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ARTICLE TYPE

N-Arylalkylbenzo[*d*]thiazole-2-carboxamides as anti-mycobacterial agents: Design, new methods of synthesis and biological evaluation

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Abstract: Benzothiazole-2-carboxyarylalkylamides are reported as new class of potent anti-mycobacterial agents. Forty one target compounds have been synthesized following a green synthetic strategy using water as the reaction medium to construct the benzothiazole scaffold followed by (i) microwave-assisted catalyst-free, and (ii) ammonium chloride-catalysed solvent-free amide coupling. The anti-mycobacterial potency of the compounds was determined against $H_{37}Rv$ strain. Twelve compounds exhibited promising anti-TB activity in the range of 0.78-6.25 µg/mL and were found to be non-toxic (< 50% inhibition at 50 µg/mL) to HEK 293T cell lines with the therapeutic index (TI) of 8-64. The most promising anti-TB compound 5bf showed MIC 0.78 µg/mL (TI > 64). The molecular docking studies of 5bf predicts it to be a ligand for the *M. tuberculosis* HisG, the putative drug target for tuberculosis, and could serve as guiding principle for lead optimization.

Introduction

The human tuberculosis (TB), caused by infection with *Mycobacterium tuberculosis* (Mtb),[1] is world's most debilitating disease accounting for the death of 1.3 million people in 2012 and 8.6 million new cases.[2] The majority of Mtb infected people contain the pathogen as asymptomatic latent TB infection (LTBI) and about 2 billion people with LTBI are in the risk zone of disease re-activation.[1,3] The options for treating TB is limited to the following therapeutic regimen:[4] (i) first –line drugs isoniazid (INH), rifampicin (R), pyrazinamide (Z), ethambutol (E), and rifapentine (P) or rifabutin (Rfb) (Group 1), (ii) second-line drugs aminoglycosides streptomycin (S), kanamycin (Km), amikacin (Amk), the polypeptides capreomycin (Cm), viomycin (Vim) (Group 2), the fluoroquinolones (e.g., ciprofloxacin (Cfx), levofloxacin (Lfx), moxifloxacin (Mfx), ofloxacin (Ofx), gatifloxacin (Gfx) (Group 3), and para-amino salicylic acid (Pas), cycloserine (Dcs), teridizone (Trd), ethionamide (Eto), prothionamide (Pto), thioacetazone (Thz), and linezolid (Lzd) (Group 4), and (iii) third-line drugs clofazimine (Cfz), amoxicillin plus clavulanate (Amx/Clv), imipenem plus cilastatin (lpm/Cln), clarithromycin (Clr) (Group 5). The rise of drug resistance Mtb strains is a severe obstacle for the treatment against TB with about 440,000 cases of multidrug-resistant TB (MDR-TB) (resistance to at least R and INH)[5] responsible for most of deaths for TB, extensively drug-resistance TB (XDR-TB) (MDR-TB plus resistance to a fluoroquinolone and at least one second line injectable agent i.e. Amk, Km and/or Cm) reported in 84 countries[6] and the recent reports on totally drug-resistant TB (TDR-TB) that are resistant to all first- and second-line TB drugs.[7] Treatment of drug sensitive TB requires 6 months with first-line therapy involving 2 months of four drugs (INH, R, Z, and E) followed by 4 months of INH plus R through directly observed treatment short course strategy (DOTS) with a cure rate of > 95%. The treatment of drug-resistant TB requires 18-24 months or longer, involving the use of the second-line drugs which are more toxic and expensive. The dual pandemics of TB and human immunodeficiency virus-1 (HIV) compound the problem causing morbidity and mortality.[8] The major challenges associated with the available therapy are: drug intolerance and toxicities, drug-drug interaction particularly with the anti-retroviral therapy (ART) drugs to treat patients co-infected with TB and HIV.[2,8,9] All these press the need to develop novel, more effective and well tolerated drugs to curb the TB pandemic.[10,11]

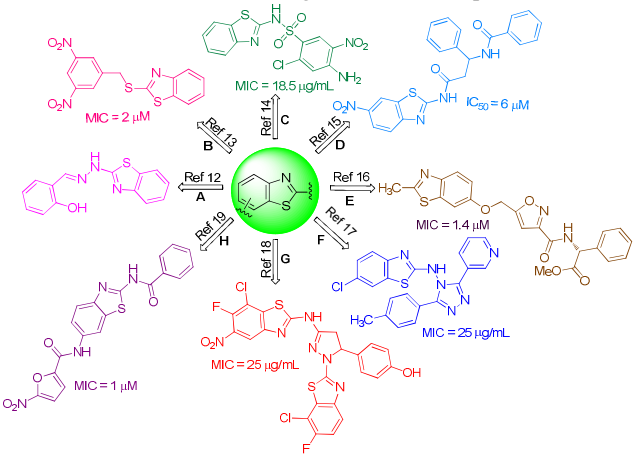

Figure 1. Various benzothiazole scaffolds with anti-tuberculosis activity.[12-19]

The benzothiazole scaffold has been recognized as an essential

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pharmacophoric feature for anti-tuberculosis activity.[12-19] However, the design of the target compounds in these reports is focused on the C-2 heteroatom (predominantly nitrogen) substitution of the benzothiazole moiety (Motifs A, C, D, F-H; Figure 1). The finding on the Mtb growth inhibitory potential of 2-methylbenzothiazoles (Motif E; Figure 1) is the lone example of C-2 carbo substitution which however focused on functional building through the benzenoid nucleus.[16] Most of these cases the nitro aryl containing fragments is a predominant structural feature (Motifs B-D, G and H). The nitro aromatic group is involved in DNA adduct formation, methaemoglobinemia and are potentially mutagenic.[20]

Results and Discussion

In the present study we adopted scaffold hopping strategy[21] and designed the C-2 carboxamide (reverse amide)[22] substituted benzothiazole scaffold (Figure 2).

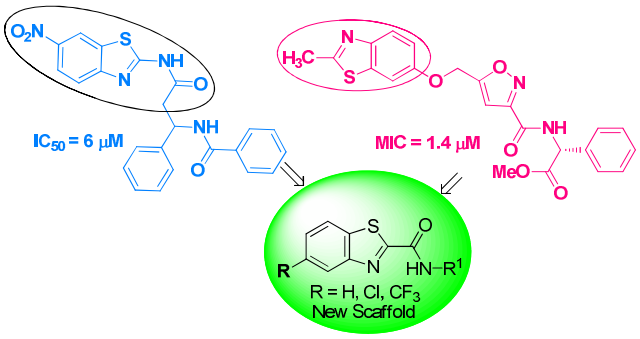
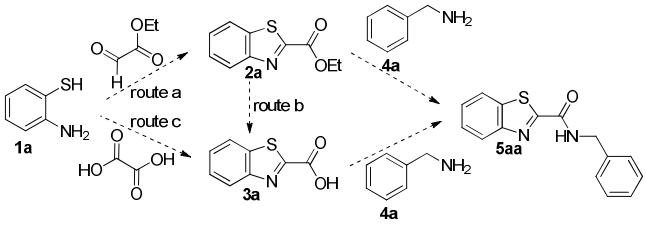


Figure 2. New benzothiazole scaffold with C-2 reverse amide substitution (present work).

The design for the new scaffold (*N*-arylalkylbenzo[*d*]thiazole-2-carboxamides) is devoid of the nitroaryl moiety thus would be free from nitroaryl-derived toxicity and gains boost from the recent pharmaceutical use of benzothiazoles for treating the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms[23] as it would augment the anti-tubercular potency of the newly designed 2-carboxamido benzothiazoles in view of the Mtb-HIV co-infection.

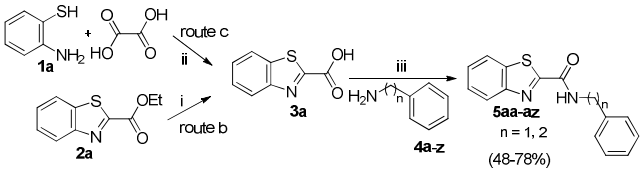
Chemistry

The synthetic design of the target compounds is depicted in Scheme 1. The key intermediate ethyl benzothiazole-2-carboxylate **2a** can be prepared by the reaction of 2-aminothiophenol **1a** with (i) ethyl carboethoxyformidate in refluxing ethanol[24] and (ii) ethyl triethoxyacetate at 130°C for 18 h.[25] The lack of commercial availability of the coupling agents (ethyl carboethoxyformidate and ethyl triethoxyacetate) necessitates a more convenient method of preparation. The acid-catalyzed condensation of **1a** with commercially available diethyl oxalate in 1:2 molar ratio followed by thermal decomposition of the intermediate at 225°C under nitrogen forms **2a** in moderate yield.[26] Earlier we reported that benzothiazoles are conveniently synthesized by condensation of **1a** with aldehydes in water under heating[27] or even at rt in the presence of catalytic amount of SDOSS[28] that constitute a green protocol. The treatment of **1a** with ethyl glyoxalate in water in the presence of SDOSS (10 mol%) afforded **2a** in 83% yield after 5 h (route a, Scheme 1). Hydrolysis of **2a** with LiOH·H_2O in aqueous THF at 10°C for 30 min afforded **3a** in 97% yield (route b, Scheme 1).



Scheme 1. Synthetic strategies for the synthesis of *N*-arylmethylbenzo[*d*]thiazole-2-carboxamides.

In order to avoid the two-step synthesis for **3a** a direct one pot preparation from oxalic acid was planned. Benzazoles can be prepared in one-pot directly from carboxylic acids through in situ carboxyl activation by thionyl chloride[29,30] but the microwave-assisted direct condensation[31,32] with carboxylic acids appears to be more appealing in the context of green synthesis. However, the treatment of **1a** with oxalic acid (1.4 equiv, route c) under microwave irradiation afforded **3a** in moderate yield (60%). Therefore, the two stage process of water-SDOSS mediated condensation of ethyl glyoxalate with **1a** followed by hydrolysis (routes a and b) was preferred and **3a** was obtained in 80.5% yield. The desired amides **5aa-az** were formed by DCC-assisted coupling of **3a** with various substituted arylalkyl amines **4a-z** (Scheme 2).



Scheme 2. Synthesis of **5aa-az** via DCC-assisted coupling of **3a** with the amines **4a-z** (Method A).

Reagents and condition: (i) LiOH·H_2O (1 equiv), Water (2 mL), THF, 10°C, 30 min, 97%. (ii) Oxalic acid (1.4 equiv), neat, 100°C, 4 h, 60%. (iii) DCC (1.2 equiv), DCM, Et_3N (4 equiv), rt, 12 h.

Although the DCC-assisted amide formation (Scheme 2) afforded the synthetic targets, in view of the longer reaction time and the generation of waste it was planned to develop a better methodology to comply with the timely compound supply[33] for biological evaluation and enrich the medicinal chemists' tool box.[34] Microwave-assisted activation would enable the condensation of **2a** with an amine.[35] The reported microwave-assisted amide formation requires stoichiometric amount of KOBu^t.[36] Herein we describe a base-free protocol by the treatment of **2a** with the amines **4a-z** in MeCN at 100°C under microwave irradiation (Scheme 3) to afford the desired amides **5aa-az** in 51-97% yields in 15 min (Table 1) (Method B).

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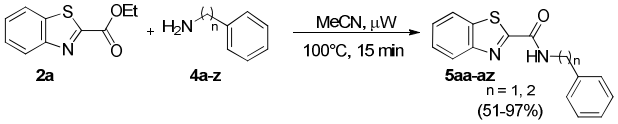
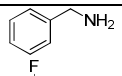
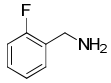
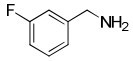
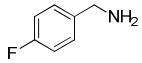
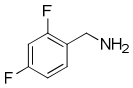
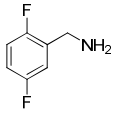
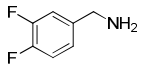
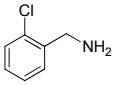
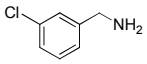
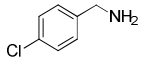
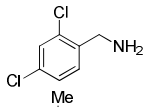
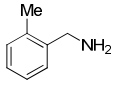
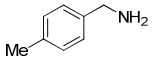
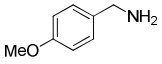
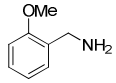
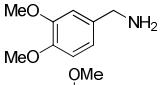
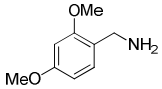
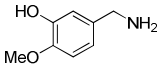
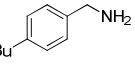
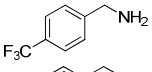
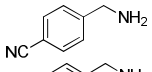
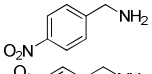
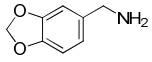


Scheme 3. Microwave-assisted synthesis of **5aa-az** by direct condensation of the amines **4a-z** with **2a** (Method B).

Table 1. Synthesis of the *N*-arylalkyl benzo[*d*]thiazole-2-carboxamides **5aa-az** by the newly developed methods A[a] and B[b] (Schemes 2 and 3, respectively).

Entry	Amine	Compd No.	Yield (%)[c] Method A	Method B
1		**5aa**	78	85
2		**5ab**	66	83
3		**5ac**	55	87
4		**5ad**	70	87
5		**5ae**	54	95
6		**5af**	60	96
7		**5ag**	58	97
8		**5ah**	68	68
9		**5ai**	71	85
10		**5aj**	73	84
11		**5ak**	49	63
12		**5al**	65	75
13		**5am**	51	79
14		**5an**	75	85
15		**5ao**	76	80
16		**5ap**	48	64
17		**5aq**	51	74
18		**5ar**	58	58
19		**5as**	58	60
20		**5at**	61	64
21		**5au**	55	64
22		**5av**	51	51
23		**5aw**	55	55

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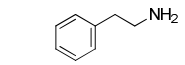
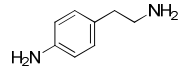
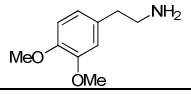
24		**5ax**	65	72[d]
25		**5ay**	53	65[d]
26		**5az**	58	70[d]

[a] **3a** was treated with the amine (1.3 equiv) in the presence of DCC (1.2 equiv) and Et_3N (4 equiv) in DCM at rt for 12 h. [b] **2a** was treated with the amine (1.2 equiv) in MeCN (except for entries 24-26) under microwave irradiation (100 °C) for 15 min. [c] Isolated yield. [d] MeOH was used as the solvent instead of MeCN.

All of the synthesized twenty six benzo[*d*]thiazole-2-carboxamide **5aa-az** were subjected to in vitro anti-TB activity against *M.tuberculosis* $H_{37}Rv$ (ATCC 27294 strain).[37] The minimum inhibitory concentration (MIC), the minimum concentration in μg/mL of the compound required for 99% inhibition of bacterial growth, of **5aa-az** and those of the standard drugs (INH, R, E, Z and Cfx) determined in triplicate at pH 7.4, are provided in Table 2. All of these synthesized compounds showed MIC values in micromolar range (3.125-50 μg/mL). Out of these, seven compounds (**5aa**, **5ac**, **5ad**, **5af, 5ah**, **5aw** and **5ax**) exhibited MIC in the range of 3.125–6.25 μg/mL with **5aa** and **5ax** being the most active (MIC 3.125 μg/mL) in the series and was found to be more potent than the standard drug Z (MIC 6.25 μg/mL).[38]

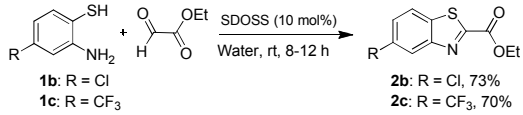
Table 2. Antimycobaterial activity of **5aa-az**, and a few standard anti-TB drugs.

Compound	MIC[a] (μg/mL)[a]	Compound	MIC[a] (μg/mL)
5aa	3.125	**5aq**	50
5ab	25	**5ar**	25
5ac	6.25	**5as**	50
5ad	6.25	**5at**	12.5
5ae	25	**5au**	12.5
5af	6.25	**5av**	12.5
5ag	25	**5aw**	6.25
5ah	6.25	**5ax**	3.125
5ai	50	**5ay**	25
5aj	50	**5az**	25
5ak	50	INH	0.098
5al	12.5	R	0.197
5am	50	E	1.56
5an	25	Z	6.25
5ao	50	Cfx	1.56
5ap	12.5		

[a] 99% inhibition of growth of *M.tuberculosis* $H_{37}Rv$ (ATCC 27294 strain).

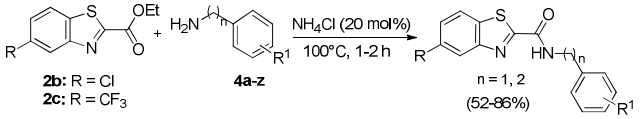
While establishing the structure activity relationship (SAR) of the amides **5aa-az** with respect to their anti-TB activity it was realized that the unsubstituted amides **5aa** and **5ax** are more potent compared to their substituted analogues and this leaves little scope for further optimization of the lead. To further improve the anti-TB activity it became apparent to increase the diversity through structural modification in the benzenoid moiety of the benzothiazole scaffold. Thus, we explored the potential of the *N*-arylalkylbenzo[*d*]thiazole-2-carboxamides having Cl and CF_3 group in the benzenoid nucleous of the benzothiazole ring.

The desired starting materials chloro/trifluoromethyl substituted 2-carboethoxybenzothiazoles **2b** and **2c** were prepared following the similar green protocol of SDOSS-water promoted cyclocondensation of ethyl glyoxalate with **1b** and **1c** respectively, as mentioned above for the synthesis of **2a** (route a, Scheme 1)



Scheme 4. Synthesis of the chloro/trifluoromethyl substituted 2-carboethoxybenzothiazoles **2b** and **2c**, respectively.

During the preparation of the 5Cl/CF_3 substituted *N*-arylalkylbenzo[*d*]thiazole-2-carboxamides we revisited the earlier method of microwave-assisted amide formation (Method B, table 1) and realized the dependence on the use of organic solvents (MeCN/MeOH). In an attempt to avoid the use of volatile organic solvent, to comply with the green chemistry principle,[39] a new synthetic protocol (Method C) for the preparation of the desired chloro/trifluoromethyl substituted *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides was developed under solvent-free condition in the presence of catalytic amount (20 mol%) of NH_4Cl at 100 °C (Scheme 5).



Scheme 5. Synthesis of the chloro/trifluoromethyl substituted *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides by NH_4Cl-catalysed direct condensation of **2b** and **2c** with the corresponding amines under solvent-free condition (Method C).

This method was found to be more advantageous compared to Method A and Method B. The product was isolated by diluting the reaction mixture with cold water followed by filtration of the solid precipitate to furnish the final product that did not require any further purification (Table 3).

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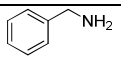
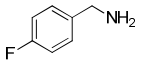
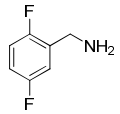
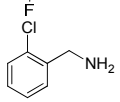
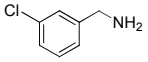
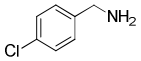
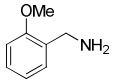
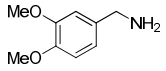
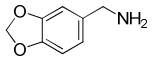
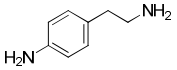
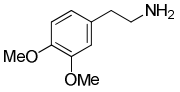
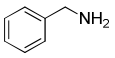
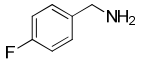
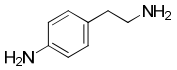
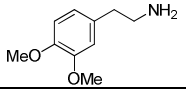
Table 3. Synthesis of the additional *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides with chloro/trifluoromethyl substitution in the benzene ring of the benzothiazole scaffold by the newly developed method C (Scheme 5).[a]

	Amine	R	Compd no.	Yield (%)[b]
1		Cl	**5ba**	79
2		Cl	**5bd**	75
3		Cl	**5bf**	52
4		Cl	**5bh**	62
5		Cl	**5bi**	59
6		Cl	**5bj**	56
7		Cl	**5bo**	63
8		Cl	**5bp**	63
9		Cl	**5bw**	65
10		Cl	**5by**	73
11		Cl	**5bz**	86
12		CF_3	**5ca**	83
13		CF_3	**5cd**	78
14		CF_3	**5cy**	54
15		CF_3	**5cz**	70

[a] **2b**/**2c** was treated with the amine (1.0 equiv) in the presence of NH_4Cl (20 mol%) under neat condition at100 °C for 1-2 h. [b] Isolated yield.

These newly synthesized fifteen compounds (Table 3) were subjected to in vitro biological evaluation and were found to have significant improvement in their anti-TB activity with MIC ranging from 0.78-50 μg/mL (Table 4) compared to the MIC ranges of 3.125-50 μg/mL for the 2-carboxamido benzothiazoles without any substitution in the benzene ring of the benzothiazole scaffold (Table 2). Among the eleven chloro substituted derivatives, five compounds showed improved potency (0.78-6.25 μg/mL). The most active compound **5bf** (MIC 0.78 μg/mL) turned out to be eight fold more potent than its unsubstituted counterpart **5af**. However, the CF_3 substituted derivatives (**5ca**, **5cd**, **5cy** and **5cz**) did not show any improvement in anti-TB potency.

Table 4. Antimycobaterial activity of the additional *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides with chloro/trifluoromethyl substitution in the benzene ring of the benzothiazole scaffold.

Compound	MIC[a] (μg/mL)	Compound	MIC[a] (μg/mL)
5ba	6.25	**5bw**	25
5bd	25	**5by**	1.56
5bf	0.78	**5bz**	12.5
5bh	12.5	**5ca**	6.25
5bi	25	**5cd**	12.5
5bj	25	**5cy**	50
5bo	12.5	**5cz**	25
5bp	6.25		

[a] 99% inhibition of growth of *M.tuberculosis* $H_{37}Rv$ (ATCC 27294 strain.

The in vitro cell viability of the compounds with MIC ≤ 12.5 μg/mL was evaluated against HEK-293T (Human Embryonic Kidney) cell lines at 50 μg/mL concentration by using [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)] MTT assay. The % inhibitory cytotoxicity data are summarized in Table 5 and graphically represented in Figure 3 along with the MIC values of the respective compounds. In general, all of these eleven compounds were found to be non-toxic (< 50% inhibition) and **5bf** the most active compound has therapeutic index greater than 64. The compound **5bf** emerged as the most promising anti-TB lead compound from this series.

Table 5. In vitro cell viability of compounds with MIC ≤ 12.5 μg/mL.

Compound	HEK 293T % Inhibition[a]	Mtb MIC (μg/ mL)[b]
5aa	41.21	3.125
5ac	44.56	6.25
5ad	50.34	6.25
5af	52.12	6.25
5ah	35.62	6.25
5al	42.6	12.5
5ap	19.12	12.5
5at	36.70	12.5
5au	36.00	12.5
5av	38.12	12.5
5aw	16.12	6.25
5ax	21.98	3.125
5ba	40.12	6.25
5bf	32.16	0.78
5bh	35.97	12.5
5bo	38.92	12.5
5bz	30.95	12.5
5bp	36.13	6.25
5by	25.9	1.56

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5bz	30.94	12.5
5ca	40.08	6.25
5cd	38.74	12.5

[a] % inhibition at 50 µg/mL concentration determined against HEK 293T cells lines. [b] Against *Mycobacterium tuberculosis* $H_{37}Rv$ strain.

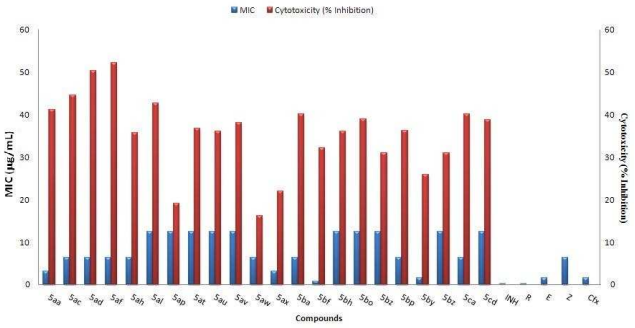

Figure 3. Graphical representation of the antitubercular activity and cytotoxicity profile of the compounds with MIC ≤ 12.5 µg/mL in comparison with the standard drugs.

A complete SAR can be drawn taking into account the MIC values (Tables 2 and 4) and the cytotoxicity data of the selected compounds (Table 5). The presence of the chloro group in the benzene ring of the benzothiazole scaffold increases the potency. Better anti-TB activity is exhibited by the benzylamides than the corresponding phenethyl amides (**5ap** vs **5az** and **5bp** vs **5bz**). The detrimental effect of the increase in the amide chain length on the anti-TB activity was also observed for compounds that did not have the chloro substitution in the benzene ring of the benzothiazole scaffold.

The antimycobacterial activity of C-2 *N*-carboxamide substituted benzothiazoles have been demonstrated due to their interaction with ATP phosphoribosyl transferase (HisG) that catalyzes the first step in the biosynthesis of histidine,[15] the putative drug target. As the designed molecules resemble the reverse amide scaffold we planned to correlate/rationalise the biological activity of the best active compound (**5bf**) on its binding affinity with HisG through molecular docking (PDB structure 1NH8).

To obtain an in-depth understanding on the interaction of **5bf** on to the HisG active site, we docked compound **5bf** utilizing PDB 1NH8, centered about Tyr116. An automated docking analysis of all compounds was performed into the crystallographic structure of HisG, using AutoDock Vina 4.2.[40] These molecules were found to fit reasonably well into the catalytic site, with the ligand mainly locating into the ATP binding site. The predicted binding mode for compound **5bf** is shown in (Figure 4a). The benzothiazole ring was found to interact with the same hydrophobic pocket next to Leu12, Leu71 and Pro50 as observed by Huang *et. al*.[16] The H-bond interactions is formed between carbonyl oxygen of the amide and the backbone amide of Ala11. Figure 4b shows the favourable lock and key model of the **5bf** into the active cavity. Figure 4c shows two previously identified HisG inhibitors in complex with 1NH8 as taken from ref 15.

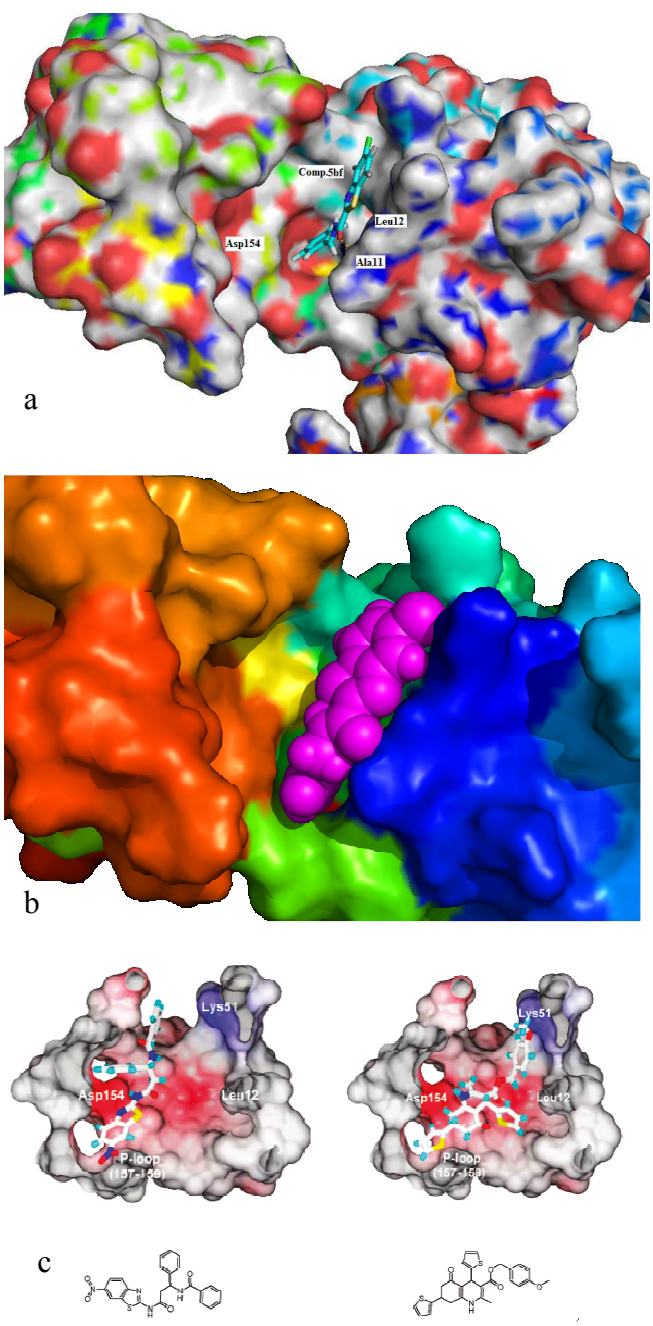

Figure 4. (a) Docking pose of **5bf** with HisG PDB:1NH8 as determined using Autodock Vina 4.2. Structure is represented using Pymol. (b) Ligand-protein surface docking pose (c) Docked structures of two reported HisG inhibitors.[15]

The literature report[15] reveals that the nitrobenzothiazole fragment is the essential feature for inhibitory potential against HisG. A careful analysis of this benzothiazole scaffold (Figure 5) lead to derive a topological model (common pharmacophoric feature) that includes the presence of aryl groups at either end of the molecule and a hydrophobic aryl group in the middle. This topology mimics the natural ligand phosphoribosyl ATP (PRATP) of HisG. In the newly found **5bf** the benzothiazole moiety represents the adenosine ring system of ATP and the benzylamine moiety resembles the ribose ring of PRATP. suggesting HisG as putative target in Mtb for the compound **5bf**.

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Thus, this modelling study suggests that the compounds of the benzothiazole-2-carboxamide series might be acting on Mtb HisG.

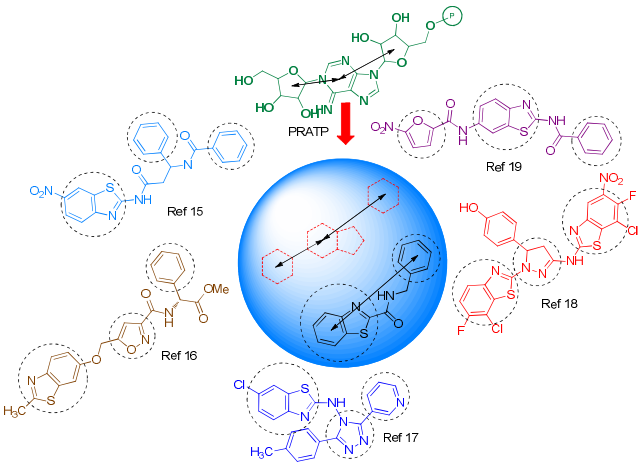

Figure 5. Comparative analysis of pharmacophoric features between natural ligand of HisG: Phosphoribosyl ATP (PRATP) and literature reported Mtb inhibitors.

Conclusion

The present work reveals *N*-arylmethylbenzo[*d*]thiazole-2-carboxamide as a new anti-TB scaffold. Forty one compounds in the series have been prepared by three newly developed synthetic methods and evaluated in vitro for their potential as anti-TB drug candidate. Twelve compounds displayed good in vitro antimycobacterial activity, with MIC in low micromolar range against replicating TB and are, in general, non-toxic to HEK 293T cell lines (< 50% inhibition at 50 µg/mL). The most potent compound **5bf** exhibits MIC of 0.78 µg/mL (therapeutic index > 60), more than that of the standard drugs E, Z and Cfx. The significant increase in anti-TB activity with the 5-Cl substituted benzothiazole derivatives shows further scope for improvement in anti-TB activity. The molecular docking study with **5bf** suggests that the anti-TB benzothiazole-2-carboxamides might be acting on Mtb HisG. The docking information may provide valuable guiding principle for future design to evolve more potent anti-TB molecules. In fine, this study has provided novel anti-TB lead and can be a useful starting point for further exploration in this area.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Procedure for the synthesis, molecular modelling, spectral characterization and biological evaluation is described]. See DOI: 10.1039/b000000x/

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Graphical Abstract

N-Arylalkylbenzo[*d*]thiazole-2-carboxamides as anti-mycobacterial agents: Design, new methods of synthesis and biological evaluation

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