Synthesis and Evaluation of Antimicrobial Activity of thiazolidine-4-one

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Abstract

Nitrogen and sulphur containing heterocycles are of high therapeutic importance due to broad spectrum of biological activities. The world of medicinal chemistry always looks for newer analogues to be developed to overcome the microbial resistance /higher therapeutic value. In view of this, a virtual library of nitrogen and sulphur containing heterocycles were designed and subjected for molecular docking analysis to find out probable potent erivatives. The docking analysis was done against targets like Shikimate Kinase (Tubercular activity), Glucosamine-6-Phosphate (Antimicrobial activity) and "Alpha Glucosidase" (Antidiabetic activity). Promising potent derivatives from thiazolidine-4-ones, isoxazolines and triazoles were synthesized by conventional synthetic methods. The structures of synthesized compounds were confirmed by spectral study i.e. IR, ^{1}HNMR and Mass analysis. Antitubercular, antidiabetic, antimicrobial and antioxidant activities (in-vitro) were carried out as per standard literature procedures. The results were compared with standard drugs.

Keywords: heyerocyclic, antitubercular, biological activity, SAR

Introduction:

Heterocyclic compounds are considered an important branch of organic compounds due to their application in drugs, agricultural fertilizers and industrial studies (1) a variety of atoms, such as N, O, S, P, Si and as can be incorporated into the ring structures (2). The most common heterocyclic are those with five- or six membered rings (3). Heterocyclic compound containing atom other than carbon in their ring, have long been proven to have vivid biological activities. The biological activities of heterocyclic rings, such as triazoles, indoles, pyrones, morpholines, pyridines, and pyrazoles, have been reviewed widely (4,5). The 4-thiazolidinone is one of class represent an important analogue to thiazolidine heterocyclic compounds (6). The cyclization reaction for synthesis of thiazolidin-4-one compounds was carried out by conventional (7-12) or microwave irradiation techniques (13-15). Thiazolidinone is another heterocyclics have biological important which contain of sulfur atom at position 1, nitrogen atom of at position 3, and a carbonyl group at the 2, 4, or 5 positions. The various derivatives: 2-thiazolidinone or 4-thiazolidinone or 5-thiazolidinone or 2-thioxo-4-thiazolidinone and thiazolidine-2,4-dione are associated with number of pharmacological properties.

Material and Methods:

GlcN-6-P synthase as described by the reported reference. The pdb enzyme file of receptor was downloaded from the RCSB Protein Data Bank (PDB code 1MOQ) and used as a fixed molecule. The docking study of the potent active isoxazoline, thiazolidine and triazole derivatives toward antimicrobial species inside the active pocket of L-Glutamine: D-fructose-6-phosphate amidotransferase, the active target for antimicrobial agents was explored.

Anti-Tubercular

Shikimate kinase (SK) is an essential enzyme in several pathogenic bacteria and does not have any counterpart in human cells, thus making it an attractive target for the development of new antibiotics. The important interactions of the substrate and product binding and the enzyme movements that are vital for catalytic turnover of the Mycobacterium tuberculosis *shikimate kinase* enzyme (Mt-SK) have been investigated by structural and computational studies. Literature reveals triazole derivatives along with various heterocyclic analogs were designed and assayed successfully against *shikimate kinase* thus the PDB 1L4u was selected as a target for docking of compounds for anti-tubercular screening.

Result and Discussion:

***Shikimate kinase* (SK) (for antitubercular activity):** *Shikimate kinase* is an essential enzyme in several pathogenic bacteria and does not have any counterpart in human cells, thus making it an attractive target for the development of new antibiotics. The crucial interactions of the substrate and product binding and the enzyme activities that are essential

for catalytic turnover of the Mycobacterium tuberculosis *shikimate kinase* enzyme (Mt-SK) have been investigated by structural and computational studies. Literature reveals triazole derivatives along with various heterocyclic analogs were designed and assayed successfully against *shikimate kinase* thus the PDB 1L4u was selected as a target for docking of compounds for anti-tubercular screening.

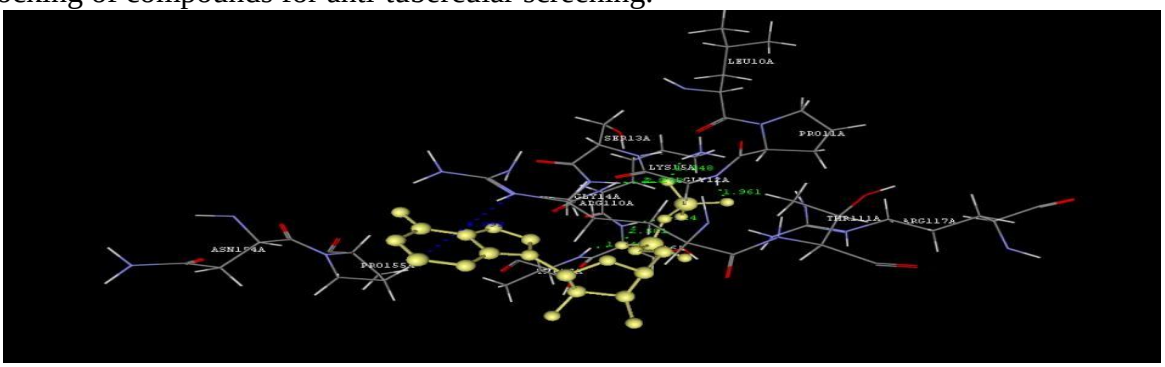

Figure 1.1: Docking interactions for the reference molecule with Shikimate kinase (Yellow colour ball and stick)

The docking scores and the interactions of top scoring compounds are as indicated in Table (additional Information). The best docked compound SS12 has docking score 0 f -59.584312, suggesting good binding of the compound to the targets. The compound SS 12 shows Hydrogen Bonding Interactions with GLY12, ARG117, and Hydrophobic interactions with THR17, ARG110 and PRO155. The best docked pose of the molecule SS 12 is as shown in **Figure 1.2**.

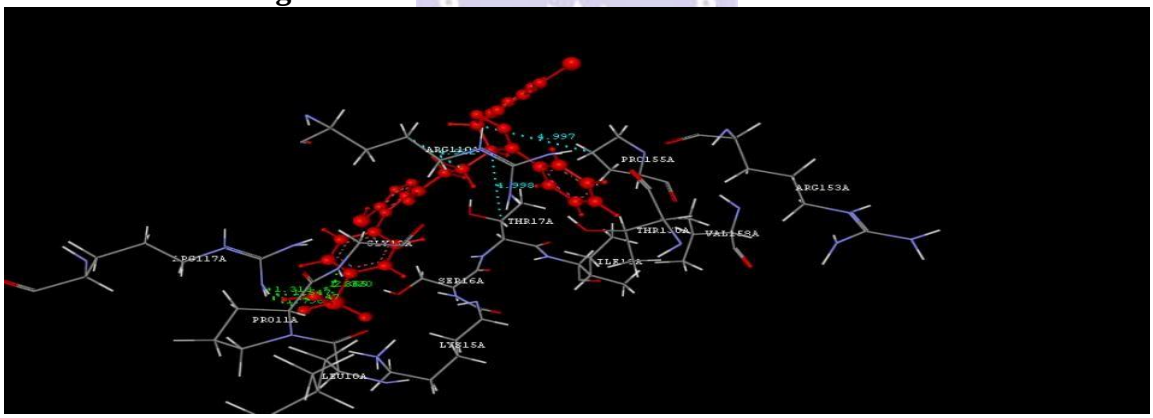

Figure 1.2: Docking interactions for the SS 12 molecule with Shikimate Kinase (RED colour ball and stick)

The docking study of the potent active derivatives toward antimicrobial species inside the active pocket of L-Glutamine: D-fructose-6-phosphate amidotransferase, the active target for antimicrobial agents was explored. As described by the X-ray study, the binding pocket of target enzyme including the following subsequent residues, cysteine 300, glycine 301, threonine 302, serine 303,serine 347, glutamine 348, serine 349, threonine 352, valine 399, serine 401, alanine 602 and lysine 603 as shown in Figure 1.3

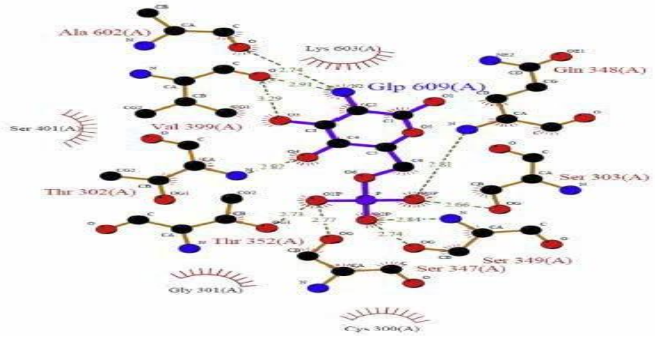

Figure 1.3: The binding of glucosamine-6-phosphate inside the active site of target enzyme

DPPH ASSAY (ANTIOXIDANT ACTIVITY) FOR THIAZOLIDINE-4-ONES

Radical scavenging activities are of great significance due to the deleterious role of free radicals in biological systems. The *in vitro* antioxidant properties of the newly synthesized compounds at different concentrations were examined by a well- documented assay like DPPH free radical scavenging assay. The effect of antioxidants on DPPH radicals is considered due to their hydrogen donating ability. Antioxidant molecule can quench DPPH free radicals and convert them to a colourless/bleached product ultimately resulting in a decrease in the absorbance. The *in vitro* antioxidant activity of the synthesized compounds SG1-SG21 compared to ascorbic acid as standard are shown in Table 15. Our results indicate that newly synthesized compounds showed moderate to good antioxidant activity at low concentrations as compared to ascorbic acid. In an attempt to establish some structure activity relationship based on the position and presence of different substituents and to understand as to how different functionalities have an effect on the antioxidant properties, a series of new Thiazolidine-4-ones were synthesized. The DPPH radical scavenging efficacy of SG2-SG21 did not show a regular trend. The scavenging of DPPH radicals by most of these compounds occurred in a concentration-dependent manner from 2 to 32 µg/ml with SG1 analogue showing maximum effect of 83.54 %, respectively. Whereas for its unsubstituted counterpart and chloro analogue, the moderate free radical scavenging activity was SG17 (20.22□0.134) and 58.63 %, at a concentration of 32 µg/ml, respectively.

Table 1: Data of % Scavenging Activity at Different Concentrations for selected Thiazolidine-4-one

Sr. No	Sample	% Scavenging Activity At Different Concentrations				
		2□g/mL	4□g/mL	8□g/mL	16□g/mL	32□g/mL
1.	**Ascorbic Acid**	19.70□0.36	25.92□1.19	37.96□0.38	55.77□0.26	89.61□0.36
2.	SG1	19.28□0.51	30.53***□0.55	32.72***□0.56	47.59***□0.84	83.54***□0.40
3.	SG2	18.50□1.82	30.12***□0.33	41.24***□0.61	56.21□0.77	62.22***□0.52
4.	SG3	18.49□1.82	25.63□0.40	32.61***□0.58	47.72***□0.71	63.62***□0.53
5.	SG16	17.48*□0.60	26.53□0.51	30.94***□0.51	39.21***□0.76	67.99***□0.63
6.	SG17	17.20**□0.80	32.59***□0.54	41.26***□0.54	53.81***□0.32	58.63***□0.77
7.	SG18	18.41□1.77	29.53***□0.43	39.6***□0.77	47.45***□0.71	59.06***□0.98
8.	SG19	27.2***□0.96	36.53***□0.70	43.16***□0.35	53.53***□0.30	67.19***□1.03
9.	SG20	19.75□0.13	29.05***□0.58	31.42***□0.61	38.64***□0.63	56.59***□0.72
10.	SG21	22.23**□1.27	36.13***□0.48	40.83***□0.67	57.26**□0.17	63.07***□0.68

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