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Antitubercular and Molecular Docking Studies of Some 5 - Arylmethylene – Pyrimidine -2, 4, 6-Triones

GajananHegde*[1], Bharath Raj B[2]
[1]Department of Chemistry, Gokhale Centenary College, Ankhola,Karnataka, India
[2]Karnataka Veterinary,Animal and Fisheries Sciences University, Bidar, Karnataka, India

ABSTRACT

A series of 5-arylmethylene-pyrimidine -2, 4, 6-triones (**3a-3j**) were synthesized by condensation of aromatic aldehydes (**1**) and barbituric acid (**2**) in aqueous medium in presence of Amberlite IR-120 H catalyst. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR and mass spectroscopic studies. All the synthesized compounds were subjected to anti-tuberculosis screening and molecular docking studies. Among them **3a** and **3i** were found to possess broad-spectrum antituberculosis activity and all the synthesized compounds are found to be promising potential specific inhibitors under molecular docking studies.

Keywords:5-arylmethylene-pyrimidine-2,4,6-triones, aromatic aldehydes, barbituric acid, antituberculosis activity , Molecular docking studies

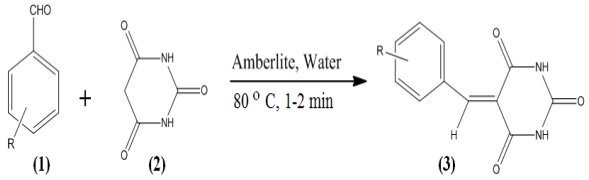
I. INTRODUCTION

The pyrimidinetriones (barbituric acid) scaffold represents common motif in many pharmaceutical active and remarkable compounds demonstrating a wide range of pharmacological activities[1-3]. Traditionally, they have been reported to show activity as anticancer[4], antispasmodic, local anaesthetic and sedatives[5-6]. Arylidene-pyrimidine-2,4,6-trione, arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione and its derivatives were found to have hypotensive, transiquilizer and good anti-bacterial agents[7-8].

The Knoevenagel condensation is one such reaction which facilitates C-C double bond formation and has been widely used in synthesis of fine chemicals[9], hetero Diels-Alder reactions[10] and in synthesis of carbocyclic[11] as well as heterocyclic compounds[12] of biological significance. These reactions are usually catalyzed by bases[13-15]. Literature search reveals that a fair amount of work has been reported on the condensation reactions of barbituric acid with carbonyl compounds in the presence of various catalysts[16-19].

Amberlite has been explored as effective heterogeneous and reusable catalysts in organic synthesis[20]. As heterogeneous catalyst, it has many advantages in contrast to traditional catalysts. It is relatively non toxic, easy to handle and readily separable from the products[21].

Prompted by the enormous significance of pyrimidinetriones and their derivatives due to their biological activities a plan as drawn to synthesize 5 - arylmethylene – pyrimidine -2, 4, 6-triones via condensation reaction with aromatic aldehydes and barbituric acid in water using eco friendlyAmberlite catalyst (**Scheme 1**) and to study their antituberculosis activity and molecular docking studies.



R = 4-NO_2, 4-Cl,4-F,4-OH,4-CH_3,4-$N(CH_3)_2$,3-Cl ,3-NO_2,3-OCH_3,2-OH

Scheme 1

II. EXPERIMENTAL

Melting points of the compounds **(3a-3j)** were determined in open capillary tubes and are uncorrected. The purity of synthesized compounds was checked by TLC observing single spot on Merk silica gel 60 F254 coated alumina plates. IR spectra (cm^{-1}) were recorded on Shimadzu Fourier transform (FT)-IR-577 Infrared Spectrophotometer in KBr pellets. The ^1H NMR and Spectra were recorded on Brucker AMX-400 (400 MHz) spectrometer using DMSO-d_6 as solvent and TMS as an internal standard. Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

General procedure for the synthesis of 5 - arylmethylene – pyrimidine -2, 4, 6-triones:

Barbituric acid (1 mmol) was dissolved in boiling water, then aromatic aldehyde (1 mmol) was added in the presence of amberlite catalyst (0.1g) at 80°C. Reaction were monitored using thin – layer chromatography (TLC, 2:8:: ethylacetate : petroleum ether). After the completion of reaction (in 1 – 2 min) product formed was separated just by filtration. The catalyst settles down, and easily separated by filtration. The final product was washed with hot water. The separated catalyst was washed with ethyl acetate and reused for atleast three times without the significant loss in its activity. The product after removal of solvent was recrystallized from glacial acetic acid.

Table 1.Synthesis of 5 - arylmethylene – pyrimidine -2, 4, 6-triones catalysed by Amberlite IR- 120H

Sl.No	Aldehyde	Product	Time (sec)	Yield (%)	Melting Point (°C)	
					Found	Reported Ref. 20-24
01	4-NO_2	3a	60	92	273-275	272-274
02	4-Cl	3b	60	95	297-299	279-281
03	4-F	3c	60	86	296-228	295-297
04	4-OH	3d	80	90	248-250	297-298
05	4-CH_3	3e	80	92	296-298	276-277
06	4-$N(CH_3)_2$	3f	90	94	265-266	262-263
07	3-Cl	3g	60	92	253-255	264
08	3-NO_2	3h	60	86	232-234	231-33
09	3-OCH_3	3i	80	91	187-189	187-190
10	2-OH	3j	80	89	248-250	249-251

Table 2. Results of Anti-TB of 5 - arylmethylene – pyrimidine -2, 4, 6-triones (3a-3j) and Reference standards by MicroplateAlamer Blue Assay (MABA) Method (MIC Test)

Test Samples	100µg/mL	50µg/mL	25µg/mL	12.5µg/mL	6.25µg/mL	3.12µg/mL
3a	S	S	S	S	R	R
3b	R	R	R	R	R	R
3c	R	R	R	R	R	R
3d	R	R	R	R	R	R
3e	R	R	R	R	R	R
3f	R	R	R	R	R	R
3g	R	R	R	R	R	R
3h	R	R	R	R	R	R
3i	S	S	S	R	R	R
3j	R	R	R	R	R	R
Pyrazinamide	S	S	S	S	S	S
Streptomycin	S	S	S	S	S	S
Ciprofloxacin	S	S	S	S	S	R

Note:S-Sensitive; **R**- Resistant; Strain: Mycobacterium tuberculosis (H37 RV) strain

Molecular docking

To validate drug-target association, automated docking was performed with the AutoDock 4 (ScrippsResearch Institute, USA) using an empirical free energy function and Larmarckian Genetic Algorithm, with an initial population of 150 randomly placed individuals, a maximum number of 250000 energy evaluations, a mutation rate of 0.02, and a crossover rate of 0.80. The grid map was centered at the active site binding pocket of the protein by AutoGrid 4 involving Cys 1, Trp74, Thr 76, His 77, Gly 99, and Asp 123 as previously reported by other groups (Wojciechowski et al., 2005; Banerjee et al., 2011; Satyendra et al., 2012). Ten independent GA (Genetic Algorithm) runs were performed for each ligand. Results differing by <2.0 A ° in positional root-mean-square deviation (RMSD) were clustered together and represented by the result with the most favorable free energy of binding. All torsions were allowed to rotate during docking.

Absorption-Distribution-Metabolism-Excretion and toxicity (ADME/Tox)

The ADME properties of all the ligands were calculated by using ADMETSAR (Version 3.4). The ADMET Structure-Activity Relationship (ADMETSAR) server, entitled admetSAR, is a comprehensive knowledge and tool for predicting Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of drug candidates and environmental chemicals. The Simplified Molecular-Input Line-Entry System (SMILES) format of each ligand was submitted to ADMETSAR webserver for the prediction of ADMET properties.

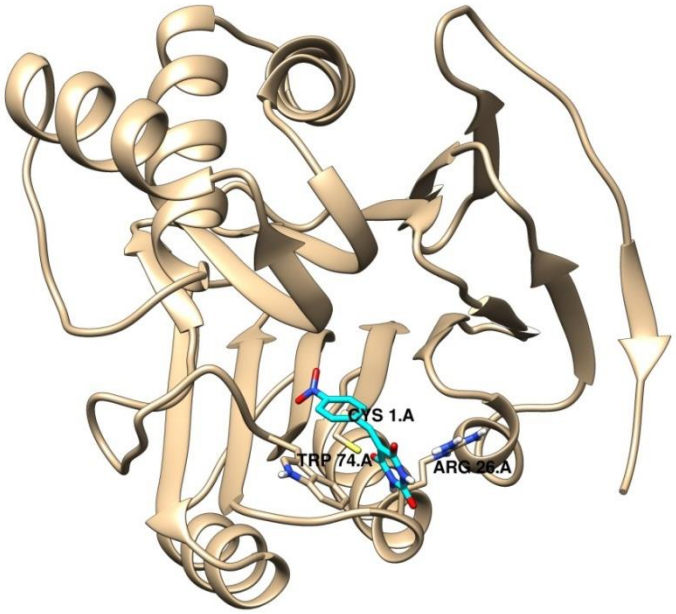


Figure 1. G6P-Ligand (APTN-4) interactions

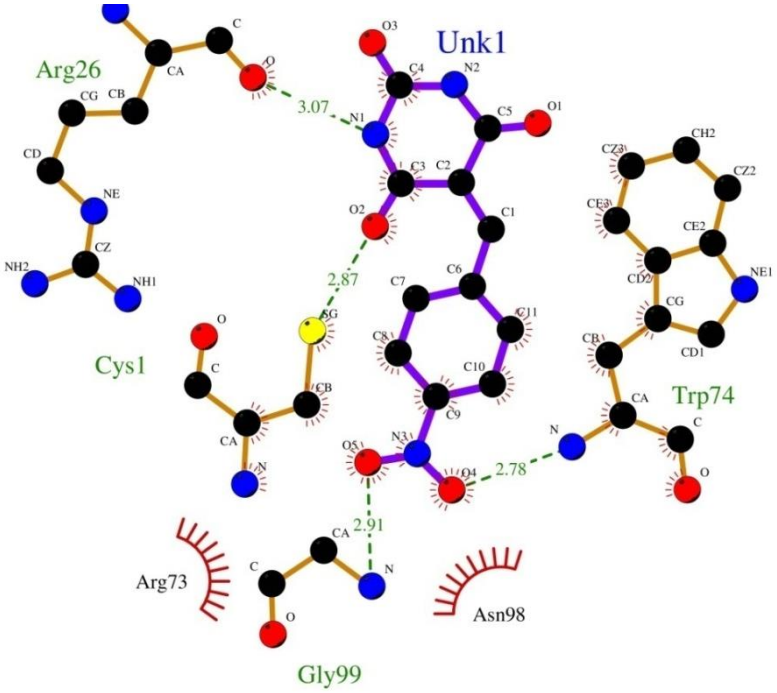


Figure 2. Interacting amino acids as predicted from the ligplot

III. RESULTS AND DISCUSSION:

The anti tuberculosis study results shows that, among the synthesized compounds **3a** and **3i** were found to possess broad-spectrum antituberculosis activity compared with available standards up to 12.5 and 25 µg/mL respectively .

The molecular docking study of all the compounds *in silico* analysis was undertaken to identify whether the molecular docking of benzofuran derivatives (APTNP 1-10) with G6P provides any correlating information with their *in vitro* antibacterial activity. Computationally the molecular docking investigations revealed lower binding energy values of benzofuran

derivatives (APTNP 1-10) in comparison to the standard compounds used streptomycin and fluconazole (Table 1) indicating higher binding affinity with Glucosamine 6-phosphate synthase. The RMSD value obtained for docking and re-docking of benchmark compound streptomycin revealed a score as low as 0.46 suggestive of the confidence in following Autodock protocol Å suggestive of the confidence in following Autodock protocol. This represents that the docking procedure will constantly reproduce the receptor bound conformation with present ligand molecules. The molecular docking analysis revealed that among all the ligands, the ligand APTN-4 with the least binding energy of -8.36 kcal/mol and exhibiting most favorable hydrogen-bonded interactions with the active site residues of the target protein G6P, was predicted to be good lead molecule (Table 1). Most of the benzofuran derivatives (APTNP 1-10)were found to be interacting via hydrogen bond interactions with key active site residues Cys 1 and TRP 74 (Figure 1) of G6P suggesting their strong inhibitory potential. Fig. 2 shows interacting amino acids of G6P by APTNP 4 as predicted by ligplot. Furthermore, ADME/Tox analysis of the benzofuran derivatives was performed to check for the drug likeliness property and human intestinal absorption (HIA). This analysis also revealed that compound 4i was non toxic and has the best human intestinal absorption of 99.7% in comparison to all other ligands (Table 2). Nevertheless both streptomycin and fluconazole had poor HIA in comparison to benzofuran derivatives (APTNP 1-10). In general, all the ligand molecules (APTNP 1-10) were showed promising results against G6P than standard compounds. Hence, they may act as potential specific inhibitors. Further, findings demonstrated that computational analysis was in good agreement with *in vitro* observations.

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