Global Journal of
Pharmacy & Pharmaceutical Sciences
ISSN: 2573-2250

Juniper Publishers
key to the Researchers

Review Article
Volume 11 Issue 4 June 2024
DOI: 10.19080/GJPPS.2024.11.555818

Glob J Pharmaceu Sci

Unveiling the Potential of Heterocycles: Innovations in Anti-Tubercular Therapeutics

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Submission: June 1, 2024; **Published:** June 10, 2024

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Abstract

Tuberculosis (TB) remains a significant global health concern, with the emergence of drug-resistant strains posing formidable challenges to effective treatment. In the pursuit of novel therapeutic options, researchers have turned to advanced heterocycles as promising scaffolds for the design and synthesis of anti-tubercular agents. This review provides an overview of the current landscape of TB, highlighting the urgent need for innovative treatment strategies. Focusing on heterocyclic compounds such as pyrazoline, pyrrole, benzimidazoles, benzothiazoles, and selective purines, we discuss recent advances in their utilization for TB drug discovery. Through structure-activity relationship studies and innovative synthetic methodologies, these heterocyclic compounds have demonstrated potent anti-mycobacterial activity against both drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis. The review concludes with insights into the future directions and potential challenges in harnessing the therapeutic potential of advanced heterocycles for combating TB.

Keywords: Tuberculosis; Mycobacterium tuberculosis; Pyrazoline; Pyrrole; Benzimidazoles; Benzothiazoles; Selective purines

Abbreviations: TB: Tuberculosis; MDR-TB: Multidrug-Resistant TB; WHO: World Health Organization; INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; DOT: Directly Observed Therapy; SARs: Structure-Activity Relationships; XDR: Extensively Drug-Resistant

Introduction

Tuberculosis (TB) is a significant global health threat that has been a major cause of morbidity and mortality for centuries. It is an airborne infectious disease caused by the *Mycobacterium tuberculosis* complex, which primarily affects the lungs but can also cause disease in almost any part of the body [1-4]. The disease is highly prevalent among low socioeconomic and marginalized populations, and its impact is exacerbated by the emergence of drug-resistant strains, such as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) [1-3] (Figure 1).

According to the World Health Organization (WHO), in 2021 (from latest WHO issued Global TB Report 2023), an estimated 10.6 million people fell ill with TB, resulting in 1.6 million deaths and around 8.1% of new TB cases were among people living with HIV [5]. Despite significant progress in TB control over the past decade, including a 47% decline in TB mortality since 1990, the disease remains a major killer, particularly in low-income and middle-income countries [2]. The WHO has set targets to reduce TB deaths by 90% by 2030 and achieve an 80% reduction in TB incidence by 2030 as part of the End TB strategy [2].

The causative organism, *M. tuberculosis*, is a highly infectious and adaptable pathogen that can remain dormant in the host for extended periods, making it challenging to diagnose and treat effectively [1,3,4]. Current treatments for TB include a combination of antibiotics, which can be effective for sensitive strains but are often inadequate for drug-resistant forms of the disease [1-3]. Novel diagnostic modalities, such as interferon-gamma release tests and nucleic acid amplification techniques, have improved the accuracy of diagnosis, but more research is needed to develop effective treatments for MDR-TB and XDR-TB [1,3,4].

The Currently available Treatments for Tuberculosis (TB) Include

Treatment for Drug-Sensitive TB

The standard treatment regimen for drug-sensitive TB involves a combination of four antibiotics taken for at least 6 months: [6-8] Isoniazid (INH); rifampicin (RIF); pyrazinamide (PZA); ethambutol (EMB). The treatment is divided into two phases: [6] Initial phase (2 months): INH, RIF, PZA, EMB and

continuation phase (4 months): INH, RIF. This regimen can be administered daily or intermittently under directly observed therapy (DOT) to ensure treatment adherence and success [6,9].

Treatment for Drug-Resistant TB

Management of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) is more challenging and usually requires: [7] Injectable agents (amikacin, kanamycin or capreomycin) for 4-6 months; toxic second-line oral drugs for 18-24 months and novel drugs like bedaquiline and delamanid are being evaluated in clinical trials to improve the treatment of drug-resistant TB [7].

Treatment for Latent TB Infection:

Latent TB infection can be treated with: [8,9] Isoniazid (INH) for 6-9 months and rifampicin (RIF) for 4 months; a once-weekly regimen of rifapentine plus isoniazid for 12 weeks and directly observed therapy (DOT) is recommended for all patients to ensure treatment adherence and completion [8,9]. The choice of regimen depends on factors such as drug susceptibility, HIV status, and potential drug interactions [8] (Figure 2).

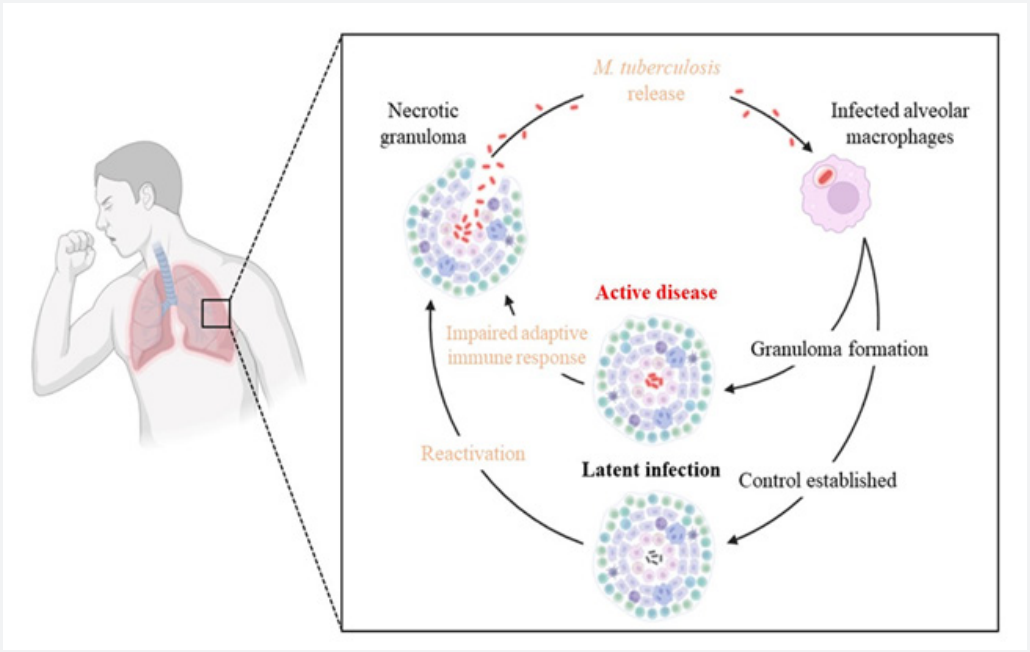

Figure 1: Pathogenesis of tuberculosis.

Heterocycles used in the Treatment of Tuberculosis

Heterocyclic compounds have played a significant role in the development of anti-tubercular drugs due to their diverse biological activities and structural versatility [10-12]. These compounds contain one or more heteroatoms, such as nitrogen, oxygen, or sulphur, within a cyclic structure and have been extensively explored for their potential in treating tuberculosis (TB) [10,11].

Several classes of N-heterocycles, including indoles, triazoles, thiazoles, and pyrazoles, have demonstrated promising anti-TB effects [10,11]. These compounds have been investigated for their ability to inhibit the growth of *Mycobacterium tuberculosis*, the causative agent of TB, and to overcome drug resistance [10-12].

Recent advances in the research of heterocyclic compounds have focused on their antimycobacterial activity, mechanisms of action, toxicity, and structure-activity relationships (SARs) [12]. Novel heterocyclic compounds with improved properties, such as lower toxicity, shortened duration of therapy, rapid bactericidal action, and enhanced activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, have entered clinical trials in recent years [12-14].

The development of heterocyclic-based anti-TB drugs is crucial to address the global health burden of TB, which remains a major cause of morbidity and mortality worldwide [10-12]. This review aims to provide a comprehensive overview of the contribution of various heterocyclic rings towards the treatment of tuberculosis, highlighting the recent advances, challenges, and future prospects in this field.

Advanced Pyrazoline-based Anti-Tubercular Agents

Ali MA, et al. (2007) synthesized a series of novel pyrazoline containing heterocycles 1a-k and 2a-k (Figure 3), via the reaction of hydrazine hydrate with chalcones, followed by condensation

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with appropriate aryl isothiocyanate. The synthesized molecules were evaluated for their in vitro anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system. The 2,6-dichloro substituted derivative exhibited the highest activity, while substituents such as 4-Cl, 2-Cl, and 3-NO_2 resulted in only mild inhibition. In contrast, the 4-OMe phenyl substitution (2a), as well as the 3',4'-diOMe phenyl (2e) and 3',4',5'-triOMe phenyl substitutions (2f), demonstrated moderate activity. However, the 3',4'-diOMe phenyl (1e) and 3',4',5'-triOMe phenyl substitutions (1f) showed lower activity. These findings indicate that substitution at the 2,6 positions enhances activity. Among these molecules, (2i) exhibited the highest activity against $H_{37}Rv$ strain of *M. tuberculosis*, with a minimum inhibitory concentration of 0.0034 mM [15].

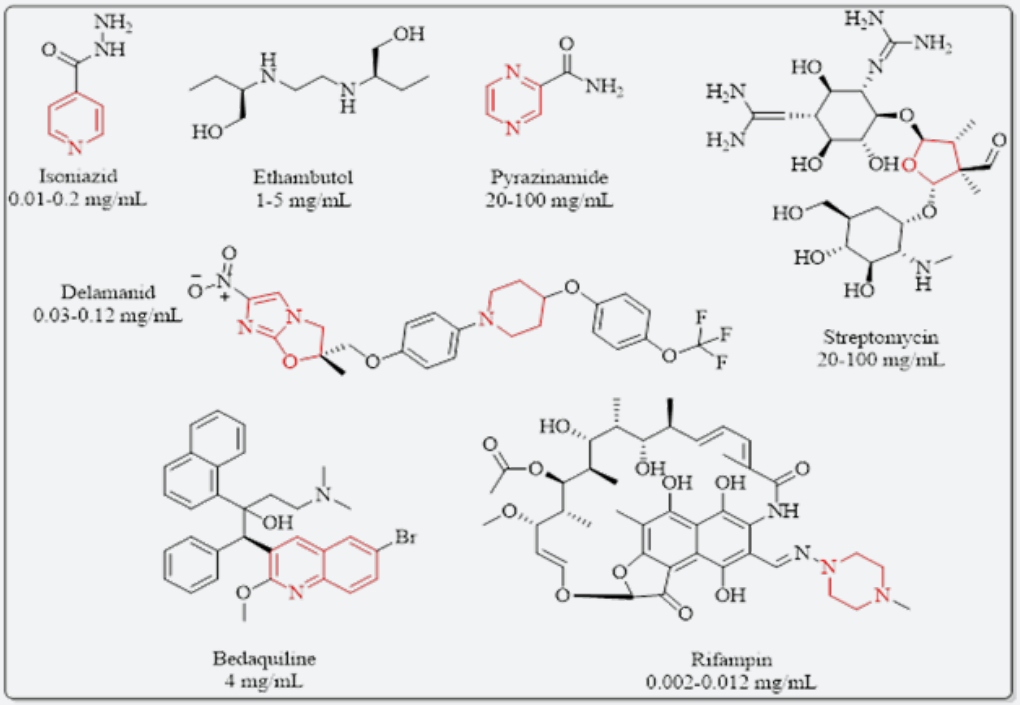

Figure 2: Currently available therapeutics for treatment of tuberculosis.

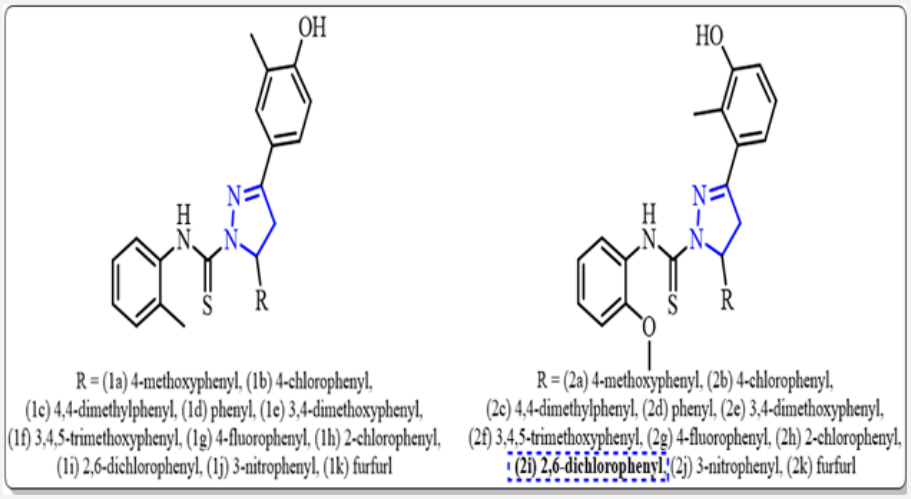

Figure 3: Pyrazoline-based anti-tubercular agents.

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Advanced pyrrole-based anti-tubercular agents

Biava et al. (2002) synthesized a series of 1,5-diarylpyrroles derivatives and identified that 1-(4-fluorophenyl)-2-ethyl-3-(thiomorpholine-4-yl)-methyl-5-(4-methylphenyl)-1-pyrrole (3) displayed potent anti-tubercular activity with a MIC value of 0.25 mg/mL against both susceptible and RIF resistant strains of *M. tuberculosis*. Furthermore, several other pyrrole derivatives, including molecules 4 [16], 5[17], and 6[18], exhibited notable efficacy against *M. tuberculosis* H_{37}Rv, with MIC ranging from 0.06 to 0.5 mg/mL.

In the SAR studies, specific alterations to the pyrrole ring were identified as pivotal for combatting mycobacterial infections: a) Incorporating a substituted phenyl ring at 1st and 5th positions, with -F, -Cl, or -Me groups being the most efficacious; b) Introducing an -$MeNH_2$ group at 3rd position, particularly in the form of a thiomorpholino methyl side chain, proved to be highly effective. Additionally, it was observed that enhancing the lipophilicity of these pyrrole derivatives generally correlated with enhanced anti-microbial activity. Notably, modifications at 2nd position exhibited comparatively lesser impact on activity when contrasted with those at 1st, 3rd and 5th positions [19] (Figure 4).

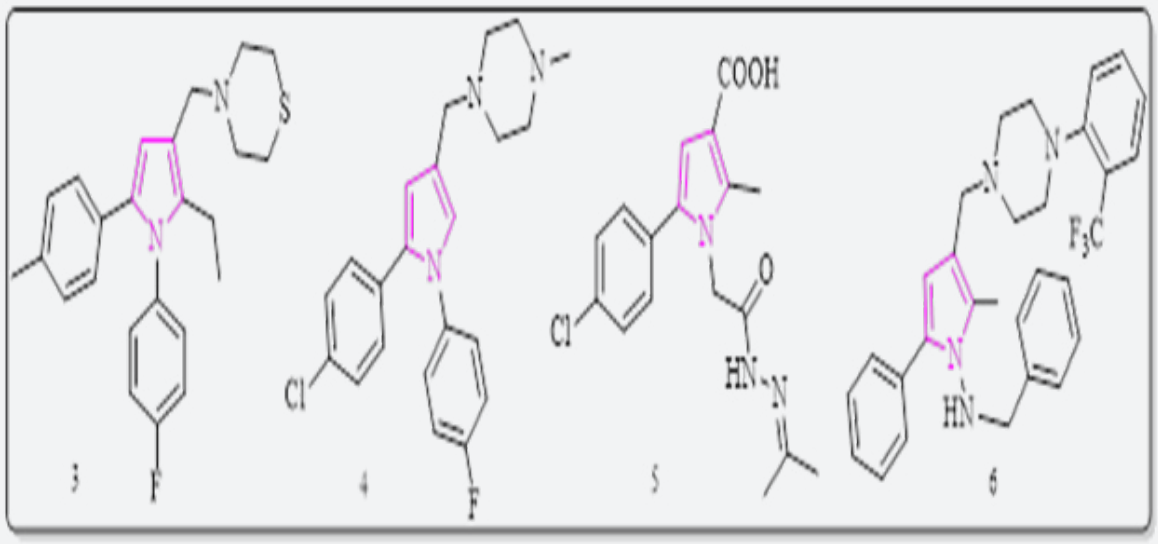

Figure 4: Pyrrole-based anti-tubercular agents.

Advanced Benzimidazoles-Based Anti-Tubercular Agents

A novel series of 5-(nitro/bromo)styryl-2-benzimidazoles [7-18] was synthesized by Shingalapur R. V. et al. (2009) through a mild and efficient synthetic method involving the condensation of 5-(nitro/bromo)-o-phenylene diamine with trans cinnamic acids in ethylene glycol. These molecules were screened for in vitro anti-tubercular activity against *M. tuberculosis* H_{37}Rv. Remarkably, molecules five synthesized molecules [11,13-15,17] exhibited potent anti-tubercular efficacy. Consequently, this investigation highlights the superior activity of bromine-containing compounds compared to their nitro-substituted counterparts [20] (Figure 5).

Advanced Benzothiazoles-Based Anti-Tubercular Agents

Khokra et al. (2011) introduced a novel series of benzothiazole derivatives possessing anti-mycobacterial properties. Within this series, analogue 56, characterized as 4-amino-N-(1,3-benzothiazol-2-yl)-benzenesulfonamide, exhibited significant activity against *M. tuberculosis* H37Rv. Similarly, analogue 19, featuring a 2-hydrazino benzothiazole structure with a 1,2,4-triazole moiety, demonstrated antimycobacterial activity. Additionally, derivatives of 5-(2-methylbenzothiazol-5-yloxymethyl)-isoxazole-3-carboxamide were found to be active against replicating *M. tuberculosis* H_{37}Rv. Among these derivatives, [20] emerged as the most potent, inhibiting *M. tuberculosis* growth at micromolar concentrations with a MIC value of 0.61 mg/mL [21] (Figure 6).

Advanced selective purines-based anti-tubercular agents

Brændvang M. et al. (2005) synthesized a series of molecules denoted as 21a-t and 22a-u (Figure 7), comprising 6-Aryl and 6-heteroaryl 9-benzylpurines, which exert a novel and selective mechanism against *M. tuberculosis*, as well as both gram positive and gram negative strains bacteria. These compounds were synthesized utilizing a palladium catalyzed coupling reaction,

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facilitating the formation of C-C and C-N bonds between aryl/heteroaryl groups and purines. Notably, 21f (1.56 mg/mL) from 21 series and 22i (0.39 mg/mL) from 22 series demonstrated good and excellent activity, respectively against *M. tuberculosis*. Augmented activity was observed upon the introduction of -Cl at the 2nd position and a couple of -OMe group at the phenyl ring. Introducing an electron donating group (EDG) on the phenyl ring led to an increased activity. The inclusion of nitrogen into the heterocyclic system was found to attenuate the anti-tubercular activity. Furthermore, EWG or substitutions at the m-position were discouraged [22].

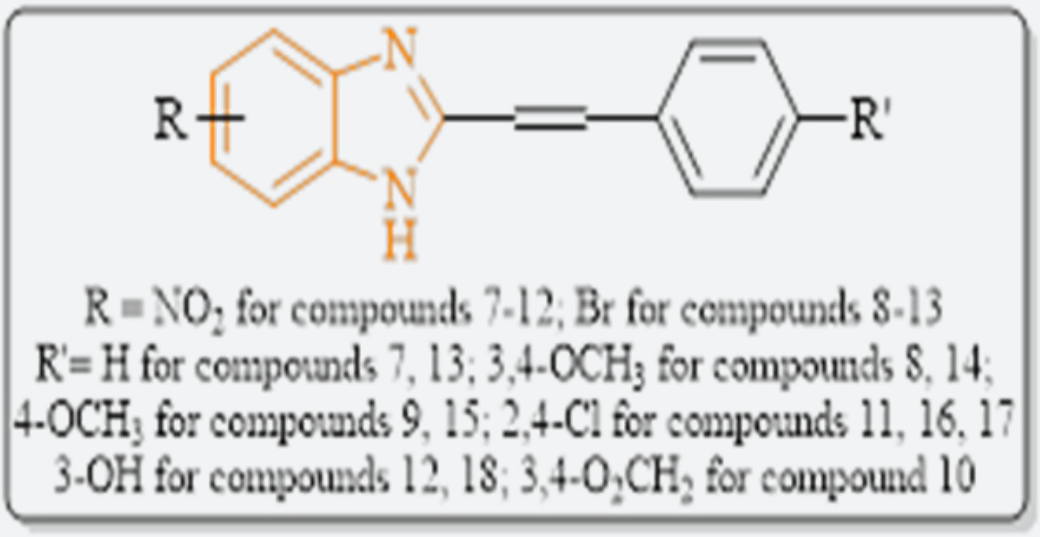

Figure 5: Benzimidazoles-based anti-tubercular agents.

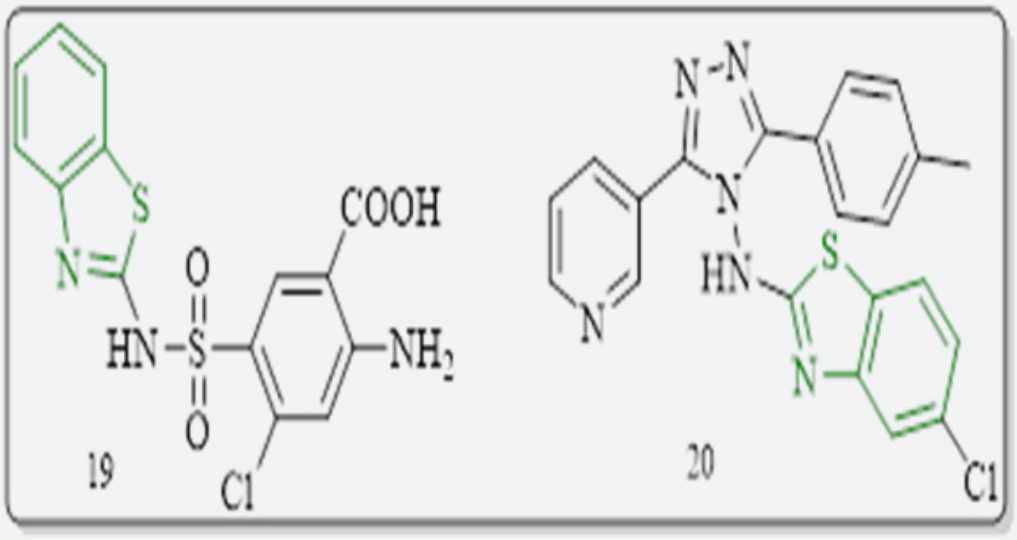

Figure 6: Benzthiazoles-based anti-tubercular agents.

Conclusion

In conclusion, the diverse array of advanced heterocycles, including pyrazoline, pyrrole, benzimidazoles, benzothiazoles, and selective purines, offer promising avenues for the design and synthesis of novel anti-tubercular agents. Each class of heterocycle brings unique structural features and pharmacological properties, allowing for the exploration of various chemical

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scaffolds to target *Mycobacterium tuberculosis*. Through systematic structure-activity relationship studies and innovative synthetic methodologies, researchers have been able to develop potent compounds with enhanced efficacy against tuberculosis. Furthermore, the versatility of heterocyclic compounds provides opportunities for the discovery of new drug candidates with improved pharmacokinetic profiles and reduced toxicity. Continued research efforts in this field hold great potential for addressing the challenges posed by drug-resistant tuberculosis and advancing the development of effective treatments for this global health burden.

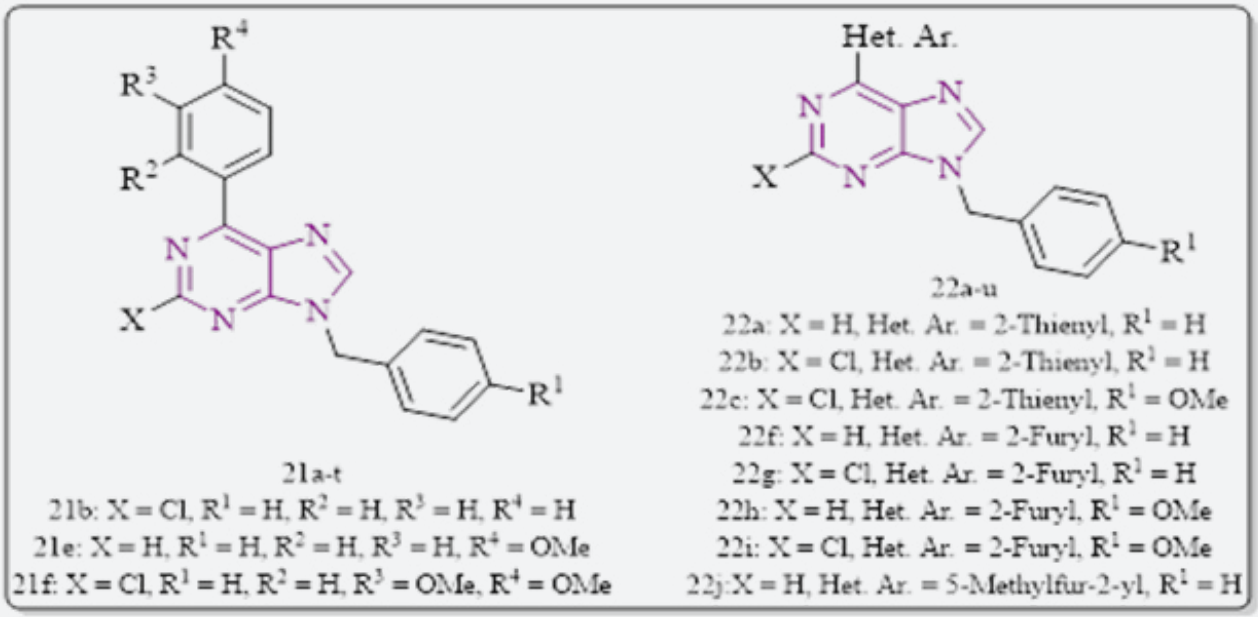

Figure 7.

Funding

This research received no external funding.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

Declarations & Author's Contributions

V.G. carried out all the literature searches. V.G. and R.R. carried out the writing of the manuscript. All the authors have read and approved the final version of the manuscript.

Acknowledgement

The authors are highly grateful to Jamia Hamdard, New Delhi and Bharat Institute of Technology, Meerut, Uttar Pradesh.

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