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Graphical Abstract

Benzo[*d*]thiazole-2-carbanilides as New Anti-TB Chemotypes: Design, Synthesis and Biological Evaluation

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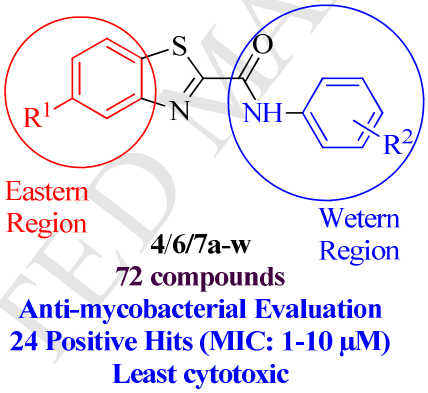

The benzo[*d*]thiazole-2-carbanilides have been identified as new chemotypes with potent anti-TB activities.

Benzo[*d*]thiazole-2-carbanilides as New Anti-TB Chemotypes: Design, Synthesis, Biological Evaluation, and Structure-Activity Relationship

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Abstract

Tuberculosis is the second leading cause of deaths worldwide. The inadequacy of existing drugs to treat TB due to developed resistance and TB-HIV synergism urges for new anti-TB drugs. Seventy-two benzo[*d*]thiazole-2-carbanilides have been synthesized through CDI-mediated direct coupling of benzo[*d*]thiazole-2-carboxylic acids with aromatic amines using a three step methodology which includes a green protocol for synthesis of ethyl benzo[*d*]thiazole-2-carboxylates, precursor of the desired carboxylic acids. The compounds were evaluated in vitro for anti-tubercular activity against *M. tuberculosis* $H_{37}Rv$ (ATCC27294 strain). Thirty-two compounds exhibiting MIC values in the range of 0.78-6.25 µg/mL (1.9-23 µM) were subjected to cell viability test against RAW 264.7 cell lines and thirty compounds were found to be non-toxic (< 50% inhibition). The most active compounds with MIC of 0.78 µg/mL (e.g., **4i**, **4n**, **4s**, **4w**, **6f**, **6h**, **6u**, **7e**, **7h**, **7p**, **7r** and **7w**) exhibit therapeutic index of 64. The structure activity relationship of the *N*-arylbenzo[*d*]thiazole-2-carboxamides has been established for anti-mycobacterial activity. Molecular docking suggests that the compounds **7w**, **4i** and **4n** bind to the catalytic site of the enzyme ATP Phosphoribosyltransferase (HisG) and might be attributed to their anti-TB potential. These can serve as a new starting point for the development of anti-TB agents with therapeutic potential.

Keywords. Benzo[*d*]thiazole-2-carbanilides, new anti-TB chemotypes, anti-TB ($H_{37}Rv$) activity, CDI-mediated amide coupling, molecular docking, ATP Phosphoribosyltransferase (HisG).

1. Introduction

Tuberculosis (TB), a widespread infectious disease, has been the curse to humanity for many years. In view of the extreme alarming situation, the World Health Organization (WHO) declared TB as a worldwide health unseen crisis in 1993. [1] The discovery of pathogenic *Mycobacterium tuberculosis* (Mtb) by Robert Koch [2] that earned him the Nobel Prize in physiology or medicine in 1905 [3] paved the way to find therapeutic agents to cope up with this disease. However, the drive under the directly observed treatment short course (DOTS) chemotherapy with the conventional first and second line anti-TB drugs is not sufficient to meet the desired cure rate of TB. [4] To tackle the pandemic of TB, several therapeutic leads e.g., linezolid, sutezolid, gatifloxacin and moxifloxacin have been repurposed in clinical trials for the treatment of TB (Figure 1). [5] Recently, bedaquiline (a diarylquinoline class of compound marketed as Sirturo^{TM}) [6] and delamanid (a nitro-dihydro-imidazooxazole class of compound, Figure 1) [7] have been approved for the treatment of MDR-TB (multi-drug resistant TB) in the United States and European countries, respectively in combination therapy with other drugs. However, bedaquiline causes serious side effects such as QT prolongation and hepatotoxicity. [8,9] To avoid synergistic drug-drug interaction (which also aggravate the QT prolongation) for the use of bedaquiline special precaution is required with CYP3A4 inhibitors. [10] Delamanid causes QT prolongation and CNS toxicity. [11] These press the need for the search of new class of compounds as potential anti-tuberculotic agents.

Insert Figure 1 here.

1.1 Design

The design of benzo[*d*]thiazole-2-carbanilides (**I**, Figure 2) as new anti-TB chemotypes with a wider chemical space could be derived through structural modification of the newly found anti-TB scaffolds *N*-arylalkylbenzo[*d*]thiazole-2-carboxamide [12] and benzo[*d*]thiazol-2-yl(piperazin-1-yl)methanones. [13]

Insert Figure 2 here.

2. Results and discussion

2.1 Chemistry

For the synthesis of the designed molecules the key intermediate ethyl benzo[*d*]thiazole-2-carboxylates (**2**) were prepared adopting a green protocol reported [12–14] from this laboratory which involves the cyclocondensation of 2-amino thiophenols (**1**) and ethyl glyoxalate in water in the presence of catalytic amount of SDOSS as the dioxygen activator (Table 1. [15]

For the synthesis of benzo[*d*]thiazole-2-carbanilide (**4a**) we planned to adopt the NH_4Cl-catalysed trans-amidation methodology as reported for the reaction of **2a** with arylalkyl amines [12] and alicyclic amines. [13] However, the treatment of **2a** with aniline (**3a**) in the presence of NH_4Cl (20 mol%) under neat condition at 100 °C for 12 h did not produce any significant amount of **4a**. The use of trifluoroacetic acid (TFA) either in catalytic amount (20 mol%) or as solvent under heating at 100 °C (oil bath) for 12 h also did not afford **4a**. The inefficiency of the Lewis acid-catalyzed trans-anilidation of **2a** with aromatic amines containing halogen (ESI: Table S1) or electron withdrawing substituents and poor yields obtained through the base-promoted reaction (ESI: Table S2) led us to use an alternate methodology for the preparation of the synthetic target using 1,1'-carbonyldiimidazole (CDI) assisted coupling of carboxylic acids with anilines. [16]

The precursor benzothiazole-2-carboxylic acid (**5a**), obtained through hydrolysis of **2a** (98% yield), [12] on treatment with CDI (1.5 equiv) in dry THF at rt for 12 h, followed by removal of

THF under reduced pressure, and treatment of the residue with the **3a** (1.1 equiv) in the presence of (DBU, 0.5 equiv) at 60-80 °C in dry THF gave **4a** in 85% yield (83% overall yield from **2a**).

The ethyl 5-chloro benzo[*d*]thiazole-2-carboxylate **2b** and ethyl 5-trifluoromethyl benzo[*d*]thiazole-2-carboxylate **2c** obtained from the corresponding 2-amino-4-chlorobenzenethiol **1b** and 2-amino-4-(trifluoromethyl) benzenethiol **1c**, respectively, were subjected to hydrolysis to form corresponding carboxylic acids **5b**,**c**. The CDI-mediated direct condensation of **5b**,**c** with **3a-x** afforded the corresponding benzo[*d*]thiazole-2-carbanilides **4**, **6**, and **7a-x** in 60-80% yields (Table 1).

Insert Table 1 here.

2.2 Biological Evaluation

2.2.1 Determination of MIC ($H_{37}Rv$)

The synthesized seventy-two benzo[*d*]thiazole-2-carbanilides were tested in vitro for anti-TB activity against *M. tuberculosis* $H_{37}Rv$ (ATCC27294 strain) [17] along with a few standard anti-TB drugs e.g., Isoniazid (INH), Rifampin (R), Ethambutol (E), Pyrazinamide (Z), and Ciprofloxacin (Cfx) at pH 7.4 in triplicate (Table 2, Figure 3). The most active compounds (**4i**, **4n**, **4s**, **4w**, **6f**, **6h**, **6u**, **7e**, **7h**, **7p**, **7r** and **7w**) showed the Minimum Inhibitory Concentration (MIC) of 0.78 µg/mL and were more potent than the standard drugs E, Cfx and Z. Thirteen compounds (**4j**, **4u**, **4x**, **6b**, **6k**, **6f**, **6m**, **6n**, **6q**, **7b**, **7c**, **7f** and **7g**) with the MIC value of 1.56 µg/mL were equipotent to E and Cfx but more potent than Z, two compounds (**4g** and **4m**) having MIC of 3.125 µg/mL were more potent than Z, and five compounds (**4e**, **4l**, **4r**, **6c** and **7o**) having MIC of 6.25 µg/mL showed potency similar to that of Z.

Insert Table 2 here.

Insert Figure 3 here.

2.2.2 In vitro cell viability tests

The in vitro cell viability of a few selected benzothiazole-2-anilides with MIC ≤ 6.25 µg/mL was determined against RAW 264.7 cell lines using MTT assay at 50 µg/mL (Table 2, Figure 4) that revealed the non-cytotoxic nature of these compounds. The most active compounds **4i**, **4n**, **4s**, **4w**, **6f**, **6h**, **6u**, **7e**, **7h**, **7p**, **7r** and **7w** (MIC of 0.78 µg/mL) exhibited therapeutic index of 64 and emerged as the most promising anti-TB leads.

Insert Figure 4 here.

2.2.3 Structure Activity Relationship (SAR)

The structure activity relationship (SAR) of the *N*-arylbenzo[*d*]thiazole-2-carbanilides could be drawn by correlating the MIC (µg/mL) values of the compounds with the specific changes in the structure made by various substitution on the core moieties. For this purpose the main structural scaffold is segregated into two different regions: (a) the eastern region (benzenoid nucleous of the benzo[*d*]thiazole moiety) and (b) western region (*N*-aryl part of the carbanilide moiety) (Structure **I**, Figure 2).

2.2.3.1 SAR analysis based on the modifications made on the core moieties

For the SAR analysis the various possible changes made in the western regions were considered with respect to the R^1 substituent present at the fifth position of the benzo[*d*]thiazole (i.e. eastern region) i.e., R^1 = H, Cl, CF_3.

2.2.3.2 Modifications made on the western region

2.2.3.2.1 When R^1 = H:

i. Incorporation of 4-Me on the phenyl ring of the anilide moiety increases the anti-TB activity to 12.5 µg/mL in **4b** (compared to the parent compound **4a** that has MIC of 25 µg/mL). With the 2-Me and 3-Me substitution, the activity decreased

[**4c**, **4d**; MIC of >25 µg/mL]. However, the activity increased with 2,4,6-trimethyl substitution (**4x**, MIC of 1.56 µg/mL).

ii. Introduction of methoxy group increases the anti-TB activity compared to that of the parent compound. Out of the three substitution made, the MIC values increased (and the anti-TB potential decreased) in the order: *o*-OMe < *p*-OMe < *m*-OMe [**4g** < **4e** < **4f**]. The incorporation of 3,4,5-trimenthoxy substitution resulted into the most potent compound **4w** with MIC of 0.78 µg/ml.

iii. Incorporation of the electron withdrawing chlorine at the *meta* position of the phenyl ring resulted the potent compound **4i** with MIC of 0.78 µg/mL than at the *para*- or the *ortho*- position [**4h**, MIC of >25 µg/mL; **4j**, MIC of 1.56 µg/mL].

iv. Incorporation of 2-fluoro substitution (**4m**, MIC of 3.125 µg/mL) increases the anti-TB activity by two fold compared to that of the 3-fluoro substitution (**4l**, MIC of 6.25 µg/mL) but with the 4-fluoro substitution the activity detoriated (**4k**, MIC > 25 µg/mL)

v. The introduction of the strong electron withdrawing CF_3 group in general increased the anti-TB activity. The *p*-CF_3 analogue **4n** showed the best activity with the MIC value of 0.78 µg/mL. The *o*-CF_3 and *m*-CF_3 substitution were found to be not so effective in improving the anti-TB potency (with **4o** and **4p** exhibiting MIC of 12.5 µg/mL), though better than that of **4a**.

vi. The compound with the 4-bromo substitution (**4q**, MIC of >25 µg/mL) showed lesser activity compared to that of the parent compound **4a**.

vii. In case of the nitro group, *m*-nitro derivative **4s** turned out to be the the most active compound with the MIC of 0.78 µg/mL as compared to the corresponding

p-nitro analogue **4r** (MIC of 6.25 µg/mL) along with an improved therapeutic index from 8 for **4r** to 64 for **4s**.

viii. The activity increased by sixteen fold on incorporation of morpholine ring at the *para* position (**4u**, MIC of 1.56 µg/mL) and by two fold at the *ortho* position (**4v**, MIC of 12.5 µg/mL). The inferior activity of the *ortho*-morpholino derivative could be due to the steric effect of the morpholine. It appears that the CF_3 group counterbalances the electronic effect of the morpholine group as the 3-fluoro-4-morpholinyl derivative **4t** exhibited poor activity (MIC of > 25 µg/mL).

2.2.3.2.2 When R^1 = Cl:

i. The methyl substitution (R^2 = Me) at *para*- and *meta*- position resulted an increase of the activity the best activity as the corresponding compounds **6b** and **6c** exhibited MIC of 1.56 and 6.25 µg/mL, respectively. However, no effect on the activity was reflected for the *o*-Me and 2,4,6-trimethyl derivatives **6d** and **6x** that have MIC value of 25 µg/mL similar to that of the parent compound **4a**.

ii. Incorporation of the OMe group at the *meta* position significantly improved the activity in **6f** with MIC of 0.78 µg/mL. But the anti-TB activity remained unaffected in the corresponding *para*- and *meta*- derivatives **6a** and **6d** as well as in the 3,4,5-trimenthoxy compound **6w** as these showed MIC of 25 µg/mL similar to that of the parent compound **4a**.

iii. The incorporation of chlorine at the *para* position resulted **6h** as one of the most potent compounds with MIC of 0.78 µg/mL. No influence on the activity was observed for the *o*- and *m*- chloro analogues **6i** and **6j** that have MIC value similar (25 µg/mL) to that of **4a**.

iv. Substitution with fluorine, in general, increased the activity with similar extent irrespective of being at *para*, *meta*, or *ortho* position with the corresponding compounds **6k**, **6l**, and **6m** all exhibiting MIC of 1.56 µg/mL.

v. Introduction of the trifluoromethyl group at the *para* position increased the activity (**6n**, MIC of 1.56 µg/mL) but no effect was observed for the *met* and *ortho* trifluoromethyl analogues **6o** and **6p** each of which has MIC of 25 µg/mL similar to that of **4a**.

vi. Substitution with bromine at the *para* position resulted in an increase of the activity (**6q**, MIC of 1.56 µg/mL).

vii. For substitution with the nitro group the 3-nitro compound **6s** has activity (MIC of 12.5 µg/mL) better than that of **4a** while the 4-nitro substitution has no overall effect on the activity as **6s** has MIC of 25 µg/mL.

viii. The substitution with the morpholine ring at the *para* position increased the activity giving **6u** as one of the most active compounds in this study with MIC of 0.78 µg/mL. In **6t** that has the 3-fluoro substituent in addition to the 4-morphonilyl group the anti-TB activity is less effectively increased (MIC of 12.5 µg/mL) suggesting that the electronic effect of the CF_3 group is in dissonance with that of the morpholinyl group towards the increase of the anti-TB activity. The 2-morphonilyl substitution has no effect on the activity as the resultant compound **6v** showed anti-TB activity (MIC of 25 µg/mL) similar to that of **4a** and the lack of any influence of the *ortho* substitution could be due to the steric effect.

2.2.3.2.3 When $R^1 = CF_3$:

i. The activity increased with similar extent by substitution with methyl group (R^2 = Me) at the *para*- and *meta*- position and the resultant compounds **7b** and **7c** showed MIC of 1.56 µg/mL. However the 2-methyl and 2,4,6-trimethyl substitutions did not have any effect of the activity as the corresponding compounds **7d** and **7x** have MIC value (25 µg/mL) similar to that of **4a**.

ii. The incorporation of methoxy substituent, in general, is associated with an increase of activity. The most pronounced effect is exhibited by *para* substitution (**7e**, MIC of 0.78 µg/mL) while the *meta* and *ortho* substitution increase the activity to equally (**7f** and **7g** both having MIC of 1.56 µg/mL), although being inferior to the *para* substitution. The best activity is observed with the 4-methoxy substituent (**8e**, MIC of 0.78 µg/mL). The 3,4,5-trimethoxy substituted compound **7w** also exhibited increased activity (MIC of 0.78 µg/mL) being one of the most potent anti-TB compounds that emerged from this work.

iii. The influence of the chloro substitution in increasing the anti-TB potential follows the order 2-Cl < 3-Cl < 4-Cl. The compound **7h** having 4-chloro substituent appeared one amongst the most potent compounds from this study having MIC of 0.78 µg/mL. The *meta*-chloro analog **7i** is less effective having MIC of 0.78 µg/mL and no improvement of the activity is noticed for the ortho-chloro substitution as the corresponding compound **7j** has anti-TB activity (25 µg/mL) similar to that of **4a**.

iv. Substitution with fluorine either at the *para* (**7k**, MIC 25 µg/mL) or the *ortho* (**7m**, MIC 25 µg/mL) position did not have any influence on the activity as

compared to the parent compound **4a**. The anti-mycobacterial activity increased by two fold with the 3-fluoro substituent (**7l**, MIC of 12.5 µg/mL).

v. Significant increase of the activity took place on incorporation of the lipophilic trifluoromethyl group at the *meta* and *ortho* position with the corresponding compounds **7o** and **7p** exhibiting the anti-TB activity with MIC of 6.25 and 0.78 µg/mL, respectively. The *para*-substitution has little effect on the activity as **7n** has MIC (25 µg/mL) comparable to that of **4a**.

vi. The 4-bromo substitution did not show any increasing effect on the activity (**7q**, MIC of 25 µg/mL).

vii. Incorporation of the strong electron withdrawing nitro group at the *para* position gave **7r** as one of the most potent compounds with MIC of 0.78 µg/mL but *meta*-nitro derivative was less active (**7s**, MIC of 25 µg/mL) being similar to **4a**.

viii. Incorporation of the morpholine ring was either ineffective (**7u**, MIC of 25 µg/mL) or exhibited moderate effect (**7t** and **7v**, MIC of 12.5 µg/mL) in increasing the activity.

2.3 Molecular Docking

The promising anti-TB activity of the benzo[*d*]thiazole-2-carbanilides (Table 2) and the devoid of cytotoxicity encouraged us further to understand the possible mode of anti-TB action of these compounds. We were attracted by the findings on the HisG inhibitory activity of three nitro substituted 2-amido/amino benzothiazoles. [18] However, the lack of anti-TB (whole cell) activity and the potential mutagenicity, due to the presence of the nitro group, [19] of these compounds encouraged us to consider these benzo[*d*]thiazole-2-carbanilides to be alternative and more effective ligands of HisG and that the anti-TB activity of benzo[*d*]thiazole-2-carbanilides

might be attributed due to HisG inhibition. The topological features of the *N*-arylalkylbenzo[*d*]thiazole-2-carboxamide match with those of PRATP (natural ligand of HisG) [12]. The benzo[*d*]thiazole-2-carbanilides are devoid of the potential mutagenic aromatic nitro functionality and hence would represent new structural scaffold for Mtb HisG inhibition.

In this context, the molecular docking provides insight into the structure-activity correlation that might help to optimize the lead structure and to understand the mechanism of action of active compounds [12,20–22]. Therefore, the binding site of the potent compounds **7w**, **4i**, and **4n** on the ATP phosphoribosyltransferase enzyme (PDB: 1NH8) was predicted by molecular docking using AutoDock Vina 4.2 (Figure 5) [23]. The molecular docking analysis shows that the compounds **7w**, **4i**, and **4n** bind to the substrate binding catalytic site of the enzyme with differential binding energies. The compound **7w** binds to the catalytic site formed by the Domain I and Domain II of the ATP phosphoribosyl transferase enzyme [24] with a binding energy of -8 kcal/mol to the substrate binding (PRPP and ATP) pocket of the enzyme (Figure 5a) and is involved in HB formation with the backbone nitrogen of Ala11 and Leu12. The fluorine of the trifluoromethyl group present in **7w** undergoes electrostatic interaction with the oxygen of Asp154. The fluorine forms HB with Ala 115 and Gly138. The compound **7w** also exhibits hydrophobic interactions with Tyr116, Val155, Pro50, Leu71, Ala11, Leu12 and Gly10 in the catalytic site. The compound **4i** binds to the substrate binding site with a binding energy of -7.6 kcal/mol (Figure 5b). The chlorine of **4i** forms a strong HB with Gly88 and also experiences electrostatic interaction with oxygen of Gly88. This compound is stabilized by the hydrophobic interactions with Gly10, Leu12, Pro50, Gly68, Leu71 and Tyr116. The compound **4n** also binds to the substrate binding pocket of the enzyme with a binding energy of -7.4 kcal/mol (Figure 5c). The fluorine of **4n** undergoes electrostatic interactions with the oxygen of Gly88 and forms

strong HB with the hydroxyl (OH) group of Ser90 and the benzothiazole ring is engaged with hydrophobic interactions with the Ala11, Leu12, Pro50 and Leu71 in the binding pocket. Further, we also docked the 2-amido nitrobenzothiazole that has been reported [18] as the most effective Mtb HisG inhibitor to compare its binding mode with that of the benzo[*d*]thiazole-2-crbanilides. The 2-amido nitrobenzothiazole derivative binds to the catalytic site of the enzyme (Figure 5d) with a binding energy of -7.8 kcal/mol which is less as compared to that of **7w**. The oxygen of the nitro group of this 2-amido nitrobenzothiazole forms HB with the backbone nitrogen of Gly157, Ser158, Gly159, Arg160, and Thr161 as well as with the Tyr116 and Asp70. Further, this compound is also involved in stabilized hydrophobic interactions with the Pro50, Leu10 and Leu11. We next considered the molecular docking of the next best reported HisG inhibitor [18] that is devoid of the nitro group and the 2-amidothiazole moiety (Figure 5d) and observed that docks onto the catalytic site of the enzyme, stabilized by the hydrophobic interactions with Gly10, Ala11, Leu12, Pro50, Leu71, Tyr116, Val155 in the catalytic site, with a binding energy of -7.1 kcal/mol which is inferior compared to that of the newly found anti-TB compounds **7w**, **4i**, and **4n**. Thus, the molecular docking studies suggest that the compound **7w** binds to the enzyme more strongly as compared to the previously reported HisG inhibitors [18], and the compounds **4i** and **4n** also bind to the catalytic site of the enzyme with good affinities as compared to the next best inhibitor that does not bear the 2-amidothazole moiety and the mutagenic nitro aromatic group.

The compounds **7w**, **4i**, and **4n** show a very good alignment with the PR-ATP (phosphoribosyl pyrophosphate-adenosine triphosphate), the natural substrate of HisG where the benzothiazolyl moiety occupies the same space of the active site which is occupied by the adenosine moiety of PR-ATP [12] (Figure 6a). These topological features were not observed with the two reported

inhibitors of Mtb HisG [18] selected for molecular docking (supporting information: Figure S1a). The benzothizole-2-carbanilide ligands **7w**, **4i**, and **4n** fit into the active site of HisG (Figures 6b, 6c; see also the supporting information: Figure S1b) better than that of the two reported [18] Mtb HisG inhibitors suggesting HisG to be the putative target for the anti-TB activity of these compounds.

Insert Figure 6 here.

3. Conclusions

In this study benzo[*d*]thiazole-2-carbanilides have been revealed as new anti-TB chemotypes. Seventy-two compounds have been synthesized and tested in vitro against *M. tuberculosis* ($H_{37}Rv$) to assess their anti-TB potential. Twenty-four compounds (e.g., **4i**, **4j**, **4n**, **4s**, **4u**, **4w**, **4x**, **6b**, **6f**, **6h**, **6k**, **6l**, **6m**, **6n**, **6q**, **6u**, **7b**, **7e**, **7f**, **7g**, **7h**, **7p**, **7r** and **7w**) exhibited MIC values of 1-10 µM. The in vitro cell viability of a few selected benzo[*d*]thiazole-2-carbanilides with MIC of $\leq$ 6.25 µg/mL against RAW 264.7 cell lines revealed the non-cytotoxic nature of these compounds. The structure activity relationship for the anti-mycobacterial activity of these *N*-arylbenzo[*d*]thiazole-2-carbanilides has been analysed. Molecular docking analysis of the most potent compounds **7w**, **4i** and **4n** shows that these compounds bind to the substrate binding pocket of ATP phosphoribosyl transferase enzyme (HisG) with docking energies better than that of the reported HisG inhibitors. This reflects that these compounds might inhibit the growth of *Mycobacterium tuberculosis* possibly by targeting the HisG enzyme.

4. Experimental Section

4.1 General Chemistry

Chemicals and all solvents were commercially available, and used directly without further purification. ^{1}H NMR and ^{13}C NMR spectra were determined using spectrometer at 400 and 100 MHz, respectively, with TMS (tetramethyl silane) as an internal standard and solvents ($CDCl_3$, DMSO and MeOD) with residual undeuterated solvent ($CDCl_3$: 7.26/77.0, DMSO-d_6: 2.5/39.5 and MeOD: 3.31, 49.00). Coupling constants (*J*) were reported in hertz (Hz). The ^{13}C NMR spectra were fully decoupled. The abbreviations used to characterize the signals are as follows: s = singlet, m = multiplet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, quin = quintet, br s = broad singlet. For triplet with the splitting pattern of 1:2:1, only one average coupling constant is reported but for doublet of doublet with the splitting pattern of 1:2:2:1, two different coupling constants are reported. Mass spectra were recorded in the APCI mode at an ionization potential (70 eV) with LCMS MSD and GCMS in the EI mode mass spectrometers. Infra-red (FTIR) spectra (neat or KBr) were determined using FT-IR spectrometer (4000-600 cm^{-1}). Melting points have been determined using digital melting point apparatus. Evaporation of solvent was done at reduced pressure, using a rotary evaporator. HPLC of all the target compounds has been performed using C18 column (4.6 × 250 mm, 5 micron,) and acetonitrile:water (95:50) as the mobile phase at 40 ºC (column temperature) utilizing 20 µL of the sample with flow rate of 1 mL min^{-1} using binary pump. Photo diode array detector was used for at wavelengths (254 nM and 215 nM). The intermediates **2a-c**, **5a** [12] and final compounds **4a**, **4b** and **4i** [31] are reported in the literature.

Synthetic procedure for preparation of 5-substituted benzo[*d*]thiazole-2-carboxylate (2a-c): To a magnetically stirred miceller solution of SDOSS (44 mg, 10 mol %) in demineralised water

(2 mL), was added 2-aminothiophenol **1a** (1 mmol,) and ethyl glyoxalate (1.2 equiv) and the mixture was stirred at rt. After completion of the reaction (5 h, TLC), the reaction mixture was extracted with EtOAc up to four times. Combined EtOAc extracts were dried over anhydrous Na_2SO_4, and concentrated under vacuum rotary evaporation. The crude product was purified by passing through a column of silica gel (60-120 mesh) and eluted with hexane-EtOAc (90:10) to afford the pure **2a**.

4.1.1 Ethyl benzo[*d*]thiazole-2-carboxylate (**2a**): Yield: 172 mg, 83% (yellow solid), mp 68-72 $^{\circ}$C. IR (KBr) ν: 1750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.25 (d, *J* = 8.16 Hz, 1H), 7.97 (d, *J* = 7.92 Hz, 1H), 7.60-7.52 (m, 2H), 4.56 (q, *J* = 7.12 Hz, 2H), 1.49 (t, *J* = 7.12, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.68, 158.57, 153.22, 136.78, 127.54, 127.09, 125.52, 122.08, 63.13, 14.29. MS (APCI) *m/z* 208.21 $(M + H)^+$.

4.1.2 Ethyl 5-chlorobenzo[*d*]thiazole-2-carboxylate (2b): Yield: 176 mg, 73% (yellowish solid), mp 91-93 $^{\circ}$C. IR (KBr) ν: 1743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.24 (d, *J* = 1.88 Hz, 1H), 7.91 (d, *J* = 8.68 Hz, 1H), 7.53 (dd, *J* = 8.64, 1.96 Hz), 4.57 (q, *J* = 7.16 Hz, 2H), 1.50 (t, *J* = 7.12 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.35, 160.31, 153.95, 134.98, 133.28, 128.26, 125.05, 122.89, 63.37, 14.27. MS (ESI) (*m/z*) 242.23 $(M)^+$.

4.1.3 Ethyl 5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxylate (2c): Yield: 193 mg, 70% (white solid), mp 73-75 $^{\circ}$C. IR (KBr) ν: 1736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.53 (s, 1H), 8.13 (d, *J* = 8.52 Hz, 1H), 7.79 (dd, *J* = 8.52, 1.32 Hz, 1H), 4.60 (q, *J* = 7.12 Hz, 2H), 1.52 (t, *J* = 7.12 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.80, 160.01, 152.87, 139.93, 130.22, 129.89, 123.62, 123.59, 122.77, 122.49, 63.22, 14.05. MS (APCI) (*m/z*) 275.97 $(M+H)^+$.

Synthesis of 5-substituted benzo[*d*]thiazole-2-carboxylic acid (5a): To the solution of **2** (207 mg, 1 mmol) in THF (0.5 mL) at 10 ˚C was added $LiOH \cdot H_2O$ (42 mg, 1 mmol, 1equiv) in water (2 mL) and stirred magnetically for 30 min followed by drop wise addition of dil. HCl (1 N) until precipitation occurred. The precipitate was filtered and dried under rotary vacuum evaporation (24 psi) to afford **5a** in 98% yield, identical (spectral data) with an authentic sample. [12]

4.1.4 Benzo[*d*]thiazole-2-carboxylic acid (5a): Yield: 175 mg, 98% (white solid), mp 104-108 °C. IR (KBr) ν: 1708 cm^{-1}. ^1H NMR (400 MHz, DMSO-D_6): δ (ppm): 9.43 (s, 1H), 8.19 (d, J = 8.52 Hz, 1H), 8.12 (d, J = 8.44 Hz, 1H), 7.57 (dt, J = 1.16, 8.2 Hz, 1H), 7.51 (dt, J = 1.2, 8.08 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-D_6): δ (ppm): 161.43, 159.98, 152.97, 136.26, 127.47, 127.15, 124.68, 122.99; MS (APCI) *m/z* 180 $(M + H)^+$.

Synthesis of benzo[*d*]thiazole-2-carbanilides (4, 6, 7a-x): The benzothiazole-2-carboxylic acid **5a** (179 mg, 1 mmol) in dry THF (2 mL) was treated with CDI (245 mg, 1.5 mmol, 1.5 equiv). The mixture was stirred magnetically at rt overnight, concentrated under rotary vacuum evaporation. The residue was diluted with freshly dried THF (2 mL) and treated with anilines **3** (1.1 mmol, 1.1 equiv) and DBU (76 mg, 0.5 mmol, 0.5 equiv) under magnetic stirring at 60-80 ^oC for 6-8 h. After the completion of the reaction (TLC), solvent was evaporated from reaction mixture under reduced pressure, reaction mixture was diluted with cold water (15-20 mL) and the mixture was allowed to stir for 10 min. The solid precipitate was filtered off and air dried to furnish the pure product (**4**, **6**, **7a**-**x**).

4.1.5 *N*-Phenylbenzo[*d*]thiazole-2-carboxamide (**4a**): White solid (160 mg, 63%), mp 156-158 ºC. IR (DCM, cm^{-1}) 3359, 2922, 1677, 1595, 1532, 763, 633; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.16 (d, J = 8.12 Hz, 1H), 8.04 (d, J = 7.72 Hz, 1H), 7.80 (d, J = 7.64 Hz,

2H), 7.64-7.54 (m, 2H), 7.46-7.42 (m, 2H), 7.24-7.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 157.6, 152.7, 137.5, 137.0, 129.7, 127.1, 127.0, 125.0, 124.4, 122.6, 119.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{10}N_2OSNa$ 277.0412; Found 277.0405. HPLC analysis: retention time = 4.283 min; peak area, 99.94%.

4.1.6 *N*-(*p*-Tolyl)benzo[*d*]thiazole-2-carboxamide (4b): Yield: 210 mg (78%), mp 146–148 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.60-7.50 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.3, 157.5, 152.7, 137.4, 134.7, 134.5, 129.8, 127.0, 126.9, 124.3, 122.5, 119.8, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2NaOS$ 291.0568; Found 291.0563. HPLC analysis: retention time = 4.344 min; peak area, 99.94%.

4.1.7 *N*-(*m*-Tolyl)benzo[*d*]thiazole-2-carboxamide (4c): Yield: 211 mg (79%), mp 115-117 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.61-7.49 (m, 4H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.3, 157.5, 152.7, 139.2, 137.5, 136.9, 129.1, 127.0, 126.9, 125.8, 124.4, 122.5, 120.5, 116.9, 21.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2OSNa$ 291.0568; Found 291.0563. HPLC analysis: retention time = 4.228 min; peak area, 99.90%.

4.1.8 *N*-(*o*-Tolyl)benzo[*d*]thiazole-2-carboxamide (4d): Yield: 192 mg (72%), mp 106–109 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.26 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 8.0 Hz ,1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.61-7.50 (m, 2H), 7.31-7.25 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):

164.3, 157.6, 152.8, 137.5, 135.1, 130.6, 128.4, 127.0, 127.0, 126.9, 125.4, 124.5, 122.5, 121.8, 17.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2OSNa$ 291.0568; Found 291.0563. HPLC analysis: retention time = 4.470 min; peak area, 95.92%.

4.1.9 *N*-(4-Methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (4e): Yield: 220 mg (75%), mp 135-139 ºC. IR (KBr) ν: 3372, 1687, 1524, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.17 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.71-7.67 (m, 2H), 7.61-7.49 (m, 2H), 6.96-6.92 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.4, 157.3, 156.9, 152.8, 137.4, 130.2, 127.0, 126.9, 124.3, 122.5, 121.4, 114.4, 55.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2O_2SNa$ 307.0517; Found 307.0507. HPLC analysis: retention time = 4.897 min; peak area, 99.91%.

4.1.10 *N*-(3-Methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (4f): Yield: 233 mg (82%), mp 125-128 ºC. IR (KBr) ν: 3365, 1674, 1544, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.26 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.61-7.50 (m, 3H), 7.32-7.22 (m, 2H), 6.74-6.74 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 160.3, 157.6, 152.7, 138.2, 137.5, 129.9, 127.1, 127.0, 124.4, 122.5, 112.0, 111.2, 105.3, 55.4.HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2O_2SNa$ 307.0517; Found 307.0507. HPLC analysis: retention time = 3.818 min; peak area, 97.30%.

4.1.11 *N*-(2-Methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (4g): Yield: 213 mg (75%), mp 117-120 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.88 (s, 1H), 8.54 (dd, J = 1.6, 8.0 Hz, 1H), 8.17 (d, J = 8.1 Hz 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.60-7.49 (m, 2H), 7.13 (dt, J = 1.6, 7.7 Hz, 1H), 7.04 (dt, J = 1.2, 7.8 Hz, 1H), 6.96 (dd, J = 1.2, 8.1 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.5, 157.5, 152.9, 148.7,

137.4, 124.7, 124.6, 126.9, 126.8, 124.7, 124.6, 122.4, 121.9, 121.1, 120.0, 110.2, 56.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}N_2O_2SNa$ 307.0517; Found 307.0507. HPLC analysis: retention time = 4.893 min; peak area, 99.91%.

4.1.12 *N*-(4-Chlorophenyl)benzo[*d*]thiazole-2-carboxamide (4h): Yield: 250 mg (87%), mp 145-150 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.74-7.71 (m, 2H), 7.62-7.51 (m, 2H), 7.39-7.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.7, 157.6, 152.6, 137.4, 135.6, 130.0, 129.3, 127.2, 127.1, 124.4, 122.6, 121.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9ClN_2OSNa$ 311.0022; Found 311.0015. HPLC analysis: retention time = 7.235 min; peak area, 99.54%.

4.1.13 *N*-(3-Chlorophenyl)benzo[*d*]thiazole-2-carboxamide (4i): Yield: 219 mg (76%), mp 131-133 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.28 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.88 (t, J = 2.0 Hz, 1H), 7.63-7.51 (m, 3H), 7.32 (t, J = 8.0 Hz, 1H), 7.17-7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.5, 157.7, 152.6, 138.1, 137.5, 135.0, 130.2, 127.1, 125.0, 124.5, 122.5, 121.9, 119.9, 117.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9ClN_2OSNa$ 311.0022; Found 311.0015. HPLC analysis: retention time = 7.203 min; peak area, 99.72%.

4.1.14 *N*-(2-Chlorophenyl)benzo[*d*]thiazole-2-carboxamide (4j): Yield: 192 mg (67%), mp 141–144 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.92 (s, 1H), 8.58 (dd, J = 1.3, 8.2 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.61-7.51 (m, 2H), 7.45 (dd, J = 1.2, 8.0 Hz,1H), 7.35 (t, J = 8.2 Hz 1H), 7.12 (dt, J = 1.2, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.5, 157.8, 152.8, 137.5, 134.0, 129.3, 127.4, 127.1, 127.1, 125.3, 124.8, 123.5, 122.4, 121.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for

$C_{14}H_9ClN_2OSNa$ 311.0022; Found 311.0015. HPLC analysis: retention time =5.203 min; peak area, 98.23%.

4.1.15 *N*-(4-Fluorophenyl)benzo[*d*]thiazole-2-carboxamide (4k): Yield: 212 mg (78%), mp 142–145 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.25 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.77-7.71 (m, 2H), 7.61-7.51 (m, 2H), 7.13-7.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.9, 161.0, 158.5, 157.6, 152.7, 137.4, 133.1, 133.1, 127.1, 127.0, 124.4, 122.5, 121.6, 121.5, 116.1, 115.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9FN_2OSNa$ 295.0371; Found 295.0311. HPLC analysis: retention time = 4.269 min; peak area, 99.06%.

4.1.16 *N*-(3-Fluorophenyl)benzo[*d*]thiazole-2-carboxamide (4l): Yield: 206 mg (76%), mp 108–110 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.32 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 2.2, 10.7 Hz, 1H), 7.62-7.51 (m, 2H), 7.43-7.32 (m, 2H), 6.92-6.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.3, 163.6, 161.9, 157.7, 152.6, 138.5, 138.4, 137.5, 130.4, 130.3, 127.1, 124.5, 122.6, 115.2, 115.17, 111.9, 111.6, 107.5, 107.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9FN_2OSNa$ 295.0371; Found 295.0311. HPLC analysis: retention time = 3.856 min; peak area, 96.22%.

4.1.17 *N*-(2-Fluorophenyl)benzo[*d*]thiazole-2-carboxamide (4m): Yield: 184 mg (68%), mp 132–135 ºC. IR (KBr) ν: 3378, 1685, 1544, 1285 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.55 (s, 1H), 8.51 (dt, J = 1.8, 8.1 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.62-7.51 (m, 2H), 7.24-7.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):165.4, 157.7, 154.0, 152.7, 151.5, 137.5, 127.1, 127.1, 125.7, 125.6, 125.2, 125.1, 124.8, 124.8, 124.7, 122.5, 121.5, 115.2, 115.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9FN_2OSNa$ 295.0371; Found 295.0311. HPLC analysis: retention time = 4.422 min; peak area, 96.65%.

4.1.18 *N*-(4-(Trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (4n): Yield: 174 mg (54%), mp 150-153 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.43 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.61-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.3, 157.9, 152.6, 140.0, 137.5, 127.3, 127.2, 126.9, 126.7, 126.6, 126.6, 126.5, 126.5, 124.5, 122.6, 119.5, 119.0, 114.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_9F_3N_2OSNa$ 345.0285; Found 345.0283. HPLC analysis: retention time = 4.516 min; peak area, 96.03%.

4.1.19 *N*-(3-(Trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (4o): Yield: 183 mg(53%), mp 148-151 ºC. IR (KBr) ν: 3362, 1697, 1558, 1314 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.40 (s, 1H), 8.15-8.12 (m, 1H), 8.08 (s, 1H), 8.02-7.97 (m, 2H), 7.63-7.52 (m, 3H), 7.45 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.3, 157.9, 152.6, 137.6, 137.5, 132.2, 131.9, 131.6, 131.2, 130.9, 129.8, 128.9, 127.2, 127.2, 125.1, 124.5, 122.8, 122.6, 122.4, 121.5, 121.5, 121.5, 116.6, 116.6, 116.6, 116.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_9F_3N_2OSNa$ 345.0285; Found 345.0283. HPLC analysis: retention time = 4.393 min; peak area, 97.62%.

4.1.20 *N*-(2-(Trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (4p): Yield: 184 mg (59%), mp 116–119 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.82 (s, 1H), 8.51 (d, J = 8.3 Hz, 1H), 8.19-8.17 (m, 1H), 8.02-7.99 (m, 1H), 7.71-7.51 (m, 4H), 7.30 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.1, 158.1, 152.7, 137.5, 134.6, 133.1, 127.2, 127.1, 126.4, 126.4, 126.3, 126.3, 125.4, 124.9, 124.8, 123.4, 122.7, 122.4, 120.4, 120.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_9F_3N_2OSNa$ 345.0285; Found 345.0283. HPLC analysis: retention time = 4.388 min; peak area, 98.31%.

4.1.21 *N*-(4-Bromophenyl)benzo[*d*]thiazole-2-carboxamide (4q): Yield: 261 mg (79%), mp 149-152 ºC. IR (KBr) ν: 3328, 1648 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.28 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 7.9 Hz 1H), 7.69-7.66 (m, 2H), 7.62-7.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.7, 157.6, 152.6, 137.5, 136.1, 132.3, 127.1, 127.1, 124.4, 122.6, 121.4, 117.7. HRMS (ESI): *m/z* for $C_{14}H_9BrN_2OSNa$ $[M + Na]^+$, calc.: 354.9517; observed: 354.9510. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{12}N_2ONa$ 271.0847; Found 271.0846. HPLC analysis: retention time = 4.397 min; peak area, 97.99%.

4.1.22 *N*-(4-Nitrophenyl)benzo[*d*]thiazole-2-carboxamide (4r): Yield: 245 mg (82%), mp 151-155 ºC. IR (KBr) ν: 3398, 1668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.58 (s, 1H), 8.31 (d, *J* = 9.1 Hz, 2H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 2H), 7.65-7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.7, 152.5, 150.1, 144.3, 142.7, 136.3, 132.9, 127.5, 127.4, 125.3, 124.6, 122.6, 121.0, 119.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9N_3O_3SNa$ 322.0262; Found 322.0267. HPLC analysis: retention time = 3.713 min; peak area, 97.56%.

4.1.23 *N*-(3-Nitrophenyl)benzo[*d*]thiazole-2-carboxamide (4s): Yield: 250 mg (84%), mp 200–202 ºC. IR (KBr) ν: 3398, 1668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.50 (s, 1H), 8.65 (t, *J* = 2.1 Hz, 1H), 8.19-8.15 (m, 2H), 8.07-8.02 (m, 2H), 7.65-7.55 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.0, 158.0, 152.5, 138.1, 137.5, 130.2, 127.4, 127.3, 125.3, 124.6, 122.6, 119.5, 114.6, 107.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_9N_3O_3SNa$ 322.0262; Found 322.0267. HPLC analysis: retention time = 3.658 min; peak area, 96.88%.

4.1.24 *N*-(3-Fluoro-4-morpholinophenyl)benzo[*d*]thiazole-2-carboxamide (4t): Yield: 239 mg (67%), mp 186–188 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.69 (dd, *J* =

2.4, 14.0 Hz, 1H), 7.61-7.47 (m, 2H), 7.37 (dd, *J* = 1.4, 8.6 Hz, 1H), 6.96 (t, *J* = 9.0 Hz, 2H), 3.88 (t, *J* = 4.5 Hz, 4H), 3.09 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.8, 157.4, 156.6, 154.2, 152.67, 137.4, 137.1, 137.0, 132.1, 132.0, 127.1, 127.0, 124.4, 122.5, 118.9, 118.9, 115.7, 109.0, 108.7, 67.0, 51.0. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{18}H_{16}FN_3O_2SNa$ 380.0845; Found 380.0835. HPLC analysis: retention time = 4.337 min; peak area, 96.98%.

4.1.25 *N*-(4-Morpholinophenyl)benzo[*d*]thiazole-2-carboxamide (4u): Yield: 210 mg (62%), mp 220-230 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.17 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 7.9 Hz 1H), 7.69 (td, *J* = 3.2, 9.0 Hz, 2H), 7.60-7.49 (m, 2H), 6.95 (td, *J* = 3.2, 9.0 Hz, 2H), 3.88 (t, *J* = 4.7 Hz, 4H), 3.17 (t, *J* = 4.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6, 159.4, 153.6, 137.2, 135.4, 133.0, 128.9, 128.0, 127.9, 127.4, 124.0, 123.2, 44.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}N_3O_2SNa$ 362.0939; Found 362.0936. HPLC analysis: retention time = 3.997 min; peak area, 99.61%.

4.1.26 *N*-(2-Morpholinophenyl)benzo[*d*]thiazole-2-carboxamide (4v): Yield: 200 mg (59%), mp 190-193 ºC. IR (KBr) ν: 3373, 1664, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.64 (s, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.62-7.50 (m, 2H), 7.25-7.16 (m, 3H), 4.04 (t, *J* = 4.5 Hz 4H), 2.99 (t, *J* = 4.6 Hz 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 157.4, 152.9, 141.8, 137.4, 132.5, 127.0, 126.9, 125.7, 124.7, 124.5, 122.5, 120.5, 119.6, 67.7, 52.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}N_3O_2SNa$ 362.0939; Found 362.0936. HPLC analysis: retention time = 5.074 min; peak area, 98.60%.

4.1.27 *N*-(3,4,5-Trimethoxyphenyl)benzo[*d*]thiazole-2-carboxamide (4w): Yield: 189 mg (55%), mp 160-162 ºC. IR (KBr) ν: 3368, 1665, 1510, 1319 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ

(ppm): 9.21 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.62-7.54 (m, 2H), 7.10 (s, 2H), 3.92 (s, 6H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 157.5, 153.5, 152.7, 137.4, 135.2, 133.0, 127.1, 127.0, 124.3, 122.6, 97.4, 61.0, 56.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}N_2O_4SNa$ 367.0728; Found 367.0723. HPLC analysis: retention time = 4.232 min; peak area, 96.56%.

4.1.28 *N*-Mesitylbenzo[*d*]thiazole-2-carboxamide (4x): Yield: 177 mg (60%), mp 155-157 ºC. IR (KBr) ν: 3369, 1672, 1515, 1320 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.59-7.52 (m, 2H), 6.96 (s, 2H), 2.31 (s, 3H), 2.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.8, 158.2, 152.9, 137.5, 137.4, 135.2, 130.1, 129.1, 126.9, 126.9, 124.4, 122.5, 21.0, 18.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}N_2OSNa$ 319.0881; Found 319.0877. HPLC analysis: retention time = 4.283 min; peak area, 97.48%.

4.1.29 5-Chloro-*N*-phenylbenzo[*d*]thiazole-2-carboxamide (6a): Yield: 216 mg (75%), mp 160-162 ºC. IR (KBr) ν: 3366, 1681, 1536, 1308 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.52 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 157.2, 153.5, 136.8, 135.7, 133.2, 129.3, 127.6, 125.2, 124.1, 123.3, 119.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}N_2OSNa$ 311.0022; Found 311.0011. HPLC analysis: retention time = 4.345 min; peak area, 99.39%.

4.1.30 5-Chloro-*N*-(*p*-tolyl)benzo[*d*]thiazole-2-carboxamide (6b): Yield: 247 mg, (82%), mp 140-142 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 8.09 (s, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.49 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

(ppm): 166.2, 157.0, 153.5, 135.6, 134.9, 134.3, 133.1, 129.8, 127.5, 124.0, 123.3, 119.9, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2OSNa$ 325.0178; Found 325.0172. HPLC analysis: retention time = 4.771 min; peak area, 96.12%.

4.1.31 5-Chloro-*N*-(*m*-tolyl)benzo[*d*]thiazole-2-carboxamide (6c): Yield: 229 mg (76%), mp 138-142 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.17 (s, 1H), 8.10 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.5 (dd, J = 1.9, 8.6 Hz, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 157.1, 153.5, 139.3, 136.7, 135.6, 133.1, 129.1, 127.6, 126.0, 124.0, 123.3, 120.5, 117.0, 21.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2OSNa$ 325.0178; Found 325.0172. HPLC analysis: retention time = 4.613 min; peak area, 98.55%.

4.1.32 5-Chloro-*N*-(*o*-tolyl)benzo[*d*]thiazole-2-carboxamide (6d): Yield: 225 mg (74%), mp 179-181 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.20 (s, 1H), 8.18-8.14 (m, 2H), 7.92 (d, J = 8.6 Hz, 1H), 7.50 (dd, J = 1.6, 8.6 Hz, 1H), 7.31-7.25 (m, 2H), 7.14 (t, J = 7.4 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 157.2, 153.5, 135.7, 134.9, 133.1, 130.7, 128.3, 127.6, 127.1, 125.5, 124.2, 1233, 121.8, 17.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2OSNa$ 325.0178; Found 325.0172. HPLC analysis: retention time = 4.500 min; peak area, 96.45%.

4.1.33 5-Chloro-*N*-(4-methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (6e): Yield: 248 mg (78%), mp 160-163 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.12 (s, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.9 Hz, 2H), 7.49 (dd, J = 1.8, 8.6 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.3, 157.0, 156.9, 153.5, 135.6, 133.1, 130.0, 127.5, 124.0, 123.3, 121.5,

114.4, 55.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2O_2SNa$ 341.0127; Found 341.0119. HPLC analysis: retention time = 4.697 min; peak area, 96.46%.

4.1.34 5-Chloro-*N*-(3-methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (6f): Yield: 252 mg (79%), mp 139-142 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.55-7.51 (m, 2H), 7.33 (t, J = 8.1 Hz, 1H), 7.25 (d, J = 8.2 Hz, 2H), 6.78 (dd, J = 2.1, 8.1 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.0, 159.3, 156.2, 152.4, 137.0, 134.6, 132.2, 129.9, 126.6, 123.1, 122.3, 111.1, 110.3, 104.4, 54.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2O_2SNa$ 341.0127; Found 341.0119. HPLC analysis: retention time = 4.927 min; peak area, 96.04%.

4.1.35 5-Chloro-*N*-(2-methoxyphenyl)benzo[*d*]thiazole-2-carboxamide (6g): Yield: 216 mg (69%), mp 163-167 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.84 (s, 1H), 8.51 (dd, J = 1.2, 8.0 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.49 (dd, J = 1.8, 8.6 Hz, 1H), 7.14 (dt, J = 1.4, 8.0 Hz, 1H), 7.03 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.3, 157.1, 153.7, 148.6, 135.6, 133.0, 127.4, 126.6, 124.9, 124.3, 123.2, 121.2, 120.0, 110.2, 55.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{11}ClN_2O_2SNa$ 341.0127; Found 341.0119. HPLC analysis: retention time = 5.030 min; peak area, 95.03%.

4.1.36 5-Chloro-*N*-(4-chlorophenyl)benzo[*d*]thiazole-2-carboxamide (6h): Yield: 270 mg (84%), mp 170-181 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 8.09 (d, J = 1.88 Hz, 1H), 7.91 (d, J = 8.64 Hz, 1H), 7.64-7.70 (m, 2H), 7.50 (dd, J = 2.0, 8.6 Hz, 1H), 7.39-7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6, 157.2, 153.4, 135.6, 135.4, 133.3, 130.2, 129.3, 127.8, 124.1, 123.3, 121.1. HRMS (ESI-TOF) m/z: [M

+ Na]$^+$ Calcd for $C_{14}H_8Cl_2N_2OSNa$ 344.9632; Found 344.9651. HPLC analysis: retention time = 7.025 min; peak area, 99.03%.

4.1.37 5-Chloro-*N*-(3-chlorophenyl)benzo[*d*]thiazole-2-carboxamide (6i): Yield: 279 mg (86%), mp 168-170 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.24 (s, 1H), 8.10 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.90 (t, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.53 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H) 7.20 (dd, *J* = 1.0, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.4, 157.2, 153.4, 137.9, 135.7, 135.0, 133.3, 130.3, 127.8, 125.2, 124.1, 123.3, 120.0, 117.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_8Cl_2N_2OSNa$ 344.9632; Found 344.9651. HPLC analysis: retention time = 5.027 min; peak area, 98.06%.

4.1.38 5-Chloro-*N*-(2-chlorophenyl)benzo[*d*]thiazole-2-carboxamide (6j): Yield: 250 mg (74%), mp 195-197 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.90 (s, 1H), 8.58 (dd, *J* = 1.4, 8.3 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.53 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.48 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.16 (dt, *J* = 1.5, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.4, 157.3, 153.5, 135.7, 133.8, 133.2, 129.4, 127.9, 127.7, 125.5, 124.4, 123.5, 123.2, 121.3. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_8Cl_2N_2OSNa$ 344.9632; Found 344.9651. HPLC analysis: retention time = 7.232 min; peak area, 99.68%.

4.1.39 5-Chloro-*N*-(4-fluorophenyl)benzo[*d*]thiazole-2-carboxamide (6k): Yield: 220 mg (72%), mp 163-165 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.50 (s, 1H), 8.49 (dt, *J* = 1.6, 8.1 Hz, 1H), 8.16 (d, *J* = 1.9 Hz, 1H), 7.93 (t, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.24-7.14 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.2, 157.3, 154.0, 153.5, 151.6, 135.7, 133.3, 127.8, 125.6, 125.5, 125.4, 125.3, 124.8, 124.8,

124.3, 123.2, 121.5, 115.3, 115.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8ClFN_2OSNa$ 328.9928; Found 328.9922. HPLC analysis: retention time = 4.804 min; peak area, 95.27%.

4.1.40 5-Chloro-*N*-(3-fluorophenyl)benzo[*d*]thiazole-2-carboxamide (6l): Yield: 215 mg (71%), mp 147-150 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.25 (s, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.71 (td, J = 1.9, 10.5 Hz, 1H), 7.51 (dd, J = 2.0, 8.6 Hz, 1H), 7.42-7.33 (m, 2H), 6.93-6.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5, 164.3, 161.9, 157.3, 153.4, 138.3, 138.2, 135.7, 133.3, 130.5, 130.4, 127.8, 124.1, 123.3, 115.3, 115.2, 112.1, 111.9, 107.6, 107.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8ClFN_2OSNa$ 328.9928; Found 328.9922. HPLC analysis: retention time = 4.037 min; peak area, 96.91%.

4.1.41 5-Chloro-*N*-(2-fluorophenyl)benzo[*d*]thiazole-2-carboxamide (6m): Yield: 205 mg (67%), mp 152-155 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.49 (s, 1H), 8.48 (t, J = 8.1 Hz, 1H), 8.15 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.50 (dd, J = 1.6, 8.6 Hz, 1H), 7.23-7.12 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.2, 157.3, 154.0, 153.5, 151.5, 135.6, 133.3, 127.8, 125.5, 125.4, 125.4, 125.3, 124.8, 124.8, 124.3, 123.2, 121.5, 115.3, 115.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8ClFN_2OSNa$ 328.9928; Found 328.9922. HPLC analysis: retention time = 4.425 min; peak area, 95.46%.

4.1.42 5-Chloro-*N*-(4-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (6n): Yield: 230 mg (65%), mp 134-137 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.40 (s, 1H), 8.44 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 7.4 Hz, 1H), 7.71 (d, J =8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6, 157.3, 152.1, 140.6, 139.7, 130.2, 129.8, 127.3, 126.7, 126.6, 126.6, 126.6, 125.2, 123.6, 123.5,

123.5, 123.5, 123.4, 121.9, 121.9, 121.8, 121.8, 119.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa^+$ 378.9890; Found 378.9886. HPLC analysis: retention time = 4.764 min; peak area, 97.96%.

4.1.43 5-Chloro-*N*-(3-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (6o): Yield: 240 mg (67%), mp 144-147 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^1H NMR (400 MHz, DMSO) δ (ppm): 11.56 (s, 1H), 8.43 (s, 1H), 8.48 (d, J = 8.5 Hz, 2H), 8.27 (s, 1H), 8.21 (d, J = 7.7 Hz, 1H), 7.73-7.66 (m, 2H), 7.56 (d, J = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.9, 158.8, 153.9, 139.1, 135.7, 132.5, 130.5, 130.1, 129.8, 127.9, 125.2, 124.9, 123.8, 123.2, 121.5, 121.4, 121.4, 121.3, 117.6, 117.5, 117.5, 117.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa$ 378.9896; Found 378.9873. HPLC analysis: retention time = 4.900 min; peak area, 99.48%.

4.1.44 5-Chloro-*N*-(2-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (6p): Yield: 179 mg (51%), mp 141-143 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.5 (s, 1H), 8.39 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.70-7.62 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0, 158.8, 153.9, 139.1, 135.7, 132.5, 130.5, 129.8, 127.9, 125.3, 124.9, 123.8, 121.4, 117.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa$ 378.9896; Found 378.9891. HPLC analysis: retention time = 4.898 min; peak area, 99.00%.

4.1.45 5-Chloro-*N*-(4-bromophenyl)benzo[*d*]thiazole-2-carboxamide (6q): Yield: 288 mg (79%), mp 155-157 ºC. IR (KBr) ν: 3328, 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 8.10 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.67-7.65 (m, 2H), 7.54-7.49 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5, 157.2, 153.4, 135.9, 135.7, 133.3, 132.3, 127.8,

124.1, 123.3, 121.4, 117.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8BrClN_2OSNa$ 388.9127; Found 388.9119. HPLC analysis: retention time = 4.676 min; peak area, 95.90%.

4.1.46 5-Chloro-*N*-(4-nitrophenyl)benzo[*d*]thiazole-2-carboxamide (6r): Yield: 185 mg (56%), mp 215-217 ºC. IR (KBr) ν: 3398, 1668 cm^{-1}. ^1H NMR (400 MHz, DMSO+$CDCl_3$) δ (ppm): 10.80 (s, 1H), 8.91 (s, 1H), 8.27 (d, J = 6.4 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.60-7.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO+$CDCl_3$) δ (ppm): 170.5, 163.1, 158.3, 153.2, 143.6, 140.3, 137.7, 134.5, 132.5, 131.1, 128.7, 128.3, 124.0, 120.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8ClN_3O_3SNa$ 355.9873; Found 355.9869. HPLC analysis: retention time = 3.918 min; peak area, 97.94%.

4.1.47 5-Chloro-*N*-(3-nitrophenyl)benzo[*d*]thiazole-2-carboxamide (6s): Yield: 226 mg (68%), mp 262-263 ºC. IR (KBr) ν: 3367, 1658 cm^{-1}. ^1H NMR (400 MHz, DMSO+$CDCl_3$) δ (ppm): 10.88 (s, 1H), 8.26 (d, J = 9.2 Hz, 2H), 8.17-8.14 (m, 3H), 8.02 (d, J = 8.7 Hz, 1H), 7.56-7.54 (m, 1H). ^{13}C NMR (100 MHz, DMSO+$CDCl_3$) δ (ppm): 170.4, 166.6, 163.2, 158.4, 148.5, 148.4, 140.3, 137.8, 132.6, 129.5, 128.7, 128.4, 125.2, 117.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_8ClN_3O_3SNa$ 355.9873; Found 355.9869. HPLC analysis: retention time = 3.365 min; peak area, 95.92%.

4.1.48 5-Chloro-*N*-(3-fluoro-4-morpholinophenyl)beno[*d*]thiazole-2-carboxamide (6t): Yield: 243 mg (62%), mp 203-205 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 2.3, 13.9 Hz, 1H), 7.50 (dd, J = 1.9, 8.6 Hz, 1H), 7.36 (dd, J = 5.3 Hz, 1H), 6.96 (t, J = 9 Hz, 1H), 3.88 (t, J = 4.5 Hz, 4H), 3.09 (t, J = 9.1 Hz, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6, 159.4, 153.6, 137.2, 135.4, 133.0, 128.9, 128.0, 127.9, 127.4, 124.0, 123.2, 44.0. HRMS

(ESI-TOF) m/z: $[M]^+$ Calcd for $C_{18}H_{15}ClFN_3O_2SNa^+$ 414.0450; Found 414.0447. HPLC analysis: retention time = 4.340 min; peak area, 99.91%.

4.1.49 5-Chloro-*N*-(4-morpholinophenyl)benzo[*d*]thiazole-2-carboxamide (6u): Yield: 212 mg (57%), mp 170-175 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.11 (s, 1H), 8.10 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.49 (dd, J = 2.0, 8.6 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 3.88 (t, J = 4.7 Hz, 4H), 3.17 (t, J = 4.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 156.8, 153.5, 148.8, 135.6, 133.1, 129.5, 127.5, 124.0, 123.3, 121.1, 116.2, 66.9, 49.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{16}ClN_3O_2SNa$ 396.0549; Found 396.0543. HPLC analysis: retention time = 5.074 min; peak area, 98.62%.

4.1.50 5-Chloro-*N*-(2-morpholinophenyl)benzo[*d*]thiazole-2-carboxamide (6v): Yield: 249 mg (67%), mp 165-172 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.61 (s, 1H), 8.50 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.50 (dd, J = 1.9, 8.6 Hz, 1H), 7.26-7.15 (m, 3H), 4.04 (t, J = 4.4 Hz, 4H), 2.99 (t, J = 4.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 156.9, 153.6, 141.8, 135.6, 133.1, 132.4, 127.5, 124.9, 124.1, 123.3, 120.6, 119.6, 67.7, 52.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{16}ClN_3O_2SNa$ 396.0549; Found 396.0543. HPLC analysis: retention time = 4.284 min; peak area, 96.08%.

4.1.51 5-Chloro-*N*-(3,4,5-trimethoxyphenyl)benzo[*d*]thiazole-2-carboxamide (6w): Yield: 219 mg (58%), mp 220-222 ºC. IR (KBr) ν: 3367, 1671, 1512, 1323 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.51 (dd, J = 2.0, 8.6 Hz, 1H), 7.08 (s, 2H), 3.92 (s, 6H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 157.1, 153.6, 153.5, 135.6, 135.4, 132.2, 132.9, 127.7, 124.0, 123.3, 97.5, 61.0, 56.2.

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}ClN_2NaO_4S$ 401.0339; Found 401.0333. HPLC analysis: retention time = 3.995 min; peak area, 97.09%.

4.1.52 5-Chloro-*N*-mesitylbenzo[*d*]thiazole-2-carboxamide (6x): Yield: 190 mg (58%), mp 157-159 ºC. IR (KBr) ν: 3369, 1672, 1515, 1320 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.66 (s, 1H), 8.12 (d, J = 1.92 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.50 (dd, J = 2.0, 8.6 Hz, 1H), 6.96 (s, 2H), 2.31 (s, 3H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.7, 157.1, 153.7, 137.6, 135.6, 135.2, 133.0, 129.9, 129.1, 127.5, 124.1, 123.2, 21.0, 18.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}ClN_2OSNa$ 353.0491; Found 353.0485. HPLC analysis: retention time = 4.345 min; peak area, 99.39%.

4.1.53 *N*-Phenyl-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7a): Yield: 250 mg (78%), mp 131–133 ºC. IR (KBr) ν: 3289, 1661, 1542, 1317 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.41 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.78-7.75 (m, 3H), 7.43 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 157.0, 153.2, 140.6, 136.7, 130.0, 129.6, 129.3, 125.3, 123.3, 123.3, 123.3, 123.2, 121.8, 121.8, 121.7, 121.7, 119.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_9F_3N_2OSNa$ 345.0285; Found 345.0280. HPLC analysis: retention time = 4.289 min; peak area, 99.56%.

4.1.54 *N*-(*p*-Tolyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7b): Yield: 262 mg (78%), mp 181-185 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.17 (s, 1H), 8.39 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 10.5 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 156.8, 152.3, 140.6, 135.1, 134.2, 129.9, 129.8, 123.3, 123.2, 123.2, 123.1, 123.1, 121.7,

121.7, 121.6, 121.6, 119.9, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2OSNa$ 359.0442; Found 359.0433. HPLC analysis: retention time = 4.456 min; peak area, 97.71%.

4.1.55 *N*-(*m*-Tolyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7c): Yield: 266 mg (79%), mp 128-130 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.18 (s, 1H), 8.40 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 156.9, 152.2, 139.3, 136.6, 129.9, 129.6, 129.1, 126.1, 125.3, 123.4, 123.3, 123.3, 123.3, 123.2, 123.2, 123.2, 122.6, 121.7, 120.5, 117.0, 21.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2OSNa$ 359.0442; Found 359.0433. HPLC analysis: retention time = 4.971 min; peak area, 97.20%.

4.1.56 *N*-(*o*-Tolyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7d): Yield: 249 mg (72%), mp 136-139 ºC. IR (KBr) ν: 3365, 1684, 1543, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.23 (s, 1H), 8.44 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 7.85 Hz, 1H), 7.32-7.26 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.1, 160.0, 148.0, 146.5, 143.3, 134.5, 130.2, 128.2, 128.1, 127.6, 127.6, 127.2, 122.6, 122.4, 115.9, 114.9, 114.9, 114.3, 55.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2OSNa$ 359.0442; Found 359.0437. HPLC analysis: retention time = 4.228 min; peak area, 99.90%.

4.1.57 *N*-(4-Methoxyphenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7e): Yield: 299 mg (85%), mp 163-166 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.14 (s, 1H), 8.39 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.75 (dd, *J* = 1.0, 8.4 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm): 166.7, 157.1, 156.7, 152.3, 140.6, 129.9, 129.6, 125.3, 123.3, 123.2, 123.1, 123.1, 122.6, 121.7, 121.6, 121.6, 121.6, 121.5, 114.5, 55.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2NaO_2S$ 375.0391; Found 375.0381. HPLC analysis: retention time = 3.829 min; peak area, 99.47%.

4.1.58 *N*-(3-Methoxyphenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7f): Yield: 290 mg (82%), mp 135-137 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.24 (s, 1H), 8.43 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 1.1, 8.5 Hz, 1H), 7.54 (t, *J* = 2.1 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 6.79 (dd, *J* = 1.8, 7.6 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 160.4, 157.0, 152.2, 140.6, 137.9, 130.0, 129.7, 125.3, 123.3, 123.3, 123.3, 123.2, 123.2, 122.6, 121.8, 121.8, 121.7, 121.7, 112.1, 111.4, 105.5, 55.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2O_2SNa$ 375.0391; Found 375.0385. HPLC analysis: retention time = 3.825 min; peak area, 99.47%.

4.1.59 *N*-(4-Methoxyphenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7g): Yield: 264 mg (75%), mp 157-160 ºC. IR (KBr) ν: 3370, 1684, 1534, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.87 (s, 1H), 8.52 (dd, *J* = 1.5, 8.0 Hz, 1H), 8.47 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 1.3, 8.5 Hz, 1H), 7.15 (dt, *J* = 1.6, 7.8 Hz, 1H), 7.04 (dt, *J* = 1.1, 7.92 Hz, 1H), 6.97 (dd, 1.1, 8.1 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.8, 156.9, 152.4, 148.7, 140.6, 129.8, 126.6, 125.4, 125.0, 123.1, 123.1, 123.0, 122.6, 122.0, 121.9, 121.9, 121.9, 121.2, 120.0, 110.3, 55.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{11}F_3N_2O_2SNa$ 375.0391; Found 375.0387. HPLC analysis: retention time = 4.624 min; peak area, 95.40%.

4.1.60 *N*-(4-Chlorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7h): Yield: 308 mg (87%), mp 170-172 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.23 (s, 1H), 8.39 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.77-7.71 (m, 3H), 7.38 (dd, J = 1.9, 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 157.0, 152.1, 140.6, 135.3, 130.4, 130.1, 129.7, 129.4, 123.4, 123.4, 123.3, 123.3, 122.5, 121.8, 121.8, 121.7, 121.7, 121.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa$ 378.9896; Found 378.9884. HPLC analysis: retention time = 4.329 min; peak area, 96.27%.

4.1.61 *N*-(3-Chlorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7i): Yield: 270 mg (76%), mp 123-126 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.24 (s, 1H), 8.40 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.89 (t, J = 2.0 Hz, 1H), 7.77 (dd, J = 1.3, 8.5 Hz, 1H), 7.63-7.60 (m, 1H), 7.34 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.9, 157.1, 152.1, 140.6, 137.8, 135.1, 130.3, 130.1, 129.8, 125.4, 125.2, 123.4, 123.4, 123.4, 123.4, 121.8, 121.8, 121.8, 120.0, 117.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa$ 378.9896; Found 378.9881. HPLC analysis: retention time = 4.370 min; peak area, 96.12%.

4.1.62 *N*-(2-Chlorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7j): Yield: 239 mg (67%), mp 176-178 ºC. IR (KBr) ν: 3338, 1689, 1590, 1538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 7.77-7.73 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.9, 157.1, 152.3, 140.6, 133.7, 129.4, 127.9, 125.6, 123.6, 123.4, 123.4, 123.3, 123.3, 122.2, 122.2, 122.1, 122.1, 121.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8ClF_3N_2OSNa^+$ 378.9890; Found 378.9885. HPLC analysis: retention time = 5.185 min; peak area, 96.63%.

4.1.63 *N*-(4-Fluorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7k): Yield: 266 mg (78%), mp 120-122 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.40 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.77-7.73 (m, 3H), 7.12 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 161.1, 158.7, 156.9, 152.2, 140.6, 132.8, 130.0, 129.7, 123.4, 123.3, 123.3, 123.2, 121.8, 121.7, 121.7, 121.7, 121.6, 116.2, 116.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8F_4N_2NaOSNa$ 363.0191; Found 363.0182. HPLC analysis: retention time = 3.854 min; peak area, 92.70%.

4.1.64 *N*-(3-Fluorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7l): Yield: 259 mg (76%), mp 110-114 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.27 (s, 1H), 8.41 (d, *J* = 8.1 Hz, 2H), 7.78-7.70 (m, 2H), 7.7-7.34 (m, 2H), 6.94-6.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.9, 164.3, 161.9, 157.1, 152.1, 140.6, 138.2, 138.1, 130.5, 130.4, 130.1, 129.7, 125.2, 123.4, 123.4, 123.4, 123.3, 122.5, 121.8, 121.8, 121.8, 121.7, 115.3, 115.2, 112.2, 112.0, 107.6, 107.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8F_4N_2NaOSNa$ 363.0191; Found 363.0189. HPLC analysis: retention time = 4.028 min; peak area, 97.27%.

4.1.65 *N*-(2-Fluorophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7m): Yield: 250 mg (74%), mp 145-149 ºC. IR (KBr) ν: 3373, 1690, 1544, 1275 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.51 (s, 1H), 8.51-8.45 (m, 2H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 1.2, 8.5 Hz, 1H), 7.24-7.13 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.7, 157.1, 154.0, 152.2, 151.6, 140.6, 130.0, 129.7, 125.5, 125.4, 125.4, 125.3, 124.8, 124.8, 123.4, 123.3, 123.3, 122.5, 122.0, 122.0, 121.5, 115.3, 115.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8F_4N_2OSNa$ 363.0191; Found 363.0185. HPLC analysis: retention time = 3.855 min; peak area, 95.37%.

4.1.66 5-(Trifluoromethyl)-*N*-(4-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (7n): Yield: 280 mg (72%), mp 155-159 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.43 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.61-7.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.6, 157.9, 152.6, 140.0, 137.5, 127.3, 127.3, 126.9, 126.7, 126.6, 126.6, 126.5, 126.5, 124.5, 122.6, 119.5, 119.0, 114.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_8F_6N_2OSNa$ 413.0159; Found 413.0162. HPLC analysis: retention time = 4.365 min; peak area, 96.99%.

4.1.67 5-(Trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (7o): Yield: 276 mg (71%), mp 145-147 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.37 (s, 1H), 8.41 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):165.7, 157.3, 152.1, 140.6, 137.3, 132.0, 131.7, 130.2, 129.9, 129.8, 125.2, 123.5, 123.5, 123.5, 123.4, 122.9, 122.4, 121.9, 121.9, 121.8, 121.8, 116.8, 116.7, 116.7, 116.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_8F_6N_2OSNa$ 413.0159; Found 413.0162. HPLC analysis: retention time = 5.022 min; peak area, 98.50%.

4.1.68 5-(Trifluoromethyl)-*N*-(2-(trifluoromethyl)phenyl)benzo[*d*]thiazole-2-carboxamide (7p): Yield: 260 mg (67%), mp 121-124 ºC. IR (KBr) ν: 3372, 1687, 1548, 1334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.38 (s, 1H), 8.43 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.80 (dd, J = 1.3, 8.5 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.7, 157.3, 152.1, 140.6, 137.3, 132.0, 131.7, 130.2, 129.9, 125.2, 123.5, 123.5, 123.5, 123.4, 122.9, 121.9, 121.9, 121.8, 121.8, 116.8, 116.7,

116.7, 116.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_8F_6N_2OSNa$ 413.0159; Found 413.0162. HPLC analysis: retention time = 4.345 min; peak area, 99.65%.

4.1.69 *N*-(4-Bromophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7q): Yield: 259 mg (65%), mp 176-179 ºC. IR (KBr) ν: 3328, 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.22 (s, 1H), 8.40 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 1.0, 8.4 Hz, 1H), 7.68-7.66 (m, 2H), 7.55-7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.0, 157.0, 152.1, 140.6, 135.8, 132.3, 132.0, 130.1, 129.8, 123.4, 123.3, 123.3, 123.8, 121.8, 121.7, 121.7, 121.4, 118.0, 116.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8BrF_3N_2NaOSNa$ 422.9391; Found 422.9388. HPLC analysis: retention time = 4.706 min; peak area, 98.46%.

4.1.70 *N*-(4-Nitrophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7r): Yield: 245 mg (67%), mp 175-180 ºC. IR (KBr) ν: 3398, 1668 cm^{-1}. ^1H NMR (400 MHz, DMSO+$CDCl_3$) δ (ppm): 11.51 (s, 1H), 8.45 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.24 (s, 4H), 7.85 (s, 1H). ^{13}C NMR (100 MHz, DMSO+ $CDCl_3$) δ (ppm): 171.4, 163.4, 157.3, 148.9, 148.5, 145.4, 139.6, 134.1, 129.5, 129.1, 128.2, 123.2, 128.2, 128.1, 126.3, 126.3, 126.3, 126.2, 125.6, 118.6, 112.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_8F_3N_3NaO_3S$ 390.0136; Found 390.0144. HPLC analysis: retention time = 3.667 min; peak area, 96.23%.

4.1.71 *N*-(3-Nitrophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7s): Yield: 189 mg (51%), mp 188-189 ºC. IR (KBr) ν: 3398, 1668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.48 (s, 1H), 8.70 (t, J = 2.1 Hz, 1H), 8.44 (s, 1H), 8.19-8.16 (m, 2H), 8.10 (dd, J = 1.4, 8.2 Hz, 1H), 7.81 (dd, J = 1.1, 8.5 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.2, 157.4, 154.5, 152.1, 148.8, 140.6, 137.9, 136.0, 130.2, 125.4, 123.7, 123.6, 123.6, 123.6, 123.4, 121.9, 121.9, 121.9, 121.8, 119.8, 114.8. HRMS (ESI-TOF) m/z: [M

+ Na]$^+$ Calcd for $C_{15}H_8F_3N_3O_3SNa$ 390.0136; Found 390.0106. HPLC analysis: retention time = 3.668 min; peak area, 96.24%.

4.1.72 *N*-(3-Fluoro-4-morpholinophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7t): Yield: 250 mg (59%), mp 201-205 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.18 (s, 1H), 8.39 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.69 (dd, J = 2.3, 13.9 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 6.97 (t, J = 9.0 Hz, 1H), 3.89 (t, J = 4.4 Hz, 4H), 3.10 (t, J = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.2, 156.8, 156.6, 152.2, 140.6, 137.4, 137.3, 131.7, 131.6, 129.7, 123.4, 123.3, 122.5, 121.7, 121.7, 119.0, 118.9, 115.8, 115.8, 109.0, 108.8, 67.0, 51.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{15}F_4N_3O_2SNa$ 448.0719; Found 448.0709. HPLC analysis: retention time = 4.059 min; peak area, 99.67%.

4.1.73 *N*-(4-Morpholinophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7u): Yield: 227 mg (56%), mp 191-194 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 8.41 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 1.2, 8.5 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 3.92 (t, J = 4.7 Hz 4H), 3.20 (t, J = 4.8 Hz 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.8, 156.6, 152.3, 148.9, 140.6, 129.3, 123.3, 123.2, 123.1, 123.1, 123.0, 121.7, 121.6, 121.6, 121.5, 121.2 116.2, 66.9, 49.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{16}F_3N_3O_2SNa$ 430.0813; Found 430.0808. HPLC analysis: retention time = 4.051 min; peak area, 98.01%.

4.1.75 *N*-(2-Morpholinophenyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7v): Yield: 276 mg (68%), mp 179-182 ºC. IR (KBr) ν: 3373, 1164, 1532, 1260 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.65 (s, 1H), 8.55-8.53 (m, 1H), 8.43 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H),

7.79 (dd, *J* = 1.2, 8.5 Hz, 1H), 7.30-7.19 (m, 3H), 4.07 (t, *J* = 4.4 Hz, 4H), 3.02 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0, 156.8, 152.5, 141.9, 140.6, 132.3, 130.0, 129.6, 125.8, 125.0, 123.3, 123.2, 123.2, 123.1, 123.1, 121.8, 121.8, 121.8, 120.7, 120.7, 119.7, 67.8, 52.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{16}F_3N_3O_2SNa$ 430.0813; Found 430.0805. HPLC analysis: retention time = 4.612 min; peak area, 95.47%.

4.1.76 5-(Trifluoromethyl)-*N*-(3,4,5-trimethoxyphenyl)benzo[*d*]thiazole-2-carboxamide (7w): Yield: 255.67 mg (62%), mp 225-227 ºC. IR (KBr) ν: 3364, 1668, 1514, 1325 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.17 (s, 1H), 8.40 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.77 (dd, *J* = 1.2, 8.5 Hz, 1H), 7.09 (s, 2H), 3.92 (s, 6H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 156.9, 153.6, 152.2, 140.6, 135.5, 132.8, 129.7, 123.4, 123.3, 123.3, 123.3, 123.2, 121.7, 121.6, 121.6, 121.6, 97.5, 61.0, 56.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}F_3N_2O_4SNa$ 435.0602; Found 435.0597. HPLC analysis: retention time = 4.610 min; peak area, 94.94%.

4.1.77 *N*-Mesityl-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (7x): Yield: 207 mg (57%), mp 159-161 ºC. IR (KBr) ν: 3369, 1672, 1515, 1320 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 8.44 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 1.0, 8.4 Hz, 1H), 6.99 (s, 2H), 2.34 (s, 3H), 2.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.1, 157.6, 152.4, 140.6, 137.7, 135.1, 129.9, 129.5, 129.1, 125.3, 123.3, 123.2, 123.1, 123.1, 123.1, 121.8, 121.8, 121.8, 121.7, 21.0, 18.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}F_3N_2NaOS$ 387.0755; Found 387.0748. HPLC analysis: retention time = 4.235 min; peak area, 97.63%.

4.2. Biological Evaluation

4.2.1 Determination of Minimum Inhibitory Concentration

Two-fold serial dilutions of each test compound/drug were prepared and incorporated into agar medium with oleic acid, albumin, dextrose, and catalase growth supplement to get final concentrations of 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 μg/mL. Inoculum of *M. tuberculosis* ATCC 27294 was prepared from fresh agar slants with growth supplement adjusted to 1 mg/ mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of ~107 colony forming unit (cfu)/mL. Five microliters of this bacterial suspension was spotted onto agar tubes containing different concentrations of the drug as discussed above. The tubes were incubated at 37 °C, and final readings (as MIC in μg/mL) were determined after 28 days. The MIC is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.[17] Isoniazid (INH), Rifampin (R), Ethambutol (E), Pyrazinamide (Z) and Ciprofloxacin (Cfx) was procured from commercial sources.

4.2.2 In vitro Cell Viability Assay

In-vitro cell viability of the anti-TB compounds with MIC ≤ 6.25 μg/mL was determined against RAW 264.7 cell lines at 50 μg/mL concentration. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)] assay into a formazan product using the non-radioactive cell proliferation assay.

4.3. Molecular Docking

Molecular docking simulations for identification of putative binding site of the compounds (**7w**, **4i**, **4n**) on Mtb HisG was done using the Autodock Vina[23]. The 3D co-ordinates of the compounds were prepared using PRODRG server[26]. The crystal structure for *Mycobacterium tuberculosis* HisG obtained from RSC PDB (PDB entry 1NH8) [24] was used as a model for analysis. Mtb HisG (1NH8) also contained AMP bound to its active site, which was extracted prior to docking. The surface of HisG was covered in a grid space of 58Å×74 Å×80Å with a grid spacing of 1.0 Å. The compounds were considered as a flexible molecule and were docked onto HisG, which was taken as a rigid molecule. Other parameters were kept as default. Docking experiments were performed with an exhaustiveness of 30. The receptor and ligand molecules were converted into .pdbqt format using Autodock Tools 1.5.6 [27]. Out of the nine possible ligand conformations generated at the end of each run, the ligand conformation with the highest affinity was selected as a model for the binding site of compound on HisG and was further studied using PyMOL [28].

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.

Author Contributions

All authors contributed equally to this work.

Notes

The authors declare no competing financial interest. Synthesis and biological evaluation of *N*-aryl benzo[*d*]thiazole-2-carboxamides as anti-tubercular agents have been filed in Indian Patent

Office [Indian Patent Application No. TEMP/E-1/10432/2017-DEL filed on 2017/03/23 (IP36982/CBR)].

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5. References

[1] WHO declares tuberculosis a global emergency [press Release]. Geneva: World health organization, Apr 23, 1993, WHO/31.

[2] Brock, T. D. Robert Koch: A Life in Medicine and Bacteriology; Science Tech Publishers: Madison, WI, 1988.

[3] Nobel Foundation. The Nobel Prize in Physiology or Medicine 1905. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1905/%3E (accessed Sep 14, 2015).

[4] K. Dheda, C.E. Barry 3rd, G. Maartens, Tuberculosis, Lancet 387 (2015) 1211–1226.

[5] P.S. Jadhavar, M.D. Vaja, T.M. Dhameliya, A.K. Chakraborti, Oxazolidinones as Anti-tubercular Agents : Discovery, Development and Future Perspectives, Curr. Med. Chem. 22 (2015) 4379–4397.

[6] FDA news release. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm (accessed Dec 12, 2015).

[7] Otsuka Pharmaceutical Media Release. Otsuka Wins European Marketing Authorization for Deltyba(TM) (delamanid). http://www.otsuka.co.jp/en/company/release/2014/0430_01.html (accessed May 18, 2016).

[8] Highlights of Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf. (accessed June 14, 2016)

[9] M.V. Worley, S.J. Estrada, Bedaquiline : A Novel Anti-tubercular Agent for the Treatment of Multidrug-Resistant Tuberculosis, Pharmacotherapy 34 (2014) 1187–1197.

[10] The Use of Delamanid in the Treatment of Multidrug-resistant Tuberculosis. http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf. (accessed June 14, 2016)

[11] E. Harausz, H. Cox, M. Rich, C.D. Mitnick, P. Zimetbaum, J. Furin, QTc Prolongation and Treatment of Multidrug-Resistant Tuberculosis, Int. J. Tuberc. Lung Dis. 19 (2015) 385–391.

[12] P. Shah, T.M. Dhameliya, R. Bansal, M. Nautiyal, D.N. Kommi, P.S. Jadhavar, J.P. Sridevi, P. Yogeeswari, D. Sriram, A.K. Chakraborti, *N*-Arylalkylbenzo[*d*]thiazole-2-

carboxamides as Anti-mycobacterial Agents: Design, New Methods of Synthesis and Biological Evaluation, Med. Chem. Commun. 5 (2014) 1489–1495.

[13] S. Pancholia, T.M. Dhameliya, P. Shah, P.S. Jadhavar, J.P. Sridevi, P. Yogeshwari, D. Sriram, A.K. Chakraborti, Benzo[*d*]thiazol-2-yl(piperazin-1-l)methanones as New Anti-mycobacterial Chemotypes: Design, Synthesis, Biological Evaluation and 3D-QSAR Studies, Eur. J. Med. Chem. 116 (2016) 187–199.

[14] T.M. Dhameliya, S.S. Chourasiya, E. Mishra, P.S. Jadhavar, P.V. Bharatam, A.K. Chakraborti, Rationalization of Benzazole-2-carboxylate versus Benzazine-3-one/Benzazine-2,3-dione Selectivity Switch during Cyclocondensation of 2‑Aminothiophenols/Phenols/Anilines with 1,2-Biselectrophiles in Aqueous Medium, J. Org. Chem. 82 (2017) 10077–10091.

[15] N. Parikh, D. Kumar, S.R. Roy, A.K. Chakraborti, Surfactant Mediated Oxygen Reuptake in Water for Green Aerobic Oxidation: Mass-spectrometric Determination of Discrete Intermediates to Correlate Oxygen Uptake with Oxidation Efficiency, Chem. Commun. 47 (2017) 1797–1799.

[16] C. Larrivée-Aboussafy, B.P. Jones, K.E. Price, M.A. Hardink, R.W. McLaughlin, B.M. Lillie, J.M. Hawkins, R. Vaidyanathan, DBU Catalysis of *N*,*N*'-Carbonyldiimidazole-mediated Amidations, Org. Lett. 12 (2010) 324–327.

[17] P. Wayne, National Committee for Clinical Laboratory Standards (NCCLS). Antimycobacterial Susceptibility Testing for *Mycobacterium tuberculosis*, Tentative Standard M24-T. (1995).

[18] Y. Cho, T.R. Ioerger, J.C. Sacchettini, Discovery of Novel Nitrobenzothiazole Inhibitors for Mycobacterium tuberculosis ATP Phosphoribosyl Transferase (HisG) through Virtual Screening, J. Med. Chem. 51 (2008) 5984–5992.

[19] V. Purohit, A.K. Basu, Mutagenicity of nitroaromatic compounds, Chem. Res. Toxicol. 13 (2000) 673–692.

[20] P.S. Jadhavar, T.M. Dhameliya, M.D. Vaja, D. Kumar, J.P. Sridevi, P. Yogeeswari, D.Sriram. A.K. Chakraborti, Synthesis, Biological Evaluation and Structure-Activity Relationship of 2-Styrylquinazolones as Anti-tubercular Agents, Bioorg. Med. Chem. Lett. 26 (2016) 2663–2669.

[21] S. Dastmalchi, M. Hamzeh-Miverhoud, B. Sokouti, Applied Case Studies and Solutions in Molecular Docking-Based Drug Design, IGI Global, Hershey PA, 2016.

[22] K. Seth, S. K. Garg, R. Kumar, P. Purohit, V. S. Meena, R. Goyal, U. C. Banerjee, A. K. Chakraborti, 2‑(2-Arylphenyl)benzoxazole As a Novel Anti-Inflammatory Scaffold: Synthesis and Biological Evaluation, ACS Med. Chem. Lett. 5 (2014) 512−516.

[23] O.Trott, A.J. Olson, AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization and Multithreading. J. Comb. Chem. 31 (2010) 455–461.

[24] Y. Cho, V. Sharma, J.C. Sacchettini, Crystal Structure of ATP Phosphoribosyltransferase from *Mycobacterium tuberculosis*. J. Biol. Chem. 278 (2003) 8333–8339.

[25] E.P. Papadopolus, C.M. Schupbach, Reactions of Azoles with Isocyanates at Elevated Temperature, J. Org. Chem. 44 (1979) 99–104.

[26] A.W. Schűttelkopf, D.M. van Aalten, PRODRG: A tool for high-throughput crystallography of protein-ligand complexes. Acta Crystallogr. D60 (2004) 1355–1363.

[27] G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, Software News and Updates AutoDock4 and AutoDockTools4 : Automated Docking with Selective Receptor Flexibility, J. Comput. Chem. 30 (2009) 2785–2791.

[28] DeLano WL (2002). The PyMOL Molecular Genetics Graphics System, DeLano Scientific LLC, San Carlos, CA.

[29] **FIGURE CAPTIONS**

Figure 1. The pipeline and approved anti-TB drug candidates.

Figure 2. The design of benzo[*d*]thiazole-2-carbanilides (**I**) as new anti-TB chemotypes.

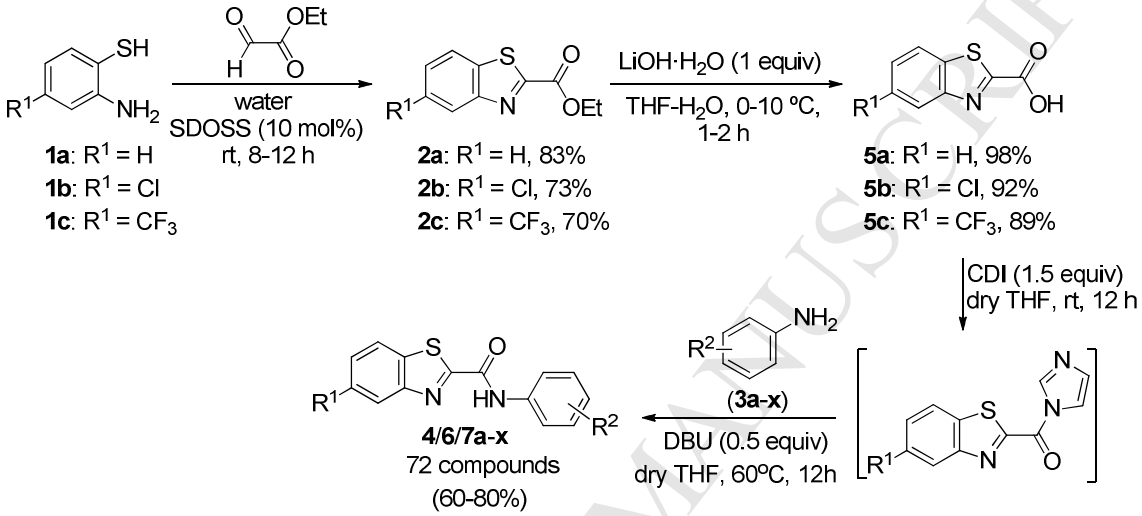
Figure 3. Graphical representation of anti-TB activity profile of the compounds with MIC ≤ 6.25 µg/mL along with the standard drugs.

Figure 4. Graphical representation of cytotoxicity profile of compounds with MIC ≤ 6.25 µg/mL.

Figure 5. (a-c) Docking pose of **7w, 4i** and **4n** with HisG (PDB: 1NH8) as determined using Autodock Vina. (d) Docked structures of two reported HisG inhibitors [18]. Yellow dashed shows HB and dashed blue shows electrostatic interactions.

Figure 6. (a) Docking alignment of PR-ATP, natural substrate of HisG (PDB: 1NH8) with **7w, 4i** and **4n.** (b) Superimposed docked poses of nitrobenzothiazole derivative with **7w, 4i** and **4n.** (c) Superimposed docked poses of thiophene derivative with **7w, 4i** and **4n.** Different ligands have been coded with respective colors: PR-ATP (orange), **7w** (magenta), **4i** (pink), **4n** (blue), nitrobenzothiazole derivative (yellow) and thiophene derivative (white).

Table 1. Synthesis of *N*-arylbenzothiazole-2-carbanilides from benzothiazole-2-carboxylic acid **5a-c** via CDI mediated amide coupling.



Entry	Compd No.	R^1	R^2	Yield[b] (%)
1	**4a**	H	H	70
2	**4b**	H	4-CH_3	78
3	**4c**	H	3- CH_3	79
4	**4d**	H	2- CH_3	72
5	**4e**	H	4-OCH_3	85
6	**4f**	H	3-OCH_3	82
7	**4g**	H	2-OCH_3	75
8	**4h**	H	4-Cl	87
9	**4i**	H	3-Cl	76
10	**4j**	H	2-Cl	67
11	**4k**	H	4-F	78

12	**4l**	H	3-F	76
13	**4m**	H	2-F	68
14	**4n**	H	4-CF_3	54
15	**4o**	H	3-CF_3	53
16	**4p**	H	2-CF_3	59
17	**4q**	H	4-Br	79
18	**4r**	H	4-NO_2	82
19	**4s**	H	3-NO_2	84
20	**4t**	H	3-Fluoro-4-morpholinyl	67
21	**4u**	H	4-Morpholinyl	62
22	**4v**	H	2-Morpholinyl	59
23	**4w**	H	3,4,5-$(OCH_3)_3$	55
24	**4x**	H	2,4,6-$(CH_3)_3$	60
25	**6a**	Cl	H	75
26	**6b**	Cl	4-CH_3	82
27	**6c**	Cl	3- CH_3	76
28	**6d**	Cl	2- CH_3	74
29	**6e**	Cl	4-OCH_3	78
30	**6f**	Cl	3-OCH_3	79
31	**6g**	Cl	2-OCH_3	69
32	**6h**	Cl	4-Cl	84
33	**6i**	Cl	3-Cl	86
34	**6j**	Cl	2-Cl	74
35	**6k**	Cl	4-F	72
36	**6l**	Cl	3-F	71
37	**6m**	Cl	2-F	67
38	**6n**	Cl	4-CF_3	65

39	**6o**	Cl	3-CF_3	67
40	**6p**	Cl	2-CF_3	51
41	**6q**	Cl	4-Br	59
42	**6r**	Cl	4-NO_2	56
43	**6s**	Cl	3-NO_2	68
44	**6t**	Cl	3-Fluoro-4-morpholinyl	62
45	**6u**	Cl	4-Morpholinyl	57
46	**6v**	Cl	2-Morpholinyl	67
47	**6w**	Cl	3,4,5-$(OCH_3)_3$	58
48	**6x**	Cl	2,4,6-$(CH_3)_3$	76
49	**7a**	CF_3	H	78
50	**7b**	CF_3	4-CH_3	78
51	**7c**	CF_3	3- CH_3	79
52	**7d**	CF_3	2- CH_3	72
53	**7e**	CF_3	4-OCH_3	85
54	**7f**	CF_3	3-OCH_3	82
55	**7g**	CF_3	2-OCH_3	75
56	**7h**	CF_3	4-Cl	87
57	**7i**	CF_3	3-Cl	76
58	**7j**	CF_3	2-Cl	67
59	**7k**	CF_3	4-F	78
60	**7l**	CF_3	3-F	76
61	**7m**	CF_3	2-F	74
62	**7n**	CF_3	4-CF_3	72
63	**7o**	CF_3	3-CF_3	71
64	**7p**	CF_3	2-CF_3	67
65	**7q**	CF_3	4-Br	65

66	**7r**	CF_3	4-NO_2	67
67	**7s**	CF_3	3-NO_2	51
68	**7t**	CF_3	3-Fluoro-4-morpholinyl	59
69	**7u**	CF_3	4-Morpholinyl	56
70	**7v**	CF_3	2-Morpholinyl	68
71	**7w**	CF_3	3,4,5-$(OCH_3)_3$	62
72	**7x**	CF_3	2,4,6-$(CH_3)_3$	57

[a]Reaction of 5-substituted-benzo[*d*]thiazole-2-carboxylic acid (**5a-c**) with CDI (2.5 equiv) in freshly dried THF for 12 h at rt followed by removal of THF, addition of fresh dry THF aromatic amine and DBU; [b]Isolated yield of final compounds. [c]Characterized by IR, NMR (^{1}H and ^{13}C) and MS (EI/ ESI).

Table 2. The anti-TB activity and in vitro cell viability of **4**, **6**, and **7a-x** and a few standard anti-TB drugs against *M. tuberculosis* H_{37}Rv (ATCC 27294).

Entry	Compd No.	MIC (µg/mL)[a]	MIC (µM)[a]	RAW 264.7 % inhibition[b]
1	**2a**	25	120.63	-
2	**2b**	3.125	12.93	37.40
3	**2c**	6.25	22.71	29.12
4	**4a**	25	98.31	-
5	**4b**	12.5	46.58	-
6	**4c**	>25	>93.17	-
7	**4d**	>25	>93.17	-
8	**4e**	6.25	21.98	24.56
9	**4f**	>25	>87.93	-
10	**4g**	3.125	10.99	16.70

11	**4h**	>25	>86.58	-
12	**4i**	0.78	2.70	26.78
13	**4j**	1.56	5.40	24.00
14	**4k**	>25	>91.81	-
15	**4l**	6.25	22.95	20.90
16	**4m**	3.125	11.48	24.89
17	**4n**	0.78	2.42	13.56
18	**4o**	12.5	38.78	-
19	**4p**	12.5	38.78	-
20	**4q**	>25	>75.03	-
21	**4r**	6.25	20.88	35.64
22	**4s**	0.78	2.61	38.42
23	**4t**	>25	>69.95	-
24	**4u**	1.56	4.60	18.90
25	**4v**	12.5	36.83	-
26	**4w**	0.78	2.26	30.12
27	**4x**	1.56	5.26	17.90
28	**6a**	25	86.58	-
29	**6b**	1.56	5.15	22.65
30	**6c**	6.25	20.64	52.16
31	**6d**	25	82.57	-
32	**6e**	25	78.42	-
33	**6f**	0.78	2.45	18.67
34	**6g**	25	78.42	-
35	**6h**	0.76	2.35	28.90
36	**6i**	25	77.35	-
37	**6j**	25	77.35	-

38	**6k**	1.56	5.09	34.56
39	**6l**	1.56	5.09	29.07
40	**6m**	1.56	5.09	18.14
41	**6n**	1.56	4.37	40.97
42	**6o**	25	70.08	-
43	**6p**	25	70.08	-
44	**6q**	1.56	4.24	53.12
45	**6r**	25	74.91	-
46	**6s**	12.5	37.45	-
47	**6t**	12.5	31.90	-
48	**6u**	0.78	2.09	42.32
49	**6v**	25	66.87	-
50	**6w**	25	65.99	-
51	**6x**	25	75.57	-
52	**7a**	25	77.57	-
53	**7b**	1.56	4.64	47.80
54	**7c**	1.56	4.64	34.56
55	**7d**	25	74.33	-
56	**7e**	0.78	2.21	35.68
57	**7f**	1.56	4.43	26.75
58	**7g**	1.56	4.43	43.21
59	**7h**	0.78	2.19	36.70
60	**7i**	12.5	35.04	-
61	**7j**	25	70.08	-
62	**7k**	25	73.47	-
63	**7l**	12.5	36.73	-
64	**7m**	25	73.47	-

65	**7n**	25	64.05	-
66	**7o**	6.25	16.01	19.80
67	**7p**	0.78	2.00	27.80
68	**7q**	25	62.31	-
69	**7r**	0.78	2.12	32.65
70	**7s**	25	68.06	-
71	**7t**	12.5	29.38	-
72	**7u**	25	61.36	-
73	**7v**	12.5	30.68	-
74	**7w**	0.78	1.89	23.45
75	**7x**	25	68.61	-
76	**INH**	0.098	-	-
77	**R**	0.197	-	-
78	**E**	1.56	-	-
79	**Z**	6.25	-	-
80	**Cfx**	1.56	-	-

[a]99% inhibition of *M. tuberculosis* H_{37}Rv ATCC 27294 strain. [b]% inhibition at 50 µg/mL concentration determined against RAW 264.7 cell lines.

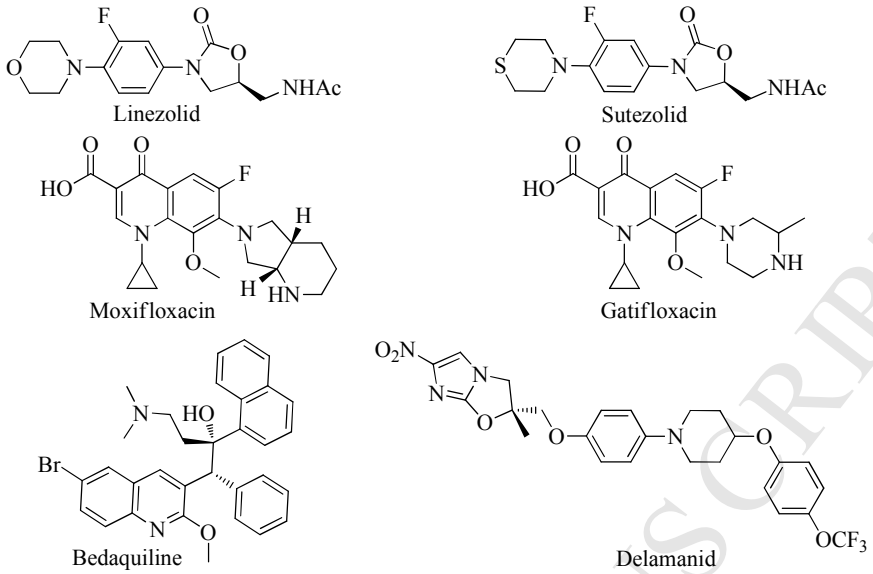


Figure 1. The pipeline and approved anti-TB drug candidates.

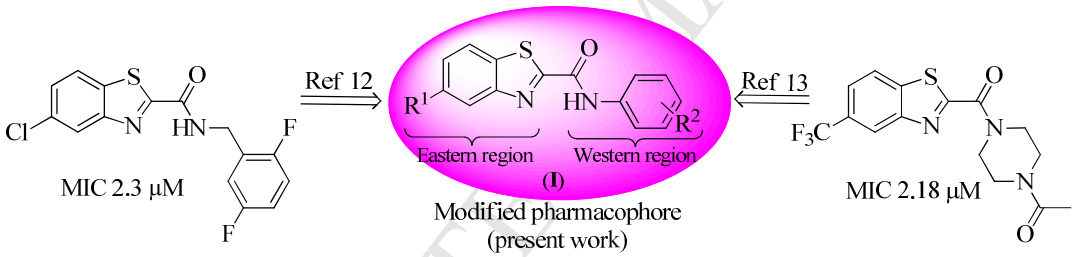


Figure 2. The design of benzo[*d*]thiazole-2-carbanilides (**I**) as new anti-TB chemotypes.

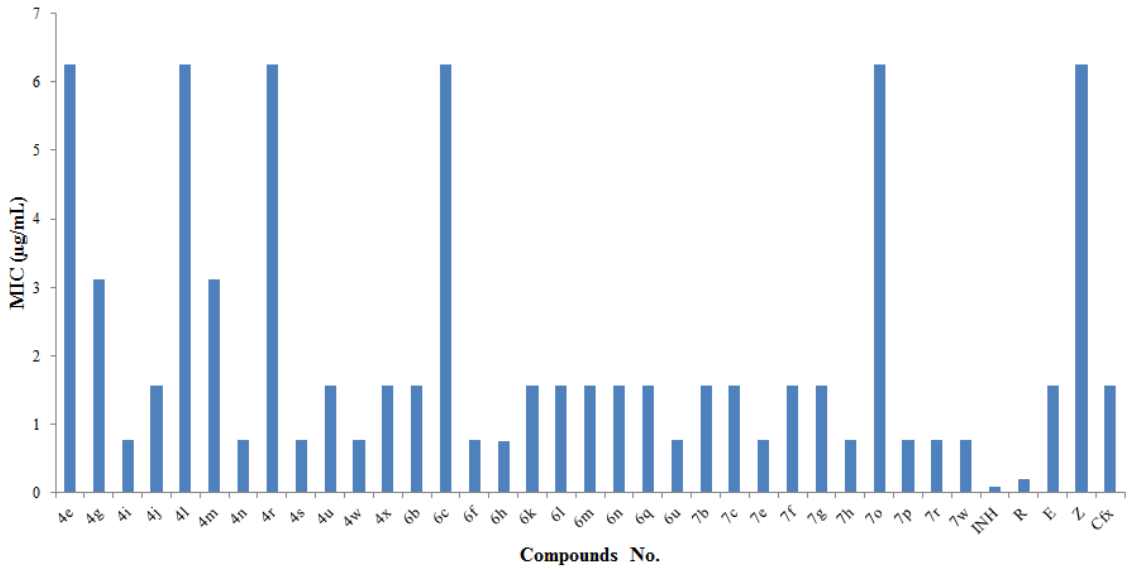


Figure 3. Graphical representation of anti-TB activity profile of the compounds with MIC ≤ 6.25 µg/mL along with the standard drugs.

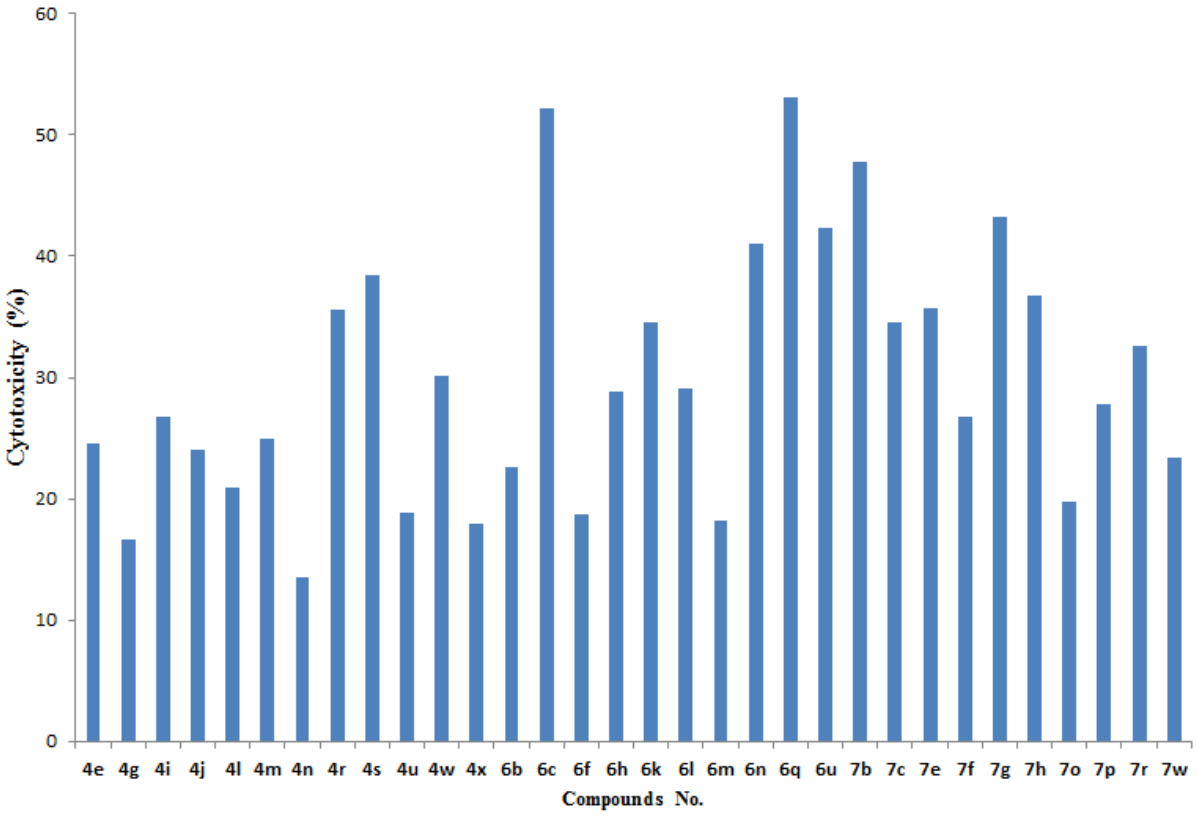


Figure 4. Graphical representation of cytotoxicity profile of compounds with MIC ≤ 6.25 µg/mL.

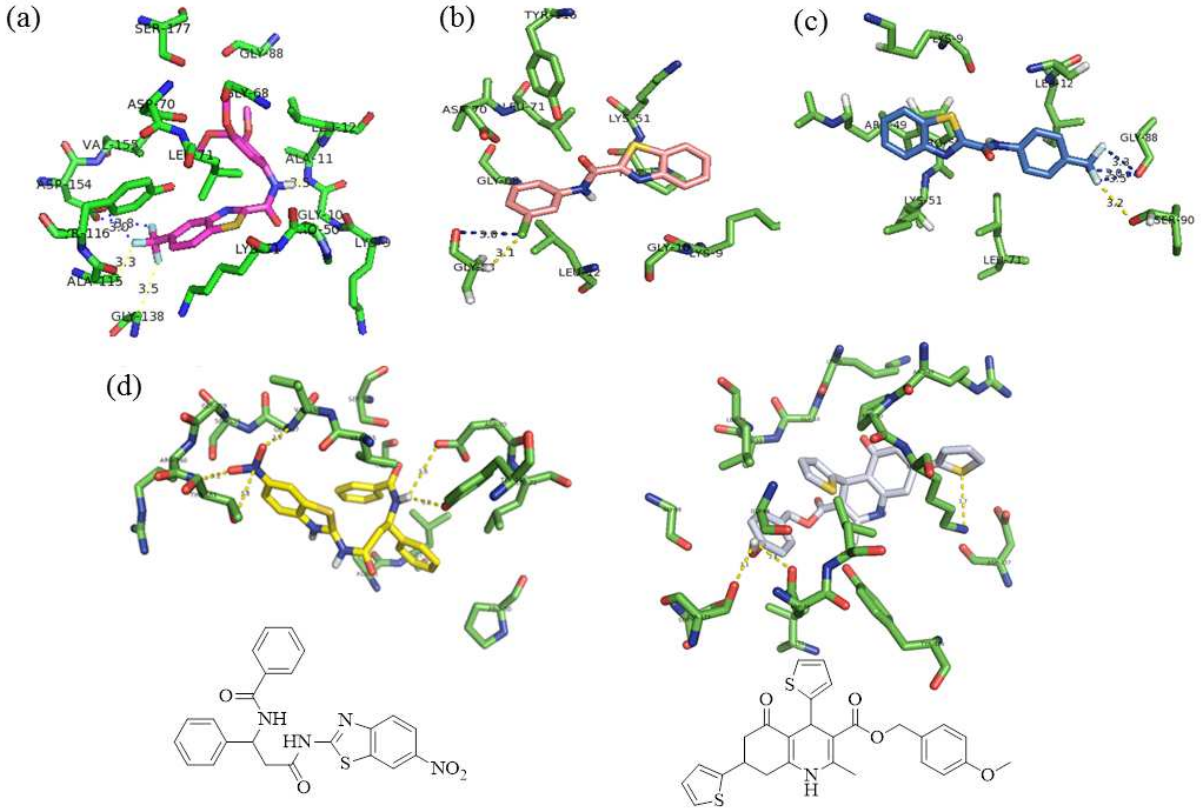


Figure 5. (a-c) Docking pose of **7w**, **4i** and **4n** with HisG (PDB: 1NH8) as determined using Autodock Vina. (d) Docked structures of two reported HisG inhibitors [18]. Yellow dashed shows HB and dashed blue shows electrostatic interactions.

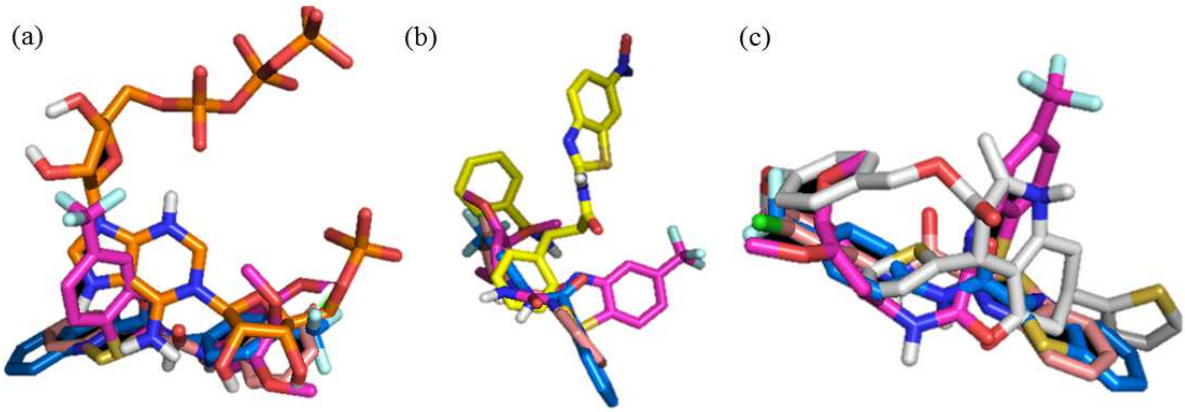


Figure 6. (a) Docking alignment of PR-ATP, natural substrate of HisG (PDB: 1NH8) with **7w**, **4i** and **4n**. (b) Superimposed docked poses of nitrobenzothiazole derivative with **7w**, **4i** and **4n**. (c) Superimposed docked poses of thiophene derivative with **7w**, **4i** and **4n**. Different ligands have been coded with respective colors: PR-ATP (orange), **7w** (magenta), **4i** (pink), **4n** (blue), nitrobenzothiazole derivative (yellow) and thiophene derivative (white).

Highlights

Benzo[*d*]thiazole-2-carbanilides as New Anti-TB Chemotypes: Design, Synthesis and Biological Evaluation

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- Benzo[*d*]thiazole-2-carbanilides reported as new chemotypes as anti-TB agents.
- The designed compounds were synthesized using CDI mediated amidation following a green synthetic protocol.
- Thirty-two compounds were found with potent MIC values (*M. tuberculosis*).
- The most active compounds with MIC of 0.78 µg/mL exhibited therapeutic index of 64.
- The SAR analysis of benzo[*d*]thiazole-2-carbanilides has been performed.
- Molecular docking of the three most active benzo[*d*]thiazole-2-carbanilides have been performed onto the active site of HisG and compared to two reported HisG inhibitors.