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REVIEW

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Recent advances in the synthesis of new benzothiazole based anti-tubercular compounds

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This review highlights the recent synthetic developments of benzothiazole based anti-tubercular compounds and their in vitro and in vivo activity. The inhibitory concentrations of the newly synthesized molecules were compared with the standard reference drugs. The better inhibition potency was found in new benzothiazole derivatives against M. tuberculosis. Synthesis of benzothiazole derivatives was achieved through various synthetic pathways including diazo-coupling, Knoevenagel condensation, Biginelli reaction, molecular hybridization techniques, microwave irradiation, one-pot multicomponent reactions etc. Other than recent synthetic developments, mechanism of resistance of anti-TB drugs is also incorporated in this review. Structure activity relationships of the new benzothiazole derivatives along with the molecular docking studies of selected compounds have been discussed against the target DprE1 in search of a potent inhibitor with enhanced anti-tubercular activity.

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Introduction

Tuberculosis (TB) is one of the most precarious and contagious infectious illnesses in the world caused by Mycobaterium tuberculosis, Mtb.^{1,2} Moreover, the rapid growth of drug resistant bacteria has contributed to a rise in incidence of both extensively drug resistant (XDR) and multidrug resistant (MDR) tuberculosis.3 Under this situation, only the recently developed Delamanid, Pretomanid,⁴ Bedaquiline⁵ and Fluoroquinolone antibiotics⁵ have proven to be effective novel pharmaceuticals

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with distinct modes of action to treat TB infection. This highlights the inherent challenges of creating and evaluating novel chemical agents by medicinal chemists, as well as the constraints brought on by a deficit of drug discovery research in the pharmaceutical sector.6 New drug development is the main objective of medicinal chemistry, which operates at the interface between synthetic organic chemistry and molecular biology. One of the most common, yet equally significant, sections of organic chemistry is the synthesis and study of heterocyclic chemistry, which has been the subject of extensive research for more than a century.7 Benzothiazole is a heterocyclic compound with benzene nucleus attached to a five membered ring having nitrogen and sulphur atoms placed at 1



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derived materials, natural product-inspired hybrid analogues and molecular modeling, especially in protein-ligand interaction via in silico docking tools.

Review

and 3 positions.⁷ Benzothiazole analogues are most ubiquitous and an integral part of many pharmaceutical agents.^{8,9} Benzothiazole is considered as a fundamental building block in the search of a novel class of drug molecules with diverse pharmacological activities like anti-tubercular,^{5,10-14} anti-convulsant,^{15,16} anti-HIV,¹⁷ anti-mosquito,¹³ anti-microbial,¹⁶ antitumor,^{18,19} analgesic,²⁰ anti-leishmanial,²¹ and antiinflammatory.^{22,23} Additionally, the logical design and development of novel anti-TB agents incorporating a benzothiazole nucleus can assist in addressing the need for an effective antimicrobial therapy for the treatment tuberculosis.¹⁰ Anti-TB drugs are basically divided into two categories, (i) first line drugs, (ii) second line drugs.



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ology in organic synthesis, the synthesis of carbohydrate fusedlinked heterocyclic molecules as bioactive molecules. He is also interested in synthesis of natural product inspired bioactive scaffolds as antiviral agents.



Prof. Ram Sagar received his MSc degree from University of Lucknow, Lucknow, UP, India. Prof. Sagar has completed his PhD degree in Organic Chemfrom istry Central Drug Research Institute (CDRI) Lucknow and University of Agra in 2006. After his PhD, he pursued his Research Associate with Prof. Y. D. Vankar at IIT Kanpur during 2006-2007. Then he pursued his first post-doctoral

research at Seoul National University South Korea with Prof. Seung Bum Park during 2007-2008. He moved to University of Oxford in 2008 and worked with Prof. Benjamin G. Davis as BBSRC postdoctoral fellow until August 2012. He returned to India in August 2012 and held a faculty position at Shiv Nadar University (SNU), Greater Noida. He moved to Department of Chemistry, Banaras Hindu University (BHU) as Associate Professor in February 2018 and worked there till December 2020. He subsequently got full professor at Jawaharlal Nehru University (JNU), New Delhi in December 2020 and presently working as Professor of Chemistry in School of Physical Sciences. His current research interests include devising newer methods for the efficient synthesis of natural product inspired small molecules, glycohybrids and glycopeptides implicated in various diseases including tuberculosis and cancer. His interested also lies the preparation of carbohydrate based materials.



Fig. 1 Molecular structure of first line anti-tubercular drugs.

First-line medications (FLD), such as Isoniazid (INH), Rifampicin (RIF) and its derivatives, Pyrazinamide (PZA), Ethambutol (EMB), Streptomycin (STM) (Fig. 1) can be used to treat TB infection.²⁴

However, as drug-resistant bacteria proliferate, causing relapse and disease progression, there are numerous cases and fatalities reported due to a decline in the effectiveness of these first-line medications. The combination of these drugs is used to increase patient adherence to the treatment and avoid the emergence of new resistant strains of bacteria that utilize different mechanisms of action. The rise of multidrug resistant tuberculosis (MDR-TB), which is resistant to at least Isoniazid (INH) and Rifampicin (RIF) is extremely concerning since it necessitates the use of second-line medications that are more toxic and expensive as compared to first line anti-tuberculosis drugs (Fig. 2). Whereas XDR-TB refers to resistance to three or more of the six classes of second-line medications.²⁵ Active TB patient shows symptoms and can spread the disease while latent TB patient has no symptoms and cannot spread the disease.²⁶

Among the new class of drugs Delamanid and Pretomanid belongs to nitroimidazole class of antibiotics while Bedaquiline belongs to diarylquinoline class of antibiotics (Fig. 3). These drugs are crucial for the treatment of MDR-TB. Bedaquiline blocks the



Fig. 2 Molecular structures of second line anti-tubercular drugs.



Fig. 3 Molecular structure of newly approved anti-tubercular drugs against MDR and XDR TB.

proton pump for ATP synthase while Delamanid and Pretomanid prevents the production of mycolic acid in cell walls.^{27,28}

Drug resistance for TB and mechanism of resistance

Spontaneous change in Mtb strains make them resistant to at least one anti-TB medication. Basically, drug resistance develops due to gene mutations. Thus, exposure to a single anti-TB medicine could slow the expansion of the Mtb population but not totally eradicate it. Like first-line medications, second-line medications are also linked to genetic alterations. Resistance to Rifampicin and its derivatives (rifabutin, rifapentine, and rifalazil) is linked to genetic changes in the *rpoB* gene, genetic alterations involving the *embCAB* operon cause Ethambutol resistance, mutations in the *rpsl* are linked to Streptomycin resistance, mutations in *gyrA* are linked to resistance to the drugs belonging to group quinolones, while mutations in *rrs* are linked to Kanamycin and Amikacin resistance (Table 1).²⁶

Because of development of MDR and XDR-TB the medicinal chemists are in continuous search of new molecules which can combat drug resistance tuberculosis. Several research groups throughout the globe are working towards this objective utilizing various natural product inspired molecular scaffolds. The benzothiazole is one of such privileged drugs like scaffold. There are several compilations of reports on benzothiazole nucleus and associated various biological activities. But detailed review on the recent synthetic developments of benzothiazole derivatives and their anti-TB activity was of absolute necessity. Keeping this in mind the current review focused on the recent developments towards synthesis of new benzothiazole derivatives and associated anti-TB activity.

Recent synthesis of benzothiazole based anti-tubercular molecules

R. Chikhale and co-workers took decaprenylphosphoryl- β -D-ribose 20-epimerase (DprE1) as a possible therapeutic target for the creation of anti-tubercular drugs and synthesized novel derivatives of benzothiazolylpyrimidine-5-carboxamides **7a-g** from three component one-pot classical Biginelli reaction between benzothiazolyloxobutanamide **4**, substituted aromatic benzaldehydes **5** and thiourea **6** (Scheme 1, Table 2).⁴² Benzothiazolyloxobutanamide **4** was prepared from 2-aminobenzothiazole **3a** in presence of sodium hydroxide and ethylacetate. Compound **3a** in turn was prepared from aniline **1** *via* a two-step reaction involving an intermediate **2**.

All synthesized compounds were evaluated for their antitubercular activity against the pathogenic strain of Mtb H_{37} Rv ATCC 27294. MIC and IC₅₀ values revealed that compounds **7a** and **7g** had comparative better activity than INH (Table 2). DprE1 selectivity and pharmacokinetics studies of these derivatives were carried out which showed compounds **7a** and **7g** were highly selective with better bioavailability (>52%) by oral dose. A pharmacophore model of these compounds suggested that, presence of aromatic, aliphatic carbon center and hydrogen bond donor is essential for better anti-tubercular activity and DprE1 inhibition.

Table 1 Classification of anti-TB drugs according to their mechanism of resistance and route of intake

Drugs lines	Groups	Drugs	Mechanism of resistance	References
First line anti-TB drugs	Group 1 (oral)	Isoniazid	Mutations in <i>katG</i> and <i>inhA</i>	29
C		Rifampicin/Rifampin	Mutations in <i>rpoB</i> gene	30
		Pyrazinamide	Mutations in RpsA, pncA	31 and 32
		Rifapentine	Mutations in <i>rpoB</i> gene	33
		Rifabutin	Mutations in <i>rpoB</i> gene	34
		Ethambutol	embCAB operon	24
	Injectable	Streptomycin	Mutations in <i>rpsL</i>	35
Second-line anti-TB drugs	Group 2 (injectable)	Kanamycin	Mutations in rrs	36
C C		Amikacin	Mutations in rrs	
		Viomycin	Mutations in rrs	
		Capreomycin	Mutations in <i>thyA</i>	
	Group 3 (oral and injectable)	Moxifloxacin	Mutations in gyrA	37
		Levofloxacin	Mutations in gyrA	
	Group 4 (oral)	Linezolid	Mutations in G2576T (238)	38
		Prothionamide	Mutations in <i>etha</i>	39
		Ethionamide	Mutations in <i>etha</i> and <i>inhA</i>	40
		Terizidone	Non	
		Cycloserine	Mutation in <i>alrA</i>	41
		Para-aminosalicylic acid (PAS)	Mutations in <i>thyA</i>	41



Scheme 1 Synthesis of benzothiazolylpyrimidine-5-carboxamide analogues.

Table 2 Anti-tubercular activity of benzothiazolylpyrimidine-5-carboxamide analogues^a

Compounds	R	IC_{50} (μM)	MIC (µM)
7a	н	7.7 ± 0.8	0.08
7b	2-Cl	NT	0.32
7 c	4-Cl	NT	0.32
7d	2,4-Di Cl	NT	0.25
7e	4-F	9.2 ± 1.5	0.09
7 f	CF_3	11.1 ± 1.8	0.09
7g	$4-N(Me)_2$	10.3 ± 2.6	0.08
INH	_	0.2	—
^{<i>a</i>} NT: not tested.			

Docking studies of compound 7a against 4FDN protein of potential therapeutic site DprE1 revealed that it displays better binding affinity of -8.4 kcal mol⁻¹ with several amino acids at active site of the protein chain. This finding suggests that, this could be a potential target of 7a and responsible for its antitubercular activity (Fig. 4 and 5).

Shaikh and co-workers synthesized some acetamide linked benzothiazole derivatives through various intermediates. Initial



Fig. 4 3D representation of ligand 7a and its interactions at the active site of 4FDN protein.



Fig. 5 2D representation of docking results showing interactions of ligand 7a with 4FDN protein.



step involved the synthesis of (E)-5-arylidenethiazolidine-2,4diones 9a-n (Scheme 2) from the Knoevenagel condensation reaction of 1,3-thiazolidine-2,4-dione 8 with various aromatic aldehydes in ethanol solvent in the presence of a piperidine catalyst. Next to this the reaction of aniline 1 with acetic acid in presence of bromine and ammonium thiocyanate lead to the formation of 2-amino-6-thiocyanato benzothiazole 10. The later 10 on further reaction with chloroacetyl chloride produced 2-



Scheme 3 Synthesis of 6-thiocyanatobenzo[d]thiazol-2-amine 10 and 2-chloro-N-(6-thiocyantobenzo[d]thiazol-2-yl)acetamide 11.



Scheme 4 Synthesis of 2,4-thiazolidinediones incorporated 2-amino-6-thiocyanato benzothiazole derivatives.

Table 3 Anti-tubercular activity of the synthesized compounds

Compounds	R	$\frac{\rm MIC}{(\mu g \ m L^{-1})}$	Inhibition (%)	Compounds	R	$\frac{\rm MIC}{(\mu g \ m L^{-1})}$	Inhibitior (%)
9a	Н	250	98	12a	н	100	99
9b	2-Cl	500	97	12b	2-Cl	500	98
9c	4-Cl	250	99	12c	4-Cl	50	99
9d	4-F	100	98	12d	4-F	100	99
9e	3-Br	250	99	12e	3-Br	25	99
9f	4-Me	200	99	12f	4-Me	1000	98
9g	4-OMe	250	98	12g	4-OMe	100	99
9h	4-N(Me) ₂	1000	98	12h	$4-N(Me)_2$	62.5	99
9i	4-OH	250	99	12i	4-OH	500	98
9j	3-OMe-4-OH	100	99	12j	3-OMe-4-OH	500	99
9k	$2-C_4H_3O$	1000	98	12k	$2-C_4H_3O$	500	99
91	$3-OC_6H_5$	200	98	12l	$3-OC_6H_5$	250	99
9m	3,4,5-Tri-OMe	50	99	12m	3,4,5-Tri-OMe	1000	98
9n	4-N[(CH ₂) ₅ CH ₃] ₂	500	98	12n	4-N[(CH ₂) ₅ CH ₃] ₂	250	97
10	_	500	99	RIF	_	40	99
11	_	62.5	99				

chloro-*N*-(6-thiocyanatobenzo[*d*]thiazol-2-yl)acetamide **11** (Scheme 3). Finally the reaction of (*E*)-5-arylidenethiazolidine-2,4-diones **9a–n** and 2-chloro-*N*-(6-thiocyanatobenzo[*d*]thiazol-2-yl)acetamide **11** in presence of anhydrous K_2CO_3 in DMF (Scheme 4) furnished the desired compounds **12a–n** (Scheme 4, Table 3).⁴³

Biological evaluation of the synthesized compounds showed moderate to good anti-tubercular activity against *M. tuberculosis* $H_{37}R_V$ with reference drug Rifampicin. The L–J agar (MIC) method was used to assess drug susceptibility and the MIC of the test compounds against *M. tuberculosis* $H_{37}R_V$ (Table 3). The compounds **10**, **11** and **12g** showed better activity (MIC = 25–50 µg mL⁻¹). All other compounds showed moderate to modest anti-tubercular activity against *M. tuberculosis* $H_{37}R_V$. MIC values of 62.5–100 µg mL⁻¹ were similar for compounds **9f**, **9l**, **12b**, **12c**, **12f**, **12i** and **12j** while the remaining compounds showed minimal to moderate activity (MIC = 200–1000 µg mL⁻¹). Abdel-Aziz and co-workers synthesized few benzothiazole based halophenyl bis-hydrazones and their sulfone derivatives **15**, **16a–b**. Bis-hydrazone derivative of benzothiazole **15** was produced by the reaction of benzo[d]thiazole-2-carbohydrazide

Table 4Anti-tubercular activity of halophenyl bis-hydrazone and itssulfone derivatives

Ar	MIC ($\mu g \ mL^{-1}$)
_	NA
Ph	NA
4-Me-C ₆ H ₄	125
_	0.40
_	3.21
	Ar — Ph 4-Me-C ₆ H ₄ —

^{*a*} NA: not active.



Scheme 5 Synthesis of benzothiazole based halophenyl bis-hydrazone.



Scheme 6 Synthesis of sulfone derivative of benzothiazole based halophenyl bis-hydrazone compounds.

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Scheme 7 Synthesis of benzothiazole based derivatives of coumarin substituted quinazolines.

13 with 2-oxo-*N*'-(4-substituted phenyl)propane hydrazonoyl chloride **14** in tetrahydrofuran (THF) under reflux conditions (Scheme 5). Resulting bis-hydrazones **15** on further reaction with sodium benzenesulfinate or sodium 4-methylbenzenesulfinate furnished the corresponding sulfones **16a** and **16b** respectively (Scheme 6, Table 4).⁴⁴

These benzothiazole based halophenyl bis-hydrazones derivatives when tested against mycobacterial strain were

Table 5	Anti-tubercular activity of benzothiazole based derivatives of
coumari	n substituted quinazolines

22aH>6.2525022bCl>6.252522cBr>6.2512.522dF>6.253.1222eNO2>6.25100	$C method mL^{-1}$
22bCl>6.252522cBr>6.2512.522dF>6.253.1222eNO2>6.25100	
Image: Definition of the second system of the se	
22d F >6.25 3.12 22e NO2 >6.25 100	
22e NO ₂ >6.25 100	
22f CN >6.25 200	
22g Me >6.25 250	
22h OMe >6.25 100	
22i OEt >6.25 50	
22j OH 6.25 6.25	
EMB — 3.12 —	
PZA — 6.25 —	
RIF — 0.25 —	
INH — 0.20 —	

found to be less active against *M. tuberculosis* as compared to standard reference drugs Isoniazid and Pyrazinamide (Table 4).

A. B. Patel and co-workers synthesized benzothiazole based derivatives of coumarin substituted quinazolines **22a-j** (Scheme 7, Table 5). 2-Aminobenzoic acid **17** was used to create the first analogue, 2,4-dihydroquinazoline **18** which on further reaction with POCl₃ in DMA (dimethylacetamide) gave 2,4-dichlor-oquinazoline **19**. The intermediate analogue **21** was formed by the condensation of 4-hydroxycoumarin **20** with 2, 4-dichlor-oquinazoline **19** in the presence of potassium carbonate base. Intermediate **21** on reaction with various 2-aminobenzothiazole derivatives **3a-f** furnished the desired compounds **22a-j** in good yields.⁴⁵

According to the results of *in vitro* screening against $H_{37}Rv$ strain of *M. tuberculosis*, all newly synthesized compounds demonstrated moderate to good suppression of *M. tuberculosis* $H_{37}Rv$ at 3.12–25 µg mL⁻¹ (Table 5). For the first selection of active compounds, the primary screening was carried out using the BACTEC MGIT technique⁴⁵ at a concentration of 6.25 µg mL⁻¹. Using primary screening **22d** and **22j** showed the maximum inhibition (99%) of all the investigated drugs. However, analogue **22d** with a fluoro group attached to the benzothiazole ring demonstrated the best inhibition against *M. tuberculosis* $H_{37}Rv$ with MIC value of 3.12 µg mL⁻¹, according to the results of secondary biological screening using the Lowenstein–Jensen MIC method.⁴⁵



Scheme 8 Synthesis of benzo[d]thiazole-2-carboxamide analogues.

Compounds	R	Z	R^1	Yields (%)	$\begin{array}{l} \text{MIC} \\ \left(\mu g \ m L^{-1} \right) \end{array}$	Compounds	R	Z	R^1	Yields (%)	MIC $(\mu g m L^{-1})$
23a	Н	_	_	83	25	25h	Cl	NR ¹	4-OMe-C ₆ H ₄	54	3.125
23b	Cl	_	_	73	3.125	25i	Cl	NR^1	4-COMe-C ₆ H ₄	54	1.56
23c	CF_3		_	70	6.25	25j	Cl	NR^1	4-Pyridyl	58	12.5
24a	Н	0	_	88	1.56	25k	Cl	NR^1	2-Pyrazinyl	47	6.25
24b	Н	S	_	83	25	251	Cl	NR^1	$CH(C_6H_5)_2$	77	0.78
24c	Н	CH_2	_	67	25	26a	CF ₃	0	_ ` `	88	0.78
24d	Н	$NR^{\overline{1}}$	Ме	56	3.125	26b	CF ₃	S	_	92	0.78
24e	Н	NR^1	СОМе	55	1.56	26c	CF ₃	CH_2	_	74	12.5
24f	Н	NR^1	C_6H_5	76	1.56	26d	CF ₃	NR^1	Ме	77	6.25
24g	Н	NR^1	2-OMe-C ₆ H ₄	55	3.125	26e	CF ₃	NR^1	COMe	88	1.56
24h	Н	NR^1	4-OMe-C ₆ H ₄	53	12.5	26f	CF ₃	NR^1	C_6H_4	72	12
24i	Н	NR^1	4-COMe-C ₆ H ₄	51	1.56	26g	CF ₃	NR^1	2-OMe-C ₆ H ₄	77	25
24j	Н	NR^1	4-Pyridyl	54	3.125	26h	CF ₃	NR^1	4-OMe-C ₆ H ₄	88	3.125
24k	Н	NR^1	2-Pyrazinyl	77	6.25	26i	CF ₃	NR^1	4-COMe-C ₆ H ₄	77	6.25
241	Н	NR^1	$CH(C_6H_5)_2$	63	0.78	26j	CF ₃	NR^1	4-Pyridyl	74	3.125
25a	Cl	0	_	77	6.25	26k	CF ₃	NR^1	2-Pyrazinyl	75	3.125
25b	Cl	S	_	67	6.25	26l	CF ₃	NR^1	$CH(C_6H_5)_2$	74	25
25c	Cl	CH_2	_	77	12.5	INH	_	_	_	_	0.098
25d	Cl	NR^1	Ме	60	25	RIF	_	_	_	_	0.19
25e	Cl	NR^1	СОМе	82	12.5	EMB	_	_	_	_	1.56
25f	Cl	NR^1	C_6H_5	78	6.25	PYZ	_	_	_	_	6.25
25g	Cl	NR^1	2-OMe-C ₆ H ₄	57	3.125	CIP	_	_	_	_	1.56



Fig. 6 Synthesis of benzo[*d*]thiazol-2-yl (piperazin-1-yl) methanones by the molecular hybridization method.

K. Chakraborti and co-workers designed and synthesized some new anti-mycobacterial chemotypes as benzo[*d*]thiazol-2yl(piperazin-1-yl)methanones **24a–l**, **25a–l** and **26a–l** (Scheme 8, Table 6) from the molecular hybridization of *N*-benzyl benzo[*d*] thiazole-2-carboxamides and alicyclic piperazines (Fig. 6) in solvent free conditions from good to moderate yields. Intermediates 5-substituted benzo[*d*]thiazole-2-carboxylate **23a–c** were formed from the reaction of 2-aminothiophenol **17a–c** with ethyl glyoxylate in presence of micellar solution of SDOSS (sodium dioctyl sulfosuccinate). The intermediates **23a–c** on further coupling with alicyclic amines produced the diverse library of compounds **24a–l**, **25a–l** and **26a–l**.⁴⁶

Synthesized benzo[*d*]thiazole-2-carboxamide derivatives were tested *in vitro* for their anti-tubercular activity against H_{37} Rv strain of *M. tuberculosis* (Table 6). From this structurally diverse library, eighteen compounds 24a, 24d–f, 24g, 24i–j, 24l, **25g-i**, **25l**, **26a-b**, **26e**, **26h**, **26j-k** showed MICs value in the range of 0.78–3.125 μ g mL⁻¹. The compounds **24l**, **25l**, **26a**, and **26b** with MIC value of 0.78 μ g mL⁻¹ were found to be more powerful than the standard medicines Ethambutol (1.56 μ g mL⁻¹), Ciprofloxacin (1.56 μ g mL⁻¹), and Pyrazinamide (6.25 μ g mL⁻¹). The compounds **26a** and **26b** were found to be less cytotoxic against RAW 264.7 cell lines (mouse macrophage cell line) with inhibition of 24.56% and 18.12% having therapeutic index >60. As Mtb grow inside macrophages therefore any new molecule should remain nontoxic to these cells. SAR study revealed that, presence of –CF₃ group on **26a** and **26b** improve their anti-tubercular activity.

Amongst the all-tested compounds the most active compound **26a** was choosen for molecular docking studies to find its binding target. It shown better affinity towards 4P8N protein of DprE1 enzyme (Fig. 7 and 8) with a good binding



Fig. 7 3D representation of ligand **26a** and its interactions with 4P8N protein.



Fig. 8 2D representation of docking results showing interactions of compound 26a with 4P8N protein.

affinity of $-8.9 \text{ kcal mol}^{-1}$ and MIC value of $0.78 \mu \text{g mL}^{-1}$. This compound **26a** may be considered as lead compound in further search of a better ligand to fit within the target site of DprE1 of *M. tuberculosis*.

N. Bhoi and co-workers designed 4*H*-pyrimido [2,1-*b*] benzothiazole with an isoniazid nucleus 33a-n and its biological profile was investigated (Scheme 9, Table 7). The traditional approach was used to complete the synthesis in the hopes of finding novel analogue leads that could work as an antimycobacterial agent. Synthesis of adduct **31a-n** involved the dropwise addition of hydrazine hydrate solution in presence of catalytic amount of H_2SO_4 to the previously synthesized derivatives **30a-n**. Further reaction of adduct **31a-n** with triethylamine and hydrochloride salt of isonicotinoyl chloride **32** produced the *N*-isonicotinoyl-2-methyl-4-(pyridin-2-yl)-4*H*-

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Table 7	Anti-mycobacterial	activity of	isoniazid	linked	4H-pyrimido
[2,1-b] be	enzothiazole analog	ues			

Compounds	R	Yields (%)	Inhibition (%)	MIC value (μg mL ⁻¹)
339	н	71.2	60.01	125
33h	6-Br	68.4	73.17	62.5
33c	6-Me	74.1	54.47	500
33d	4-Me	65.2	47.15	1000
33e	6-NO ₂	69.2	56.91	250
33f	6-Cl	75.6	71.54	125
33g	4-Cl	66.1	81.30	50
33h	6-F	78.5	80.48	25
33i	6-OMe	79.6	49.59	500
33j	6-OEt	80.0	63.41	62.5
33k	6-OCF ₃	67.6	79.67	6.25
331	6-OH	71.2	68.29	100
33m	4-OMe	70.2	50.40	125
33n	5,6 di Me	69.5	82.11	12.5
INH	—	—	99.18	0.20

benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbohydrazide analogues **33a–n**.^{47,48}

In a standard primary screen, all the newly synthesized compounds **33a–n** were evaluated *in vitro* for their antimycobacterial activity against *M. tuberculosis* H_{37} Rv using a well-known Lowenstein–Jensen (L–J) method. The results of anti-mycobacterial activity indicated that the synthesized compounds displayed diverse tuberculostatic activity (Table 7). Among them, compound **33k** was found to be most potent compound with MIC value 6.25 mg mL⁻¹, while compound **33n** (MIC 12.5 mg mL⁻¹) showed good anti-mycobacterial activity. Compounds **33b**, **33g–h** and **33j** were found to display good to moderate anti-mycobacterial activity.



Scheme 9 Synthesis of isoniazid linked 4H-pyrimido [2,1-b] benzothiazole.



Scheme 10 Designing approach for the synthesis of new class of benzothiazoles.

Samala and co-workers developed benzo[*d*]imidazo[2,1-*b*] thiazole derivatives from previously reported imidazo[1,2-*a*] pyridine-based pantothenate synthetase (PS) inhibitors for *M. tuberculosis* (Schemes 10 and 11, Table 8). Synthesis of final desired compounds involved three steps process. Step one was initiated from the reaction between 2-aminobenzothiazole **3a** and 2-chloroethylacetoacetate **34** in 1,2-dimethoxyethane at 90 ° C to give tricyclic compound **35**. Step 2 involved two reaction pathways on ester group. Among these two pathways one was the conversion of ester group to acid hydrazide **36** and another one was the conversion of ester to acid **37**. Compound **36** reacted with substituted aromatic carboxylic acids and



Scheme 11 Synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole derivatives.

 Table 8
 Anti-tubercular activities of benzo[d]imidazo[2,1-b]thiazole derivatives



Compound	s R	Yields (%)	PanC IC ₅₀ (µM)	MIC against Mtb (μM)	Compou	nds R	Yields (%)	PanC IC ₅₀ (µM)	MIC against Mtb (μM)
38a	Phenyl	80	1.10 ± 0.4	35.67	39d	3,4,5- Trimethoxyphenyl	91	2.07 ± 0.20	29.45
38b	4-Tolyl	87	5.83 ± 0.24	17.15	39e	4- <i>N</i> , <i>N</i> - Dimethylphenyl	82	1.46 ± 0.12	4.13
38c	4-Phenoxyphenyl	74	0.53 ± 0.13	3.53	40a	4-Bromophenyl	63	0.52 ± 0.04	16.18
38d	1-Naphthyl	69	1.39 ± 0.08	15.60	40b	Phenyl	81	1.03 ± 0.11	40.67
38e	Cyclohexyl	89	2.91 ± 0.11	17.53	40c	4-Ethoxyphenyl	83	2.10 ± 0.09	41.95
39a	4-Bromophenyl	87	1.02 ± 0.13	15.12	40d	Benzyl	72	0.84 ± 0.1	19.44
39b	4-	93	5.31 ± 0.11	16.53	40e	Cyclohexyl	81	1.02 ± 0.11	19.94
	Trifluoromethylpher	nyl							
39c	Phenyl	90	2.15 ± 0.8	9.35	INH	_	_	>25	0.72
	-				EMB	_		>25	7.64



Scheme 12 Synthesis of 2-(4-amino-2-aryl/alkyl aminothiazol-5-oyl)benzothiazole derivatives.

Table 9Anti-tubercular activity of 2-(4-amino-2-aryl/alkyl amino-
thiazol-5-oyl)benzothiazole derivatives a

		Zone of inhibition (mm)						
Compounds	R	0.5 mg	1 mg	1.5 mg	2 mg	Control		
43a	C ₆ H ₅	NA	NA	2	3	3		
43b	4-ClC ₆ H ₄	NA	1	2	4	3		
43c	4-MeOC ₆ H ₄	NA	NA	NA	2	3		
43d	$4-EtOC_6H_4$	3	5	6	8	3		
43e	4-MeC ₆ H ₄	NA	3	4	4	2		
43f	C_2H_5	3	6	7	8	3		
43g	$N-C_3H_7$	NA	NA	NA	NA	NA		
43h	N-C ₄ H ₉	NA	NA	2	2	4		
43i	Allyl	2	3	3	5	2		

^a NA: not active.

substituted aldehydes to furnish desired compounds **38a–e** and **39a–e** respectively while compound **37** reacted with aromatic/ aliphatic primary amines in order to furnish desired compounds **40a–e**.^{49,50}

Synthesized compounds were evaluated *in vitro* for their anti-TB activity against replicative and non-replicative Mtb (Table 8). All of the synthesized compounds were found to be active against Mtb with MICs ranging from 3.53 to 41.95 μ M. Compound **38c** with MIC of 3.53 μ M emerged as a powerful molecule against Mtb (Table 8).⁵⁰ The cytotoxicity study of the compound **38c** was done against RAW 264.7 cell lines (mouse macrophage cell line) which showed better results with cytotoxicity of 10.4% at 50 μ M.

A. Yardily and co-workers synthesized 2-(4-amino-2-aryl/alkyl aminothiazol-5 oyl)benzothiazole derivatives **43a-i** from the



Scheme 13 Synthesis of series of (Z)-3-(4-(benzo[d]thiazol-2-ylthio) phenyl)-5-benzylidene-2-(pyridine-4-yl)thiazolidine-4-one.

Table 10 Ant	Table 10 Anti-tubercular activity of thiazolidine-4-one substituted benzothiazoles											
Compounds	R^1	R^2	% inhibition	MIC values (μM)	Compounds	\mathbb{R}^1	R^2	% inhibition	MIC values (µM)			
47	_	_	74	>100	48g	Н	Cl	99	<50			
48a	Н	Н	69	>100	48h	Н	Br	10	>100			
48b	н	OH	71	>100	48i	Pyridine-2	-carbaldehyde	100	<50			
48c	Ме	OMe	13	>100	48j	Pyridine-4	-carbaldehyde	99	<50			
48d	н	NO_2	95	>100	INH		,	99	0.25			
48e	н	F	98	<50	RIF	_	99	40				
48f	F	н	100	<50								



Scheme 14 Synthesis of benzothiazole based Schiff base.

 Table 11
 Anti-tubercular activity of Schiff base and the formed metal complexes

Compounds	$MIC \ (\mu g \ mL^{-1})$
52	1.6
53	0.8
54	1.6
55	0.8
STM	6.25



reaction of amidinothioureas **41a–i** and 2-(2-bromoacetyl)benzothiazole **42** in the presence of triethylamine at 35 °C (Scheme 12, Table 9).⁵¹

All the synthesized compounds were evaluated for their antitubercular activity. Compounds **43d**, **43f**, and **43i** demonstrated the highest activity against *M. tuberculosis* when compared to control penicillin (Table 9).⁵¹

V. M. Patel and co-workers aimed to create powerful antimycobacterial molecules based on thiazolidine-4-one motif through Knoevenagel condensation *via* conventional heating as well as microwave irradiation as a green protocol (Scheme 13, Table 10). 4-(Benzo[d]thiazol-2-ylthio) aniline **45** was synthesized from the reaction of mercaptobenzothiazole **44** with 4iodoaniline in the presence of CuI and TBAB (tetrabutylammonium bromide). Compound **45** on further reaction with pyridine-4-carbaldehyde in presence of glacial acetic acid formed (*E*)-*N*-(4-(benzo[*d*]thiazol-2-ylthio)phenyl)-1-(pyridin-4yl)methanimine **46**. Compound **46** on reaction with thioglycolic acid in presence of ZnCl₂ gave **47**, which on further reaction with substituted benzaldehydes in presence of piperidine and acetic acid furnished the target compounds **48a–j** (Scheme 13).⁵²

In vitro anti-tubercular activity of the synthesized benzothiazole derivatives **47**, **48a–j** was assessed by using MABA approach against H_{37} Rv strain of *M. tuberculosis* taking Isoniazid and Rifampicin as the standard reference drugs (Table 10).

S. S. Jawoor and co-workers created the ligand **52** by the dropwise addition of 2-hydrazinobenzothiazole **51a** in ethanol to a solution of 8-formyl-7-hydroxy-4-methylcoumarin **50** in ethanol (Scheme 14, Table 11). Later on novel $Co(\pi)$, $Ni(\pi)$, and $Cu(\pi)$ complexes of the Schiff base **53–55** (Fig. 9) were synthesized by the reaction of an ethanolic solution of the ligand **52** with $CoCl_2 \cdot 6H_2O/NiCl_2 \cdot 6H_2O/CuCl_2 \cdot 2H_2O$ under reflux conditions in search of potent anti-tubercular molecules.⁵³

Synthesized metal complexes 53–55 along with ligand 52 were evaluated for their anti-tubercular activity against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA) technique while taking Streptomycin (STM) as the reference drug. The MIC results showed that the metal complexes had higher anti-tubercular activity than that of the free ligand (Table 11).

Reshma and co-workers synthesized some benzothiazole derivatives from a pre-existing lead to create a potent molecule against Mtb LAT, a critical enzyme for controlling the amino acid pool, which is essential for antibiotic resistance and persistence. It serves as potential target in management of latent tuberculosis. The initial step in the synthetic process involved the construction of the benzothiazole ring 57 by condensation of the 2-amino thiophenol **17a** with malononitrile **56** in the presence of catalytic amounts of acetic acid in ethanol.



Scheme 15 Synthesis of acrylonitrile derivatives of benzothiazole.

 Table 12
 Anti-mycobacterial activity of acrylonitrile derivatives of benzothiazole

Compounds	R	MIC (μ M)	LAT IC50 (μM)	Compounds	R	$MIC \left(\mu M \right)$	LAT IC50 (µM)
59a	€∕ОН	>89.93	10.38 ± 1.21	59m	NH You NH	>99.60	17.05 ± 1.21
59b	÷ F	89.29	4.11 ± 0.78	59n	NO ₂	>84.18	19.59 ± 0.32
59c	-€О−	20.29	$\textbf{7.83} \pm \textbf{0.31}$	590	NO ₂	>79.87	54.76 ± 0.21
59d	но он	10.61	23.19 ± 0.89	59p	Hz ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	>83.06	$\textbf{37.91} \pm \textbf{0.48}$
59e		>77.64	61.41 ± 1.56	59q	же основности соон	>67.20	3.74 ± 0.27
59f		>71.02	64.89 ± 2.31	59r	усторон соон	>67.20	14.06 ± 0.16
59g	<u>∔</u> ()-0_()	67.95	47.93 ± 1.82	59s	жо-соон соон	60.09	1.15 ± 0.27
59h		81.69	65.98 ± 0.63	59t	жсs-соон	64.43	5.73 ± 0.79
59i	÷ OH	4.64	3.08 ± 0.37	59u	ж s соон	2.01	6.72 ± 0.27
59j	OH Jrt	2.32	53.78 ± 0.96	59v	ж s соон	>57.60	2.62 ± 0.37
59k	Jun O	49.60	16.23 ± 0.26	INH	_	0.4	_
59l	J-S Mar	>93.28	92.57 ± 1.94	RIF	_	0.5	_



Scheme 16 Synthesis of 2-arylidene-benzylidene hydrazinyl benzothiazole derivatives.



Scheme 17 Synthesis of metal complex.

Synthesis of final products **59a–v** was achieved by Knoevenagel condensation reaction between 2-(benzo[d]thiazol-2-yl) acetonitrile **57** and aryl/heteroaryl aldehydes **58a–v** (Scheme 15, Table 12).⁵⁴

The MABA approach was used to screen all substances for their effectiveness against the replicative stage of Mtb. Compound **59u** was found to be most potent with a MIC value of 2.01 μ M. Compounds **59d**, **59i**, **59j** also demonstrated good activity with MIC values of 10.61, 4.64 and 2.32 μ M respectively (Table 12).⁵⁴ Molecular docking of these active compounds with LAT from Mtb revealed that, these molecules binds to the hydrophobic pocket having Leu414, Val63 and Phe167.

A. C. Pinheiro and co-workers synthesized 2-arylidenebenzylidene hydrazinyl benzothiazole derivatives **61a-i** from the reaction between 2-hydrazinobenzothiazole **51a**, and substituted benzaldehydes **60** in refluxing methanol from moderate to good yields and investigated their antimycobacterial activity (Schemes 16 and 17, Table 13).⁵⁵

 Table 13
 Anti-tubercular activity of 2-arylidene-benzylidene hydrazinyl benzothiazole derivatives and metal complex

Table	14	Anti-mycobacterial	activity	of	N-arylbenzothiazole-2-
carbar	nilide	25			

Compounds	R^{1}/X	MIC (μM)	
61a	Ph	>100	
61b	$2-ClC_6H_4$	>100	
61c	$2-NO_2C_6H_4$	10.5	
61d	$2-OHC_6H_4$	11.6	
61e	$4-OMeC_6H_4$	8.8	
61f	2-OH-4-OMeC ₆ H ₃	167	
61g	$2-OH-5-NO_2C_6H_3$	>100	
61h	Pyridin-2-yl	4.9	
62	2-OH-5-MeC ₆ H ₃	12.4	
EMB	_	15.3	
INH	_	0.46	

The most potent anti-mycobacterial compounds were **61c** (aryl = $2-O_2NC_6H_4$), **61d** (aryl = $2-HOC_6H_4$), **61e** and **61h** and all these compounds showed greater anti-mycobacterial activities as compared to standard drug Ethambutol. Based on the MIC values of the ligand and its complex, which ranged from 4.9 to 12.4 µM for the *M. tuberculosis* H₃₇Rv strain, complex **62** was found to be less active than that of ligand **61d**. The diminished potency of the complex can be explained by the fact that less of the active ligand is available for activity against *M. tuberculosis* ATTC 27294 due to strong complexation by Cu(n) (Table 13).

T. M. Dhamelia and co-workers synthesized benzo[d] thiazole-2-carbanilides **66a–d**, **67a–c**, **68a–e** (Scheme 18, Table 14) from CDI mediated direct reaction between benzo[d] thiazole-2-carboxylic acids **64a–c** and aromatic amines **1a–l** *via* three step synthetic pathway which involved green protocol for the synthesis of ethylbenzo[d]thiazole-2-carboxylates **63a–c**, which were the precursors of desired carboxylic acids **64a–c**.⁵⁶

The anti-tubercular efficacy of the synthesized compounds was assessed *in vitro* against *M. tuberculosis* H_{37} Rv (ATCC 27294 strain). With a therapeutic index of 64, the most potent molecules **66a–d**, **67a–c**, **68a–e** were found to have MICs of 0.78 µg mL⁻¹ (Table 14). Molecular docking of these active compounds suggested that, they bind to the catalytic site of enzyme ATP phosphoribosyl transferase and this binding might be responsible for their anti-tubercular activity.

Compounds	\mathbb{R}^1	\mathbb{R}^2	${\rm MIC} \atop \left(\mu g \ m L^{-1} \right)$
53a	-H	_	25
53b	-Cl	_	3.125
53c	-CF ₃	_	6.25
56a	-Н	3-Cl	0.78
56b	-H	4-CF ₃	0.78
56 c	-H	3-NO ₂	0.78
56d	-H	3,4,5-Tri-OMe	0.78
57a	-Cl	3-OMe	0.78
57 b	-Cl	4-Cl	0.76
57 c	-Cl	4-Morpholinyl	0.78
58a	-CF ₃	4-OMe	0.78
58b	$-CF_3$	4-Cl	0.78
58c	$-CF_3$	2-CF ₃	0.78
58d	$-CF_3$	$4-NO_2$	0.78
58e	$-CF_3$	3,4,5-Tri-OMe	0.78
NH	—	—	0.098
RIF	—	_	0.197
EMB	—	—	1.56





Matada and co-workers synthesized new dispersion azo dye ligand and its bioactive Cu(n), Co(n), Ni(n), and Fe(n) complexes **72a–d** (Fig. 10). Synthesis of azo dye ligand **71** was achieved *via*



Scheme 18 Synthesis of N-arylbenzothiazole-2-carbanilides.



Scheme 19 Synthesis of Azo dye ligand.

Table 15 Anti-tubercular activity of azo-dye ligand and metal complexes at variable concentrations^a

Ligands/complexes	$100 \ \mu g \ mL^{-1}$	$50~\mu g~mL^{-1}$	$25 \ \mu g \ m L^{-1}$	$12.5~\mu g~mL^{-1}$	$6.25~\mu g~mL^{-1}$	$3.12~\mu g~mL^{-1}$	$1.6~\mu g~mL^{-1}$	$0.8~\mu g~mL^{-1}$
71 L	S	S	S	S	S	R	R	R
$72a [Cu(L)_2]$	S	S	S	S	S	S	R	R
$72b [Co(L)_2]$	S	S	S	S	S	S	R	R
$72c [Fe(L)_2]$	S	S	S	S	S	S	S	R
$72d [Ni(L)_2(H_2O)_2]$	S	S	S	S	S	R	R	R
^{<i>a</i>} S: sensitive, R: resi	stance.							

diazo-coupling reaction between 5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine **69** and 2-thioxodihydropyrimidine-4,6(1H,5H)-dione **70** at 0-10 °C (Scheme 19, Table 15).⁵⁷

The Microplate Alamar Blue Assay (MABA) was used to investigate the anti-tubercular activity of the azo dye ligand (L) and its metal chelates against *M. tuberculosis* (H_{37} Rv strain,

ATCC 27294) (Table 15). The newly synthesized azo-dye showed tridentate behavior, and when it interacted with the different metal ions, it formed a six-membered chelate ring with octahedral geometry, apart from the Cu(II) complex, which had distorted octahedral geometrical environment (Fig. 10).

Bhat and co-workers synthesized 1-phenyl-2-(1-phenylethylidene) hydrazines $75a{\rm -}i$ from the reaction of



Scheme 20 Synthesis of pyrazole conjugated benzothiazole derivatives

 Table 16
 Anti-tubercular activity of pyrazole conjugated benzothiazole derivatives

Compounds	R	MIC ($\mu g \ mL^{-1}$)	Compounds	R	MIC ($\mu g \ mL^{-1}$)
78a	Н	12.5	79a	Н	25
78b	p-OCH ₃	6.25	79b	p-OCH ₃	25
78c	p-OH	6.25	79c	p-OH	25
78d	p-CH ₃	1.6	79d	p-CH ₃	25
78e	<i>p</i> -Cl	1.6	79e	p-Cl	100
78f	<i>p</i> -Br	6.25	79f	<i>p</i> -Br	50
78g	p-NO ₂	6.25	79g	$p-NO_2$	100
78h	m-NO ₂	50	79h	<i>m</i> -NO ₂	50
78i	$p-N(CH_3)_2$	25	79i	$p-N(CH_3)_2$	50
PYZ	_	3.125	CIP	_	3.125



Scheme 21 Synthesis of substituted benzothiazoles.

 Table 17
 Anti-tubercular activity of substituted benzothiazoles

Compounds	R^1	\mathbb{R}^2	R ³	MIC (µg H ₃₇ Rv Sj	mL ⁻¹) pec. 210
82 83 84 PZA INH RIF	Cl Cl CF ₃ —	H H — —	-(CH ₂) ₃ -Cy -(CH ₂) ₃ -Cy -(CH ₂) ₃ -Cy 	100 100 25 0.125 1.2	100 100 100 >400 12.5 2.5

phenyl hydrazines 74 and different acetophenones 73a–i. Then 75a-i reacted with POCl₃ under reflux conditions to give pyrazole-conjugated benzothiazoleanalogues 76a–i which further reacted with 2-hydrazinyl benzothiazole 51a and benzothiazole-2-carbohydrazide 77 to furnish the desired compounds 78a–i and 79a–i respectively (Scheme 20, Table 16).⁵⁸

In vitro screening was done for the anti-tubercular activity of the synthesized compounds **78a–i** and **79a–i** using Microplate Alamar Blue Assay (MABA) technique. Compared to benzothiazole carbohydrazide derivatives, which had MIC values of 100 to 25 μ g mL⁻¹, benzothiazole hydrazine compounds displayed

greater activity (MIC values 25 to 1.6 μ g mL⁻¹) (Table 16). Molecular docking of most active compounds 78d and 78e were in accordance with anti-tubercular activity with docking score of -7.68 and -8.12 kcal mol⁻¹ and these molecules were non-toxic in cytotoxicity assay.

Krause and co-workers synthesized some benzothiazole derivatives **82–84** (Scheme 21, Table 17) from the reaction of Methanesulfonic acid (MSA) and the appropriate carboxylic acid at 140 °C for 72 hours with 2-amino-4-chlorothiophenol or 2-amino-4-trifluoromethylthiophenol and the silica gels.⁵⁹

The synthesized compounds **82–84** were evaluated for their anti-tubercular activity against $H_{37}Rv$ strain of Mtb and a wild strain Spec. 210 extracted from tuberculosis patients. Rifampicin, Pyrazinamide and Isoniazid were used as standard reference drugs. All these benzothiazole analogues were found to possess moderate anti tubercular activity (Table 17).

J. Graham and co-workers identified numerous hits with moderate activity from the screening of available libraries against *M. tuberculosis* and developed numerous benzothiazo-leamide anti-tubercular agents **86a–j** after extensive medicinal chemistry optimization. Under amide coupling conditions, utilizing 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo [4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) in the presence of *N*,*N*-diisopropylethylamine (DIEA) in



Scheme 22 Synthesis of benzothiazole amide derivatives.

Table 18	Structure activity	relationship of	cyclohexane	derivatives	towards M.	tuberculosis	$H_{37}Rv$
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Compounds	R^1	R ²	$MIC \left(\mu g \ mL^{-1}\right)$	Compounds	R^1	R^2	$MIC \left(\mu g \ mL^{-1}\right)$
86a	5-CF ₃	t t	≤0.12	86f	5,7-Di-F		0.25
86b	5,7-Di-Me	1	0.25	86g	OCF ₃	y pr	0.5
86c	5,7-Di-F		0.25	86h	5-Br	5-5-5- 	≤0.12
86d	CF ₃		2	86i	5,7-Di-Cl	4	≤0.12
86e	CF ₃	\$	4	86j	4,5,6-Tri-F		≤0.12

dichloroethane (DCE), the synthesis began with substituted 2amino-benzothiazole **3** intermediates and variously substituted cycloalkyl carboxylic acids **85a-j** (Scheme 22, Table 18).⁶⁰

Anti-tubercular activity of the synthesized compounds **86a-j** was evaluated by introducing differently substituted cyclohexane and bycyclo derivatives to the benzothiazole moiety. In order to predict the structure activity relationship with respect to cyclohexane derivatives, their MIC values were compared (Table 18). The preliminary mechanism of action studies revealed that these molecules targeting MmpL3, a mycobacterial mycolic acid transporter. These compounds were having better *in vivo* efficacy. Deng and co-workers reported the novel selective triplecleavage of bromodifluoroacetamides **87** by S_8 for the first time. Using a cascade protocol, they synthesized 2-amido substituted benzothiazoles **88–89** in good to outstanding yields. In the absence of ligands, exogenous oxidants, or transition metal catalysts, this transformation simultaneously broke the three halogen–carbon bonds of the halogenated difluoro compounds **87** with a broad substrate range, to assemble the desired N-containing heterocycles **88–89** in good to exceptional yields (Scheme 23). Activity against *M. tuberculosis* was observed in some of the synthesized compounds.⁶¹



Scheme 23 Synthesis of amido substituted benzothiazole analogues.



Scheme 24 Synthesis of oxazolone linked benzothiazole analogues.

Table 19 Anti-mycobacterial activity of oxazolone linked benzothiazole analogues (30 μ g mL⁻¹)^a

Compounds	Ar	Yields (%)	Inhibition (%)	Compounds	Ar	Yields (%)	Inhibition (%)
92a 92b 92c 92d	4-OH (C_6H_4) 4-OCH ₃ (C_6H_4) 3-OCH ₃ , 4-OH (C_6H_3) 4-CH (C, H_1)	96 88 89 86	99.4 96.5 80	92e 92f 92g BIF	3,4-OCH ₂ O-(C ₆ H ₃) 4-N(CH ₃) ₂ C ₆ H ₄ 3-Indole	89 88 85	26.1 49.1 16.1

a % inhibition = (activity of mycobacteria without compounds – activity of mycobacteria in presence of compounds)/(activity of mycobacteria without compounds – blank) × 100.



Scheme 25 Synthesis of acetamide derivatives of benzothiazole.

Table 20 Anti-tubercular activity of acetamide derivatives of benzothiazole a

Compounds	\mathbb{R}^1	\mathbb{R}^2	MIC (µM) H ₃₇ Rv	IC_{50} (μ M) DprE ₁
96a	Me	Me	2.41	NT
96b	OMe	OMe	3.74	NT
96c	F	Н	3.23	NT
96d	SMe	Н	2.48	NT
96e	OMe	Н	2.81	NT
96f	Н	OH	2.10	NT
96g	Н	OMe	1.01	14.1 ± 1.7
96h	OH	OMe	2.06	NT
96i	Cl	Н	0.91	12.7 ± 0.9
96j	Н	NO_2	3.35	NT
96k	Н	Н	0.82	14.8 ± 2.4
96l	COMe	Н	2.79	NT
96m	F	F	3.04	NT
96n	NH_2	Н	2.16	NT
960	Н	Br	1.04	11.2 ± 1.5
INH	_	_	0.31	—

^{*a*} NT: not tested.

A. P. Chavan and co-workers synthesized a new series of 4-(substituted benzylidene)-3-((benzo[d]thiazol-2-ylthio)methyl) isoxazol-5(4H)-one 92a–g by the reaction of mercapto benzothiazole 44 with 4-[(4-methoxyphenyl)-methylidene-]-3-chloromethyl-5(4H)-isoxazolone 91a–g, prepared from 90, in the presence of NaHCO₃ in ethanol in good yields (Scheme 24, Table 19).⁶²

The anti-tubercular activity of synthesized compounds **92a–g** was carried out against *M. tuberculosis* H_{37} Ra (ATCC 25177) using XTT reduction menadione assay (XRMA). Among the synthesized derivatives compound **92b** was found to be most potent against *M. tuberculosis* and all compounds from **92a–g** were found to be non-cytotoxic (Table 19).

Gawad and co-workers created a pharmacophore model by utilizing a ligand-based drug discovery method with a single ligand (Scheme 25, Table 20). The essential elements causing DprE1 inhibitory action were considered while creating the pharmacophore. The first step in the synthesis of 6-nitrobenzo[*d*] thiazol-2-amine **3** [27] involved simmering 4-nitroaniline **1a**, potassium thiocyanate, and dropwise addition of bromine while



Scheme 26 Synthesis of triazolo-pyrazinyl linked benzothiazole analogues.

 Table 21
 Anti-tubercular activities of triazolo-pyrazinyl linked benzothiazole analogues



using acetic acid as a diluent. A suitable aryl benzaldehyde and 6 nitrobenzo[*d*]thiazol-2-amine **3** were condensed in ethanol with a catalytic quantity of glacial acetic acid to create *N*-benzylidene-6nitrobenzo[*d*]thiazol-2-amine **93**. Finally 2-(6-nitrobenzo[*d*]thiazol-2-ylthio)-*N*-benzyl-*N*-(6-nitrobenzo[*d*]thiazol-2-yl)acetamide derivatives **96a–o** were formed after a series of reduction, acetylation and nucleophilic substitution (SN²) reaction.⁶³

Using Isoniazid as a standard reference, anti-mycobacterial activity of the synthesized compounds was tested against *M. tuberculosis* H_{37} Rv (ATCC 27294). Compounds **96g**, **96i**, **96k** and **96o** were found to have MIC values in between 0.82–1.04 μ M, which was reported to be somewhat closer to the MIC of the standard reference Isoniazid, which is 0.31 μ M. From this, authors concluded that by altering aliphatic and aromatic carbon centres more powerful DprE1 inhibitors can be synthesized (Table 20). Molecular docking of the synthesized compounds was done against BTZ043 to evaluate their DprE1

inhibition ability. Docking results suggested that di-halogen substituted compound was found to exhibit strong enzyme inhibition.

D. J. Jethava and co-workers synthesized *N*-(benzo[*d*]thiazol-2-yl)-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo [4,3-*a*] pyrazin-7 (8*H*)-yl) acetamide derivatives **98a–e** after acetylation of benzothiazole **3a–e** in presence of base NEt₃ followed by nucleophilic substitution from triazolo-triazine **97** in presence of potassium carbonate in DMF solvent (Scheme 26, Table 21).⁶⁴

Using the well-known Lowenstein–Jensen (L–J) technique, all novel compounds were tested against the *M. tuberculosis* H_{37} Rv strain with Isoniazid as a positive control. A common MIC value of 500 mg mL⁻¹ for the intended pathogenic strain of *M. tuberculosis* H_{37} Rv was observed for compounds **98a**, **98d** and **98e** (Fig. 11, Table 21).

Hazra and co-workers synthesized N-((1-(7-chloro-6-fluoro-5nitrobenzo[d] thiazol-2-yl) phenyl-1H-pyrazol-4-yl)methylene)-3substituted isonicotino hydrazide **102a–c** and N-((1-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)ethylene) isonicotinohydrazide **106a–c** for improved anti-tubercular efficacy. Initial step involved the reaction of 7-chloro-6-fluoro-5nitro-2-hydrazinylbenzo[d]thiazole **99** and 7-chloro-6-fluoro-4nitro-2-hydrazinylbenzo[d]thiazole **103** with substituted acetophenones in presence of glacial acetic acid to produce **100a–c** and **104a–c** respectively. Compounds **102a–c** and **106a–c** underwent Vilsmeyer–Haack reaction in presence of POCl₃ in DMF to produce **101a–c** and **105a–c** respectively. The later **101a– c** and **105a–c** after being treated with isoniazid in presence of glacial acetic acid furnished the desired compounds **102a–c** and **106a–c** respectively (Schemes 27 and 28, Table 22).⁶⁵

The compounds **102a–c** and **106a–c** were found to be effective anti-tubercular agents (MIC = 40.19 to 64.96 nM) through *in vitro* anti-mycobacterial activity against *M. tuberculosis* H_{37} Rv (ATCC 27294). All the substances examined had low cytotoxicity when evaluated on the THP-1 cell line. Even though this concentration is much higher than the concentration evaluated for the anti-tubercular action, the presence of a nitro group in the compound is demonstrated to increase the toxicity (Table 22).

Sahoo and co-workers synthesized a variety of new analogues of 5-(pyridine-4-yl)-1,3,4-oxadiazole-2(3H)-thione **109a-j** (Scheme 29, Table 23) by combining 1,3,4-oxadiazole **108a** and benzo[*d*]thiazole *via* Mannich reaction under conventional heating and improved microwave irradiations.⁶⁶

All the synthesized compounds were evaluated *in vitro* for their anti-tubercular activity against $H_{37}Ra$ strain of *M*.



Fig. 11 Mechanistic pathway showing synthesis of compound 98a.



Scheme 27 Synthesis of new series of *N*-((1-(7-chloro-6-fluoro-5-nitrobenzo[*a*]thiazol-2-yl)phenyl-1*H*-pyrazol-4-yl)methylene)-3-substituted isonicotinohydrazide.

tuberculosis. Compound **109c**, with a methyl group at the *ortho* position of an aromatic ring, displayed higher anti-tubercular activity. Change in the activity was also observed with the addition of various electron-releasing and electron-withdrawing substituents to the benzo[d]thiazole ring (Table 23). All the

synthesized compounds were found to be non-cytotoxic (<50% inhibition at 50 μ g mL⁻¹) to HEK 293T cell lines with therapeutic index ranging from 8–64.

P. T. Acharya and co-workers synthesized a series of *N*-(1, 3-benzothiazole-2-yl)-2(pyridine-3-yl) formohydrazido acetamide



Scheme 28 Synthesis of new series of *N*-((1-(7-chloro-6-fluoro-4-nitrobenzo[*d*]thiazol-2-yl)phenyl-1*H*-pyrazol-4-yl)methylene)-3-substituted isonicotinohydrazide.

 Table 22
 Anti-tubercular activity of 5-nitro and 4-nitro substituted isonicotino-hydrazide analogues of benzothiazole

Compounds	R	MIC (nM)		
102a	Н	95.80		
102b	2,4 di Cl	42.31		
102c	4-F	46.30		
106a	Н	47.90		
106b	2,4 di Cl	42.31		
106c	4-F	46.30		
PYZ	_	60.095		
STM	_	14.387		

derivatives **113a–i** by using a simple and effective conventional technique (Scheme 30, Table 24). Initial step involved the synthesis of *N*-(1,3 benzothiazole-2-yl)-2chloroacetamide **111a–i** from the acetylation of 2-amino benzothiazole derivatives **110a–i** in presence of TEA in chloroform. Next step involved the reaction of nicotinohydrazide **112** with **111a–i** in presence of base K_2CO_3 under reflux conditions to produce the desired compounds **113a–i**.⁶⁷

All synthesized compounds **113a–i** were tested *in vitro* for their anti-tuberculosis activity against the $H_{37}Rv$ strain of *M. tuberculosis* using Lowenstein–Jensen media (conventional method). Compound **113a** displayed promising activity against $H_{37}Rv$ strains with mean IC₅₀ of 50 mg mL⁻¹. Compounds **113g–h** showed potent anti-tubercular action with mean IC₅₀ of 62.5 mg mL⁻¹ (Table 24). All the synthesized compounds were found to exhibit good pharmacokinetics properties (ADME) with good oral absorption percentage in the tolerable range of 65–100%. Docking of the synthesized compound **113a** was found to exhibit good binding affinity of -8.423 kcal mol⁻¹ to the active site of 1ENY with reference to the standard drug Isoniazid (-6.33 kcal mol⁻¹). Here PDB 1ENY was chosen in order to target enoyl-acyl-carrier protein reductase.

B. N. Ravi and co-workers described the synthesis of bioactive Ni(π) complexes **116a–c** from azo dye ligands **115a–c**. Azo dyes were formed from the diazo-coupling of 6-nitro-1,3benzothiazole **3e** with substituted pyridinone derivatives **114a–c** in presence of NaNO₂ in HCl at low temperature range (Scheme 31, Table 25). These Ni(π) complexes possess a structure of [Ni(L)₂(H₂O)₂] with a metal–ligand ratio of 1:2 (Fig. 12)



Scheme 29 Synthesis of 3-((substituted-benzo[d]thiazol-2-ylamino)methyl)-5-(pyridine-4-yl)-1,3,4-oxadiazole-2(3H)-thione.

Table 23	Anti-tubercular	activity	of	3-((substituted-benzo[a]thiazol-2-ylamino)methyl)-5-(pyridine-4-yl)-1,3,4-oxadiazole-2(3H)-thione
analogues				

Compounds	R^1	R^2	Conventional method yields (%)	Microwave irradiation yields (%)	MIC (µM)
108a	_	_	90	_	>100
109a	н	Н	63	85	>50
109b	Н	CH_3	66	82	>100
109c	CH_3	Н	59	80	>50
109d	Н	NO_2	58	75	>50
109e	NO_2	Н	55	78	>100
109f	н	F	63	80	>100
109g	F	Н	60	75	>100
109h	Н	Br	58	78	>100
109i	Н	Cl	54	75	>100
109j	Н	OCH ₃	60	80	>100
INH	_	_		_	0.25
RIF	_	_		_	40



Scheme 30 Synthesis of acetamide derivatives of benzothiazole.

 Table
 24
 Anti-tubercular
 activity
 of
 acetamide
 derivatives
 of

 benzothiazole

Compounds	R	Х	$MIC (mg mL^{-1})$
			- 0
113a	Н	Н	50
113b	OCH_3	Н	250
113c	OC_2H_5	Н	100
113 d	OH	Н	250
113e	Cl	Н	500
113f	F	Н	250
113g	Н	Ν	62.5
113h	OCH_3	Ν	62.5
113i	OC_2H_5	Ν	100
INH	—	—	0.20

where L is the deprotonated azo dye ligand which show bidentate behavior. 68

By using the Microplate Alamar Blue Assay (MABA), the antitubercular activity of the azo dye ligands and their Ni(n) complexes was assessed against *M. tuberculosis* (H_{37} Rv strain, ATCC 27294). Some Ni(II) complexes of azo dyes showed good inhibitory activity with MIC value of 1.60 µg mL⁻¹. Additionally, all other substances showed good to moderate activity, with MIC values in between 6.25–3.12 µg mL⁻¹. The increased lipophilicity of the metal ion caused by the overlapping of the ligand's orbitals and partial sharing of the metal ion's positive charge with the donor atoms was responsible for the greater activity metal chelates than the ligand (Table 25).

Velappan and co-workers synthesized 2-aryl benzothiazole based dual targeted compounds **118a–d**, **120a**, **123a–d** through the reaction of 2-amino thio phenol **1** with various heterocyclic derivatives (Scheme 32, Table 26).⁶⁹

Their anti-tubercular activity was checked by using MABA for replicating form of Mtb and Low Oxygen Recovery Assay (LORA) for non-replicating form of Mtb. Compound **118a** ($R=C_8H_{17}$) showed MIC value of 30.12 µg mL⁻¹ against replicating Mtb. Contrarily, compound **118b** ($R=C_9H_{19}$) was discovered to be the most effective against the non-replicating Mtb. The MIC values



Scheme 31 Synthesis of azo-dye ligands.

Table 25 Anti-mycobacterial activity of the synthesized azo-dyes and their Ni(II) complexes^a

Compounds	$100 \ \mu g \ m L^{-1}$	$50~\mu g~mL^{-1}$	$25~\mu g~mL^{-1}$	$12.5~\mu g~mL^{-1}$	$6.25~\mu g~mL^{-1}$	$3.12~\mu g~mL^{-1}$	$1.60~\mu g~mL^{-1}$	$0.80~\mu g~mL^{-1}$
115a	S	S	S	S	S	S	S	R
115b	S	S	S	S	S	S	S	R
115c	S	S	S	S	S	R	R	R
116a	S	S	S	S	S	S	S	R
116b	S	S	S	S	S	R	R	R
116c	S	S	S	S	S	S	S	R
STM	S	S	S	S	S	R	R	R
CIP	S	S	S	S	S	S	R	R
PYZ	S	S	S	S	S	S	R	R

^a S: sensitive, R: resistance.



Fig. 12 Structure for Ni(II) complexes of azo dyes.

were determined in between 56–32 μ g mL⁻¹ against replicating Mtb and 40–28 μ g mL⁻¹ against non-replicating Mtb for molecules having geranyl **118c** and farnesyl **118d** chains. On the other hand, they discovered that the activity of the *meta*-isomers

against replicating Mtb reduced as the length of the alkyl chain increased, with the best activity being observed for **120a** with a methyl chain. The alkenyl chain once more exhibited better anti-tubercular action ($<50 \ \mu g \ mL^{-1}$). **123a-c** did not show any significant difference in activity against replicating and non-replicating Mtb. It was concluded that their effectiveness against replicating and non-replicating forms of Mtb is significantly influenced by their isomers (*meta* or *para*) and the presence of heteroatom's in the aromatic ring (Table 26).

Maliyappa and co-workers created four heterocyclic azo dyes **125a–d** using the standard diazo-coupling process between aniline derivatives and 5-methyl-2-(6-methyl-1,3-benzothiazol-2yl)-2,4-dihydro-3*H* pyrazol-3-one **124** at lower temperature. Initial step involved the diazotization of substituted anilines in presence of NaNO₂/H₂SO₄. Diazotized product on further coupling with benzothiazole derivatives in presence of base KOH at low temperature furnished the desired compounds **125a–d** (Scheme 33, Table 27).⁷⁰



Scheme 32 Synthesis of 2-aryl substituted benzothiazole analogues.

 Table 26
 Anti-tubercular activity of 2-aryl substituted benzothiazole analogues^a

	$\frac{\text{MIC} (\mu \text{g mL}^{-1}) \text{ against } \text{H}_{37}\text{Rv}}{}$				
Compounds	MABA	LORA			
118a	30.12	47.31			
118b	39.52	40.63			
118c	56.13	40.09			
118d	31.49	27.81			
120a	29.51	70.42			
123a	>100	NT			
123b	>100	NT			
123c	>100	NT			
123d	52.37	43.11			
INH	0.40	>100			
RIF	0.01	0.04			

The synthesized compounds were screened for their antimycobacterial activity against Mtb by using MABA method. From the synthesized compounds **125a–b** showed better activity than **125c–d** (Table 27).

Abozeid and co-workers synthesized benzothiazole based naphthyl ketone **129** scaffold by refluxing formylchromone **126** and cyanoacetanilide **127** in ethanol in the presence of triethyl amine as catalyst (Scheme 34).⁷¹

The synthesized compound was tested *in vitro* against Mtb using Isoniazid as positive control. Compound **129** was found to exhibit anti-tubercular activity against Mtb with a MIC value of 1.95 μ g mL⁻¹. Molecular docking of this active compound **129** against InhA enzyme showed better binding affinity of -9.3 kcal mol⁻¹.

J. K. Suyambulingam and co-workers synthesized two Schiff bases, 2-[6-methylbenzothiazol-2-ylimino] methyl phenol **131a** and 3-bromo-2-[6-methylbenzothiazol-2-ylimino] methyl phenol **131b** utilizing a straightforward condensation reaction between amino benzothiazole derivative **3c** and salicylaldehyde/ bromosalicylaldehyde **130a-b** (Scheme 35, Table 28).⁷²

Anti-tubercular activity of the synthesized compounds was evaluated against H_{37} Rv strain of *M. tuberculosis*. Compound **131a** showed moderate activity while compound **131b** was

Table 27 Anti-mycobacterial activity of the synthesized azo dye ligands $^{\alpha}$

Compounds	$12.5~\mu g~mL^{-1}$	$6.25~\mu g~mL^{-1}$	$3.12~\mu g~mL^{-1}$	$1.6 \ \mu g \ mL^{-1}$
125a	S	S	S	S
125b	S	S	S	S
125c	S	S	R	R
125d	S	S	R	R
PZA	S	S	S	R
^{<i>a</i>} S: sensitive	, R: resistant.			

found to exhibit better activity with a MIC value of 1.6 μ g mL⁻¹ which was lesser than standard drugs like Pyrazinamide, Streptomycin and Ciprofloxacin which have MIC values 3.125 μ g mL⁻¹, 6.25 μ g mL⁻¹, 3.125 μ g mL⁻¹ respectively (Table 28).

In order to find the inhibition potency of benzothiazole based Schiff bases the molecular docking of compound **131b** was performed against 4P8N protein of *M. tuberculosis* DprE1. It was observed from the docking results that compound **131b** interacts better with active site of 4P8N protein with a binding affinity of -9.2 kcal mol⁻¹. The interactions involved were different types of pi-pi and hydrogen bond interactions (Fig. 13 and 14). The increase in protein–ligand interaction surface results in strong van der Waal's interactions and hence greater binding affinity.

Nagaraja and co-workers synthesized 4-hydroxy coumarin containing benzothiazole based azo dye **132**. Initial step involved the diazotization of 2-amino substituted benzothiazoles in presence of NaNO₂/H₂SO₄. Final step involved diazocoupling of 4-hydroxy coumarin **20** and diazotized benzothiazole analogue to furnish the desired compound **132** (Scheme 36).⁷³

By using the MABA method, the compound **132** was tested for its anti-tubercular activity against *M. tuberculosis*. The outcome was compared to standard medications Pyrazinamide, Ciprofloxacin, and Streptomycin. Synthesized compound was found to be sensitive at a concentration range of 100–1.6 μ g mL⁻¹ and resistant at 0.8 μ g mL⁻¹.

M. Bhat and co-workers synthesized a series of azo-ester derivatives of benzothiazole 134a-k via Steglich esterification



Scheme 33 Synthesis of azo dye ligands.



Scheme 34 Synthesis of benzothiazole based naphthyl ketone.



Scheme 35 Synthesis of benzothiazole based Schiff bases.

reaction by using dicyclohexylcarbodiimide (DCC) as a coupling reagent and 4-(dimethylamino)pyridine (DMAP) as nucleophile. Initial step involved the formation of diazotized product **133a-k** from the diazotization of 2-amino substituted benzothiazoles **3a-k**. Compound **133a-k** on further coupling with phenol in presence of base NaOH gave the azo-dye complex **134a-k**. This complex on further reaction with suspension of substituted carboxylic acid in presence of DCC and DMAP furnished the desired compounds **134a-k** (Scheme 37, Table 29).⁷⁴

By using the Microplate Alamar blue assay technique for *M. tuberculosis*, the produced compounds were tested for antitubercular activity. Among the synthesized compounds **134d** and **134j** showed better anti-tubercular activity with a MIC value of 1.6 μ g mL⁻¹ which was less than that of standard drugs like Streptomycin (MIC 6.25 μ g mL⁻¹) and Pyrazinamide (MIC 3.125 μ g mL⁻¹). Rest of the synthesized compounds displayed moderate activity (Table 29).

In order to predict the interaction of ligand 134j with *M. tuberculosis* DprE1 we performed docking against 4P8N protein. Along with different types of interactions with the protein chain compound 134j was found to exhibit best docking results with a binding affinity of -10.3 kcal mol⁻¹ towards 4P8N (Fig. 15 and 16).

Chen and co-workers synthesized the benzothiazole based sulfonamide compounds **137a–d** by treating different aryl amines **136a–d** with 4-acetamido benzene sulfonyl chloride **135** followed by base catalyzed hydrolysis of the acetyl group (Scheme 38, Table 30).⁷⁵

After screening of the synthesized compounds against *M. tuberculosis* H_{37} Rv the selected compounds were tested against an isolated clinical strain of XDR-TB. Isoniazid (INH) and sulfaphenazole (SPA) were used as reference standards for anti-



Fig. 13 $\,$ 3D representation of ligand 131b and its interactions with active site of 4P8N protein.



Fig. 14 2D representation of docking results showing interactions of compound 131b with 4P8N.

able 28 Anti-tubercular activity of Schiff bases ^a								
Compounds	$100 \ \mu g$ mL ⁻¹	$50~\mu g$ mL ⁻¹	25 μg mL ⁻¹	$\begin{array}{c} 12.5 \ \mu g \\ m L^{-1} \end{array}$	$6.25~\mu g$ mL $^{-1}$	$\begin{array}{c} 3.12 \ \mu g \\ mL^{-1} \end{array}$	$1.6~\mu m g$ mL $^{-1}$	$0.8~\mu g$ mL $^{-1}$
131a 131b	S S	S S	S S	S S	S S	R S	R S	R R

^a S: sensitive, R: resistant.

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Scheme 36 Synthesis of coumarin based azo dye

tubercular evaluation of the synthesized compounds. Among the synthesized compounds compound **137a** displayed modest activity (MIC = 14.26 μ g mL⁻¹). Altering the position and introduction of phenyl group to benzothiazole moiety leads to decrease in anti-tubercular activity of the compounds **137b** and **137d** compounds (Table 30).

S. V. Mamatha and co-workers synthesized the target compounds **142a–d**, **143a–d**, **144a–d**, **145a–d** *via* several steps. Initial step involved the reaction of aniline derivatives **138a–d** with bromine in acetic acid in presence of potassium thiocyanate to give 2-amino substituted benzothiazoles **139a–d**. The later on reaction with hydrazine hydrate produced hydrazine benzothiazoles **140a–d**. Compounds **140a–d** underwent cyclization with carbon disulfide in presence of NaOH to produce triazol-2-thiol derivatives **141a–d** which ultimately furnished the



Fig. 15 3D representation of ligand 134j and its interactions with active site of 4P8N protein.

desired compounds **142a–d**, **143a–d**, **144a–d**, **145a–d** after being alkylated with several heterocyclic compounds (Scheme 39, Table 31).⁷⁶

Microplate Alamar Blue Assay (MABA) was used to test the anti-mycobacterial activity of synthesized compounds **142a–d**, **143a–d**, **144a–d** and **145a–d** against *M. tuberculosis* and MIC values are summarized in Table 31. The best action was demonstrated by the benzothiazolyltriazoles with piperidine



Scheme 37 Synthesis of benzothiazole azo-ester derivatives.

Table 29	Anti-tubercular	activity of	benzothiazole	azo-ester	derivatives

Compounds	\mathbb{R}^1	R ²	Yields (%)	$MIC \left(\mu g \ mL^{-1}\right)$	Compounds	\mathbb{R}^1	R ²	Yields (%)	MIC ($\mu g \ mL^{-1}$)
134a	OEt		55	2.5 ± 0.24	134h	OEt	OCH3	83	25 ± 0.25
134b	OEt	N	92	6.25 ± 0.18	134i	Н		81	12.5 ± 0.13
134c	OEt		78	25 ± 0.39	134j	Н	F	86	1.6 ± 0.08
134d	OEt	F	80	1.6 ± 0.15	134k	Н		67	25 ± 0.24
134e	OEt	F-	71	25 ± 0.43	STM	_	_	_	6.25 ± 0.16
134f	OEt	F3CO	92	50 ± 0.40	CIP	_	_	_	3.125 ± 0.22
134g	OEt		88	50 ± 0.37	PZA	_	_	_	3.125 ± 0.35



Fig. 16 2D representation of docking results showing interaction of compound 134j with 4P8N protein.



Scheme 38 Synthesis of benzothiazole based sulfonamide compounds.

 Table 30
 Anti-tubercular activity of benzothiazole based sulfonamides against XDR-TB

Compounds	R	$MIC (\mu g \ mL^{-1})$
137a	S →	14.26
137b	S I I	>32
137c	C S S S S S S S S S S S S S S S S S S S	>32
137d	, , , , , , , , , , , , , , , , , , ,	>32
SPA	N N	5.51

(142b–d), pyrrolidine (144a–c) and pyrimidine (145b and 145d) moieties with MIC values ranging from 3.12 to 1.6 μ g mL⁻¹. A unique and promising hit molecule that shown good anti-TB properties as well as good docking score was compound 144b which possess benzothiazolyltriazole with a pyrrolidine moiety (Table 31). Molecular docking studies of these compounds against inhA of *M. tuberculosis* suggested that compound 144b is superior compound with a binding affinity of -8.654 kJ mol⁻¹ as compared to the standard dug Isoniazid (-6.617 kJ mol⁻¹).

B. Manjunatha and co-workers described the synthesis of various azo dyes **147a–e** based on coumarin and benzothiazole in this study. Synthetic process involved the diazotization of 2-amino benzothiazole derivatives **146a–e** in presence of NaNO₂/

HCl. Diazotized solution was then added to 4-hydroxycoumarin **20** in order to obtain azo dyes **147a–e** while maintaining the pH of the reaction mixture (Scheme 40, Table 32).⁷⁷

In vitro screening of the synthesized compounds was done against $H_{37}Rv$ strain of *M. tuberculosis* using MABA technique. Using Streptomycin as a reference point, the study's findings were interpreted in terms of minimum inhibitory concentration (MIC). The results of the anti-TB activity tests showed that compounds **147a–c** and **147e** had outstanding and comparable sensitivity (MIC = 1.6 µg mL⁻¹). However, among the synthesized dyes, compound **147d** with an ethoxy substitution at the benzothiazole's 6th position exhibited lower sensitivity (MIC = 3.2 µg mL⁻¹) (Table 32).

Ethambutol, an anti-TB medicine, is known to target the arabinosyl transferases EmbA, EmbB, and EmbC, which are known to be involved in the manufacturing of the cell walls in *M. tuberculosis*. The donor and acceptor interactions as observed from docking predicts the mechanism of inhibition of arabinosyl transferases. Herein we observed the better interaction of ligand **147e** to the active site of 7BVF protein (cryo-EM structure of *M. tuberculosis* in complex with Ethambutol) with a binding affinity of -9.4 kcal mol⁻¹ (Fig. 17 and 18). These findings certainly will help in predicting the biochemical function and development of new anti-tubercular agents.

Satyadev and co-workers synthesized benzothiazole-linkedchalcones **151a–n** from the reaction of 1-(2-aminobenzo[*d*] thiazol-5-yl)ethan-1-one **149** with aldehydes **150a–n** in ethanol with pyridine as catalyst (Schemes 41 and 42, Table 33).⁷⁸ The intermediate **149** in turn was synthesized from the reaction of 3aminoacetophenone **148** with Br_2 and potassium thiocyanate in glacial acetic acid.

In vitro screening of the synthesized compounds showed that **149**, **151j** and **151l** were found to be most potent anti-tubercular compounds with a MIC value of 6.25 μ g mL⁻¹. Moreover, compounds **151d** and **151e** had notable inhibitory action with values of 12.5 and 12.5 μ g mL⁻¹ respectively. Rest other compounds showed moderate to less activity (Table 33).

Van Der Westhuyzen and co-workers discovered a powerful benzoheterocyclic oxime carbamate hit series **154–165** (Schemes 43 and 44, Tables 34 and 35) through the screening of a library of small polar compounds against *M. tuberculosis.*⁷⁹ The reaction between 2-(benzo[*d*]thiazol-2-yl)acetonitrile **152** and sodium nitrite produced oxime **153**. This oxime-based compound on further reaction with dimethyl carbamoyl chloride, mesyl chloride and alkyl chlorides in presence of base under reflux conditions produced the desired compounds **154**, **155–156** and **157–165** respectively.

Biological activity results of these compounds **154–165** predicted that due to inability to penetrate the Mtb cell wall the free oxime **153** was very poor active whereas its carbamate derivative **154** shown great potency with MIC value lower than 0.16 μ M. Whereas sulfamoyl masked derivatives **155** and **156** possess good anti-tubercular activity with MIC value of 0.30 μ M and 5.0 μ M respectively. When the oxime moiety was masked with alkyl ethers the anti-tubercular activity was decreased this may be due to these alkyl ethers groups are not falling inside the cell (intracellular) and releasing free oxime. These results indicated

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Scheme 39 Schematic pathway for the synthesis of triazole conjugated benzothiazole derivatives.

Table 31	Anti-tubercular	activity of	triazole	conjugated	benzothiazole	derivatives
				, ,		

Compounds	$MIC \left(\mu g \ mL^{-1}\right)$	Docking score (kJ mol ⁻¹)	Compounds	$MIC \left(\mu g \; mL^{-1} \right)$	Docking score (kJ mol ⁻¹)
142a	25	-5 999	144c	16	-5 568
142b	1.6	-7.443	144d	12.5	-5.698
142c	1.6	-5.986	145a	50	-6.186
142d	1.6	-7.865	145b	1.6	-6.176
143a	50	-5.036	145c	50	-6.392
143b	50	-4.864	145d	1.6	-6.338
143c	50	-4.034	INH	0.40	-6.617
143d	6.25	-5.833	PZA	3.125	_
144a	1.6	-6.424	CIP	3.125	_
144b	3.12	-8.643	STM	6.25	_

that the active anti-tubercular species is benzothiazole oxime 153. This study further suggested that there is need to work on these benzothiazole oxime derivatives 154–165 to optimize this chemical series and/or develop formulation strategies to improve permeation across the Mtb cell-wall (Tables 34 and 35).⁷⁹

A commercially available aldehyde **165** or ketone **167** reacted with hydroxylamine under basic conditions to create free oximes **166**, **168** with the nitrile group in **153** replaced by H and



Scheme 40 Schematic pathway for the synthesis of coumarin azo dyes.

 Table 32
 Anti-tubercular activity of synthesized coumarin dyes^a

Compounds	R	$100 \ \mu g \ m L^{-1}$	$50~\mu g~mL^{-1}$	$25 \ \mu g \ m L^{-1}$	$12.5 \ \mu g \ m L^{-1}$	$6.25~\mu g~mL^{-1}$	$3.12~\mu g~mL^{-1}$	$1.6 \ \mu g \ m L^{-1}$	$0.8~\mu g~mL^{-1}$
147a	н	S	S	S	S	S	S	S	R
147b	6-Cl	S	S	S	S	S	S	S	R
147c	$6-NO_2$	S	S	S	S	S	S	S	R
147d	6-OEt	S	S	S	S	S	R	R	R
147e	$4-CH_3$	S	S	S	S	S	S	S	R



Fig. 17 Surface representation of docking between ligand 147e and 7BVF protein.



Fig. 18 2D view showing interaction between ligand 147e and various amino acids of 7BVF protein.

Me respectively. A CF_3 substituted oxime **170** was prepared from hydrated compound **169** using hydroxyl amine under reflux condition. A reaction of 2-benzothiazoleacetonitrile **152** and hydroxylamine, followed by cyclization with acetic anhydride, was used to create 1, 2, 4-oxadiazole **171** which further get



Scheme 41 Synthesis of 1-(2-aminobenzo[*d*]thiazol-5-yl) ethan-1-one.

converted to respective oxime **172**. Ester **173** and hydrazine were combined to create intermediate **174**. After being acylated, the hydrazide was subsequently reacted with POCl₃ and Lawesson's reagent to produce oxadiazole and thiadiazoles **179–181** (Scheme 44, Table 35).⁷⁹

M. J. Zala and co-workers synthesized some novel pyrazolylpyrazoline derivatives **187a–d** from green method of synthesis. The Vilsmeier–Hack reaction was used to create the starting material, 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4carbaldehyde **182**. Further reaction of **182** with substituted thiophenols **183** and **184** in presence of K₂CO₃ and DMF produced substituted aromatic aldehydes **185a–b** as key intermediates. Substituted aldehydes **185a–b** underwent multicomponent one pot reaction with 2-acetyl pyrrole or 2-acetyl-1,3thiazole **186a–b** in presence of sodium hydroxide in ethanol at room temperature under sonification to furnish desired pyrazolylpyrazoline derivatives **187a–d** after getting cyclized with 1,3-benzothiazol-2-ylhydrazine **51a** (Scheme 45, Table 36).⁸⁰



Scheme 42 Synthesis of benzothiazole linked substituted chalcones.

 Table 33
 Anti-tubercular activity of benzothiazole linked substituted chalcones

Compounds	R	MIC ($\mu g \ mL^{-1}$)	
151a	C_6H_5	25	
151b	$4 - MeC_6H_4$	25	
151c	$4-OHC_6H_4$	100	
151d	$4-OMeC_6H_4$	12.5	
151e	4-NMe ₂ C ₆ H ₄	12.5	
151f	$4-NO_2C_6H_4$	50	
151g	$4-ClC_6H_4$	25	
151h	Furan-2-yl	25	
151i	Furan-3-yl	50	
151j	Thiophen-2-yl	6.25	
151k	Thiophen-3-yl	50	
151l	Pyridin-2-yl	6.25	
151m	Pyridin-3-yl	100	
151n	Pyridin-4-yl	50	
PZA	_	3.125	



Scheme 43 Synthesis of benzothiazole oxime derivatives.



Scheme 44 Synthesis of oxadiazole and thiadiazole linked benzothiazole analogues.

Using a Lowenstein–Jensen medium, the synthesized compounds were assessed for their *in vitro* anti-tubercular activity against the H_{37} Rv strain (Table 36). **187b** and **187d** exhibited excellent activity with inhibition of 96% and 98% respectively. It is quite interesting to note that the compound

187d can be introduced as new anti-tubercular compound in upcoming years.

Docking studies of ligand **187d** revealed that it interacts in an efficient manner with the active site of 4DRE protein of inhA in *M. tuberculosis*. Basically, the enol-acyl carrier protein

 Table 34
 Anti-tubercular activity of benzoheterocyclic oxime carbamate analogues

Compounds	R	MIC (µM)
153	_	>160
154	$-CON(CH_3)_2$	<0.16
155	$-SO_2N(CH_3)_2$	0.30
156	$-SO_2CH_3$	5.0
157	-CH ₂ COOCH ₂ CH ₃	>160
158	-CH ₂ CON(CH ₂ CH ₃) ₂	>160
159	-CH ₃	160
160	–Propyl	>160
161	-Bn	20
162	2-Picolyl	>160
163	3-Picolyl	>160
164	4-Picolyl	20
RIF		0.009
INH	_	0.14

reductase inhA of *M. tuberculosis* is an attractive, validated target for anti-TB drug development. Moreover, direct inhibitors of inhA remain effective against inhA variants with mutations associated with Isoniazid resistance. With very good binding affinity of -10.5 kcal mol⁻¹ ligand **187d** can act as an

 Table 36
 Anti-tubercular evaluation of pyrazolyl-pyrazoline derivatives of benzothiazole

Compounds	R	Х	Y	% inhibition
187a	Ме	NH	СН	91
187b	Me	S	Ν	96
187c	F	NH	CH	75
187d	F	S	Ν	98
RIF	_	_	_	98
INH	—	—	—	99

Table 35 Anti-tubercular activity of oxadiazole and thiadiazole linked benzothiazole analogues

Optimization of r	nitrile functior	nality		2				
\mathbb{R}^{N} \mathbb{R}^{2} \mathbb{R}^{0} \mathbb{R}^{1}								
Compounds	\mathbb{R}^1	R ²	MIC (µM)	Compounds	R ¹	R^2	MIC (µM)	
166	Н	Н	>160	180	Н	N-N N-N S	2.5	
168	Н	Ме	>125	181	н	N-N S	0.78	
170	Н	CF_3	37	RIF	_	~	0.009	
172	Н	N O N N	>160	INH	_	_	0.14	
179	Н	N N	160					



Scheme 45 Synthesis of pyrazolyl-pyrazoline derivatives of benzothiazole.



Fig. 19 3D view of interactions shown by ligand 187d and active site of 4DRE protein.



Fig. 20 2D view of interactions between ligand 187d and various amino acids of 4DRE protein chain.

alternative in case of Isoniazid resistance due to mutations in *inhA* gene (Fig. 19 and 20).

P. R. Kadam and co-workers performed a one pot three component Knoevenagel condensation reaction between 4-

hydroxycoumarin **20**, substituted aldehydes, and 2-mercapto benzothiazole **44** in presence of L-proline as catalyst to synthesize 3-[(1,3-benzothiazol-2-ylsulfanyl) (phenyl)methyl]-2*H*chromen-4-ol derivatives **188a–f** (Scheme 46, Table 37).⁸¹

In vitro anti-tubercular evaluation of all the synthesized compounds against $H_{37}Rv$ strain of *M. tuberculosis* was done using Microplate Alamar Blue Assay (MABA) technique. Due to the presence of the –OCH₃ group, compound **188d** demonstrated good activity with a MIC value of 1.6 µg mL⁻¹ compared to the reference drug Streptomycin. Compound **188c** and **188b** demonstrated inhibition at 6.25 µg mL⁻¹ and 12.5 µg mL⁻¹ while compounds **188a** and **188f** demonstrated activity at 50 and 25 µg mL⁻¹ (Table 37).

R. Moodley and co-workers synthesized a series of novel benzothiazole-urea-quinoline hybrid molecules *via* a three-step synthetic process that included an amidation coupling reaction as a crucial step. Initial step started from the reaction of 4,7dichloroquinoline and various excess diamines to give the intermediate 4-aminoquinoline diamines **190a–e** and **191** (Routes A and B respectively). Using the 1,1'carbonyldiimidazoles (CDIs), several 2-amino-6-substituted benzothiazoles **192a–g** were converted to benzothiazole-1*H*-imidazole-1-carboxamide intermediates **193a–g** also in excellent yields. The last step involved the synthesis of desired compounds **194a–y** from the coupling of 4-aminoquinoline diamines with benzothiazole-1*H*-imidazole-1-carboxamide derivatives **193a–g** (Scheme 47, Table 38).⁸²

All the synthesized compounds were evaluated *in vitro* against H_{37} Rv strain of *M. tuberculosis* over seven days of incubation in two different media 7H9/CAS/GLU/Tx and 7H9/ADC/GLU/Tw. The main difference among the media was that the former contained tyloxapol (Tx) and casitone (CAS), whereas the later contained Tween-80 (Tw) and albumin-dextrose-catalase



Scheme 46 Synthesis of [(1,3-benzothiazol-2-ylsulfanyl) (phenyl)methyl]-2H-chromen-4-ol derivatives.

Table 37	Anti-tubercular activity of [(1,3-benzothiazol-2-ylsulfanyl) (phenyl)methyl]-2H-chromen-4-ol analogues ^{a}
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Compounds	R	$100 \ \mu g \ m L^{-1}$	$50 \ \mu g \ m L^{-1}$	$25 \ \mu g \ m L^{-1}$	$12.5 \ \mu g \ m L^{-1}$	$6.25~\mu g~mL^{-1}$	$3.12~\mu g~mL^{-1}$	$1.6 \ \mu g \ m L^{-1}$	$0.8 \ \mu g \ m L^{-1}$
188a	Н	S	R	R	R	R	R	R	R
188b	Br	S	S	S	S	R	R	R	R
188c	Cl	S	S	S	S	S	R	R	R
188d	OCH_3	S	S	S	S	S	S	S	R
188e	OH	S	S	S	S	R	R	R	R
188f	CH_3	S	S	S	R	R	R	R	R

^{*a*} S: sensitive, R: resistance.



Scheme 47 Synthesis of benzothiazole-urea-quinoline hybrid analogues.

 Table 38
 Anti-tubercular activity of benzothiazole-urea-quinoline hybrid analogues^a

Compounds	x	Diamine linker	^b 7H9/CAS/GLU/Tx 7 days (μM)	^c 7H9/ADC/GLU/Tw 7 days (μM)	Compounds	x	Diamine linker	^b 7H9/CAS/GLU/Tx 7 days (μM)	^c 7H9/ADC/GLU/Tw 7 days (μM)	
194a	Н	H ₂ N-NH ₂	21.001	>125	1940	Cl	$H_2N_{\widetilde{M_4}}NH_2$	7.455	23.529	
194b	CF_3		4.943	6.85	194p	Br		7.812	15.609	
194c	F		>125	>125	194q	F		>125	>125	
194d	NO_2		>125	>125	194r	Cl	$H_2N_{4}NH_2$	7.597	14.617	
194e	CF_3	H ₂ NNH ₂	NT	NT	194s	Br		8.76	20.954	
194f	Cl	$\varphi_2 = \varphi_2$	125	>125	194t	F		6.974	31.25	
194g	Br		8.89	14.898	194u	CF_3	H ₂ N NH ₂	0.968	5.732	
194h	F		62.5	62.5	194v	F		>125	>125	
194i	CF_3		7.812	12.837	194w	Br		8.191	14.001	
194j	Cl	M3 112	4.389	11.748	194x	CH_3		7.219	10.35	
194k	CH_3		31.25	62.33	194y	Cl		2.331	8.455	
194l	Н		9.628	9.447	RIF	_		0.03	0.001	
194m	Br		15.924	16.863						
194n	\mathbf{F}		>125	125						
^a NT: not tes	^a NTP. not tasted ^b Durate in deficient Mth madia ^c Durate in wich Mth madia									

^{*a*} NT: not tested. ^{*b*} Protein-deficient Mtb media. ^{*c*} Protein rich Mtb media.

(ADC). Compound **194u** was found to be most active against tuberculosis with MIC value of 0.968 μ M with MIC₉₀ values between 1–10 μ M. Thirteen compounds **194b**, **194g**, **194i–j**, **194l**, **194o–p**, **194r–t** and **194x–y** demonstrated potential antitubercular activity (Table 38). From cytotoxicity assay it was observed that compound **194t** exhibited the highest cell viability at the MIC₉₀ (92%) as compared to **194r** (72%) and **194s** (76%). *In silico* ADME and drug likeness properties suggested high percentage human oral absorption (>80%). Most of these compounds fulfilled Lipinski's rules for drug-like properties.

Conclusions and future perspectives

It became evidenced from above discussions that, benzothiazole nucleus is an important structural motif in medicinal chemistry for the search of new anti-tubercular compounds. Therefore, various analogues of benzothiazole nucleus have been synthesized and evaluated for their anti-tubercular activity by several research groups. There is much scope in benzothiazole derivatives as a source of molecular targets and research into this nucleus has recently received a lot of attention.

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Carbanilide derivatives of benzothiazole exhibited excellent anti-tubercular activity with MIC of 0.78 μ g mL⁻¹ as compared to Ethambutol (1.56 μ g mL⁻¹). Benzothiazole based Schiff bases were also potent against Mtb with MIC of 0.8-1.6 $\mu g m L^{-1}$ which was better than standard drug Streptomycin (6.25 µg mL^{-1}). Azo-ester complexes of benzothiazoles emerges as potential anti-TB molecules with good docking score and MIC value of 1.6 μ g mL⁻¹, this activity was much better than the standard drugs Streptomycin (MIC 6.25 µg mL⁻¹) and Pyrazinamide (MIC 3.125 μ g mL⁻¹). Further coumarin based azo dye molecules were found as excellent anti-tubercular compounds along with good docking score and MIC value of 1.6 μ g mL⁻¹ as compared to the standard drug Streptomycin $(6.25 \ \mu g \ m L^{-1})$. Pyrazole conjugates of benzothiazole derivatives were identified another potent molecules having better potency than standard drugs like Streptomycin and Ciprofloxacin with a MIC value of 1.6 μ g mL⁻¹. Among the hydrazine sub-series, compound containing CF₃ was found to exhibit outstanding activity in both mediums. It is also evidenced from this discussion that, most of the synthesized compounds having C-6 substitution of benzothiazole ring is more potent than C-6 unsubstituted compounds. Benzothiazole based azo dyes and their metal complexes were also observed to inhibit the growth of M. tuberculosis. We performed docking of some selected most active compounds in order to find potent inhibitory action against DprE1, enol-acyl carrier protein reductase inhA and arabinosyl transferase. From the molecular docking studies it can be concluded that the selected compounds can be taken as lead to work and develop potent anti-tubercular molecules, which may works against drug resistance strains as well. As highlighted in current review that, recently benzothiazole derivatives are becoming molecules of interest for drug development against tuberculosis. However, further research is needed to completely understand the molecular mechanism of these active compounds to fully comprehend the molecular basis of the anti-tubercular activity in order to develop new antitubercular drugs that can obliterate mycobacterial infections.

Conflicts of interest

There are no conflicts to declare.

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