International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 7, 2024

Original Article

A SIMULATION APPROACH FOR NOVEL 1,3,4 THIADIAZOLE ACETAMIDE MOIETIES AS POTENT ANTIMYCOBACTERIAL AGENTS

SAIRA SUSAN VARGHESE*, SANTHOSH M. MATHEWS

Pushpagiri College of Pharmacy, Medicity Campus, Perumthuruthy PO, Thiruvalla, India
***Corresponding author: Saira Susan Varghese; Email: walks.2.remember@gmail.com**

Received: 25 Apr 2024, Revised and Accepted: 28 May 2024

ABSTRACT

Objective: To design novel series of 1,3,4 thiadiazoles and to evaluate their anti-mycobacterial potency via *in silico* modeling.

Methods: *In silico* modeling comprising of lipinski rule evaluation, ADMET prediction, Molecular docking and Simulation studies aimed to identify potent 1,3,4 thiadiazoles.

Results: The various physiochemical parameters and molecular descriptors of the proposed 1,3,4 thiadiazoles were predicted. And they exhibited good binding score compared with standard drug INH. The simulation studies showed minimal fluctuation of the ligand-receptor complexes.

Conclusion: The MD simulation and binding affinity of designed 1,3,4 thiadiazoles proved their efficiency as InhA inhibitors. The potency of the selected derivatives can be confirmed by further *in vitro* and *in vivo* experiments.

Keywords: Simulation studies, 1,3,4 thiadiazoles, Antimycobacterial activity

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i7.51356 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

Tuberculosis is major health crisis affecting more than a quarter of world population. It is one of the major reasons of increased mortality rate worldwide. The mycobacterium tuberculosis mainly affects lungs and can spread to other organs of the body [1, 2]. The development of first-line drugs such as Isoniazid (INH), Rifampicin, Streptomycin, Ethambutol and Bacillus Calmette Guerin (BCG) vaccine have declined the mortality rates due to tuberculosis [3]. But the emergence of drug-resistant strains and HIV patients are more prone to develop tuberculosis as co-infection created a high prevalence rate for tuberculosis. The second-line drugs are more toxic and require long treatment mode for complete cure of tuberculosis. So there is urgency to design and develop new anti-tubercular agents with more efficacy and less toxicity [4, 5].

1,3,4 thiadiazoles are promising heterocycles with excellent chemical properties and vivid pharmacological activities [6]. The presence of nitrogen and sulfur as heteroatoms and the high aromaticity of the ring provides prominent stability and reduce toxicity to 1,3,4 thiadiazoles. The presence of sulfur atom provides improved lipophilicity, which favour penetration through cell membranes. The electron-deficient nature effective nucleophilic substitution at 5th and 2nd position enables them to be highly reactive [7]. The bioisosteric potency as well as the mesoionic nature of 1,3,4 thiadiazoles contributes high versatility of this moiety in drug discovery. So the 1,3,4 thiadiazole is privileged heterocyclic moiety having antimicrobial, antioxidant, antitubercular, anticancer, anticonvulsant and herbicidal activities [8, 9].

Various computational approaches like *in silico* modeling, molecular docking and simulation studies help to identify potent pharmacophore which can facilitate drug discovery process. The software based approaches produces a clear-cut knowledge about the interactions of the ligands and binding sites. The comparison of binding affinities can provide evidence for mechanism of action. In another hand simulation studies generate the Root mean Square Fluctuation (RMSF), Root mean Square Deviation (RMSD), hydrogen bond efficiency and component analysis of the most stable energy stabilized protein-ligand complex [10].

MATERIALS AND METHODS

Preparation of ligands

A series of ten novel 1,3,4 thiadiazoles were designed using ACD/Chem sketch Software. The scheme involved refluxing of various substituted aromatic carboxylic acids with thiosemicrbazide in the presence of conc. Sulfuric acid followed with the treatment of chloro acetyl chloride and aniline [11]. The various molecular descriptors such as average mass, parachor, molar refractivity, index of refraction, polarizibility and density were identified for the proposed derivatives [12].

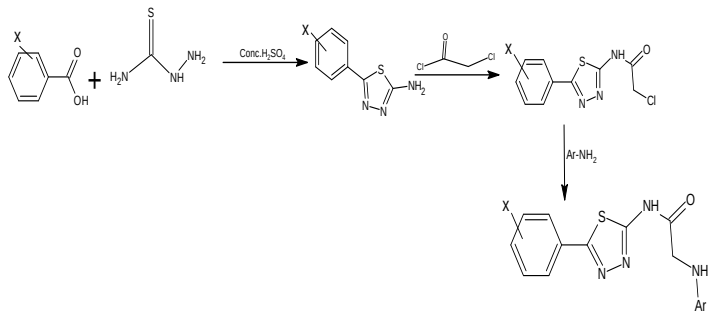


Fig. 1: Scheme for proposed 1,3,4 Thiadiazole derivatives

Evaluation of lipinski's rule

Molinspiration software was used to evaluate the lipinski's rule of five. As per the 'Rule of five' for an orally active compound it should possess molecular weight less than 500 Daltons, log p values less than 5, number of hydrogen bond donors less than 5, number of hydrogen bond acceptors less than 10, polar surface area less than140 A° and number of rotatable bonds less than 10. The compounds having more than two violations will be considered as orally inactive [13]. Various other physiochemical parameters that could affect the pharmacokinetic features of the drug were also studied.

***In silico* ADMET prediction**

The pkCSM software was used for Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) prediction. The absorption parameters such as water solubility, Cacao and skin permeability, Human intestinal absorption values and distribution criteria like volume of distribution, fraction of unbound drug, Blood Brain Barrier (BBB) and Central Nervous System (CNS) permeability were predicted. The software also identified whether the proposed 1,3,4 thiadiazoles are CYP450 substrate or inhibitor. The total renal clearance and toxicity prediction on Salmonella Mutagenicity Assay (AMES) toxicity, hepatotoxicity and skin sensitization were performed [14-16].

Molecular docking approach

All the proposed 1,3,4 thiadiazoles were docked using AutodockVina. They were docked with the X-ray crystal structure of InhA (PDB: IP44) which was downloaded from protein data bank (www. resb. org). The three-dimensional structure of the ligand was developed using Chemsketch software. The Chemistry at Harvard Molecular Mechanics (CHARMm) force field was used to minimize total energy and optimize ligands. The designed ligand structures were converted into the pdb file format by BIOVIA Discovery Studio Visualizer [17-19]. The preparation of protein was done by Discovery Studio 2019 Client. And it was compared with the standard drug INH.

MD simulation studies

Molecular dynamics simulation studies of the ligand-receptor complex was identified to confirm the mode of action of proposed 1,3,4 thiadiazoles. The Desmond dynamic package in Academic version of Schrodinger software was used to identify the binding affinity of ligand-receptor complexes [20]. The simulation studies were performed in linux atmosphere and the time-related changes of the complexes were calculated. A water model was established using SPC water model. The electric charges were maintained with the addition of counter ions. The energy of the system was decreased prior to the commencement of simulation procedure. The entire simulation process was performed at temperature of 300 K and one atmospheric pressure by employing Nose Hoover method [21-24]. The most stable confirmations were identified.

RESULTS AND DISCUSSION

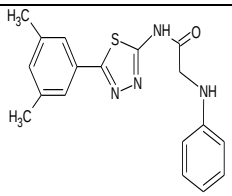
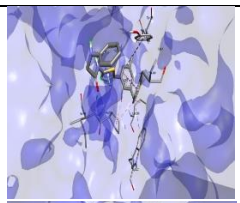
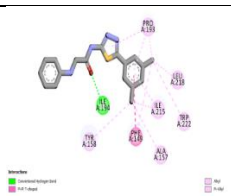
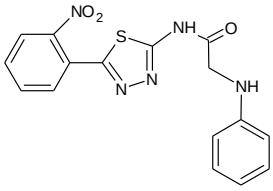
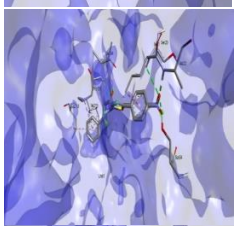
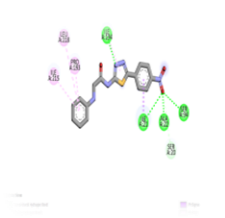
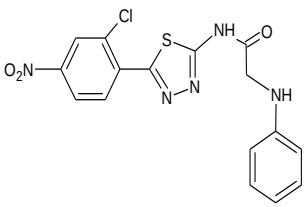
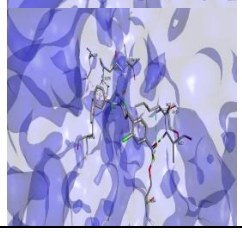
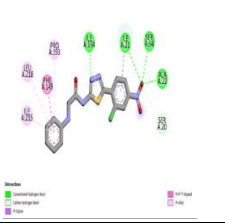
***In silico* ADMET studies**

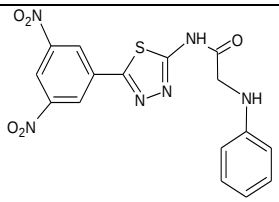
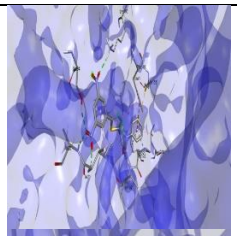
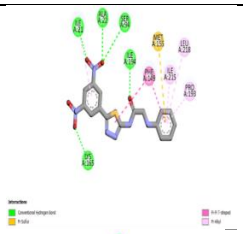
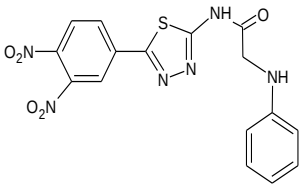
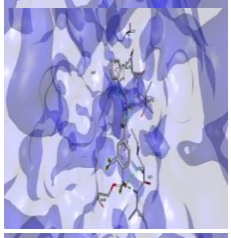
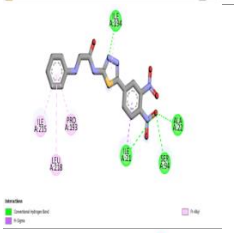
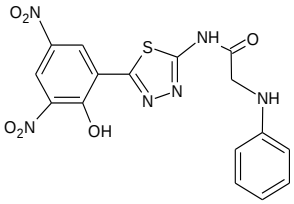
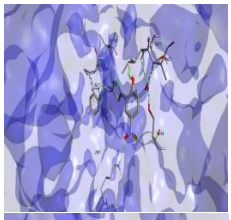
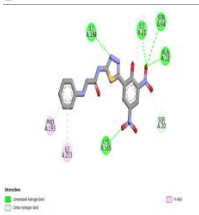
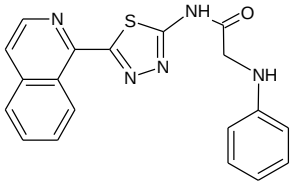
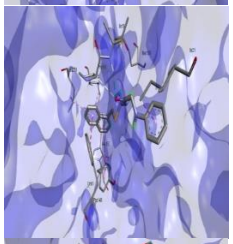
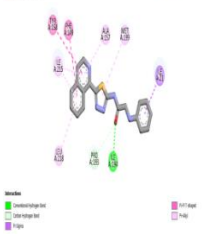
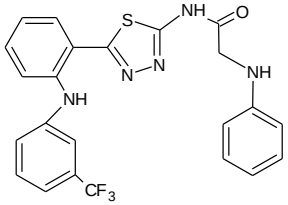
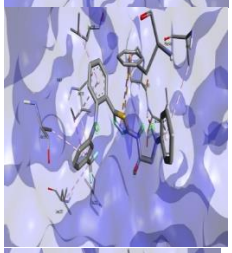
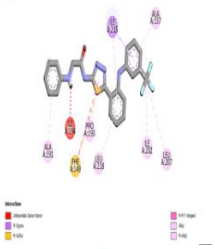
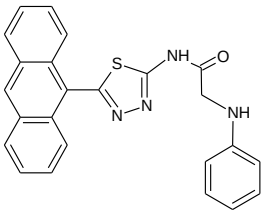
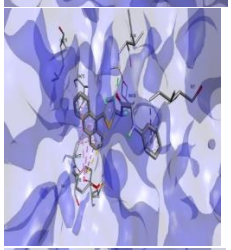
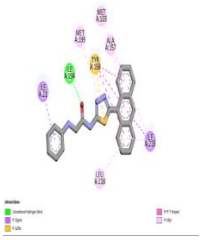
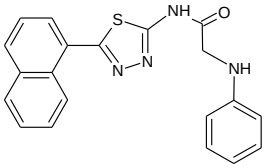
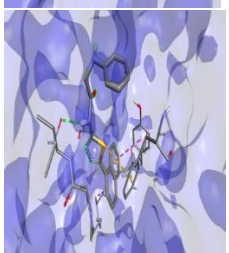
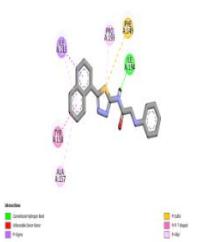
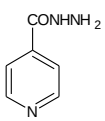
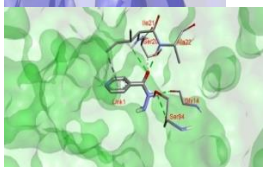
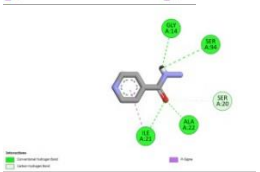
The designed 1,3,4 thiadiazoles were evaluated for various physiochemical properties and they exhibited promising data. All the proposed derivatives followed the lipinski's Rule and are orally active. The pkCSM software was used to ascertain the various ADMET parameters. The molecular weight of proposed 1,3,4 thiadiazoles ranges from 330-365 daltons. And the presence of 2-3 hydrogen bond donors and 6-8 hydrogen bond acceptors was estimated. All the compounds showed topological polar surface area less than140 A° and log P values less than 5. The oral bioavailabilitythe selected derivatives ranged from 82% to 91%. The water solubility and $Caco_2$ permeability values were found significant. The BBB and CNS permeability revealed the distribution efficiency of selected compounds. Total renal clearance, Mutagenicity, hepatotoxicity, skin sensitivity prediction was satisfactory [25, 26].

Molecular docking

In silico molecular docking approach was employed to identify the interactions of ten selected 1,3,4 thiadiazoles. The PyRxprogramme in AutodockVina was exploited to understand the intermolecular interaction of the protein and bioactive molecules [27, 28]. The first line anti tubercular drug, INH was considered as the standard drug, which inhibits mycolic acid synthesis. So Enoyl Acyl Carrier Protein Reductase (InhA) with PDB: IP44 was selected as the protein target. The binding affinity of INH with its target receptor InhA was-7.6 kcal/mol. All the ten 1,3,4 thiadiazoles were docked with InhA to establish antimycobacterial activity. And they exhibited excellent binding affinity greater than-9.0 kcal/mol. The 2D and 3D fitting pose interaction of the ligand-receptor complex is shown in table 1.

Table 1: The 2D and 3D structure with the binding affinity of proposed 1,3,4 thiadiazoles

Compound ID	Structure	3D Structure	2D Structure	Binding score (kcal/mol)
TDZ1				-9.0
TDZ2				-9.1
TDZ3				-9.3

Compound ID	Structure	3D Structure	2D Structure	Binding score (kcal/mol)
TDZ4				-9.1
TDZ5				-9.5
TDZ6				-9.1
TDZ7				-9.2
TDZ8				-10.7
TDZ9				-10.6
TDZ10				-9.5
INH				-7.6

The presence of heterocyclic aromatic rings in the 1,3,4 thiadiazole were responsible for the major liphophilic interactions experienced in the molecular docking studies. Some amino acids in the ligand binding position of InhA were identified [29, 30]. Some prominentnon-covalent interactions were noticed between proposed ligands and binding sites of InhA. Several amino acids were involved in the ligand interactions with InhA which are described in table 2. So they impart inhibitory effects in the ligand binding domain of InhA.

The presence of four prominent hydrogen bonds in the INH with amino acids SER94, ILE21, ALA22, GLY14 and one C-H bond with SER20 were key structural features for InhA inhibitory effects. Most of the selected derivatives formed hydrogen bonds as well as C-H bonds similar to INH.

Compound TDZ 8 showed a maximum binding affinity of-10.6 kcal/mol compared to the standard medication INH with binding affinity of –7.6 kcal/mol. The presence of nitro group in compounds TDZ 2, TDZ 3, TDZ4, TDZ 5 and TDZ 6 contributed more than three hydrogen bond with amino acid residues SER94, ILE21, ILE 194, ALA22, in the ligand binding site of InhA ligand complex. The docking analysis of the INH and compound TDZ 2, TDZ 3, TDZ4, TDZ 5 and TDZ 6 depicted the presence of hydrogen bonds with the same amino acid residues SER94, ILE21, ALA22. This signifies the effectiveness of the selected 1,3,4 thiadiazoles as InhA inhibitors. Several C-H bonds, pi-pi interactions and alkyl bonds were also evident in these compounds which are depicted in table 2.

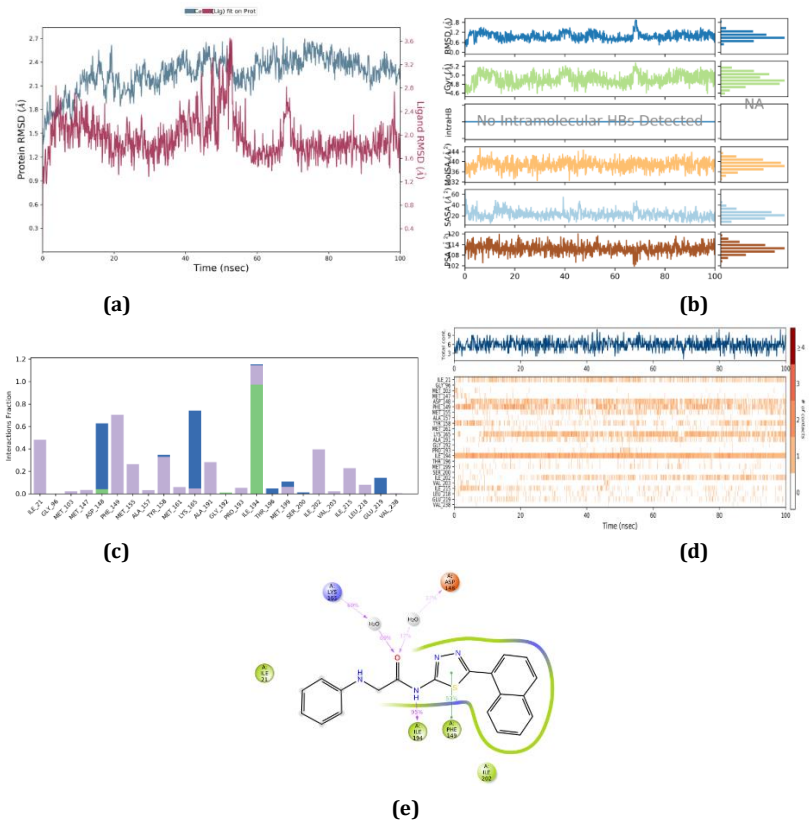
The outcome of molecular docking proved the potency of selected 1,3,4 thiadiazoles as antimycobacterial agents.

Table 2: Docking interactions of the ligand with various amino acid residues

Ligand	Binding energy	Pi-alkyl	Hydrogen bond	C-H bond	Pi-sigma	Pi-Pi	Alkyl	Pi-sulphur
TDZ 1	-9.0	PRO 193 LEU 218 TRP 222	ILE 194			PHE 149	ILE 215 ALA 157 TYR 158	
TDZ 2	-9.1	LEU 218 ILE 215 PRO 193 ILE 194	ILE 194 ILE 21 ALA 22 SER 94	SER 20	ILE 21			
TDZ 3	-9.3	ILE 215 LEU 218 PRO 193 ILE 194	ILE 194 ILE 21 SER 94 ALA 22	SER 20	ILE 21	PHE 149		
TDZ 4	-9.1	ILE 21 ILE 215 LEU 218 PRO 193	ILE 21 ALA 22 SER 94 ILE 194			PHE 149		MET155
TDZ 5	-9.5	ILE 215 PRO 193 LEU 218 ILE 194	ILE 194 ILE 21 SER 94 ALA 22		ILE 21			
TDZ 6	-9.1	PRO 193 ILE 215 ILE 21	ILE 194 LYS 165 ILE 21 SER 94 ALA 22	SER 20				
TDZ 7	-9.2	ILE 215 LEU 218 ALA 157 MET199	ILE 194	PRO193	ILE 21	TYR 158 PHE 149		
TDZ 8	-10.7	ALA 157 ILE 202 LEU 207			ILE 215	PHE 149	PRO 193 ALA 191 LEU 218	PHE 149
TDZ 9	-10.6		ILE 194		ILE 21 ILE 215	MET199 MET103 ALA 157 LEU 218		TYR 158
TDZ 10	-9.5	ALA 157 PRO 193	ILE 194		ILE 215	TYR 158		PHE 149
INH	-7.6		GLY14 SER94 ALA22 ILE21	SER20				

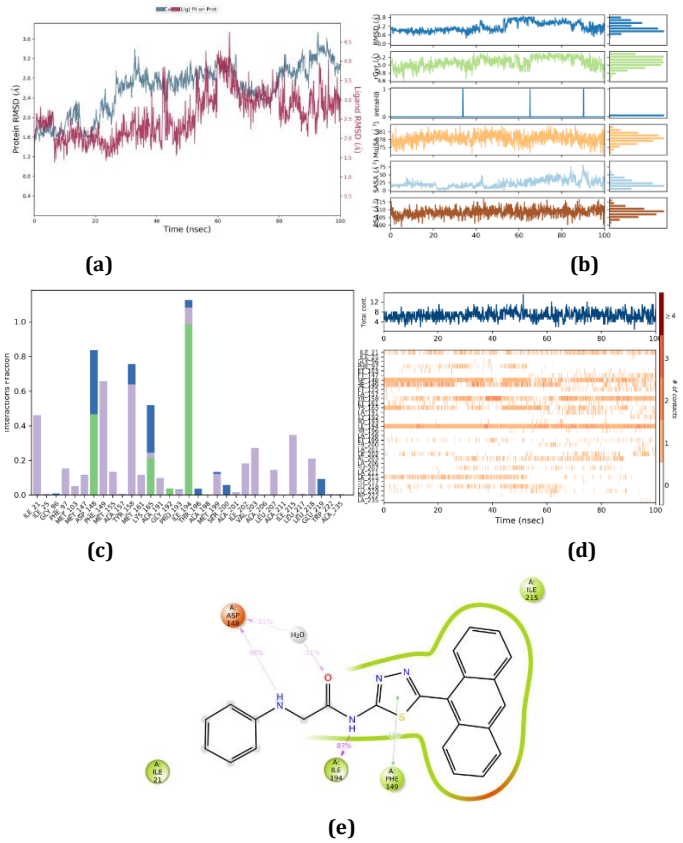
MD simulation studies

The molecular dynamic simulation studies were performed for five 1,3,4 thiadiazoles with most significant docking score. To identify the molecular interactions of selected ligands with InhA protein a 100 ns molecular dynamic simulation was performed. The MD simulation trajectory events of InhA-TDZ 10 exhibited minimum fluctuations at the beginning and was stabilized at 2.8A°, having an average RMSD of 2.2 A° depicted in fig. 1 a. Fig. 1b showed hydrophobic interactions, ionic bonds, absence of hydrogen bonds. The RMSD of TDZ 9 and TDZ 8 showed fluctuations which were stabilized at 3.0 A° and 2.8 A° respectively (fig. 2a,3a). TDZ4 and TDZ 3 trajectory showed highest stability throughout the entire simulation process with average RMSD of 3 A° and 2.8 A° (fig. 4a,5a). The RMSF of all the ligands and proteins showed no fluctuations indicating the binding of corresponding amino acids with the suitable functional groups of ligands. The histogram and timeline representation of all protein–ligand complex were depicted. The 2D fitting pose interactions of all the five ligands with InhA protein complex exhibited valuable information regarding the intermolecular interactions and development of new antimycobacterial agents.



(a) (b) (c) (d) (e)

Fig. 1: (a) RMSD (b) ligand properties (c) Protein–ligand histogram (d) Time line representation of protein ligand complex (e) Fitting pose interaction in 2D view of TDZ10



(a) (b) (c) (d) (e)

Fig. 2: (a) RMSD (b) ligand properties (c) Protein–ligand histogram (d) Time line representation of protein ligand complex (e) Fitting pose interaction in 2D view of TDZ9

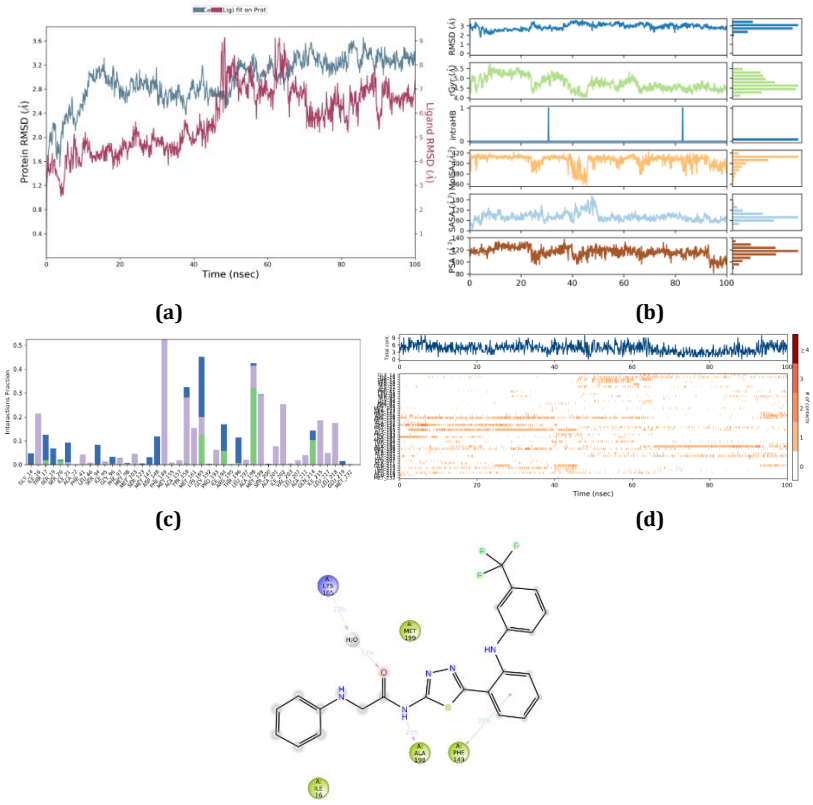


Fig. 3: (a) RMSD (b) ligand properties (c) Protein–ligand histogram (d) Time line representation of protein ligand complex (e) Fitting pose interaction in 2D view of TDZ8

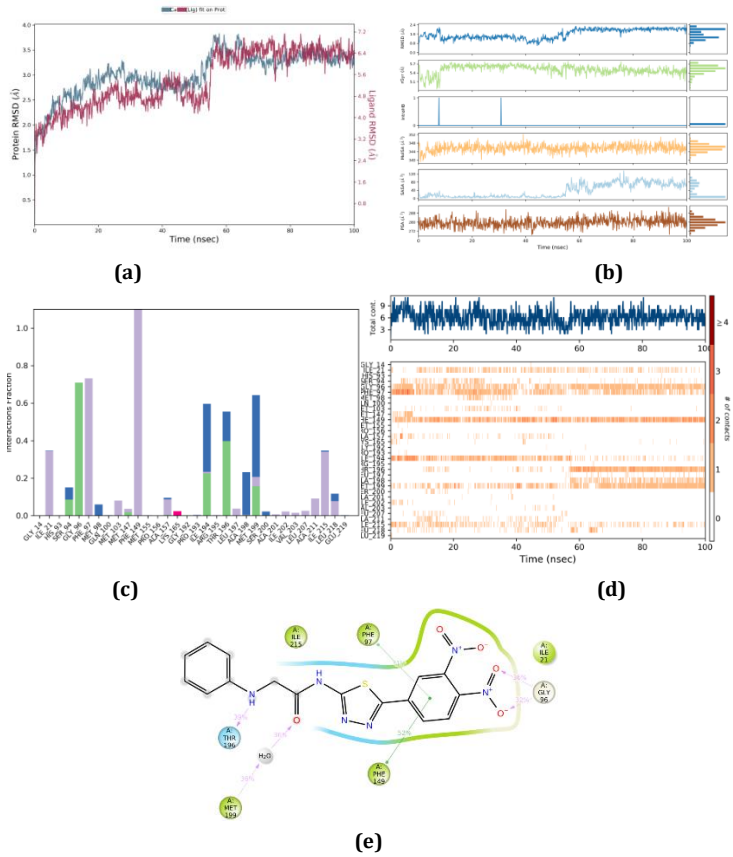


Fig. 4: (a) RMSD (b) ligand properties (c) Protein–ligand histogram (d) Time line representation of Protein ligand complex (e) Fitting pose interaction in 2D view of TDZ4

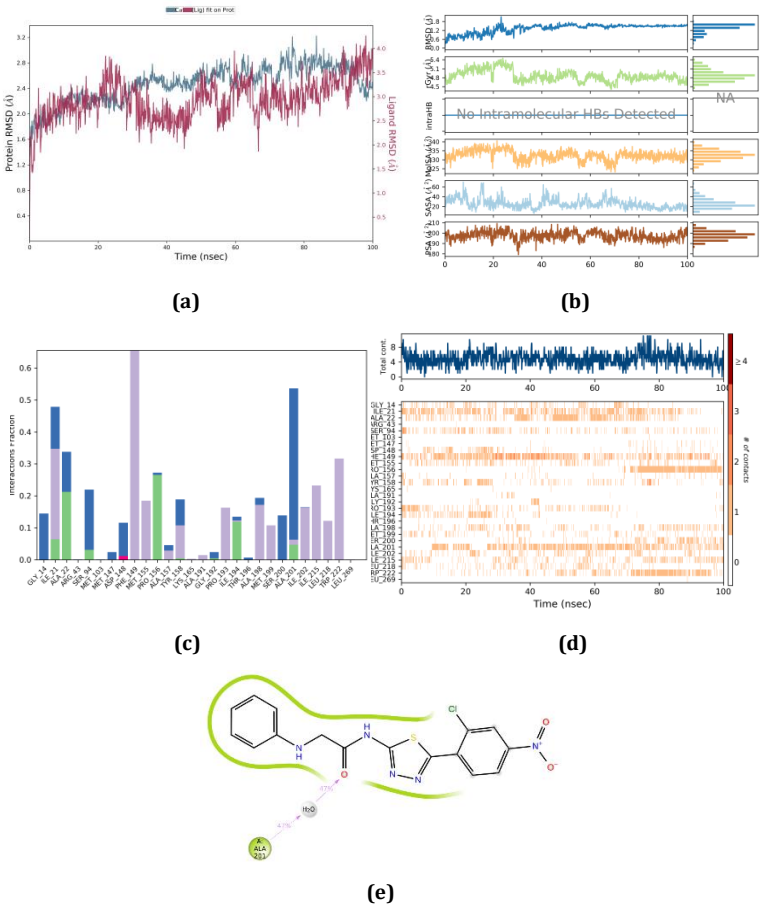


Fig. 5: (a) RMSD (b) ligand properties (c) Protein–ligand histogram (d) Time line representation of protein ligand complex (e) Fitting pose interaction in 2D view of TDZ3

DISCUSSION

Ten 1,3,4 thiadiazoles were selected by monitoring various pharmacokinetic parameters. As they satisfied the lipinski's rule, *in silico* docking was performed to identify the binding affinity of selected ligands towards InhA protein. InhA inhibitors can be therapeutically employed as antimycobacterial agents. All the compounds showed excellent binding affinity than INH.

MD simulation of five 1,3,4 thiadiazoles with most prominent docking score was selected to comprehend the molecular level interactions with InhA receptor. The trajectory analysis of the ligand-InhA complex exhibited minimal fluctuations in RMSD. The presence of water bridges, hydrogen bounds, ionic interactions and hydrophobic interactions are also evident. The molecular dynamics modeling exhibited substantial reduction in volatility and deviation. The presence of prominent pi-pi stacking and binding affinity proves that the designed 1,3,4 thiadiazoles can be effective as InhA inhibitors.

CONCLUSION

The various *in silico* screening approaches like lipinski's rule determination, ADMET screening and the prominent pharmacokinetic values signifies the potency of selected 1,3,4 thiadiazoles. Molecular docking performed with InhA protein exhibited significant docking score than INH. Simulation studies also confirmed the stability of selected derivatives as antimycobacterial agents. The potency of the selected derivatives can be confirmed by further *in vitro* and *in vivo* experiments.

ACKNOWLEDGMENT

The authors are thankful to Pushpagiri college of pharmacy, Thiruvalla, Kerala. As they provide necessary facilities and support for the successful completion of the research work. Also delighted to thank, Prof. Dr. Presennakumaran PN, HOD Department of Pharmaceutical Chemistry, Pushpagiri college of pharmacy for the essential technical and moral support.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Experimental design, guidance and supervision of the research work was performed by Dr. Santhosh M Mathews. Various *in silico* analysis including molecular docking and simulation studies and writing of this manuscript was done by Mrs. Saira Susan Varghese. Both the authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors report no competing interest to declare.

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