



Design, synthesis, biological evaluation and molecular docking studies of thiophene derivatives

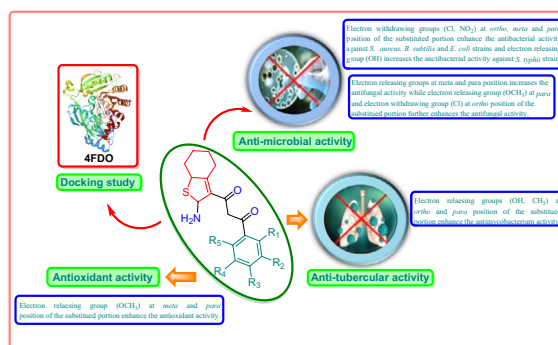
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Abstract

A series of 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]-3-yl)-3-substitued-phenylpropane-1,3-dionederivatives were synthesized using the Gewald synthesis in first step which is followed by Baker–Venkataraman rearrangement to yield title compounds. The FTIR, MS and ¹H NMR results of the produced derivatives were validated. The biological potential such as antimicrobial, antioxidant and antimycobacterial activity against a particularly virulent strain of MTB (MTB H37Ra) of the synthesized compounds were examined. Antimicrobial screening outcomes showed that compound *S*₁₇ turned to be the most effective antibacterial agent against Gram positive bacteria such as *Staphylococcus aureus* (MIC = 16.87 μM) and *Bacillus subtilis* (MIC = 9.45 μM) and Gram negative bacteria such as *Escherichia coli* (MIC = 16.87 μM) and compound *S*₇ against *Salmonella typhi* (MIC = 9.74 μM) and compound *S*₁₆ displayed remarkable antifungal activity toward each *Candida albicans* and *Aspergillus niger* (MIC = 15.23 μM). The standard drugs, cefadroxil (antibacterial), have MIC value against *S. aureus*, *B. subtilis*, *E. coli* and *S. Typhi* are 16.40 μM, 32.80 μM, 16.40 μM and 16.40 μM, respectively, and fluconazole (antifungal) has MIC value 20.40 μM against both the *C. albicans* and *A.niger* strain. In comparison with ascorbic acid, a standard drug (IC₅₀ 44.91 μg/mL), compound *S*₁₀ demonstrated good antioxidant activity, with an IC₅₀ value of 45.29 μg/mL, according to the results of the antioxidant screening. The results of the in vitro antituberculosis screening showed that compound *S*₂₃ was found to be effective with an MIC value of 78.125 μg/mL. Molecular docking study of an enzymatic active site of “*DprE1-decaprenylphosphoryl-β-D-ribose-2'-epimerase*” shows a comparable binding mode to the native ligand with better docking score which contributes in understanding and development of models for ligand–protein interactions. Compound *S*₂₃ showed better docking score of –8.516 as compared to the Isoniazid with the docking score of –6.315 which in future will create the fundamental structural framework for MTB inhibition.

Graphic abstract



Keywords Antimicrobial · Antioxidant · Antitubercular · MABA · Molecular docking

Abbreviations

MDR Multidrug resistant
XDR Extensively drug resistant

Extended author information available on the last page of the article

TB	Tuberculosis
MTB	Mycobacterium tuberculosis
μM	Micromolar
μg	Microgram
MIC	Minimum inhibitory concentrations
FTIR	Fourier transform infrared spectroscopy
MS	Mass spectrometry
$^1\text{H NMR}$	Proton nuclear magnetic resonance
DPPH	2,2-Diphenyl-1-picrylhydrazyl
MABA	Microplate Alamar blue assay
DprE1	Decaprenylphosphoryl- β -D-ribose-2'-epimerase
BVR	Baker–Venkataraman rearrangement
DPA	Decaprenylphosphoryl-D-arabinose
TLC	Thin-layer chromatography
UV	Ultraviolet

Introduction

One of the better strategies for synthesizing new precursor molecules for drug development is to derive known active pharmacophores [1]. Even chemists and biologists find it challenging to discover the lead compounds. To make this easy, molecular docking and web-based software's were currently being used. Molecules containing thiophene moiety have remarkable biological applications having antimicrobial [2], antitubercular [3], antioxidant [4], anti-inflammatory and analgesic [5], antihypertensive [6] and anticancer activities [7] while they are also used as metal corrosion inhibitors [8, 9] or in the production of light-emitting diodes in materials science [10]. The rationale for the drug design of the synthesized compounds in the manuscript was rooted in the molecular structure of the tetrahydrobenzothiophene derivatives. These compounds were designed with specific pharmacophores, particularly the thiophene moiety, which is known for its diverse biological applications, including antimicrobial, antioxidant activities and antitubercular [11].

Tuberculosis (TB), which is among the most common infectious diseases, continues to be an important global health problem. The widespread rise of Mycobacterium tuberculosis (MTB) strains that are multidrug resistant (MDR) and extensively drug resistant (XDR), including infectious, primary and drug resistance-blocking strains, has made tuberculosis the deadliest illness [12]. Drug-resistant TB, which is notoriously difficult to treat, accounted for about half a million of the 6.4 million new TB cases in 2021 [13]. The number of new chemical entities (17) currently approved for clinical trials alone or in combination with selections from 9 existing anti-TB drugs represents a major improvement on previous years [14, 15]. Although there are first- and second-line medications available to treat the illness, tuberculosis

still has a high mortality rate and has grown to be a severe hazard to world health [16]. Due to the emergence of drug testing, significant side effects of existing drugs and drug–drug interactions, there is a need for the development of new antitubercular drugs with low toxicity and effective treatment against MDR and XDR and the underlying pathogens [17]. Based on these facts, efforts to find effective chemotherapy drugs for tuberculosis remain continued.

We are currently able to develop new drugs owing to the recent reports of the antituberculosis activity of numerous novel compounds with good minimum inhibitory concentration (MIC) values [18]. FDA-approved medications such sertoconazole, raloxifene, benocyclidine and zileuton all include the drug-like structure known as the benzo[b] thiophene moiety which have significant pharmacological value [19, 20]. Therefore, while our work on the discovery of antitubercular drugs continues, several 1,3-diketones, flavones and pyrazoles were created from tetrahydrobenzo[b] thiophenecarboxylic acid which showed good inhibitory activity [21–24].

To reveal possible mechanisms for antitubercular activity of synthesized compounds, protein–ligand binding interaction was visualized at molecular level with the help of molecular docking study [25–27]. In silico approaches to molecular docking have proved important to identify the target of different ligands and their thermodynamic intermolecular interactions with target enzymes that control their growth [28, 29]. The selection of DprE1-decaprenylphosphoryl- β -D-ribose-2'-epimerase as the target in the manuscript is justified by its pivotal role in Mycobacterium tuberculosis (MTB) cell wall synthesis. Inhibiting DprE1 disrupts the formation of decaprenylphosphoryl-D-arabinose (DPA), impacting arabinogalactan, a crucial component of the MTB cell wall. This disruption weakens the cell wall, hindering MTB growth and survival. Molecular docking studies enhance the rationale, elucidating ligand–protein interactions crucial for designing effective antitubercular drugs. The selected target's centrality in MTB viability underscores its potential as a strategic point for drug intervention, justifying its relevance in combating tuberculosis [30]. The active site of DprE1 (decaprenylphosphoryl- β -D-ribose-2'-epimerase) shows similarities to the native ligand in crystal structure by molecular docking study which further helps in understanding the ligand–protein interactions and in the design of basic structure which is required for the inhibition of tubercular bacterium [31].

Result and discussion

Chemistry

Thiophene is a five-membered, sulfur-containing heteroaromatic ring generally used as building block in drugs.

It undergoes electrophilic aromatic substitution very readily. Sulfur is the least electron donor as compare to nitrogen and oxygen. Its structural metabolism leads to the formation of reactive metabolites. This compound is widely spread in nature and has diversified application in design of new drug molecule. The Gewald synthesis is a well-established method for the construction of thiophene rings, aromatic heterocyclic compounds featuring a sulfur atom within a five-membered ring. The synthetic route involves the reaction of α,β -unsaturated carbonyl compounds, such as α,β -unsaturated ketones or esters, with elemental sulfur (S_8) and α -halo ketones or α -halo esters. The process initiates with the deprotonation of the unsaturated carbonyl compound by a strong base, generating an enolate ion. Subsequent nucleophilic attack by sulfur leads to the formation of a thiolate intermediate. Intramolecular cyclization is facilitated by an α -halo ketone or ester, resulting in the formation of an intermediate that undergoes elimination of a halide ion. The final step yields ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate product. Subsequent base hydrolysis, likely employing lithium hydroxide (LiOH), transformed intermediate-1 into benzo[b]thiophene-2-carboxylic acid (Intermediate-2). The pivotal Baker–Venkataraman rearrangement ensued, facilitated by pyridine and substituted acetophenones in $POCl_3$ causing the migration of the aryl group to an adjacent position. This rearrangement mechanism led to the final compounds, 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]-3-yl)-3-substitued-phenylpropane-1,3-dione derivatives. Thiophene derivatives (S_1 – S_{23}) were synthesized by following general procedure which were discussed in Synthetic Scheme 1.

Biological evaluation

Antimicrobial activity

According to antimicrobial study findings, compound S_{17} had the highest antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli*, with MIC values of 16.87, 9.45 and 16.87 μ M, respectively. Compounds S_7 and S_{11} had the highest potency against *S. typhi*, with MIC values of 9.74 and 16.43 μ M, respectively. The synthesized compound not only exhibited notable antibacterial activity, but also good antifungal activity, with compound S_{16} emerging as the most effective antifungal agent against both *C. albicans* and *A. niger* (MIC = 15.23 μ M), and compound S_3 also showing good antifungal activity against *A. niger* with MIC value 18.85 μ M. The results of the overall antibacterial activity (Table 1) showed that compounds S_{16} and S_{17} were the most effective antimicrobial agents.

Antioxidant activity

Using the DPPH test at an absorbance of 517, in vitro antioxidant activity of each newly synthesized molecule was examined. The IC_{50} values of freshly synthesized compounds are shown in Figs. 1, 2 and 3. The entire newly synthesized molecule showed good to moderate antioxidant activity, according to the data. When compared to ascorbic acid (IC_{50} 44.91 μ g/mL) as the reference drug, compounds S_3 and S_{10} showed the best antioxidant activity, with IC_{50} values of 47.70 μ g/mL and 45.29 μ g/mL, respectively. These substances could serve as a starting point for more research. Table 2 displays the results.

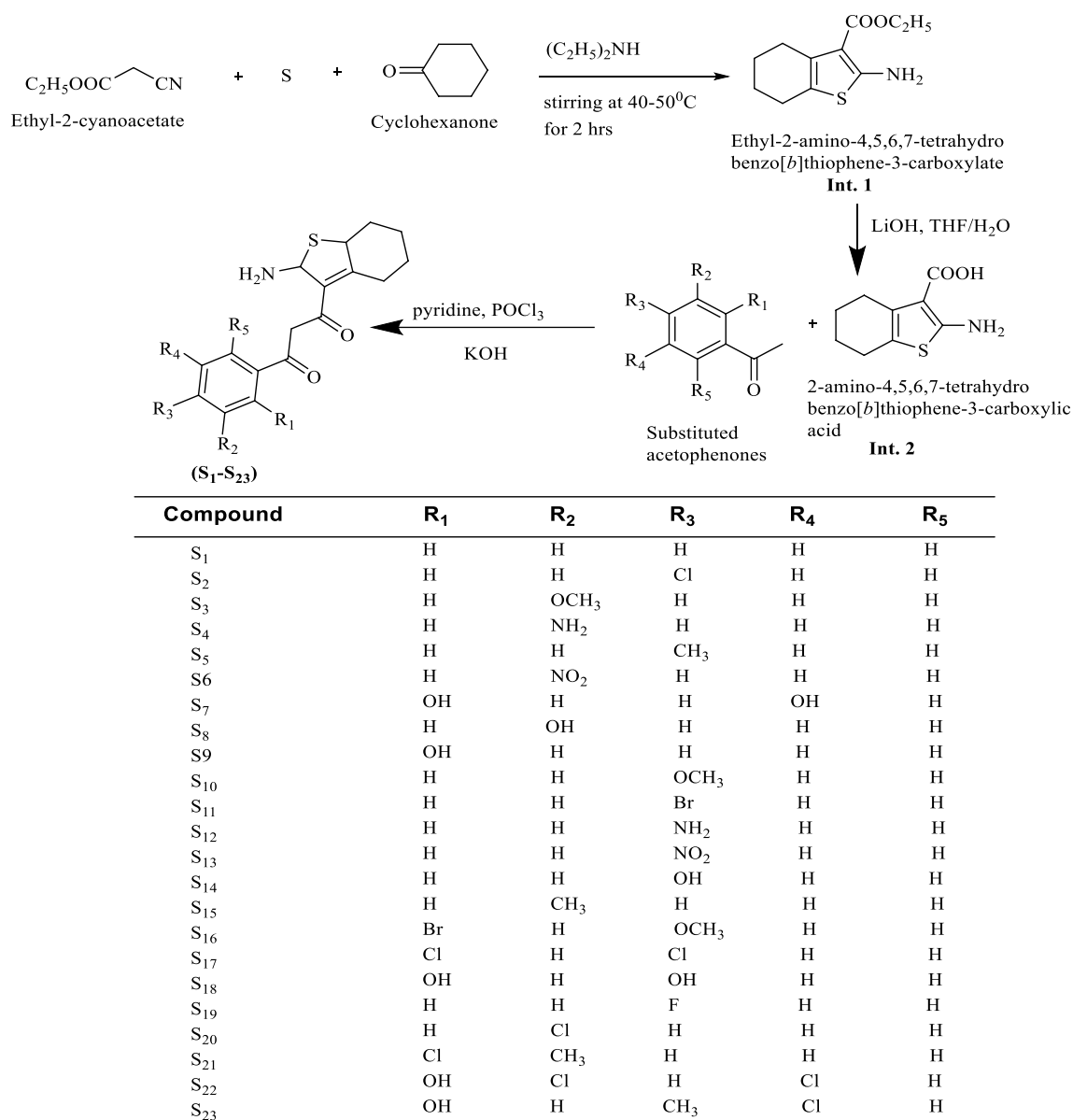
Antitubercular activity

Avirulent strain of MTB (MTB H37Ra; ATCC 25177) was used to test the derived molecules for in vitro antitubercular potency by assessing growth inhibition using the MABA method. The results of each experiment were run in triplicate, and Table 3 and Fig. 4 show the minimum inhibitory concentrations (MICs) in (μ g/mL). A few of the compounds were determined to have good to moderate antitubercular action, according to the outcome. When compared to isoniazid, the standard treatment, compound S_{23} and compound S_{22} both showed good antitubercular activity with MIC values of 78.125 μ g/mL and 156.25 μ g/mL, respectively.

Molecular docking

A molecular docking study was carried out in order to identify the best potential binding modes for newly derived molecules with the enzyme (DprE1). It plays a key role in the synthesis of decaprenylphosphoryl-D-arabinose (DPA) which is sole source of D-arabinofuranosyl residues known to be used in the synthesis of arabinogalactan, the fundamental building block of the mycobacterial cell wall core. DprE1 is thus a promising target for antimycobacterial drug design because it is also necessary for cell growth and survival. The Schrodinger suite release 2019–1 49 was used to simulate docking. The most active molecule, S_{23} , had a docking score of -8.516 while the native ligand had a docking score of -6.316 . All of the compounds' docking scores are displayed in Table 4. The interacting amino acid residues were identified as Gly55, Gly57, Gly125, Lys418, Tyr 415, Gly117, Gln336 and His132 of DprE1. Isoniazid, compound S_{13} and compound S_{23} binding modalities are shown in Fig. 5.

While the NH_2 group substituted on tetrahydrobenzothiophene exhibits the interaction with Gln336 and Lys418 and the hydroxyl and amino groups substituted phenyl ring display interaction with the GLY125 and Tyr 415, both oxygen atoms interact with Tyr 415, Gly55, Gly57, Gly125 and His132. Although the binding



Scheme 1 Synthesis of 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-phenylpropane-1,3-dione derivatives

patterns of all tetrahydrobenzo[*b*]thiophene-2-carboxylic acid molecules were discovered to be comparable, the molecule *S*₂₃ stronger binding to the active site of DprE1 is enhanced by the existence of considerably stronger noncovalent interactions.

Molecular dynamic simulation

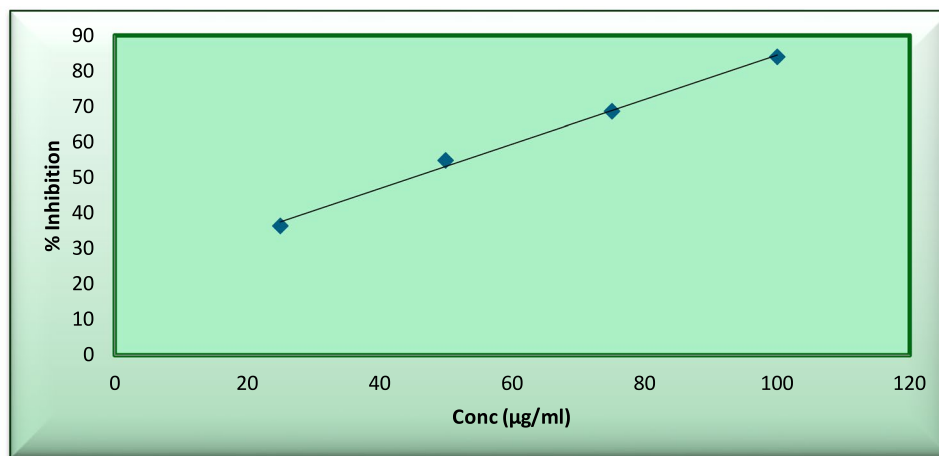
The complex of compound showed highest docking score (compound *S*₂₃) with DprE1 undergoes molecular docking simulation study using Desmond MD engine for a period of 100 ns. In order to comprehend the binding mode sustainability as the simulation progressed, an MD simulation

was run in order to determine the dynamic nature and alterability of the ligand binding site, the plasticity of the pocket and the contact stability between compound *S*₂₃ and pocket-specific amino acids. To understand the binding mode sustainability with the progression of the simulation, root mean square fluctuation (RMSF) of compound *S*₂₃ has been recorded (Fig. 6). We analyzed 1000 frames produced out of 100-ns simulation, and we found contact sustainability with the aforesaid pertinent amino acids, such as Gly55, Arg58, Ser59, Try60, Asn63, Met74, Thr122 and Asn178 (Fig. 7). These contacts were sustained through the mediation of H-bonds, hydrophobic interactions, ionic bonds and water bridges. It was also specifically observed

Table 1 Antimicrobial testing of newly synthesized compounds (MIC = μM) (S_1 - S_{23})

Compound	Minimum inhibitory concentration (MIC = μM)					
	Bacterial species				Fungal species	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. typhi</i>	<i>A. niger</i>	<i>C. albicans</i>
S_1	41.47	41.47	41.47	41.47	41.47	41.47
S_2	37.21	18.60	37.21	37.21	74.43	74.43
S_3	37.71	75.43	37.71	37.71	18.85	37.71
S_4	39.50	39.50	39.50	19.75	39.50	39.50
S_5	39.62	39.62	39.62	79.25	79.25	79.25
S_6	39.50	19.75	19.75	39.50	39.50	39.50
S_7	37.49	37.49	37.49	9.74	37.49	37.49
S_8	19.69	39.38	39.38	39.38	39.38	19.69
S_9	39.38	39.38	39.38	39.38	78.79	39.38
S_{10}	75.43	37.71	18.85	37.71	37.71	75.43
S_{11}	32.86	32.86	65.75	16.43	32.86	32.86
S_{12}	39.50	39.50	39.50	19.75	19.75	79.00
S_{13}	72.17	36.08	36.08	36.08	36.08	36.08
S_{14}	39.38	39.38	19.69	39.38	39.38	39.38
S_{15}	39.62	39.62	39.62	39.62	39.62	39.62
S_{16}	30.46	30.46	30.46	30.46	15.23	15.23
S_{17}	16.87	9.45	16.87	33.75	33.75	33.75
S_{18}	37.49	37.49	37.49	37.49	37.49	37.49
S_{19}	39.13	39.13	19.56	39.13	39.13	39.13
S_{20}	37.21	37.21	37.21	74.43	37.21	74.43
S_{21}	71.45	71.45	35.72	35.72	35.72	35.72
S_{22}	64.71	129.42	16.17	32.35	64.71	32.35
S_{23}	34.16	34.16	68.33	34.16	34.16	34.16
Cefadroxil	16.40	32.80	16.40	16.40	–	–
Fluconazole	–	–	–	–	20.40	20.40

The synthesized compounds have shown the very good antimicrobial activity which can be very fruitful for developing of new antimicrobial drug (in bold)

Fig. 1 Standard graph of ascorbic acid

from the simulation study that the protein RMSD value did not cross the 3 Å limit (Fig. 8). This fact signified that the protein structure did not go through a large conformational change. In secondary structure element elucidation, where

the reference frame, frame at 50 ns and frame at 100 ns were aligned with each other (Fig. 9). Furthermore, the depiction of Fig. 8 suggested and affirmed the fact that RMSD of compound S_{23} did not cross the limit of 3 Å and thus suggest

Fig. 2 Graph of potent antioxidant compounds S_3 and S_{10}

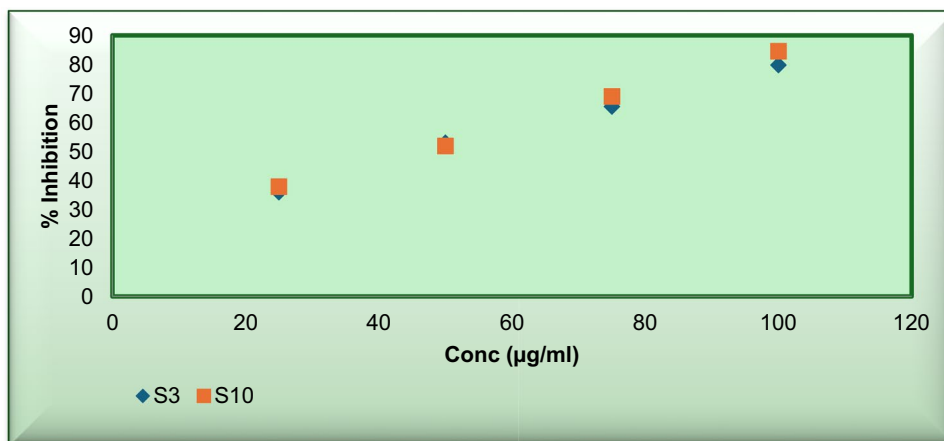
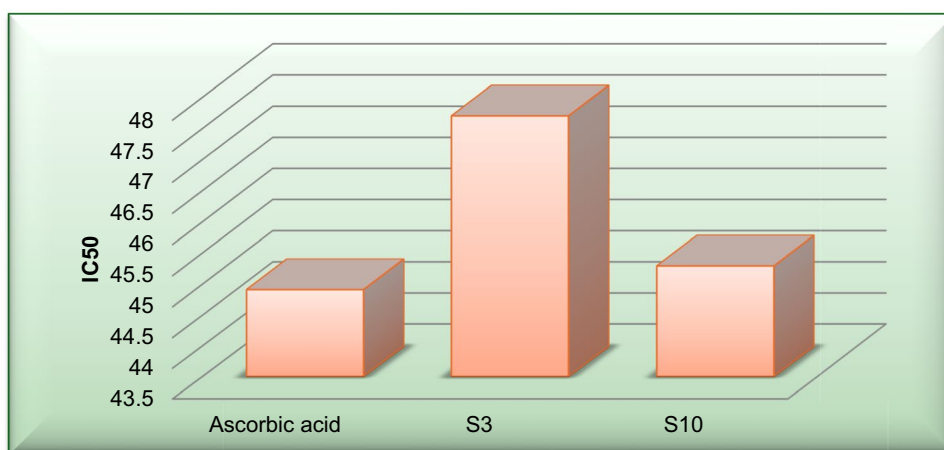


Fig. 3 IC_{50} values of S_3 and S_{10} compounds in comparison with ascorbic acid



the controlled dynamicity of ligand in the orthosteric site of the DprE1. This overall state-of-the-art molecular dynamic simulation confirmed protein–ligand complex stability over the course of the simulation timeline.

Structure activity relationships (SARs)

From the results of antimicrobial, antioxidant and antitubercular tests of the newly synthesized 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-substituted phenylpropane-1, 3-dione derivatives, it was found that tetrahydrobenzo ring attached at 2 and 3 position of thiophene heterocyclic ring plays a significant role in enhancing all the biological activity. The presence of an electron-withdrawing group ($-Cl$, NO_2 compound S_{17}) in the *ortho*, *meta* and *para* positions of the substituted part increases the antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* strains, and an electron-releasing group (OH compound S_7) in the *meta* position increases antibacterial activity of the synthesized compound against *S. typhi* strain. While in case of antifungal activity, the electron-releasing group (OCH_3) in the *para* and the

electron-withdrawing group (Cl) in the *ortho* position (compound S_{16}) of the substituted moiety increases the activity. It was found that electron-releasing group (OCH_3 , compound S_{10}) in the *meta* and *para* position of the substituted part plays a very crucial role in increasing the antioxidant activity. The most potent antimycobacterial activity was found with the compound S_{23} which has an electron-releasing group in the *ortho* (OH) and *para* (CH_3) position of the substituted part. Thus, from these results, we can conclude that compounds require different mechanisms to be effective for different targets.

Experimental

General procedure

The investigation employed only laboratory- and analytical-grade materials that were locally sourced. Thin-layer chromatography (TLC) was used to observe the forward reaction stages using commercial silica gel plates (Merck) and silica gel F254 on aluminum sheets. Using the open capillary

Table 2 Antioxidant screening results of newly synthesized molecules (S_1 – S_{23})

Compound	% Inhibition				IC ₅₀ µg/ml
	25 µg/ml	50 µg/ml	75 µg/ml	100 µg/ml	
S_1	15.98	25.87	48.87	67.87	77.05
S_2	21.87	38.24	56.98	76.32	64.79
S_3	35.96	53.07	65.45	79.74	47.70
S_4	33.98	47.92	60.87	69.23	56.28
S_5	24.87	35.95	50.74	67.94	71.39
S_6	15.75	32.87	48.94	65.93	76.24
S_7	21.96	38.93	56.32	68.95	68.00
S_8	18.76	37.90	55.92	65.23	71.39
S_9	16.73	35.27	47.23	59.83	80.61
S_{10}	37.90	51.94	68.93	84.54	45.29
S_{11}	24.32	41.97	65.23	74.96	60.25
S_{12}	15.84	33.96	47.54	66.83	75.96
S_{13}	23.84	39.92	57.92	72.05	64.96
S_{14}	36.92	47.23	59.34	73.12	54.00
S_{15}	20.04	36.67	60.23	81.93	62.90
S_{16}	30.97	48.93	63.24	78.03	53.98
S_{17}	18.04	37.93	59.45	67.54	68.77
S_{18}	16.67	33.53	54.93	71.84	70.26
S_{19}	27.93	41.43	67.03	80.32	56.79
S_{20}	15.74	25.56	46.82	59.43	84.06
S_{21}	32.05	48.65	62.94	78.47	53.51
S_{22}	36.92	47.26	62.73	78.28	51.23
S_{23}	37.72	45.28	67.92	80.02	49.58
Ascorbic acid	36.52	54.78	68.79	83.95	44.91

The synthesized compounds having the good antioxidant activity (in bold)

Table 3 MIC value of all compounds tested against MTB

S.No.	Comp. no.	MIC (mg/mL)	MIC (µg/mL)
i.	S_3	0.625	625
ii.	S_5	2.5	2500
iii.	S_6	2.5	2500
iv.	S_{10}	1.25	1250
v.	S_{12}	0.3125	312.5
vi.	S_{13}	0.3125	312.5
vii.	S_{15}	5.0	5000
viii.	S_{21}	0.625	625
ix.	S_{22}	0.15625	156.25
x.	S_{23}	0.078125	78.125
xi.	Isoniazid	0.0025	2.5

technique, melting points were examined. Parts per million (5 ppm) downfield tetramethylsilane (internal standard) are used to express the ¹H nuclear magnetic resonance spectra, which were obtained using a Bruker Avance 400 NMR

spectrometer and the suitable chloroform solvent. Data from the ¹H NMR are presented as multiplicity (singlet, doublet, triplet or multiplet) and number of protons. On a Bruker FTIR spectrometer, infrared (IR) spectra were taken.

General procedure for the synthesis of 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-phenylpropane-1,3-dione (S_1 – S_{23})

Step I: Synthesis of ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate: Mixture of ethyl cyanoacetate (5.32 mL, 0.05 mol) and cyclohexanone (5.2 mL, 0.05 mol) was taken in conical flask and allowed to stirred at room temperature followed by the addition of elemental sulfur (1.92 g, 0.06 mol). Then diethylamine (5.26 mL, 0.05 mol) as an amine catalyst was added in it [32]. The reaction mixture was then stirred at 40 °C to 50 °C for 2 h, which undergoes Gewald reaction (the most versatile reaction and involves one-pot cyclocondensation of ketones with activated nitrile derivatives and elemental sulfur to provide 2-aminothiophenes) leading to the formation of intermediate-1 (10 mmol).

Step II: Intermediate I was treated with 103 mmol lithium hydroxide in THF (40 ml) for 24 h at 50 °C. The mixture was then cooled to 0 °C and neutralized with acetic acid to pH 7. The precipitate obtained was collected by filtration, washed with water and dried in vacuum. This gives the formation of benzo[b]thiophene-2-carboxylic acid (intermediate 2) [33].

Step III: Synthesis of 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-substitued-phenylpropane-1,3-dione derivatives: "Further, the reaction between intermediate 2 (0.05 mol) and substituted aromatic acetophenone (0.05 mol) in pyridine, KOH and POCl₃ provided intermediate esters under refluxed condition. In the next step, these intermediate undergoes Baker–Venkataraman rearrangement (BVR) when it was refluxed for 4 h, affording the formation of 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-substitued-phenylpropane-1,3-dione derivatives. The resulting mixture was cooled, poured onto crushed ice to give a solid precipitate, filtered, washed with 1% potassium bicarbonate and subsequently with water, dried and recrystallized from ethanol."

Spectral data of newly synthesized thiophene compounds

Compound S_1 : 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-phenylpropane-1,3-dione, IR, cm⁻¹: 2828 (C–H str.), 1519 (C=C str.), 1190 (C–N str.), 3384 (N–H str.), 1699 (C=O str., carbonyl), 674 (C–S–C str., thiophene ring), 3553 (OH str., aromatic), MS m/z: 302.

Compound S_2 : 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-(4-chlorophenyl)

Fig. 4 MIC values of compounds compared to standard drug

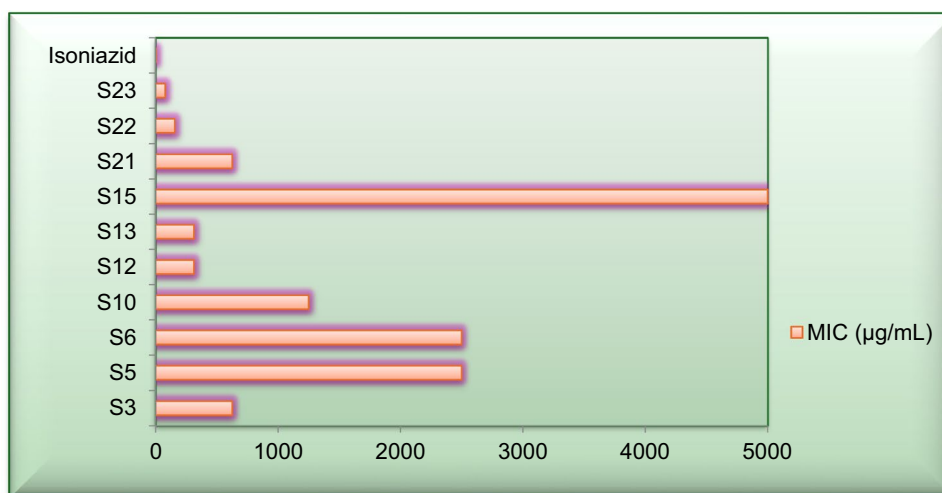


Table 4 Docking score of newly synthesized derivatives

S. No.	Ligand code	Docking score	Glide score	Glide emodel
1	S ₂₃	-8.516	-8.565	-55.018
2	S ₁₃	-8.134	-8.183	-60.666
3	S ₁₂	-7.648	-7.697	-45.125
4	S ₃	-7.097	-7.146	-52.504
5	S ₁₀	-6.84	-8.343	-50.098
6	S ₂₂	-6.557	-8.055	-63.488
7	S ₁₅	-6.549	-8.054	-56.64
8	S ₂₁	-6.527	-6.578	-48.756
9	S ₅	-6.45	-6.498	-45.381
10	S ₆	-6.41	-6.459	-58.157
11	Isoniazid	-6.315	-6.316	-35.288

propane-1,3-dione, IR, cm^{-1} : 2938 (C–H str.), 1521 (C=C str.), 1257 (C–N str.), 3306 (N–H str.), 1679 (C=O str., carbonyl), 685 (C–S–C str., thiophene ring), 779 (C–Cl str., aromatic), MS m/z: 336.

Compound S₃: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-methoxyphenyl)propane-1,3-dione, IR, cm^{-1} : 3040 (C–H str.), 1457 (C=C str.), 1100 (C–N str.), 3396 (N–H str.), 1688 (C=O str., carbonyl), 672 (C–S–C str., thiophene ring), 2995 (OCH₃ str., aromatic), ¹H NMR (CDCl₃, δ ppm): 7.20–7.81 (m, 2H, Ar–H), 6.83 (d, 2H, –NH₂), 4.72 (t, 1H, –CH), 3.56 (t, 1H, –CH cyclo), 1.16 (q, 2H, –CH₂cyclo), 1.49 (m, 2H, –CH₂ cyclo), 2.59 (t, 2H, –CH₂cyclo), 3.67 (s, 1H, –CH), 3.68 (s, 3H, –OCH₃), MS m/z: 332.

Compound S₄: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-aminophenyl)propane-1,3-dione, IR, cm^{-1} : 3083 (C–H str.), 1531 (C=C str.), 1259 (C–N str.), 3511 (N–H str.), 1685 (C=O str., carbonyl), 675 (C–S–C str., thiophene ring), 3617 (OH str., aromatic), MS m/z: 317.

Compound S₅: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(p-tolyl)propane-1,3-dione, IR, cm^{-1} : 2800 (C–H str.), 1576 (C=C str.), 1269 (C–N str.), 3332 (N–H str.), 1685 (C=O str., carbonyl), 640 (C–S–C str., thiophene ring), 1354 (CH₃ str., aromatic), ¹H NMR (CDCl₃, δ ppm): 7.19–7.32 (m, 2H, Ar–H), 5.01 (d, 2H, –NH₂), 3.68 (t, 1H, –CH), 1.70 (q, 2H, –CH₂cyclo), 1.29 (m, 2H, –CH₂ cyclo), 1.72 (t, 2H, –CH₂cyclo), 3.69 (s, 1H, –CH), 2.66 (s, 3H, –CH₃), MS m/z: 316.

Compound S₆: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-nitrophenyl)propane-1,3-dione, IR, cm^{-1} : 2847 (C–H str.), 1532 (C=C str.), 1256 (C–N str.), 3312 (N–H str.), 1688 (C=O str., carbonyl), 681 (C–S–C str., thiophene ring), 1419 (N–O str., aromatic), ¹H NMR (CDCl₃, δ ppm): 7.58–7.82 (m, 2H, Ar–H), 5.9 (d, 2H, –NH₂), 3.63 (t, 1H, –CH), (t, 1H, –CH cyclo), 1.81 (q, 2H, –CH₂cyclo), 1.30 (m, 2H, –CH₂ cyclo), 2.57 (t, 2H, –CH₂cyclo), 3.64 (s, 1H, –CH), MS m/z: 317.

Compound S₇: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(2,5-dihydroxyphenyl)propane-1,3-dione, IR, cm^{-1} : 2859 (C–H str.), 1538 (C=C str.), 1270 (C–N str.), 3362 (N–H str.), 1686 (C=O str., carbonyl), 708 (C–S–C str., thiophene ring), 3600 (OH str., aromatic), MS m/z: 334.

Compound S₈: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-hydroxyphenyl)propane-1,3-dione, IR, cm^{-1} : 2854 (C–H str.), 1593 (C=C str.), 1285 (C–N str.), 3337 (N–H str.), 1680 (C=O str., carbonyl), 688 (C–S–C str., thiophene ring), MS m/z: 318.

Compound S₉: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(2-hydroxyphenyl)propane-1,3-dione, IR, cm^{-1} : 2949 (C–H str.), 1592 (C=C str.), 1261 (C–N str.), 3330 (N–H str.), 1680 (C=O str., carbonyl), 719 (C–S–C str., thiophene ring), 3658 (OH str., aromatic), MS m/z: 318.

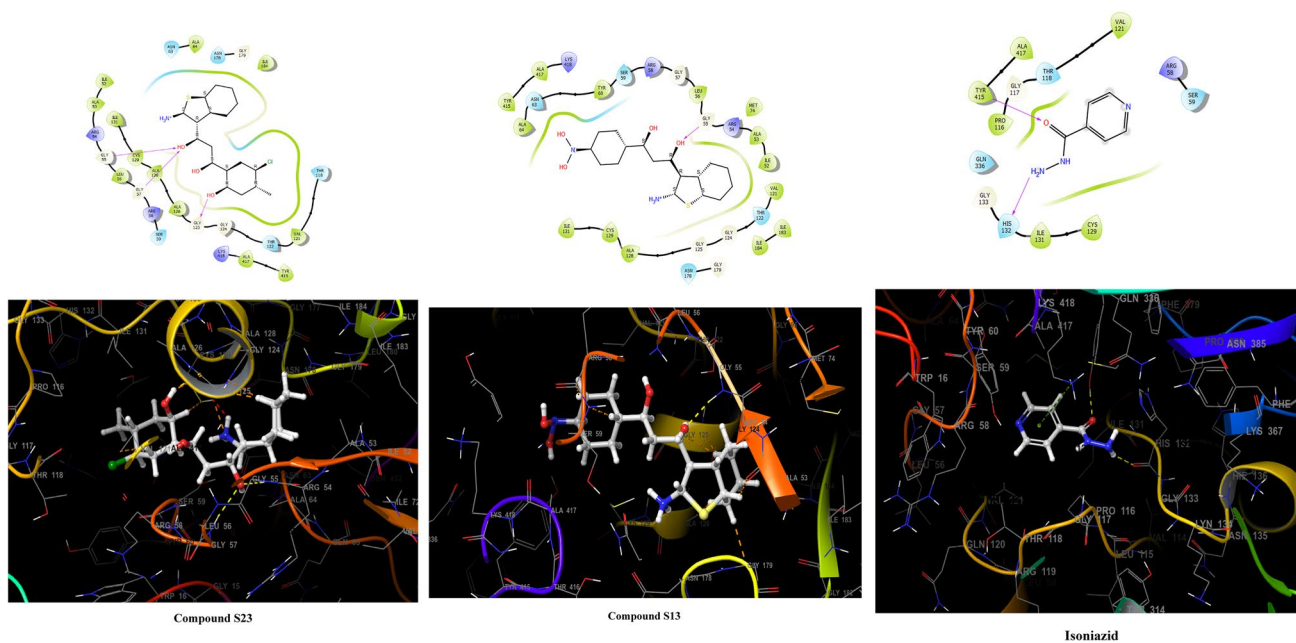
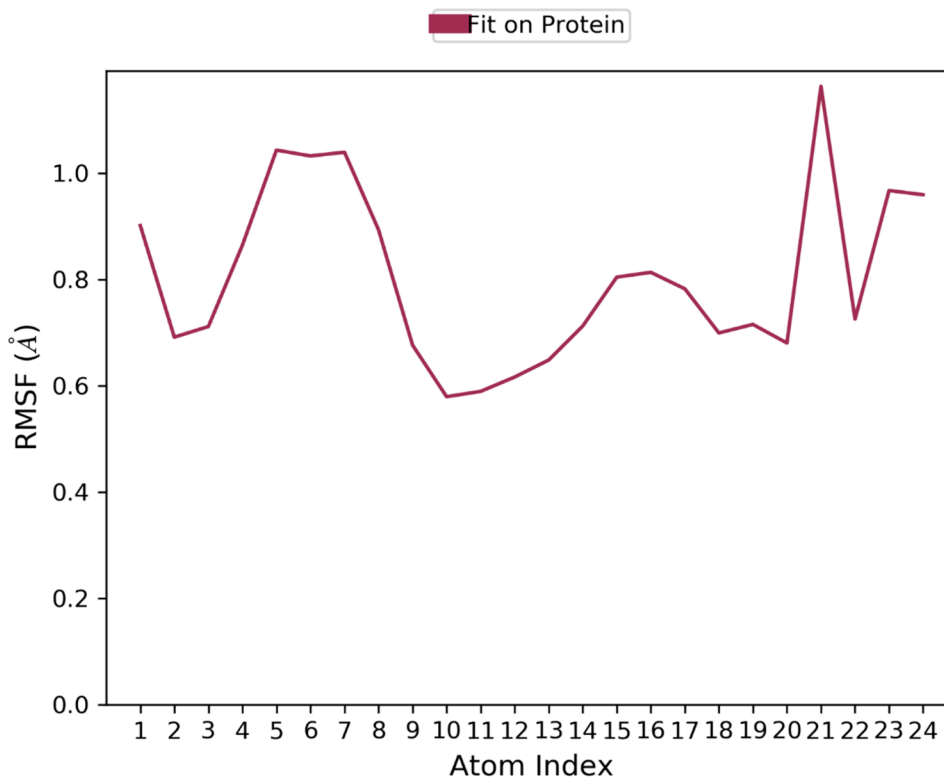


Fig. 5 Isoniazid, S_{23} and S_{13} binding models with DprE1 target activity

Fig. 6 Simulation root mean square fluctuation (RMSF) of compound S_{23}



Compound S_{10} : 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-methoxyphenyl)propane-1,3-dione, IR, cm^{-1} : 2956 (C–H str.), 1597 (C=C str.), 1267 (C–N str.), 3360 (N–H str.), 1668 (C=O str., carbonyl), 694 (C–S–C str., thiophene ring), 2810 (O–CH₃

str., aromatic), ¹H NMR (CDCl₃, δ ppm): 7.25 (m, 2H, Ar–H), 3.74 (d, 2H, –NH₂), 3.71 (t, 1H, –CH), 3.58 (t, 1H, –CH cyclo), 1.93 (q, 2H, –CH₂cyclo), 1.88 (m, 2H, –CH₂ cyclo), 2.54 (t, 2H, –CH₂cyclo), 3.73 (s, 1H, –CH), 3.85 (s, 3H, –OCH₃), MS *m/z*: 332.

Fig. 7 Representation of contact consistency with the key amino acids

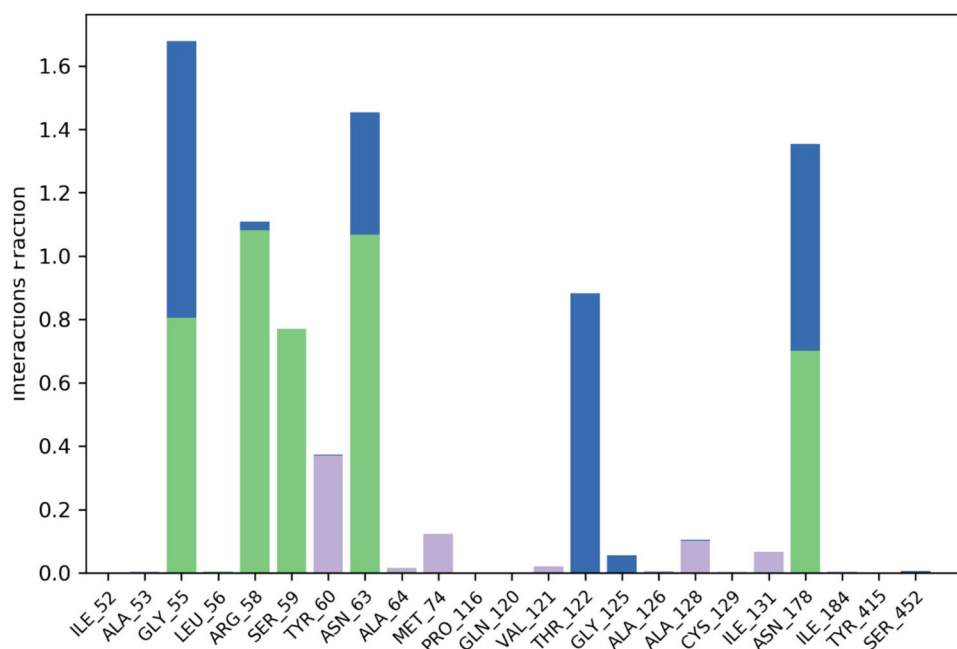
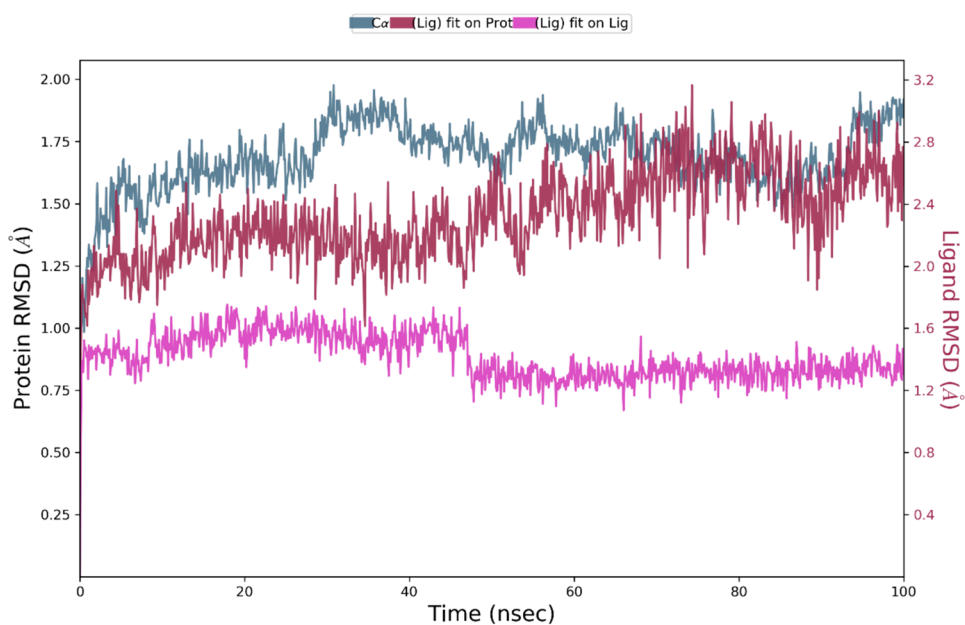


Fig. 8 Graphical elucidation of the RMSD of the protein and the ligand



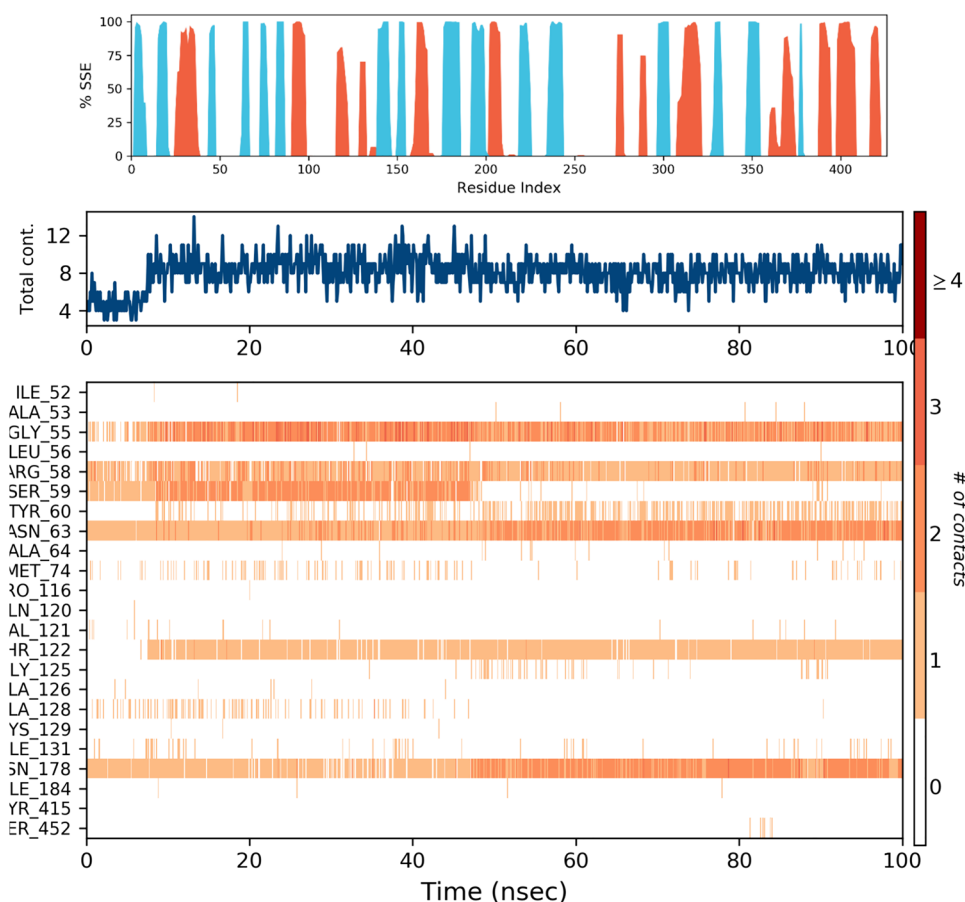
Compound S₁₁: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-bromophenyl)propane-1,3-dione, IR, cm⁻¹: 2839 (C–H str.), 1589 (C=C str.), 1268 (C–N str.), 3399 (N–H str.), 1682 (C=O str., carbonyl), 680 (C–S–C str., thiophene ring), 645 (C–Br str., aromatic), MS m/z: 381.

Compound S₁₂: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-aminophenyl)propane-1,3-dione, IR, cm⁻¹: 2866 (C–H str.), 1521 (C=C str.), 1265 (C–N str.), 3497 (N–H str.), 1648 (C=O str., carbonyl), 664 (C–S–C str., thiophene ring), 1 H NMR(CDCl₃,

δppm): 7.25 (m, 2H, Ar–H), 4.27 (d, 2H, –NH₂), 4.25 (t, 1H, –CH), 4.21 (t, 1H, –CH cyclo), (q, 2H, –CH₂cyclo), (m, 2H, –CH₂ cyclo), (t, 2H, –CH₂cyclo), 4.23 (s, 1H, –CH), 5.91 (t, 2H, –NH₂), MS m/z: 317.

Compound S₁₃: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-nitrophenyl)propane-1,3-dione, IR, cm⁻¹: 2929 (C–H str.), 1587 (C=C str.), 1262 (C–N str.), 3396 (N–H str.), 1687 (C=O str., carbonyl), 696 (C–S–C str., thiophene ring), 1480 (N–O str., aromatic), 1H NMR (CDCl₃, δppm): 7.25–9.19 (m, 2H, Ar–H), 4.31 (d, 2H, –NH₂), 4.28 (t, 1H, –CH), 3.70 (t, 1H,

Fig. 9 Secondary structure element elucidation where alpha sheet is displayed by the deep orange color, and the beta sheet is presented in white



–CH cyclo), 1.95 (q, 2H, –CH₂cyclo), 1.32 (m, 2H, –CH₂ cyclo), 2.84 (t, 2H, –CH₂cyclo), 4.22 (s, 1H, –CH), MS m/z: 347.

Compound S₁₄: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-hydroxyphenyl)propane-1,3-dione, IR, cm⁻¹: 3075 (C–H str.), 1596 (C=C str.), 1274 (C–N str.), 3400 (N–H str.), 1687 (C=O str., carbonyl), 668 (C–S–C str., thiophene ring), 3604 (OH str., aromatic), MS m/z: 318.

Compound S₁₅: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(*m*-tolyl)propane-1,3-dione, IR, cm⁻¹: 3019 (C–H str.), 1648 (C=C str.), 1002 (C–N str.), 3516 (N–H str.), 1696 (C=O str., carbonyl), 672 (C–S–C str., thiophene ring), 1420 (CH₃ str., aromatic), ¹H NMR (CDCl₃, δppm): 7.25 (m, 2H, Ar–H), 5.91 (d, 2H, –NH₂), 4.27 (t, 1H, –CH), 4.21 (t, 1H, –CH cyclo), 1.77 (q, 2H, –CH₂cyclo), 1.30 (m, 2H, –CH₂ cyclo), 2.46 (t, 2H, –CH₂cyclo), 4.25 (s, 1H, –CH), 2.68 (s, 3H, –CH₃), MS m/z: 316.

Compound S₁₆: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-bromo-5-methoxyphenyl)propane-1,3-dione, IR, cm⁻¹: 3019 (C–H str.), 1526 (C=C str.), 1262 (C–N str.), 3347 (N–H str.), 1679 (C=O str., carbonyl), 673 (C–S–C str., thiophene ring),

618 (C–Br str., aromatic), 2877 (O–CH₃ str., aromatic), MS m/z: 411.

Compound S₁₇: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(2,4-dichlorophenyl)propane-1,3-dione, IR, cm⁻¹: 2932 (C–H str.), 1580 (C=C str.), 1262 (C–N str.), 3321 (N–H str.), 1679 (C=O str., carbonyl), 742 (C–S–C str., thiophene ring), 819 (C–Cl str., aromatic), MS m/z: 371.

Compound S₁₈: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(2,4-dihydroxyphenyl)propane-1,3-dione, IR, cm⁻¹: 2772 (C–H str.), 1519 (C=C str.), 1261 (C–N str.), 3467 (N–H str.), 1679 (C=O str., carbonyl), 673 (C–S–C str., thiophene ring), 3503 (OH str., aromatic), MS m/z: 334.

Compound S₁₉: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(4-fluorophenyl)propane-1,3-dione, IR, cm⁻¹: 2839 (C–H str.), 1591 (C=C str.), 1275 (C–N str.), 3345 (N–H str.), 1684 (C=O str., carbonyl), 685 (C–S–C str., thiophene ring), 1041 (C–F str., aromatic), MS m/z: 320.

Compound S₂₀: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophen-3-yl)-3-(3-chlorophenyl)propane-1,3-dione, IR, cm⁻¹: 2826 (C–H str.), 1541 (C=C str.), 1261 (C–N str.), 3398 (N–H str.), 1678 (C=O str.,

carbonyl), 752 (C–S–C str., thiophene ring), 677 (C–Cl str., aromatic), 3398 (OH str., aromatic), MS m/z: 336.

Compound S₂₁: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-(2-chloro-3-methylphenyl)propane-1,3-dione, IR, cm⁻¹: 3008 (C–H str.), 1588 (C=C str.), 1227 (C–N str.), 3486 (N–H str.), 1682 (C=O str., carbonyl), 721 (C–S–C str., thiophene ring), 635 (C–Cl str., aromatic), 1356 (CH₃ str., aromatic), 1H NMR (CDCl₃, δppm): 7.25 (m, 2H, Ar–H), 5.91 (d, 2H, –NH₂), 4.27 (t, 1H, –CH), 4.21 (t, 1H, –CH cyclo), 1.78 (q, 2H, –CH₂cyclo), 1.30–1.33 (m, 2H, –CH₂ cyclo), 2.46 (t, 2H, –CH₂cyclo), 4.23 (s, 1H, –CH), 2.48 (s, 3H, CH₃), MS m/z: 350.

Compound S₂₂: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-(3,5-dichloro-2-hydroxyphenyl)propane-1,3-dione, IR, cm⁻¹: 3085 (C–H str.), 1508 (C=C str.), 1276 (C–N str.), 3391 (N–H str.), 1691 (C=O str., carbonyl), 682 (C–S–C str., thiophene ring), 3654 (OH str., aromatic), 788 (C–Cl str., aromatic), 1H NMR (CDCl₃, δppm): 7.25 (m, 2H, Ar–H), 5.91 (d, 2H, –NH₂), 4.25 (t, 1H, –CH), 2.7 (t, 1H, –CH cyclo), 1.76 (q, 2H, –CH₂cyclo), 1.57 (m, 2H, –CH₂ cyclo), 2.46 (t, 2H, –CH₂cyclo), 4.21 (s, 1H, –CH), 4.27 (s, 1H, –OH), MS m/z: 387.

Compound S₂₃: 1-(2-amino-2,4,5,6,7,7a-hexahydrobenzo[b]thiophen-3-yl)-3-(5-chloro-2-hydroxy-4-methylphenyl)propane-1,3-dione, IR, cm⁻¹: 2803 (C–H str.), 1541 (C=C str.), 1229 (C–N str.), 3395 (N–H str.), 1692 (C=O str., carbonyl), 756 (C–S–C str., thiophene ring), 3742 (OH str., aromatic), 1341 (CH₃ str., aromatic), 650 (C–Cl str., aromatic), 1H NMR (CDCl₃, δppm): 7.25 (m, 2H, Ar–H), 5.70 (d, 2H, –NH₂), 4.08 (t, 1H, –CH), 3.59 (t, 1H, –CH cyclo), 1.68 (q, 2H, –CH₂cyclo), 1.37 (m, 2H, –CH₂ cyclo), 2.57 (t, 2H, –CH₂cyclo), 4.07 (s, 1H, –CH), 4.11 (s, 1H, –OH), 2.06 (s, 3H, –CH₃), MS m/z: 366.

Screening for antimicrobial activity

MIC (minimal inhibitory concentration) determination

The synthesized compounds were evaluated by microbroth dilution method using 96 flat bottom microtiter plates as described by CLSI guideline, 2020 [34]. Fluconazole (an antifungal) and cefadroxil (an antibacterial) were used as standard drugs. The selected strains for screening were as “Gram positive bacteria: *Staphylococcus aureus* (MTTC 3160), *Bacillus subtilis* (MTCC 441), Gram negative bacteria *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 3216) and fungal strains *Aspergillus niger* (MTTC 281) and *Candida albicans* (MTCC 227)” [35]. The synthesized compounds were diluted first in 10 wells (from 1000 µg/mL

to 1.9 µg/mL) and 11th well was kept as positive control and 12th well was left as media control. The overnight grown culture was adjusted to 0.5 McFarland turbidity standards. In each well 10 µL broth was added except 12th well. The presence of turbidity shows the bacterial growth, and the absence of turbidity was interpreted as the MIC. By the addition of *p*-iodonitrotetrazolium violet dye (INT; 0.2 mg/mL), viability of microorganisms was also confirmed.

Screening for antioxidant activity by DPPH (1,1-diphenyl-2-picrylhydrazyl) method

The newly synthesized substance's antioxidant activity was assessed spectrophotometrically utilizing the DPPH free radical scavenging technique. When DPPH reacts with hydrogen donors, it is reduced to the equivalent hydrazine and its dark purple color turns to yellow, indicating a considerable reduction in absorption at 517 nm. DPPH is a stable free radical with an absorption maximum at 517 nm. Solution of DPPH (3 g/mL) in methanol was prepared. As a blank control, methanol and DPPH (1:1) solution were utilized. Each synthetic molecule and the standard (ascorbic acid) was diluted in methanol to four different concentrations (25 g/mL, 50 g/mL, 75 g/mL and 100 g/mL), and one milliliter of each concentration was added to one milliliter of the DPPH solution. The mixture was vigorously agitated and left at room temperature in the dark for 30 min, after which the UV absorbance at 517 nm was measured [36]. The percent (%) inhibition of free radical DPPH is calculated as:

$$\% \text{ Inhibition} = \frac{(A_{\text{Blank}} - A_{\text{Sample}})}{A_{\text{Blank}}} \times 100 \quad (1)$$

A_{Blank} = absorbance of the blank reaction, A_{Sample} = absorbance of the test compounds.

The graph plotting percent inhibition and various concentrations of produced compounds served as the basis for calculating the IC₅₀ value.

Screening for antitubercular activity

The antimycobacterium activity of compounds was assessed against *M. tuberculosis* using the microplate Alamar blue assay. This method uses a thermally stable reagent, has a good correlation with proportionate and is nontoxic. All of the sterile 96-well plates' outside perimeter wells received 200 µL of sterile deionized water in order to reduce the amount of medium that dries out in the test wells during incubation. 100 µL of the Middlebrook 7H9 broth were added to the 96-well plate, and compounds were serially diluted right there on the plate. The range of final drug testing was 100–0.2 g/mL. The plate was incubated for five days at 37 °C with Parafilm wrapping and sealing it. After that, 25 µL of a

freshly prepared 1:1 solution of 10% tween 80 and Alamar blue reagent was added to the plate. While a blue color in the well indicated no bacterial growth, a pink color indicated growth. The MIC is the lowest drug concentration that prevents the color shift from blue to pink [37].

Computational study

The Schrodinger suite release 2019–1 49 was employed to carry out molecular docking of certain legends into the active binding regions of protein on default setting. The right 2D orientation of the chemical structures of the chosen ligands was shown using the ChemOffice program "Chem Draw 16.0," and ChemBio3D was used to lower the energy required for each molecule. The molecules with the least amount of energy were chosen to perform a docking. The three-dimensional structure of the receptor protein was retrieved from <https://www.rcsb.org/with> a PDB ID of 4FDO (Resolution: 2.40 Å.

R-Value Free: 0.205, R-Value Work: 0.167, R-Value Observed: 0.169) by doing a search on the protein data bank repository. The co-crystallized ligand, along with a few water molecules and cofactors, had to be released in order to effectively prepare the target protein in line with the standard protocol [38]. Target protein preparation was followed by rendering utilizing the glide grid module for grid creation. Grid is a particular location on the receptor protein where the medication will bind. The macromolecule's target area was placed inside the grid so that it covered the whole structure. It was determined that the glide dock module of the Schrodinger suit provided the docking technique that could be used to dock the ligand and protein most successfully. Each ligand was examined in up to nine different conformations throughout the docking process. Investigating ligand-receptor interactions in both 3D and 2D was done using the Discovery studio visualizer. The target receptor-friendly (lower) free binding energy conformations were those that were selected using this method. The ligands are depicted in various colors, and the residues that interact with H-bonds and one another are indicated as balls and sticks [39].

Docking validation

To confirm the Docking procedure, the co-crystallized ligand (PDB ID: 4FDO) was extracted from its crystal structure and docked again into the active site of enzyme. The computed RMSD value between the co-crystallized ligand and the top-ranked docked conformation was 0.132, as predicted.

Molecular dynamic simulation

Molecular dynamic simulation was performed on Desmond version 2022.4. The complex of compound S_{23} with DprE1 was taken for the system buildup for MD simulation. System ionization was carried out by use of the default force field, OPLS4. In relation to transmembranes (TMs), the palmitoyl-oleoyl-phosphatidylcholine (POPC) bilayer membrane was positioned by adhering to the OPM information source. The system was neutralized by adding Na⁺ and Cl⁻ ions after it was solvated using the TIP3P water model4 inside the 10 Å orthorhombic box. In particular, the addition of ions was rationally avoided in the 4 Å space surrounding the compound S_{23} . The System Builder program for the Desmond MD engine was used to set up the system. Following its conclusion, a 100-ns MD simulation using the chosen ensemble of NPγT was run in an isothermal-isobaric thermodynamic environment. Throughout the simulation, 1.01325 bar of applied pressure and 300 K of temperature were maintained. Using VMD and the Desmond MD engine's simulation interaction diagram module, the MD trajectory was further examined after the MD simulation was finished.

Discussion

A series of 1-(2-amino -2,4,5,6,7,7a-hexahydrobenzo[b]-3-yl)-3-substitued-phenylpropane-1,3-dione derivatives were synthesized using the Gewald synthesis in the first step, followed by Baker–Venkataraman rearrangement to yield title compounds. The FTIR, MS and 1H NMR results of the produced derivatives were validated. The biological potential of the synthesized compounds was examined in vitro using various techniques, including the tube dilution method for testing antimicrobial activity, the DPPH method for testing antioxidant activity and the microplate Alamar blue assay (MABA) method for testing antimycobacterial activity against a particularly virulent strain of MTB (MTB H37Ra). Antimicrobial screening outcomes showed that compound S_{17} turned out to be the most effective antibacterial agent against *Staphylococcus aureus* (MIC = 16.87 μM), *Bacillus subtilis* (MIC = 9.45 μM) and *Escherichia coli* (MIC = 16.87 μM), while compound S_7 exhibited outstanding activity against *Salmonella typhi* (MIC = 9.74 μM), and compound S_{16} displayed remarkable antifungal activity toward both *Candida albicans* and *Aspergillus niger* (MIC = 15.23 μM). Compound S_{10} demonstrated good antioxidant activity (IC₅₀ = 45.29 μg/mL), outperforming ascorbic acid. From the results of antitubercular activity, compound S_{23} exhibited promising efficacy with an MIC value of 78.125 μg/mL. Molecular docking studies were conducted to elucidate the binding

modes of the synthesized compounds with the enzymatic active site of “DprE1-decaprenylphosphoryl- β -D-ribose-2'-epimerase.” The docking results revealed a comparable binding mode to the native ligand with a favorable docking score, shedding light on the potential of these compounds as inhibitors of DprE1 and contributors to the development of effective antitubercular drugs. The synthesized compounds showed very good binding affinity in comparison with a positive control (Isoniazid). Compound S_{23} was found to have very good docking score of -8.516 as compared to the Isoniazid with the docking score of -6.315 . So from the study of both docking and as well as in vitro analysis of synthesized compounds it gives the clear idea that compound S_{23} was found to be very effective as antitubercular drug. This study underscores the significance of understanding ligand–protein interactions at the molecular level for rational drug design against *Mycobacterium tuberculosis*.

Conclusion

In summary, we can say that new tetrahydrobenzothiophene compounds were created, forming a new class of inhibitors with strong antibacterial, antioxidant and antitubercular characteristics. Compound S_{23} was discovered to be the most effective against a variety of Gram positive and Gram negative bacterial strains with electron-releasing groups; however, substitution with electron-releasing groups increased the antibacterial activity against *S. Typhi* strain. Because of presence of methoxy group at the *para* position and a chloro group at the *ortho* position, compound S_{16} has become the most potent antifungal agent. Due to the presence of an electron-releasing group, compound S_{10} was found to be more powerful in antioxidant test results. Significant antitubercular action was shown by compound S_{23} against the MTB H37Ra strain. According to the results of the antitubercular screening, the produced compounds with electron-releasing groups (*o*-OH, *p*-CH₃) on the benzylidene part were found to have substantial action. Molecular docking study reveals that tetrahydrobenzo[b]thiophene-2-carboxylic acid derivatives shown high binding affinity against active site of the DprE1 enzymes because of hydrogen bonding with the glycine 55, glycine 57 and glycine 125 residue of receptor protein. The docking score of synthesized compound S_{23} was more than that of standard drug (Isoniazid). This provides a solid foundation for the development of the lead compounds for this series that will constitute effective antitubercular medicines. Therefore, these thiophene derivatives undoubtedly have a higher chance of being discovered as a lead molecule for the development of new medicinal medicines.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13738-024-03088-6>.

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Author's contributions PKV designed and finalized the scheme; RS did research work; and MS and SK did review work and wrote the paper. All authors read and approved the final manuscript.

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Data availability All data are provided in the manuscript or cited in the references.

Declarations

Conflict of interest The author(s) have no conflicts of interest.

Consent to participate Not applicable.

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