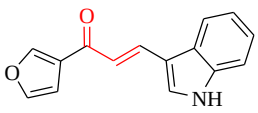
2. Literature

The reported literature provides a vast database of compounds as anti-TB agents. These reported compounds exhibit activity on one or the other targets like ATP synthase, DprE1, MmpL3, InhA etc. Thus, with an aim to better understand the already reported research work, the literature section is divided into: discussion related to anti-TB agents and Recent development of DprE1 inhibitors.

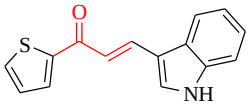
2.1 Anti-tubercular agents

2.1.1 Chalcones as anti-tubercular agents

In 2020, Ramesh D *et al*.[1] designed and synthesized indole chalcones as potential agents against *Mtb*. Three compounds (**43-45)** demonstrated anti-TB activity with MIC values of 210, 197, and 236 µM respectively. Docking studies indicated that compound (**43**) binds to Kas A protein. Further, these were found to be non-cytotoxic. Additionally, the activity of these three compounds is linked to the size of heterocycle and their metal chelation ability.



(43)



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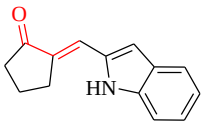
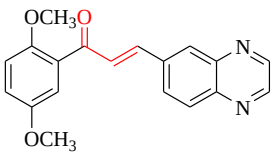


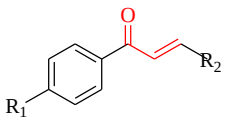
(45)

Muradas T C *et al*.[2] developed quinoxaline based chalcones against *Mtb*. During the primary screening six compounds showed *Mtb* inhibition in laboratory strains. Based on the data, compound (**46)** was taken as a hit obtained for further investigation. It showed MICs of 1.56 µg/mL and 3.135 µg/mL against *Mtb* and clinical isolates respectively. Interestingly, this chalcone depicted synergistic effects when combined with moxifloxacin. It was noteworthy that compound (**46)** did not inhibit the cytochrome P_{450} isoforms. A mechanistic point of view implied that the mechanism of action of compound (**46**) is other than those used by INH as compound (**46)** was found not to affect the biosynthesis of mycolic acid or non-hydroxylated fatty acid.

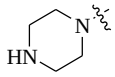
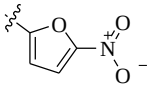
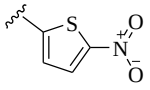
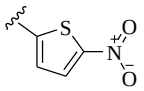
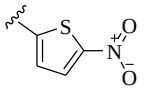


(46)

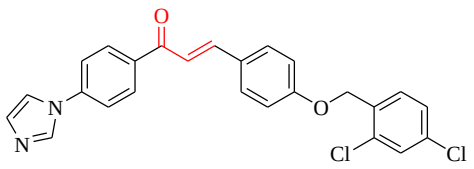
In 2017 Gomes M N *et al.*[3] reported series of potent chalcone derivatives with anti-tubercular activity. Initially, SAR rules along with binary QSAR models using literature were developed. Based on these, 33 compounds were scrutinized for synthesis and biological evaluation. The results of the biological activity revealed that 10 heteroaryl chalcones were exhibiting nanomolar activity against replicating *Mtb*. Four of these compounds, (**47a-47d)** were exhibiting more potency than standard drug INH. The most potent compounds (**47b)** was found to have MABA MIC and LORA MIC 0.19 µM and 1.73 µM respectively[3].



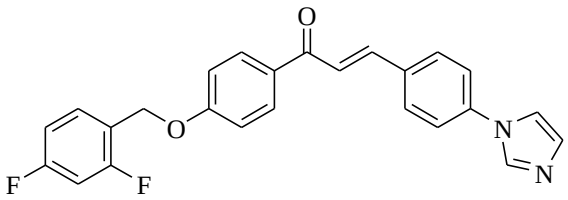
(47)

	R_1	R_2
47a		
47b		
47c	$-C(CH_3)_3$	
47d	$-(CH_2)_3CH_3$	

Marrapu V K *et al.*[4] in 2011 developed novel chalcone derivatives with potent anti-TB activity. Total 27 compounds were tested for *in vitro* anti-TB activity. Ten compounds demonstrated MIC values within the range of 3.12-0.78 µg/mL while, six compounds were found to be non-toxic. These six compounds were further evaluated for *ex vivo* to check the potential to kill intracellular bacilli, wherein two compounds (**48** and **49)** showed 99% and 71% killing respectively. Moreover, compound (**49)** demonstrated moderate *in vivo* activity in mice against virulent *Mtb*.



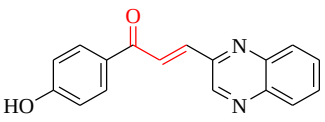
(**48**)



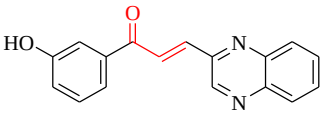
(**49**)

In 2017, Desai V *et al.*[5] developed novel quinoxalinyl chalcone hybrid molecules as anti-TB agents. These derivatives were found to act as ACP reductase inhibitors. All the compounds were evaluated for anti-TB activity by MABA. Compounds (**50** and **51)** containing

-OH group, exhibited noticeably good MIC value of 3.12 µg/mL. Compounds (**50** and **51)** demonstrated good inhibitory activity against enzyme enoyl ACP reductase.

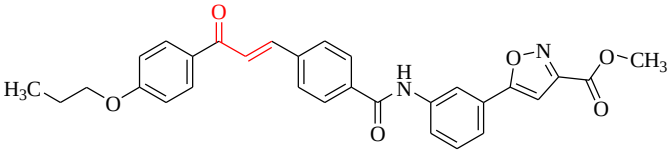


(50)



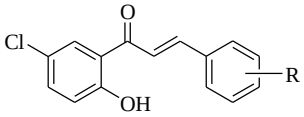
(51)

Sahoo S K *et al.*[6] synthesized and reported SAR of chalcone derivatives as active moiety against drug-resistant *Mtb*. A total of 35 compounds were synthesized, out of which 32 derivatives showed potent *in-vitro* activity with MIC values in the range of 0.12-16 µg/mL. Compound (**52)** can be seen as a potential hit for the development of newer agents. SAR studies revealed that halogen and alkyl substitution compounds were the most potent compounds. The *p*-substituted compounds were the most active derivatives whereas the *m*-substituted analogs were the least potent derivatives. Increased alkyl appendages among *p*-alkoxy derivatives enhanced the potency of the compounds as seen with compound (**52)**. The study revealed that isoxazole methyl ester provides anti-TB activity whereas chalcone moiety improvises potency and selectivity. The most potent compound (**52**) demonstrated MIC value of 0.12 µg/mL.



(52)

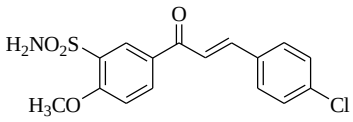
Ammaji S *et al.*[7] reported a series of chalcones as anti-TB and anti-oxidant agents. Two compounds (**53a** and **53b**) were found to exhibit MIC values of 14±0.11 µM and 14±0.017 µM respectively. The docking results revealed that these chalcones may target isocitrate lyase to exhibit anti-TB activity.



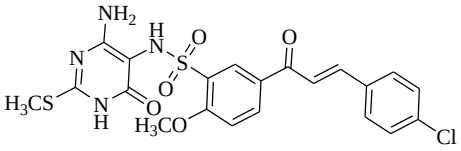
(53)

	R
53a	4-F
53b	3-OCH_3

Castano L F *et al.*[8] synthesized new chalcone-sulphonamide hybrid compounds and examined their anti-TB and anti-cancer activity. New sulphonamide-chalcone derivatives were synthesized using 4-methoxy acetophenone. Two compounds (**54** and **55**) showed significant growth inhibition of Mtb showing MIC ≤20 µM.

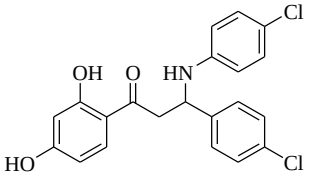


(**54**)



(**55**)

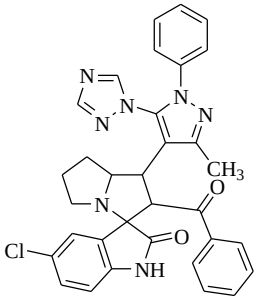
Zhang M *et al*.[9] reported some chalcones and their derivatives as exhibiting anti-TB activity. In the study, previously reported chalcone like anti-bacterial agents were used for generation of a pharmacophore model. Based on the hits, new chalcones derivatives and their thiol-Michael addition analogues were synthesized and evaluated for anti-bacterial activity. Amine-Michael addition analogue (**56**) showed MIC value of 50 µg/mL against Mtb.



(**56**)

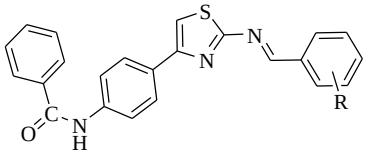
2.1.2 Five membered heterocycles as anti-TB agents

Pogaku *et al*.[10] reported the synthesis of novel pyrazole based derivatives as anti-TB agents. Molecular hybridization approach was used to design a hybrid molecule containing triazole, pyrazole, and spirooxindolopyrrolizidines in a single framework. Compound (**57)** exhibited outstanding activity of MIC value 0.78 µg/mL comparable to the standard drug ethambutol (1.56 µg/mL). All the synthesized compounds exhibited low/no cytotoxicity.



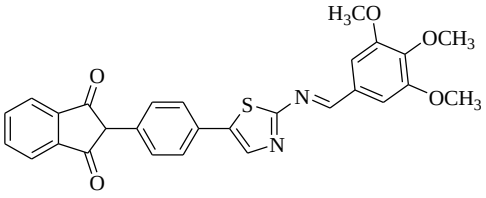
(57)

Rachel C and Kachroo M synthesized 2-amino thiazole-based Schiff bases and evaluated for their anti-TB activity. Three compounds **(58a, 58b** and **59)** demonstrated considerable anti-TB activity with a MIC value of 6.25 µg/mL. Drug likeness predictions revealed that all these compounds comply with Lipinski rule of five and have drug-like properties.



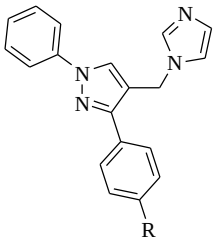
	R
58a	2-NO_2
58b	4-OH

(58)



(59)

Taban I M *et al.*[11] reported pyrazole derivatives as anti-mycobacterial agents. Three series of biarylpyrazole with imidazole or triazole group were reported. The compounds (**60a** and **60b**) were found to have MIC values of 6.25 µg/mL. It was speculated that the anti-mycobacterial activity might be a result of increased lipophilicity as suggested by Hansch analysis.

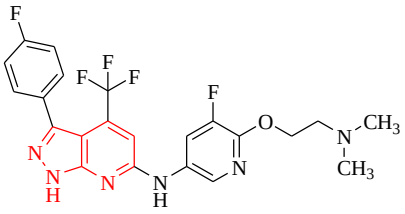


	R
60a	Br
60b	I

(**60**)

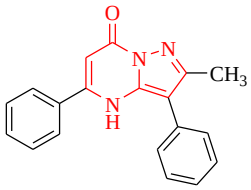
2.1.3 Bicyclic compounds as anti-TB agents

Choi P J *et al.*[12] synthesized pyrazolopyridines as potential ATP synthesis inhibitor of *Mycobacterium tuberculosis*. MIC for compound **(61)** were determined by using MABA and LORA for aerobic and anaerobic bacteria respectively. Results for both the compounds showed moderate MIC_{90} of 8 µg/mL against aerobic cultures and 11 µg/mL against anaerobic cultures.

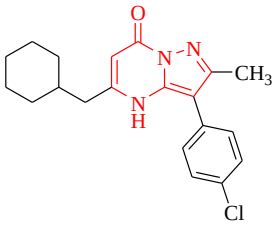


(61)

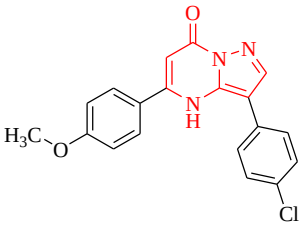
Oh S *et al.*[13] reported the SAR of pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones as anti-tubercular agents. A HTS study of a small molecule database was carried out that yielded compounds (**62-64**) with pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one scaffold as hits. Compounds (**62)** showed MIC value of 12.5 µM, whereas both compound (**63**) and (**64**) showed MIC value of 9.38 µM.



(62)

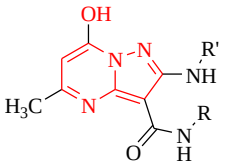


(63)



(64)

Modi P *et al.*[14] in 2019 reported some new pyrazolo[1,5-*a*]pyrimidine derivatives (**65**) as anti-tubercular agents. A total of 26 compounds were designed based on molecular docking. Most of the compounds demonstrated potent activity in MABA assay. Compounds (**65a-65d)** exhibited excellent activity without any cytotoxicity. Molecular dynamics simulation were carried out for 10ns to assess the stability of protein ligand complex. Molecular docking revealed that these derivatives were interacting with InhA enzyme effortlessly. SAR studies concluded that the derivatives with electron withdrawing substitutions elevate the potency. The activity of the synthesized compounds is shown in **Table 2.1**.

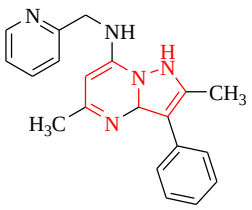


(65a-65d)

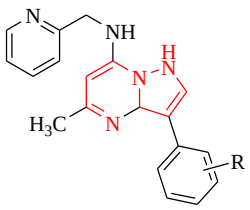
Table 2.1: Results of biological evaluation of compounds (**65a-65d**).

	R	R’	MIC (µg/mL)			Cytotoxicity IC_{50} (µg/mL)
			H37Rv	MDR-TB	XDR-TB	
65a	4-CH_3	4-Cl	3.12	6.25	>100	20.99
65b	NH_2	3, 4-di-Cl	6.25	12.5	50	29.02
65c	2-OCH_3	3-CH_3	3.12	6.25	12.5	21.26
65d	4-F	3, 4-di-F	0.8	3.12	25	13.57
Isoniazid			0.5	6.25	50	ND

Candice S D M *et al.*[15] reported aminopyrazolo[1,5-*a*]pyrimidines (**66** and **67**) as *Mtb* inhibitors. A HTS was carried out to obtain aminopyrazolo[1,5-*a*]pyrimidines as a hit. All the synthesized compounds showed potent *in vitro* anti-TB activity. To study the SAR of these derivatives, substitutions at 7 and 3 position were explored to identify some promising compounds (**66** and **67a-67c)** with MIC_{99} values within the range of 1.25-5 µM. It was observed that 2-pyridylmethylamine moiety at C-7 is important for the activity, whereas C-3 position offered greater degree of flexibility.



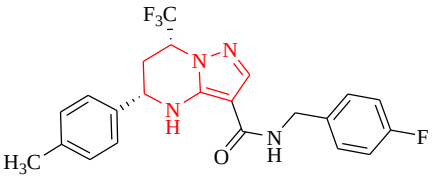
(**66**)



(**67**)

	R_1
67a	-3Cl
67b	-2F
67c	3-Cl, 4-F

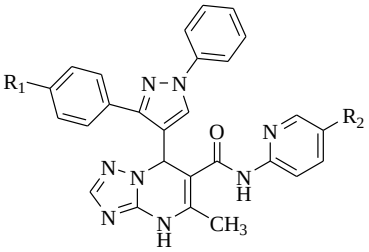
Yokokawa F *et al*.[16] in 2013 discovered tetrahydro-pyrazolopyrimidine carboxamide derivatives as potential anti-TB agents. Whole-cell high throughput screening of *Mtb* provided the hit molecule tetrahydropyrazolo[1,5-*a*]pyrimidine moiety. A series of compounds for this scaffold was synthesiszed and studied for their SAR and structure-property relationship (SPR). Compound (**68**) emerged as potential derivatives, with promising Drug Metabolism and Pharmacokinetics (DMPK) profile in mouse and showed potent oral *in vivo* activity, achieving reduction in 3.5 log CFU of *Mtb*.



(68)

	R_1	R_2
69a	-H	-Br
69b	$-NO_2$	-Br
69c	-Cl	-Br
69d	-F	-H
69e	-F	-Br

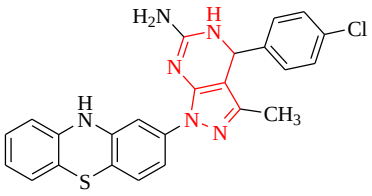
Bhatt J D *et al*.[17] reported pyrazole based triazolo[1,5-α]pyrimidine derivatives as anti-TB agents. Molecular docking and *in vitro* screening for the synthesized compounds yielded five potent derivatives **(69a-69e)** with no cytotoxicity against Vero cells. The docking with enzyme InhA revealed that two compounds (**69c** and **69e**) were showing good binding affinity. The MIC for compounds (**69c** and **69e)** was found to be 0.78±0.039 and 0.39±0.019 µg/mL respectively.



(69)

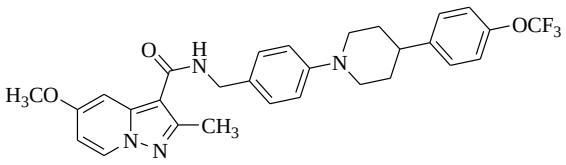
Siddiqui AB *et al*.[18] in 2014 discovered 4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine with phenothiazines as anti-TB agents. These hybrid derivatives were synthesized via a

modified Biginelli reaction. Among all the synthesized derivatives, compound (**70**) demonstrated most prominent anti-TB activity against *Mtb* having MIC value of of 0.02 µg/mL.



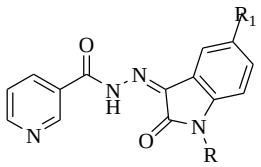
(**70**)

In 2015, Tang J *et al.*[19] reported pyrazolo[1,5-*a*]pyridine-3-carboxamide as anti-TB agents. All the synthesized compounds showed promising activity with nanomolar MIC values against *Mtb*. The most potent compound (**71**) exhibited MIC value of 11.1 nM.



(**71**)

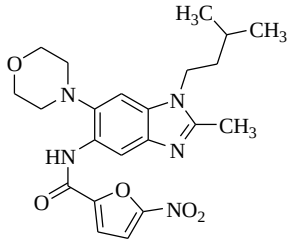
Recently, Elsayed Z M *et al.*[20] reported isatin-nicotinohydrazide hybrid molecules (**72**) as anti-TB compounds. From the reported compounds, compound (**72a-72c**) was found to exert potent anti-TB activity with MIC value of 0.24 µg/mL. Compounds (**72b** and **72c**) were also found to be active against resistant *Mtb* strains. The molecular docking studies indicated that these compounds were probably inhibiting DprE1 to exert the anti-TB action.



(**72**)

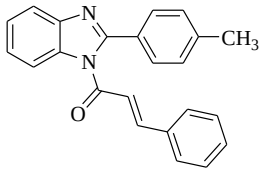
	R_1	R
72a	-H	$-CH_2C_6H_5$
72b	-Br	$-CH_2CH_2CH_3$
72c	-Br	$-CH_2CH(CH_3)_2$

Gong Y *et al.*[21] in 2014 reported benzimidazole derivatives as anti-TB agents. It was found that benzimidazole derivatives having 5-nitrofuranyl moiety exhibited potency against *Mtb*. Compound (**73**) were found to have MIC90 <0.049 µg/mL.



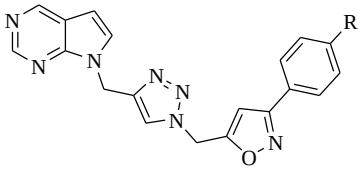
(**73**)

Kalalbandi VK A *et al*.[22] synthesized a series of benzimidazole derivatives containing 21 compounds. These compounds exhibited promising inhibition of *Mtb* in MABA method. The most potent compound (**74**) showed MIC value of 1.6 µg/mL.



(**74**)

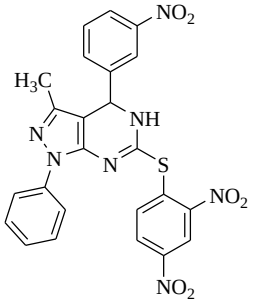
Raju KS *et al*.[23] reported novel 1,2,3-triazole derivatives as anti-TB agents. Most of the synthesized compounds exhibited promising anti-mycobacterial activity. The most active compounds (**75a-75b**) demonstrated MIC value of 0.78 µg/mL.



	R
75a	H
75b	F

(**75**)

Trivedi A *et al*.[24] reported various 6-substituted pyrazolo[3,4-*d*]pyrimidine derivatives as anti-TB agents. The most potent compound (**76**) showed MIC value of <6.25 µg/mL and IC_{50} value of 1.4 µg/mL.



(**76**)

2.2 DprE1 inhibitors as Anti-TB agents

A lot many compounds have been reported as DprE1 inhibitors. These are further categorized in covalent or non-covalent inhibitors depending of their mechanism of action. Regardless of their mode of binding, various scaffolds such as benzothiazinones **(25, 26** and **35),** benzothiazoles **(30, 36** and **37),** quinoxalines **(32** and **38**), imidazopyridine **(42),** azaindoles **(24),** pyrazolopyridine **(40)** have been reported as DprE1 inhibitors. It can be noted that most of the reported compounds are fused bicyclic heterocycles. Five membered heterocycles such as triazole **(31)**, thiadiazole **(39)** etc. have shown considerable DprE1 activity. Further, four DprE1 inhibitors are in clinical trials (**24-27**). These molecules can be taken up for design of new DprE1 inhibitors. Some of the established DprE1 inhibitors are shown in **Figure 2.1**[25–38].

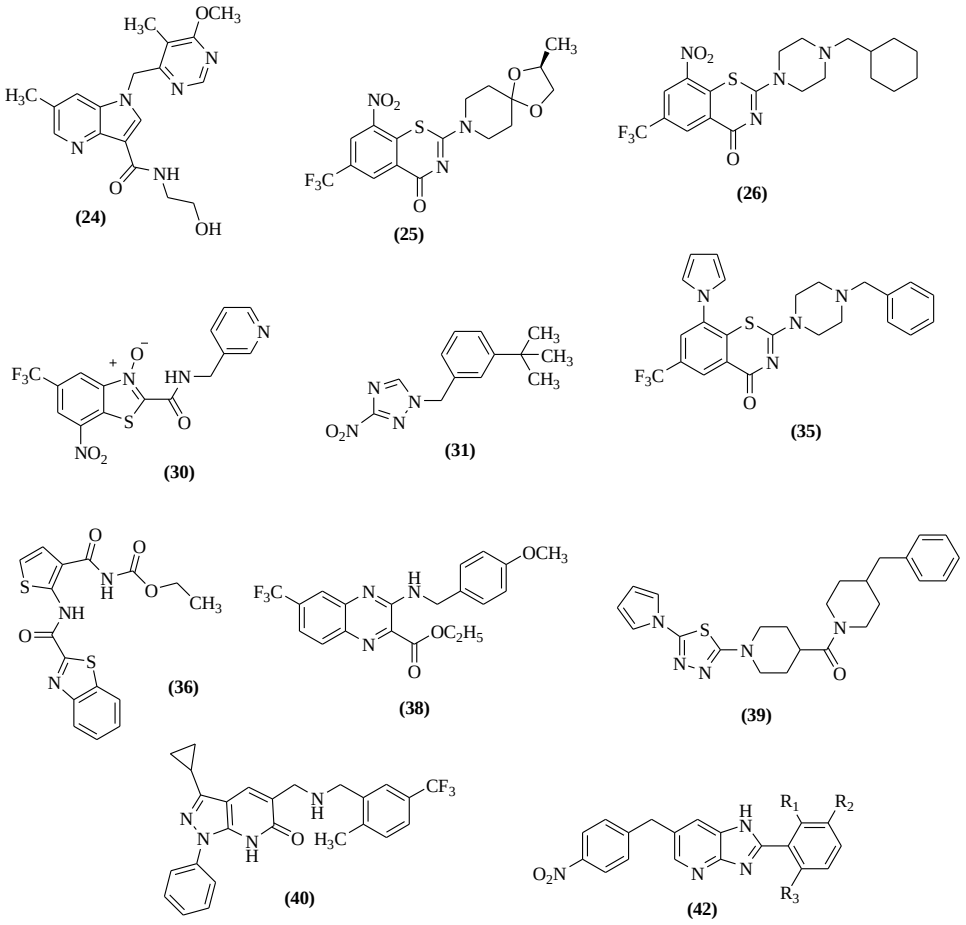
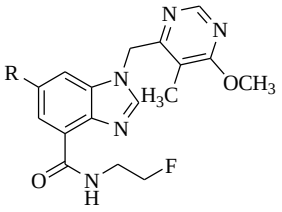


Figure 2.1: A few reported DprE1 inhibitors

2.2.1 Benzimidazole based DprE1 inhibitors

Manjunatha *et al.*[29] undertook TBA7371 **(24)** as the template molecule and used it for scaffold morphing to generate benzimidazole as a novel scaffold for DprE1 inhibition. These benzimidazole derivatives depicted enhanced aqueous solubility and increased plasma function. From the docking studies, it was evident that benzimidazole derivative (**77, 78**) were showing similar interactions as TBA7371 (**24**). Further, it was observed that benzimidazole was having hydrophobic interactions with CH-π with Trp230 and Try314 residues.

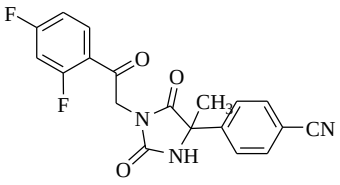


	R
77	H
78	-CH_3

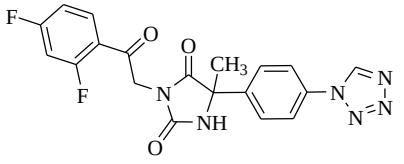
(**77, 78**)

2.2.2 Hydantoin based DprE1 inhibitors

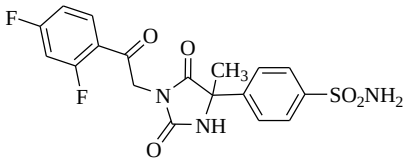
A Target based HTS study by GSK led to emergence of novel hydantoin derivatives as DprE1 inhibitors. The initial hit **(79)** so obtained showed promising inhibitory activity against DprE1 with pIC_{50} value of 7.0. The authors tried to optimize the hit and explored the SAR of these hydantoin derivatives. During the SAR studies, it was observed that most of the changes in the basic structure of the hit, led to reduced or loss of activity.[39] Further in 2020, the authors continued their work of SAR exploration and optimization of the hit.[40] But, only compound (**80** and **81**) showed increase in activity.



(**79**)



(**80**)

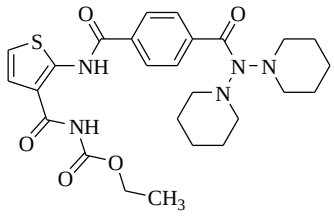


(**81**)

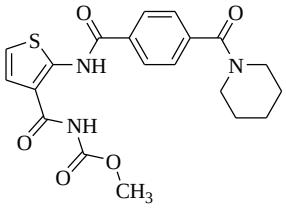
2.2.3 Thiophene based DprE1 inhibitors

Wang P. *et al.*[41] in 2021, discovered novel thiophene-acrylamide derivatives as DprE1 inhibitors exhibiting anti-TB activity. The authors implemented scaffold hopping to derive

thiophene-arylamide derivatives from TCA1 (**36**). The docking of TCA1 indicated towards the importance of 2,3 disubstituted thiophene moiety in maintaining key interactions of co-crystal structure. Compound (**82**) with benzamide moiety served as a new insight into the discovery of novel anti-tubercular agents. Docking results revealed that the H-bond interaction with Try60 provided additional binding affinity. Compound (**83)** (MIC = 0.19 µM) with acceptable PK profiles was proved to be efficacious *in vivo* in an acute mouse model.



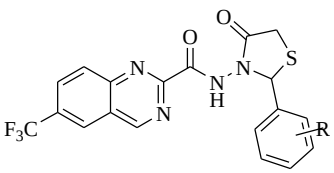
(**82**)



(**83**)

2.2.4 Quinazoline based DprE1 inhibitors

In 2020, Gawad J and Bonde C[42] reported novel quinazoline-2-carboxamide derivatives as potential DprE1 inhibitor. The authors utilized structure-based drug discovery approach to develop pharmacophore model followed by virtual screening and molecular docking to develop these derivatives. A total of 18 compounds were synthesized and anti-tubercular activity for all the compounds was carried out. Four compounds **84(a-d)** have shown remarkable glide score and exhibited good *in vitro* anti-tubercular activity having MIC value of 1.27, 1.12, 1.18 and 0.96 µM. So, these four compounds were further evaluated for DprE1 inhibition. Among those, two compounds **84b** and **84d** having hydroxyl and nitro group had shown strong DprE1 inhibition with IC_{50} value 11.6±1.3 µM and 14.9 ±1.9 µM.



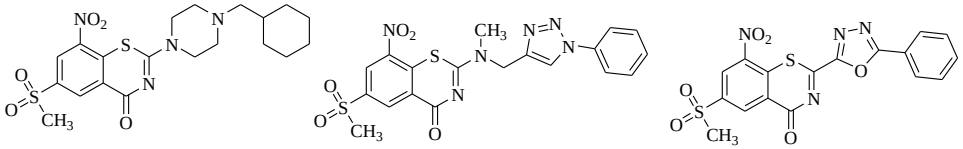
(**84a-84d**)

	R
84a	2,5-dimethyl
84b	4-hydroxy
84c	2,4-dihydroxy
84d	2-bromo-4-nitro

2.2.5 Benzothiazinone based DprE1 inhibitors

In 2021, Fan D *et al*.[43] reported SAR of nitrobenzothiazinones as DprE1 inhibitors. It is speculated that the low solubility of PBTZ169 (**26**) might lead to reduced bioavailability of the drug in the body. In order to resolve the issue, the authors studied the BTZ and possible side chains. When BTZ core combined with 6-methanesulfonyl substitution, it exhibited high activity and better physiochemical parameters. When 6-trifluroromethyl group was replaced

with sulphonyl, the resulted compound MsPBTZ169 (**85**) demonstrated reduced activity but improved aqueous solubility. Taking MsPBTZ169 as starting point, other compounds with 1,2,3-triazole (**86)** and 1,3,4-oxadizole (**87)** linker compounds were designed and synthesized. These derivatives depicted *in vivo* metabolic stability, selectivity and low toxicity. All these results indicated towards the applicability of such changes to alter the physicochemical properties of BTZ based compounds.



MsPBTZ169 (**85**) (**86**) (**87**)

Liu *et. al.*[44] reported new benzothiazin-4-ones as covalent inhibitors of DprE1. The authors attempted to replace nitro group with an electrophillic warhead to achieve the covalent interaction with nucleophilic Cys387 (**Figure 2.2**). To successfully achieve this hypothesis, the authors designed and synthesized a number of covalent inhibitors and tested their anti-tubercular activity and DprE1 inhibitory activity. Mass spectroscopy was used to study the chemical reactivity and formation of covalant adduct between the warhead and the enzyme. Five out of seven type A compounds exhibited excellent DprE1 inhibitory activity. Compounds with less bulky groups such as acrylamide showed IC_{50} < 0.4 µM.

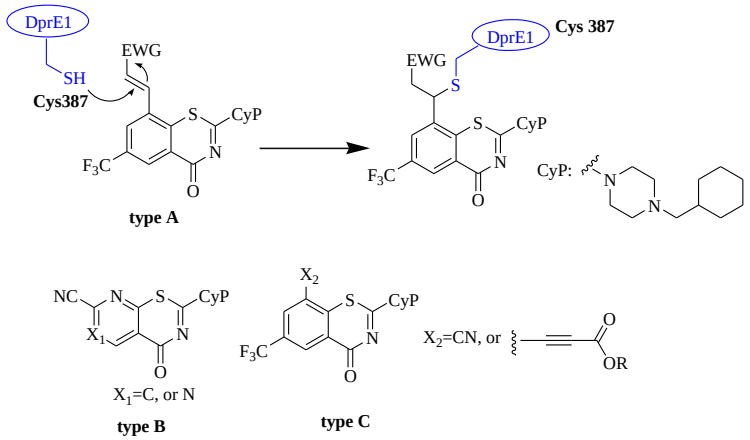
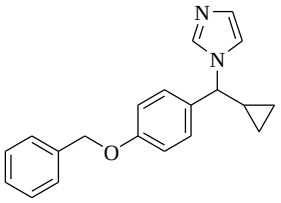


Figure 2.2: Rationale for design of covalent inhibitors

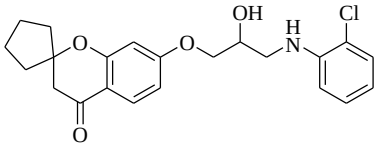
2.2.6 Imidazole based DprE1 inhibitors

In 2021, Kumar N *et al.*[45] performed virtual screening to identify and optimize DprE1 inhibitors. A database of anti-TB agents containing 78,713 molecules were subjected to molecular docking and their binding affinity and pharmacokinetic was used to screen out ten

bioactive molecules. These ten molecules were checked for drug likeness and as a result, four compounds **(88-91)** were obtained as potential DprE1 inhibitors. It was noteworthy that three out of four hits were having five membered heterocycles.



(88)



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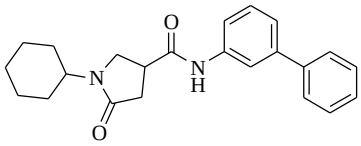

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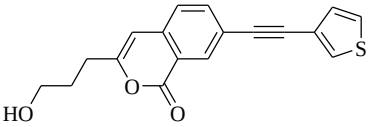
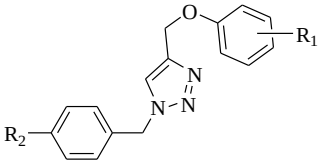


(91)

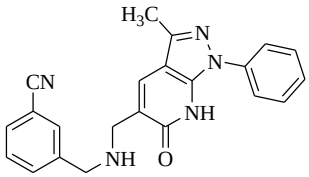
2.2.7 Triazole and pyrazolopyridones based DprE1 inhibitors

In 2020, Panigrahi D *et al.*[46] undertook some fifty 1,2,3-triazole and pyrazolopyridone derivatives to carry out pharmacophore modelling, QSAR study, molecular docking, *in silico* ADME predictions. Five compounds **(92-96)** were obtained as suitable hits forming significant binding with the active site residues by forming H-bond interactions.



(92-95)

	R_1	R_2
92	4-CH_3	4-Cl
93	4-Cl	4-Br
94	3-NO_2	4-NO_2
95	2, 4, 6-trichloro	4-Cl

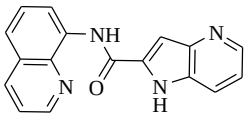


(**96**)

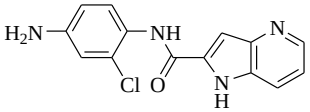
2.2.8 Azaindole based DprE1 inhibitors

TBA7371 **(24)** is an azaindole derivative with *in vivo* activity and is under clinical trial. Suma *et al.*[47] used TBA7371 as the prototype to develop new DprE1 inhibitor. The authors generated structure-based pharmacophore model to identify the compounds with the same

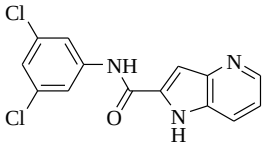
structural features. A ZINC database of 156 azaindole derivatives were used to generate a four-feature model 4-AARR with two H-bond acceptors and two aromatic rings. Two compounds (**97-98**) were obtained as hits and further studied for ADME predictions by Qikprop. These compounds were further subjected to induced fit docking and molecular simulations to establish one hit molecule. Finally, it was concluded that the compound with ID-ZINC000170252277 (**99**) can be taken as a starting point for further study of azaindoles as DprE1 inhibitors.



ZINC000170252294 (**97**)



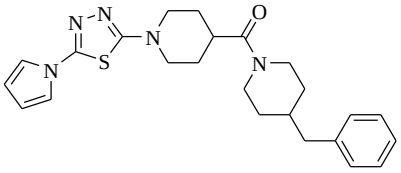
ZINC000170251946 (**98**)



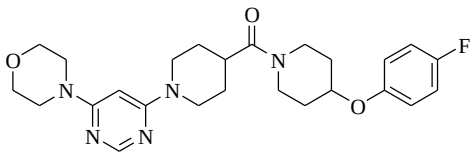
ZINC000170252277 (**99**)

2.2.9 Pyrrolothiadiazole based DprE1 inhibitors

Borthwick J A *et al.*[48] identified pyrrolothiadiazole (**100)** compounds as DprE1 inhibitor. This hit was further optimized by the authors to yield a new series of compound with favorable physiochemical properties and high *in vivo* efficacy. The optimized compound (**101)** showed good $DprE_1$ inhibitory activity with pIC_{50} value and MIC_{90} value of 7.3 and 1.7 µM respectively.[48]



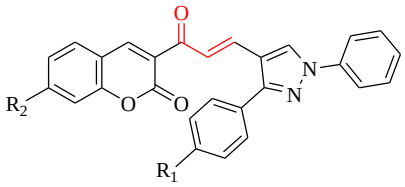
(**100**)



(**101**)

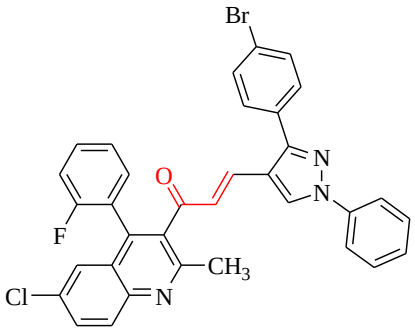
2.2.10 Chalcone based DprE1 inhibitors

Kumar G *et al.*[49] in 2020 reported hybrid chalcones as potential anti-tubercular agent. Two series of chalcones viz. pyrazole-coumarin chalcone derivatives and pyrazole-quinoline chalcone derivatives were reported. A total of 32 compounds were checked for anti-TB activity against *Mtb* wherein three compounds (**102a**, **102b** and **103)** demonstrated MIC value of 3.125 µg/mL. Molecular docking of the synthesized compounds with DprE1 revealed noticeable binding within the enzyme with binding affinities between -7.047 and -9.353 Kcal/mol. The active compounds were found to interact with the enzyme via hydrogen bonding, van der Waals interaction and π-π interaction. These results suggested that the mechanism of action for these derivatives could be DprE1 inhibition.



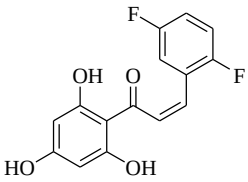
(102)

	R_1	R_2
102a	$-CH_3$	$-OCH_3$
102b	-OH	-H



(103)

Yalcin G *et al*.[50] in 2018 performed molecular docking of fluoro-substituted chalcones as potential DprE1 inhibitors. The chalcones demonstrated binding affinity lesser than -8.0 kcal/mol. The compound (**104**) having a double bond were showing effective inhibition and the structural motif had influence on the binding profile of molecules. Further, hydroxyl group is explicit for binding as it forms hydrogen bond with three amino acids (ASN 385, HIS 132 and GLN 336). It was found that fluorine molecule was crucial for binding.



(**104**)

- Summary of literature review

1. Many chalcone derivatives have been reported to exert anti-TB activity along with some reports claiming DprE1 inhibition.
2. Many bicyclic heterocycles such as pyrazolopyrimidine, pyridopyrimidines, pyrrolopyrimidines etc have been reported to show promising anti-TB activity.
3. A majority of DprE1 inhibitors have bicyclic heterocycles motifs in their structure.
4. Five membered heterocycles such as pyrazoles, triazoles can act as promising lead for anti-TB agents.

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