liver damage, cardiac arrhythmias, gastrointestinal difficulties, ototoxicity, neurotoxicity, and mental disorders, increases when anti-TB medication is pro long. In addition to these issues, combination therapy presents furthers to conventional treatments, including synergistic side effects and drug to drug interactions. For example coadministration of rifampicin with nevirapine has the potential to reduce nevirapine plasma concentrations [44]. The finding is in line with study that delamanid is a nitro dihydro imidazooxazole derivative that inhibit mycolic corrosive amalgamation with potent in vitro and vivo movement against medication safe strains of mycobacterium tuberculosis. [45] Thus the study conclude that rifamycin is considered as one of the effective antibiotic for the treatment of Tuberculosis.[46] New rifamycin derivatives with different properties have been synthesized,the first of which to reach clinical trials was rifabutin, a spiropiperidyl derivative of the parent compound rifamycin.

References

1.Review: Tuberculosis : Pathogenesis, Current Treat ment Regimens and New Drug Targets.(Shahinda S. R. Alsayed 1,* and Hendra Gunosewoyo 1,2,*). https://p mc.ncbi.nl m.nih.gov/articles/P MC10049048/.

2.Acharya, B.; Acharya, A.; Gauta m, S.; Ghimire, S.P.; Mishra, G.; Parajuli, N.; Sapkota, B. Advances in diagnosis of Tuberculosis: An update into molecular diagnosis of Mycobacterium tuberculosis. Mol.Biol.Rep.2020,47,4065–4075. [CrossRef]

3.Zumla, A; Nahid, P; Cole, S.T. Advances in the develop and treat

4.The study was carried out at Grasment of new tuberculosis drugs mentregimens. Nat. Rev.DrugDiscov.2013,12,388 microbePrivateLi–404. [CrossRef]. Mited (GMPL), which was established in2016 in the tranquil surroundings of Hyderabad, India's Gene meValley. https://phar mabharath.co m/company/grasmicrobe-private-li mited.

5.Smith I. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clin Microbiol Rev 2003; 16(3): 463-496.

6.World Health Organisation. Global Tuberculosis Report 2022. World Health Organization; Geneva, Switzerland: 2022. [(accessed on 1 February 2023)].Licence: CC BY-NC-SA 3.0 IGO. Available online: https://www.who.int/publications/i/item/9789240061729. [Google Scholar]

7.Flynn J.L., Chan J. Tuberculosis: Latency and Reactivation. Infect. Immun. 2001;69:4195–4201. doi: 10.1128/IAI.69.7.4195-4201.2001. [DOI] [PMC free article] [PubMed] [Google Scholar]

8.WHO T. Global tuberculosis report 2012 World Health Organization. Geneva: http://appswhoint/iris/bitstream/ 10665/91355/1/9789241564656_eng. pdf. 2012.

9.WHO Consolidated Guidelines on Tuberculosis Module 4: Treatment Drug-Susceptible Tuberculosis Treatment; World Health Organization: Geneva, Switzerland, 2022. [Google Scholar]

10.Sensi, P. History of the development of rifampin. Rev. Infect. Dis. 5 (Suppl 3), S402–S406 (1983). CAS PubMed Google Scholar

11.Maggi, N. et al. Rifampicin: a new orally active rifamycin. Chemotherapia11, 285–292 (1966). CAS Google Scholar

12.Arioli, V. et al. Antibacterial activity of DL 473, a new semisynthetic rifamycin derivative. J. Antibiot. 34, 1026–1032 (1981). CAS Google Scholar

13.O'Brien, R. J., Lyle, M. A. & Snider, D. E. Jr. Rifabutin (ansamycin LM 427): a new rifamycin-S derivative for the treatment of mycobacterial diseases. Rev. Infect Dis. 9, 519–530 (1987). CAS PubMed Google Scholar

14.Wehrli, W., Knüsel, F., Schmid, K. & Staehelin, M. Interaction of rifamycin with bacterial RNA polymerase. Proc. Natl Acad. Sci. USA 61, 667–673 (1968). CAS PubMed PubMed Central Google Scholar

15. Campbell, E. A. et al. Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. Cell 23, 901–912 (2001). Google Scholar

16. Arbex MA , Varella Mde C, Siqueira HR et al. . Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first-line drugs. J Bras Pneumol2010; 36: 626–40.Google Scholar CrossrefPubMed WorldCat

17.Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle1978; 59: 13–32.Google Scholar CrossrefPubMed WorldCat

18.Dworkin MS , Adams MR, Cohn DL et al. . Factors that complicate the treatment of tuberculosis in HIV-infected patients. J Acquir Immune Defic Syndr2005; 39: 464–70. Google Scholar CrossrefPubMed WorldCat

19.Ruslami R , Nijland HM, Alisjahbana B et al. . Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. Antimicrob Agents Chemother2007; 51: 2546–51. Google Scholar CrossrefPubMed WorldCat

20.Jeong I , Park JS. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci2015; 30: 167–72.Google Scholar CrossrefPubMed WorldCat

21.Steele MA , Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A metaanalysis. Chest1991; 99: 465–71.Google Scholar CrossrefPubMed WorldCat
22.reen RA , Miller RF, Gorsuch T et al. . Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax2006; 61: 791–4. Google Scholar CrossrefPubMed WorldCat
23.Marks DJ , Dheda K, Dawson R et al. . Adverse events to antituberculosis therapy: influence of HIV and antiretroviral drugs. Int J STD AIDS2009; 20: 339–45.Google Scholar CrossrefPubMed WorldCat
24.Schifitto G , McDermott MP, McArthur JC et al. . Incidence of and risk factors for HIVassociated distal sensory polyneuropathy. Neurology2002; 58: 1764–8. Google Scholar CrossrefPubMed WorldCat
25.Yee D , Valiquette C, Pelletier M et al. . Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med2003; 167: 1472–7.Google Scholar CrossrefPubMed WorldCat
26.Gort A , Falguera M, Schoenenberger JA. Rifampicin toxicity in HIV-infected patients: a study of its incidence and the risk factors. An Med Interna1997; 14: 559–64. Google Scholar PubMed WorldCat
27.Shang P, Xia Y, Liu F et al. . Incidence, clinical features and impact on anti-tuberculosis treatment of anti-tuberculosis drug induced liver injury @ATLI# in China. PLoS One2011; 6: e21836.Google Scholar CrossrefPubMed WorldCat
28.Krishnamurthy DV , Selkon JB, Ramachandran K et al. . Effect of pyridoxine on vitamin B6 concentrations and glutamic-oxaloacetic transaminase activity in whole blood of tuberculous patients receiving high-dosage isoniazid. Bull World Health Organ1967; 36: 853–70. Google Scholar PubMed WorldCat
29.Semenya, S.S.; Maroyi, A. Medicinal plants used for the treatment of tuberculosis by Bapedi traditional healers in three districts of the Limpopo Province, South Africa. AJTCAM 2013, 10, 316–323. [Google Scholar] [CrossRef] [Green Version]
30.Xu, Y.; Liang, B.; Kong, C.; Sun, Z. Traditional Medicinal Plants as a Source of Antituberculosis Drugs: A System Review. BioMed Res. Int. 2021, 2021, 9910365. [Google Scholar] [CrossRef] [PubMed]
31.Acharya B., Acharya A., Gautam S., Ghimire S.P., Mishra G., Parajuli N., Sapkota B. Advances in diagnosis of Tuberculosis: An update into molecular diagnosis of Mycobacterium tuberculosis. Mol. Biol. Rep. 2020;47:4065–4075. doi: 10.1007/s11033-020-05413-7. [DOI] [PubMed] [Google Scholar]
32. . Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. Int J Tubercle Lung Disease 1999; 3: Suppl. 2, S231–S279.Google Scholar
33. Caminero JA, ed. Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis. Paris, International Union Against Tuberculosis and Lung Disease, 2013. Google Scholar
34.Caminero JA, Matteelli A, Lange C. Treatment of TB. In: Lange C, Migliori GB, eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society, 2012; pp. 154–166. Google Scholar
35.The Joint United Nations Programme on HIV/AIDS. AIDS epidemic update 2016http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016 (2016).
36. Tiberi, S. et al. The cursed duet today: tuberculosis and HIV-coinfection. Presse Med. 46, e23–e39 (2017). PubMed Google Scholar
37. Egelund, E. F., Dupree, L., Huesgen, E. & Peloquin, C. A. The pharmacological challenges of treating tuberculosis and HIV coinfections. Expert. Rev. Clin. Pharmacol. 10, 213–223 (2017). CAS PubMed Google Scholar
38. Regazzi, M., Carvalho, A. C., Villani, P. & Matteelli, A. Treatment optimization in patients

coinfected with HIV and Mycobacterium tuberculosis infections: focus on drug-drug interactions with rifamycins. Clin. Pharmacokinet. 53, 489–507 (2014). CAS PubMed Google

39.https://gsrs.ncats.nih.gov/ginas/app/ui/substances/5ARN4FK9X2.

40.Review Article Traditional Medicinal Plants as a Source of Antituberculosis Drugs : A SystemReviewYuhuiXu,1BowenLiang,2ChengchengKong,3,4andZhaogangSun3,4. https://doi.org/10.1155/2021/9910365

41.Kirby-BauerDiskDiffusionSusceptibilityTestProtocol||Created:Tuesday,08Dece 2009Author • JanHudzicki.

42.In vitro evaluation of theinhibitoryeffectof3, 5-dichloro-2-pyridoneonMycobacterium tuberculosisH37RvLinLing1,ChenLing2,Hua Wu1*

43.Antituberculosis Drug Non adherence and Its Associated Factors: Evidence from Debre Berhan Town, North Shewa Zone, Ethiopia To mas Getahun, 1 Hail emikael Debebe, 2Helen Getahun,2YonasAbebe,3KidistAssefa,4 and Mizan Habtemichael3. https://doi.org/10.1155/2023/7645058.

44.Recent advancements in the quest of benzazoles as Anti-Mycobacterial tuberculosis agents AuthorlinksopenoverlaypanelKshitij I Patel a nirjhar saha b, tejas M.dhameliya c, asit K. chakraborti a b. https://doi.org/10.1016/j.bioorg.2024.108093

45.Current Affairs, Future Perspectives of Tuberculosis and Antitubercular Agents Author links open overlay panelJineetkumar Gawad, Chandrakant Bonde.

46.Marsili L, Pasqualucci CR, Vigeyani A, Gioia B, Schioppacassi G, Oronzo G. New rifamycins modified at positions 3 and 4: synthesis, structure and biological evaluation. Journal of Antibiotics (Tokyo) 1981;34(8): 1033–8