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Design, synthesis and biological evaluation of some 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide derivatives as selective DprE1 inhibitors

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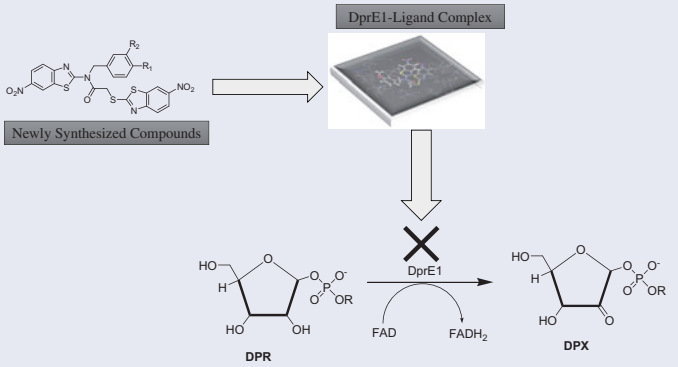
ABSTRACT

Tuberculosis (TB) is an infectious disease and caused by various strains of mycobacteria. In the present study, pharmacophore model was developed using single ligand by ligand-based drug discovery approach. The key features responsible for DprE1 inhibitory activity were taken into consideration for developing pharmacophore. After the virtual screening, top 1000 hits were further subjected to docking study using GLIDE module, Schrödinger. Docking studies have shown promising interaction with amino residues with better glide score. Ligand-based drug design approach yielded a series of 15, 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide derivatives. All synthesized derivatives were characterized using NMR, mass, CHN analysis. The synthesized compounds were screened for *In vitro* antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$). Four compounds, **5g** (MIC-1.01 μM); **5i** (MIC-0.91 μM); **5k** (MIC-0.82 μM); and **5o** (MIC-1.04 μM) has shown promising activity compared to MIC of standard isoniazid (INH) and DprE1 enzyme inhibition was compared to BTZ043. Two halogen-substituted compounds have exhibited drastic enzyme inhibition.

GRAPHICAL ABSTRACT



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Introduction

Tuberculosis (TB) is an infectious airborne disease, mostly affecting young adults in their productive years. It is a serious concern to mankind claiming nearly 2 million lives and causing 9.8 million new infections each year. In the last few decades, there is a substantial increase in the incidences of tuberculosis due to the development of resistant *Mycobacterium tuberculosis*.[1] According to the recent World Health Organization (WHO) report, TB infection is one of the leading cause of death worldwide. Treatment of TB has been always depending on the drugs used for a long time, such as isoniazid, rifampicin, ethambutol, and pyrazinamide etc. While the multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis have proven these drugs to be less effective and nowadays ineffective.[2,3] Increase in drug-resistant strains of *M. tuberculosis* strictly needs the designing of novel antitubercular molecules to serve the society in a better way. TB is also a reason for decreasing the life expectancy and standards of health not only in developing countries but also in developed as well.[4,5]

Unfortunately, no new and effective anti-TB drugs have been developed in the past couple of decades. The research on drugs against drug-resistant strains of *M. tuberculosis* remains a significant challenge. Research groups have to find new targets with attractive and promising microbiological properties for tackling tuberculosis with target-based drug discovery. Among the explored targets, decaprenyl-phosphoryl-β-D-ribose-2-epimerase (DprE1), which is the key enzyme involved in the arabinogalactan biosynthesis of Mycobacterium cell wall, DprE1 is essential for the survival of *M. tuberculosis*. The enzyme is crucial and conservative for mycobacterial cell wall biosynthesis.[6–8] DprE1 catalyzes the FAD-dependent oxidation of decaprenylphosphoryl-β-D-ribose (DPR) to decaprenyl-phosphoryl-2′-keto-D-erythro-pentofuranose (DPX). DPX is then reduced by decaprenyl-phospho-2′-keto- D- arabinose reductase (DprE2) to generate DPA, which is the indispensable component of Mycobacterium cell wall. Since there is no alternative way to synthesize DPX, DprE1 becomes a druggable target. Targeting DprE1 with small-molecule inhibitors has emerged as a promising strategy for anti-TB therapy. For the past few years, DprE1 inhibitors, like BTZs and TCA1, were found to cause Mycobacterium death by covalently or non-covalently binding to the enzyme DprE1.[9,10] Benzothiazole derivatives are used as a component like local anesthetics, hypoglycemic agents, carbonic anhydrase inhibitors, enzyme inhibitors, antimicrobial agents, anticancers, antitubercular agents, central dopaminergic agents.[11–22] Previously, several successful attempts were made to construct benzothiazole[23–26] and benzothiazole containing compounds for therapeutic purpose. Here, we have made a successful attempt to design and synthesize some new benzothiazole substituted compounds as antitubercular agents with specific DprE1 inhibitory activity which will cause the death of *M. tuberculosis*.

Results and discussion

Pharmacophore modeling, virtual screening and docking studies

Pharmacophore model was generated with single ligand by using Develop common pharmacophore hypothesis of maestro. Single ligand was used to develop

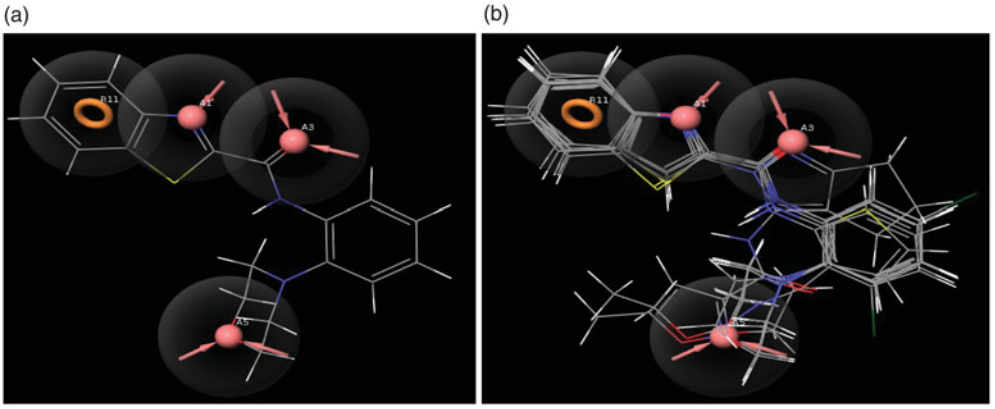


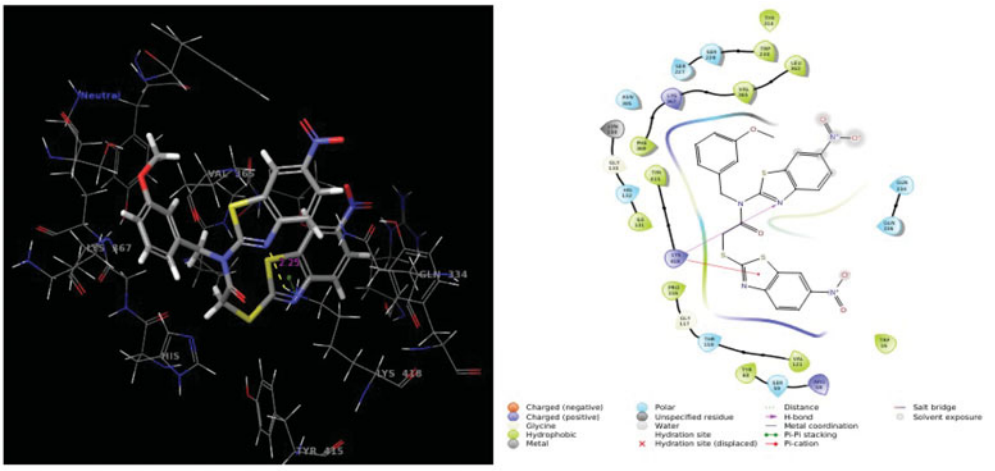
Figure 1. Selected Pharmacophore hypotheses (a) and overlapping of four compounds (b).

Table 1. Data of the *in vitro* studies for MIC for M. tuberculosis ($H_{37}Rv$), IC_{50} for DprE1 inhibition study.

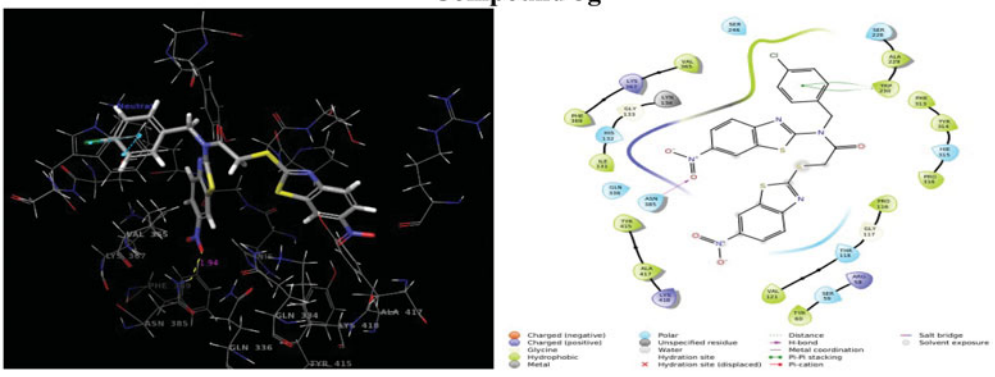
Compound ID	Glide Score	Antitubercular activity MIC (μM) on $H_{37}RV$	IC_{50} (μM) DprE1
5a	−6.342	2.41	NT*
5b	−6.229	3.74	NT
5c	−6.969	3.23	NT
5d	−5.969	2.48	NT
5e	−6.937	2.81	NT
5f	−6.166	2.10	NT
5g	−7.708	1.01	14.1 ± 1.7
5h	−6.545	2.06	NT
5i	−8.348	0.91	12.7 ± 0.9
5j	−6.599	3.35	NT
5k	−7.641	0.82	14.8 ± 2.4
5l	−5.522	2.79	NT
5m	−6.854	3.04	NT
5n	−6.234	2.16	NT
5o	−7.211	1.04	11.2 ± 1.5
Isoniazid (INH)	–	0.31	–
BTZ-043	–	–	0.084
Co-crystal Ligand	−5.725	–	–

NT: not tested.

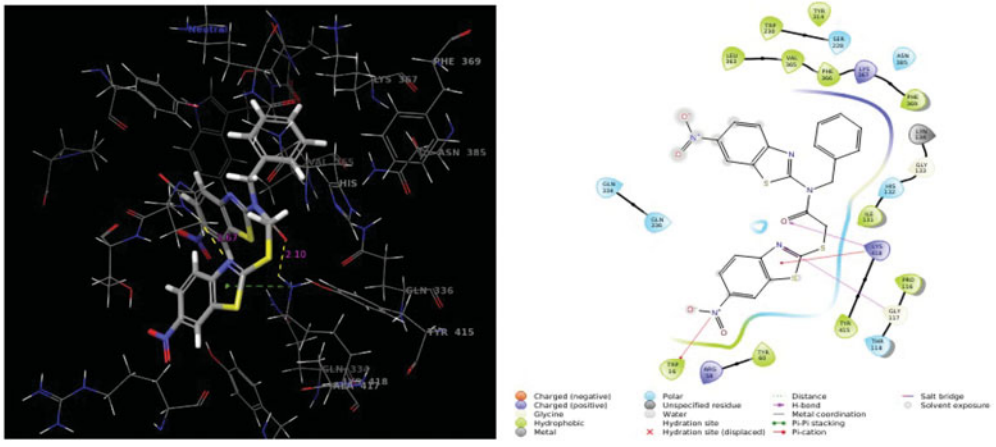
pharmacophore. The features necessary to exhibit DprE1 inhibitory activity were considered. The developed model (Fig. 1) was subjected to virtual screening. Model was screened for a database of compounds provided by Schrödinger, USA, comprising of around 8,20,000 compounds. After screening, top 1000 hits were subjected to molecular docking studies. The molecular docking study was carried out to discover the flexible binging modes for ligands with an enzyme (DprE1). The docking simulations were run by the Glide docking tool of Maestro molecular modeling interphase (Schrödinger, USA). All the docking parameters were kept as default. OPLS2005 force field was applied. The receptor employed here was specifically DprE1 (PDB code: 4KW5) obtained from RCSB Protein Data Bank (RCSB-PDB). The initial crystal structure consisted of the bound ligands (glycerol moieties), it was removed and the missing loops were added. The docking scores of all the compounds were presented in (Table 1). The



Compound 5g

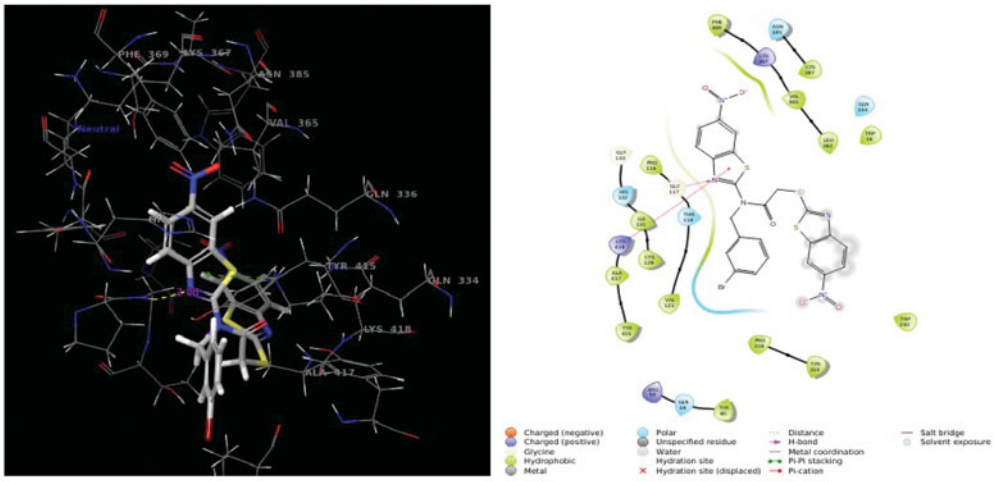


Compound 5i



Compound 5k

Figure 2. Binding modes of compounds **5c**, **5g**, **5i**, and **5o** with DprE1 target cavity, which represents hydrogen bonds, hydrophobic interactions and pi-pi interactions.



Compound 5o

Figure 2. Continued.

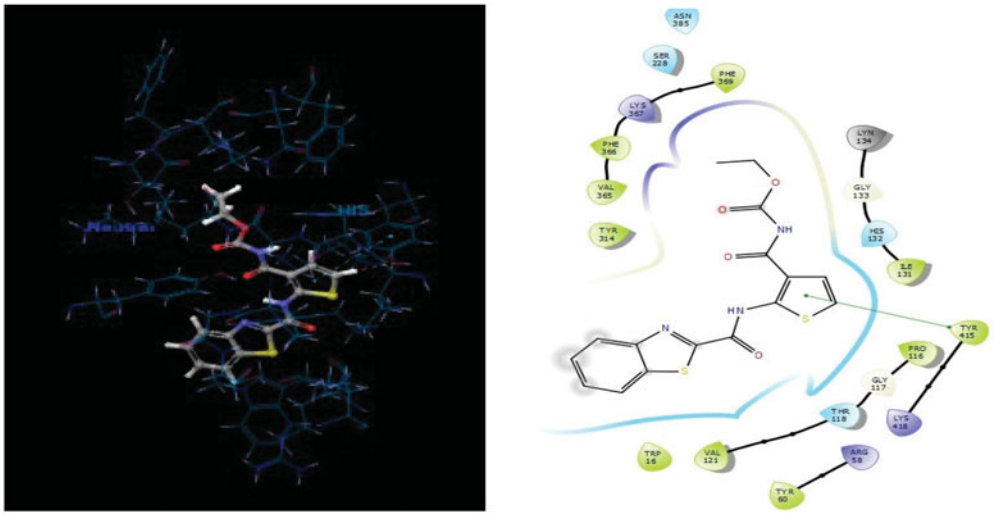


Figure 3. Binding modes of co-crystal ligand (PDB ID-4KW5).

interacting amino acid residues were identified as Lys418, Trp230, Asp389, Phe313, Asn385, etc. The results were promising and interesting compared to previously reported findings. Among all compounds, here we have discussed four compounds with maximum docking score as well as antitubercular activity (Fig. 2) along with 2 D and 3 D docking poses of co-crystallised ligand (Fig. 3). In compound **5g**, Lys418 has shown H-bond with one nitrogen of benzothiazole ring and pi-pi stacking with substituted benzothiazole. In compound **5i**, Trp230 has shown overlapping pi-pi stacking with substituted chlorobenzyl and oxygen of nitro of benzothiazole has formed H-bond with Asn385. Meanwhile, compound **5k**, emphasized that substituted benzothiazole has

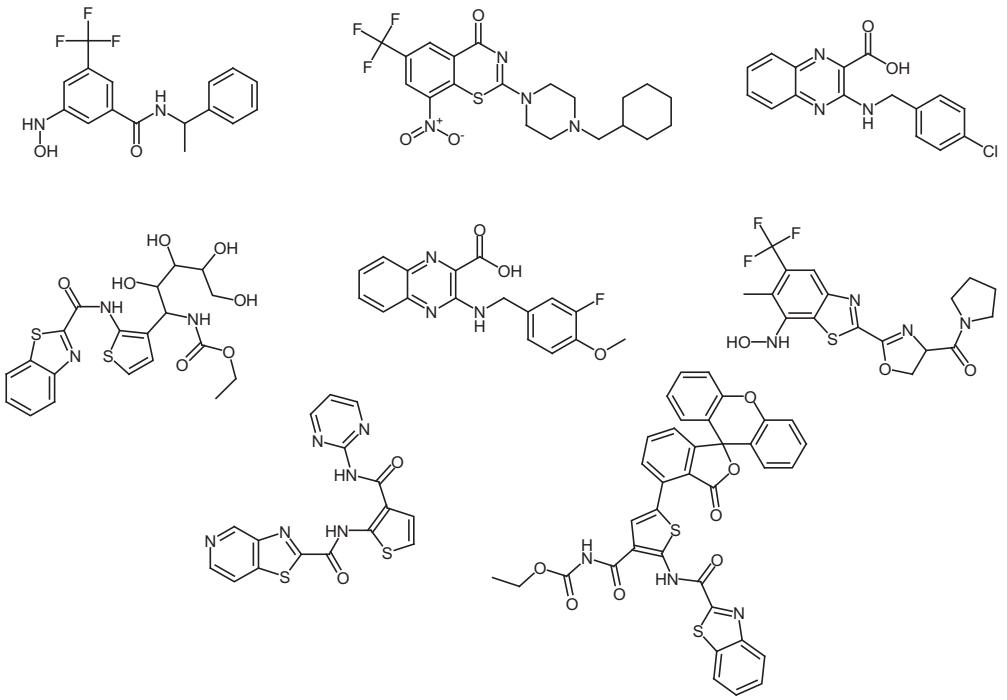
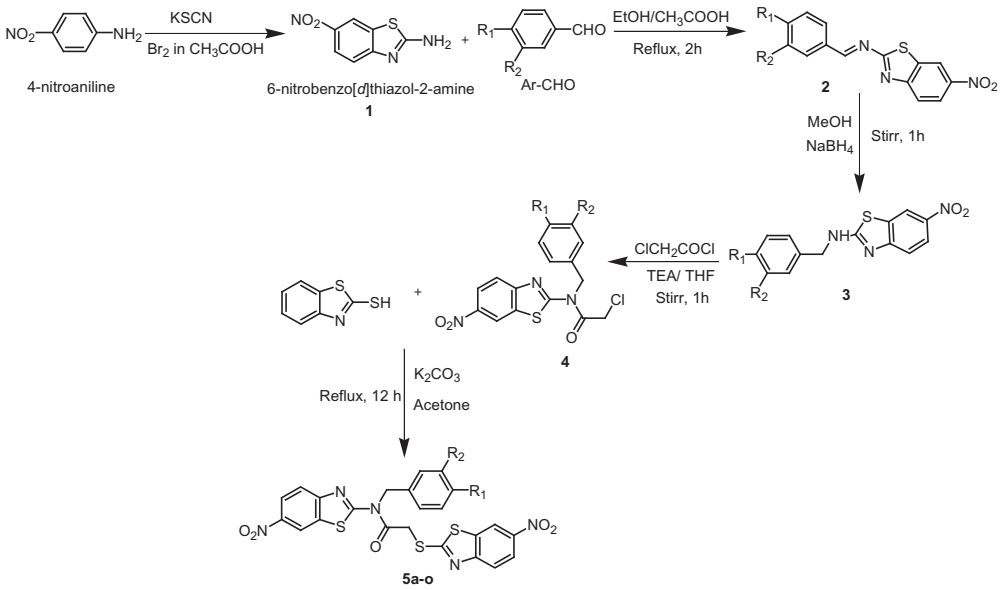


Figure 4. Representative compounds from top 1000 hits after virtual screening.

exhibited fantastic interactions, the nitrogen of nitro has formed H-bond withTrp16, Lys418 has shown dual interaction, it has formed H-bond with the oxygen of amide and has formed a salt bridge with substituted benzothiazole ring. Gly117 has formed H-bond with the nitrogen of benzothiazole. Lastly, in compound **5o**, Lys418 has shown pi-pi stacking with benzothiazole ring and Gly117 has formed H-bond with the nitrogen of benzothiazole ring. Interactions produced by these molecules are quite similar to the lead molecule TCA1, this directs that substitution with benzothiazole nucleus may contribute towards the DprE1 selectivity leading to the development of the target-specific lead molecules for this series forming potent antitubercular agents. After the virtual screening, from top 1000 hits, some of the representative compounds were presented in Figure 4. Among these structures, different structural building blocks were present but benzothiazole was present in more number of structures. Also, by considering the literature and the importance of benzothiazole nucleus for therapeutic applications, we decided to synthesize its substituted derivatives.

Chemistry

Target molecules (5a–o) were synthesized in five steps as shown in Scheme 1. Initially, 6-nitrobenzo[d]thiazol-2-amine **(1)**[27] was synthesized by stirring 4-nitroaniline, potassium thiocynate and dropwise added bromine using acetic acid as diluent. N-benzylidene-6-nitrobenzo[d]thiazol-2-amine **(2)** was synthesized via condensation of appropriate aryl benzaldehyde and 6-nitrobenzo[d]thiazol-2-amine in ethanol with a catalytic amount of glacial acetic acid. Compound **(2)** in methanol was reduced to N-



Scheme 1. Synthesis of 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide derivatives.

benzyl-6-nitrobenzo[d]thiazol-2-amine **(3)** by using $NaBH_4$. In the third step, N-benzyl-2-chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide **(4)** was synthesized by acetylation of the compounds **(3)** in tetrahydrofuran (THF) with chloroacetyl chloride. Finally, bimolecular nucleophilic substitution (S_N2) reaction between appropriate benzo[d]thiazole-2-thiol and the compound **(4)** in the presence of potassium carbonate dissolved in acetone has given the desired compound **(5)**. Substitution with different aryl aldehydes has produced 15 new 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide derivatives **(5a–o)**.

The IR spectrum showed absorption bands at 1550–1500 cm^{-1} (N–O str) confirms the presence of nitro group, 1690 cm^{-1} (C=O str) confirms the amide, bands in the range 2000–1650 cm^{-1} indicates the presence of aromatic rings, 1440–1000 cm^{-1} illustrates fluoro (C–F) substitution and 690–515 cm^{-1} confirms the presence of bromo compound. ^1H NMR study displays the protons between δ 7.1 and 8.8 belongs to the aromatic ring of substituted benzothiazole. The ^{13}C NMR studies indicate the aromatic carbons. The compounds were also confirmed by mass and CHN analysis.

Biological evaluation

Mycobacterium tuberculosis $H_{37}Rv$ (ATCC 27294) to determine MIC of test compounds with Isoniazid as a standard reference. After the incubation period of culture in the presence or absence of test compounds, the viability of bacteria was determined by observing the color change from blue to pink of Resazurin mixture which acts as an indicator of the inhibitory activity and potency. It was found that compounds **5g**, **5i**, **5k**, and **5o** exhibited MIC between 0.82 and 1.04 μM which is found to be a bit closer to the standard reference isoniazid with MIC of 0.31 μM. The compounds with good MIC were found

to be substituted with halogens like chlorine and bromine which are good dual-acting substitutions causing an electron withdrawing nature on the ring nucleus.

DprE1 activity and inhibition studies

This enzymatic assay was carried out on the selected compounds which have shown good MIC in the cell cultures.[28–30] The UV-spectrophotometric method for 2,6 dichlorophenolindophenol (DCPIP) and DprE1 activity assay was carried out on the b-D-ribofuranose (FPR) substrate as described earlier by Liav A. et al. the mixture was incubated for 7 min at different concentrations of test compounds **5g**, **5i**, **5k**, and **5o**. The inhibition concentration and enzyme activity in the absence of inhibitor were determined and reported in Table 1. Compounds **5g** and **5i** exhibited IC_{50} of 14.1 ± 1.7 µM and 12.7 ± 0.9 µM, respectively, whereas **5k** and **5o** had IC_{50} of 14.8 ± 2.4 and 11.2 ± 1.5 respectively.

Conclusion

In this paper, we have reported a series of 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide derivatives (**5a–o**). Newly synthesized compounds were analyzed for their *in vitro* antitubercular activity on the strain $H_{37}RV$ of *M. tuberculosis*. Among those compounds, four has shown comparatively impressive activity. The active compounds, **5g**, **5i**, **5k**, and **5o** have shown good potency towards *M. tuberculosis* strain. Pharmacophore model was generated using single ligand, after the virtual screening, molecular docking studies were also carried out using the reported crystal structure of DprE1, we studied flexible binding modes for the synthesized compounds in comparison with the co-crystal reference molecule TCA1. Interestingly, four compounds (**5g**, **5i**, **5k**, and **5o**) have shown better glide score and antitubercular activity. Knowledge from the molecular docking studies emphasizes that further modifications are also possible in the series of molecules to develop better compounds for potential DprE1 inhibitory activity. These most active four compounds were analyzed for DprE1 enzyme specific studies. Interestingly, two compounds, i.e. **5i** and **5o** have shown DprE1 inhibition. Previously, it was reported that nitro group is essential for DprE1 inhibitory activity, as it gets reduced and forms adduct with Cys387 to exhibit activity. Currently, presented molecular docking findings strikes on interactions of synthesized chemical structures with various amino acid residues but does not showed any interaction with Cys387 residue but has come up with promising glide score. By modifying aliphatic and aromatic carbon centers, more potent DprE1 inhibitors can be designed in the future.

Experimental

Materials and methods

Protein structure was downloaded from RCSB protein data bank along with co-crystallized ligand present in it. Protein was prepared by using the protein preparation wizard and ligands were prepared by using Ligprep tool (Maestro 11.8.012).[31]

Pharmacophore hypothesis virtual screening and molecular docking studies

The crystal structure of *M. tuberculosis* decaprenyl-phosphoryl-ribose 2′-epimerase (DprE1) complexed with co-crystallized ligand (PDB ID: 4KW5) was downloaded from PDB data bank. Key features responsible for DprE1 enzyme inhibition were manually identified and considered during selection of pharmacophore features. Pharmacophore model was generated using PHASE module of Schrodinger. All calculations were performed on a commercially available Maestro, Schrödinger, USA. Developed pharmacophore hypothesis was screened for a library of around 8.2 lakhs of compounds. All the parameters were kept as default. Molecular docking studies were performed by using Glide module of Maestro 11.8.012. Docking of the top 1000 hits from virtual screening was carried out on Glide docking module of Maestro 11.8.012 as per the Glide protocol of Schrödinger. All the default parameters were used. For ligand preparation, the pH was 7.0 ± 2.0, force field OPLS2005 was applied and ionization was done using Epik. For protein preparation, the pH was 7.0 ± 2.0, force field was OPLS2005, ionization was done using Epik and the water molecules within 3 Å were kept and rest were deleted.

General procedure for synthesis of 6-nitrobenzo[d]thiazol-2-amine (1)

A mixture of 4-nitroaniline (30 mmol) and potassium thiocyanate (30 mmol) was taken in three-neck flask, bromine in acetic acid (2.6 mL of bromine in 12.5 mL of acetic acid) was added dropwise using dropping funnel for initial 1 h. The reaction mixture was continuously stirred for 6–7 h. After completion, the reaction mixture was filtered. Filtrate was placed in ice-cold water and neutralized with ammonia solution. The precipitate was filtered, recrystallized with ethanol.[32]

Synthesis of substituted N-benzylidene-6-nitrobenzo[d]thiazol-2-amine (2)

Different substituted aromatic benzaldehydes (20 mmol), 6-nitrobenzo[d]thiazol-2-amine (20 mmol) and glacial acetic acid (0.5 mL) in catalytic amount were refluxed in ethanol (50 ml) for 2 h. After completion of the reaction, the mixture was cooled, precipitated product was filtered, and recrystallized from ethanol.[33–35]

Synthesis of N-benzyl-6-nitrobenzo[d]thiazol-2-amine (3)

The compound **2** (10 mmol) was dissolved in methanol (50 ml). The reduction was carried out by using sodium borohydride which was divided into four portions (4 × 0.15 g) and added to the methanolic solution after intervals of every 15 min. After addition of the last portion, reaction mixture was allowed to stir for 1 h at room temperature. The excess of solvent was evaporated under reduced pressure, crude product was washed with ether, dried, and recrystallized from ethanol.[36–38]

Synthesis of N-benzyl-2-chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide (4)

The compound **3** (2 mmol) was dissolved in tetrahydrofuran (25 ml) and further triethylamine (1.5 ml) was added. The mixture was cooled in an ice bath and chloroacetyl

Table 2. Synthesis of compounds from **5a–o**.

Compound ID	R_1	R_2
5a	$-CH_3$	$-CH_3$
5b	$-OCH_3$	OCH_3
5c	–F	–H
5d	$-SCH_3$	–H
5e	$-OCH_3$	–H
5f	–H	–OH
5g	–H	$-OCH_3$
5h	–OH	$-OCH_3$
5i	–Cl	–H
5j	–H	$-NO_2$
5k	–H	–H
5l	$-COCH_3$	–H
5m	–F	–F
5n	$-NH_2$	–H
5o	–H	–Br

chloride (0.5 ml) was added dropwise with stirring. After the addition of chloroacetyl chloride, the reaction mixture was stirred for additional 1 h at room temperature. The solvent was evaporated, product was washed with water, ether then dried and recrystallized from ethanol.[39,40]

Synthesis of 2-(6-nitrobenzo[d]thiazol-2-ylthio)-N-benzyl-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide (5)

The compound **4** (2 mmol), benzo[d]thiazole-2-thiol (mercaptobenzothiazole) and potassium carbonate (eq.) in acetone (20 ml) was refluxed for 12 h. After TLC screening, the solvent was evaporated under reduced pressure. The product **5** was washed with water, dried, and recrystallized from ethanol. Various aryl aldehydes yielded different derivatives (Table 2).[41] Yield: 41%. M.P. 172 C–174 °C. IR $\nu = 1520\ cm^{-1}$ (N–O), $1660\ cm^{-1}$ (C=O), 1690, 1720, $1750\ cm^{-1}$ (aromatic rings), $1420\ cm^{-1}$ (C–H). ^{1}H NMR: (600 MHz, DMSO) $\delta = 2.22$ (3H, s), 2.24 (3H, s), 4.24 (2H, s), 5.14 (2H, s), 7.16 (1H, dd, $J = 8.2$, 2.5 Hz), 7.15 (1H, dd, $J = 8.2$, 2.0 Hz), 7.21 (1H, dd, $J = 2.0$, 1.5 Hz), 7.98 (1H, dd, $J = 9.8$, 1.3 Hz), 8.12 (1H, dd, $J = 10.7$, 2.5 Hz), 8.32–8.38 (2 H, m), 8.64–8.72 (1H, m). ^{13}C NMR (100 MHz, DMSO) δ (ppm) 19.4, 32.1, 51.7, 117.9, 121.9, 127.6, 133.9, 138.3, 142.3, 150.8, 164.9, 165.6. MS *m/z*: found for $C_{25}H_{19}N_5O_5S_3$ found 565.9 $(M-H)^-$: 564.05. Anal Found: C, 53.08; H, 3.39; N, 12.38, calcd: C, 53.10; H, 3.41; N, 12.40.

Full experimental detail, ^{1}H and ^{13}C NMR spectra, biological testing. This material can be found via the "Supplementary Content" section of this articles webpage.

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