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Original article

Sulfur rich 2-mercaptobenzothiazole and 1,2,3-triazole conjugates as novel antitubercular agents

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ABSTRACT

A series of benzfused heterocyclic derivatives such as amide conjugates of 2-(benzo[d]thiazol-2-ylthio) acetic acid with aromatic/aliphatic/cyclic secondary amines (**5a**–**5o & 8a**–**8m**); 1,2,3-triazole conjugates of 2-mercaptobenzothiazoles and amide conjugates of indole-3-glyoxalic acid with cyclic secondary amines (**14a**–**14g**) have been synthesized and were screened for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth microdilution assay method. Compounds **8b, 8f, 8g** and **8l** inhibited the growth of the H37Rv strain at concentrations of 8 μg/mL. These compounds (**8b, 8f, 8g** and **8l**) have been further identified as bactericidal and are completely killing the microbes at 32–64 μg/mL concentrations. Molecular docking studies of the active compounds reveal that these compounds are targeting DprE1 and may act as DprE1 inhibitors.

1. Introduction

Despite being an ancient disease, tuberculosis (TB) remains the leading infectious disease killer in the world. The emergence of resistance to new generation TB drugs ("multiple drug resistant" *Mycobacterium tuberculosis*, MDR-TB) alarming the serious problem in TB control and demanding the need for new drugs more potent than earlier with safe ADME profile. The increasing number of MDR-TB cases has caused great concern because they are often associated with HIV infection. Due to the unusual structure and chemical composition of the mycobacterial cell wall, effective tuberculosis (TB) treatment is difficult, making many antibiotics ineffective and hindering the entry of new drugs [1]. No new chemical entity has been emerged in last 50 years after the discovery of rifampicin. Therefore new drugs are required to counter the tuberculosis (TB) pandemic. Several strategies are being pursued in order to identify new leads, although only a few leads are being optimized to generate drug candidates [2]. Most of the efforts have been directed towards identifying and validating drug targets and making derivatives of existing drugs [3].

Several heterocyclic moieties consisting of nitrogen, sulfur, oxygen hetero-atoms have been explored for the development of new generation anti-tubercular agents [1,4–7]. Azoles are one of the most important classes of nitrogen containing heterocycles that demonstrated the potential anti-tubercular activity. Azole derivatives inhibit the growth of bacteria by blocking lipid biosynthesis and/or additional mechanisms which is one of the most attractive strategies for effective anti-TB drug (development of cell wall biosynthesis inhibitors). From the literature it has been observed that sulfur is unusually common in most of the anti-tubercular drugs, therefore sulfur-containing heterocycles are being explored comprehensively [8]. Interestingly, it has also been observed that the introduction of sulfur atom in the cyclic systems along with nitrogen has resulted in the improved anti-tubercular activities [8b]. Thiazoles are five membered heterocycles of azole family consisting nitrogen and sulfur atoms, are one of the key building blocks in drug discovery that can be well illustrated by the

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0223-5234/

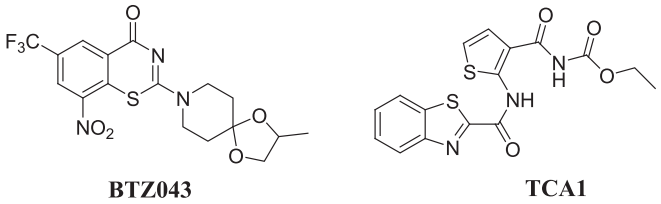
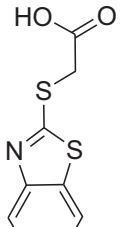
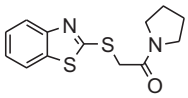
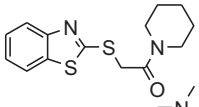
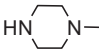
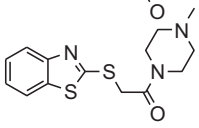
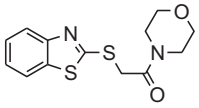
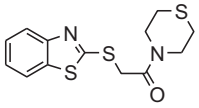
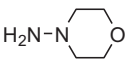
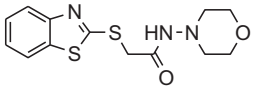
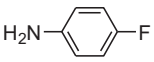
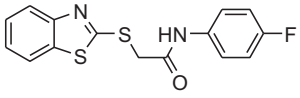
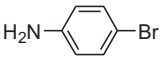
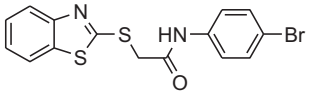
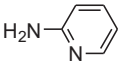
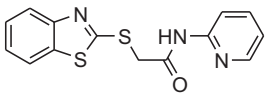
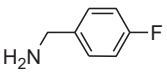
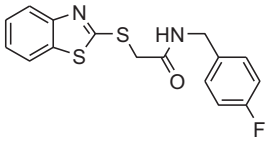
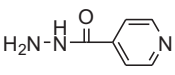
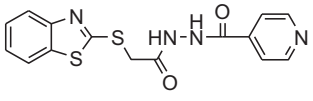


Fig. 1. Structures of BTZ043 & TCA1.

large number of drugs in the market [8]. Thiazoles are considered as important frameworks in the TB drug development and various derivatives of thiazoles have been made [8,9] including benzothiazole derivatives. Benzothiozoles are a kind of sulfur containing benzfused heterocycles showing a broad spectrum of biological properties including antitumor [10–12], antiviral [13], anti-HIV [14], antimicrobial [15] activities. In addition, the benzothiazole moiety has also been recognized for anti-TB design. Conjunction of benzothiazoles with 1,2,4-triazole system has resulted in the potential anti-tubercular activity [16a]. Benzo[*d*]isothiazole, Benzothiazole and Thiazole Schiff Bases have also been explored for their

Table 1
Amide conjugates of 2-mercaptobenzothiazoles.

Sr. No.	Carboxylic acid (**3**)	Amines (**4**)	Benzothiazole conjugates (**5**)	Yields[a] (%)
a				98
b				94
c				91
d				95
e				83
f				88
g				87
h				84
i				82
j				95
k				74

[a] Isolated yields.

antitubercular potentials and none of them found active [16b]. Recently hydrazinyl benzothiazole derivatives have been reported as novel antitubercular agents [16c]. Though several reports are present with the anti-tubercular potentials of benzothiazole derivatives; most of them are more labile to hydrolysis. Lower half life of the compounds may cause bacterial resistance to the corresponding drug. Thus there remains a compelling need of compounds with potential microbial growth inhibition and better ADME values with mycobactericidal activities and with an improved safety profile.

After consistent efforts, a new class of new compounds called nitro-benzothiazinones (BTZ) have been emerged that were potent against mycobacteria and come up with a new lead BTZ043 which is in clinical trials with an MIC of 1 ng/mL [17]. The compound has been found to target a component of Mycobacterium's cell-wall-building machinery *i.e.* inhibiting the conversion of decaprenylphosphoryl-β-D-ribose (DPR) to decaprenylphosphoryl-β-Darabinofuranose (DPA), a precursor of mycobacterial cell wall arabinan [17,18]. Recently Feng Wang et al. have discovered that a benzothiazole derivative TCA-1 is inhibiting DprE1 with a different binding mechanism [19].

Keeping in view the promising results from BTZ043 and TCA1 (Fig. 1) and the antitubercular potential of the sulfur rich heterocycles, in continuation of our earlier studies, we aim to explore the antitubercular potential of some other benzfused heterocycles consisting of sulfur/nitrogen heteroatoms (2-mercaptobenzothiazole & indole derivatives).

As piperazine, morpholine, thiomorpholine, 1,2,3-triazoles and aromatic rings are considered to be important ligands in the tuberculosis drug development; 2-mercaptobenzothiazoles have been conjugated to these ligands through an amide linkage. Recent studies reveals that 1,2,3-triazoles are also potential ligands to improve the activity profile against mycobacterial strains [4,20]. Thus 2-mercaptobenzothiazole have also been conjugated to 1,2,3-triazoles using click chemistry protocol as earlier reported by our group in which anti-inflammatory profile of these conjugates has been explored [21].

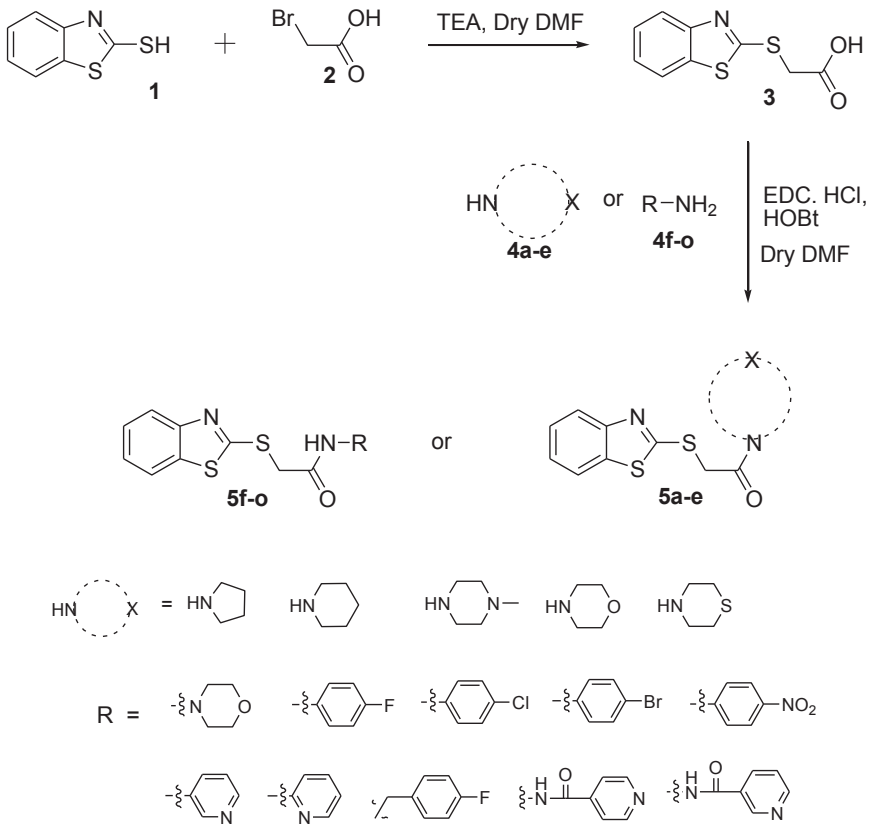
At the same time the studies have also been carried out with the benzfused heterocycles without sulfur atom in the ring system (indole derivatives). As indole moiety is known for its broad spectrum of pharmacological activities over the years and being a part of several drugs [22], some of the indole conjugates with cyclic secondary amines have also been studied for their antitubercular ability. A focused library of 24 compounds from the benzthiazole series and seven compounds from indole series have been synthesized. Hitherto for the first time, we report the antitubercular activity of benzothiazoles and 1,2,3-triazole based *bis*-heterocycles against *M. tuberculosis* H37Rv.

2. Results and discussion

2.1. Chemistry

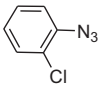
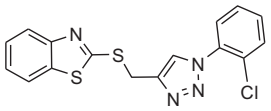
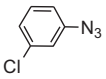
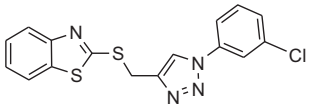
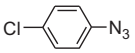
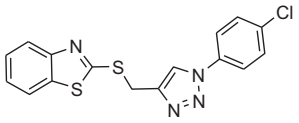
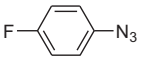
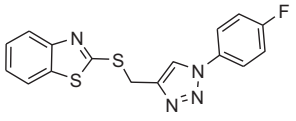
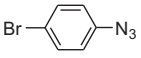
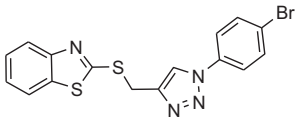
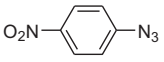
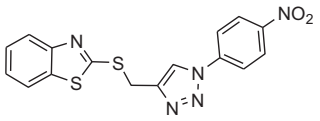
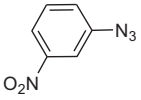
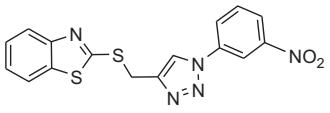
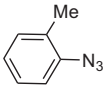
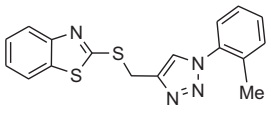
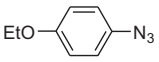
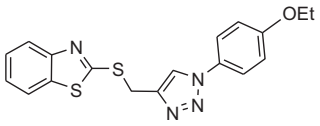
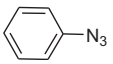
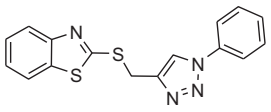
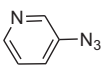
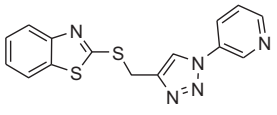
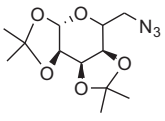
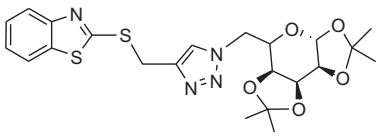
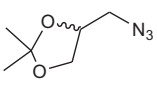
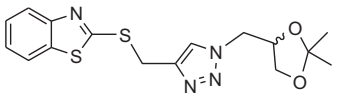
In view of the biological importance of benzfused sulfur heterocycles, a focused library of sulfur rich 2-mercaptobenzothiazole derivatives have been synthesized (Table 1) to explore their antitubercular potentials. 2-mercaptobenzothiazole was reacted with α-bromo acetic acid to obtain 2-(benzo[d]thiazol-2-ylthio)acetic acid (compound **3**). Compound **3** was conjugated with various cyclic secondary amines like N-methyl piperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and various primary amines including anilines, 4-amino morpholine and isoniazid through an amide linkage using EDC coupling (Scheme 1).

As 1,2,3-triazole moiety and an amide group are considered as biological isosters; 1,2,3-triazololly moiety has been introduced in



Scheme 1. Synthetic approach for 2-mercaptobenzothiazole conjugates.

Table 2
1,2,3-Triazole conjugates of 2-mercaptobenzothiazole.

Sr. No.	Azide (**7**)	*Bis*-heterocycles (**8**)	Reaction time (h)	Yields[a] (%)
a			8	95
b			7	93
c			7	89
d			8	95
e			6	97
f			8	93
g			7	92
h			8	88
i			7	94
j			8	92
k			8	95
l			9	90
m			9	87

[a] Isolated yields.

place of amide bond. Synthesis of these *bis*-heterocycles (Table 2) has been carried out by the recently reported procedures by our group (Scheme 2) [21].

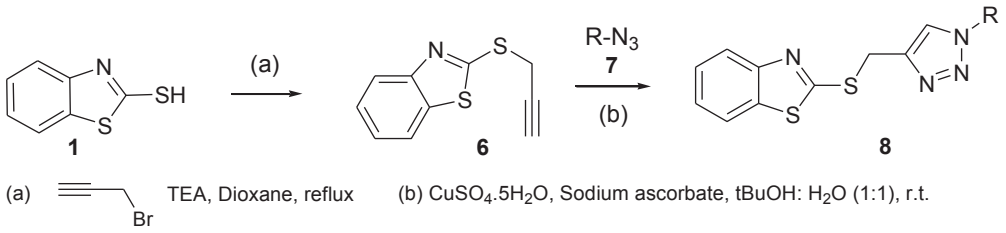
In the same way indole conjugates have been made by the EDC coupling of indole-3-glyoxalic acid with various 1°/2°-amines. Indole-3-glyoxalyl chloride was obtained by the reaction of oxalyl chloride with indole in ether at 0 °C which was transformed to indole-3-glyoxalic acid by reacting with saturated $NaHCO_3$/2N HCl (Scheme 3). All the synthesized compounds (Table 3) were tested for their antitubercular activity.

All the products were characterized by ^{1}H NMR, ^{13}C NMR, IR, MALDI-MS/ESI-MS. In the ^{1}H NMR spectra, the formation of triazoles was confirmed by the resonance of H–C(5) of the triazole ring in the aromatic region. The structure was further supported by the ^{13}C NMR spectra, which showed the C-atom signals corresponding to triazole derivatives. MALDI-MS/ESI-MS of all compounds showed [M+1] or [M+2].

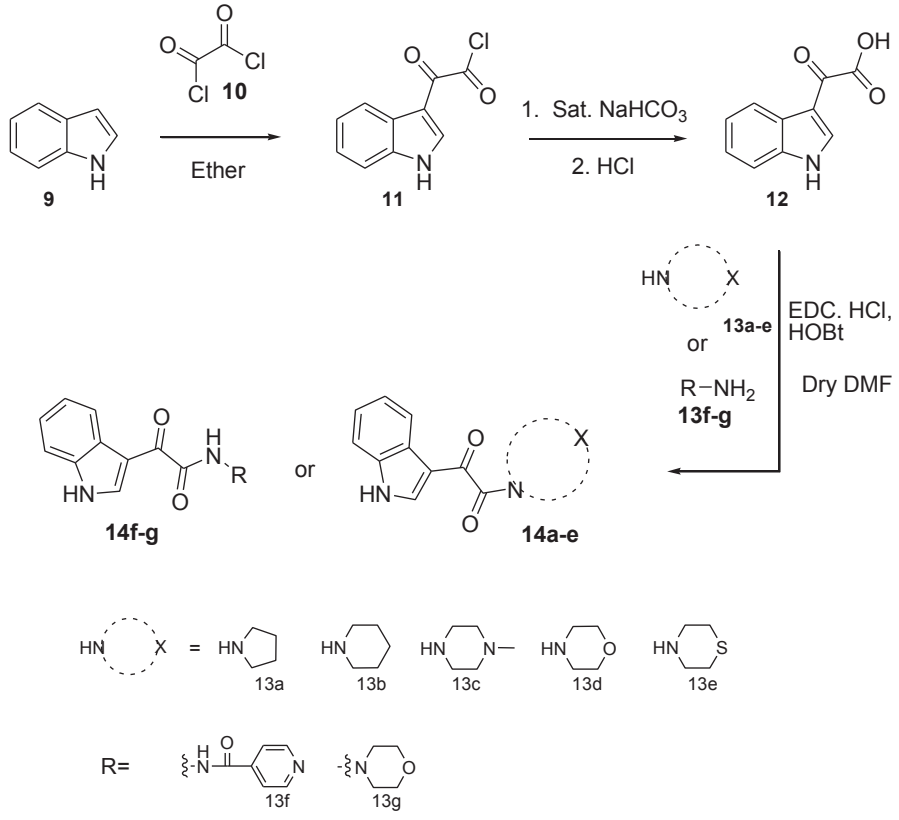
2.2. In vitro anti-tubercular activity

Keeping in view the biological importance of thiol rich heterocycles as antimycobacterial agents, a focussed library of benzothiazole and indole derivatives have been synthesized and tested for their *in vitro* antitubercular activity against *M. tuberculosis* H37Rv by microdilution assay. The results have been shown in Table 4. Among the conjugates of secondary cyclic amines with 2-(benzo[*d*]thiazol-2-ylthio)acetic acid (**3**); compound **5e**, a thiomorpholine conjugate has shown the inhibition at 64 μg/mL concentration. When it was conjugated with aromatic/heteroaromatic amines, the activity profile has not been improved and persisted with the similar activity with the inhibitory concentration of 64 μg/mL while aliphatic amines are inactive. Aromatic amide conjugates with halo substitution (flouro & bromo) on para position of the aromatic ring (**5g** & **5i**) and heteroaromatic amide conjugate i.e. 2-amino pyridine (**5l**) have shown activity with MIC of 64 μg/mL. As the 1,2,3-triazoles are considered to be biological isosteres of amides; amide bond has been replaced with 1,2,3-triazoles. It is well explored that incorporation of 1,2,3-triazoles on bioactive ligands may enhance the biological potentials of the counter part as they emerged as potent bio-active ligands on their own right [4,20,23].

After replacing the amide bond with 1,2,3-triazolyl ring the activity of the resultant conjugates enhanced to 8 μg/mL. Compounds **8b, 8f, 8g** and **8l** from the benzothiazole and 1,2,3-triazole conjugates inhibited the growth of *M. tuberculosis* H37Rv at 8 μg/

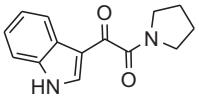
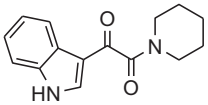
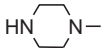
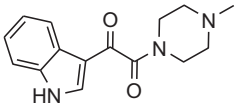
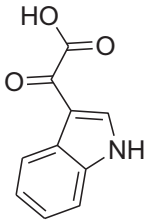
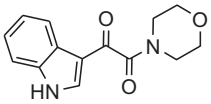
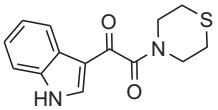
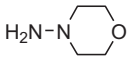
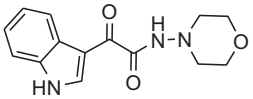
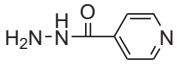
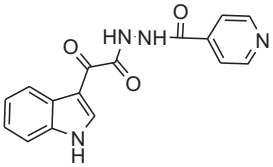


Scheme 2. Synthesis of 1,2,3-triazole conjugates of 2-mercaptobenzothiazole.



Scheme 3. Synthetic approach for indole-3-glyoxalicacid conjugates.

Table 3
Amide conjugates of indole-3-glyoxalic acid.

Sr. No.	Azide (**3**)	*Bis*-heterocycles (**14**)	Yields[a] (%)
a			96
b			94
c			91
d			95
e			82
f			92
g			82

[a] Isolated yields.

mL whereas compounds **8a**, **8e** and **8k** showed the inhibition at 16 μg/mL. While isoniazid conjugate of 2-(benzo[*d*]thiazol-2-ylthio)acetic acid has shown the activity at 64 μg/mL. When the same kind of conjugates has been made with indoleglyoxalic acid, no significant activity was observed. An isoniazid conjugate of indoleglyoxalic acid has been exhibited moderate activity with MIC 64 μg/mL against *M. tuberculosis* H37Rv.

From the above results it is demonstrated that the sulfur rich benzfused heterocyclic moiety is showing better activity compared to indole derivatives. Further the compounds showing promising activity (**8b, 8f, 8g and 8l**) have been tested for their bactericidal activity and were found to be bactericidal (Table 5).

Table 4
In vitro anti-tubercular activity of synthesized conjugates against *Mycobacterium tuberculosis* H37Rv.

Sr. No.	Compound	H37Rv MIC (μ g/mL)	Sr. No.	Compound	H37Rv MIC (μg/mL)
1	5a	<128	19	8h	<128
2	5b	<128	20	8i	<128
3	5c	<128	21	8j	<128
4	5d	<128	22	8k	**16**
5	5e	64	23	8l	**8**
6	5f	<128	24	8m	<128
7	5g	64	25	14a	<128
8	5h	<128	26	14b	<128
9	5i	64	27	14c	<128
10	5j	<128	28	14d	<128
11	5k	<128	29	14e	<128
12	8a	**16**	30	14f	<128
13	8b	**8**	31	14g	64
14	8c	<128	32	Rifampicin	0.06
15	8d	<128	33	Isoniazid	0.125
16	8e	**16**			
17	8f	**8**			
18	8g	**8**			

Bold values represent compounds with significant activity.

2.3. Molecular docking study

To investigate the binding effects between compounds **8b, 8f, 8g, 8l** and DprE1 molecular docking study was performed. The binding models of compounds **8b, 8f, 8g** and **8l** are depicted in Fig. 2. In the binding model, Tyr60, Gly117, Ala375, Ser378, Asn385, Lys418 and Trp437 of DprE1 formed hydrogen bonds with compound **8f**. Along with this compound **8f** has formed a hydrophobic

Table 5
MBC results.

Sr. No	Compound	MIC (μg/mL)	MBC (μg/mL)
1	8b	8	>64
2	8f	8	32
3	8g	8	64
4	8l	8	32

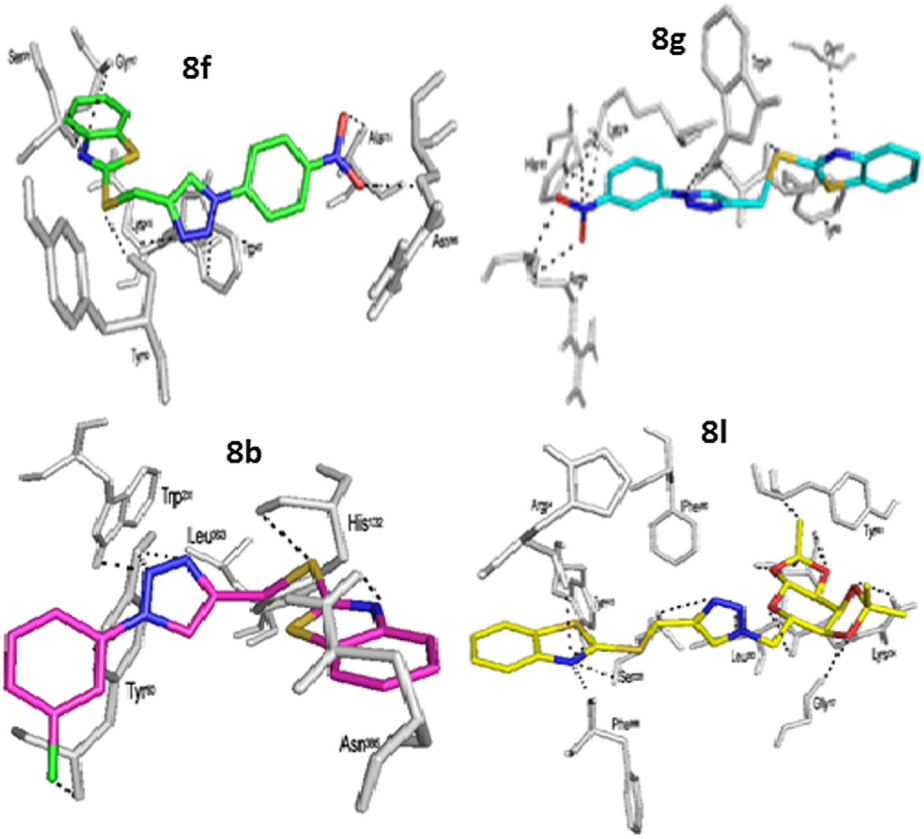


Fig. 2. Molecular docking of the active compounds with DprE1.

interaction with the Tyr60, Trp437 and Ala375. The potential inhibitory property possessed by this compound, may be attributed to the above hydrogen bonds and hydrophobic interactions. The docking calculations also reveal that the complex has the lower free energy of binding (−9.16 kcal/mol).

As it has shown in Fig. 2, for compound **8g**, due to hydrogen bonding between Arg54, Tyr60, Gly117, His132, Lys134 and Trp231 conformational locking happened. Moreover compound **8g** even able to form hydrophobic interactions with Tyr60, Lys134 and Trp231. The lower free energy of binding shown by compound **8g** with DprE1 is −9.49 kcal/mol. The calculated lowest energy for compound **8b** is −7.89 kcal/mol. The schematic diagram of docking pose of compound **8b** is shown in Fig. 2. In this docking model compound **8b** has shown hydrogen bonding interactions with Tyr60, His132, Trp231 and Asn385. Compound **8b** has shown even hydrophobic interactions with Tyr60 and Leu363 of DprE1.

Among the four docked compounds, compound **8l** has developed highest docking interactions of −11.59 kcal mol with DprE1. In this docking model (Fig. 2) compound **8l** interacted with Arg54, Tyr60, Gly117, Lys134, Ser228, Leu363 and Tyr415 through hydrogen bonding interactions. Hydrophobic interactions were developed by the compound **8l** with Phe360, Leu363 and Phe366 of DprE1. The maximum inhibitory potential shown by this compound may be due the development of tight interactions with the receptor.

3. Conclusion

In the present study a focussed library of 2-mercaptobenzothiazole and Indole moieties were conjugated to various bio-active ligands through an amide linkage/triazolly ring by EDC coupling/click chemistry. All the synthesized compounds have been evaluated for their anti-tubercular activity. From the structure activity relationship the 2-mercaptobenzothiazoles conjugated to 1,2,3-triazole ring were more active when compared to the aromatic/aliphatic/cyclic secondary amines attached through an amide linkage. Chloro and nitro-substitution on aromatic ring is exhibiting potential activity (compounds **8b, 8f and 8g).** The bactericidal activities of these compounds demonstrated the utility of sulfur rich benzothiazoles as potent ligands against tuberculosis. From the molecular docking studies it is identified that 1,2,3-triazole conjugates of benzothiazoles may be acting as DprE1 inhibitors and are effective against drug-susceptible and MDR forms of TB. Further studies on these structures are in progress to obtain lead compounds.

4. Experimental

4.1. Chemistry

All commercial chemicals used as starting materials and reagents in this study were purchased from Merck (India), Spectrochem, and Sigma–Aldrich which were of reagent grade. All melting points were uncorrected and measured using Electrothermal IA 9100 apparatus (Shimadzu, Japan); IR spectra were recorded on Bruker ALPHA FT-IR spectrometer (Germany), ^{1}H NMR spectra were determined on a Bruker (200, 300 and 400 MHz) spectrometer and chemical shifts were expressed as ppm against TMS as internal reference. Mass spectra were recorded on 70 eV (EI Ms-QP 1000EX, Shimadzu, Japan), Column Chromatography was performed on (Merck) Silica gel 60 (particle size 0.06e 0.20 mm).

4.1.1. General procedure for the amide coupling of 2-(Benzo[d] thiazol-2-ylthio)acetic acid with 1°/2° amines

To the THF (5 mL) and DMF (0.5 mL) solution of 2-(Benzo[d] thiazol-2-ylthio)acetic acid (100 mg; mM) was added EDC.HCl

(1.5 molar equivalents) and HOBt (10 mg). The reaction mixture was stirred for five minutes under nitrogen atmosphere at room temperature. Then 1.2 molar equivalents of amine (1°/2°) were added to the reaction mixture and the reaction mixture was continued to stir for further 12–16 h. After the completion of the reaction monitored by TLC, the reaction mixture was quenched with excess of water (100 mL) and extracted with ethylacetate (2 × 20 mL). Combined organic layers were dried over anhydrous sodium sulfate and evaporated to obtain the target compound.

4.1.1.1. 2-(Benzo[d]thiazol-2-ylthio)-1-(pyrrolidin-1-yl)ethanone (5a). M.P. 69–71 °C; IR (KBr) (cm^{-1}): 3058, 2929, 2857, 1713, 1614, 1556, 1505, 1454, 1424, 1371, 1308, 1272, 1235, 1166, 1125, 1076, 1019, 992, 901, 855, 752, 724; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.99–2.07 (m, 4H), 3.52 (t, 2H, $J = 6.60$ Hz), 3.67 (t, 2H, $J = 6.90$ Hz), 4.29 (s, 2H), 7.26–7.32 (m, 1H), 7.38–7.43 (m, 1H), 7.75 (d, 1H, $J = 7.80$ Hz), 7.82 (d, 1H, $J = 7.80$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.41, 2622, 36.93, 46.41, 47.13, 121.12, 121.36, 124.35, 126.01, 135.51, 152.92, 165.46, 165.94; ESIMS: 279 (M^++1), 280 (M^++2); Anal. Calcd. for $C_{13}H_{14}N_2OS_2$: C, 56.09; H, 5.07; N, 10.06; S, 23.04%, Found: C, 56.15; H, 5.04; N, 10.11; S, 23.05%.

4.1.1.2. 2-(Benzo[d]thiazol-2-ylthio)-1-(piperidin-1-yl)ethanone (5b). M.P. 74–76 °C; IR (KBr) (cm^{-1}): 2935, 2861, 2825, 2780, 1614, 1446, 1425, 1368, 1258, 1237, 1215, 1178, 1124, 1100, 1076, 1021, 1006, 955, 909, 855, 758, 727; ^1H NMR (DMSO, 400 MHz) δ (ppm): 1.21 (m, 2H), 1.43 (m, 4H), 3.44 (t, 2H, $J = 6.00$ Hz), 3.49 (t, 2H, $J = 6.00$ Hz), 4.51 (s, 2H), 7.34 (t, 1H, $J = 7.20$ Hz), 7.45 (t, 1H, $J = 8.00$ Hz), 7.82 (d, 1H, $J = 8.00$ Hz), 7.99 (d, 1H, $J = 7.60$ Hz); ^{13}C NMR (DMSO, 100 MHz): δ 24.32, 25.55, 36.74, 43.41, 47.46, 49.22, 121.10, 121.32, 124.36, 126.04, 135.21, 153.04, 165.34, 165.97; ESIMS: 293 (M^++1), 294 (M^++2); Anal. Calcd. for $C_{14}H_{16}N_2OS_2$: C, 57.50; H, 5.52; N, 9.58; S, 21.93%, Found: C, 57.51; H, 5.50; N, 9.61; S, 21.99%.

4.1.1.3. 2-(Benzo[d]thiazol-2-ylthio)-1-(4-methylpiperazin-1-yl) ethanone (5c). M.P. **79–81 °C**; IR (KBr) (cm^{-1}): 32955, 2923, 2796, 1633, 1614, 1574, 1557, 1455, 1446, 1425, 1377, 1308, 1270, 1227, 1140, 1036, 989, 779, 750; ^1H NMR (DMSO, 400 MHz) δ (ppm): 2.19 (s, 3H), 2.27–2.38 (m, 4H), 3.46–3.55 (m, 4H), 4.51 (s, 2H), 7.34 (t, 1H, $J = 7.20$ Hz), 7.45 (t, 1H, $J = 7.60$ Hz), 7.82 (d, 1H, $J = 7.60$ Hz), 7.99 (d, 1H, $J = 7.60$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.12, 42.08, 45.96, 46.09, 54.41, 54.91, 121.16, 121.36, 124.46, 126.09, 135.45, 152.87, 165.64; ESIMS: 308 (M^++1), 309 (M^++2); Anal. Calcd. for $C_{14}H_{17}N_3OS_2$: C, 54.69; H, 5.57; N, 13.67; S, 20.86%, Found: C, 54.66; H, 5.61; N, 13.61; S, 20.89%.

4.1.1.4. 2-(Benzo[d]thiazol-2-ylthio)-1-morpholinoethanone (5d). M.P. 107–109 °C; IR (KBr) (cm^{-1}): 2963, 2918, 2858, 1633, 1614, 1455, 1424, 1408, 1261, 1215, 1111, 1067, 1035, 1018, 1002, 989, 959, 797, 757; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.68–3.72 (m, 8H), 4.37 (s, 2H), 7.31 (t, 1H, $J = 7.60$ Hz), 7.42 (t, 1H, $J = 7.60$ Hz), 7.76 (d, 1H, $J = 8.00$ Hz), 7.83 (d, 1H, $J = 8.00$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 35.09, 55.86, 56.92, 66.18, 66.43, 121.03, 121.47, 125.06, 126.11, 126.62, 151.95, 166.10; ESIMS: 295 (M^++1), 296 (M^++2); Anal. Calcd. for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52; S, 21.78%, Found: C, 52.99; H, 4.83; N, 9.49; S, 21.76%.

4.1.1.5. 2-(Benzo[d]thiazol-2-ylthio)-1-thiomorpholinoethanone (5e). M.P. 97–98 °C; IR (KBr) (cm^{-1}): 3031, 2965, 2914, 2845, 1643, 1634, 1455, 1448, 1422, 1393, 1386, 1181, 999, 990, 950, 907, 772, 763, 725; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.65 (t, 2H, $J = 5.10$ Hz), 2.74 (t, 2H, $J = 5.10$ Hz), 3.92 (t, 4H, $J = 5.10$ Hz), 4.38 (s, 2H), 7.30 (t, 1H, $J = 7.20$ Hz), 7.42 (t, 1H, $J = 7.20$ Hz), 7.76 (d, 1H, $J = 8.10$ Hz), 7.84 (d, 1H, $J = 8.10$ Hz); ^{13}C NMR (DMSO, 100 MHz): δ 26.93, 27.30, 37.30, 44.95, 48.92, 121.44, 122.27, 124.91, 126.83, 135.21, 153.08, 165.49, 166.73; ESIMS: 311 (M^++1), 312 (M^++2), 313 (M^++3), 208 (M^+−102); Anal. Calcd. for $C_{13}H_{14}N_2OS_3$: C, 50.29; H, 4.55; N, 9.02; S, 30.98%, Found: C, 50.33; H, 4.52; N, 8.97; S, 31.01%.

4.1.1.6. 2-(Benzo[d]thiazol-2-ylthio)-N-morpholinoacetamide (5f). M.P. 124–127 °C; IR (cm^{-1}): 2987, 2921, 2691, 1666, 1509, 1410, 1379, 1108, 1073, 1361, 1305, 1108, 1073, 993, 890, 855, 750, 721; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.85 (brs, 4H), 3.75 (brs, 4H), 3.83 (s, 2H), 7.30 (t, 1H, $J = 7.20$ & 8.10 Hz), 7.42 (t, 1H, $J = 7.20$ & 7.80 Hz), 7.72 (d, 1H, $J = 7.80$ Hz), 7.88 (d, 1H, $J = 8.10$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.09, 55.86, 66.18, 121.47, 125.07, 126.11, 126.62, 151.84, 166.15, 166.93; ESIMS: 310 (M^++1), 311 (M^++2); Anal. Calcd. for $C_{13}H_{15}N_3O_2S_2$: C, 50.46; H, 4.89; N, 13.58; S, 20.73%, Found: C, 50.41; H, 4.95; N, 13.61; S, 20.77%.

4.1.1.7. 2-(Benzo[d]thiazol-2-ylthio)-N-(4-fluorophenyl)acetamide (5g). M.P. **87–89** °C; IR (cm^{-1}): 3042,3011, 2987, 1677, 1615, 1555, 1505, 1454, 1427, 1415, 1208, 1189, 1156, 1123, 1100, 1076, 996, 840, 810, 789, 754, 723; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.00 (s, 2H), 6.88–6.94 (m, 2H), 7.33 (t, 1H, $J = 7.50$ & 7.80 Hz), 7.38–7.48 (m, 3H), 7.74 (d, 1H, $J = 8.10$ Hz), 7.88 (d, 1H, $J = 8.10$ Hz), 10.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.23, 115.55, 115.78, 120.99, 121.07, 121.15, 121.54, 125.15, 126.74, 134.25, 135.46, 151.98, 158.06, 166.57, 167.61; ESIMS: 319 (M^++1), 320 (M^++2); Anal. Calcd. for $C_{15}H_{11}FN_2OS_2$: C, 56.59; H, 3.48; F, 5.97; N, 8.80; S, 20.14%, Found: C, 56.66; H, 3.42; F, 6.01; N, 8.83; S, 20.18%.

4.1.1.8. 2-(Benzo[d]thiazol-2-ylthio)-N-(4-bromophenyl)acetamide (5h). M.P. **92–94** °C; IR (cm^{-1}): 2914, 2849, 1620, 1601, 1538, 1521, 1487, 1455, 1423, 1394, 1386, 1327, 1309, 1261, 1233, 1153, 1099, 1069, 1042, 1017, 1003, 952, 935, 813, 748, 720; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.05 (s, 2H), 7.37–7.48 (m, 5H), 7.53 (t, 1H, $J = 7.50$ & 7.20 Hz), 7.82 (d, 1H, $J = 7.80$ Hz), 7.94 (d, 1H, $J = 8.40$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.19, 121.58, 122.39, 125.06, 126.91, 132.14, 135.28, 138.62, 152.98, 165.94, 166.94; ESIMS: 380 (M^++1), 381 (M^++2), 382 (M^++3); Anal. Calcd. for $C_{15}H_{11}BrN_2OS_2$: C, 47.50; H, 2.92; Br, 21.07, N, 7.39; S, 16.91%, Found: C, 47.47; H, 2.96; Br, 21.09, N, 7.40; S, 16.92%.

4.1.1.9. 2-(Benzo[d]thiazol-2-ylthio)-N-(pyridin-2-yl)acetamide (5i). M.P. **96–98** °C; IR (cm^{-1}): 2963, 2915, 1683, 1580, 1520, 1506, 1427, 1311, 1258, 1092, 1055, 992, 951, 859, 816, 795,779,751; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.12 (s, 2H), 7.01 (t, 1H, $J = 5.70$ Hz), 7.27 (t, 1H, $J = 7.80$ Hz), 7.40 (t, 1H, $J = 7.80$ Hz), 7.68–7.74 (m, 2H), 7.96 (d, 1H, $J = 8.10$ Hz), 8.19 (t, 1H, $J = 8.70$ Hz), 10.57 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.96, 113.93, 120.20, 121.57, 122.36, 125.01, 126.89, 135.26, 138.81, 148.58, 152.14, 153.00, 166.54, 166.66; ESIMS: 302 (M^++1), 303 (M^++2); Anal. Calcd. for $C_{14}H_{11}N_3OS_2$: C, 55.79; H, 3.68; N, 13.94; S, 21.28%, Found: C, 55.81; H, 3.64; N, 14.03; S, 21.26%.

4.1.1.10. N-(4-fluorobenzyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (5j). M.P. **95–97** °C; IR (cm^{-1}): 3272, 3051, 2988, 2930, 2880, 1634, 1548, 1539, 1506, 1456, 1424, 1392, 1308, 1216, 1158, 1132, 1096, 1074, 993, 823, 752, 720; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.96 (s, 2H), 4.34 (d, 2H, $J = 5.40$ Hz), 6.78 (t, 2H, $J = 8.40$ Hz), 7.04–7.09 (m, 2H), 7.25–7.31 (m, 1H), 7.33–7.39 (m, 1H), 7.62 (d, 1H, $J = 8.10$ Hz), 7.70 (d, 1H, $J = 7.80$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.05, 43.21, 115.31, 115.52, 121.27, 121.31, 124.92, 126.38, 129.11, 129.19, 135.39, 152.21, 166.13, 168.10; ESIMS: 333 (M^++1), 334 (M^++2); Anal. Calcd. for $C_{16}H_{13}FN_2OS_2$: C, 57.81; H, 3.94; F, 5.72, N, 8.43; S, 19.29%, Found: C, 57.57; H, 3.96; F, 5.78, N, 8.39; S, 19.32%.

4.1.1.11. 2-(Benzo[d]thiazol-2-ylthio)-N′-(pyridin-4-yl)acetohydrazide (5k). semi solid; IR (cm^{-1}): 3201, 2973, 1695, 1659, 1555,

1539, 1515, 1505, 1480, 1455, 1425, 1379, 1292, 1234, 1143, 1076, 1062, 1019, 998, 968, 905, 846, 755, 726; ^{1}H NMR (DMSO, 300 MHz) δ (ppm): 4.23 (s, 2H), 7.29 (t, 1H, *J* = 6.90 Hz), 7.40 (t, 1H, *J* = 7.20 Hz), 7.68 (d, 1H, *J* = 4.80 Hz), 7.78 (d, 1H, *J* = 8.10 Hz), 7.95 (d, 1H, *J* = 7.80 Hz), 8.67 (d, 1H, *J* = 4.80 Hz), 10.50 (s, 1H), 10.79 (s, 1H); ESIMS: 317 (M^++1); 318 (M^++2); Anal. Calcd. for $C_{14}H_{12}N_4OS_2$: C, 53.14; H, 3.82; N, 17.71; S, 20.27%, Found: C, 53.17; H, 3.78; N, 17.73; S, 20.26%.

4.1.2. Click chemistry-general procedure for 1,2,3-triazolyl conjugates of benzothiazole

1,2,3-Triazolyl conjugates of 2-mercaptobenzothiazole were prepared as per the previously reported method by us [20].

4.1.3. General procedure for the amide coupling of indoleglyoxalic acid with 1°/2° amines

4.1.3.1. 1-(1H-indol-3-yl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (14a). M.P. **195–197** °C; IR (cm^{-1}): 3749, 3648, 3141, 3032, 2971, 2360, 2327, 1715, 1621, 1541, 1507, 1456, 1438, 1414, 1339, 1315, 1245, 1170, 1132; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.55–1.62 (m, 4H), 3.18–3.26 (m, 4H), 6.88–6.91 (m, 2H), 7.12 (t, 1H, *J* = 3.33 & 5.70 Hz), 7.71 (s, 1H), 7.89 (t, 1H, *J* = 3.33 & 5.70 Hz), 11.48 (brs, 1H); ^{13}C NMR (DMSO, 100 MHz): δ 24.01, 26.01, 45.41, 47.00, 113.08, 113.13, 121.42, 122.92, 123.93, 125.65, 137.32, 137.79, 165.72, 186.85; ESIMS: 243 (M^++1), 244 (M^++2); Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%, Found: C, 69.46; H, 5.79; N, 11.54%.

4.1.3.2. 1-(1H-indol-3-yl)-2-(piperidin-1-yl)ethane-1,2-dione (14b). M.P. **159–161** °C; IR (cm^{-1}): 2923, 2868, 1607, 1519, 1435, 1242, 1123, 952, 772, 734, 641; ^{1}H NMR (DMSO, 400 MHz) δ (ppm): 1.41 (m, 2H), 1.59 (m, 4H), 3.26 (t, 2H, *J* = 5.20 Hz), 3.56 (t, 2H, *J* = 5.20 Hz), 7.21–7.28 (m, 2H), 7.51 (d, 1H, *J* = 7.20 Hz), 8.07–8.11 (m, 2H), 12.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.36, 25.52, 26.36, 41.70, 46.91, 113.12, 113.58, 121.32, 122.95, 123.99, 125.30, 137.25, 137.37, 166.19, 187.28; ESIMS: 257 (M^++1), 258 (M^++2); Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%, Found: C, 70.32; H, 6.24; N, 10.91%.

4.1.3.3. 1-(1H-indol-3-yl)-2-(4-methylpiperazin-1-yl)ethane-1,2-dione (14c). M.P. **145–146 °C**; IR (KBr) (cm^{-1}): 3853, 3749, 3648, 3162, 3115, 2930, 2800, 2369, 2318, 1716, 1614, 1541, 1507, 1456, 1285, 1238, 1132, 1007, 951, 928, 840, 729; ^{1}H NMR (DMSO, 300 MHz) δ (ppm): 2.18 (s, 2H), 2.24 (t, 2H, *J* = 4.80 Hz), 2.40 (t, 2H, *J* = 4.80 Hz), 2.32 (t, 2H, *J* = 5.40 & 4.20 Hz), 2.61 (t, 2H, *J* = 5.10 & 4.20 Hz), 7.23–7.31 (m, 2H), 7.52–7.55 (m, 1H), 8.09–8.14 (m, 2H), 12.31 (s, 1H); ^{13}C NMR (DMSO, 100 MHz): δ 45.88, 46.06, 54.45, 55.04, 113.15, 113.56, 121.38, 123.01, 124.05, 125.31, 137.39, 137.53, 166.24, 186.76; ESIMS: 272 (M^++1), 273 (M^++2); Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49%, Found: C, 66.37; H, 6.34; N, 15.51%.

4.1.3.4. 1-(1H-indol-3-yl)-2-morpholinoethane-1,2-dione (14d). M.P. **199–201** °C; IR (cm^{-1}): 3741, 3682, 3102, 2923, 2847, 2370, 2327, 1623, 1541, 1526, 1499, 1442, 1462, 1244, 1154, 1140, 1107, 1031, 960, 776, 748; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.98 (t, 2H, *J* = 4.80 Hz), 3.13 (t, 2H, *J* = 4.80 Hz), 3.24–3.26 (m, 4H), 6.73–6.80 (m, 2H), 7.00 (t, 1H, *J* = 4.80 & 3.90 Hz), 7.48 (s, 1H), 7.71 (t, 1H, *J* = 3.60 & 4.80 Hz), 11.52 (s, 1H); ^{13}C NMR (DMSO, 100 MHz): δ 41.45, 46.48, 66.35, 66.66, 113.15, 113.60, 121.41, 123.07, 124.10, 125.35, 137.42, 137.79, 166.34, 186.51; ESIMS: 259 (M^++1), 260 (M^++2); Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85%, Found: C, 65.09; H, 5.52; N, 10.88%.

4.1.3.5. 1-(1H-indol-3-yl)-2-thiomorpholinoethane-1,2-dione (14e). M.P. **181–184** °C; IR (KBr) (cm^{-1}): 3749, 3648, 3161, 2919, 2853, 2362, 2325, 1601, 1519, 1546, 1435, 1258, 1240, 1137, 962, 926, 770, 738; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.58 (t, 2H, *J* = 5.20 Hz), 2.66 (t, 2H, *J* = 4.80 Hz), 3.66 (t, 2H, *J* = 4.80 Hz), 3.92 (t, 2H, *J* = 4.80 Hz), 7.19–7.26 (m, 2H), 7.33 (d, 1H, *J* = 7.60 Hz), 7.78 (s, 1H), 8.23 (d, 1H, *J* = 7.20 Hz); ^{13}C NMR (DMSO, 100 MHz): δ 26.91, 27.65, 113.15, 113.50, 121.38, 123.05, 124.08, 125.32, 137.43, 137.82, 166.59, 186.61; ESIMS: 275 (M^++1), 276 (M^++2); Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69%, Found: C, 61.24; H, 5.11; N, 10.17; S, 11.71%.

4.1.3.6. 2-(1H-indol-3-yl)-N-morpholino-2-oxoacetamide (14f). M.P. **203–205** °C; IR (cm^{-1}): 3742, 3636, 2968, 2932, 2868, 2817, 2365, 2319, 1648, 1598, 1575, 1525, 1435, 1264, 1233, 1159, 1100, 1062, 1046, 981, 952, 900, 834, 782, 754; ^{1}H NMR (DMSO, 400 MHz) δ (ppm): 2.82 (t, 4H, *J* = 4.40 Hz), 3.64 (t, 4H, *J* = 4.40 Hz), 7.19–7.27 (m, 2H), 7.50–7.52 (m, 1H), 8.17–8.19 (m, 1H), 8.58 (s, 1H), 9.79 (s, 1H), 12.22 (s, 1H); ^{13}C NMR (DMSO, 100 MHz): δ 54.80, 55.88, 66.06, 66.39, 112.78, 112.95, 121.63, 123.04, 123.92, 126.41, 136.82, 138.63, 161.75, 183.52; ESIMS: 274 (M^++1), (M^++1) 275; Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38%, Found: C, 61.48; H, 5.56; N, 15.41%.

4.1.3.7. N′-[2-(1H-indol-3-yl)-2-oxoacetyl]pyridine-4-carbohydrazide (14g). M.P. **263–265** °C; IR (KBr) (cm^{-1}): 3838, 3749, 3689, 3628, 3106, 2360, 1716, 1698, 1647, 1557, 1541, 1521, 1507, 1473, 1456, 1418, 1396, 1336, 1233, 1117, 1008, 819, 759, 646; ^{1}H NMR (DMSO, 300 MHz) δ (ppm): 7.27–7.33 (m, 2H), 7.59 (t, 1H, *J* = 3.90 Hz), 8.10 (d, 2H, *J* = 6.00 Hz), 8.23 (t, 1H, *J* = 3.60 & 5.40 Hz), 8.67 (d, 1H, *J* = 3.30 Hz), 8.96 (d, 2H, *J* = 6.00 Hz), 10.96 (s, 1H); 11.18 (s, 1H) 12.45 (d, 1H, *J* = 2.40 Hz); ^{13}C NMR (DMSO, 100 MHz): δ 112.89, 113.25, 121.67, 123.28, 124.19, 124.73, 126.19, 136.98, 138.90, 145.22, 145.49, 162.63, 163.69, 182.15; ESIMS: 309 (M^++1), 310 (M^++2); Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17%, Found: C, 62.28; H, 3.93; N, 18.19%.

4.2. Pharmacology

4.2.1. Drugs

Isoniazid and rifampicin were used in the biological assays.

4.2.2. Antimycobacterial activity and determination of minimum bactericidal concentration

The antimycobacterial activities of novel conjugates of 2-mercaptobenzothiozoles (5a–5o and 8a–m) and indole-3-glyoxalic acids (14a–14g) were evaluated against *M. tuberculosis* H37Rv using microplate dilution assay [24,25]. All the compounds were initially screened against *M. tuberculosis* H37Rv at the single concentration of 64 μg/mL in triplicate in a microtiter plate. The active compounds from this screening were further tested for Minimum Inhibitory Concentration (MIC) determination using the broth microdilution assay. The microtiter plates were incubated for 2–3 weeks at 37 °C in CO_2 incubator and read visually for the absence of growth turbidity. Further, the bactericidal effect (minimum bactericidal concentration, MBC) of active compounds was assessed by plating the bacterial suspensions from microtiter plate which exhibited MIC, at the end of the experiment on 7H11 agar medium for viable count enumeration. A total of 0.02 mL of *M. tuberculosis* suspension from wells showing MIC and above concentrations was plated onto 7H10 agar medium, and the resulting bacterial counts were enumerated after 20 days of incubation at 37 °C. The MBC was defined as the minimal concentration which effectively reduced by at least 99% the viable counts in the compound-containing sample compared with those in control vials (compound free wells) [26,27].

4.2.3. Protein structure preparation

The DprE1 crystal structure (PDB: 4FDO) elucidated by Batt et al. [28] was used as receptor for docking analysis with the compounds **8b, 8f, 8g, 8l**. The structure contains chain A of protein, water molecules and connecting atoms. Water molecules and connecting atoms were removed and chain A was retained to be used as a receptor for docking. Before DprE1 was used for docking with ligands it was energy minimized by Gromacs 4.0.5 [29].

4.2.4. Docking studies

The four compounds that gave better activity in *In-vitro* studies were used as ligands for docking studies. The 3D structures of ligands in energy minimized form were obtained from ProDrg [30]. Docking studies were carried out with AutoDock 4.2 along with AutoDock Tools 1.5.4 [31]. Docking calculations were performed with Lamarkian genetic algorithm. 100 docked conformations were generated, with each using 25 million evaluations for 27,000 generations of population size 300. Docking results were clustered at a 2A RMS cutoff. Conformations of the docking compounds were generated using Pymol 1.1 [32].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.02.017.

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