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Design, synthesis, antimycobacterial activity and molecular docking studies of novel 3- (N-substituted glycinamido) benzoic acid analogues as anti tubercular agents

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Abstract

We have recently identified mycolic acid methyl transferase (MmaA1) enzyme inhibitors as potential antitubercular agents using *in silico* modelling techniques. In continuation of that study, we synthesised a series of novel 3- (N-substituted glycinamido) benzoic acid derivatives with an aim to optimise the lead molecule. The newly synthesised compounds were evaluated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H_{37}Rv. Among these, 5 compounds A3, A4, A5, A6 and A10 exhibited most potent activity with an MIC value of 1.6 µg/ml. Further molecular docking studies were carried out to investigate the binding mode of the ligands with MmaA1 protein. The docking studies revealed that the ligands made strong interactions with the catalytic site residues TRP30, TYR 32, GLY 71, TRP 74, GLY 76, ALA 77 and GLU 136 of MmaA1 protein. Druglikeness and leadlikeness properties of the compounds were also studied using computational tools. The results of *in silico* and *in vitro* studies indicate that these novel compounds are propitious leads for tuberculosis therapy.

Keywords

Tuberculosis; 3- (N-substituted glycinamido) benzoic acid; methyl transferases; MABA assay; molecular docking

Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis is distinguished by its lipid rich cell wall. It contains a complex structure of covalently linked peptidoglycan, arabinogalactan and mycolic acids[1-3]. Mycolic acids are very long chain (C40-C60) fatty acids which often carry substitutions like alcohol, ether and cyclopropyl groups.[4,5] These substitutions bring about necessary functional changes in mycolic acids, including maintenance of cell wall rigidity, physical strength of cell wall and virulence[6,7].

Mycolic acid methyl transferases belong to the mycolic acid cyclopropane synthases family and are involved in the synthesis of methoxy mycolic acids. Mycolic acid methyl transferase (MmaA1) belongs to a gene cluster that encodes four closely related methyl transferases (MmaA1-4) that introduce post synthetic modifications in the meromycolate chain of mycobacteria[8]. The methyl transferases share a common cofactor, S-adenosyl methionine (SAM). These SAM dependent enzymes bring about post synthetic modifications and unsaturations in the synthesis of mycolic acids[9,10]. MmaA1 protein is required for the synthesis of trans and keto mycolic acids in the mycobacteria. The MmaA1 protein converts cis-olefin oxygenated precursors of mycolates to trans-olefins with an adjacent methyl branch to form trans mycolic acids. Increased trans mycolic acid synthesis leads to increased cell wall rigidity, increased drug resistance and altered colony morphology.

Our research group has recently reported the identification of 3-(2-morpholinoacetamido)-N-(3,4-dihydro-4-oxoquinazolin-7-yl)benzamide and its intermediates as inhibitors of MmaA1 protein using structure-based drug design studies.[11] This molecule exhibited an activity of 100 µg/ml, whereas the intermediate compound 3-(2-chloroacetamido) benzoic acid or 3-(N-substituted glycinamido) benzoic acid exhibited an MIC of 25 µg/ml against *M. tuberculosis* H_{37}Rv. With an aim to optimize the structure further, we proceeded to synthesise the derivatives of 3-(N-substituted glycinamido) benzoic

acid (Fig 1). The synthesised compounds were screened for *in vitro* anti TB activity along with molecular docking studies and *in silico* ADME studies. The results of our study are discussed here in this publication.

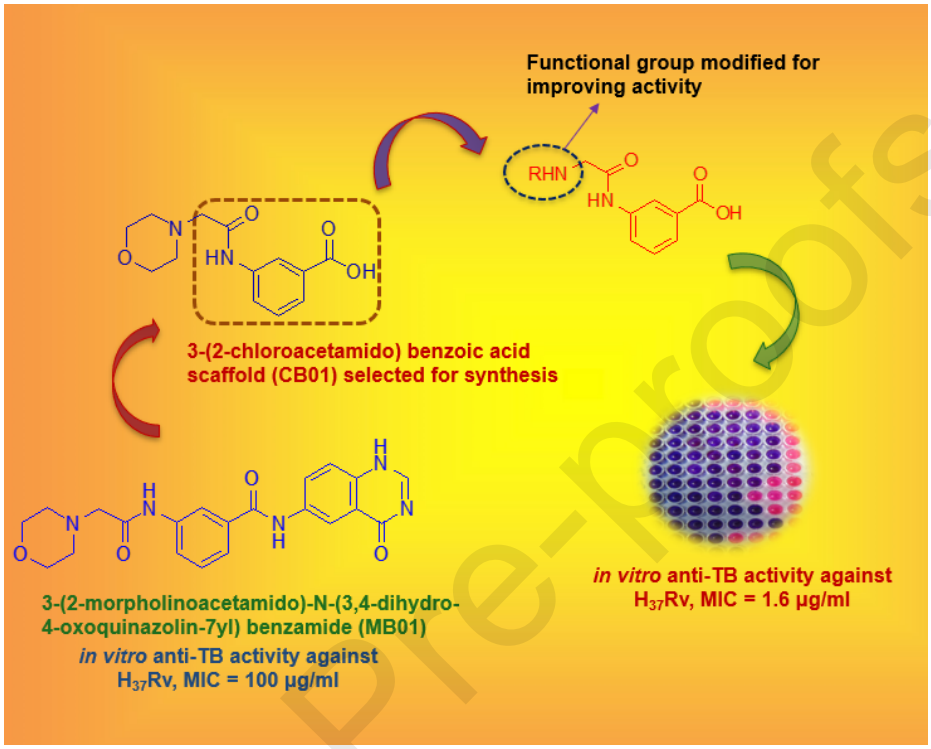
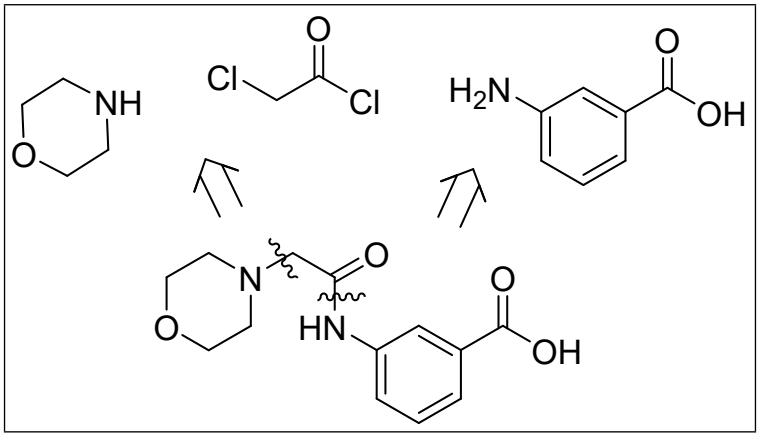


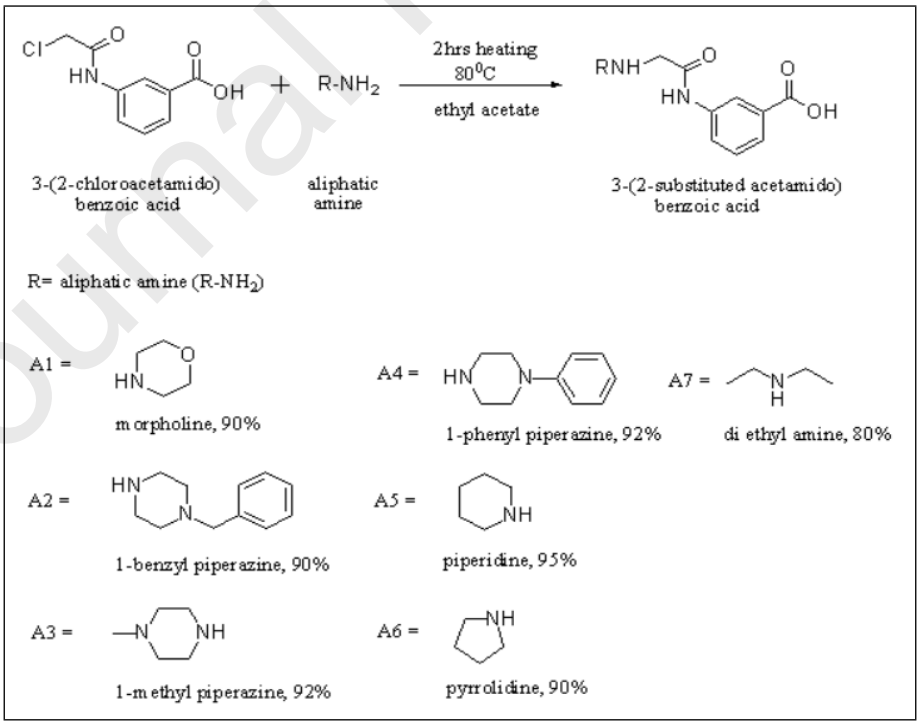
Fig.1: Design of scaffold for synthesis of 3-(N-substituted glycinamido) benzoic acid derivatives

The retrosynthetic analysis (scheme 1) of the chosen scaffold has given us simple and easily accessible starting materials. Here, Schotten Baumann reaction of 3-amino benzoic acid with chloroacetyl chloride has given us the first starting material 3-(2-chloroacetamido) benzoic acid. This, then undergoes nucleophilic substitution reaction with corresponding amine to realize the target compound.

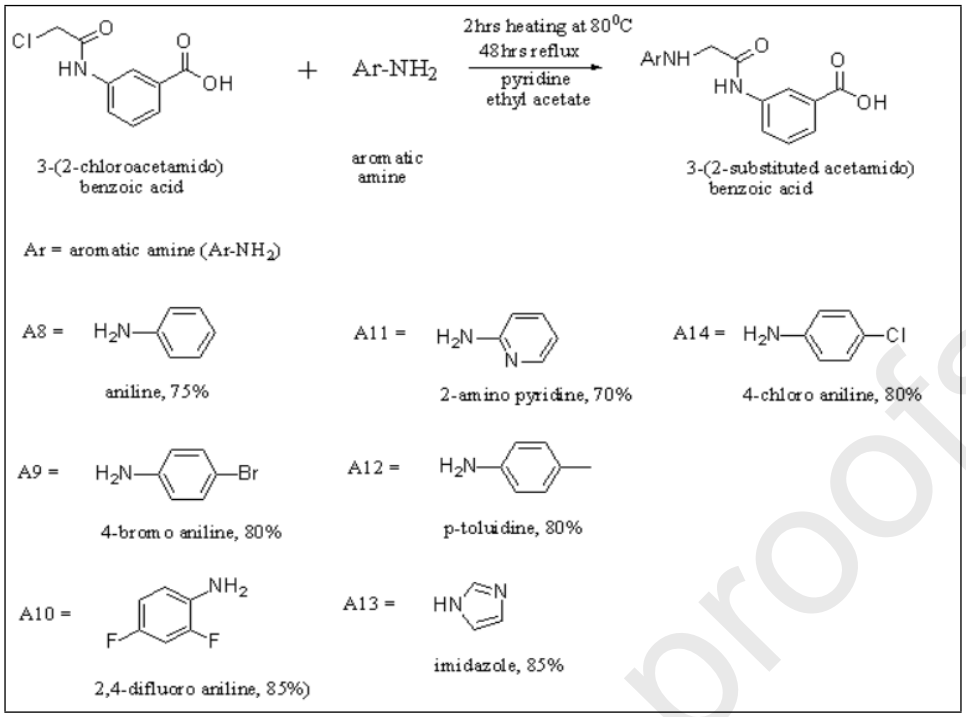


Scheme 1: Retrosynthetic route of 3-(2-chloroacetamido) benzoic acid

The synthesis of 3-(N-substituted glycinamido) benzoic acid derivatives was brought about by two different procedures resulting in excellent yields (70-95%). The synthesis of aliphatic amine substituted 3- (N-substituted glycinamido) benzoic acid derivatives is given in Scheme 2. The synthetic procedure for aromatic amine substituted 3-(N-substituted glycinamido) benzoic acid derivatives is given in Scheme 3. The detailed procedures for the synthesis are given in the supplementary information.



Scheme 2: Synthesis of aliphatic amine substituted of 3- (N-substituted glycinamido) benzoic acid derivatives and their yields



Scheme 3: Synthesis of aromatic amine substituted derivatives of 3- (N-substituted glycinamido) benzoic acid and their yields

The newly synthesised compounds were evaluated against $H_{37}Rv$ for their anti-TB activity using MABA assay [12,13]. The results showed the compounds A3-A6 and A10 to have the highest anti-TB activity with an MIC of 1.6 µg/ml (fig 2). They are more than twice as potent as the standard drugs Pyrazinamide (MIC = 3.12 µg/ml), Ciprofloxacin (MIC= 3.12 µg/ml) and Streptomycin (MIC= 6.25 µg/ml).

The compounds obtained from aliphatic amines have shown better activity than those obtained from aromatic amines. Here, replacement of morpholine (A1) with piperidine (A5) significantly improved potency from MIC 25 µg/ml to 1.6 µg/ml. In case of anilines, presence of halogens improved bioactivity in the order 2,4-di F > 4-Br > 4-Cl. In contrast, presence of electron donating groups on aromatic ring, significantly reduced the potency. This suggests that the scaffold 3- (N-substituted glycinamido) benzoic acid is very important

for activity and further substitutions of the scaffold with aliphatic heterocyclic groups and substituted aromatic amine groups help in enhancing its activity.

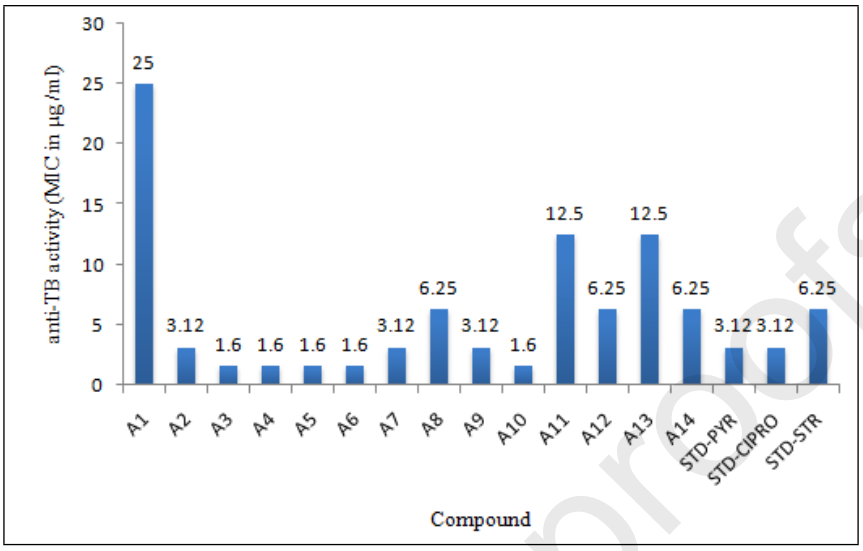


Fig 2: MABA assay results of the compounds A1-A14

Further, molecular docking studies [14] were performed using PyRx[15] at the active site of the MmaA1 protein with all the 14 synthesised molecules to understand the binding mode of the ligands towards the MmaA1 protein. Docking was carried out using AutoDock Vina[16] module in PyRx. The ligand input files were prepared using OpenBabel[17]. OpenBabel was used to convert ligands to Sybyl Mol2 format, the input format for PyRx. The ligands were subject to minimisation for 200 steps using Steepest descent method with a step size of 0.02 and 20 steps of Conjugate gradient minimisation in Chimera[18].

For the docking study, regular protocol i.e., considering the protein structure rigid and ligands flexible was implemented. A total of 9 conformations were generated for each docked pose of the ligand. The output files are evaluated by visual inspection of the docking conformations and binding affinity. The active site information was taken from our previous study.[11] The active site residues of the MmaA1 protein are ASP 19, TRP 30, TYR 32, GLY 71, TRP 74, GLY 76, ALA 77 and PHE 135 which were predicted from CASTp[19], SiteMap[20]

and protein-ligand docking using PatchDock[21] with S-adenosyl-N-decyl-aminoethyl (SADAE). SADAE is a potent bi-substrate inhibitor of *M. tuberculosis* mycolic acid methyl transferases.[22] S-adenosyl-N-decyl-aminoethyl (SADAE) is a molecule in which the amino acid moiety of S-adenosyl methionine is substituted by a lipid chain. The adenosine moiety of SADAE replaces the cofactor, S-adenosyl methionine (SAM) and the lipid chain is deeply buried in the hydrophobic environment created by the residues lining the substrate-binding pocket. Therefore, docking of the MmaA1 protein was carried out with SADAE and all the designed molecules to ascertain whether they bind at the same active site and occupy similar conformation as that of SADAE.

The docking results were prioritised based on their binding affinity. Analysis of the docking results show that the ligands A1- A14 bind with the predicted active site residues, i.e., TRP 30, VAL 31, TYR 32, GLY 71, TRP 74, GLY 76, ALA 77 and PHE 135 of MmaA1 protein. The active site of MmaA1 protein is lined by non-polar hydrophobic amino acids, i.e., TYR, TRP, GLY, VAL and PHE. Hence the active site is buried inside the protein core and occupies a large volume which is divided into co-factor binding site and hydrophobic binding site. The ligand A4 is the highest scoring ligand with a binding affinity of -9.9 kcal/mol. It binds at the SAM (co-factor) binding site in the active site of the protein. It is involved in hydrogen bond interactions with the residues TRP 30 and TYR 74 and pi-pi interactions with TYR 32 of MmaA1 protein which is shown in figures 3(a) and (b).

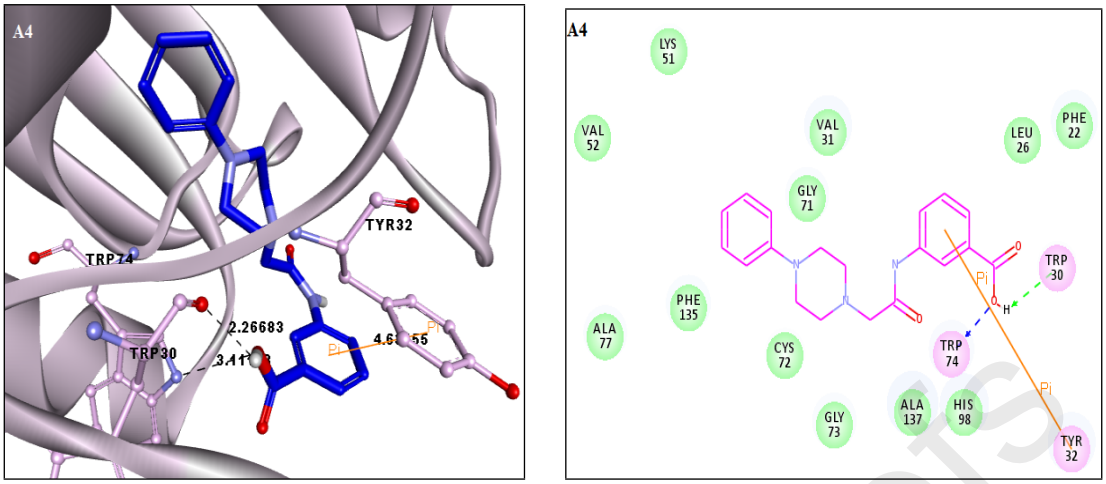


Fig 3(a): Docking interactions of ligand A4 with the residues of MmaA1protein at the active site. The ligand A4 is represented as blue colour ball and stick model and the protein is represented as grey colour cartoon, the active site residues of the MmaA1 protein interacting with the ligand as grey colour ball and sticks.

(b): 2-D view of the interactions of A4 with the active site residues of MmaA1 protein

The docked complex of SADAE with MmaA1 protein shows that SADAE sits both in the co-factor binding (SAM binding site) site and the putative substrate binding pocket. All the ligands show similar conformation at the active site of the MmaA1 protein which is represented in figure 4.

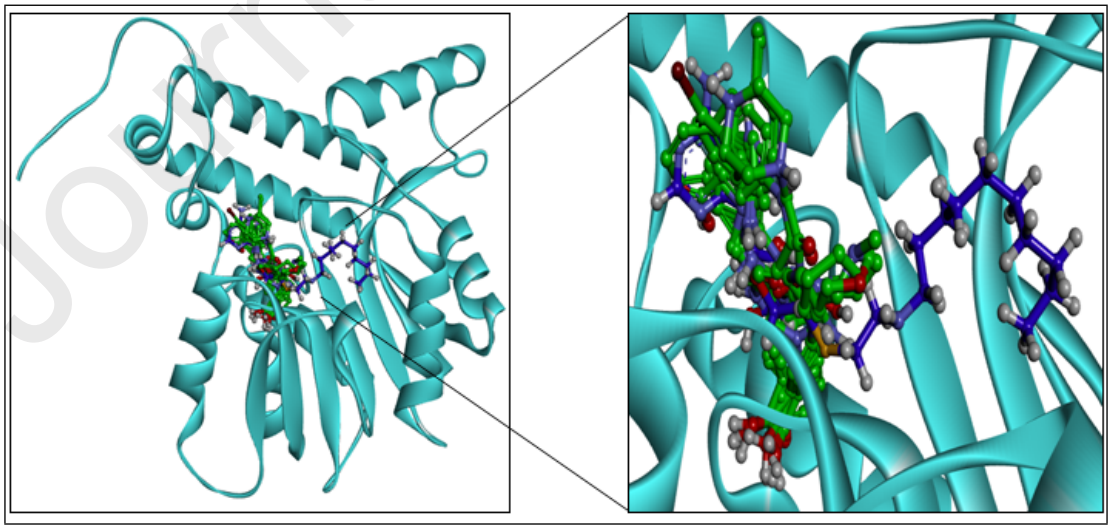


Fig. 4: Binding mode of all the compounds at the active site of MmaA1 protein along with SADAE. The right side figure shows the magnified view at the active site of

MmaA1 protein. The figure shows the ligands are aligned to the adenine moiety of SADAE. SADAE is represented as blue color ball and stick model, the ligands A1-A14 are represented in green color ball and stick model.

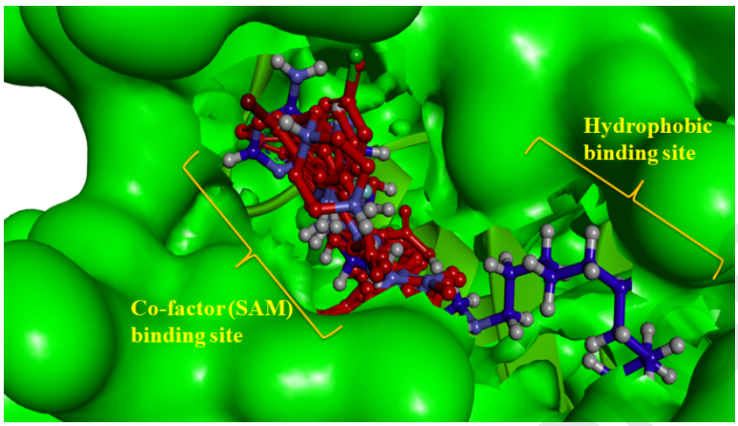


Fig 5. Alignment of the docked compounds at the active site of MmaA1 protein shown in surface representation. SADAE is represented as blue color ball and stick model and the compounds A1-A14 shown as red color ball and stick model.

The docked complexes of A1-A14 show that they occupy the cofactor binding site replacing the adenosine moiety of the SAM similar to SADAE (fig 5). Therefore, the alignment of the molecules with SADAE was studied and it revealed that they are aligned to the adenosine moiety of SADAE, resulting in the opening of the hydrophobic tunnel in the active site. Figure 6(a) shows the alignment of the top ranked ligand A4 with SADAE in the active site, indicating that A4 occupies only the SAM binding site whereas SADAE has an extended conformation into the hydrophobic site due to its lipid moiety. While the docked conformation of ligand A4 shows that the hydrophobic site is in open conformation while it is occupying only the SAM binding site, represented in figure 6(b). The hydrogen bonding and pi-pi interactions with the residues TRP 30, TYR 32, TRP 74 might be responsible for the opening of the hydrophobic tunnel in the active site. But here, in this study we were

interested only in the binding interactions and activity of the designed molecules. The active site dynamics of the protein are beyond the scope of present study.

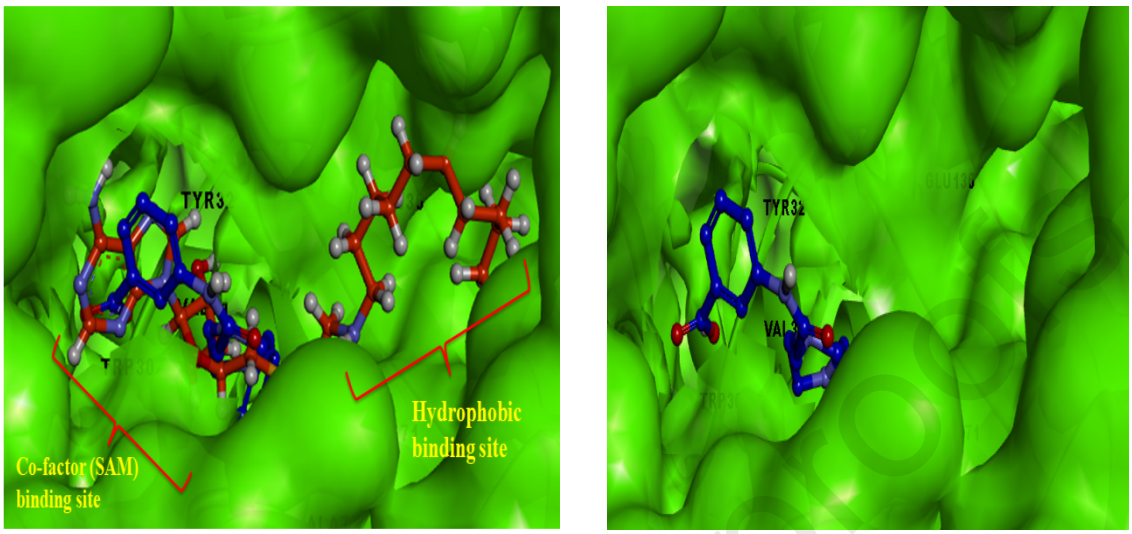


Fig. 6(a): Docked conformation of the top-ranking ligand 3-(2-(4-phenyl piperazin-1-yl) acetamido) benzoic acid (A4) and SADAE in the active site of the MmaA1 protein. A4 is represented as blue colour ball and stick model and SADAE is represented as red colour ball and stick model.
(b): Conformation of the top-ranking ligand 3-(2-(4-phenylpiperazin-1-yl) acetamido) benzoic acid (A4) without SADAE at the active site of MmaA1 protein.

From the docking analysis of the ligands, A4 (ΔG = -9.9 kcal/mol), A10 (ΔG = -9.4 kcal/mol) and A7 (ΔG = -7.1 kcal/mol), (Table 2 in supplementary information) it is evident that the binding site residues TRP 30, TYR 32, TRP 74 appear to play a crucial role in ligand binding affinity and contribute to higher docking scores (ΔG value). In the docking poses it is observed that, the poses obtained at receptor site (co-factor site) showed the best score among the docked conformers. In case of ligand A4, it showed a dock score of -9.9 kcal/mol when bound at the receptor site and a ΔG value of -8.5 kcal/mol when bound away from the active site pocket (supplementary data).

The carboxylic acid group in the benzoic acid moiety of the 3-(N- substituted glycinamido benzoic acid) appears to be important for binding with the MmaA1 protein. Especially, when the C=O group is involved in H-bond interactions with the residues TRP 30 and TRP 74 and pi-pi interactions with TRP 32 of the MmaA1 protein the binding affinity (ΔG) is higher (>9) but when it interacts with other residues such VAL 31, CYS 72, GLY 75, GLY 76 and ALA 77 the binding affinity (ΔG) is found to be lower. In case of aromatic amine substituted derivatives the benzene ring (aromatic moiety) is involved in pi-pi interactions with VAL 31 and TYR 32 which is favourable for increased binding affinity (ΔG).

Further docking analysis has shown the parent compound (3-(2-morpholinoacetamido)-N-(1, 4-dihydro-4-oxoquinazolin-6-yl) benzamide) has a binding affinity of -10.7 Kcal/mol, whereas the scaffold (3-(2-chloroacetamido) benzoic acid) has -7.4 Kcal/mol. Substituting the chloro group with the different substituents led to varying values of binding affinity. For ex. substituting the chloro group with phenyl piperazine, 2,4-difluoro aniline, aniline, 4-chloroaniline, p-toluidine and benzyl piperazine showed higher docking scores (>9). Whereas substituents like piperidine, pyrrolidine, di-ethyl amine and morpholine resulted in lower docking scores (fig 7). This shows that the substituting the chloro group with bulkier groups and substituted aromatic groups results in good binding affinity with the protein. This supports that the presence of bulkier groups is essential for good binding affinity when compared to smaller substituents.

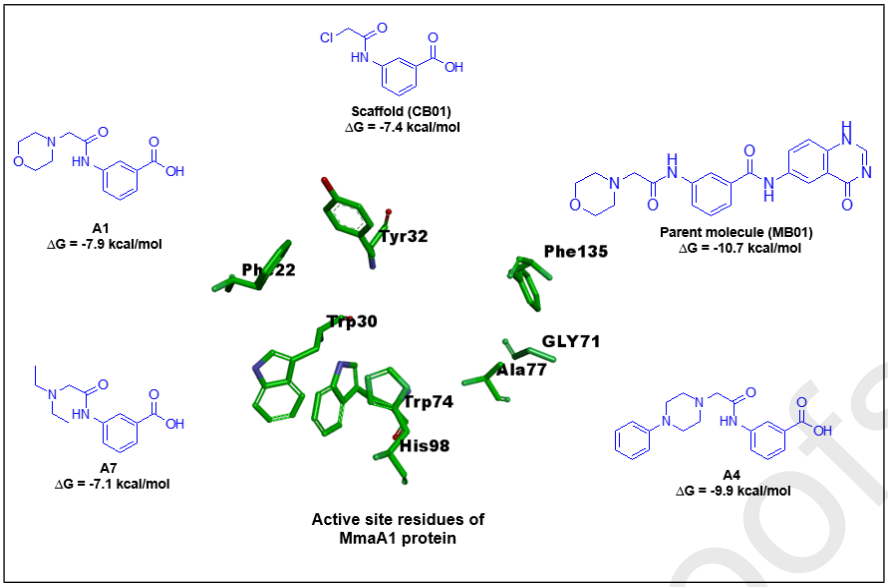


Fig 7: Binding energitics of the ligands with MmaA1 protein at the active site. The active site residues of the protein are shown as green colour sticks. The ΔG values for the different ligands are given.

Compounds with undesirable properties and poor ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiles are responsible for clinical failures at later stages of drug discovery[23-25]. Identifying and eliminating potentially toxic molecules at early stages is therefore very essential[26]. ADMET properties for the compounds were predicted using molinspiration[27], PreADMET[28] and SwissADME.[29] All the important ADME parameters like leadlikeness, druglikeness, blood brain permeation (BBB), GI absorption and CYP inhibition[30-32] were predicted. The number of rotatable bonds (<10), low polar surface area (<140 Å^2) and fewer H-bond donors and acceptors are important predictors for oral bioavailability.[33] The results show that the compounds are well absorbed and do not permeate through BBB which is a very essential prerequisite for any drug/lead like compound. The results show all the ligands have drug like properties and A1, A3-A5, A7, A8, A10 - A13 have lead like properties. (details given in Supplementary data)

In summary, novel 3- (N-substituted glycinamido) benzoic acid derivatives were synthesised and evaluated for their anti-TB activity. Five compounds A3, A4, A5, A6 and

A10 exhibited excellent anti-TB activity of MIC 1.6 μg/ml against *M. tuberculosis* $H_{37}Rv$. Molecular docking was carried out to understand the molecular interactions of the molecules with the MmaA1 protein which revealed the residues TRP 30, VAL 31, TYR 32, GLY 71, TRP 74, GLY 76, ALA 77 and PHE 135 of MmaA1 protein to have important hydrogen bonding interactions and pi-pi interactions with the ligands resulting in good docking scores ranging from -9.9 to -7.1. The *in silico* ADMET results have shown the compounds A1, A3-A5, A7, A8, A10 - A13 to have druglikeness and leadlikeness properties. Our study resulted in identification of derivatives of 3- (N-substituted glycinamido) benzoic acid as a new class of MmaA1 enzyme inhibitors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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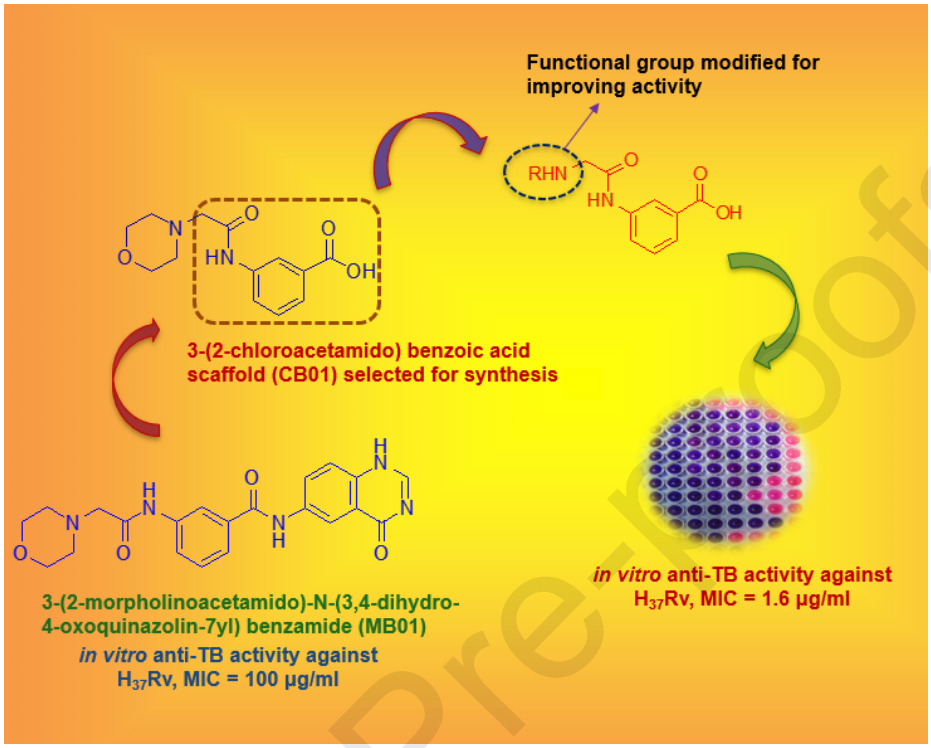
Design, synthesis, antimycobacterial activity and molecular docking studies of novel 3-(N-substituted glycinamido) benzoic acid analogues as anti tubercular agents



Design, synthesis, antimycobacterial activity and molecular docking studies of novel 3-(N-substituted glycinamido) benzoic acid analogues as anti tubercular agents

- Novel derivatives of 3-(N-substituted glycinamido) benzoic acid have been synthesised using various aliphatic and aromatic amines
- The synthesised compounds exhibited potent antimycobacterial activity carried out using MABA assay
- Molecular docking studies revealed important binding interactions of the compounds within the active site of the MmaA1 protein
- *in silico* ADMET studies aided in identifying promisable lead compounds