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Current development of 5-nitrofuran-2-yl derivatives as antitubercular agents

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ABSTRACT

Pulmonary tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and still remains one of the foremost fatal infectious diseases, infecting nearly a third of the worldwide population. The emergencies of multidrug-resistant and extensively drug-resistant tuberculosis (MDR and XDR-TB) prompt the efforts to deliver potent and novel anti-TB drugs. Research aimed at the development of new anti-TB drugs based on nitrofuran scaffold led to the identification of several candidates that were effective against actively growing as well as latent mycobacteria with unique modes of action. This review focuses on the recent advances in nitrofurans that could provide intriguing potential leads in the area of anti-TB drug discovery.

1. Introduction

Tuberculosis (TB) is a worldwide pandemic, considered one of the most dreaded diseases, and remains among the top ten causes of mortality [1]. The causative agent of pulmonary TB, *Mycobacterium tuberculosis* (MTB), is an obligate human pathogen that infects an increasing number of populations. The WHO reported that the number of cases has continually been escalating, from 8.6 million in 2012 to 9 million in 2013 to an estimated 9.6 million new cases in 2014, and one of the health targets is to end the disease by 2030 [2–5]. It is known that comorbidities can significantly affect one's health, and the association of TB with the emergence of HIV infection could result in disease reactivation [6]. Moreover, the emergence of multi-, extensively and totally drug-resistant mycobacteria complicates the situation [7]. However, in the last 50 years, only a few drugs have been approved by drug authorities such as the United States Food and Drug Administration for TB therapy, reflecting the inherent difficulties of developing new anti-TB agents [8]. Despite the introduction of Bedaquiline and Delamanid to the repertoire of anti-TB therapies for MDR-TB, many adverse effects have been noted. Consequently, there is an urgent need to develop antimycobacterial molecules with new mechanisms of action that remain active against MDR and XDR-TB [9]. Recently, three main strategies have been adopted to tackle the disease problem and discover new anti-TB agents [10,11]: (1) Application of currently used medications such as ciprofloxacin as second-line anti-TB therapy in cases of resistant MTB or intolerance to first-line medications [12], (2) Exploration of new chemical entities with new modes of actions for treatment of MDR-TB [13,14], and (3) Modification of existing drugs to improve pharmacokinetics and efficacy for TB treatment.

Antitubercular agents containing five-membered heterocyclic rings in their structures are well reviewed in the literature [15–18]. Currently, nitrofurans have gathered immense attention of medicinal chemists due to their promising anti-TB potential [19–27], activity against both actively growing and latent bacteria, activity against drug-resistant mycobacteria [28,29] and their novel mode of action. The structure-activity relationships (SARs) study of nitrofuran derivatives (Fig. 1) has revealed that the nitro functional group is essential for the anti-TB activity and that replacement of the furan ring with other similar ring systems decreased or abolished the activity [30], while exploration of anti-TB molecules incorporating nitroaromatic systems profoundly increased the activity against latent or anoxic bacteria [31]. Moreover, the development of cross-resistance with other anti-TB medications has not been documented [32].

2. 5-Nitrofuran-2-yl derivatives and their anti-TB activity

The current success of heterocyclic compounds decorated with nitro groups prompts medicinal chemists to conclude that careful

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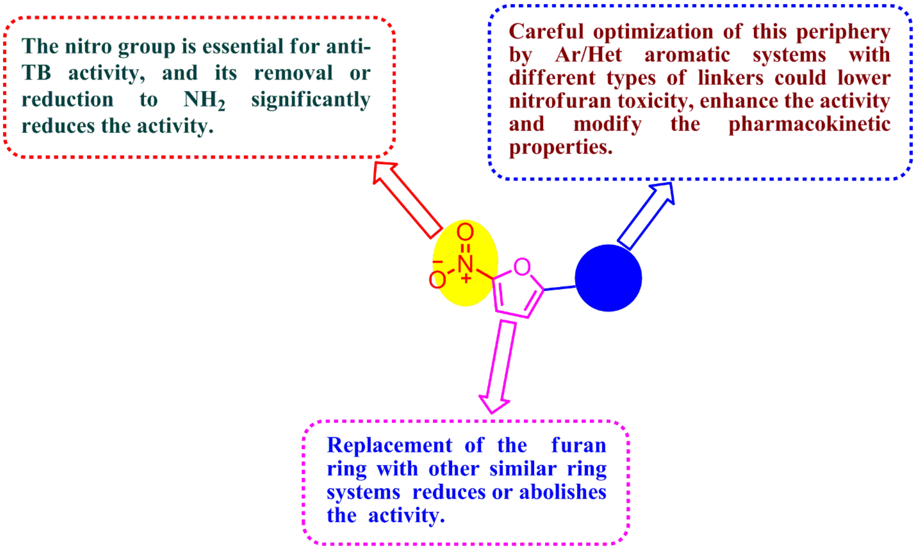

The nitro group is essential for anti-TB activity, and its removal or reduction to NH_2 significantly reduces the activity.

Careful optimization of this periphery by Ar/Het aromatic systems with different types of linkers could lower nitrofuran toxicity, enhance the activity and modify the pharmacokinetic properties.

Replacement of the furan ring with other similar ring systems reduces or abolishes the activity.

Fig. 1. SARs of 5-nitrofuran derivatives as anti-TB compounds.

optimization of the periphery of the nitrofuran ring could lessen toxicity and improve the efficacy of the newly designed chemotherapeutic candidates. This eventually led to the recent re-emergence of new nitrofuran derivatives as a very useful pharmacophore in the chemotherapeutic field [28,33], which is illustrated in this review by the recently reported compounds synthesized over the period from 2007 to date demonstrating good anti-TB activity. Moreover, an attempt has been made to shed light on some directions and approaches to advance the future development of potent yet safer 5-nitrofuran-2-yl-based anti-TB candidates.

Nearly a decade ago, 5-nitrofuran-2-yl-amide derivative **1** (Fig. 2) was reported to exert activity against MTB with the minimum inhibitory concentration (MIC) of 0.006 μg/mL [22,23,28].

Sriram et al. [34] studied the antimycobacterial activity profile of various 5-nitrofuran-2-yl derivatives **2** (Fig. 3) against tubercular and various nontuberculous mycobacterium species. The results revealed that compound **2r**, with a 3,5-disubstituted pyridine ring system, displayed growth inhibitory activity in log-phase culture of MTB (MIC = 0.22 μM). It was 3 times more active than standard isoniazid (INH) and equipotent to the reference rifampicin (RIF), with low cytotoxicity. In starved MTB H37Rv, **2r** showed an inhibitory effect with MIC of 13.9 μM and was found to be 50 times more active than INH and slightly more active than RIF. With regard to SARs, pyridylthiosemicarbazones were found to be more active than phenylthiosemicarbazones. Substitution by electron-withdrawing groups afforded highly efficacious compounds, while the electron-donating groups significantly reduced the activity. With regard to alkyl substituted compounds, dimethyl-substituted derivatives were more active than mono-substituted compounds against MTB. Additionally, these derivatives displayed significant activity against atypical MTB, and some compounds were even more active than the reference drug INH.

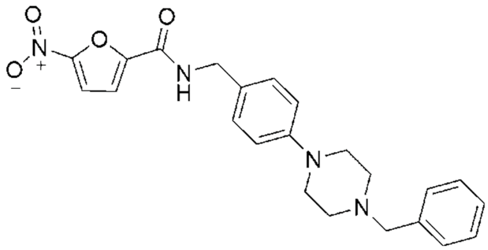
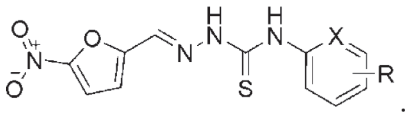

1

Fig. 2. Chemical structure of 5-nitrofuran-2-yl-amide derivative 1.

Further SARs and mechanistic studies are crucial to design potent anti-TB lead employing different aromatic/heteroaromatic systems rather than benzene and pyridine with variation in the nature, size and positions of substituents in such interesting molecular frameworks. This will offer the opportunity to study the effects of changes in steric, electronic and hydrophobic properties of substituents on the anti-TB activity of these 5-nitrofuran-based carbothioamides, as well as the introduction of functional groups allowing drug-target interactions that may promote the activity and lessen cytotoxicity.

Anti-TB activity profiles of nitrofuran coupled benzothiadiazines **3** and **4** (Fig. 4) were reported by Kamal et al. [35]. Compounds **3a-g** (MIC = 1–16 μg/mL) were more potent than compounds **4a-d** (MIC = 4–32 μg/mL). Compound **3f** has shown good in vitro antimycobacterial activity, with MIC = 1 μg/mL, and was four times more potent thant its thiophene analog **3g** pointing to the importance of the furan ring. The replacement of phenyl group with alkyl groups has reduced the effectiveness. Compound **4d** with electron withdrawing halogen substituent was the most efficacious among series **4** with MIC = 4 μg/mL. In the same study, substitution of nitro group in the furan ring of these derivatives with nitrophenyl ring systems afforded inactive derivatives, indicating the significance of direct attachment of nitro group with the furan ring. These compounds are expected to be with improved water solubility, so further studies on these compounds would end up with promising anti-TB candidates

Various 5-nitro-2-furoic acid hydrazones **5–7** (Fig. 5) were synthesized and tested against MTB by Sriram et al. [36]. These hydrazones showed good activity with MICs ranging from 2.65 to 48.22 μM. Two compounds (**5b** and **6k**) showed excellent activity with MIC of $<$ 5 μM when compared to INH (MIC = 0.72 μM) and RIF (MIC = 0.48 μM). Compound **5b** was found to be the most active compound in vitro, with MIC values of 2.65 and 10.64 μM against log- and starved-phase cultures of MTB, respectively. Regarding SARs, substituents with electron-withdrawing groups promoted the anti-TB activity, while substituents like hydroxyl, and methoxy groups reduced the activity. Acetophenone based hydrazones **7** were more active than their corresponding benzaldehyde derived compounds **6.** With respect to furanyl derived compounds, **5b** was ~9 times more potent than the desnitro derivative **5a.** Screening of these hydrazones against atypical mycobacteria (MC_2) afforded 10 compounds that were more potent than INH. Authors also attempted to explore the possible mechanism of action, such as enzyme inhibition, by screening compounds (**6b,g,j,k,** and **7a-e**) in MTB isocitrate lyase (ICL). All tested compounds inhibited MTB ICL with percentage inhibition ranging from 19.82% to 86.8% at 10 μM. Two



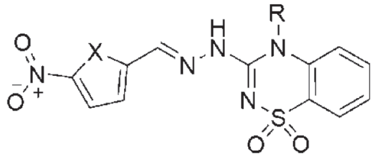
2

2a: R=H, X=H; **2b:** R=4-Me, X=H; **2c:** R=4-OMe, X=H; **2d:** R=2-Br, X=H; **2e:** R=4-Cl, X=H; **2f:** R=4-SO$_2$NH$_2$, X=H; **2g:** R=2,4-(Me)$_2$, X=H; **2h:** R=2,6-(Me)$_2$, X=H; **2i:** R=2,5-(Me)$_2$, X=H; **2j:** R=2,6-(C$_2$H$_5$)$_2$, X=H; **2k:** R=2,4-(OCH$_3$)$_2$, X=H; **2l:** R=2,4-(NO$_2$)$_2$, X=H; **2m:** R=H, X=N; **2n:** R=3-Me, X=N; **2o:** R=4-Me, X=N; **2p:** R=5-Cl, X=N; **2q:** R=4,6-(Me)$_2$, X=N; **2r:** R=3,5-Br$_2$, X=N

Fig. 3. 5-Nitrofuran-2-yl carbothioamide derivatives.

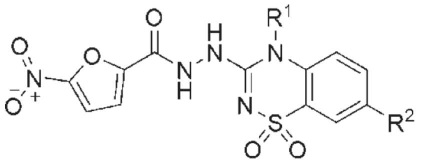
compounds (**5b** and **7c**) showed more than 50% inhibition and were found to be more potent than the standard MTB-ICL inhibitor 3-nitropropionic acid (NPA) at the tested dose level. Moreover, *in silico* studies revealed high affinity to the enzyme that was comparable to that of the standard with various electrostatic and hydrophobic patterns of interactions. On the other hand, most of these compounds were less cytotoxic to the mammalian Vero cell line. Compound **5b** emerged as a potential lead with promising activity against slowly growing or non-growing persistent MTB.

Based on stereoelectronic feature analysis, Tawari and coworkers [37] performed synthesis and in vitro anti-TB activity evaluation of 4-(5-nitrofuran-2-yl)prop-2-en-1-one derivatives **8** (Fig. 6) against MTB in addition to testing their cytotoxicity in the VERO mammalian cell line. Ten compounds (**8a-j**) showed good anti-TB activity (MIC < 5 μM) along with low cytotoxicity. Specifically, compounds **8a,b**, which decorated with small tertiary amine groups, were found to be highly potent, with MIC values of 0.19 and 0.38 μM, respectively, with reduced cytotoxicity. Compound **8a**, with good selectivity index, was nearly 10 times more potent than the first line antitubercular agent INH. The authors hypothesized that these compounds may act as prodrugs and therefore be activated by TB-nitroreductase to release toxic intermediates. Little difference in activity between unsubstituted and *p*-substituted aromatic rings was observed in compounds **8c–g** according to SARs study, while di- and tri-substitution significantly lowered the activity of these derivatives, as did replacement of the aromatic ring with a heteroaromatic system. The importance of the nitro group on the activity was assessed by synthesis of desnitro of compound **8c**, which was found to be devoid of anti-TB activity, indicating the importance of the nitro group for the activity. The significance of the electronegative furan moiety in the vicinity of the nitro group has been confirmed by synthesis of thiophene analog, **8k** (for compound **8a**), significant reduction in activity was observed, pointing to its importance in anti-TB activity. Further SARs, mechanistic studies due to emergence of multiple targets, determination of physicochemical properties and in vivo



3

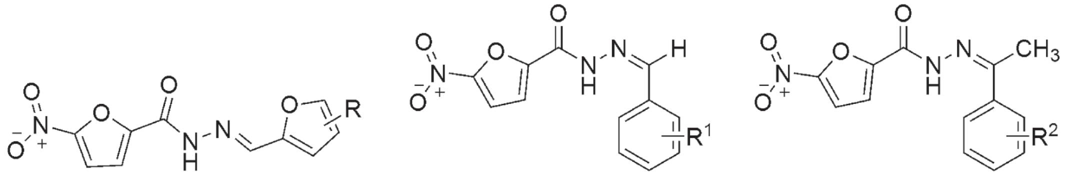
3a: R=Me, X=O; **3b:** R=Me, X=S; **3c:** R=Et, X=O; **3d:** R=Et, X=S; **3e:** R=Isopropyl, X=S; **3f:** R=Ph, X=O; **3g:** R=Ph, X=S



4

4a: R^1=Me, R^2=H; **4b:** R^1=Et, R^2=H; **4c:** R^1=Ph, R^2=H; **4d:** R^1=Me, R^2=Cl

Fig. 4. Nitroheterocyclic-based 1,2,4-benzothiadiazines.



5 **6** **7**

5a: R=H; **5b:** R=5-NO_2

6a: R^1=H; **6b:** R^1=4-NO_2; **6c:** R^1=4-Cl; **6d:** R^1=4-Br; **6e:** R^1=4-F; **6f:** R^1=4-OH; **6g:** R^1=4-Me; **6h:** R^1=4-OMe; **6i:** R^1=3-Br; **6j:** R^1=2-NO_2; **6k:** R^1=2-CF_3; **6l:** R^1=4-OH,3-Me; **6m:** R^1=2,6-$(Cl)_2$

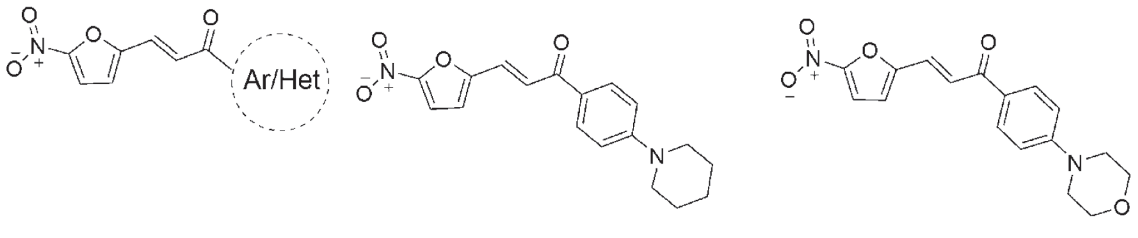
7a: R^2=H; **7b:** R^2=4-NO_2; **7c:** R^2=4-Br; **7d:** R^2=4-F; **7e:** R^2=4-Me; **7f:** R^2=2-OH

Fig. 5. 5-Nitro-2-furoic acid hydrazones.

studies are required in addition to investigations of these compounds against starved MTB.

There are many scientists in the field of anti-TB drug discovery producing candidates with in vitro activity; however, most of these compounds do not pass the subsequent phases of drug development due to different reasons. This could be exemplified by the discovery of the anti-TB activity of new nitrofuranyl amides [22,23,28] that did not perform well during in vivo studies due to their rapid clearance, which was explained by the metabolic instability of the amide bond. Accordingly, Tangallapally et al. [27] performed the synthesis of a series of compounds **9** (Fig. 7) in which the amide bond was bioisosterically replaced with an isoxazoline linker. All compounds in this series, **9a-e,** exhibited excellent activity ($MICs_{90}$ < 0.002 µg/mL); interestingly, compound **9b** was the most potent, with a MIC_{90} value of 0.00005 µg/mL (500 times more potent than the standard anti-TB drug INH). Furthermore, they demonstrated improved serum half-lives over corresponding compounds in the previous nitrofuranyl amide series pointing to the successful of the replacement strategy of the amide bond by isoxazoline. Nevertheless, these compounds did not perform well when tested for in vivo anti-TB activity, this was explained by the low solubility, low volume of distribution, high serum protein binding low bioavailability and limited tissue penetration. Further exploration performed by authors in the quest for non-nitrofuran containing isoxazolines with improved in vivo activity, led to less potent compounds such as **9f** (Fig. 7), (MIC_{90} = 1.56 µg/mL) with advantages such as solubility and less potential for side effects as no nitro group is in the structural framework. Further optimization of this series could lead to highly potent anti-TB compound with improved physicochemical and biological properties.

Increasing oral bioavailability of existing or modified compounds is an interest of some authors such as Rakesh and coworkers [24] who synthesized a series of pentacyclic nitrofurans **10** (Fig. 8). These hybrid

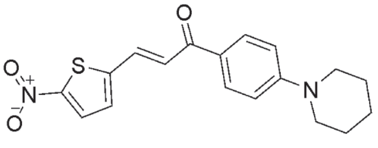


8 **8a** **8b**

8c: Ar/Het=*p*-F-Ph; **8d:**Ar/Het= *p*-CH_3-Ph; **8e:** Ar/Het= *p*-Cl-Ph;

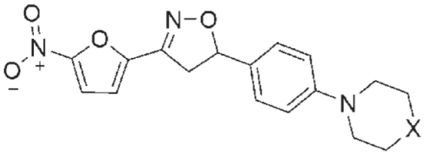
8f: Ar/Het= *p*-Br-Ph; **8g:** Ar/Het= *p*-OCH_3-Ph; **8h:** Ar/Het=Thiophene;

8i: *p*-OCF_3-$PhCH_2O$-*p*-Ph; **8j:** Ar/Het= *p*-$(CH_3CH_2)_2N$-Ph



8k

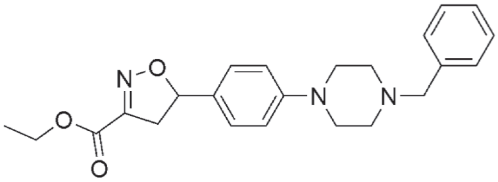
Fig. 6. 4-(5-nitrofuran-2-yl)prop-2-en-1-one derivatives.



9

9a: X=NCOOCH$(CH_3)_3$; **9b:** X= NCH_2Ph; **9c:** X=$NCOOCH_2CH_3$; **9d:** X=NCONHCH$(CH_3)_2$;

9e: X=CH_2



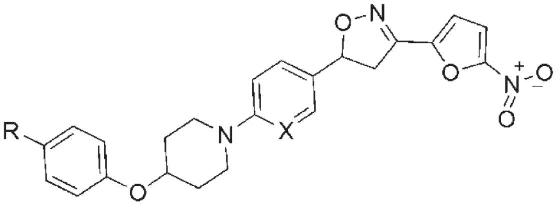
9f

Fig. 7. 5-Nitrofuran-2-yl-based isoxazolines.

architectures displayed potent inhibitory activity against MTB (MIC = 0.001–0.024 µg/mL) with reduced toxicity profile. Compound **10a** displayed inhibition of actively growing as well as dormant MTB at the nanomolar level (MIC = 0.024 µg/mL) indicating its therapeutic potential for future management of chronic tuberculosis infections. Beyond that, **10a** exerted its in vitro and in vivo inhibitory effects by a unique mechanism of action with low potential for cross-resistance with current anti-TB agents. It was also reported to be active and tolerated in acute tuberculosis infections model with an enhanced in vivo efficacy (> 90% reduction in the MTB load). In vivo pharmacokinetic experiments revealed compound **10a** with longer in vivo half-life and higher volume of distribution though with limited oral bioavailability, possibly attributable to low solubility. Moreover, **10a** displayed a prolonged post antibiotic effect compared to INH with synergy to current first-line anti-TB drugs pointing to the possibility to be complementary to the currently used anti-TB regimes. The authors believed that **10a** remained the series lead and may constitute a significantly promising lead for future development of nitrofuran-based candidates as anti-TB agents and hence further studies are needed to stress out certain limitations such as low oral bioavailability, less metabolic stability and the high serum protein binding affinity in order to enhance the in vivo efficacy of this promising lead.

The triazole nucleus is extensively explored in the literature of anti-TB compounds [38]. Based on this consideration, a series of 5-nitrofuran–triazole conjugates **11** (Fig. 9) were synthesized by Kamal et al. [39] employing a click chemistry protocol in order to obtain new and more potent anti-TB candidates. Five out of the ten compounds **11a–e** were found to be active against MTB strain H37Rv, of which compound **11e** displayed an enhanced activity with MIC value of 0.25 µg/mL. The activity of **11e** is four times more than that of linezolid, which is mainly used for drug-resistant tuberculosis, whereas the other four compounds demonstrated moderate activity. The therapeutic potential of these compounds could be reflected by the fact that the majority of these compounds are less cytotoxic than the standard drug ciprofloxacin: among them, compounds **11e,f,i** exhibited the lowest cytotoxic effects on MRC-5 and VERO cell lines. Authors proposed that these compounds may display their MTB inhibitory effect through the same mode of action as previously reported for nitrofuran-based antitubercular compounds. Based on this, in vivo efficacy and pharmacokinetic profiling are warranted to make an insight for further development of this potent anti-TB compound.

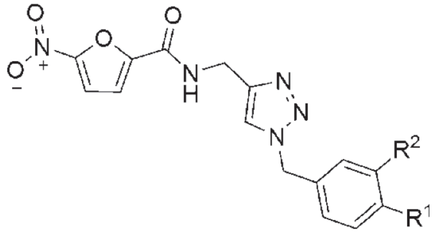
Schiff bases of isatin are known compounds with various biological activities. Aboul-Fadl et al. [40,41] hybridized a series of 5-nitrofurans with isatin in the same structural framework **12** (Fig. 10) and investigated their anti-TB activities against both standard MTB H37Rv and six single resistant MTB strains. The MIC values against the standard MTB strain ranged from 1 to 5 µg/mL. Compound **12h**, with a methyl substituent at position 5 and a benzyl group at position 1 of the



10

10a: X=CH, R=OCF_3; **10b:** X=N, R=OCF_3; **10c:** X=C-F, R=OCF_3; **10d:** X=CH, R=F; **10e:** X=N, R=F; **10f:** X=C-F, R=F

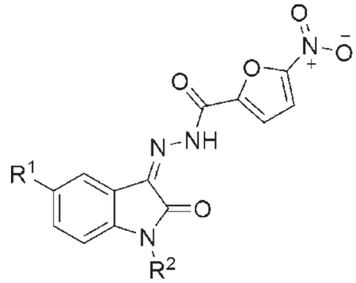
Fig. 8. Pentacyclic nitrofuran analogs.



11

11a: R^1=OH, R^2=OCH_3; **11b:** R^1=H, R^2=NO_2; **11c:** R^1= NO_2, R^2=H; **11d:** R^1= OCH_3, R^2= NO_2; **11e:** R^1=F, R^2=Cl; **11f:** R^1=CF_3, R^2=H; **11g:** R^1= OCH_3, R^2=H; **11h:** R^1= F, R^2= OCH_3; **11i:** R^1= OCH_3, R^2= F; **11j:** R^1= OCH_3, R^2= OH

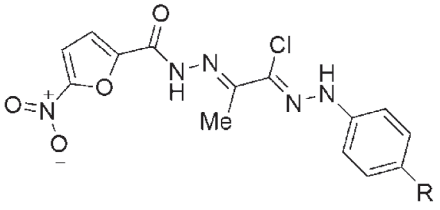
Fig. 9. 5-Nitrofuran–triazole conjugates.



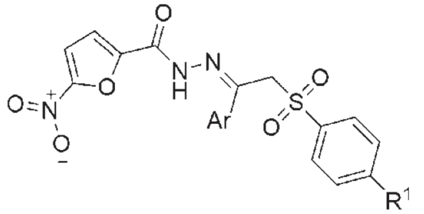
12

12a: R^1=F, R^2**=** H; **12b:** R^1= CF_3O-, R^2=H; **12c:** R^1=H, R^2=Ph; **12d:** R^1=H, R^2=$PhCH_2$- **12e:** R^1=H, R^2=$PhCH_2$-; **12f:** R^1=Cl, R^2=$PhCH_2$-; **12g:** R^1=F, R^2=$PhCH_2$-; **12h:** R^1=CH_3-, R^2= $PhCH_2$-

Fig. 10. 5-Nitrofuran-Isatin hybrids.



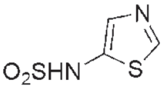
13



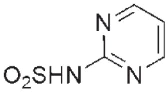
14

13a: R=H; **13b:** R=F; **13c:** R=Cl; **13d:** R=CH_3-; **13e:** R= CH_3O-; **13f:** R=SO_2NH_2;

13g: R=

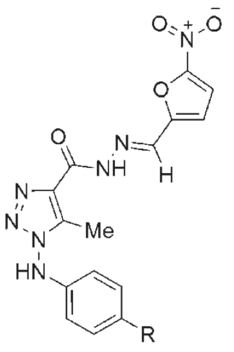


; **13h:** R=



14a: R^1=H, Ar=Ph; **14b:** R^1=H, Ar=4-FC_6H_4; **14c:** R^1=H, Ar=4-ClC_6H_4; **14d:** R^1=Me, Ar= 4-$NO_2C_6H_4$; **14e:** R^1=H, Ar=2-thiophenyl

Fig. 11. 5-Nitrofuran-2-yl hydrazones.



15

15a: R=H; **15b:** R=Cl; **15c:** R=Br; **15d:** R=F

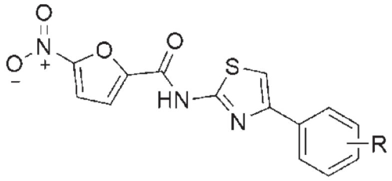
Fig. 12. 4-Acylhydrazone derivatives.

isatin ring, displayed an enhanced activity with MIC 1.25 μg/mL, while compound **12g** was found to be the most selective. The results against the single resistant strains revealed comparable activities, among which compound **12d** showed an enhanced activity against a streptomycin-resistant strain (MIC < 0.078 μg/mL), rifampin- and ofloxacin-resistant strains (MICs = 0.024 and 0.098 μg/mL, respectively). The authors stated that compound **12d** could be a potential candidate for further discovery and development of anti-TB compounds that are active against resistant MTB strains. It can be stated that, the improved anti-TB activity against resistant MTB of these hybrid molecules which obey the previously reported hypothetical pharmacophoric model for anti-TB activity [40], could be explained by virtue of the introduction of the 5-nitrofuran moiety, which can be confirmed by synthesis and anti-TB investigations of desnitro derivatives. Expansive SARs, physicochemical properties and in vivo pharmacokinetic studies are required to guide further development of these compounds into clinical trial settings.

Although nitrofuran hydrazones were moderately active against MTB [42], they could serve as a pool for the production of compounds with improved activity and low toxicity using hit-to-lead exploration. In this context, thirteen 5-nitrofuran-2-yl hydrazones **13** and **14** (Fig. 11) displayed moderate antimycobacterial activities (MIC = 3.9–125 μg/mL). Compound **13f** was the most potent (MIC = 3.90 μg/mL), indicating the importance of the sulfonamido moiety. None of the investigated compounds displayed significant cytotoxic activity, indicating selectivity and, consequently, a high therapeutic index. When the 5-nitrofuran in these compounds was replaced by a thiophene moiety, a significant reduction in activity was observed, confirming that the 5-nitrofuran group was an essential structural feature for anti-TB activity.

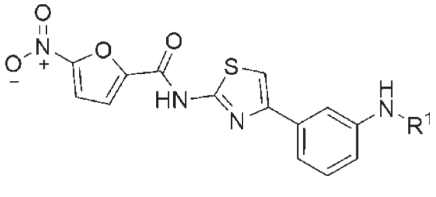
The enhanced activity of the less cytotoxic compound **13f** may be attributed to the formation of toxic free radical reported in 5-nitrofuran derivatives in addition to the influences of sulphonamido moiety. This compound can serve in future development of anti-TB compounds, however, comprehensive SARs through synthesis of various analogs could lead to a highly potent anti-TB candidate.

In silico SARs analysis of certain 4-acylhydrazone **15** (Fig. 12) [43]



16

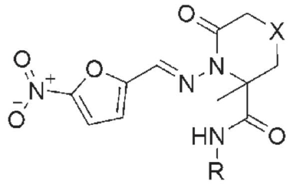
16a: R=H; **16b**: R=3-OMe; **16c:** R=4-OMe; **16d:** R=2-OMe; **16e:** R=3-F; **16f:** R=3-Cl; **16g:** R=3-Br; **16h:** R=3-OCH_2CH_3; **16i:** R=3-$OCH(CH_3)_2$; **16j:** R= 3-cyclopentyloxyl; **16k:** R= 3-acetamido; **16l:** R= 2,4,6-trimethyl; **16m:** R= 2,4,6-trifluoro



17

17a: R^1=cyclopropane carbonyl; **17b:** R^1=cyclobutanae carbonyl; **17c:** R^1=cyclopentane carbonyl; **17d:** R^1=cyclohexane carbonyl; **17e:** R^1=benzoyl; **17f:** R^1=4-F-benzoyl; **17g:** R^1=3-CF_3-benzoyl; **17h:** R^1=4-OMe-benzoyl; **17i:** R^1=methylsulfonyl; **17j:** R^1=benzyl sulfonyl

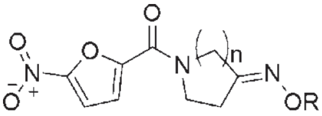
Fig. 13. 2-Aminothiazole conjugated nitrofuran derivatives.



18

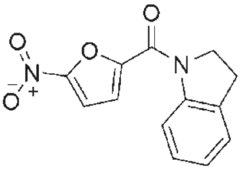
18a: R=cyclohexyl, X=direct bond; **18b:** R=4-$ClC_6H_4CH_2$, X=direct bond; **18c:** R=t-Bu, X=direct bond; **18d:** R=Bn, X=direct bond; **18e:** R=cyclohexyl, X=CH_2; **18f:** R=t-Bu, X=CH_2; **18g:** R=Bn, X=CH_2; **18h:** R=4-$ClC_6H_4CH_2$, X=CH_2; **18i:** R=cyclohexyl, X=S; **18j:** R=Bn, X=S; **18k:** R=cyclohexyl, X=O; **18l:** R=Bn, X=O; **18m:** R=t-Bu, X=O; **18n:** R=cyclohexyl, X=2-$O_2NC_6H_4SO_2N$; **18o:** R=cyclohexyl, X=$MeSO_2N$

Fig. 14. 5-Nitro-2-furfurylidene *N*-aminolactams.



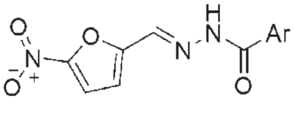
19

19a: n=1, R=Bn; **19b:** n=2, R=Bn; **19c:** n=2, R=4-FBn; **19d:** n=2, R=4-CF_3Bn; **19e:** n=2, R=4-NO_2Bn; **19f:** n=2, R=4-OCF_3Bn; **19g:** n=1, R=Me; **19h:**n=1, R=Et; **19i:** n=2, R=Me; **19j:** n=2, R=Et



20

Fig. 15. Oxime-functionalized nitrofuranylamides.

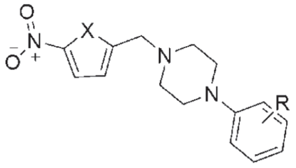


21

21a: Ar=Ph; **21b:** Ar=2-BrPh; **21c:** Ar=3-BrPh; **21d:** Ar=4-BrPh; **21e:** Ar=2,4-ClPh; **21f:** Ar=4-OCH_3Ph; **21g:** Ar=4-CH_3Ph; **21h:** Ar=3,4,5-OCH_3Ph; **21i:** Ar=1-Naphthylmethyl.

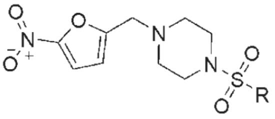
Fig. 16. 5-Nitrofuran-2-yl derivatives.

revealed the importance of 5-nitrofuran for the antimycobacterial activity by orienting the molecule for better interactions with the bacterial target. Confirming the *in silico* analysis, the MIC assays against MTB H37Rv revealed that the nitrofuran analog **15a** is the most active compound of this triazole series substituted by different aromatic systems (MIC = 2.5 μg/mL), with similar activity to the currently used



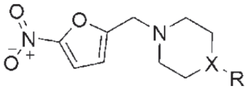
22

22a: X=S, R=H; **22b:** X=S, R=4-Cl; **22c:** X=S, R=4-Acetyl; **22d:** X=O, R=4-Me; **22e:** X=O, R=4-OMe; **22f:** X=O, R=4-t-Bu; **22g:** X=S, R=4-Cl; **22h:** X=S, R=4-Morpholinyl; **22i:** X=S, R=4-Acetyl; **22j:** X=O, R=3-OMe; **22k:** X=O, R=3-CN; **22l:** X=O, R=2-OMe



23

23a: R=Me; **23b:** R=Ph; **23c:** R=4-MePh; **23d:** R=4-OMePh; **23e:** R=4-NO_2; **23f:** R=4-CF_3; **23g:** R=4-FPh; **23h:** R=3-OMePh



24

24a: X=CH, R=Ph; **24b:** X=O

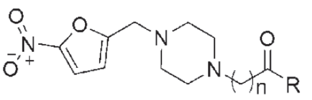
Fig. 17. 5-Nitrofuranyl methylpiperazines.

anti-TB drug ethambutol (MIC = 2 μg/mL). The derivatives **15b,d** also displayed good activity (MIC = 5.0 μg/mL). It was also observed that para-halogen substitution in the *N*-phenyl ring reduced the activity. It seems that low lipophilicity is required for optimum activity, and R group substitution and shifting to other ring positions could expand the possibilities for future development of anti-TB candidates.

2-Aminothiazole conjugated nitrofurans **16** and **17** (Fig. 13) were synthesized by Ran et al. [44] and screened for their possible anti-TB activity. The SARs of the tested compounds were deduced from their inhibitory rates (%Inh) against MTB H37Ra at the concentrations of 10 μM and 1 μM in vitro, using ciprofloxacin as standard drug. Compounds **16a-m** resulted in > 99% inhibition of bacterial growth at 10 μM, while compounds **16e, i-k** displayed > 95% inhibition at 1 μM. The role of the nitrofuran moiety was investigated by synthesizing analogs in which the nitrofuran group was replaced by furan, 4-nitrobenzene and 2-aminofuran. Despite the reduction in cytotoxicity which was investigated in Vero cells by MTT assay, a total loss of anti-TB activity was observed, confirming the necessity of 5-nitrofuran ring existence in such compounds. Moreover, a sharp loss of activity was observed at 1 μM concentration when the methoxy of **16b** was replaced by a hydrogen atom (**16a**), suggesting that the substituent on the benzene ring is an important structural feature. Shifting of the methoxy group in compound **16b** to ortho-position **16d** or para-position **16c** was also associated with a reduction in activity, indicating the beneficial effect of meta-substitution. Compounds **17a,d,e** were the most active, with > 99% inhibition at both tested concentration levels among the **17a-j** series. The MIC values of the most active eight compounds, **16e,k,l,m, 17a,d,e,j,** whose inhibitory rates were higher than 90% against H37Ra MTB, ranged from 0.27 to 1.00 μg/mL; compound **17e** was the most active among them (MIC = 0.27 μg/mL) and was approximately four times more active than the standard drug ciprofloxacin. However, the inherent problem of the metabolic instability of the amide bond previously reported [22,39] could lead to metabolic instability of this promising lead and consequently a shorter half life in the in vivo studies, and so bioisosteric replacement of this functionality could improve the potency against active as well as dormant MTB.

Krasavin et al. [45] have reported a series of 5-nitro-2-furfurylidene *N*-aminolactams with selective activity against MTB **18** (Fig. 14) using isocyanide-based multicomponent chemistry. Specifically, compounds (**18e,i,n**) which share a significant structural similarity exhibited activity against MTB, with MIC values of 22, 32 and 33 μM, respectively. In addition, these compounds displayed inhibitory activity against several MDR and poly-resistant patient-derived mutant strains, particularly, active against the MDR 2067 strain and were devoid of significant cytotoxicity. Compound **18n** was active against 2067 MDR and 5307 poly-resistant strains with an MIC of 11 μM. It is important to note that the three compounds which showed the highest anti-TB potency shared a cyclohexyl substitution at the exocyclic amide bond. Since this scaffold is amenable to chemical manipulations, authors believed that their activity could further be improved together with the reduction in toxicity through substitution of the labile hydrazone linker while keeping the pharmacophoric 5-nitrofuran-2-yl and cyclohexyl substituents. However, the amide linkage could let these compounds susceptible to the metabolizing enzyme and hence with shorter in vivo efficacy and so this amide bond should be replaced by other resistant chemical groups.

Based on the promising anti-TB activities exploited by oxime-functionalized compounds [46–49], Fana et al. [50] synthesized oxime-functionalized nitrofuranylamides **19** and **20** (Fig. 15) and tested their activities against both H37Ra MTB and drug-resistant clinical isolates.



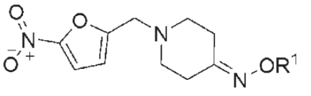
25

n=0

25a: R=Me; **25b:** R=s-Bu; **25c:** R=i-Bu; **25d:** R=t-Bu; **25e:** R=c-C_6H_{11}; **25f:** R=Ph; **25g:** R=4-OMePh; **25h:** R=4-FPh; **25i:** R=Ph(Me)N

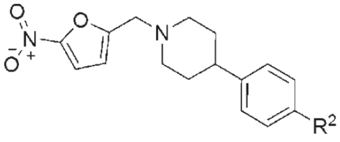
n=1

25j: R=Me; **25k:** R= EtO; **25l:** R=t-BuO; **25m:** R= $PhCH_2O$; **25n:** R=Et_2N; **25o:** R=$PhCH_2NH$



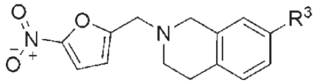
26

26a: R^1=Me; **26b:** R^1=Et; **26c:** R^1=$PhCH_2$; **26d:** R^1=4-$MeOPhCH_2$; **26e:** R^1=4-NO_2PhCH_2; **26f:** R^1=4-CF_3PhCH_2

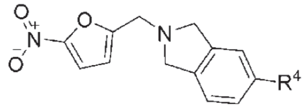


27

27a: R^2=F; **27b:** R^2=Br; **27c:** R^2=CF_3; **27d:** R^2=MeO; **27e:** R^2=CF_3O

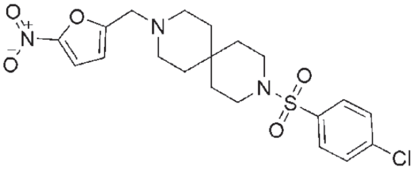


28

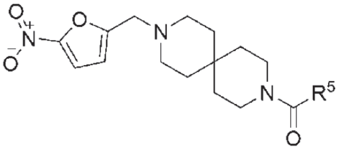


29

28a: R^3=Cl; **28b:** R^3=Br; **28c:** R^3= CN; **28d:** R^3= MeO; **29a:** R^4=H; **29b:** R^4=F; **29c:** R^4=CN

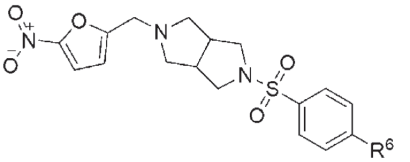


30

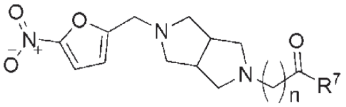


31

31a: R^5=Me; **31b:** R^5= i-Bu; **31c:** R^5=c-C_6H_{11}



32

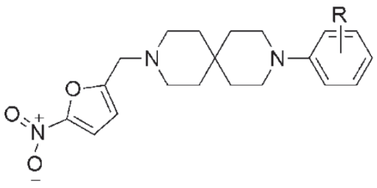


33

32a: R^6=t-Bu; **32b:** R^6=MeO; **32c:** R^6=CF_3; **32d:** R^6=NO_2; **33a:** n=0, R^7=t-Bu; **33b:** n=0, R^7=c-C_6H_{11}; **33c:** n=2, R^7=Me

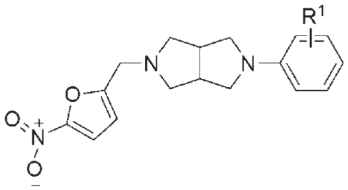
Fig. 18. Nitrofuranyl methyl *N*-heterocycles.

Six of these derivatives were active against the MTB H37Rv strain (MIC = 0.158–14.145 μg/mL). The most active agents **19a,b** (MIC = 0.291 and 0.158 μg/mL) were comparable to INH and RIF (MIC = 0.035 and 0.059 μg/mL). Similarly, the nitrofuranylamide **20** lacking the oxime group also displayed activity against the MTB H37Rv strain (MIC = 0.482 μg/mL). Compounds **19a,b,g,i** along with compound **20**, which were active against the standard strain, were evaluated against two clinically isolated 16,833 and 16,995 MDR-TB strains



34

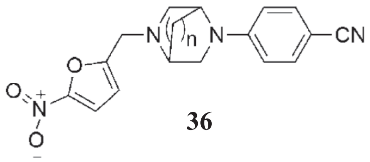
34a: R=4-OCH3; **34b:** R= 4-OCF3; **34c:** R= 4-CF3; **34d:** R=3-CF3



35

35a: R^1=H**;** **35b:** R^1=4-F; **35c:** R^1=4-CN; **35d:** R^1=4-t-Bu; **35e:** R^1=3-t-Bu; **35f:** R^1=4-OCF3;

35g: R^1=4-CF3; **35h:** R^1=3-CF3



36

36a: n=1; **36b:** n=2

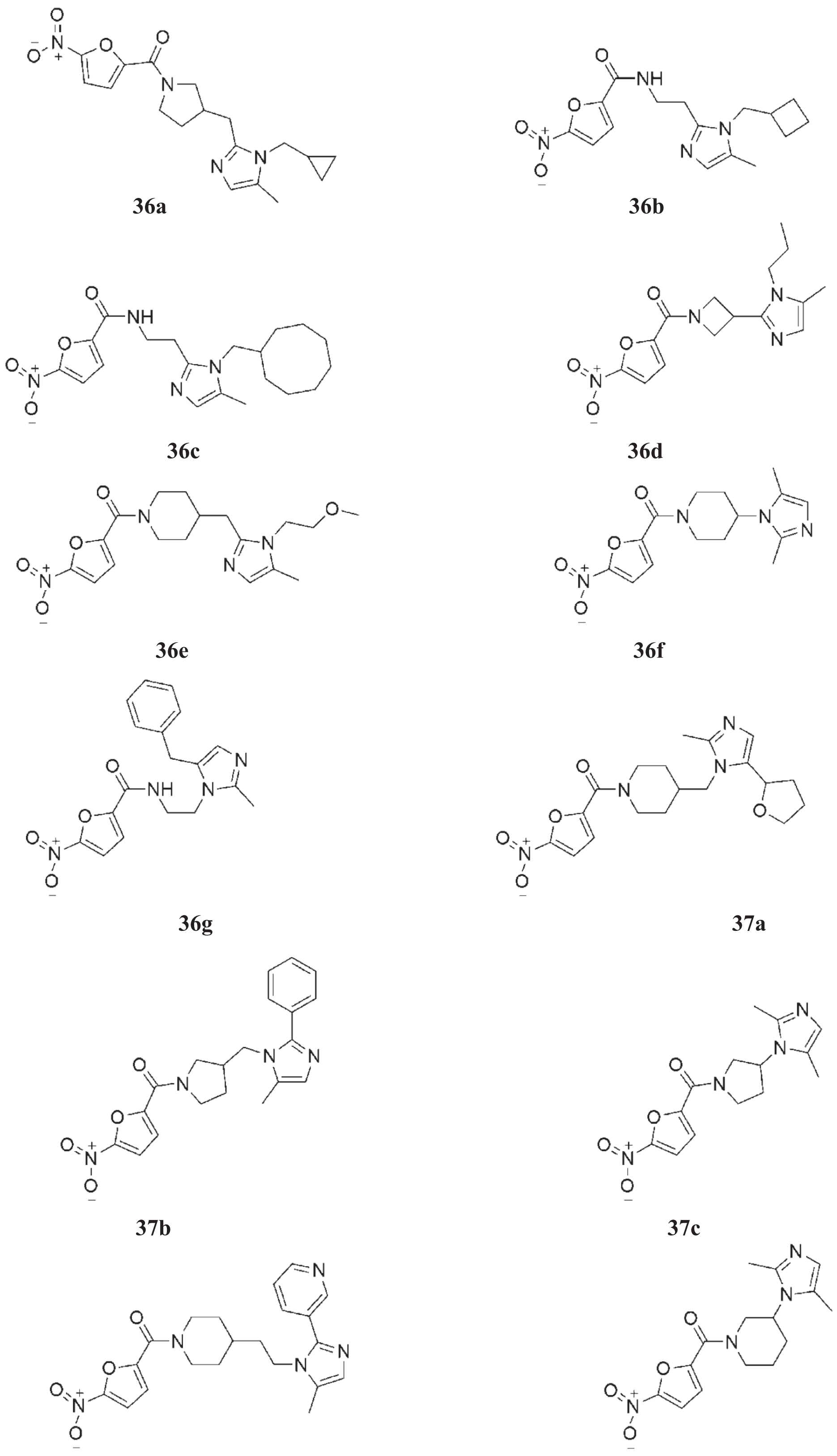
Fig. 19. Nitrofuranyl methyl *N*-heterocycle derivatives.

that were resistant to INH and RIF. Likewise, **19a,b** exhibited potent activities (MIC = 0.207–0.482 μg/mL) which were significantly higher than those of the standard drugs INH (MIC > 40 μg/mL) and RIF (MIC > 40 μg/mL) against MDR-TB 16,833 and 16,995 strains. On the other hand, the nitrofuranylamide **20** (MIC > 4 μg/mL) was inactive against the two MDR-TB strains, indicating that the oxime functionality is an important structural feature for activity against MDR-TB strains. Resistance index (RI) for compounds **19a,b,g,I** was ~1 pointing to the unique mechanism of action for these derivatives. SARs revealed that oxime-functionalized nitrofuranylamides decorated with piperidinyl were slightly more potent than the corresponding analogs with pyrrolidinyl against all tested strains and that the presence of the oxime functionality influences the activity and also compounds incorporating benzoxime functionality were more potent than their corresponding alkyloxime analogs. Beside this, dramatic reduction in anti-TB activity was observed for introduction of (F, CF_3, NO_2 and OCF_3). With regard to alkyloxime derivatives, those with shorter alkyl groups were more potent than the corresponding long chain analogs. Based on these findings, this class of compounds definitely holds promise towards the quest to discover potential anti-TB leads.

5-Nitrofuran-2-yl derivatives **21** (Fig. 16) were synthesized by Gupta et al. [51] and tested against MTB. These compounds displayed excellent anti-TB activity, and their MIC values ranged from 0.78 μg/mL-12.5 μg/mL. The most active compound **21e** (MIC = 0.78 μg/mL) was two times more potent than the anti-TB drug ethambutol (MIC = 1.56 μg/mL), while compound **21d** was relatively less potent, with equipotent activity to ethambutol. SARs revealed that *ortho-* and *para-* substitution by electron withdrawing groups is crucial for the anti-TB activity and that the 5-nitrofuran-2-yl moiety was essential for activity.

Following the screening of more than 20,000 molecules by Yempalla et al. [52], nitrofuranyl methylpiperazines **22–24** (Fig. 17) emerged as potent anti-TB compounds with MIC values in the range of 0.17–0.0072 μM. SARs studies indicated the importance of the nitro group, as well as the furan moiety, since desnitro and thiophene analogs were not active below 10 μM concentration. Additionally, *meta-* and *para*-substitutions were favorable for anti-TB activity: specifically, bulkier groups such as 4-*t*-Bu and 4-morpholinyl in compounds **22f,h** greatly enhanced the activity, with MIC values of 0.0072 and 0.02 μM against the H37Rv strain of MTB, respectively. On the other hand, *meta*-substitution by small groups could also enhance the activity as in compounds **22j,k**, with MIC values of 0.047 and 0.019 μM, respectively. Modification of the phenyl ring in compounds **22** such as via replacement by alkyl/aryl-sulfonyl groups afforded compounds **23** derivatives with high potency, especially un/substituted-phenylsulfonyl analogs **23b-h** (MICs = 0.08–1.30 μM), with compound **23 g** being the most potent. The results also demonstrated the importance of the piperazine ring in favor of piperidine and morpholine rings as in compounds **24a,b**, respectively. Encouraged by these results, further investigations were done for the most potent compounds (MIC < 0.2 μM) against nonreplicating, RIF-resistant and MDR-MTB. Compounds **22f,h,k** and **23 g** exhibited the highest potency with low cytotoxicity, and compounds **22f** and **23 g** demonstrated excellent pharmacokinetic profiles.

The structure of the anti-TB lead IIIM-MCD-211 (**22f**) was used to design nitrofuranyl methyl *N*-heterocycles **25–33** (Fig. 18) [53]. These new heterocycles were screened against MTB H37Rv, and twenty-six of these compounds displayed potent activity, with MIC values below 1 μg/mL:**25c,d,e,g,i,m, 26b-f, 27a,b,d,e, 28a-d, 29bc, 30a** and **31a-d**. Compounds **25d**, **27b** and **29a** demonstrated the highest potency (MIC = 0.031–0.062 μg/mL), less than RIF and almost comparable to reference INH and IIIM-MCD-211 (**22f**) (MIC = 0.016 μg/mL). The authors postulate that the anti-TB activity is inherent to the *N*-

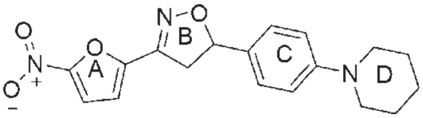


36a **36b** **36c** **36d** **36e** **36f** **36g** **37a** **37b** **37c** **37d** **37e**

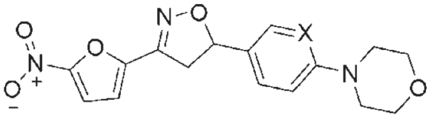
Fig. 20. 5-Nitrofuran-aminoalkylimidazole conjugates.

heterocycles and the substituents attached to them.

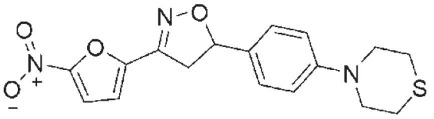
Motivated by the discovery of the highly potent and orally active anti-TB lead IIIM-MCD-211 **22f** with improved pharmacokinetic profile [52–54], a series of anti-TB nitrofuranylmethyl *N*-heterocycle derivatives **34–36** (Fig. 19) were developed and tested against the MTB H37Rv strain by Wang et al. [55]. All compounds exhibited potent activity with MIC values ranging from < 0.016–0.062 μg/mL, except compound **34a** with relatively higher MIC. Compounds **34b,c, 35e,f,h**



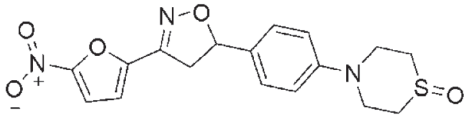
9e



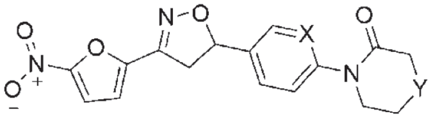
38a: X= CH; **38b:** X=N; **38C:** X=C-F



39



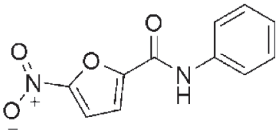
40



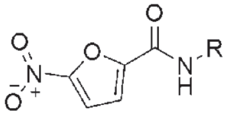
41

41a: X=CH, Y=N-Me; **41b:** X=N, Y=N-Me; **41c:** X=C-F, Y=N-Me; **41d:** X=CH, Y=O; **41e:** X=N, Y=O; **41f:** X=C-F, Y=O

Fig. 21. Nitrofuran-isoxazoline hybrids with improved pharmacokinetic properties.



42



43

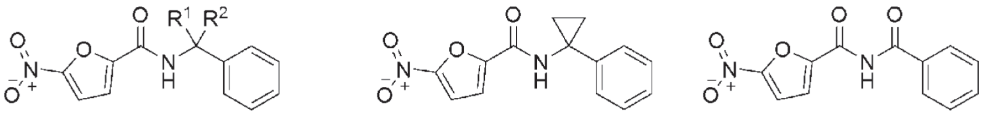
43a: R=Bn; **43b:** R=Phenylpropyl; **43c:** R=2-ClBn; **43d:** R=3-ClBn; **43e:** R=4-ClBn; **43f:** R=4-ClPh; **43g:** R=4-ClPhenethyl; **43h:** R=4-ClPhenylpropyl

Fig. 22. 2-Aroyl-5-nitrofuran-2-carboxamides 42 and 43.

and **36a**,**b** (MIC < 0.016 μg/mL) are more potent than the references INH/RIF (MIC = 0.078 μg/mL) with low cytotoxicity. Additionally, two of the most active compounds **35e,h** were further investigated against two MDR-TB clinical isolates that are resistant to INH and RIF, and their MICs were 0.016–2.22 μg/mL. SARs preliminary study revealed that *para*-substitution by electron withdrawing groups is superior to that at *meta*-position. Further modification in compounds **35e,f** by introducing *t*-Bu at the *meta*-position and an electron-withdrawing group (OCF_3) at the *para*-position, respectively, decreased the MIC values below 0.016 μg/mL. The noncytotoxic compound **35h** with potent activity against sensitive and resistant clinical isolates (MIC < 0.016 μg/mL) and with improved physicochemical properties may serve as potential lead for further exploration in the area of antitubercular drug discovery. Although comprehensive SARs are underway, investigations of in vivo efficacy and in vivo pharmacokinetic profiles of these derivatives in the future will shed the light on the possibility for further clinical development.

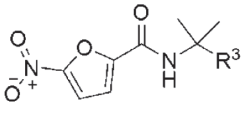
In an attempt to modify the nitrofuran periphery for potentiating the anti-TB activity and lessening the toxicity, taking into consideration the well established anti-TB activity of the nonnitrated imidazole [56], new 5-nitrofuran-aminoalkylimidazole conjugates linked by various aminoalkyl linkers **36** and **37** (Fig. 20) were developed [57]. Significant anti-TB activity was observed for all compounds against drug-sensitive H37Rv MTB. An enhancement in activity was observed when rigid cyclic structures were incorporated into the linker architectures. Of these twelve compounds, five compounds (**36a,b,d, 37d,e**) displayed the lowest MIC values (1.6–6.2 μg/mL). Compound **36d** emerged as the most potent (MIC = 1.6 μg/mL), with the same activity against three MDR-resistant clinical isolates, and with high in vivo efficacy comparable to the reference ethambutol and with a low in vivo toxicity profile. Despite the high in vitro and in vivo potency of these chimera derivatives, metabolic instability due to the presence of amide bond will constitute major difficulty facing their further development. Based on this, amide functionality should be further modified to attain potent anti-TB compounds yet metabolically stable.

Rakesh et al. [58] made an effort to enhance the pharmacokinetic properties of previously reported lead **9e** [38] and reported a series of tetracyclic isoxazoline-nitrofuran hybrids **38–41** (Fig. 21) with low solubility, strong binding to plasma protein and shorter in vivo half-life. Accordingly, solubilizing and metabolically blocking structural features were introduced in this series by modifying rings C and D. These compounds exhibited good anti-TB activity with MIC values ranging from 0.006 to 0.8 μg/mL. Compound **38a** retained high potency (MIC = 0.006 μg/mL), similar to the initial lead **9e**. SARs studies



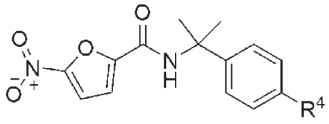
44 **45** **46**

44a: R^1=Me, R^2=H; **44b:** R^1=Me, R^2=Me; **44c:** R^1= Isopropyl, R^2=H; **44d:** R^1= Cyclopropyl, R^2= H; **44e:** R^1=t-Bu, R^2=H



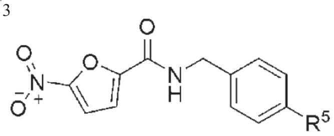
47

47a: **R^3=**2-benzothiophene; **47b:** **R^3=**2-benzofuran; **47c:** **R^3=**2-naphtyl



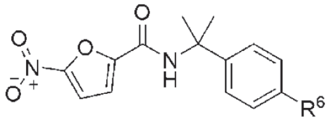
48

48a: R^4=4-Cl; **48b:** R^4=4-OMe; **48c:** R^4=4-Me_2N; **48d:** R^4=4-t-Bu; **48e:** R^4=4-OCF_3; **48f:** R^4=4-F; **48g:** R^4=4-CN; **48h:** R^4=4-CF_3



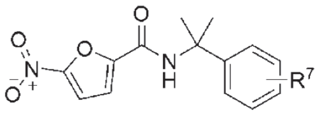
49

49a: R^5=4-ClPh; **49b:** R^5=4-ClPhO-; **49c:** R^5=4-morpholinomethyl; **49d:** R^5=4-chlorophenoxymethyl



50

50a: R^6=4-ClPh; **50b:** R^6=4-ClPhO-; **50c:** R^6=4-morpholinomethyl; **50d:** R^6=4-chlorophenoxymethyl

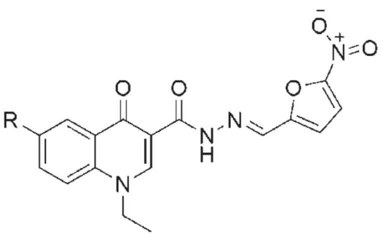


51

51a: R^7=4-methoxyphenoxymethyl; **51b:** R^7= trifluoromethoxyphenoxymethyl; **51c:** R^7=4-trifluoromethylphenoxymethyl; **51d:** R^7=2-Chlorophenoxymethyl; **51e:** R^7=2-methoxyphenoxymethyl; **51f:** R^7=2-trifluoromethoxyphenoxymethyl; **51g:** R^7=2-trifluoromethylphenoxymethyl

Fig. 23. 2-Aroyl-5-nitrofuran-2-carboxamides 44–51.

revealed that incorporation of non-polar groups elicited an increase in potency with paradoxical reduction in water solubility and metabolic stability. Compounds **38a**,**b** and **41a** exhibited better pharmacokinetic properties and still retained good to fair anti-TB activity. A relatively longer half-life and tolerability signified the propensity of compound **41a** for in vivo testing. 5-Nitrofuran and isooxazoline moieties appear to be related to the anti-TB activity, while the other rings can modify this activity and improve solubility and metabolic stability, and so ring C and D can be subjected to further modification by introduction of different substituents to improve the anti-TB activity while retaining good pharmacokinetic profile. Moreover, ring B which replaces the amide moiety can be subjected for further exploration by trying



52

52a: R=H; **52b:** R=Cl

Fig. 24. Oxoquinoline-based 5-nitrofurans.

different similar ring systems.

Despite the demonstration of excellent in vitro and in vivo efficacy, the majority of recently reported 5-nitrofuran derivatives were not transferred to clinical studies [24,39–41,50]. Recently, many authors have attempted to develop new antitubercular leads with absent or low toxicity, small MICs and acceptable pharmacokinetic profiles. In this context, *N*-benzyl-5-nitrofuran-2-carboxamide (JSF-3449) **42** (Fig. 22), which was reported earlier to possess anti-TB activity (MIC = 0.39 μM) against the H37Rv MTB [59], was subjected to an optimization by Gallardo-Macias [60] to attain new analogs **43** (Fig. 22). Anti-TB efficacy of these compounds with regard to linker length was as follows: 1 > 3 > > 0. Concerning the substituent effect, 4-substituted compound **43e** showed 4-fold enhancement in activity (MIC = 0.098 μM) with the linker maintained at 1.

Compounds **44a-e, 45** and **46** (Fig. 23) were prepared by substitution of benzylic carbon to improve metabolic stability. As a result, reduction in anti-TB activity with an improved selectivity index (**44b**, MIC = 0.78 μM) and pharmacokinetic profile was obtained. Based on these results, compounds **47a-c** (Fig. 23) were synthesized by maintaining α,α-dimethyl substitution and replacing the phenyl ring with a set of aromatic/heteroaromatic systems. This substitution afforded highly active anti-TB compounds (MIC = 0.0078–0.2 μM), and the most active of them were **47a,c** (MIC = 0.0078 and 0.078 μM), respectively. Decreased metabolic stability for **47a,b** prompted the researchers toward exploration of compounds **48** (Fig. 23) (4-substituted α,α-dimethylbenzylamide series). Compound **48e** with the 4-OCH$_3$ (MIC = 0.078 μM) analog was the most potent derivative, while the 4-CN (compound **48 g**) derivative was reported to be inactive. Nonetheless, no improvement in pharmacokinetic properties was detected for compound **48e**. Further modifications of methylene analogs by introducing bulkier substituents at position 4 of the benzylamide ring afforded the more efficacious compounds **49** (Fig. 23) (MIC = 0.039–1.2 μM). Compound **49d** demonstrated high potency in contrast to **49c**, the morpholino analog, which showed modest activity (MIC = 1.2 μM). Following this, α,α-dimethyl analogs **50** (Fig. 23) of compounds **49** were synthesized, and all compounds displayed a significant reduction in activity (MIC = 0.12–25 μM) relative to their corresponding methylene derivative. Due to its relatively high potency, compound **50d** was subjected to further manipulation by introducing various substituents in either the *meta*- or *para*-positions of the phenoxy ring to afford compounds **51** (Fig. 23). Compound **51a** displayed improved activity (MIC = 0.078 μM) compared to compound **50d** with low cytotoxicity. In addition, 2-OCH$_3$ substituted (compound **51e**; **JSF-4088**) demonstrated improved potency (MIC = 0.019 μM) and low cytotoxicity compared to compound **50d**. Despite the high potency, compound **51e** possessed a poor pharmacokinetic profile that necessitates further optimization, which remains a challenge for these highly efficacious anti-TB nitrofuran-2-carboxamide derivatives.

As discussed above, it can reasonably be concluded that, the low in vitro cytotoxicity and pharmacokinetic stability are interrelated. Thus, modification to improve these parameters would end up with setbacks in the antitubecular activity as the key factor is the substitution at the benzylic carbon.

Lately, quinoline hydrazones has gained much importance in anti-TB drug development, since they have produced outstanding results, facilitated by the synthetic flexibility of quinoline [61]. Based on this, oxoquinoline-based 5-nitrofurans **52a,b** (Fig. 24) have been found of value against the MTB H37Rv strain; **52a** was the most active compound (MIC = 6.25 μg/mL), and it could be subjected to further experimental exploration [62]. This activity could partially be explained by the expected dual inhibition mode of action of quinoline scaffold and nitrofuran moiety as pointed out from experimental and theoretical studies in this work.

3. Conclusion

Tuberculosis (TB) is a contagious disease that is considered one of the most dreaded diseases and is one of the top ten causes of mortality worldwide. The principal issues in current TB treatment that complicate the situation include the pathogen's latency, the association of TB with the emergence of HIV infection and the emergence of multi-, extensively and totally-resistant mycobacteria. Research aimed at the development of new anti-TB drugs based on the nitrofuran scaffold led to the identification of several candidates with a unique mode of action that were efficacious against actively growing as well as dormant mycobacteria. Nonetheless, these recently developed nitrofuran-based candidates were not transferred to the clinical trial setting, mainly due to poor pharmacokinetic profiles and/or toxicity; hence, optimization represents a significant challenge to this series of compounds with outstanding in vitro potency against MTB with low cytotoxicity.

Conflict of interest

The authors have declared no conflict of interest.

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