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Ionic liquid promoted one-pot synthesis of thiazole-imidazo[2,1-*b*][1,3,4]thiadiazole hybrids and their antitubercular activity†

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Abstract

In this paper, we report the facile and efficient one-pot three component synthesis of 1-((6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methylene)-2-(4-phenylthiazol-2-yl) hydrazine derivatives (**5a-w**) using an ionic liquid, 1-butyl-3-methyl imidazolium bromide ([Bmim]Br). The compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*. Compound **5s** showed the highest inhibitory activity with a MIC of 6.03 µM which is slightly lower than the MIC values of standard drugs ethambutol (15.3 µM) and ciprofloxacin (9.4 µM). Four other compounds of the series viz. **5e, 5i, 5t** and **5w** also showed significant inhibitory activity with MIC values in the range 11.7 - 13.9 µM. The structure-activity relationship revealed that a trifluoromethyl substitution at position-2 and a *p*-chlorophenyl substitution at position-6 of the imidazo[2,1-*b*][1,3,4]thiadiazole ring enhance the inhibition activity. Also, methyl, methoxy, fluoro or nitro substituents on the thiazole ring enhanced the activity of the compounds. None of the active compounds were toxic to a normal cell line (NIH 3T3) which signifies the lack of general cellular toxicity of the molecules. *In silico* molecular docking studies revealed the favourable interaction of the potent compounds with target enzymes, InhA and CP121.

Keywords: Imidazo[2,1-*b*][1,3,4]thiadiazole; 1,3-thiazole; ionic liquids; one-pot synthesis; *Mycobacterium tuberculosis*; Cytotoxicity; Molecular docking.

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1. Introduction

Tuberculosis (TB) is caused by the *Mycobacterium tuberculosis* (*Mtb*) and it mainly affects the lungs of human respiratory system. According to the report released from world health organization (WHO) in 2014,[1] around 9 million people fell sick and 1.5 million people died from the disease, 360 000 of them were HIV-positive. The current treatment with routine drugs for the treatment of multi drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) is prolonged and challenging with limited efficacy. Generally, the MDR-TB patients require treatment for 20 months and the drugs used for the treatment are more toxic and less effective than those used to treat drug-susceptible TB. Therefore, there is an emergence requirement for the development of novel pharmacophores to treat MDR-TB and XDR-TB effectively in a shorter duration and with fewer side effects.

In view of this, the imidazo[2,1-*b*][1,3,4]thiadiazole (ITD) scaffold[2-5] is a promising heterocyclic moiety to develop efficient antitubercular leads.[6,7] The derivatives with a pharmacophoric substitution at position-5 of the ring exhibited significant inhibition activity against *Mtb* H37Rv strain.[8,9] For instance, Alegaon et al. reported the synthesis and antitubercular evaluation of a series of 5-substituted ITD derivatives and the compound which contains a rhodanine acetic acid group (**I, Figure 1**) showed excellent antitubercular activity with a MIC of 3.12 μM.[10] In our earlier studies,[11,12] we incorporated a benzimidazole and 1,2,3-triazole moieties at position-5 of the ITD ring and evaluated the antitubercular activity of the hybrid molecules. Interestingly, most of the compounds (**II, III**) exhibited significant activity against *Mtb* H37Rv strain. These results motivated us to incorporate other pharmacophores at position-5 of the ITD ring and to investigate the effect of the structural modification on the antitubercular activity of the molecules. Further, the molecular design strategy which involves the hybridization of two active pharmacophores into a single molecular framework has become one of most promising approaches to develop potent antiTB agents. In this direction, we envisaged the integration of substituted thiazoles with the core ITD ring considering the fact that thiazole derivatives are being considered as important pharmacophores in the development of new antitubercular leads against *Mtb* H_{37}Rv strain.[13,14] In addition, the thiazole based molecules[15,16] exhibit low toxic level which is evident also from the safety profile of some of the marketed drugs like nitazoxanide, tizoxanide, aztreonam, meloxicam and relutex. Further, some thiazolylhydrazone derivatives (**IV-VI**) exhibited remarkable growth inhibitory activity against *Mycobacterium tuberculosis*.[17,18] For instance, Ozadali et al (2014) synthesized a series of thiazolyl hydrazone derivatives, among which compound **V** exhibited excellent activity with MIC_{MABA} of 1.03 μM.[19] So we have

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introduced the thiazole ring at position-5 of the ITD core through an amine-imine linkage. The target compounds, 1-((6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methylene)-2-(4-phenylthiazol -2-yl)hydrazines (**5a-w**) were synthesized by a one-pot three-component synthesis in an ionic liquid medium. Ionic liquids (ILs) unlike conventional organic solvents are non-volatile, green, non-hazardous, easy to handle and thermally durable.[20,21] Ionic liquids, particularly based on *N*-alkyl-3-methylimidazolium cation have exhibited great importance in modern heterocyclic chemistry and these are considered as substitution for conventional organic solvents.[22-24] So, 1-butyl-3-methylimidazolium bromide ([Bmim]Br), which is one of the widely used ILs, was employed in the present study. The one-pot reaction was carried out between three-components viz 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde, thiosemicarbazide and *p*-substituted phenacyl bromide. This method is highly atom efficient and there is no formation of by-products. Hence, the pure product was isolated straightaway (without column purification procedure) from the reaction system.

(Figure 1 here)

2. Results and discussion

2.1. Chemistry

One of the key intermediates, 5-methyl-1,3,4-thiadiazol-2-amine (**2a**) was synthesized by treating acetyl chloride with thiosemicarbazide whereas the other intermediate, 5-triflouro methyl-1,3,4-thiadiazole-2-amine (**2b**) was synthesized according to the reported procedure.[25] Compounds **3a–e** were synthesized by the reaction between **2a-b** and the corresponding substituted α-haloarylketone at 80-85 °C for 24 h. In the next step, these compounds **(3a–e)** were subjected to the Vilsmeier–Haack formylation reaction to afford 2-substituted-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes (**4a-e**).[10,11] For the synthesis of target molecules, a one pot synthetic protocol (**scheme 1**) was employed instead of conventional two step procedure[19] which generally takes a longer duration for the isolation of the final products. The solvent system, temperature and reaction time for the one-pot three-component protocol was optimized so as to get a good yield of the product. For this, the one-pot reaction of 2-methyl-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (**4a**) with thiosemicarbazide and 4-flouro phenacyl bromide (**scheme 2**) was investigated under different reaction conditions as presented in ESI (Table S1). Among these, the reaction in a mixture of [bmim]Br and ethanol at 80° C resulted in a better product (**5e**) yield. Also, the reaction under this condition was complete in a shorter duration of 30 minutes. The optimized reaction condition was applied for the reaction of all five aldehydes (**4a-e**) with

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thiosemicarbazide and different phenacyl bromides. The corresponding derivatives (**5a-w**) were isolated in good yields. The structural features, reaction time and yield of the target compounds (**5a-w**) are given in ESI (Table S2). The plausible reaction mechanism for the formation of final derivatives (**5a-w**) is shown in the **scheme 3**.

(Scheme 1 here)

(Scheme 2 here)

(Scheme 3 here)

The target molecules were analysed using spectroscopic techniques to confirm their structure. For instance, the ^{1}H NMR spectrum of compound **5e** showed a singlet with one proton at δ 12.14 ppm due to the -NH proton. Another singlet at δ 8.41 ppm is due to the -CH proton of the imine (CH=N-) linkage. The singlets at δ 2.80 and 2.38 ppm represent the methyl protons on the 1,3,4-thiadiazole and phenyl rings respectively. The spectrum displayed a multiplet in the region δ 7.93 – 7.81 ppm and two triplets at δ 7.31 and 7.24 ppm due to the aromatic protons. Also, its mass spectrum showed a molecular ion peak at *m/z* 449.0, which corresponds to M+1 peak of the molecule. The ^{1}H and ^{13}C NMR spectral data along with the elemental data of all the target molecules and some representative spectra are given in the ESI.

2.2. *In vitro* antimycobacterial activity

The target compounds (**5a-w**) were screened against *Mtb* H37Rv (ATCC27294) using the agar dilution method to evaluate their antimycobacterial activity in terms of minimum inhibitory concentration (MIC) values. The MIC is defined as the minimum concentration of a compound required to completely inhibit the bacterial growth. The MIC values of **5a-w** along with those of standard drugs for comparison are presented in **Table 1 and Figure 2**. Compound, 1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-*b*] [1,3,4] thiadiazol-5-yl) methylene)-2-(4-*p*-tolyl thiazol-2 yl)hydrazine (**5s**) is the most active derivative of the series and its MIC (6.03 μM) is lower than those of standard drugs, ethambutol and ciprofloxacin. Additionally, compounds **5e**, **5i**, **5t** and **5w** with MIC values 13.94, 12.72, 11.70 and 11.97 μM respectively are more active than ethambutol. The structural activity relationship reveals that the various substituents (R^1/R^2) on the imidazo[2,1-*b*][1,3,4]thiadiazole ring affect significantly the antitubercular activity of the compounds. The trifluoromethyl substitution at position-2 (R^1) was found to enhance the activity of the molecules. All the trifluoromethyl substituted derivatives except **5q**, showed lower MIC values than their methyl analogues. That is to say, compounds **5o**, **5p**, **5r**, **5s**, **5t**, **5u** and **5w** are more active than compounds **5f**, **5g**, **5j**, **5k**, **5l**, **5m** and **5n** respectively. Among trifluoromethyl substituted derivatives, the *p*-

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chlorophenyl substituted (*i.e* R^2 = Cl) compounds (**5s**, **5t**, **5u** and **5w**) showed better activity than the respective *p*-methoxyphenyl (*i.e* R^2 = OCH_3) analogues (**5o**, **5p**, **5q** and **5r**). A similar structure-activity relationship was observed with most of the methyl (R^1) substituted derivatives (**5f - 5n**) as well. Though the substituents (R^3) on the thiazole ring affect remarkably the activity of the compounds, we did not observe a uniform trend in the structure-activity relationship. However, compounds with methyl, methoxy, fluoro or nitro substituents on the thiazole ring showed significant activity. Hence, the imidazo[2,1-*b*][1,3,4]thiadiazole ring with a trifluoromethyl group at position-2 and a *p*-chlorophenyl substituent at position-6 could be an active core for further structural modification, particularly by introducing different pharmacophoric units at position-5 of the core structure, in order to develop promising antiTB agents.

(Figure 2 here)

2.3. Antibacterial activity

The *in vitro* antibacterial activity of compounds **5a-w** was tested using serial plate dilution method.[26] All the compounds were screened against three bacterial strains *viz. S. aureus*, *P. aeruginosa* and *E. coli.* The MIC values were evaluated at concentration range of 3.125 - 50 µg/mL and ciprofloxacin was taken as the standard drug. Compound **5w** demonstrated significant inhibition activity against all three tested bacterial strains. The antibacterial screening results are displayed in **Table 1**. It can be seen that the molecules show a better inhibition activity against *Mtb* H37Rv when compared to their activity against the other tested bacterial strains. So it may be concluded that these molecules are somewhat selective in their inhibition action against *Mtb* H37Rv strain.

(Table 1 here)

2.4. *In vitro* cytotoxicity studies

The *in vitro* cytotoxicity of the active compounds (MIC ≤ 30 µM against *M. tuberculosis*) was evaluated against NIH 3T3 mouse embryonic fibroblasts cell line using MTT assay.[27] The cell growth inhibition of potent compounds at a concentration of 50 µg/mL is shown in **Figure 3**. It can be seen that none of the active compounds are toxic to the normal cells thus proving the lack of general cellular toxicity.

(Figure 3 here)

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2.5. Molecular docking studies

In order to gain an insight about the mechanism of action of the new thiazole-ITD hybrids, the active molecules were subjected to molecular docking studies against two enzymes, enoyl-acyl carrier protein reductase (InhA) and cytochrome P450 monooxygenase (CYP121) of *M. tuberculosis,* which have been validated as effective anti-TB targets.[19] Further, Isoniazid (the first line antiTB drug) acts by inhibiting enoyl acyl carrier protein reductase (InhA). Recent studies on thiazolylhydrazone and 1,3,4-thiadiazole derivatives with InhA revealed good binding interaction of these molecules with amino acid residue of the enzyme.[28,29] InhA is one of the key enzymes involved in the type II fatty acid biosynthesis pathway. Tyr 158 is an important amino acid residue which interacts with the long chain fatty acyl substrates required for the synthesis of mycolic acids in the mycobacteria.[30,31] On the other hand, cytochrome P450 monooxygenase (CYP121) was selected based on the earlier reports on active inhibition of the target by some triazole derivatives.[28] The molecules synthesized in the present study also belong to the azole group of compounds. The molecules were docked with in the active sites of InhA (PDB code: 1P44) and CYP121 (PDB code: 4KTF) using Glide 6.6 (Schrodinger, 2015-1). The ligands from the crystal structure of the enzyme-ligand complexes were rebuilt and redocked to validate the docking procedure. The RMSD values of the docking pose from the original orientation of the ligands were found to be 0.6106 and 1.1467 Å respectively for 1P44 and 4KTF. The docking poses of molecules **5d**, **5s** and **5w** are shown in **figure 4**. Compound **5d** showed the highest docking score of -8.89 with 1P44 and exhibited H-bond interactions with residues Ala 157, Gly 104 (back bone) and Gln 100 (side chain) as well as π-π stacking interaction with residues Phe 149 and Tyr 158. The most potent anti-TB compound **5s** with a docking score of -7.23 showed π-π stacking interaction with residues Phe 149 and Tyr 158. It is interesting to note that most of the active compounds have shown interaction with amino acid residue Tyr 158. Similarly, the active compounds showed favourable interactions with enzyme 4KTF as well. Compound **5w** has the highest docking score of -9.75 whereas compound **5s** with a docking score of -8.27 showed an H-bond interaction with Ala 167 and π-π stacking interactions with Phe 168 and Trp 182. The docking score of all the active molecules and details of interacting amino acid residues are given in ESI (Table S3).

(Figure 4 here)

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3. Conclusions

We synthesized a series of 1-((6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl) methylene)-2-(4-phenylthiazol-2-yl)hydrazine derivatives via one-pot three-component approach using an ionic liquid ([Bmim]Br), with excellent product yields. The antitubercular screening of the molecules revealed that derivative **5s**, which contain a trifluoromethyl and a *p*-chlorophenyl substituents at positions-2 and 6 respectively of the ITD ring, is the most active molecule with an MIC of 6.03 μM. The inhibition activity of this molecule is higher than that of the standard drugs Ethambutol and Ciprofloxacin. Other four derivatives, **5e**, **5i**, **5t** and **5w** showed better inhibitory activity than ethambutol. The trifluoromethyl substituted derivatives exhibited superior activity when compared to the activity of methyl substituted analogues. Also, it was observed that a *p*-cholorophenyl substitution (at position-6 of the ITD ring) contributes better than a *p*-methoxyphenyl group towards the antitubercular activity. The structure-activity relationship revealed that the imidazo[2,1-*b*][1,3,4]thiadiazole ring with a trifluoromethyl group at position -2 and a *p*-chlorophenyl substituent at position -6 could be an active core for further structural modification in order to develop potent antiTB agents. Further, none of the active molecules are toxic to a normal cell line which signifies the lack of general cellular toxicity. Also, these molecules are somewhat selective in their inhibition action against *Mtb* H37Rv strain. The molecular docking studies revealed the strong interaction of the active molecules with the target enzymes, InhA and CP121. Active compounds **5d, 5e, 5h, 5i** and **5s** showed interaction with amino acid Tyr 158 which is an important residue to interact with the long chain fatty acyl substrates required for the synthesis of mycolic acids in the mycobacteria. Hence, these compounds with significant inhibition activity could serve as promising lead molecules for further development as anti-TB agents.

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Table 1. *In vitro* inhibition activity of title compounds (**5a-w**) against *Mycobacterium tuberculosis*, *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli.*

Compound	*M. tuberculosis*		*E. coli*	*S. aureus*	*P. aeruginosa*
	MIC (μg/mL)	MIC (μM)	MIC (μg/mL)	MIC (μg/mL)	MIC (μg/mL)
5a	25	56.29	50	50	25
5b	50	108.66	50	50	25
5c	25	53.87	50	50	50
5d	12.5	26.31	6.25	12.5	12.5
5e	6.25	13.94	50	50	50
5f	50	108.66	50	50	50
5g	50	105.01	12.5	50	50
5h	12.5	26.03	6.25	12.5	12.5
5i	6.25	12.72	25	25	25
5j	50	107.73	50	50	50
5k	50	107.74	50	50	50
5l	25	52.07	25	50	50
5m	50	103.1	25	25	25
5n	25	53.87	25	25	50
5o	12.5	24.13	25	50	25
5p	50	94.32	12.5	25	25
5q	50	93.63	50	50	50
5r	6.25	24.12	50	50	25
5s	3.125	6.03	25	25	25
5t	6.25	11.70	12.5	25	25
5u	50	92.94	12.5	12.5	50
5v	50	91.07	12.5	12.5	25
5w	6.25	11.97	6.25	12.5	6.25
Ciprofloxacin	3.125	9.44	6.25	6.25	6.25
Isoniazid	0.1	0.729	-	-	-
Ethambutol	3.125	15.32	-	-	-

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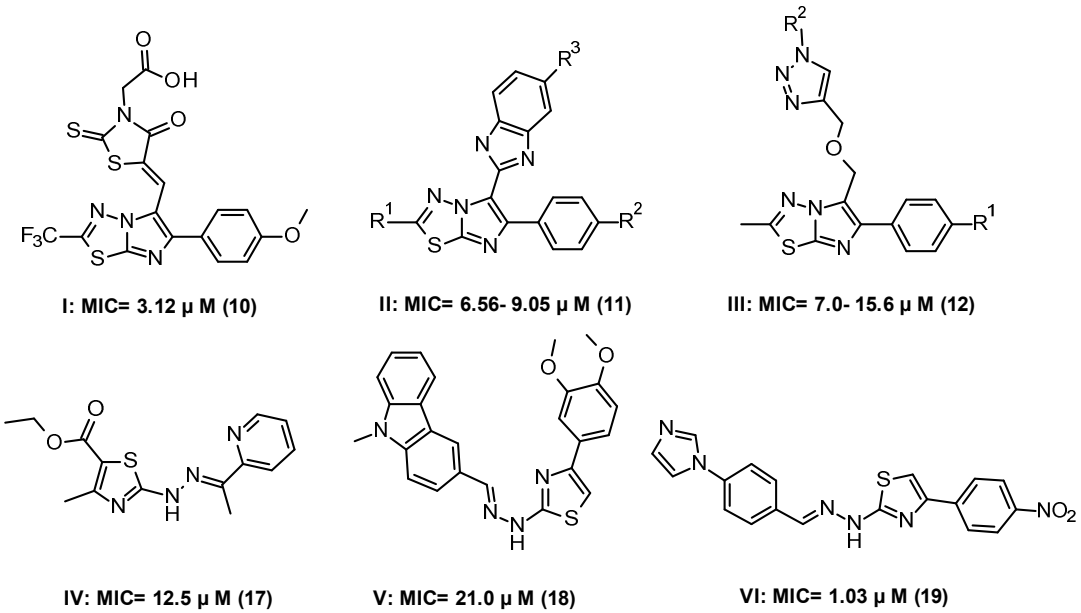

Figure 1.

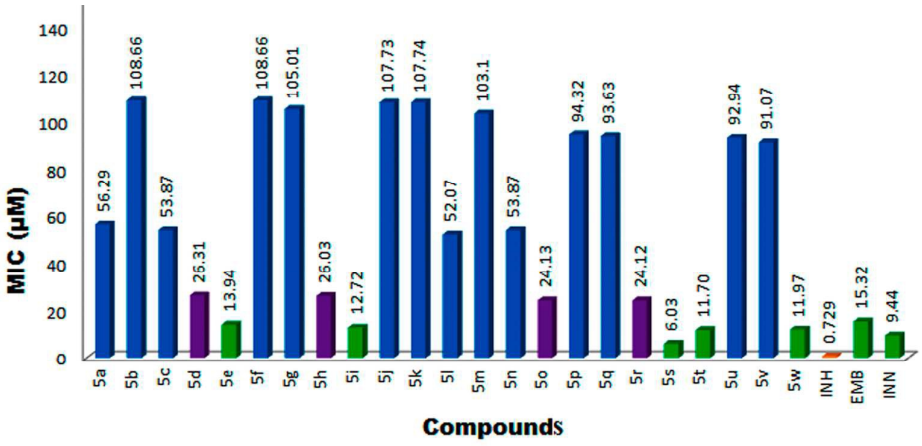

Figure 2

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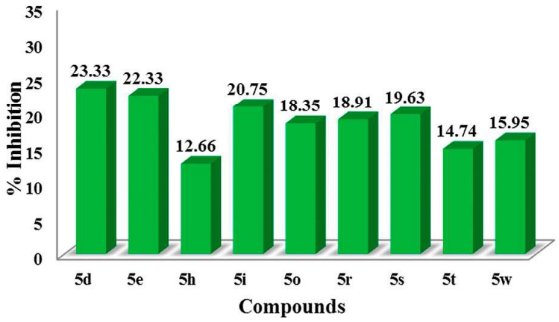

Figure 3

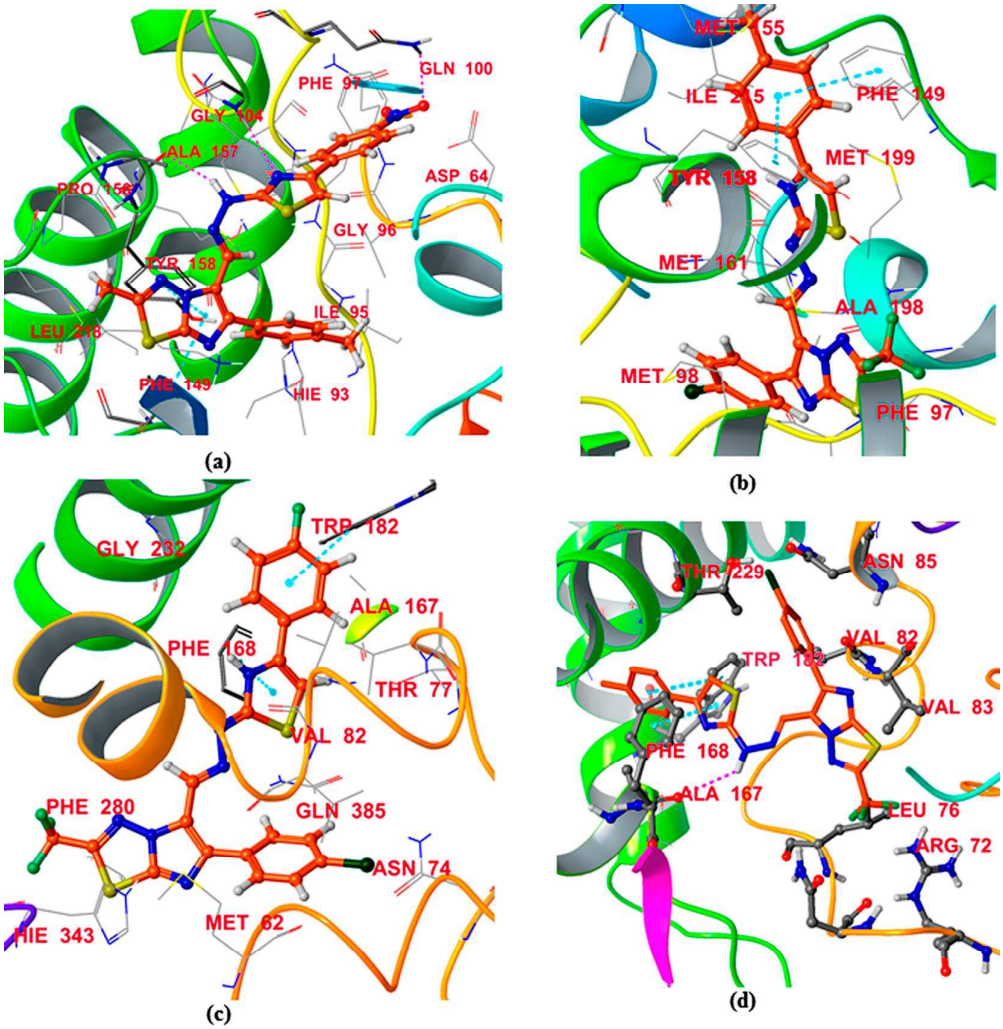

Figure 4

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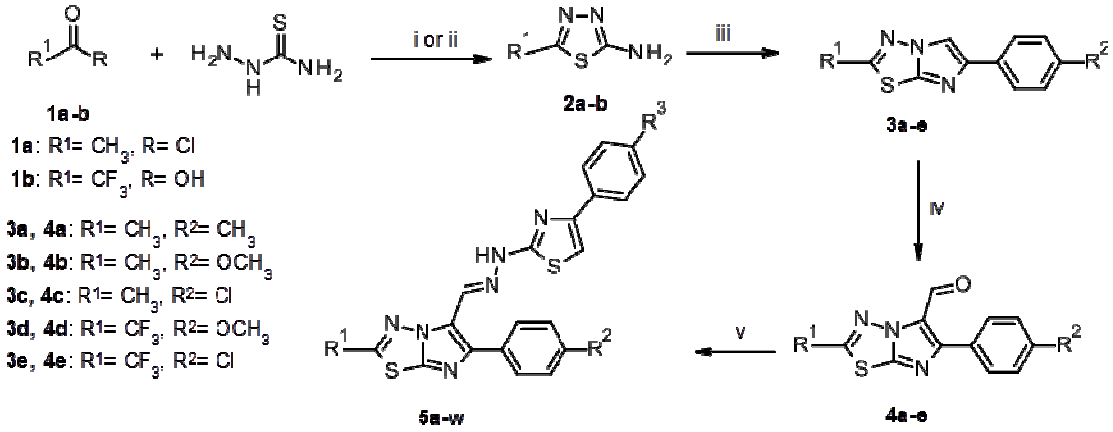
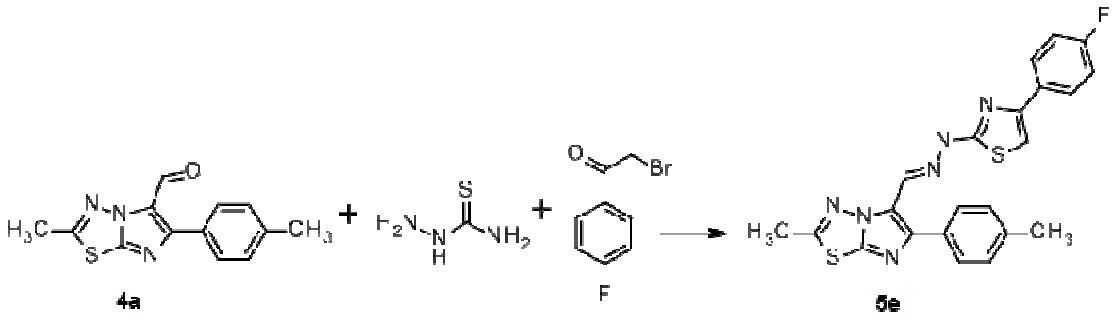


1a: R1= CH_3, R= Cl
1b: R1= CF_3, R= OH

3a, 4a: R1= CH_3, R2= CH_3
3b, 4b: R1= CH_3, R2= OCH_3
3c, 4c: R1= CH_3, R2= Cl
3d, 4d: R1= CF_3, R2= OCH_3
3e, 4e: R1= CF_3, R2= Cl

5a: R1= CH_3, R2= CH_3, R3= CH_3
5b: R1= CH_3, R2= CH_3, R3= OCH_3
5c: R1= CH_3, R2= CH_3, R3= Cl
5d: R1= CH_3, R2= CH_3, R3= NO_2
5e: R1= CH_3, R2= CH_3, R3= F
5f: R1= CH_3, R2= OCH_3, R3= CH_3
5g: R1= CH_3, R2= OCH_3, R3= OCH_3
5h: R1= CH_3, R2= OCH_3, R3= Cl
5i: R1= CH_3, R2= OCH_3, R3= NO_2
5j: R1= CH_3, R2= OCH_3, R3= F
5K: R1= CH_3, R2= Cl, R3= CH_3
5l: R1= CH_3, R2= Cl, R3= OCH_3
5m: R1= CH_3, R2= Cl, R3= Cl
5n: R1= CH_3, R2= Cl, R3= I
5o: R1= CF_3, R2= OCH_3, R3= CH_3
5p: R1= CF_3, R2= OCH_3, R3= OCH_3
5q: R1= CF_3, R2= OCH_3, R3= Cl
5r: R1= CF_3, R2= OCH_3, R3= F
5s: R1= CF_3, R2= Cl, R3= CH_3
5t: R1= CF_3, R2= Cl, R3= OCH_3
5u: R1= CF_3, R2= Cl, R3= Cl
5v: R1= CF_3, R2= Cl, R3= NO_2
5w: R1= CF_3, R2= Cl, R3= F

Scheme 1



Scheme 2

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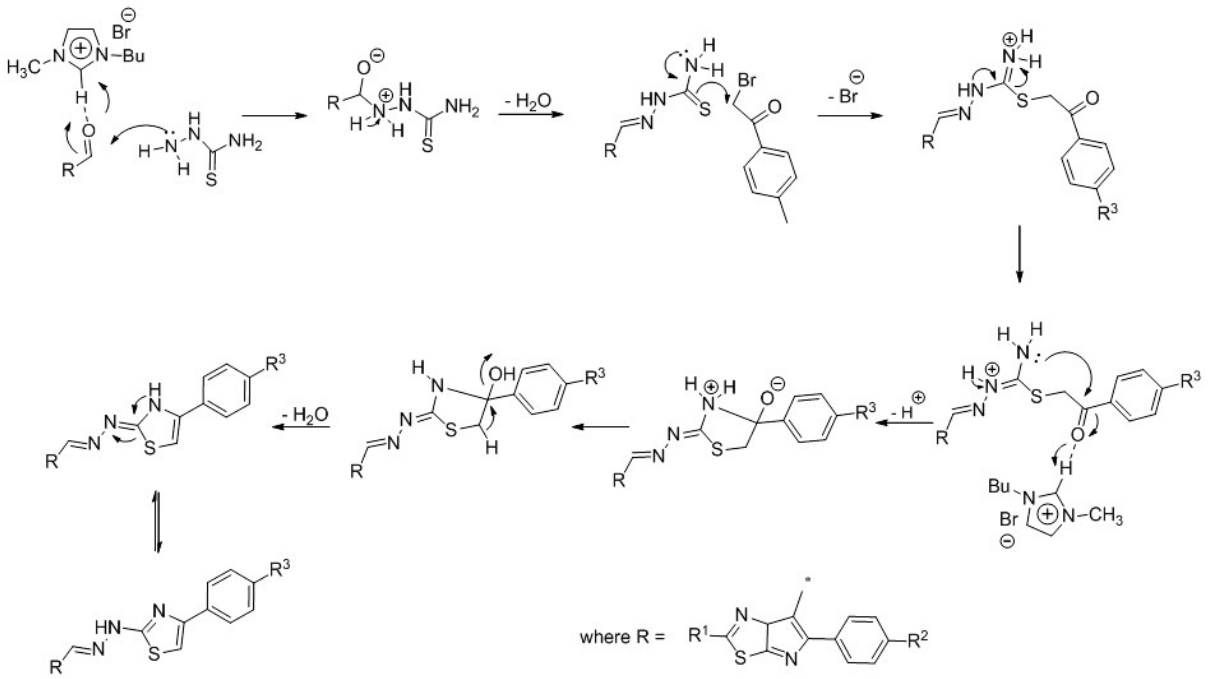

Scheme 3.

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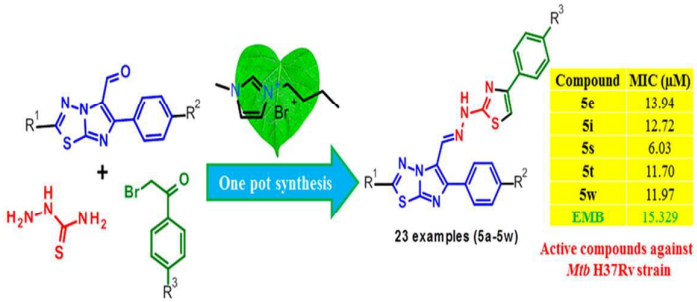
Graphical abstract

Ionic liquid promoted one-pot synthesis of thiazole-imidazo[2,1-*b*][1,3,4]thiadiazole hybrids and their antitubercular activity

Jurupula Ramprasad[a], Nagabhushana Nayak[a], Udayakumar Dalimba[a,*], Perumal Yogeeswari[b] and Dharmarajan Sriram[b]

The antiTB activity of new thiazole-imidazo[2,1-*b*][1,3,4]thiadiazoles, which are synthesized via one-pot synthesis, is comparable with that of the standard drugs.



Compound	MIC (μM)
5e	13.94
5i	12.72
5s	6.03
5t	11.70
5w	11.97
EMB	15.329