RSC Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2023, **13**, 21890

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

Rakhi Yadav, Dilkhush Meena, Kavita Singh, Rajdeep Tyagi, Yogesh Yadav and Ram Sagar *

Received 9th June 2023
Accepted 7th July 2023

DOI: 10.1039/d3ra03862a

rsc.li/rsc-advances

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.

Introduction

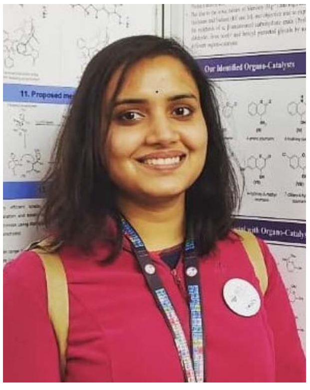
Tuberculosis (TB) is one of the most precarious and contagious infectious illnesses in the world caused by *Mycobaterium tuberculosis*, Mtb.[1,2] Moreover, the rapid growth of drug resistant bacteria has contributed to a rise in incidence of both extensively drug resistant (XDR) and multidrug resistant (MDR) tuberculosis.[3] Under this situation, only the recently developed Delamanid, Pretomanid,[4] Bedaquiline[5] and Fluoroquinolone antibiotics[5] have proven to be effective novel pharmaceuticals 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

Glycochemistry Laboratory, School of Physical Sciences, Jawaharlal Nehru University, New Delhi-110067, India. E-mail: ram.sagar@jnu.ac.in

Rakhi Yadav completed her MSc in 2020 from Kurukshetra University, Kurukshetra, Haryana, India. She joined Glycochemistry Laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a research scholar in 2022. She is currently pursuing her PhD degree under the supervision of Prof. Ram Sagar. Her expertise lies in heterocyclic molecules, medicinal chemistry, organic synthesis, and the development of new methods for the natural product inspired bioactive glycohybrids.

Dilkhush Meena completed his BSc in 2021 from Kirorimal college, University of Delhi, New Delhi-110007, India. Since then, he has been pursuing his MSc from School of Physical Sciences, Jawaharlal Nehru University, New Delhi. He is working under the supervision of Prof. Ram Sagar for his MSc Research project. He is interested in Organic Synthesis, the development of carbohydrate derived materials, natural product-inspired hybrid analogues and molecular modeling, especially in protein-ligand interaction via in silico docking tools.

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] anti-tumor,[18,19] analgesic,[20] anti-leishmanial,[21] and anti-inflammatory.[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 anti-microbial therapy for the treatment tuberculosis.[10] Anti-TB drugs are basically divided into two categories, (i) first line drugs, (ii) second line drugs.



Kavita Singh has been completed her MSc from Deen Dayal Upadhyaya University, Gorakhpur, UP, India in 2019. She qualified CSIR-JRF then joined Glycochemistry Laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a junior research fellow in 2021. She is currently persuing her PhD degree under the supervision of Prof. Ram Sagar. Her work is mainly focused on development of new methods for the synthesis of carbohydrate fused heterocyclic molecules as bioactive glycohybrids. She is also interested in medicinal chemistry and synthesis of natural product inspired bioactive scaffolds.

Yogesh Yadav has completed his MSc in 2021 from Kurukshetra University, Kurukshetra, Haryana, India. He joined Glycochemistry Laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a CSIR Junior Research Fellow in 2022. He is currently pursuing his PhD degree under the supervision of Prof. Ram Sagar. His work is mainly focused on development of new methodology in organic synthesis, the synthesis of carbohydrate fused-linked heterocyclic molecules as bioactive molecules. He is also interested in synthesis of natural product inspired bioactive scaffolds as antiviral agents.

Rajdeep Tyagi has completed his MSc in 2018 from Kirorimal college, University of Delhi, New Delhi-110007, India. He joined Glycochemistry laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a UGC junior research fellow in 2020. He is currently pursuing his PhD degree under the supervision of Prof. Ram Sagar. His expertise lies in heterocyclic molecules, medicinal chemistry, organic synthesis, and the synthesis of indole based bioactive glycohybrids. He is also interested in developing new methods for glycoconjugate synthesis and their bioapplications.

Prof. Ram Sagar received his MSc degree from University of Lucknow, Lucknow, UP, India. Prof. Sagar has completed his PhD degree in Organic Chemistry from 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.

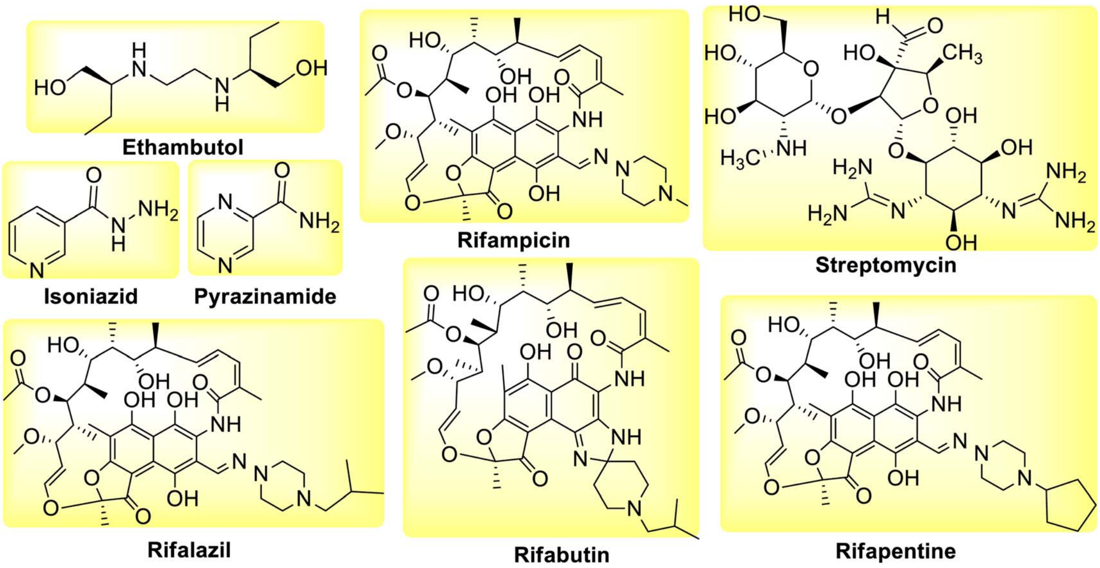


Fig. 1 Molecular structure of first line anti-tubercular drugs.

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

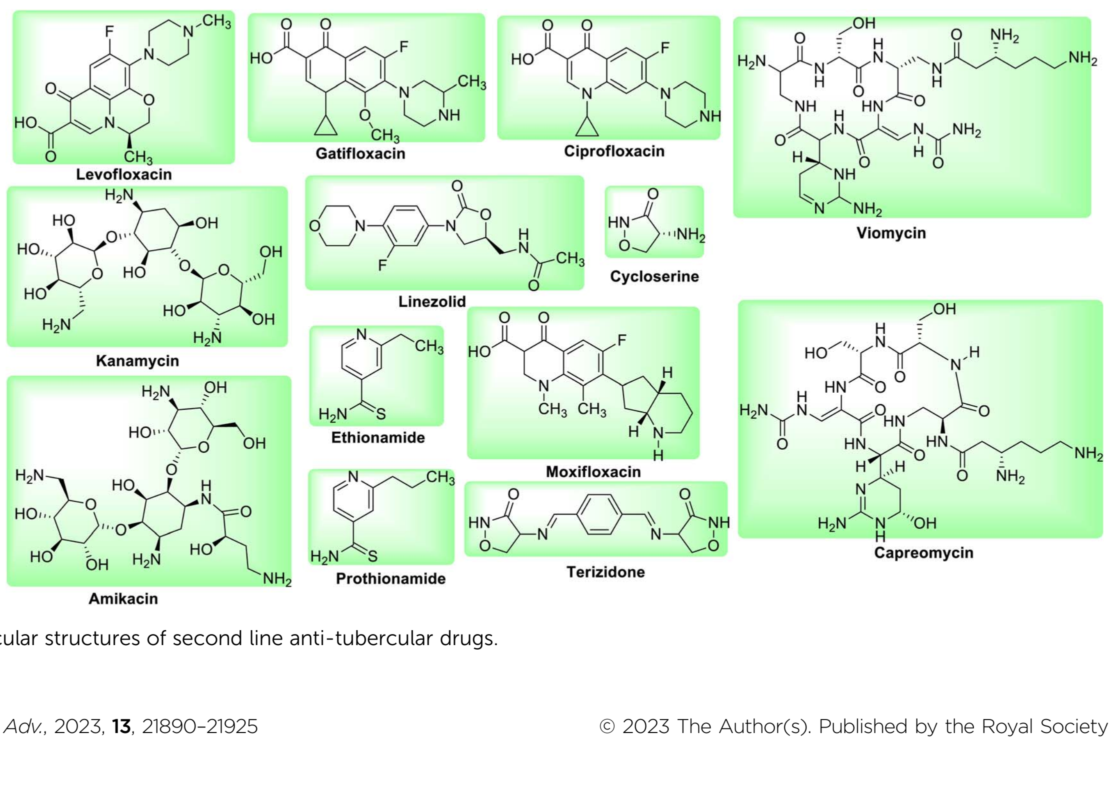


Fig. 2 Molecular structures of second line anti-tubercular drugs.

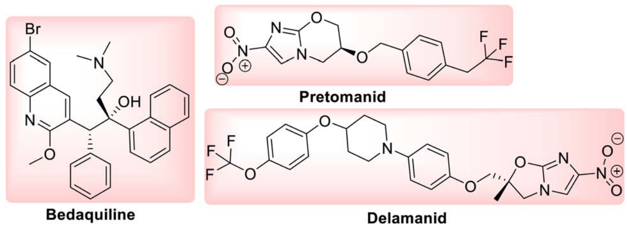


Fig. 3 Molecular structure of newly approved anti-tubercular drugs against MDR and XDR TB.

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.

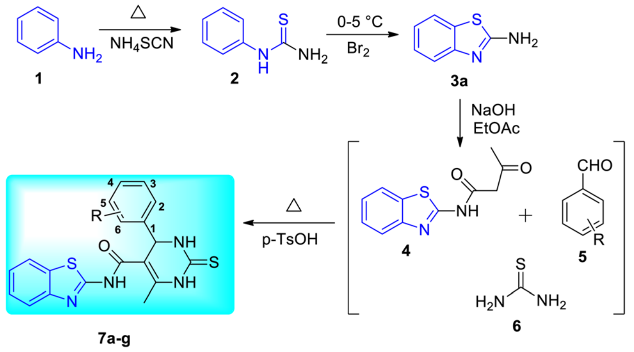
Recent synthesis of benzothiazole based anti-tubercular molecules

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 anti-tubercular activity against the pathogenic strain of Mtb $H_{37}Rv$ ATCC 27294. MIC and IC_{50} 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 *katG* and *inhA*	29
		Rifampicin/Rifampin	Mutations in *rpoB* gene	30
		Pyrazinamide	Mutations in *RpsA*, *pncA*	31 and 32
		Rifapentine	Mutations in *rpoB* gene	33
		Rifabutin	Mutations in *rpoB* gene	34
		Ethambutol	*embCAB* operon	24
	Injectable	Streptomycin	Mutations in *rpsL*	35
Second-line anti-TB drugs	Group 2 (injectable)	Kanamycin	Mutations in *rrs*	36
		Amikacin	Mutations in *rrs*	
		Viomycin	Mutations in *rrs*	
		Capreomycin	Mutations in *thyA*	
	Group 3 (oral and injectable)	Moxifloxacin	Mutations in *gyrA*	37
		Levofloxacin	Mutations in *gyrA*	
	Group 4 (oral)	Linezolid	Mutations in G2576T (23S)	38
		Prothionamide	Mutations in *etha*	39
		Ethionamide	Mutations in *etha* and *inhA*	40
		Terizidone	Non	
		Cycloserine	Mutation in *alrA*	41
		Para-aminosalicylic acid (PAS)	Mutations in *thyA*	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	H	7.7 ± 0.8	0.08
7b	2-Cl	NT	0.32
7c	4-Cl	NT	0.32
7d	2,4-Di Cl	NT	0.25
7e	4-F	9.2 ± 1.5	0.09
7f	CF_3	11.1 ± 1.8	0.09
7g	4-N(Me)$_2$	10.3 ± 2.6	0.08
INH	—	0.2	—

[a] 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 anti-tubercular activity (Fig. 4 and 5).

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

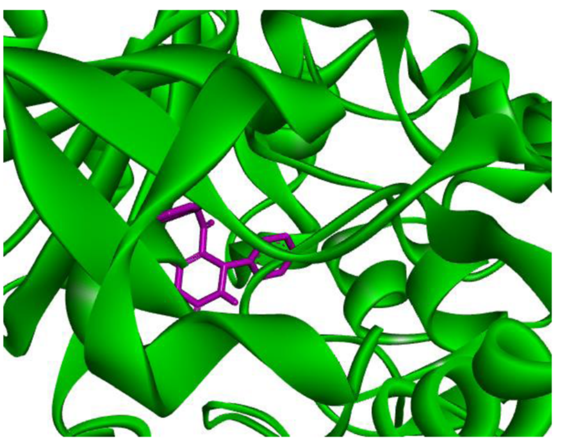


Fig. 4 3D representation of ligand **7a** and its interactions at the active site of 4FDN protein.

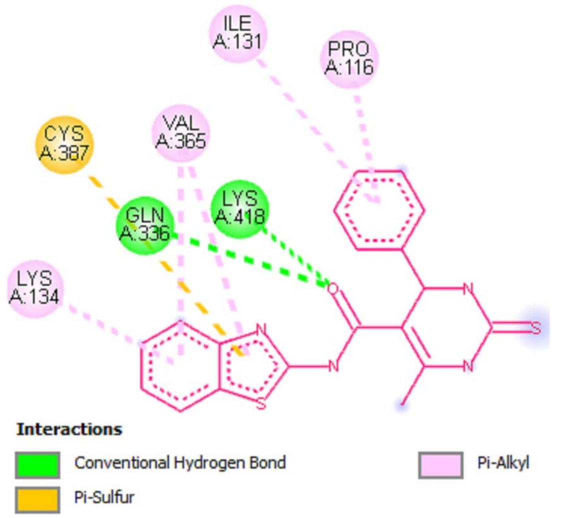
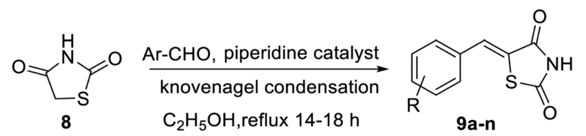
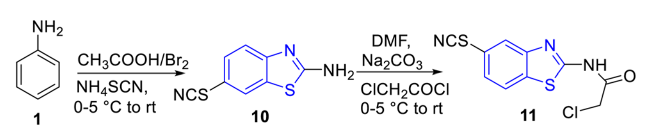


Fig. 5 2D representation of docking results showing interactions of ligand **7a** with 4FDN protein.

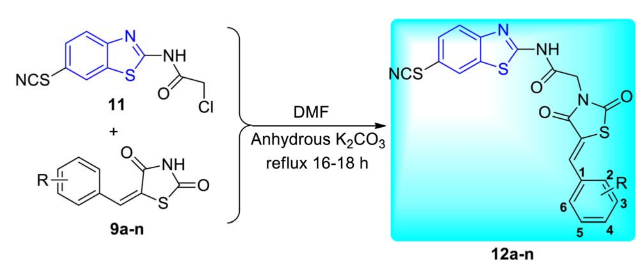


Scheme 2 Synthesis of (*E*)-5-arylidenethiazolidine-2,4-diones.

step involved the synthesis of (*E*)-5-arylidenethiazolidine-2,4-diones **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	MIC (μg mL^{-1})	Inhibition (%)	Compounds	R	MIC (μg mL^{-1})	Inhibition (%)
9a	H	250	98	**12a**	H	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
9l	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[$(CH_2)_5CH_3$]$_2$	500	98	**12n**	4-N[$(CH_2)_5CH_3$]$_2$	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]

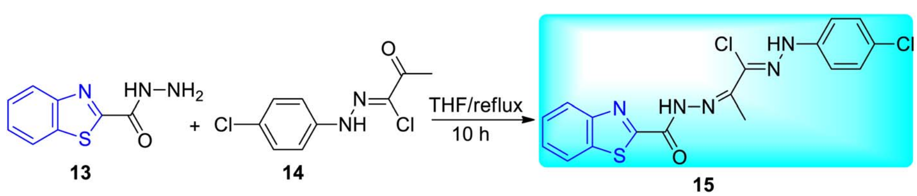
Biological evaluation of the synthesized compounds showed moderate to good anti-tubercular activity against *M. tuberculosis* $H_{37}R_V$ with reference drug Rifampicin. The L–J agar (MIC) method was used to assess drug susceptibility and the MIC of the test compounds against *M. tuberculosis* H_{37}Rv (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

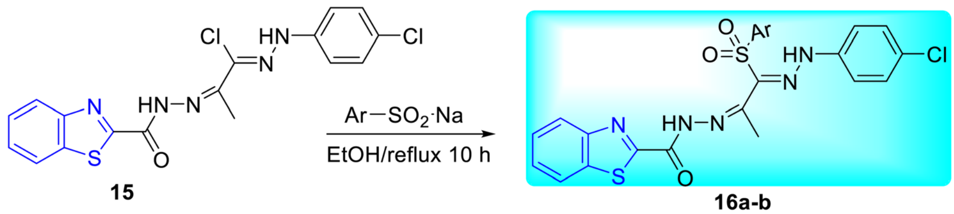
Table 4 Anti-tubercular activity of halophenyl bis-hydrazone and its sulfone derivatives[a]

Compounds	Ar	MIC (μg mL^{-1})
15	—	NA
16a	Ph	NA
16b	4-Me-C_6H_4	125
INH	—	0.40
PZA	—	3.21

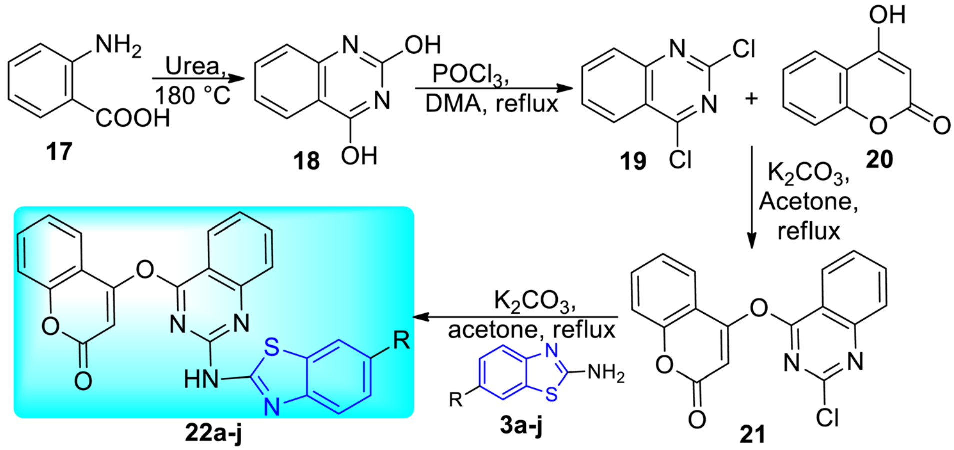
[a] NA: not active.



Scheme 5 Synthesis of benzothiazole based halophenyl bis-hydrazone.



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



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]

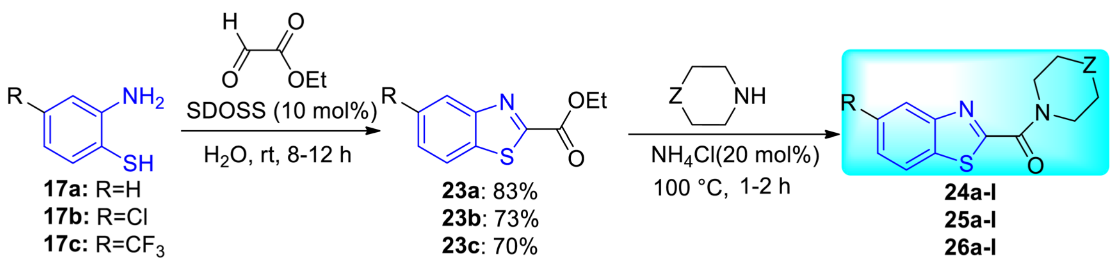
These benzothiazole based halophenyl bis-hydrazones derivatives when tested against mycobacterial strain were found to be less active against *M. tuberculosis* as compared to standard reference drugs Isoniazid and Pyrazinamide (Table 4).

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

Compounds	R	BACTEC MGIT method MIC (μg mL^{-1})	L. J. MIC method MIC (μg mL^{-1})
22a	H	>6.25	250
22b	Cl	>6.25	25
22c	Br	>6.25	12.5
22d	F	>6.25	3.12
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	—

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 $POCl_3$ in DMA (dimethylacetamide) gave 2,4-dichloroquinazoline **19**. The intermediate analogue **21** was formed by the condensation of 4-hydroxycoumarin **20** with 2, 4-dichloroquinazoline **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 technique[45] 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.

Table 6 Anti-tubercular activity of 5-substituted benzo[*d*]thiazole-2-carboxylates **23a–c** and carboxamides **24/25/26a–l**

Compounds	R	Z	R¹	Yields (%)	MIC (μg mL^{-1})	Compounds	R	Z	R¹	Yields (%)	MIC (μg mL^{-1})
23a	H	—	—	83	25	**25h**	Cl	NR¹	4-OMe-C_6H_4	54	3.125
23b	Cl	—	—	73	3.125	**25i**	Cl	NR¹	4-COMe-C_6H_4	54	1.56
23c	CF_3	—	—	70	6.25	**25j**	Cl	NR¹	4-Pyridyl	58	12.5
24a	H	O	—	88	1.56	**25k**	Cl	NR¹	2-Pyrazinyl	47	6.25
24b	H	S	—	83	25	**25l**	Cl	NR¹	$CH(C_6H_5)_2$	77	0.78
24c	H	CH_2	—	67	25	**26a**	CF_3	O	—	88	0.78
24d	H	NR¹	Me	56	3.125	**26b**	CF_3	S	—	92	0.78
24e	H	NR¹	COMe	55	1.56	**26c**	CF_3	CH_2	—	74	12.5
24f	H	NR¹	C_6H_5	76	1.56	**26d**	CF_3	NR¹	Me	77	6.25
24g	H	NR¹	2-OMe-C_6H_4	55	3.125	**26e**	CF_3	NR¹	COMe	88	1.56
24h	H	NR¹	4-OMe-C_6H_4	53	12.5	**26f**	CF_3	NR¹	C_6H_4	72	12
24i	H	NR¹	4-COMe-C_6H_4	51	1.56	**26g**	CF_3	NR¹	2-OMe-C_6H_4	77	25
24j	H	NR¹	4-Pyridyl	54	3.125	**26h**	CF_3	NR¹	4-OMe-C_6H_4	88	3.125
24k	H	NR¹	2-Pyrazinyl	77	6.25	**26i**	CF_3	NR¹	4-COMe-C_6H_4	77	6.25
24l	H	NR¹	$CH(C_6H_5)_2$	63	0.78	**26j**	CF_3	NR¹	4-Pyridyl	74	3.125
25a	Cl	O	—	77	6.25	**26k**	CF_3	NR¹	2-Pyrazinyl	75	3.125
25b	Cl	S	—	67	6.25	**26l**	CF_3	NR¹	$CH(C_6H_5)_2$	74	25
25c	Cl	CH_2	—	77	12.5	**INH**	—	—	—	—	0.098
25d	Cl	NR¹	Me	60	25	**RIF**	—	—	—	—	0.19
25e	Cl	NR¹	COMe	82	12.5	**EMB**	—	—	—	—	1.56
25f	Cl	NR¹	C_6H_5	78	6.25	**PYZ**	—	—	—	—	6.25
25g	Cl	NR¹	2-OMe-C_6H_4	57	3.125	**CIP**	—	—	—	—	1.56

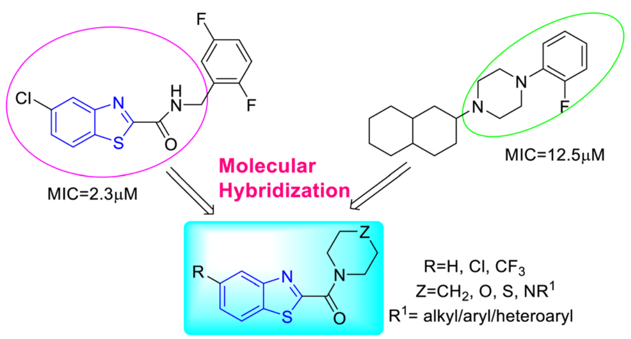


Fig. 6 Synthesis of benzo[*d*]thiazol-2-yl (piperazin-1-yl) methanones by the molecular hybridization method.

K. Chakraborti and co-workers designed and synthesized some new anti-mycobacterial chemotypes as benzo[*d*]thiazol-2-yl(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 μg mL^{-1}. The compounds **24l, 25l, 26a,** and **26b** with MIC value of 0.78 μg mL^{-1} were found to be more powerful than the standard medicines Ethambutol (1.56 μg mL^{-1}), Ciprofloxacin (1.56 μg mL^{-1}), and Pyrazinamide (6.25 μg 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 $-CF_3$ 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

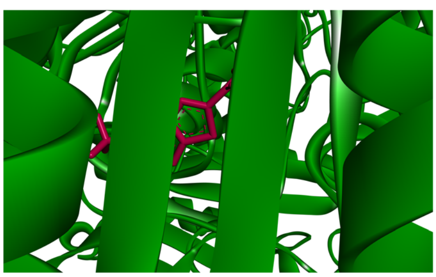


Fig. 7 3D representation of ligand **26a** and its interactions with 4P8N protein.

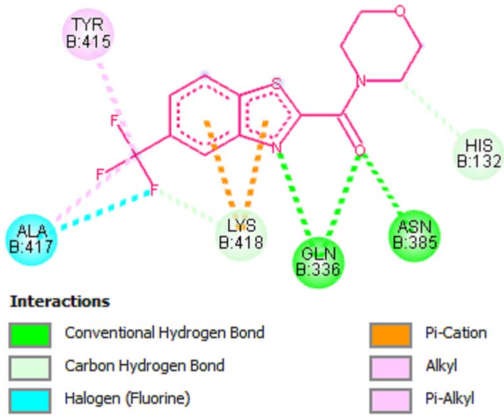


Fig. 8 2D representation of docking results showing interactions of compound **26a** with 4P8N protein.

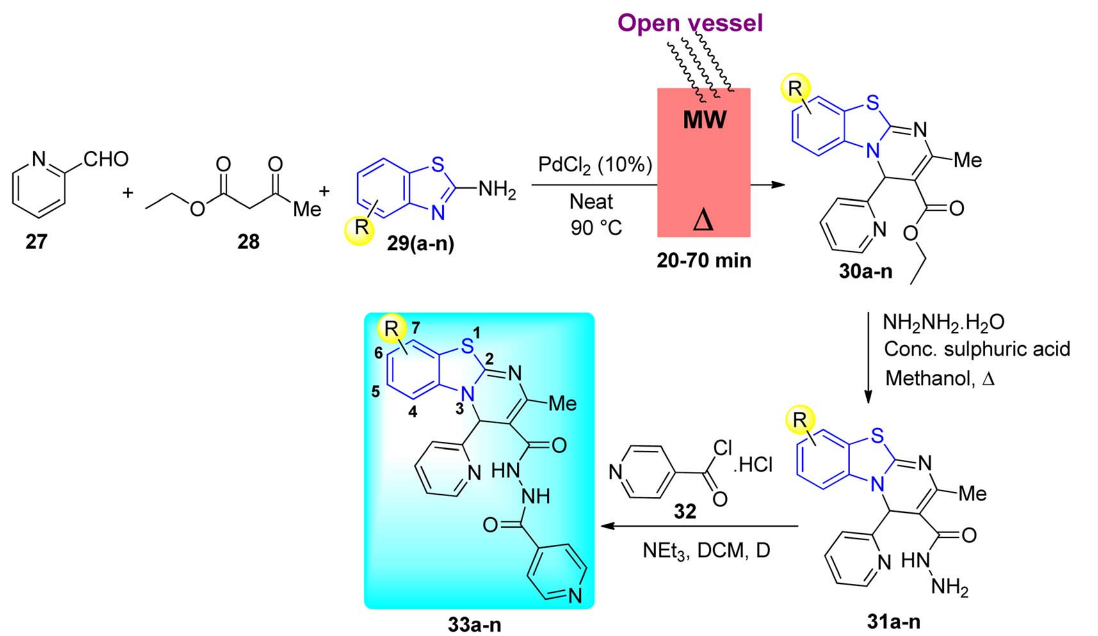
affinity of −8.9 kcal mol^{-1} and MIC value of 0.78 μg mL^{-1}. This compound **26a** may be considered as lead compound in further search of a better ligand to fit within the target site of DprE1 of *M. tuberculosis*.

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

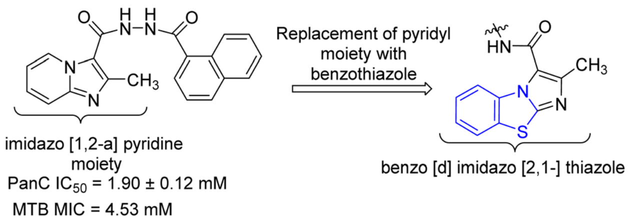
Table 7 Anti-mycobacterial activity of isoniazid linked 4*H*-pyrimido [2,1-*b*] benzothiazole analogues

Compounds	R	Yields (%)	Inhibition (%)	MIC value (μg mL^{-1})
33a	H	71.2	69.91	125
33b	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
33l	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

In a standard primary screen, all the newly synthesized compounds **33a–n** were evaluated *in vitro* for their anti-mycobacterial 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.

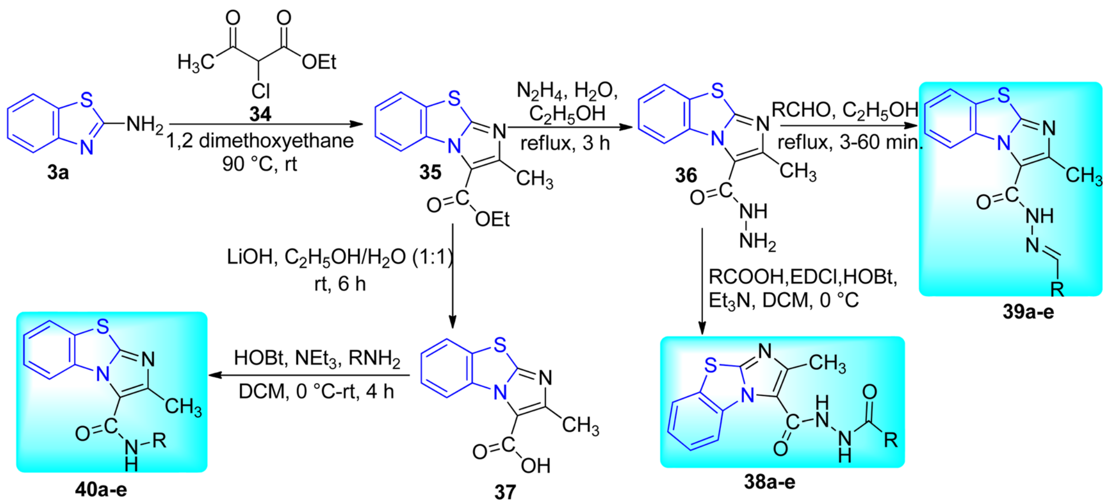


Scheme 9 Synthesis of isoniazid linked 4*H*-pyrimido [2,1-*b*] benzothiazole.



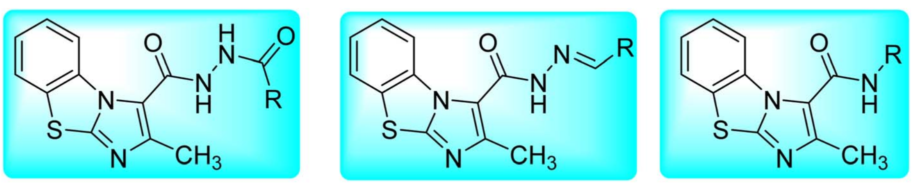
Scheme 10 Designing approach for the synthesis of new class of benzothiazoles.

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



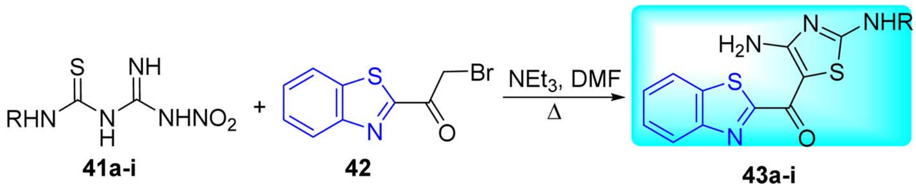
Scheme 11 Synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole derivatives.

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



38a-e **39a-e** **40a-e**

Compounds	R	Yields (%)	PanC IC_{50} (μM)	MIC against Mtb (μM)	Compounds	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-*N*,*N*-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-Trifluoromethylphenyl	93	5.31 ± 0.11	16.53	**40e**	Cyclohexyl	81	1.02 ± 0.11	19.94
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 9 Anti-tubercular activity of 2-(4-amino-2-aryl/alkyl aminothiazol-5-oyl)benzothiazole derivatives[a]

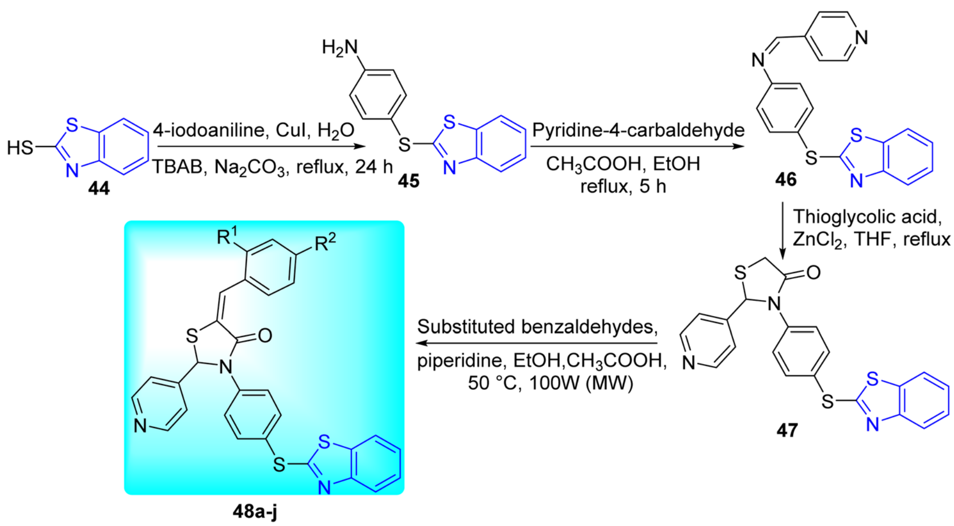
		Zone of inhibition (mm)				
Compounds	R	0.5 mg	1 mg	1.5 mg	2 mg	Control
43a	C_6H_5	NA	NA	2	3	3
43b	4-ClC_6H_4	NA	1	2	4	3
43c	4-$MeOC_6H_4$	NA	NA	NA	2	3
43d	4-$EtOC_6H_4$	3	5	6	8	3
43e	4-MeC_6H_4	NA	3	4	4	2
43f	C_2H_5	3	6	7	8	3
43g	N–C_3H_7	NA	NA	NA	NA	NA
43h	N–C_4H_9	NA	NA	2	2	4
43i	Allyl	2	3	3	5	2

[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 μM. Compound **38c** with MIC of 3.53 μM 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 μM.

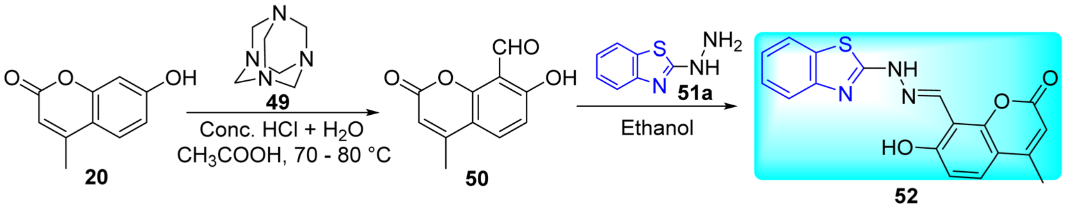
A. Yardily and co-workers synthesized 2-(4-amino-2-aryl/alkyl aminothiazol-5 oyl)benzothiazole derivatives **43a–i** from the



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 Anti-tubercular activity of thiazolidine-4-one substituted benzothiazoles

Compounds	R^1	R^2	% inhibition	MIC values (μM)	Compounds	R^1	R^2	% inhibition	MIC values (μM)
47	—	—	74	>100	**48g**	H	Cl	99	<50
48a	H	H	69	>100	**48h**	H	Br	10	>100
48b	H	OH	71	>100	**48i**	Pyridine-2-carbaldehyde		100	<50
48c	Me	OMe	13	>100	**48j**	Pyridine-4-carbaldehyde		99	<50
48d	H	NO_2	95	>100	**INH**	—		99	0.25
48e	H	F	98	<50	**RIF**	—	99	40	
48f	F	H	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 (μg mL^{-1})
52	1.6
53	0.8
54	1.6
55	0.8
STM	6.25

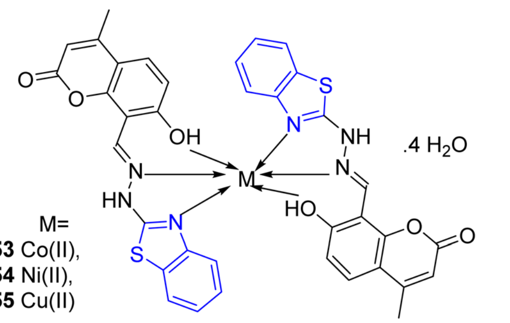


Fig. 9 Structure of metal complexes.

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 anti-tubercular activity. Compounds **43d**, **43f**, and **43i** demonstrated the highest activity against *M. tuberculosis* when compared to control penicillin (Table 9).[51]

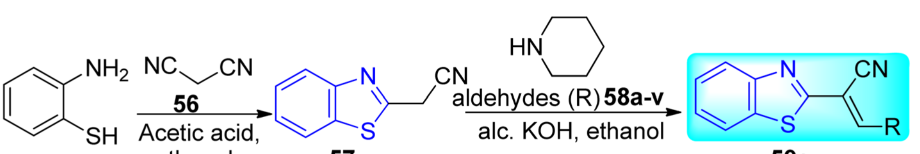
V. M. Patel and co-workers aimed to create powerful anti-mycobacterial molecules based on thiazolidine-4-one motif through Knoevenagel condensation *via* conventional heating as well as microwave irradiation as a green protocol (Scheme 13, Table 10). 4-(Benzo[*d*]thiazol-2-ylthio) aniline **45** was synthesized from the reaction of mercaptobenzothiazole **44** with 4-iodoaniline 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-4-yl)methanimine **46**. Compound **46** on reaction with thioglycolic acid in presence of $ZnCl_2$ 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(II), Ni(II), and Cu(II) 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]

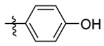
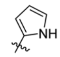
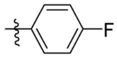
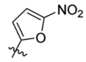
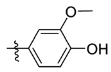
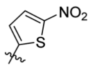
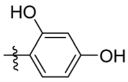
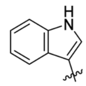
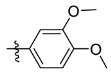
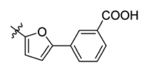
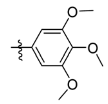
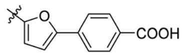
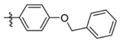
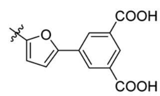
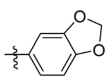
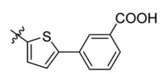
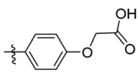
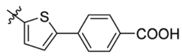
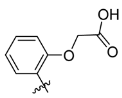
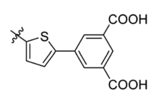
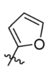
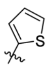
Synthesized metal complexes **53–55** along with ligand **52** were evaluated for their anti-tubercular activity against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA) technique while taking Streptomycin (STM) as the reference drug. The MIC results showed that the metal complexes had higher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

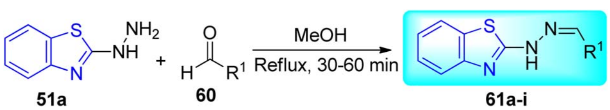
Reshma and co-workers synthesized some benzothiazole derivatives from a pre-existing lead to create a potent molecule against Mtb LAT, a critical enzyme for controlling the amino acid pool, which is essential for antibiotic resistance and persistence. It serves as potential target in management of latent 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.



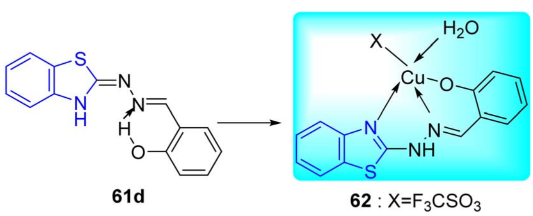
Scheme 15 Synthesis of acrylonitrile derivatives of benzothiazole.

Table 12 Anti-mycobacterial activity of acrylonitrile derivatives of benzothiazole

Compounds	R	MIC (μM)	LAT IC50 (μM)	Compounds	R	MIC (μM)	LAT IC50 (μM)
59a		>89.93	10.38 ± 1.21	**59m**		>99.60	17.05 ± 1.21
59b		89.29	4.11 ± 0.78	**59n**		>84.18	19.59 ± 0.32
59c		20.29	7.83 ± 0.31	**59o**		>79.87	54.76 ± 0.21
59d		10.61	23.19 ± 0.89	**59p**		>83.06	37.91 ± 0.48
59e		>77.64	61.41 ± 1.56	**59q**		>67.20	3.74 ± 0.27
59f		>71.02	64.89 ± 2.31	**59r**		>67.20	14.06 ± 0.16
59g		67.95	47.93 ± 1.82	**59s**		60.09	1.15 ± 0.27
59h		81.69	65.98 ± 0.63	**59t**		64.43	5.73 ± 0.79
59i		4.64	3.08 ± 0.37	**59u**		2.01	6.72 ± 0.27
59j		2.32	53.78 ± 0.96	**59v**		>57.60	2.62 ± 0.37
59k		49.60	16.23 ± 0.26	**INH**	—	0.4	—
59l		>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 μM. Compounds **59d**, **59i**, **59j** also demonstrated good activity with MIC values of 10.61, 4.64 and 2.32 μM 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-arylidene-benzylidene 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 anti-mycobacterial activity (Schemes 16 and 17, Table 13).[55]

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

Compounds	R^1/X	MIC (μM)
61a	Ph	>100
61b	2-ClC_6H_4	>100
61c	$2\text{-NO}_2C_6H_4$	10.5
61d	2-OHC_6H_4	11.6
61e	4-OMeC_6H_4	8.8
61f	2-OH-4-OMeC_6H_3	167
61g	$2\text{-OH-5-NO}_2C_6H_3$	>100
61h	Pyridin-2-yl	4.9
62	2-OH-5-MeC_6H_3	12.4
EMB	—	15.3
INH	—	0.46

The most potent anti-mycobacterial compounds were **61c** (aryl = $2\text{-O}_2NC_6H_4$), **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* $H_{37}Rv$ 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(II) (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.

Table 14 Anti-mycobacterial activity of *N*-arylbenzothiazole-2-carbanilides

Compounds	R^1	R^2	MIC (μg mL^{-1})
63a	–H	—	25
63b	–Cl	—	3.125
63c	$–CF_3$	—	6.25
66a	–H	3-Cl	0.78
66b	–H	4-CF_3	0.78
66c	–H	3-NO_2	0.78
66d	–H	3,4,5-Tri-OMe	0.78
67a	–Cl	3-OMe	0.78
67b	–Cl	4-Cl	0.76
67c	–Cl	4-Morpholinyl	0.78
68a	$–CF_3$	4-OMe	0.78
68b	$–CF_3$	4-Cl	0.78
68c	$–CF_3$	2-CF_3	0.78
68d	$–CF_3$	4-NO_2	0.78
68e	$–CF_3$	3,4,5-Tri-OMe	0.78
INH	—	—	0.098
RIF	—	—	0.197
EMB	—	—	1.56

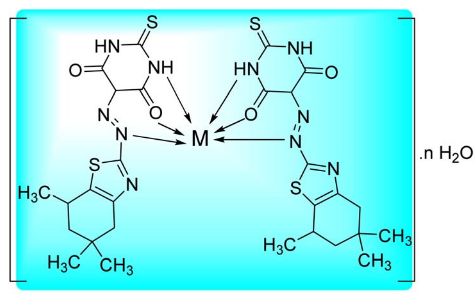
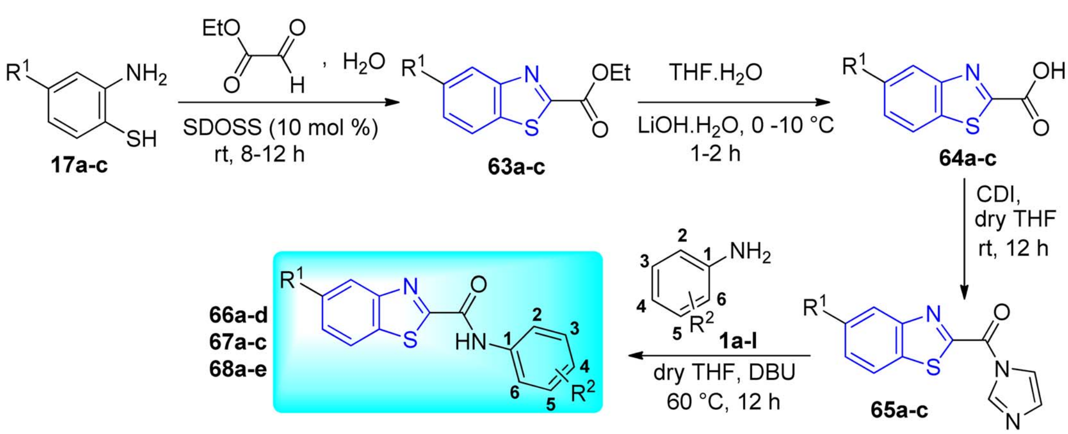
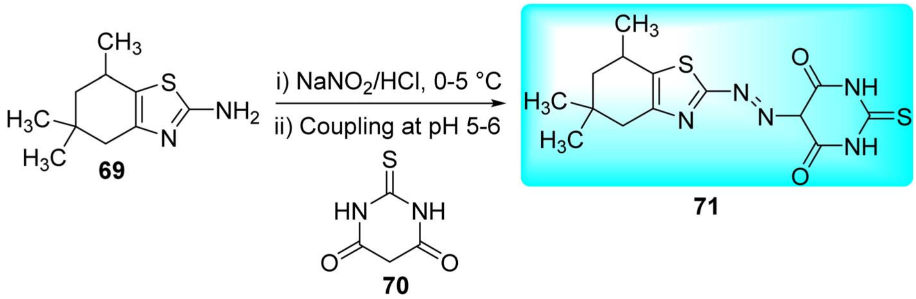


Fig. 10 Metal complexes of azo-dye ligand.

Matada and co-workers synthesized new dispersion azo dye ligand and its bioactive Cu(II), Co(II), Ni(II), and Fe(III) 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]

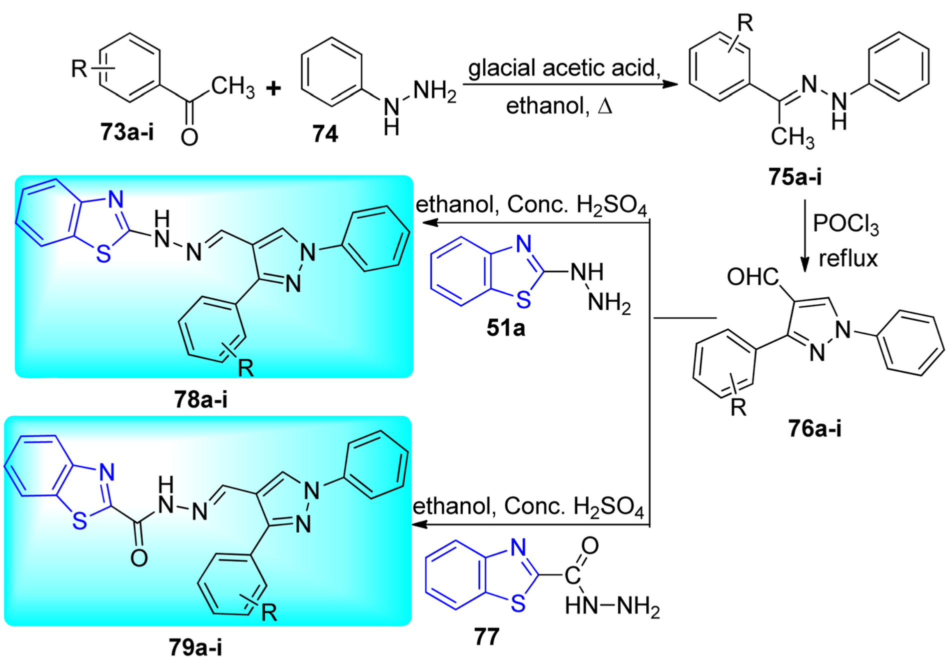
Ligands/complexes	100 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.6 μg mL^{-1}	0.8 μg mL^{-1}
71 L	S	S	S	S	S	R	R	R
72a [Cu(L)$_2$]	S	S	S	S	S	S	R	R
72b [Co(L)$_2$]	S	S	S	S	S	S	R	R
72c [Fe(L)$_2$]	S	S	S	S	S	S	S	R
72d [Ni(L)$_2$(H$_2$O)$_2$]	S	S	S	S	S	R	R	R

[a] S: sensitive, R: resistance.

diazo-coupling reaction between 5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine **69** and 2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-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).

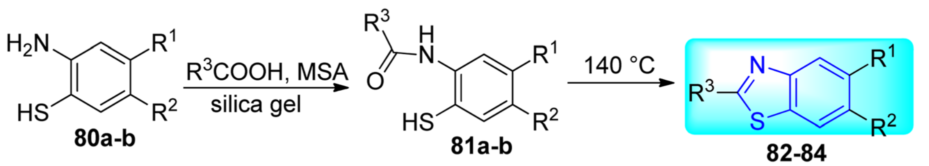
Bhat and co-workers synthesized 1-phenyl-2-(1-phenylethylidene) hydrazines **75a–i** from the reaction of



Scheme 20 Synthesis of pyrazole conjugated benzothiazole derivatives.

Table 16 Anti-tubercular activity of pyrazole conjugated benzothiazole derivatives

Compounds	R	MIC (μg mL^{-1})	Compounds	R	MIC (μg mL^{-1})
78a	H	12.5	**79a**	H	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	*p*-Cl	1.6	**79e**	*p*-Cl	100
78f	*p*-Br	6.25	**79f**	*p*-Br	50
78g	*p*-NO_2	6.25	**79g**	*p*-NO_2	100
78h	*m*-NO_2	50	**79h**	*m*-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	R^2	R^3	MIC (μg mL^{-1}) H$_{37}$Rv	Spec. 210
82	Cl	H	–$(CH_2)_3$-Cy	100	100
83	Cl	H	–$(CH_2)_3$-Cy	100	100
84	CF_3	H	–$(CH_2)_3$-Cy	100	100
PZA	—	—	—	25	>400
INH	—	—	—	0.125	12.5
RIF	—	—	—	1.2	2.5

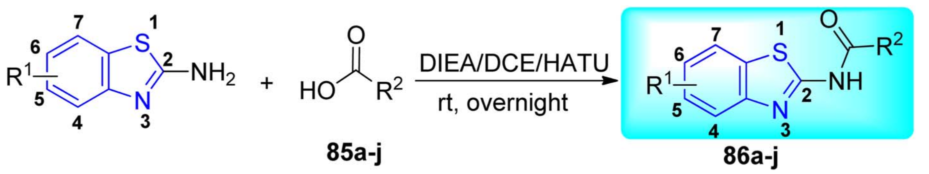
phenyl hydrazines **74** and different acetophenones **73a–i**. Then **75a–i** reacted with $POCl_3$ under reflux conditions to give pyrazole-conjugated benzothiazoleanalogues **76a–i** which further reacted with 2-hydrazinyl benzothiazole **51a** and benzothiazole-2-carbohydrazide **77** to furnish 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 μg mL^{-1}, benzothiazole hydrazine compounds displayed greater activity (MIC values 25 to 1.6 μg 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]

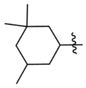
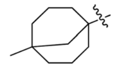
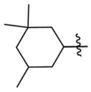
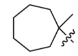
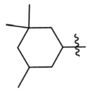
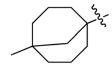
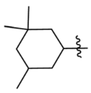
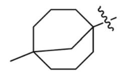
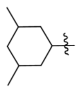
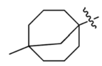
The synthesized compounds **82–84** were evaluated for their anti-tubercular activity against H$_{37}$Rv strain of Mtb and a wild strain Spec. 210 extracted from tuberculosis patients. Rifampicin, Pyrazinamide and Isoniazid were used as standard reference drugs. All these benzothiazole analogues were 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 benzothiazoleamide 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.

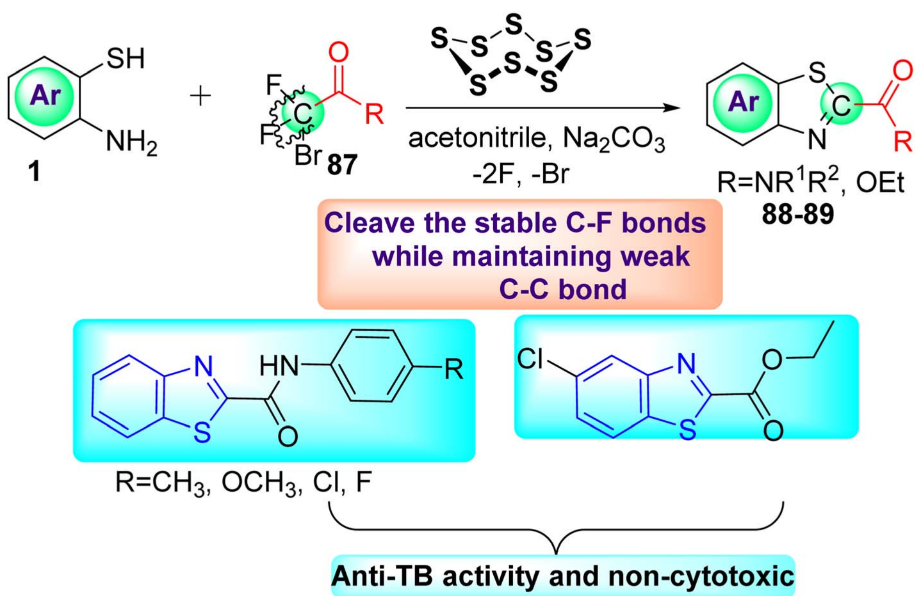
Table 18 Structure activity relationship of cyclohexane derivatives towards *M. tuberculosis* $H_{37}Rv$

Compounds	R^1	R^2	MIC ($\mu g\ mL^{-1}$)	Compounds	R^1	R^2	MIC ($\mu g\ mL^{-1}$)
86a	5-CF_3		≤0.12	**86f**	5,7-Di-F		0.25
86b	5,7-Di-Me		0.25	**86g**	OCF_3		0.5
86c	5,7-Di-F		0.25	**86h**	5-Br		≤0.12
86d	CF_3		2	**86i**	5,7-Di-Cl		≤0.12
86e	CF_3		4	**86j**	4,5,6-Tri-F		≤0.12

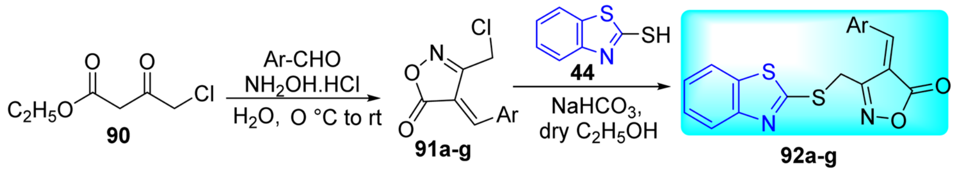
dichloroethane (DCE), the synthesis began with substituted 2-amino-benzothiazole **3** intermediates and variously substituted cycloalkyl carboxylic acids **85a–j** (Scheme 22, Table 18).[60]

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 triple-cleavage 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.

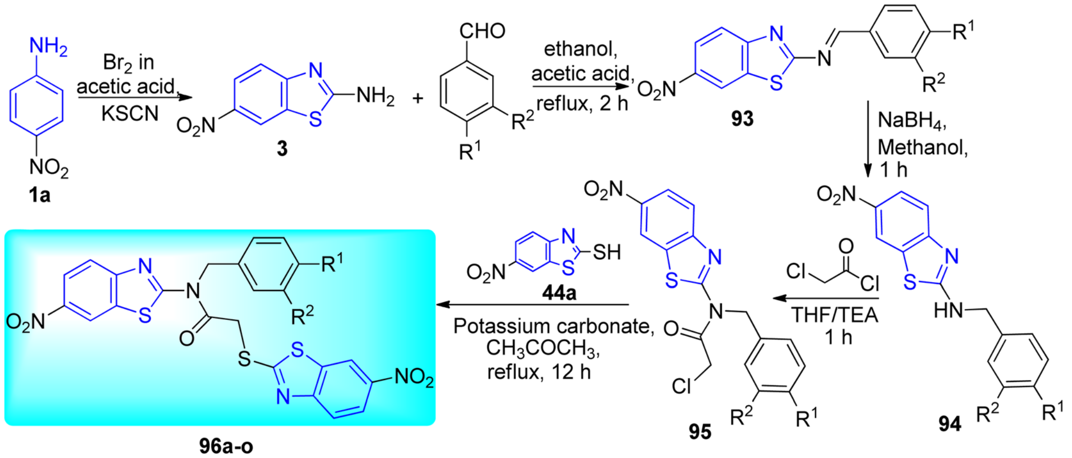


Scheme 24 Synthesis of oxazolone linked benzothiazole analogues.

Table 19 Anti-mycobacterial activity of oxazolone linked benzothiazole analogues (30 μg mL^{-1})[a]

Compounds	Ar	Yields (%)	Inhibition (%)	Compounds	Ar	Yields (%)	Inhibition (%)
92a	4-OH (C_6H_4)	96	99.4	**92e**	3,4-OCH_2O-(C_6H_3)	89	26.1
92b	4-OCH_3(C_6H_4)	88	96.5	**92f**	4-$N(CH_3)_2C_6H_4$	88	49.1
92c	3-OCH_3, 4-OH(C_6H_3)	89	80	**92g**	3-Indole	85	16.1
92d	4-CH_3(C_6H_4)	86	92.3	**RIF**	—	—	99.5

[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]

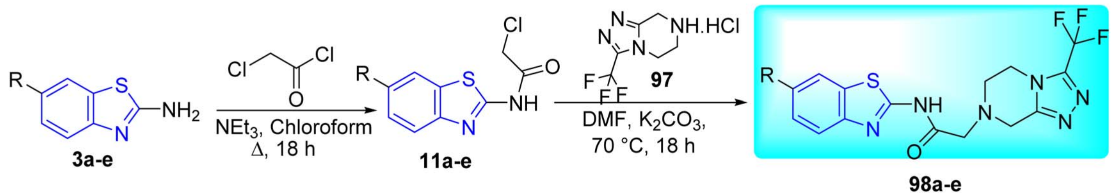
Compounds	R^1	R^2	MIC (μM) $H_{37}Rv$	IC_{50} (μM) $DprE_1$
96a	Me	Me	2.41	NT
96b	OMe	OMe	3.74	NT
96c	F	H	3.23	NT
96d	SMe	H	2.48	NT
96e	OMe	H	2.81	NT
96f	H	OH	2.10	NT
96g	H	OMe	1.01	14.1 ± 1.7
96h	OH	OMe	2.06	NT
96i	Cl	H	0.91	12.7 ± 0.9
96j	H	NO_2	3.35	NT
96k	H	H	0.82	14.8 ± 2.4
96l	COMe	H	2.79	NT
96m	F	F	3.04	NT
96n	NH_2	H	2.16	NT
96o	H	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(4*H*)-one **92a–g** by the reaction of mercapto benzothiazole **44** with 4-[(4-methoxyphenyl)-methylidene-]-3-chloromethyl-5(4*H*)-isoxazolone **91a–g**, prepared from **90**, in the presence of $NaHCO_3$ in ethanol in good yields (Scheme 24, Table 19).[62]

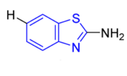
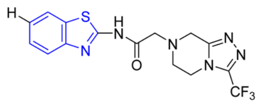
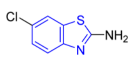
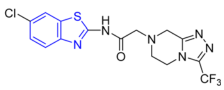
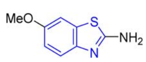
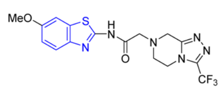
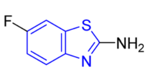
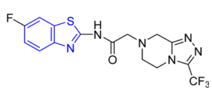
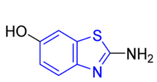
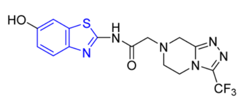
The anti-tubercular activity of synthesized compounds **92a–g** was carried out against *M. tuberculosis* $H_{37}Ra$ (ATCC 25177) using XTT reduction menadione assay (XRMA). Among the synthesized derivatives compound **92b** was found to be most potent against *M. tuberculosis* and all compounds from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

Benzothiazole derivatives	Final products	Yields (%)	MIC (μg mL^{-1})
 3a	 98a	72	500
 3b	 98b	75	250
 3c	 98c	70	250
 3d	 98d	81	500
 3e	 98e	69	500

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-6-nitrobenzo[*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 (SN^2) 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 μM, which was reported to be somewhat closer to the MIC of the standard reference Isoniazid, which is 0.31 μM. 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 NEt_3 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-5-nitrobenzo[*d*] thiazol-2-yl) phenyl-1*H*-pyrazol-4-yl)methylene)-3-substituted isonicotino hydrazide **102a–c** and *N'*-((1-(7-chloro-6-fluorobenzo[*d*]thiazol-2-yl)-3-phenyl-1*H*-pyrazol-4-yl)ethylene) isonicotinohydrazide **106a–c** for improved anti-tubercular efficacy. Initial step involved the reaction of 7-chloro-6-fluoro-5-nitro-2-hydrazinylbenzo[*d*]thiazole **99** and 7-chloro-6-fluoro-4-nitro-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 $POCl_3$ 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(3*H*)-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.*

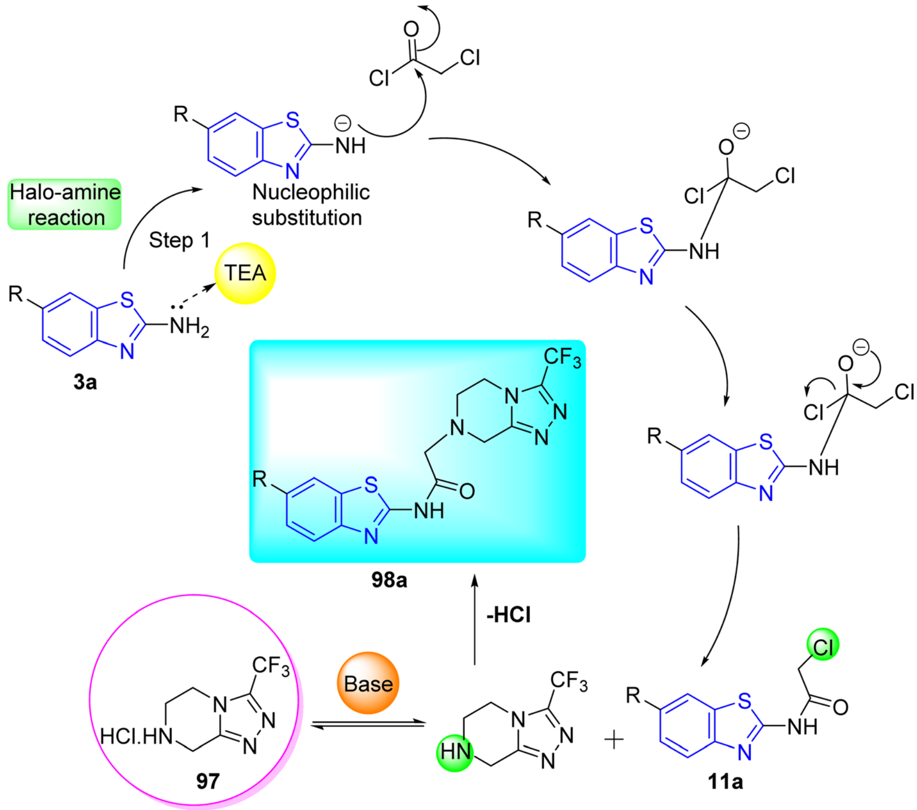
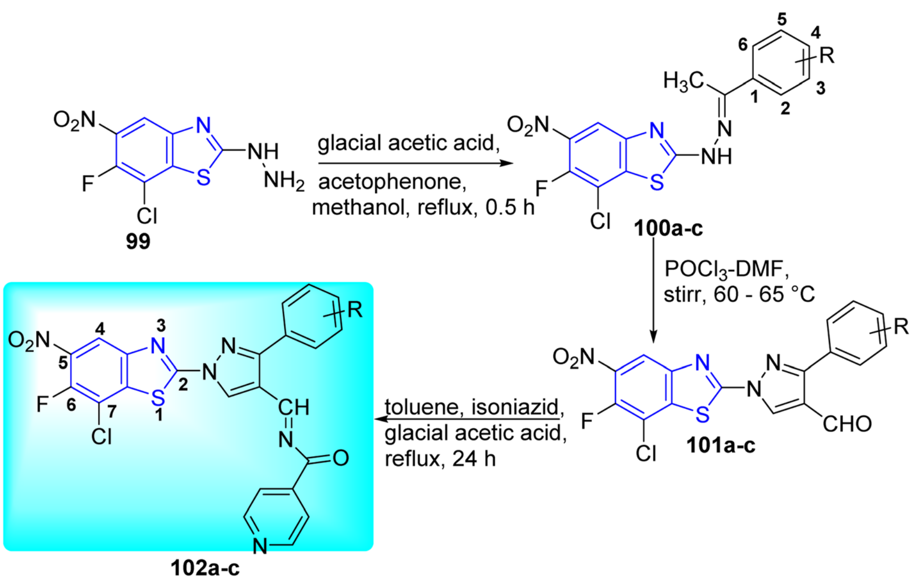


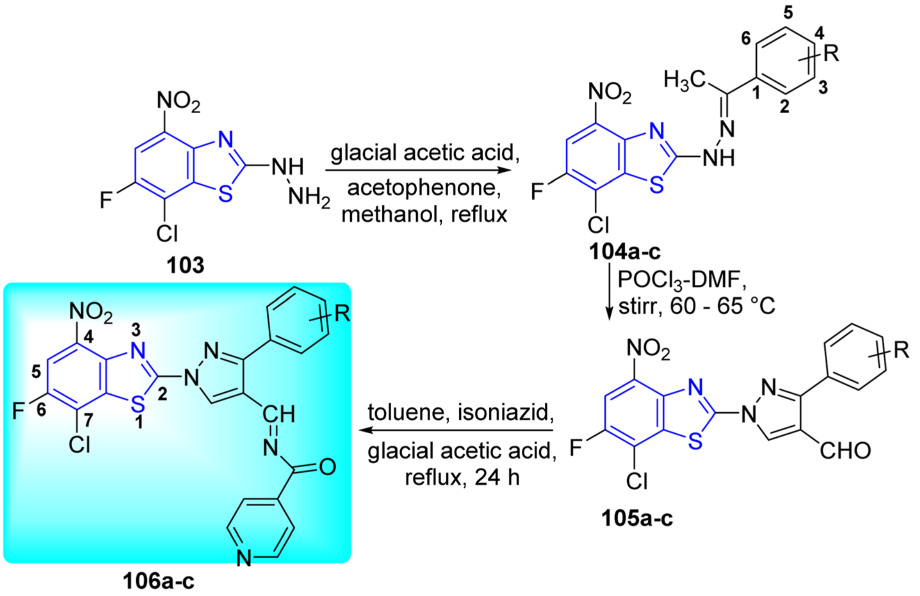
Fig. 11 Mechanistic pathway showing synthesis of compound **98a**.



Scheme 27 Synthesis of new series of *N*-((1-(7-chloro-6-fluoro-5-nitrobenzo[*d*]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 μg 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.

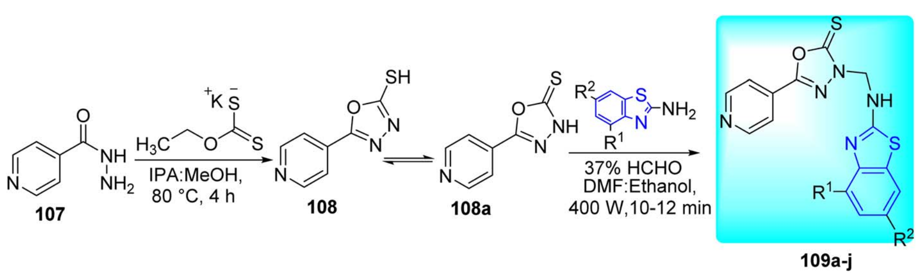
Table 22 Anti-tubercular activity of 5-nitro and 4-nitro substituted isonicotino-hydrazide analogues of benzothiazole

Compounds	R	MIC (nM)
102a	H	95.80
102b	2,4 di Cl	42.31
102c	4-F	46.30
106a	H	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 IC_{50} of 50 mg mL^{-1}. Compounds **113g–h** showed potent anti-tubercular action with mean IC_{50} 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 compounds was done against PDB 1ENY of *M. tuberculosis*. 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.

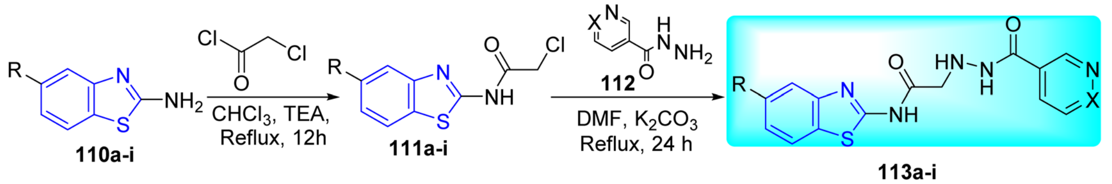
B. N. Ravi and co-workers described the synthesis of bioactive Ni(II) complexes **116a–c** from azo dye ligands **115a–c**. Azo dyes were formed from the diazo-coupling of 6-nitro-1,3-benzothiazole **3e** with substituted pyridinone derivatives **114a–c** in presence of $NaNO_2$ in HCl at low temperature range (Scheme 31, Table 25). These Ni(II) complexes possess a structure of $[Ni(L)_2(H_2O)_2]$ 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(3*H*)-thione.

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

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

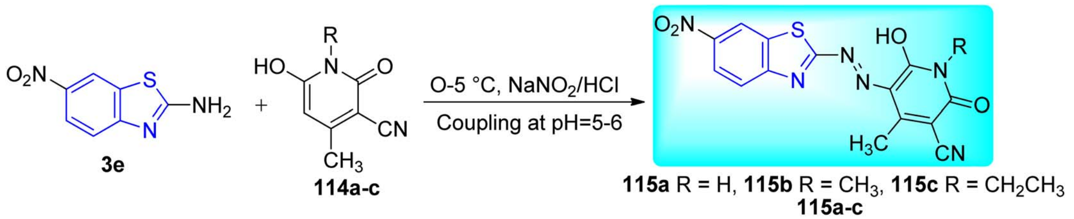
Compounds	R	X	MIC (mg mL^{-1})
113a	H	H	50
113b	OCH_3	H	250
113c	OC_2H_5	H	100
113d	OH	H	250
113e	Cl	H	500
113f	F	H	250
113g	H	N	62.5
113h	OCH_3	N	62.5
113i	OC_2H_5	N	100
INH	—	—	0.20

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

By using the Microplate Alamar Blue Assay (MABA), the anti-tubercular activity of the azo dye ligands and their Ni(II) 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

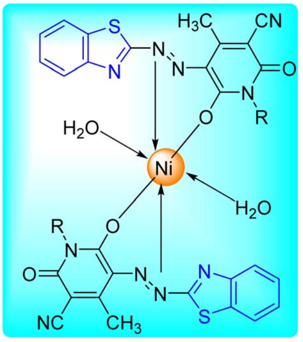


Scheme 31 Synthesis of azo-dye ligands.

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

Compounds	100 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.60 μg mL^{-1}	0.80 μg 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.

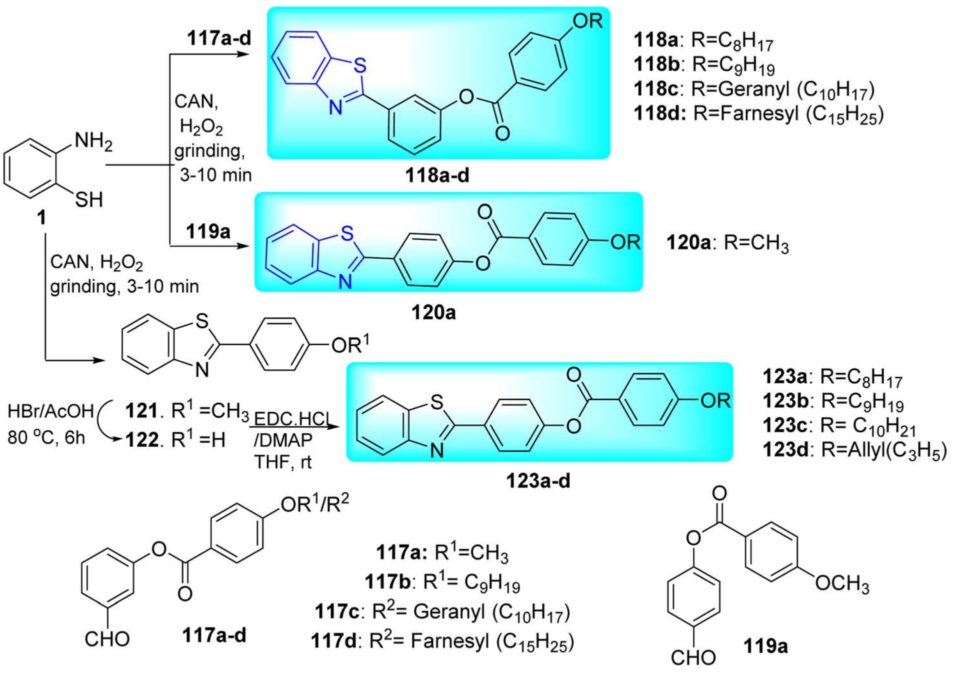


116a R = H, **116b** R = CH_3, **116c** R = CH_2CH_3
116a-c

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

were determined in between 56–32 μg mL^{-1} against replicating Mtb and 40–28 μg 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 μg 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-2-yl)-2,4-dihydro-3*H* pyrazol-3-one **124** at lower temperature. Initial step involved the diazotization of substituted anilines in presence of $NaNO_2/H_2SO_4$. 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]

Compounds	MIC (μg mL^{-1}) against $H_{37}Rv$ 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

[a] NT: not tested.

The synthesized compounds were screened for their anti-mycobacterial 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 μg 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[a]

Compounds	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.6 μg 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

[a] S: sensitive, R: resistant.

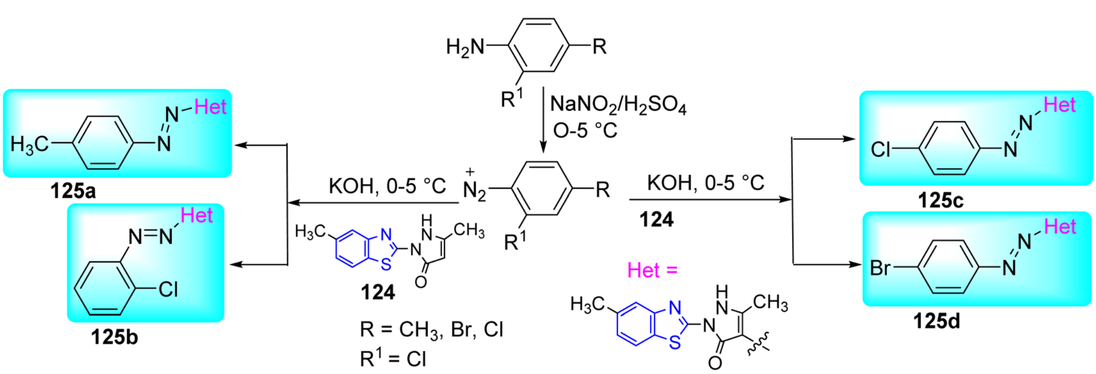
found to exhibit better activity with a MIC value of 1.6 μg mL^{-1} which was lesser than standard drugs like Pyrazinamide, Streptomycin and Ciprofloxacin which have MIC values 3.125 μg mL^{-1}, 6.25 μg mL^{-1}, 3.125 μg mL^{-1} respectively (Table 28).

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.

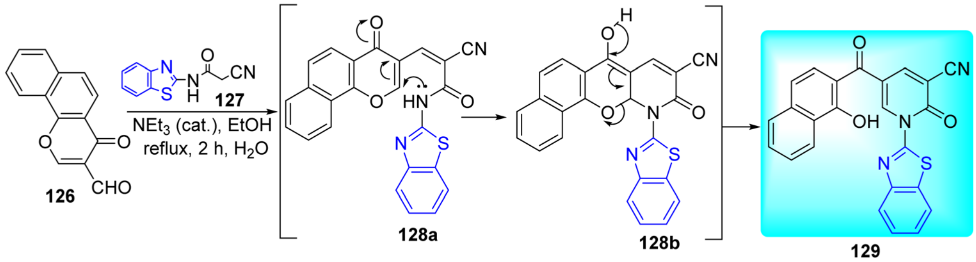
Nagaraja and co-workers synthesized 4-hydroxy coumarin containing benzothiazole based azo dye **132.** Initial step involved the diazotization of 2-amino substituted benzothiazoles in presence of $NaNO_2/H_2SO_4$. Final step involved diazo-coupling of 4-hydroxy coumarin **20** and diazotized benzothiazole 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 μg mL^{-1} and resistant at 0.8 μg mL^{-1}.

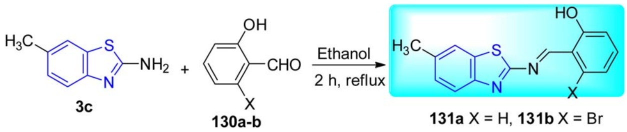
M. Bhat and co-workers synthesized a series of azo-ester derivatives of benzothiazole **134a–k** *via* Steglich esterification



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 anti-tubercular activity. Among the synthesized compounds **134d** and **134j** showed better anti-tubercular activity with a MIC value of 1.6 μg mL^{-1} which was less than that of standard drugs like Streptomycin (MIC 6.25 μg mL^{-1}) and Pyrazinamide (MIC 3.125 μg 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-

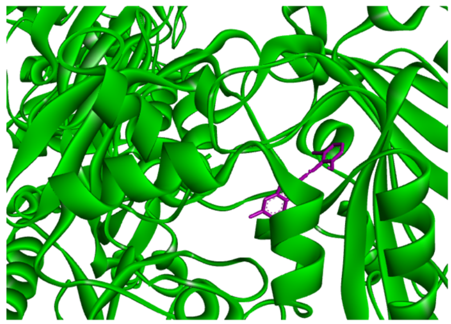


Fig. 13 3D representation of ligand **131b** and its interactions with active site of 4P8N protein.

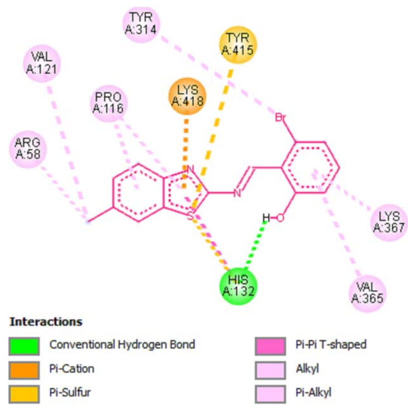
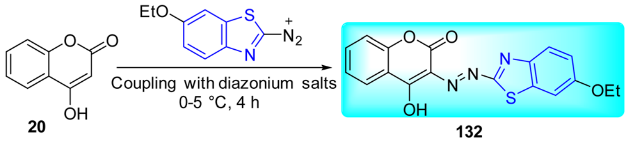


Fig. 14 2D representation of docking results showing interactions of compound **131b** with 4P8N.

Table 28 Anti-tubercular activity of Schiff bases[a]

Compounds	100 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.6 μg mL^{-1}	0.8 μg mL^{-1}
131a	S	S	S	S	S	R	R	R
131b	S	S	S	S	S	S	S	R

[a] S: sensitive, R: resistant.



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

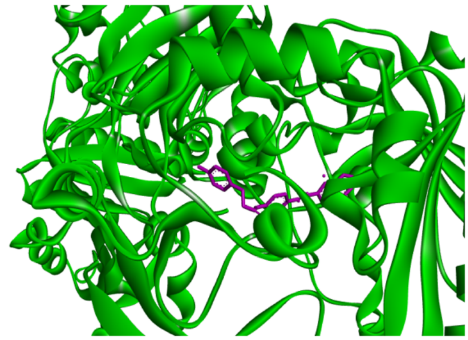
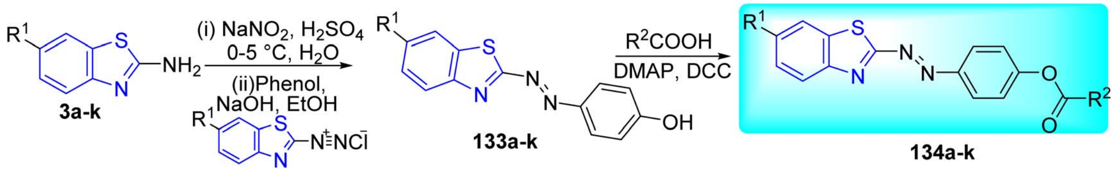


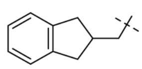
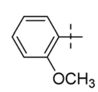
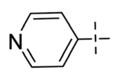
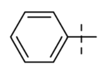
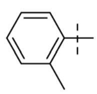
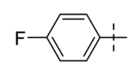
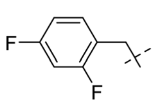
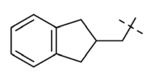
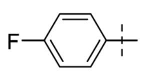
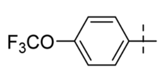
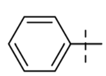
Fig. 15 3D representation of ligand **134j** and its interactions with active site of 4P8N protein.

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	R[1]	R[2]	Yields (%)	MIC (μg mL^{-1})	Compounds	R[1]	R[2]	Yields (%)	MIC (μg mL^{-1})
134a	OEt		55	2.5 ± 0.24	**134h**	OEt		83	25 ± 0.25
134b	OEt		92	6.25 ± 0.18	**134i**	H		81	12.5 ± 0.13
134c	OEt		78	25 ± 0.39	**134j**	H		86	1.6 ± 0.08
134d	OEt		80	1.6 ± 0.15	**134k**	H		67	25 ± 0.24
134e	OEt		71	25 ± 0.43	**STM**	—	—	—	6.25 ± 0.16
134f	OEt		92	50 ± 0.40	**CIP**	—	—	—	3.125 ± 0.22
134g	OEt		88	50 ± 0.37	**PZA**	—	—	—	3.125 ± 0.35

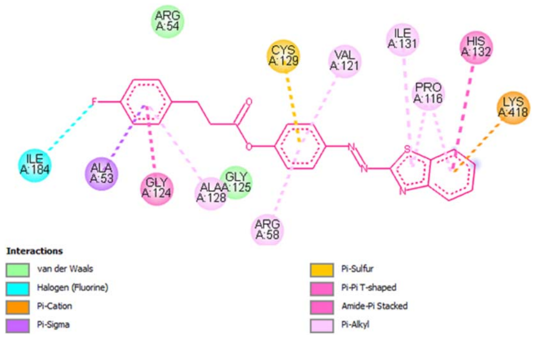
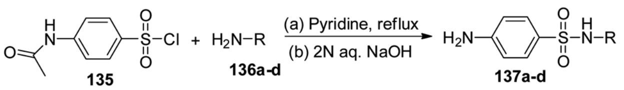
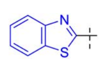
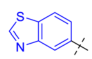
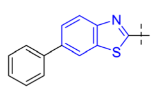
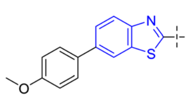
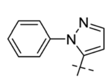


Fig. 16 2D representation of docking results showing interaction of compound **134j** with 4P8N protein.



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		14.26
137b		>32
137c		>32
137d		>32
SPA		5.51

(**142b–d**), pyrrolidine (**144a–c**) and pyrimidine (**145b** and **145d**) moieties with MIC values ranging from 3.12 to 1.6 $\mu g\ mL^{-1}$. 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 $NaNO_2$/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 $\mu g\ mL^{-1}$). However, among the synthesized dyes, compound **147d** with an ethoxy substitution at the benzothiazole's 6th position exhibited lower sensitivity (MIC = 3.2 $\mu g\ mL^{-1}$) (Table 32).

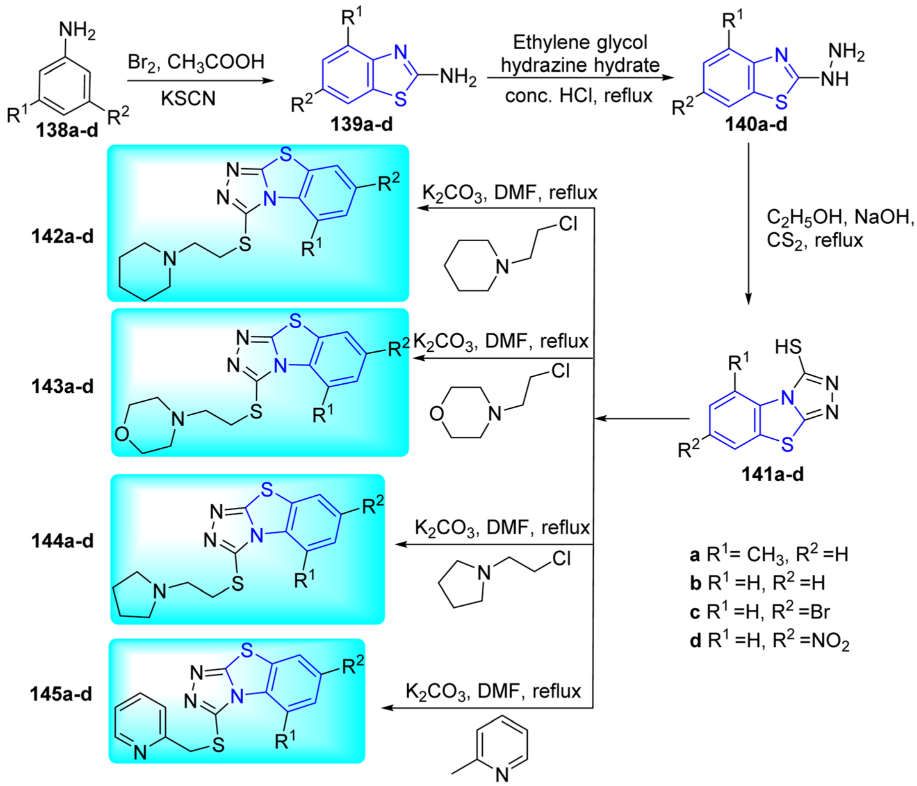
Ethambutol, an anti-TB medicine, is known to target the arabinosyl transferases EmbA, EmbB, and EmbC, which are known to be involved in the manufacturing of the cell walls in *M. tuberculosis*. The donor and acceptor interactions as observed from docking predicts the mechanism of inhibition of arabinosyl 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-linked-chalcones **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 3-aminoacetophenone **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 $\mu g\ mL^{-1}$. Moreover, compounds **151d** and **151e** had notable inhibitory action with values of 12.5 and 12.5 $\mu g\ mL^{-1}$ 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 μM. Whereas sulfamoyl masked derivatives **155** and **156** possess good anti-tubercular activity with MIC value of 0.30 μM and 5.0 μM 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



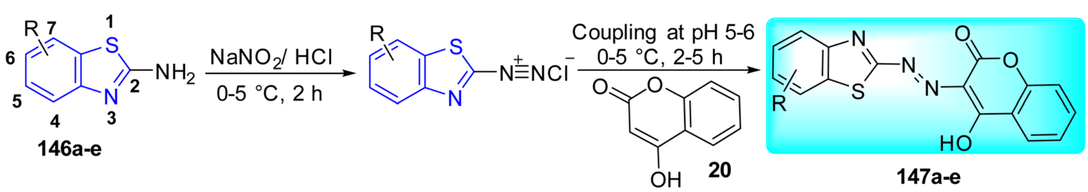
Scheme 39 Schematic pathway for the synthesis of triazole conjugated benzothiazole derivatives.

Table 31 Anti-tubercular activity of triazole conjugated benzothiazole derivatives

Compounds	MIC (μg mL^{-1})	Docking score (kJ mol^{-1})	Compounds	MIC (μg mL^{-1})	Docking score (kJ mol^{-1})
142a	25	−5.999	**144c**	1.6	−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 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.6 μg mL^{-1}	0.8 μg mL^{-1}
147a	H	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

[a] S: sensitive, R: resistant.

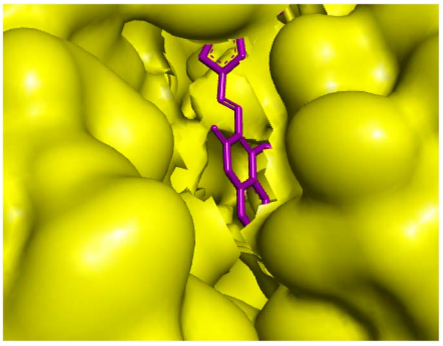


Fig. 17 Surface representation of docking between ligand **147e** and 7BVF protein.

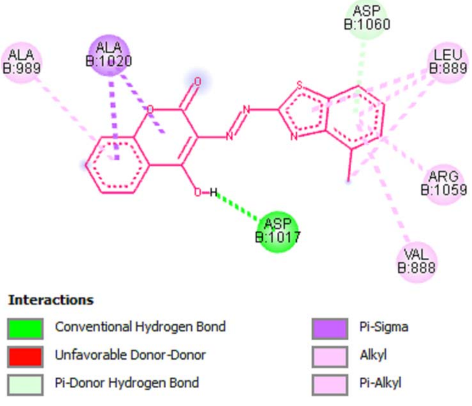
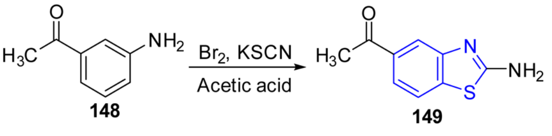


Fig. 18 2D view showing interaction between ligand **147e** and various amino acids of 7BVF protein.

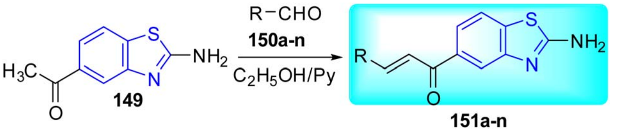
Me respectively. A CF_3 substituted oxime **170** was prepared from hydrated compound **169** using hydroxyl amine under reflux condition. A reaction of 2-benzothiazoleacetonitrile **152** and hydroxylamine, followed by cyclization with acetic anhydride, was used to create 1, 2, 4-oxadiazole **171** 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 $POCl_3$ and Lawesson's reagent to produce oxadiazole and thiadiazoles **179–181** (Scheme 44, Table 35).[79]

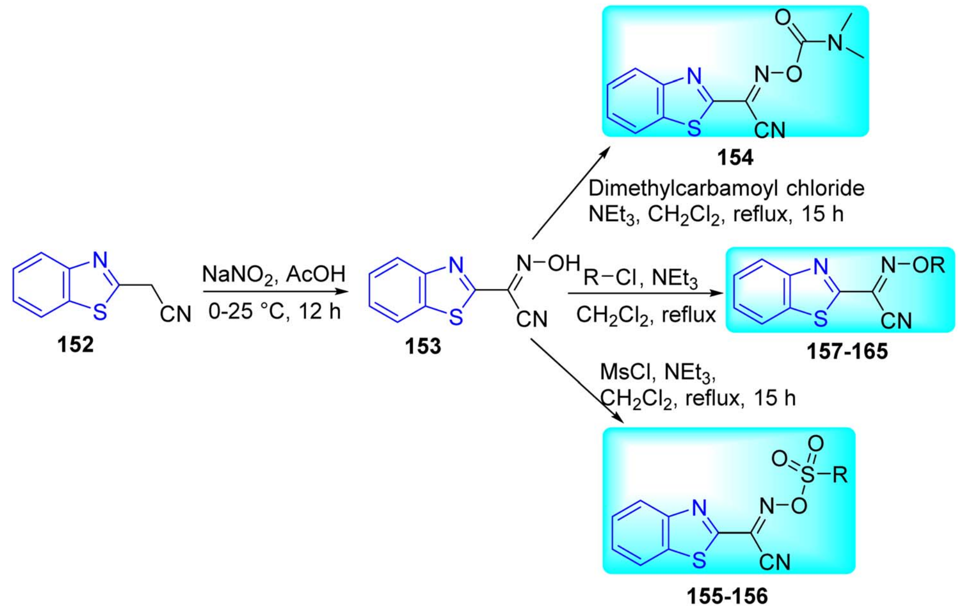
M. J. Zala and co-workers synthesized some novel pyrazolyl-pyrazoline derivatives **187a–d** from green method of synthesis. The Vilsmeier–Hack reaction was used to create the starting material, 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **182**. Further reaction of **182** with substituted thiophenols **183** and **184** in presence of K_2CO_3 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-1,3-thiazole **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]



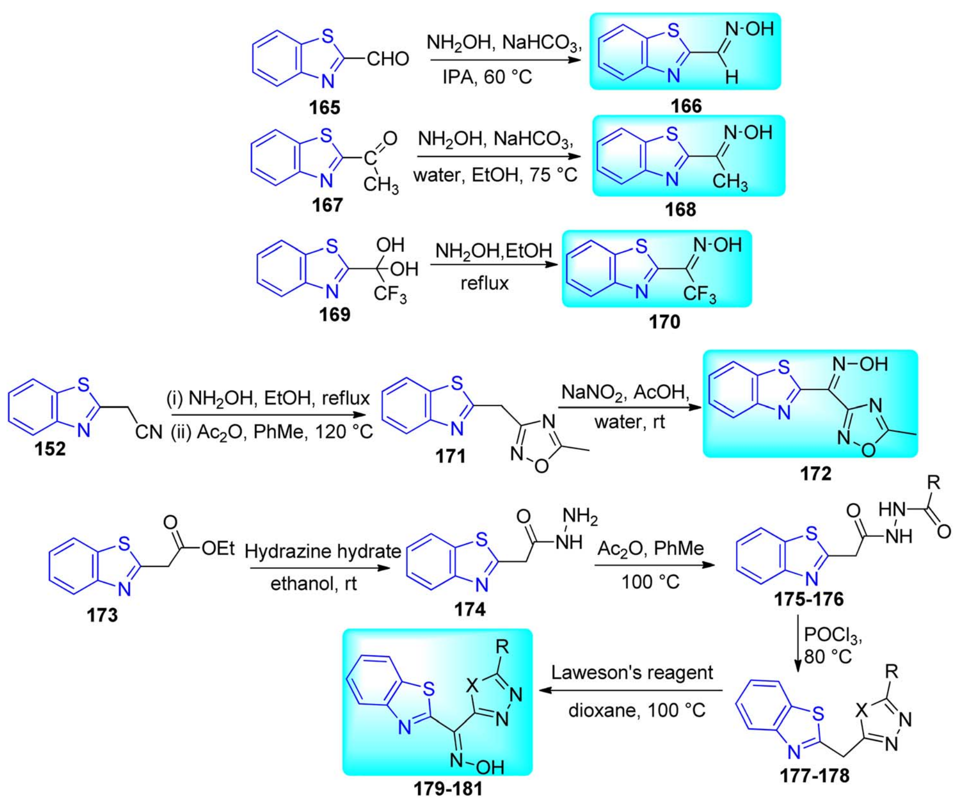
Scheme 42 Synthesis of benzothiazole linked substituted chalcones.

Table 33 Anti-tubercular activity of benzothiazole linked substituted chalcones

Compounds	R	MIC (μg 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$_2C_6H_4$	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	–$CH_2COOCH_2CH_3$	>160
158	–$CH_2CON(CH_2CH_3)_2$	>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

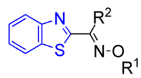
reductase inhA of *M. tuberculosis* is an attractive, validated target for anti-TB drug development. Moreover, direct inhibitors of inhA remain effective against inhA variants with mutations associated with Isoniazid resistance. With very good binding affinity of −10.5 kcal mol^{-1} ligand **187d** can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

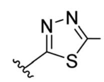
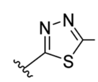
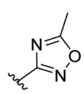
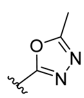
Table 36 Anti-tubercular evaluation of pyrazolyl-pyrazoline derivatives of benzothiazole

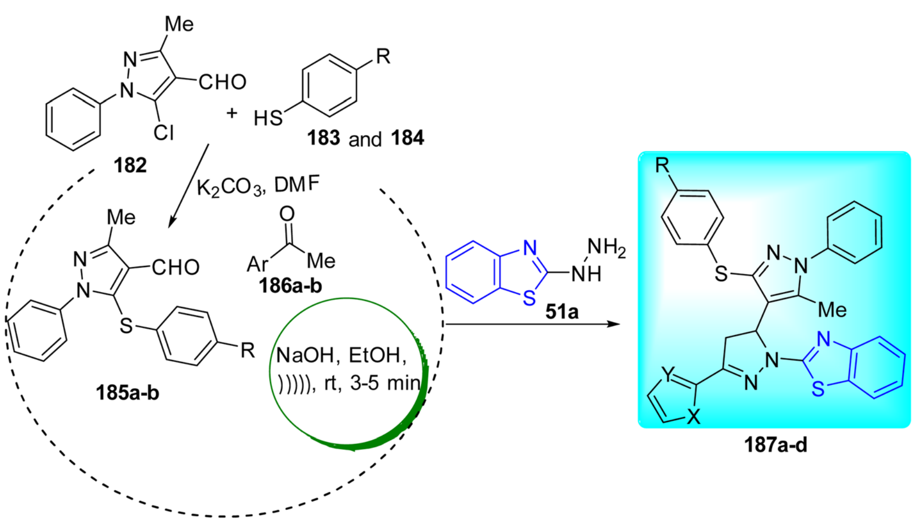
Compounds	R	X	Y	% inhibition
187a	Me	NH	CH	91
187b	Me	S	N	96
187c	F	NH	CH	75
187d	F	S	N	98
RIF	—	—	—	98
INH	—	—	—	99

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

Optimization of nitrile functionality



Compounds	R^1	R^2	MIC (μM)	Compounds	R^1	R^2	MIC (μM)
166	H	H	>160	**180**	H		2.5
168	H	Me	>125	**181**	H		0.78
170	H	CF_3	37	**RIF**	—	—	0.009
172	H		>160	**INH**	—	—	0.14
179	H		160				



Scheme 45 Synthesis of pyrazolyl-pyrazoline derivatives of benzothiazole.

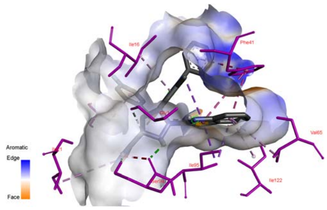


Fig. 19 3D view of interactions shown by ligand **187d** and active site of 4DRE protein.

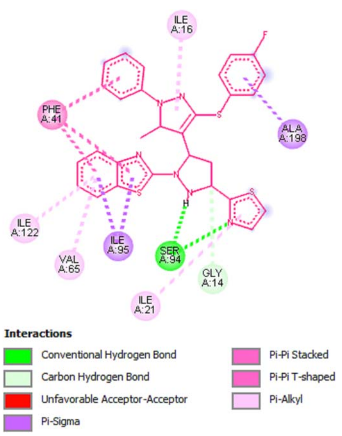


Fig. 20 2D view of interactions between ligand **187d** and various amino acids of 4DRE protein chain.

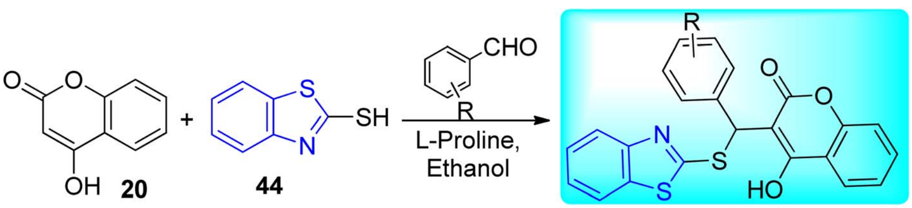
alternative in case of Isoniazid resistance due to mutations in *inhA* gene (Fig. 19 and 20).

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 $-OCH_3$ 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 4,7-dichloroquinoline 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

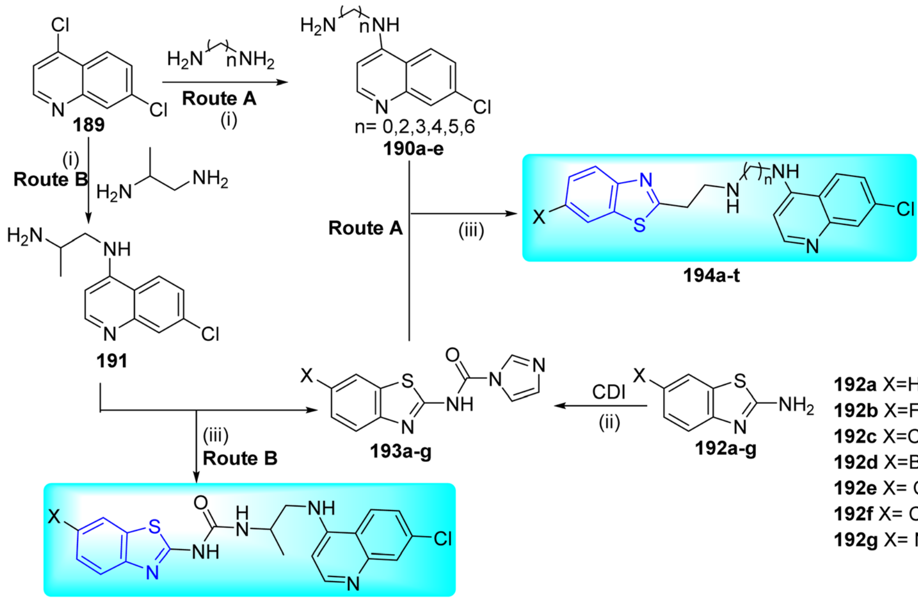


Scheme 46 Synthesis of [(1,3-benzothiazol-2-ylsulfanyl) (phenyl)methyl]-2*H*-chromen-4-ol derivatives.

Table 37 Anti-tubercular activity of [(1,3-benzothiazol-2-ylsulfanyl) (phenyl)methyl]-2*H*-chromen-4-ol analogues[a]

Compounds	R	100 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	12.5 μg mL^{-1}	6.25 μg mL^{-1}	3.12 μg mL^{-1}	1.6 μg mL^{-1}	0.8 μg mL^{-1}
188a	H	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	H	$H_2N–NH_2$	21.001	>125	**194o**	Cl	$H_2N(CH_2)_4NH_2$	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	$H_2N(CH_2)_6NH_2$	7.597	14.617
194e	CF_3	$H_2N(CH_2)_2NH_2$	NT	NT	**194s**	Br		8.76	20.954
194f	Cl		125	>125	**194t**	F		6.974	31.25
194g	Br		8.89	14.898	**194u**	CF_3	1,2-diaminopropane	0.968	5.732
194h	F		62.5	62.5	**194v**	F		>125	>125
194i	CF_3	$H_2N(CH_2)_3NH_2$	7.812	12.837	**194w**	Br		8.191	14.001
194j	Cl		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	H		9.628	9.447	**RIF**	—		0.03	0.001
194m	Br		15.924	16.863					
194n	F		>125	125					

[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 μM with MIC_{90} values between 1–10 μM. Thirteen compounds **194b, 194g, 194i–j, 194l, 194o–p, 194r–t** and **194x–y** demonstrated potential anti-tubercular activity (Table 38). From cytotoxicity assay it was observed that compound **194t** exhibited the highest cell viability at the MIC_{90} (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.

Carbanilide derivatives of benzothiazole exhibited excellent anti-tubercular activity with MIC of 0.78 μg mL^{-1} as compared to Ethambutol (1.56 μg mL^{-1}). Benzothiazole based Schiff bases were also potent against Mtb with MIC of 0.8–1.6 μg mL^{-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 μg mL^{-1}, this activity was much better than the standard drugs Streptomycin (MIC 6.25 μg mL^{-1}) and Pyrazinamide (MIC 3.125 μg 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 μg mL^{-1} as compared to the standard drug Streptomycin (6.25 μg mL^{-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 μg mL^{-1}. Among the hydrazine sub-series, compound containing CF_3 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 anti-tubercular drugs that can obliterate mycobacterial infections.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful to Jawaharlal Nehru University for providing facilities to write this detailed review on tuberculosis. RY, DM is grateful to JNU for institute fellowships. KS is thankful to CSIR and RT is thankful to UGC New Delhi for Research Fellowships. We are grateful to Ultra International and Sanganeria Foundation for supporting lab furniture to Glycochemistry Laboratory at JNU.

References

1 S. H. E. Kaufmann and A. J. McMichael, *Nat. Med.*, 2005, **11**, S33.
2 A. Zumla, P. Nahid and S. T. Cole, *Nat. Rev. Drug Discovery*, 2013, **12**, 388–404.
3 S. Landge, A. B. Mullick, K. Nagalapur, J. Neres, V. Subbulakshmi, K. Murugan, A. Ghosh, C. Sadler, M. D. Fellows, V. Humnabadkar, J. Mahadevaswamy, P. Vachaspati, S. Sharma, P. Kaur, M. Mallya, S. Rudrapatna, D. Awasthy, V. K. Sambandamurthy, F. Pojer, S. T. Cole, T. S. Balganesh, B. G. Ugarkar, V. Balasubramanian, B. S. Bandodkar, M. Panda and V. Ramachandran, *Bioorg. Med. Chem.*, 2015, **23**, 7694–7710.
4 L. D'Ambrosio, R. Centis, G. Sotgiu, E. Pontali, A. Spanevello and G. B. Migliori, *ERJ Open Res.*, 2015, **1**, 00010–02015.
5 K. N. Venugopala, M. A. Khedr, M. Pillay, S. K. Nayak, S. Chandrashekharappa, B. E. Aldhubiab, S. Harsha, M. Attimard and B. Odhav, *J. Biomol. Struct. Dyn.*, 2019, **37**, 1830–1842.
6 R. J. O'BRIEN and P. P. NUNN, *Am. J. Respir. Crit. Care Med.*, 2001, **163**, 1055–1058.
7 K. A. Gaidhani, M. Harwalkar and P. S. Nirgude, *World J. Pharm. Res.*, 2014, **3**, 5041–5048.
8 B. Berk, Y. A. Tahirovic, E. F. Bülbül and S. N. Biltekin, *Acta Pharm. Sci.*, 2017, **55**, 17–28.
9 X. Gao, J. Liu, X. Zuo, X. Feng and Y. Gao, *Molecules*, 2020, **25**, 1674, DOI: 10.3390/molecules25071675.
10 R. S. Keri, S. A. Patil, S. Budagumpi and B. M. Nagaraja, *Chem. Biol. Drug Des.*, 2015, **86**, 410–423.
11 M. A. Khedr, M. Pillay, S. Chandrashekharappa, D. Chopra, B. E. Aldhubiab, M. Attimarad, O. I. Alwassil, K. Mlisana, B. Odhav and K. N. Venugopala, *J. Biomol. Struct. Dyn.*, 2018, **36**, 2163–2178.
12 S. K. Nayak, K. N. Venugopala, D. Chopra and T. N. G. Row, *CrystEngComm*, 2011, **13**, 591–605.
13 S. K. Nayak, K. N. Venugopala, T. Govender, H. G. Kruger and G. E. M. Maguire, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2013, **69**, o70.
14 V. N. Telvekar, V. K. Bairwa, K. Satardekar and A. Bellubi, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 649–652.
15 M. Sharma, P. Chaudhary, P. K. Sharma, A. Sharma and J. Varshney, *Int. J. Pharm. Res.*, 2010, **2**, 5–11.
16 I. Yildiz-Oren, I. Yalcin, E. Aki-Sener and N. Ucarturk, *Eur. J. Med. Chem.*, 2004, **39**, 291–298.
17 L. Racanè, V. Tralić-Kulenović, D. W. Boykin and G. Karminski-Zamola, *Molecules*, 2003, **8**, 342–349.
18 R. S. Keri, B. S. Sasidhar, B. M. Nagaraja and M. A. Santos, *Eur. J. Med. Chem.*, 2015, **100**, 257–269.
19 A. El-Mekabaty, M. A. Sofan, A. M. Hasel and S. B. Said, *ChemistrySelect*, 2021, **6**, 2569–2575.
20 J. B. Baell, A. J. Harvey and R. S. Norton, *J. Comput.-Aided Mol. Des.*, 2002, **16**, 245–262.
21 F. Delmas, A. Avellaneda, C. Di Giorgio, M. Robin, E. De Clercq, P. Timon-David and J. P. Galy, *Eur. J. Med. Chem.*, 2004, **39**, 685–690.
22 K. Oketani, N. Nagakura, K. Harada and T. Inoue, *Eur. J. Pharmacol.*, 2001, **422**, 209–216.
23 R. Paramashivappa, P. Phani Kumar, P. V. Subba Rao and A. Srinivasa Rao, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 657–660.

24 H. Nath and S. Ryoo, in *Tuberculosis - Current Issues in Diagnosis and Management*, ed. B. H. Mahboub and M. G. Vats, IntechOpen Limited, London, UK, 2013, pp. 163–180, DOI: 10.5772/54960.

25 M. A. Espinal, A. Laszlo, L. Simonsen, F. Boulahbal, S. J. Kim, A. Reniero, S. Hoffner, H. L. Rieder, N. Binkin, C. Dye, R. Williams and M. C. Raviglione, *N. Engl. J. Med.*, 2001, **344**, 1294–1303.

26 H. W. Al-Humadi, R. J. Al-Saigh and A. W. Al-Humadi, *Front. Pharmacol.*, 2017, **8**, 1–10.

27 R. V. Chikhale, M. A. Barmade, P. R. Murumkar and M. R. Yadav, *J. Med. Chem.*, 2018, **61**, 8563–8593.

28 H. B. Rode, D. M. Lade, R. Grée, P. S. Mainkar and S. Chandrasekhar, *Org. Biomol. Chem.*, 2019, **17**, 5428–5459.

29 C. Vilchèze, *Appl. Sci.*, 2020, **10**, 2278.

30 A. Telenti, P. Imboden, F. Marchesi, L. Matter, K. Schopfer, T. Bodmer, D. Lowrie, M. J. Colston and S. Cole, *Lancet*, 1993, **341**, 647–651.

31 Y. Zhang, M. M. Wade, A. Scorpio, H. Zhang and Z. Sun, *J. Antimicrob. Chemother.*, 2003, **52**, 790–795.

32 W. Shi, X. Zhang, X. Jiang, H. Yuan, J. S. Lee, C. E. Barry, H. Wang, W. Zhang and Y. Zhang, *Science*, 2011, **333**, 1630–1632.

33 J. G. Y. Chan, X. Bai and D. Traini, *Expert Opin. Drug Delivery*, 2014, **11**, 421–431.

34 L. Yan, *Med. Chem.*, 2015, **5**, 412–414.

35 N. Honore and S. T. Cole, *Antimicrob. Agents Chemother.*, 1994, **38**, 238–242.

36 A. Sowajassatakul, T. Prammananan, A. Chaiprasert and S. Phunpruch, *BMC Microbiol.*, 2014, **14**, 1–7.

37 A. D. Pranger, R. Van Altena, R. E. Aarnoutse, D. Van Soolingen, D. R. A. Uges, J. G. W. Kosterink, T. S. Van Der Werfe and J. W. C. Alffenaar, *Eur. Respir. J.*, 2011, **38**, 888–894.

38 M. H. Scheetz, S. A. Knechtel, M. Malczynski, M. J. Postelnick and C. Qi, *Antimicrob. Agents Chemother.*, 2008, **52**, 2256–2259.

39 F. Wang, R. Langley, G. Gulten, L. G. Dover, G. S. Besra, W. R. Jacobs and J. C. Sacchettini, *J. Exp. Med.*, 2007, **204**, 73–78.

40 K. A. Wolff and L. Nguyen, *Expert Rev. Anti-Infect. Ther.*, 2012, **10**, 971–981.

41 D. M. Patel, S. D. Patel, P. S. Jaiswal and K. J. Brahmbhatt, *Int. J. Drug Dev. Res.*, 2012, **4**, 76–91.

42 R. Chikhale, S. Menghani, R. Babu, R. Bansode, G. Bhargavi, N. Karodia, M. V. Rajasekharan, A. Paradkar and P. Khedekar, *Eur. J. Med. Chem.*, 2015, **96**, 30–46.

43 F. M. Shaikh, N. B. Patel, G. Sanna, B. Busonera, P. La Colla and D. P. Rajani, *Med. Chem. Res.*, 2015, **24**, 3129–3142.

44 H. A. Abdel-Aziz, W. M. Eldehna, M. Fares, S. T. A. Al-Rashood, K. A. Al-Rashood, M. M. Abdel-Aziz and D. H. Soliman, *Int. J. Mol. Sci.*, 2015, **16**, 8719–8743.

45 A. B. Patel and R. M. Raval, *Res. Chem. Intermed.*, 2016, **42**, 2163–2175.

46 S. Pancholia, T. M. Dhameliya, P. Shah, P. S. Jadhavar, J. P. Sridevi, P. Yogeshwari, D. Sriram and A. K. Chakraborti, *Eur. J. Med. Chem.*, 2016, **116**, 187–199.

47 M. N. Bhoi, M. A. Borad, E. A. Pithawala and H. D. Patel, *Arabian J. Chem.*, 2019, **12**, 3799–3813.

48 M. N. Bhoi, M. A. Borad, D. J. Jethava, P. T. Acharya, E. A. Pithawala, C. N. Patel, H. A. Pandya and H. D. Patel, *Eur. J. Med. Chem.*, 2019, **177**, 12–31.

49 G. Samala, P. B. Devi, S. Saxena, N. Meda, P. Yogeeswari and D. Sriram, *Bioorg. Med. Chem.*, 2016, **24**, 1298–1307.

50 G. Samala, R. Nallangi, P. B. Devi, S. Saxena, R. Yadav, J. P. Sridevi, P. Yogeeswari and D. Sriram, *Bioorg. Med. Chem.*, 2014, **22**, 4223–4232.

51 A. Yardily, V. Anu Danie, B. A. Rosy and T. F. Abbs Fen Reji, *J. Saudi Chem. Soc.*, 2016, **20**, 278–281.

52 V. M. Patel and N. B. Patel, *Chem. Biol. Interface*, 2017, **7**, 145–153.

53 S. S. Jawoor, S. A. Patil and S. S. Toragalmath, *J. Coord. Chem.*, 2018, **71**, 271–283.

54 R. S. Reshma, V. U. Jeankumar, N. Kapoor, S. Saxena, K. A. Bobesh, A. R. Vachaspathy, P. E. Kolattukudy and D. Sriram, *Bioorg. Med. Chem.*, 2017, **25**, 2761–2771.

55 A. C. Pinheiro, M. V. N. de Souza, M. C. S. Lourenço, C. F. da Costa, T. C. Baddeley, J. N. Low, S. M. S. V. Wardell and J. L. Wardell, *J. Mol. Struct.*, 2019, **1178**, 655–668.

56 T. M. Dhameliya, R. Tiwari, A. Banerjee, S. Pancholia, D. Sriram, D. Panda and A. K. Chakraborti, *Eur. J. Med. Chem.*, 2018, **155**, 364–380.

57 M. N. Matada and K. Jathi, *J. Mol. Struct.*, 2019, **1180**, 196–208.

58 M. Bhat and S. L. Belagali, *Future Med. Chem.*, 2018, **10**, 71–87.

59 M. Krause, H. Foks, E. Augustynowicz-Kopeć, A. Napiórkowska, M. Szczesio and K. Gobis, *Molecules*, 2018, **23**, 1–15.

60 J. Graham, C. E. Wong, J. Day, E. McFaddin, U. Ochsner, T. Hoang, C. L. Young, W. Ribble, M. A. DeGroote, T. Jarvis and X. Sun, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3177–3181.

61 S. Deng, H. Chen, X. Ma, Y. Zhou, K. Yang, Y. Lan and Q. Song, *Chem. Sci.*, 2019, **10**, 6828–6833.

62 A. P. Chavan, R. R. Deshpande, N. A. Borade, A. Shinde, P. C. Mhaske, D. Sarkar and V. D. Bobade, *Med. Chem. Res.*, 2019, **28**, 1873–1884.

63 J. Gawad and C. Bonde, *Synth. Commun.*, 2019, **49**, 2696–2708.

64 D. J. Jethava, P. T. Acharya, M. S. Vasava, M. N. Bhoi, Z. A. Bhavsar, S. K. Rathwa, D. P. Rajani and H. D. Patel, *J. Mol. Struct.*, 2019, **1184**, 168–192.

65 K. Hazra and B. Nandha, *Int. J. Chem.*, 2020, **59**, 1388–1399.

66 B. M. Sahoo, B. K. Banik, A. K. Mahato, C. N. Shanthi and B. C. Mohantad, in *Green Approaches in Medicinal Chemistry for Sustainable Drug Design*, Elsevier, 2020, pp. 779–818.

67 P. T. Acharya, D. J. Jethava, M. S. Vasava, Z. A. Bhavsar, M. N. Bhoi, D. P. Rajani and H. D. Patel, *Int. J. Chem.*, 2020, **59**, 1721–1737.

68 B. N. Ravi, J. Keshavayya and N. M. Mallikarjuna, *J. Inorg. Organomet. Polym. Mater.*, 2020, **30**, 3781–3796.

69 A. B. Velappan, D. Datta, R. Ma, S. Rana, K. S. Ghosh, N. Hari, S. G. Franzblau and J. Debnath, *Bioorg. Chem.*, 2020, **103**, 104170.
70 M. R. Maliyappa, J. Keshavayya, N. M. Mallikarjuna and I. Pushpavathi, *J. Mol. Struct.*, 2020, **1205**, 127576.
71 M. A. Abozeid, A. A. El-Sawi, M. Abdelmoteleb, H. Awad, M. M. Abdel-Aziz, A. R. Hassan Abdel-Rahman and E. S. Ibrahim El-Desoky, *RSC Adv.*, 2020, **10**, 42998–43009.
72 J. K. Suyambulingam, R. Karvembu, N. S. P. Bhuvanesh, I. V. M. V. Enoch, P. M. Selvakumar, D. Premnath, C. Subramanian, P. Mayakrishnan, S. H. Kim and I. M. Chung, *J. Adhes. Sci. Technol.*, 2020, **34**, 2590–2612.
73 O. Nagaraja, Y. D. Bodke, I. Pushpavathi and S. Ravi Kumar, *Heliyon*, 2020, **6**, e042456.
74 M. Bhat and S. L. Belagali, *Anti-Infect. Agents*, 2019, **18**, 15–23.
75 H. Chen, B. Wang, P. Li, H. Yan, G. Li, H. Huang and Y. Lu, *Bioorg. Med. Chem. Lett.*, 2021, **40**, 1–6.
76 S. V. Mamatha, S. L. Belagali and M. Bhat, *Anti-Infect. Agents*, 2019, **18**, 362–374.
77 B. Manjunatha, Y. D. Bodke, O. Nagaraja, T. N. Lohith, G. Nagaraju and M. A. Sridhar, *J. Mol. Struct.*, 2021, **1246**, 131170.
78 S. A. Satyadev, *Int. J. Pharm. Res.*, 2021, **12**, 576–586.
79 R. Van Der Westhuyzen, A. Mabhula, P. M. Njaria, R. Müller, D. Ngumbu Muhunga, D. Taylor, N. Lawrence, M. Njoroge, C. Brunschwig, A. Moosa, V. Singh, S. P. S. Rao, U. H. Manjunatha, P. W. Smith, D. F. Warner, L. J. Street and K. Chibale, *J. Med. Chem.*, 2021, **64**, 9444–9457.
80 M. J. Zala and J. J. Vora, *Russ. J. Org. Chem.*, 2021, **57**, 1725–1732.
81 P. R. Kadam, Y. D. Bodke, M. D. Naik, O. Nagaraja and B. Manjunatha, *Results Chem.*, 2022, **4**, 100303.
82 R. Moodley, C. Mashaba, G. H. Rakodi, N. B. Ncube, M. V. Maphoru, M. O. Balogun, A. Jordan, D. F. Warner, R. Khan and M. Tukulula, *Pharmaceuticals*, 2022, **15**, 576.

