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SYNTHESIS, CHARACTERISATION, BIOLOGICAL EVALUATION, MTT ASSAY OF SOME NOVEL THIADIAZOLE DERIVATIVES AS ANTI-TUBERCULAR AGENTS TARGETING DECAPRENYL PHOSPHORYL BETA-D-RIBOSE2' EPIMERASE-1

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Keywords:

Thiadiazole derivatives, Anti-tubercular activity, MABA, Decaprenylphosphoryl beta-d-ribose2' epimerase-1

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ABSTRACT: Objective: The present study was designed for the synthesis, characterization, biological evaluation, and MTT assay of some novel thiadiazole derivatives as anti-tubercular agents targeting decaprenylphosphoryl beta-d-ribose2' epimerase-1($DPRE_1$). **Methods:** The molecular docking study for titled compounds was performed from Autodock 4.2. Software http://autodock.scripps.edu/, pdb file was generated by chem3D.pro software tool. The binding pose for the significant compounds was visualized by Biovia, the Discovery studio visualizer. The selected molecules were synthesized and recrystallized several times to reach the expected purity. All the purified compounds were characterized by various spectral analytical techniques and evaluated for anti-mycobacterial activity against tuberculosis H37RV strain by Microplate Alamar Blue Assay (MABA) method and cell line studies. **Results:** The experimental results showed that the Compounds SDK3 and SDK5 have an anti-tubercular activity in the Concentration of 3.12µg/mL. Cell line studies for proprietary compounds have been carried out by MTT assay using HEK (Human embryonic kidney cells) method. It also correlated with the highest docking score. **Conclusion:** The development of the SDK3 and SDK5 structures will produce molecules having better anti-mycobacterial activity.

INTRODUCTION: Tuberculosis is a chronic necrotizing bacterial infection caused by the ubiquitous organism Mycobacterium tuberculosis (Mtb) and other species; *M. caprae*, M. *microti, M. pinipedii, M. bovis, M. africanum* [1]. The Ministry of Health and Family Welfare has taken note of the WHO Global TB Report 2022, released on October 27, 2022, and has clarified that India has performed far better on major metrics as compared to other countries over time.

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India's TB incidence for the year 2022 is 210 per 100,000 population – compared to the baseline year of 2019 (incidence was 256 per lakh of population in India); there has been an 18% decline which is 7 percentage points better than the global average of 11%. These figures also place India at the 36th position in terms of incidence rates (from largest to smallest incidence numbers) [2].

The current treatment for tuberculosis includes isoniazid, pyrazinamide, ethambutol and streptomycin (first-line drugs) PAS, ethionamide, cycloserine, amikacin, kanamycin (second line drugs) [3]. WHO has launched an empiric treatment program, termed DOTS (Directly Observed Therapy Short-course) which includes a dosage regimen of isoniazid (INH), rifampin (RIF),

ethambutol (EMB), and pyrazinamide (PZA) for initial 2 months followed by intermittent therapy of INH and RIF for subsequent 4-7 months. Poor patient compliance due to prolonged therapies over the synergy of this disease with HIV infection has resulted in the emergence of multi-drug resistance tuberculosis (MDR-TB) and extreme-drug resistance tuberculosis (XDR-TB). It was also reported that about 3.6% of the new patients and 20% of the previously treated ones had MDR-TB [4].

$DPRE_1$, also known as decaprenylphosphoryl beta-d-ribose2' epimerase-1, is an indispensable flavor enzyme involved in forming mycobacterium tuberculosis. Resistance to the current use of Anti-tuberculosis therapies increasingly undetermined efforts to contain the global tuberculosis epidemic. Recently, FAD- Mycobacterium tuberculosis $DPRE_1$, which contains oxide reductase is critical to sustainability. DPA is the sole known donor substrate for a series of membrane embedded Arabinosyl transferees, Essentiality of DPA supply and lack of alternative synthetic pathways position $DPRE_1$, Which is highly conserved in mycobacterium, and $DPRE_2$ at a critical intersection of cell wall biosynthesis. A motion confirmed through mutagenesis translation. This has turned $DPRE_1$into a magical drug target.

Thiadiazole analogues have been reported as antioxidants, anti-microbial [5], anti-inflammatory, anti-tumor, anti-viral, antitubercular [6], anticonvulsant, anthelmintic, anti-diabetic, analgesic [7], *etc*., Schiff bases have become increasingly important in medicinal chemistry and pharmaceuticals field due to a wide range of biological activities. Recent studies reveal the importance of Schiff bases to produce antifungal, anti-tubercular, anticancer, and anti-inflammatory activity. Schiff bases consist of compounds, containing the imine or azomethine functional group (–C=N–). The formation of the Schiff base involves a nucleophilic addition to the carbonyl group. In these cases, the nucleophile is the amine. In the first part of this mechanism, the amine reacts with the aldehyde or ketone to produce an unstable addition compound known as carbinolamine. The carbinolamine loses water by either acid or base-catalyzed pathways. Carbinolamine is an alcohol and is subjected to acid-catalyzed dehydration. Typically the dehydration of the carbinolamine is the rate-determining stage of Schiff bases formation and that is why the reaction is catalyzed by acids.

Aim of the Study: The aim of the study was design to synthesize, characterize, biological evaluation, and MTT assay of some novel thiadiazole derivatives as anti-tubercular agents by targeting decaprenylphosphoryl beta-d-ribose2' epimerase-1($DPRE_1$).

MATERIALS AND METHODS: The chemicals used in this activity are 3-(4,5–dimethyl thiazol–2–yl)–2,5–diphenyltetrazolium bromide (MTT), phosphate-buffered saline (PBS), 4,6 diamidino 2-phenyl indole (DAPI) and trypsin which were obtained from Sigma Aldrich Co., St Louis, USA. Ethylene diamine tetra acetic acid (EDTA) and glucose were obtained from Hi Media Laboratories Ltd., Mumbai. Dimethyl sulfoxide (DMSO) and propanol were obtained from E Merck Ltd., Mumbai, India. Human embryonic Kidney Cell lines and culture medium were obtained from the National Centre for Cell Sciences, Pune, India.

Docking:

Autodock-vina Binding Affinity Prediction:

Molecular Docking Tools: The molecular docking study for titled compounds was performed from Autodock 4.2. Software http://autodock.scripps.edu/, pdb file was generated by chem3D. pro software tool. The binding pose for the significant compounds was visualized by Biovia, the Discovery studio visualizer.

Preparation of Enzymes and Ligands: The enzymes selected for this study were Decaprenylphosphoryl beta-d-ribose2' epimerase-1(PDB ID: 4P8Y). Its X-ray crystal structures were downloaded from the protein data bank http://www.rcsb.pdb.org portal. The enzyme should be refined and purified by deletion of water, heteroatoms, and addition of Kollmann charges were accomplished. The ligand was optimized by minimizing their energy, added with gasteiger charges and polarhydrogensas well torsion was set.

Molecular Stimulation: The refined proteins and ligands (energy minimized) were assessed for molecular stimulation for predicting their binding affinity and key residual sites over the enzyme.

In that grid map should be fixed with 90 points, the Lamarckian genetic algorithm was accomplished with 25,000,000 energy evaluations, for each run 5,000 generations were done and 150 docking runs were achieved [8].

***In-silco* screening of Drug Likeness:** Drug likeness is a qualitative concept used in drug design to determine how a "drug-like" substance is concerning factors such as bioavailability. It is estimated from the molecular structure even before the chemical is synthesized and tested. A drug-like molecule has properties such as hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size, and flexibility, and course presence of various pharmacophoric features that influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability, and many others [9].

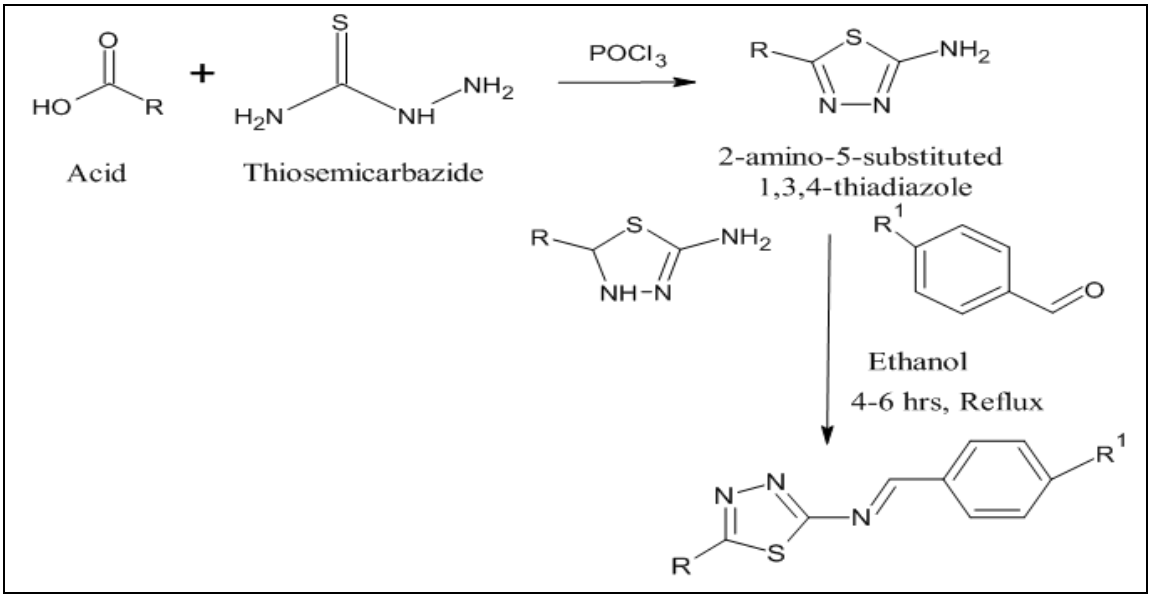
Toxicity Risk Assessment: Toxicity detection is done through Insilco using OSIRIS® Property Explorer. The OSIRIS® Property Explorer enables us to draw chemical structures and calculates on-the-fly various drug-relevant properties. When a structure is valid. Prediction results are assessed and color-coded. Properties with a high risk of undesirable effects such as mutagenicity or poor intestinal absorption are indicated in red. While a green color indicates drug-like behavior. Such of these molecules show good drug-like properties, favorable docking scores, and favorable interactions no toxicity was taken up for synthesis.

Experimental Design:

Step 1: Synthesis of 2-Amino 5-substituted Acid 1, 3, 4-thiadiazole:

Step 2: Synthesis of 5[substituted] Phenyl-N-[1E]-[substituted] Phenyl methylene]-1, 3, 4 thiadiazol-2-amine:

Synthetic Scheme:



Synthetic Procedure:

Synthesis of 2-Amino 5-substituted Acid 1, 3, 4-thiadiazole: Anequimolar quantity (0.1M) of aromatic carboxylic acid and thiosemicarbazide was added 20ml of $POCl_3$ and refluxed for one hour, The reaction mixture was Cooled and then Crushed ice (90ml) was added to the reaction mixture and refluxed for another 4 hours, cool to room temperature and filter, the filtrate was neutralized by saturated potassium hydroxide solution, filter, dried and recrystallized from a suitable solvent [10].

Synthesis of 5[substituted] phenyl-N-[1E]-[substituted] phenyl methylene]-1, 3, 4 thiadiazol-2-amine: An equimolar quantity of 2-amino 5-substituted 1,3,4-thiadiazole [0.01M] was added to various aromatic aldehydes [0.01M] and dissolved in absolute ethanol the reaction mixture was refluxed for 4-6 hours, cool to room

temperature and pouring ice product was formed, filter, dried and recrystallized using ethanol [11].

[R]:

- Benzoic Acid [Intermediate for II-Step synthesis].
- Phenoxy Acetic Acid
- Hippuric Acid.

[R_1]:

- 2-Hydroxyl Benzaldehyde
- 4- Hydroxyl Benzaldehyde
- 2,4-dichloro Benzaldehyde
- 3-NitroBenzaldehyde

Justification of Purity:

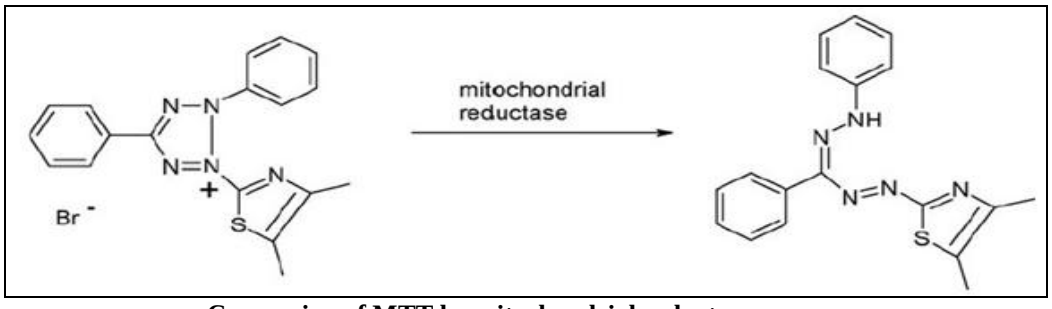
Melting Point: The melting point of the synthesized compound was determined by the open capillary tube method. The melting points were sharp and which are uncorrected.

Thin Layer Chromatography: Percolated aluminum TLC plates were used. Solutions for the reactants and products were prepared by dissolving them in methanol. A single spot not corresponding to the parent compound was noticed and hence the purity of the synthesized compounds was justified.

MABA Working Procedure: Stock solutions of the synthesized compounds and the standard drug (Pyrazinamide -3.125µg/ml, Streptomycin-6.25µg/ml, Ciprofloxacin-3.125µg/ml) used were prepared in sterile deionized water and taken at a concentration of 0.1 to 100µ1/ml. Then 200µl of sterile deionized water was added to all outer perimeter wells of the sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 well plate received 100µl of the Middle brook 7H9 broth and serial dilutions of compounds were done directly on the plate. The final drug concentrations were estimated at between 100 to 0.2µg/ml. Plates were coated and sealed with parafilm and incubated at 37°C for five days. After this time, 25µl of freshly prepared 1:1 mixture of Alamarblue reagent and 10% tween 80 was added to the plate and incubated for 24hours. The blue color in the well was interpreted as no bacterial growth, and the pink color was noted as growth. The MIC was defined as the lowest drug concentration that prevented the color change from blue to pink [12].

MTT Assay: The MTT assay is a colorimetric assay used to evaluate cell viability. NADPH-dependent cellular oxido-reductase enzyme can under specified conditions, reflect the number of viable cells present. These enzymes can reduce tetrazolium dye MTT 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide to its insoluble formazan, which is purple in color. This test can be used to measure the cytotoxicity (loss of viable cells) of potential medicinal agents and toxic materials. The produced formazan crystals are measured using spectrophotometrically at a wavelength of 540nm.

Chemical Reaction:



Conversion of MTT by mitochondrial reductase enzyme

Procedure: Exponentially growing cells were taken from T-25 tissue culture vials and a stock cell suspension $1x10^6$ was prepared with the respective media. The Cells were seeded 5000 to cells/wells in a sterile 96-well flat bottom tissue culture plate and allowed to hold for 24 hours. The test compounds were prepared just before the experiment and serially diluted with a suitable medium to obtain

the various concentrations of (31.25-250) µg/ml. The final concentration of DMSO was not more than 0.2%. After 24 hours of incubation, cells were treated with 100µl of test compounds from respective top stocks for 48 hours. At each well in the 96-wellplates, 50µl of MTT reagent (Stock: 2mg/ml in PBS) was added and incubated for 3 hours at 37ºC. The controlled cells in the group received only the medium and in the vehicle control medium with 0.2% DMSO. Each treatment was done in triplicates. After 3 hours of incubation medium along with MTT was aspirated and 100µl of 100% DMSO was added to each well to solubilize formazan crystals. The optical density (OD) was measured using a well plate reader with a reference wavelength of 540 nm. The percentage viability of individual compounds has been calculated [13].

% cell death = (OD of control - OD of test) / (OD of control) × 100

Results were expressed as Mean ± SEM.

RESULTS AND DISCUSSION: The designed molecules were docked against the selected target Decaprenylphosphoryl beta-D-ribose 2 epimerase-1. (PDB ID: 4P8Y) The best binding energy was selected based on the docking score and the interactions. The binding energy for the synthesized compounds SDK1: -9.9 kcal/mole, SDK2: -7.05 kcal/mole, SDK5:-6.97 kcal/mole, among these SDK1 has binding energy.

Interactions:

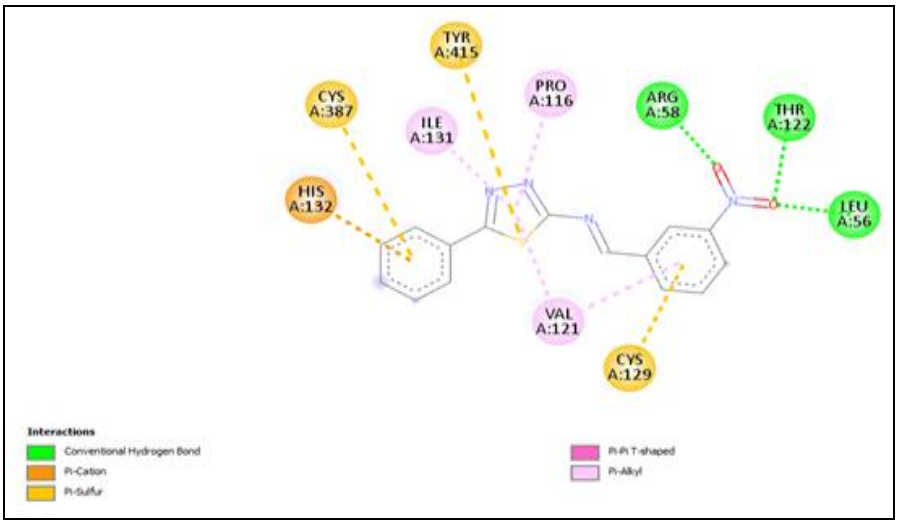


FIG. 1: SAMPLE CODE: SDK1: AMINO ACIDS INTERACTIONS

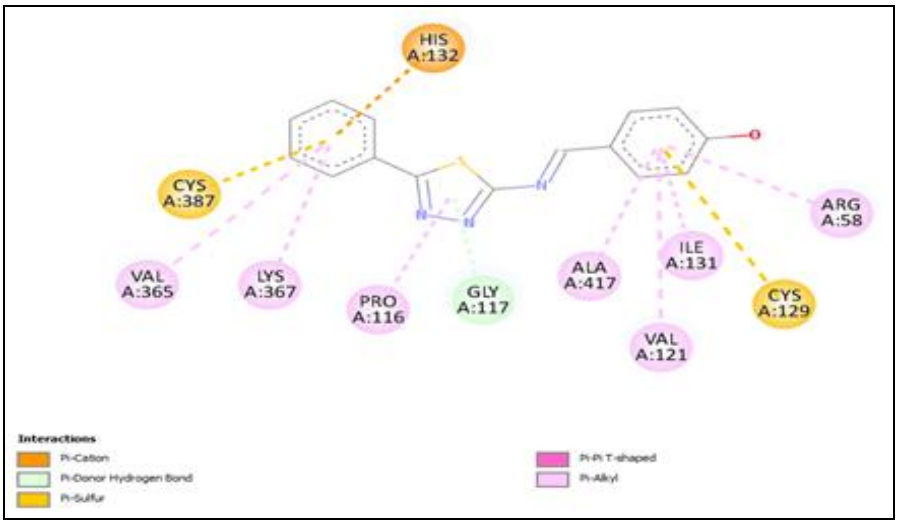


FIG 2: SAMPLE CODE: SDK2: AMINO ACIDS INTERACTIONS

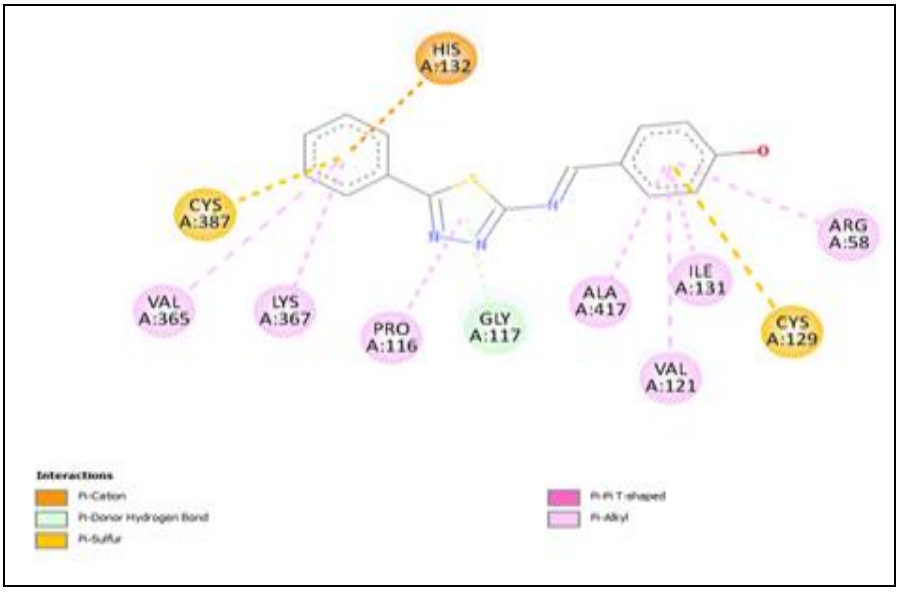


FIG. 3: SAMPLE CODE: SDK5: AMINO ACIDS INTERACTIONS

Toxicity Prediction: Toxicity Prediction results are color-coded in which the red color shows high risks with undesired effects like mutagenicity, tumorigenic, irritant and reproductive effects or poor intestinal absorption and yellow color shows moderate risks with undesired effects and the green color indicates drug-conform behavior.

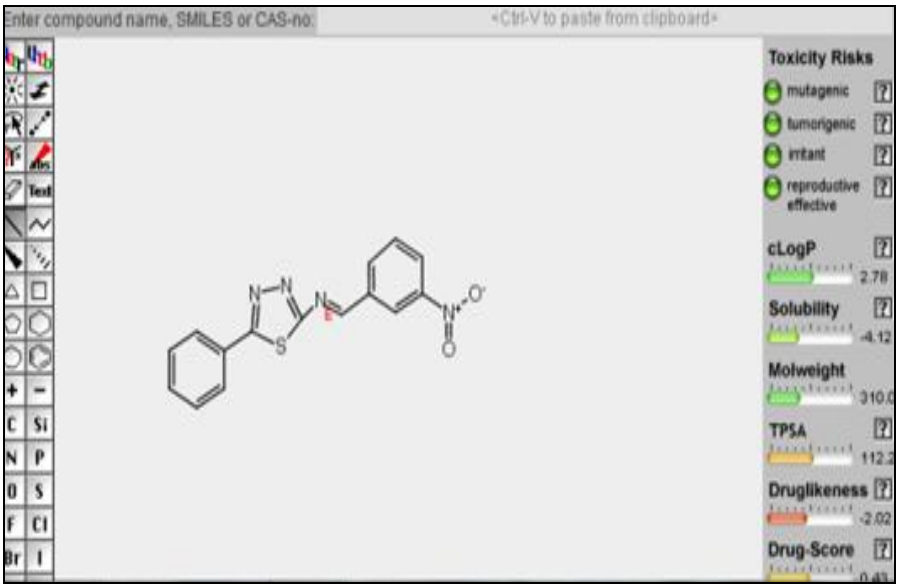


FIG. 4: SAMPLE CODE: SDK1

Spectral Analysis Data:

Compound: SDK1: (*E*)-1-(3-nitrophenyl)-*N*-(5-phenyl-1, 3, 4-thiadiazol-2-yl) methanimine IR (cm^{-1}): 3085.88[Ar CH-Stre], 2962.44 [Alip CH Stre], 1635.52[C=NStre], 756.04[C-S-C], 1512.08[N=O Stre], H^1NMR: 6-9(10H, m, Ar-H), 2.51(2H, s,-CH2). EIMS (M/Z):310.08(M+).

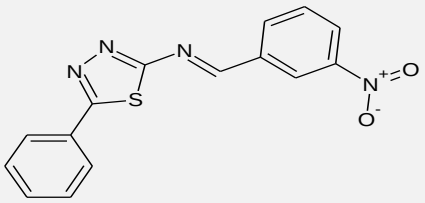
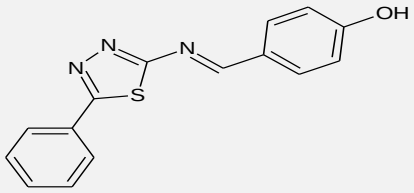
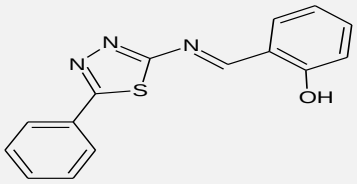
Compound: SDK2: 2-{(*E*) - [(5-phenyl-1, 3, 4-thiadiazol-2-yl) imino] methyl} phenolIR (cm-1):3085.88 [Ar- CHStret], 3440.78 [OH Stre], 1627.80 [C=N Stre], 756.04 [C-S-C] H1NMR: 6-9.2 (11H, m, Ar-H), 2.51 (2H, s, -CH2), 1.23[1H, s,OH). EIMS (M/Z):281.32 (M+).

M^+ Ions are 281.32g/mole.

Compound: SDK3: 4-{(*E*) - [(5-phenyl-1, 3, 4-thiadiazol-2-yl) imino] methyl} phenolIR (cm-1):3085.88 [Ar- CHStret], 3440.78 [OH Stre], 1627.80 [C=N Stre], 756.04 [C-S-C] H^1NMR: 6-9.2 (11H, m, Ar-H), 2.51 (2H, s, -CH2), 1.23[1H, s,OH). EIMS (M/Z):281.32 (M+).

Binding Energy with MIC Value:

TABLE 1: BINDING ENERGY WITH MIC VALUE

Compound	Structure	Binding Energy	MIC Value µg/ml
SDK1		-9.9	3.12
SDK2		-7.05	6.25
SDK5		-6.97	6.25

Physical Data of the Synthesized Compounds:

TABLE 2: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound code	Molecular Formula	Molecular weight(g/mole)	Melting point (^{o}C)	Yield (w/w)
SDK1	$C_{15}H_{11}N_3OS$	281.33	222	81%
SDK2	$C_{15}H_{11}N_3OS$	281.33	222	83%
SDK5	$C_{15}H_{10}N_4O_2S$	310.33	228	77%

* Solubility: Ethanol/Methanol (Common solvents used for all 3 compounds).

Anti-Tubercular Activity: All the compounds showed good and moderate activity against mycobacterium tuberculosis. The inhibition of the growth of bacteria was measured by µg/ml.

MABA Report of the Synthesized Compounds:

TABLE 3: MABA REPORT OF THE SYNTHESIZED COMPOUNDS

Sample code	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
SDK1	S	S	S	S	S	R	R	R
SDK2	S	S	S	S	S	R	R	R
SDK5	S	S	S	S	S	S	R	R

S- Sensitive, R- Resistant, Strain used: - M. tuberculosis [H37RV].

Toxicity Prediction Reports of Synthesized Compounds: Toxicity predictions of synthesized compounds were performed by Osiris property explorer and their toxicity characteristics were observed.

Toxicity Prediction:

TABLE 4: TOXICITY PREDICTION

Samples	SDK1	SDK2	SDK5
Mutagenic	+	+	+
Tumorigenic	+	+	+
Irritant	+	+	+
Reproductive Effect	+	+	+

[+] indicates the absence of toxicity. [-] indicates the Presence of toxicity.

Cell Line Toxicity Studies:

TABLE 5: CELL LINE TOXICITY STUDIES OF THE SYNTHESIZED COMPOUND

Sl. no.	Compound	Con(µg/ml)	Absorbance at 540 nm			% Cell death			Mean Cell Death	IC_{50}
1	SDK1	31.25	0.865	0.814	0.825	-3.47	2.63	1.32	0.16	> 250
		62.5	0.745	0.714	0.725	10.89	14.59	13.28	12.92	
		125	0.741	0.725	0.722	11.36	13.28	13.64	12.76	
		250	0.658	0.625	0.645	15.60	19.84	17.27	17.57	
2	SDK2	31.25	0.864	0.812	0.858	-3.35	2.87	-2.63	-1.04	> 250
		62.5	0.754	0.758	0.721	9.81	9.33	13.76	10.96	
		125	0.635	0.711	0.725	24.04	14.95	13.28	17.42	
		250	0.611	0.623	0.654	21.63	20.09	16.12	19.28	
3	SDK5	31.25	0.845	0.814	0.862	-1.08	2.63	-3.11	-0.52	> 250
		62.5	0.769	0.812	0.811	8.01	2.87	2.99	4.63	
		125	0.658	0.625	0.645	21.29	25.24	22.85	23.13	
		250	0.552	0.569	0.512	29.20	27.02	34.33	30.18	

TABLE 6: VEHICLE (DMSO) AND MEDIA USED FOR CELL LINE TOXICITY STUDIES

Group	Absorbance at 540			Mean	% Cell Death	% Cell Viability
Media	0.825	0.869	0.814	0.836	0	100
DMSO	0.795	0.758	0.786	0.780	6.74	93.26

The Synthesized compounds have the best docking score against specific targets. The purity of the compounds was determined by sharp melting point and single spot obtained in the Thin Layer Chromatography. The Synthesized compounds were confirmed by GC-MS analysis and the molecular weight obtained is at ± 1 variation. Then the functional group determination was obtained from FT-IR Studies. The biological evaluation of the compounds is determined by the specific organism was sensitive at 3.12 and 6.25µg/ml and showed better activity compared to standard drugs.

All the compounds gave a Docking score between -8.73 to 11.37 kcal/mole Pyrazinamide gave a docking score of 11.55kcal/mole for 4P8Y, Streptomycin gave a docking score of 10.87kcal/mole for 4P8Y and Ciprofloxacin gave docking score of 11.25k cal/mole for 4P8Y. There is a correlation between the score and activities of all the compounds which were tested and compared with the standard drugs [14].

CONCLUSION: This study proved that Decaprenylphosphoryl beta-D-ribose 2' epimerase-1' (PDBID: 4P8Y) is a critical enzyme for anti-mycobacterial activity. So fine-tuning the structures of these compounds will yield molecules with better anti-mycobacterial activity. Further structural modifications of the synthesized compounds will aid in the development of potential molecules against the tuberculosis pathogen.

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CONFLICTS OF INTEREST: Nil

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