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Design, synthesis and evaluation of antitubercular activity of 4-oxo-butanamido benzoate derivatives

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In light of the inevitable emergence of resistance, designing small molecule-based new drug candidates through structure modulation of the reported drugs has garnered considerable attention. In present study, we have synthesized and characterized 4-oxo-butanamido benzoate derivatives as anti-TB agents through molecular hybridization. A total of 15 target compounds have been synthesized. Among all the tested compounds, three compounds (SA1a, SA1b and SA2a) show potent anti-TB activity with an MIC = 1.56 µg/mL against *M. tuberculosis* H37Rv. Further evaluation includes the testing for antibacterial and antifungal activities to assess selectivity. Testing has revealed neither antibacterial activity nor antifungal activity. Docking studies have been conducted to assess binding interactions of the synthesized compounds with the five key enzymes involved in the mycolic acid biosynthesis. Docking results reveal InhA as the potential enzyme target for these compounds. In present study, compounds SA1a, SA1b and SA2a show the highest binding affinity of below –10.0 KCal/mol. The overall conclusion has highlighted the activity potency to follow the pattern *para-* ≥ *meta-* > *ortho-* derivatives, with *para* derivatives exhibiting higher activity even in docking studies.

Keywords: *Mycobacterium tuberculosis*, 2-Transenoyl-acyl carrier protein (ACP) reductase (InhA), 4-Oxo-butanamido benzoate derivatives, MABA assay, Molecular docking

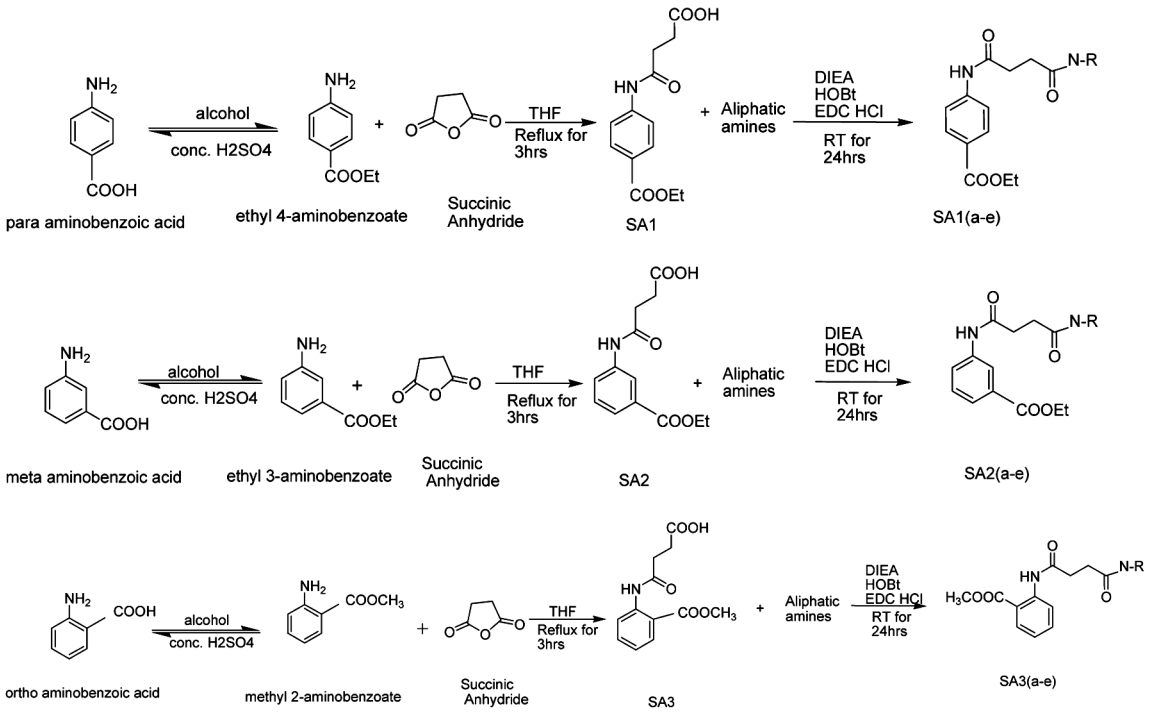
Tuberculosis (TB) is a contagious respiratory illness caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*)[1-4]. The WHO's 2024 Global TB Report[5] indicates that almost 2 billion individuals are the carriers of TB bacteria, *Mtb*. The risk of development to active TB is notably high among immune compromised persons. Globally, TB reported 10.8 million new cases in 2023, accounting for 1.25 million deaths. Countries that carry substantial burdens, such as India, Indonesia, and China bear the brunt of the epidemic. The situation is further exacerbated by the emergence of drug-resistant strains of Tuberculosis, emergence of multidrug-resistant (MDR)[6,7], extensively drug-resistant (XDR)[8,9], and total-drug-resistant (TDR)[10] strains poses a serious threat, rendering existing treatments ineffective. These findings underscore the urgent need for new therapeutic strategies.

In our ongoing effort to discover new lead molecules with selective antitubercular activity and potentially novel mechanisms of action, we recently reported anti-TB activity of 1,4-diketo compounds[11] and N-substituted glycinamide[12] derivatives with high affinity towards enzymes involved in mycolic acid biosynthesis[13]. Inspired by this discovery of anti-tubercular properties of these two scaffolds, we employed a molecular hybridization approach to synthesise 4-oxo-butanamido benzoate derivatives or Succinimides (Fig. 1) by using amino benzoic acid and aliphatic amines. As a result, we designed and synthesized a series of 15 target compounds (Scheme 1) and then assessed the structure–activity relationships (SARs) of these derivatives using the Microplate Alamar Blue Assay (MABA) to assess their antimycobacterial activity against *M. tuberculosis* H37Rv strains. Most derivatives displayed encouraging antimycobacterial activities *in vitro*. We also performed molecular docking studies of the synthesized compounds on selected proteins that are involved in the cell wall synthesis of *M. tuberculosis*.

Experimental Section

Materials and Methods

For the synthesis of the compounds commercially sourced solvents and chemicals were utilized without further purification. All reactions were monitored using an appropriate mobile phase by analytical thin-



Scheme 1 — Synthetic scheme for 4-oxo-butanamido benzote derivatives **SA1**(**a-e**); **SA2**(**a-e**); **SA3**(**a-e**)

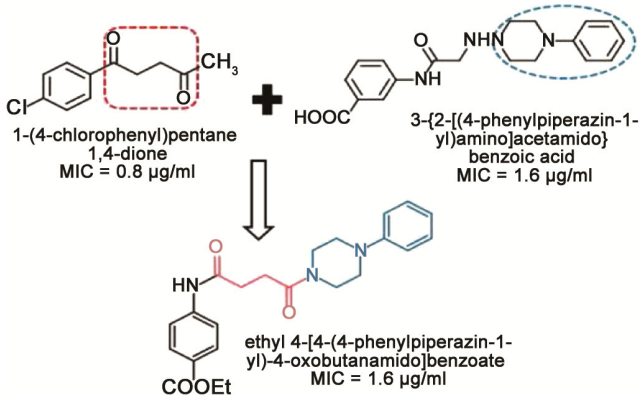


Fig. 1 — Designed strategy for the synthesis of 4-oxo-butanamido benzoate derivatives through molecular hybridization

layer chromatography (TLC) on Merck DC plates. The spots were visualised using UV (254 nm), iodine, and acid spray, respectively. The Melting points were measured on a Digimelt melting point apparatus (Stanford Research Systems, USA) and were uncorrected. ^{1}H and ^{13}C NMR spectra were acquired using the Bruker instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C). The NMR solvents used were $CDCl_3$ and DMSO-d6, and the internal standard was tetramethylsilane (TMS). For elemental analysis experiments, a Carlo Erba elemental analyzer was utilized. FTIR spectra were obtained with a Bruker (ALPHA-T) FTIR spectrometer using the KBr pellet or ATR ZnSe technique, as applicable. The Andhra University College of Pharmaceutical Sciences' biotechnology lab provided pure cultures of the experimental organisms.

Chemistry

Step-1: Esterification of benzoic acid isomers[14,15]

Amino benzoic acids (1.38 g, 10 mmol) were dissolved in 15 mL of alcohol, in a 25mL round-bottomed flask. Concentrated Sulphuric acid (1.09 mL, 15 mmol) was added drop wise to the alcoholic solution under cool conditions, and heat the mixture under gentle reflux for 40 min-2hr which is depends upon the alcohol we used in the reaction. After completion of reaction as indicated by TLC, the reaction mixture was quenched with saturated sodium bicarbonate solution and the product was extracted with ethyl acetate. Subsequent drying with anhydrous Na_2SO_4 and ethyl acetate evaporation yielded the ester in a pure form and it was utilized as such for further reactions.

Step-2: General procedure for the synthesis of Substituted Succinamic acids (SA1; SA2; SA3)[16-18]

About 10mmol of succinic anhydride was dissolved in 30 mL of anhydrous THF and then

appropriate esters of benzoic acid (10mmol) was added to the solution. The reaction mixture was heated under reflux for 3 hr. After completion of reaction as indicated by TLC, quench the reaction using ice cold water. Chilled hexane (30 mL) was added to the cold reaction flask to precipitate the corresponding succinamic acids. The product was collected by suction filtration using a Buchner funnel and then rinsed with 20 mL of hexane. Precipitate was collected, recrystallized and dried. The obtained precipitate was used for the next reaction without any further purification.

Step-3: General procedure for the Synthesis of 4-oxo-butanamido benzoate derivatives[19]

The synthesis of the title compounds SA1(a-e); SA2(a-e); SA3(a-e) involves an acid-amine coupling reaction. In a round-bottom flask (RBF), 500 mg of the corresponding succinamic acid (1.88 mmol, 0.65 eq) was placed, and 2 mL of DMF was added, followed by stirring. To this, 1.1mL of DIEA (5.709mmol, 1.97 eq) was added and chilled to 0°C while stirring for 5 minutes. Then, 733 mg EDC HCl (3.825 mmol, 1.32 eq), 586 mg HOBt (3.825 mmol, 1.32 eq), and aliphatic amine represented in Table 1 (2.898 mmol, 1 eq) were added and stirred at RT for 24 hr. Upon the completion of the reaction, as shown by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate. Wash the ethyl acetate layer with brine, dry it over anhydrous sodium sulphate and the solvent was evaporated and recrystallized from methanol to yield a pure compound.

Characterization of potent compounds (The Supplementary Information section presents the data for the remaining compounds)

Ethyl-4-[4-(4-phenylpiperazin-1-yl)-4-oxobutan-amido]benzoate, SA1a: Yield 73.6%. m.p.162°C. IR (KBr): 1233 (C-O), 1589 (C=O), 1736 (C=O), 3146 (Ar C-H), 3368 (NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (1H, s), 7.99 (2H, m, *J* = 8.3 Hz), 7.63 (2H, m, *J* = 8.4 Hz), 7.28 (2H, m, *J* = 7.74 Hz), 6.95 (3H, m, *J* = 7.71 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 3.81 (4H, m), 3.21 (4H, m), 2.94 (4H, t, *J* = 7.3 Hz), 1.39 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.12, 166.23,150.78, 142.43, 130.67, 129.30, 125.53, 120.74, 118.67, 116.74, 60.78, 49.36, 45.38, 41.94, 32.83, 28.88, 14.36; HRMS (ESI): *m/z* Calcd for $C_{23}H_{27}N_3O_4$: $[M+H]^+$ 410.20. Found 410.20. Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26;O:15.63. Found: C, 67.46; H, 6.65; N, 10.26; O, 15.63%.

Ethyl-4-[4-(4-benzylpiperazin-1-yl)-4-oxobutan-amido]benzoate, SA1b: Yield 74.3%. m.p.186°C. IR (KBr): 1293 (C-O), 1644 (C=O), 1732 (C=O), 2875, 3102 (Ar C-H), 3377 (NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (1H, s), 7.95 (2H, m, *J* = 8.5 Hz), 7.61 (2H, m, *J* = 8.47 Hz), 7.33 (3H, m, *J* = 7.74 Hz), 7.28 (2H, m, *J* = 7.71 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 3.66 (2H, m), 3.53 (4H, m), 2.77 (4H, t, *J* = 7.3 Hz); 2.45 (4H, m), 1.39 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.72, 171.24, 165.70,142.57, 137.47, 130.43, 127.35, 118.65, 62.81, 60.75, 52.61, 45.46, 42.05, 32.81, 28.80, 14.36; HRMS (ESI): *m/z* Calcd for $C_{24}H_{29}N_3O_4$: $[M+H]^+$: 424.22. Found 424.22. Anal. Calcd for $C_{23}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92; O, 15.11. Found: C, 68.06; H, 6.90; N, 9.92; O, 15.11%.

Ethyl-3-(4-oxo-4-(4-phenylpiperazin-1-yl)butan-amido)benzoate, SA2a: Yield 72.1%. m.p.158°C. IR (KBr): 1290 (C-O), 1651 (C=O), 1706 (C=O), 3121 (Ar C-H), 3379(NH) cm^{-1}; ^{1}H NMR (400 MHz,

Table 1 — Substituents used in Scheme 1

Compd	IUPAC Name	Compd	N-R
SA1	4-[4-(ethoxycarbonyl)anilino]-4-oxobutanoic acid	**SA2a**	1-Phenyl Piperazine
SA2	4-[3-(ethoxycarbonyl)anilino]-4-oxobutanoic acid	**SA2b**	1-Benzyl Piperazine
SA3	4-[2-(methoxycarbonyl)anilino]-4-oxobutanoic acid	**SA2c**	Piperidine
		SA2d	Pyrrolidine
	N-R		
SA1a	1-Phenyl Piperazine	**SA2e**	Diethyl amine
SA1b	1-Benzyl Piperazine	**SA3a**	1-Phenyl Piperazine
SA1c	Piperidine	**SA3b**	1-Benzyl Piperazine
SA1d	Pyrrolidine	**SA3c**	Piperidine
SA1e	Diethyl amine	**SA3d**	Pyrrolidine
		SA3e	Diethyl amine

$CDCl_3$): δ 8.88 (1H, s), 8.10 (1H, m,), 7.88 (1H, m, *J* = 7.79 Hz), 7.74 (1H, m, *J* = 7.82 Hz), 7.50 (1H, m, *J* = 7.81 Hz), 7.23 (3H, m, *J* = 7.7 Hz), 6.93 (2H, m, *J* = 7.74 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 3.87 (4H, m), 3.18 (4H, m), 2.82 (4H, t, *J* = 7.3 Hz), 1.94 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.62, 166.85, 150.82, 138.55, 130.75, 129.28, 124.19, 120.69, 116.72, 61.1, 52.19, 49.60, 45.38, 41.93, 32.61, 28.83, 14.3; HRMS (ESI): *m/z* Calcd for $C_{23}H_{27}N_3O_4$: $[M+H]^+$: 410.20. Found 410.21. Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26; O, 15.63. Found: C, 67.46; H, 6.65; N, 10.26; O, 15.63%.

In vitro anti-TB activity

Microplate Alamar Blue Assay (MABA)[20-22] is a fast, high-throughput, affordable dye-based cell viability assay that uses Alamar blue as indicator for anti-mycobacterial drug screening. MABA provides a quantitative evaluation of drug susceptibility of replicating *Mycobacterium tuberculosis* H37Rv (ATCC 27294). This assay was employed to assess the *in vitro* anti-tubercular activity of synthesized compounds against H37Rv strain. The results are reported as the minimum inhibitory concentration (MIC) in μg/mL. The results are presented in Fig. 2 and Table 2.

Antimicrobial activity

The agar well diffusion method[23] was used to test the bacterial susceptibility of the synthesized compounds at various concentrations. Using Rifampicin as the standard and DMSO as control, antibacterial efficacy of a test substance was assessed against *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 26). Ketoconazole was used as the standard and DMSO as control for testing antifungal activity against *Candida albicans* (ATCC 10231). At a concentration of 100 μg/mL, none of the synthesized compounds exhibited appreciable antimicrobial activity against the selected strains. The results are provided in the supporting data.

Molecular Docking Studies

Chemdraw 19.0 was used to draw the structures of compounds SA1(a-e); SA2(a-e); SA3(a-e), while Chem3D was used to optimize ligand geometry and perform MM2 energy minimization of the 3D structures[24]. 2-Transenoyl-acyl carrier protein (ACP) reductase (InhA), β-ketoacyl-ACP reductase (MabA), beta-ketoacyl-acyl carrier protein synthase III (FabH) and β-ketoacyl ACP synthase I (KasA) protein X-ray crystal structures were obtained from (www.rcsb.org/pdb/home/home.do) and mycolic acid methyl transferase (MmaA1) protein is a homology model developed in our lab from a previous study[25]. Charges were assigned for the protein and the ligand using AutoDock. The open source chemistry toolbox OpenBabel version 2.3.2 (www.openbabel.org) was utilized to perform all the file conversions necessary for the docking study. Using AutoDock Tools (ADT), a free graphical user interface included in MGL software packages (version 1.5.6rc3), the grid box parameters were generated[26]. The docking experiment was carried out using the molecular docking tool AutoDock Vina (version 1.1.2). The receptor-ligand interactions were studied using Discovery Studio Visualizer[27].

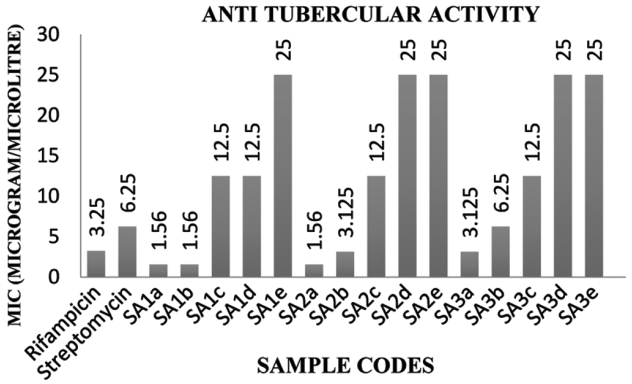


Fig. 2 — *In vitro* MABA assay results of the 4-oxo-butanamido benzoate derivatives **SA1(a-e)**; **SA2(a-e)**; **SA3(a-e)**

Table 2 — Results of Antitubercular activity of 4-oxo-butanamido benzoate derivatives (MABA Assay)

S. No	Compd	MIC (μg/mL)
1	**SA1a**	1.56
2	**SA1b**	1.56
3	**SA1c**	12.5
4	**SA1d**	12.5
5	**SA1e**	25
6	**SA2a**	1.56
7	**SA2b**	3.125
8	**SA2c**	12.5
9	**SA2d**	25
10	**SA2e**	25
11	**SA3a**	3.125
12	**SA3b**	6.25
13	**SA3c**	12.5
14	**SA3d**	25
15	**SA3e**	25
16	Streptomycin	6.25
17	Rifampicin	3.125

Results and Discussions

Chemistry

In a three-step process, 15 novel 4-oxo-butanamido benzoate derivatives SA1(a-e), SA2(a-e), and SA3 (a-e) were synthesized. Initially, amino benzoic acids underwent esterification to produce the corresponding esters. Subsequently, these esters reacted with succinic anhydride, resulting in the formation of the respective succinamic acids. The target compounds were then synthesized through an acid amine coupling reaction using aliphatic amines. The products exhibited good yields, with only one or a few compounds deviating.

The chemical structures of the synthesized compounds were confirmed using IR, ^{1}H and ^{13}C NMR, and Mass spectral data. Major IR signals were observed at 1150-1310 (C-O), 1672-1745 (Carbonyl groups), 2980-3100 (Aromatic –CH), and 3145-3500 (N-H) cm^{-1}. The ^{1}H NMR spectrum displayed methylene protons of the ethyl group at δ 4.37 as a quartet, methyl protons of the ethyl group at δ 1.3 as a triplet, methyl protons at δ 3.9, two mutually coupled triplets for methylene at δ 2.7 to 2.9 (2H, t, J = 7.3 Hz), aromatic protons at δ 6.5 to 7.8, and Acetamide (δ 8.76). The ^{13}C NMR spectrum showed characteristic peaks according to the molecular structure, with the most prominent carbon signals observed at δ 160, 170, and 171, accounting for carbonyl peaks. Signals at 60 and 14 ppm confirmed the formation of the ethyl group, while the signal at 52 ppm confirmed the formation of the methyl group. The mass spectrum of all compounds showed molecular ion peaks consistent with their molecular formulas. The elemental/CHN analysis yielded satisfactory results. The spectral characterization of all synthesized compounds is provided in Supplementary data.

In vitro anti-TB activity

For anti-tubercular activity, all the synthesized compounds SA1 (a-e); SA2 (a-e); SA3 (a-e) were subjected to *in vitro* MABA assay against *Mycobacterium tuberculosis* H37Rv. Among the synthesized compounds SA1a, SA1b and SA2a showed potent anti-TB activity with an MIC 1.56 μg/mL given in Fig. 2 and Table 2. To assess their selectivity, the 4-oxo-butanamido benzoate derivatives were further evaluated for antimicrobial activity. However, when tested at a concentration of 100 μg/mL, none of the these compounds exhibited detectable antimicrobial activity against specific strains. The results of the antimicrobial activity are given in the supplementary data.

Docking Analysis

To understand the binding mode of the 4-oxo-butanamido benzoate derivatives, all the synthesized compounds SA1(a-e); SA2 (a-e); SA3(a-e) were subjected to molecular docking studies against the five key enzymes which are involved in mycolic acid biosynthesis pathway *viz*., 2-transenoyl-acyl carrier protein (ACP) reductase (5MTP), β-ketoacyl-ACP reductase (1UZN), beta-ketoacyl-acyl carrier protein synthase III (1HZP), mycolic acid methyl transferase (MmaA1) and β-ketoacyl ACP synthase I (5LD8). The docking scores were predicted to be in the range of -6.3 to -10.4 Kcal/mol. The 4-oxo-butanamide derivatives, particularly those substituted with phenyl and benzyl piperazine amines showed good binding affinity with all the five enzymes. Notably, derivatives SA1a, SA1b, SA2a, SA2b and SA3a were found to have very strong interactions with these amino acids GLY-14, TYR-158, ILE-194, SER-20, ALA-22 and GLN-214 which are already reported to possess sceptical role in functioning of InhA, with docking scores ≥ 10.0 Kcal/mol. Hence, the docking studies align with *in vitro* activity profile observed in tests of the analogues. The Fig. 3 and Table 3 represents the docking interactions of the most potent ligands (SA1a, SA1b and SA2a) with the protein InhA. Supplementary data contains the remaining information on the docking poses with the remaining enzymes.

Molinspiration is a software tool for predicting molecular physicochemical properties such as LogP, TPSA, Lipinski Rule of Five using a methodology that calculates drug transport properties as a sum of fragment based contributions and correction factors[28-30]. It was used to predict the physicochemical properties of the 4-oxo-butanamido benzoate derivatives. The results of Molinspiration are given in the supporting data. The topological polar surface area (TPSA) of the compounds was found to be between 75.71 to 78.95 Å, which is significantly lower than the 160 Å limit suggests more polar and having good potential for hydrogen bonding interactions. The predicted percentage absorption was between 81.76 - 82.88 percent, showing good oral bioavailability of the compounds.

The Osiris Property Explorer[31,32] is based on chemical artificial intelligence and chemoinformatics

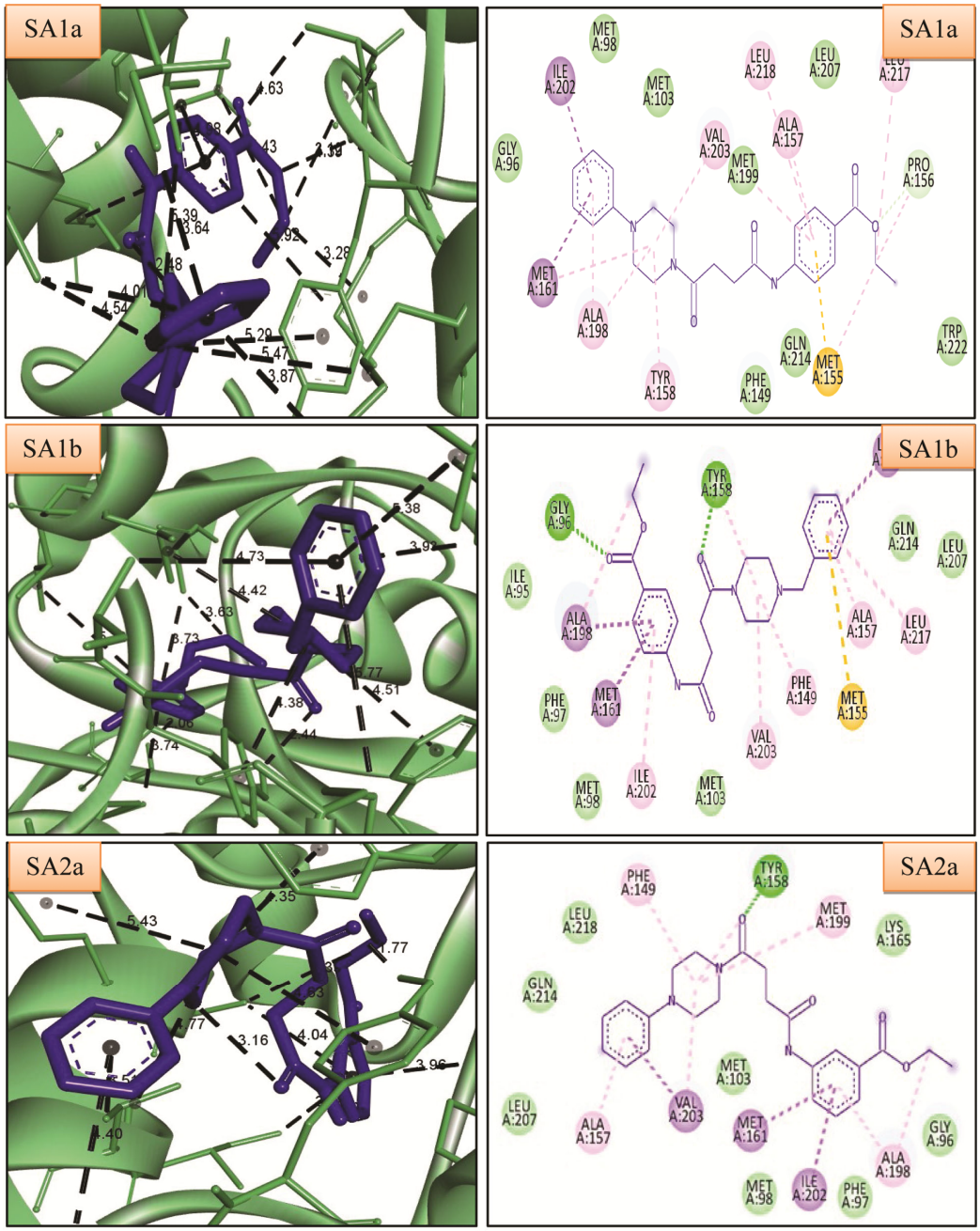


Fig. 3 — Docking poses of the potent molecules (**SA1a**, **SA1b** and **SA2a**) with InhA enzyme. The protein is shown as green color solid ribbon model and the ligand is shown as dark blue stick model. The 2D interaction diagram of the protein-ligand interaction is shown on the right side SAR of the synthesized compounds

methods to predict the toxicity risks and drug scores for small molecules. The SMILES codes for the synthesized compounds were submitted to Osiris property explorer to predict the physicochemical and toxicological properties, the results of which are given in the supporting data. In terms of mutagenicity, tumorigenicity, irritating impact, and reproductive effect, the results revealed that all the compounds were non-hazardous and likely to exhibit little or no toxicity.

The SAR of the 4-oxo-butanamido benzoate derivatives SA1(a-e); SA2(a-e); SA3(a-e), here the potency remains consistent for both *para*– and *meta*– benzoate derivatives having N-substituted piperazines, while the *ortho* position leads to a surprising drop in potency (Fig. 4). The order of

Table 3 — Molecular docking scores of 4-oxo-butanamido benzoate derivatives against enzyme (InhA)

Compd	Docking Score	Interaction residues
SA1a	–10.4	ALA-22
SA1b	–10.3	GLY-14, ILE-21, ALA-22
SA1c	–8.5	ALA-22, TYR-158, LYS-165
SA1d	–8.4	ALA-22
SA1e	–7.8	ILE-21, ALA-22, ILE-194
SA2a	–10.2	GLY-14, SER-20, ALA-22, GLY-96
SA2b	–10.2	GLN-14, SER-20, ILE-21, GLY-96
SA2c	–8.9	GLN-214
SA2d	–8.3	LYS-165, GLN-214
SA2e	–8.2	TYR-158
SA3a	–10.1	GLN-214
SA3b	–9.7	SER-94, GLY-96
SA3c	–8.8	ILE-194, GLN-214
SA3d	–8.1	LYS-165, ILE-194
SA3e	–7.4	LYS-165, ILE-194

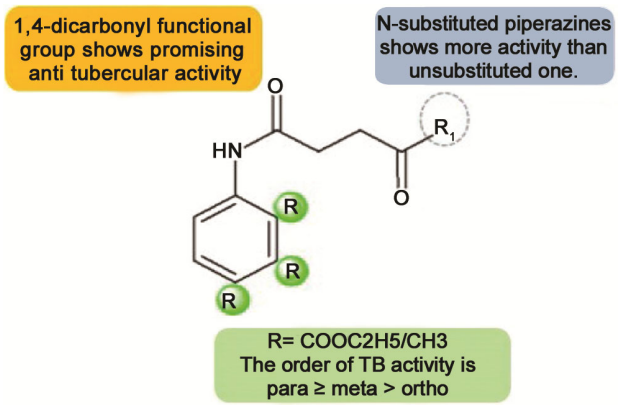


Fig. 4 — SAR Activity of 4-oxo-butanamido benzoate derivatives

potency was *para-* ≥ *meta-* > *ortho-* derivatives. Docking results align with *in vitro* assays, enhancing the study's reliability.

Conclusion

A new series of 4-oxo-butanamido benzoate derivatives obtained from molecular hybridisation are established as potential antitubercular compounds. Among the tested compounds, SA1a, SA1b and SA2a showed potent anti-TB activity against *M. tuberculosis* H37Rv with a MIC of 1.56 µg/mL. Interestingly, the intermediates (Succinamic acids) showed an activity of 6.25 µg/mL, which is appreciable but with further modification, the potency improved to 1.25 µg/mL demonstrating the progressive optimization of the structure. These compounds didn't show any noticeable antibacterial and antifungal activity at even a high concentration of 100 µg/mL in our studies. The observed structure-activity relationships among the synthesized compounds suggests that the presence of –COOEt/Me group's has a significant effect on anti-TB activity. Specifically, the order of potency was *para-* ≥ *meta-* > *ortho*-derivatives, indicating the importance of –COOEt/Me group's position. Furthermore, the presence of 1,4-dicarbonyl scaffold which is essential for activity and further substitutions with N-substituted piperazine aid in increasing the activity of the compounds. Additionally, docking studies further validated these results. Docking simulations performed on five key enzymes which are important for mycolic acid biosynthesis, revealed the multi-targeted nature of our compounds. Notably, among all enzymes, the derivatives exhibited good binding affinity with InhA protein. *In silico* ADME analysis predicted that all the synthesized compounds have a good bioactivity and very low toxicity risk. Therefore, the identified compounds can be putative leads for Tuberculosis drug discovery. Further research is required to enhance our understanding of the relationships between the structure and active site using a more extensive range of structurally related derivatives to identify even more promising leads.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Competing Interest

The authors declare that they have no conflict of interest.

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