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Research Article

Molecular Docking Studies; 1,3 Thiazines Derivatives

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Abstract

Some novel derivatives of 1,3-thiazine have been synthesized by the condensation of 2-hydroxy-3-nitro5-chlorochalcones with thiourea and phenylthiourea in ethanol containing aqueous KOH solution. The synthesized ten 1,3 thiazine derivatives were subjected to molecular docking studies against *E.coli* Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID-4 AMV) and Crystal structure of Peptide deformylase from *Staphylococcus aureus* Complex with Actinonin (PDB ID-1Q1Y) usingMolegro Virtual Docker software. All synthesized compound have been screened for in-vitro evaluation of antimicrobial activities by agar plate techniques. The results indicated that all the synthesized 1,3 thiazine derivatives shows considerable antimicrobial activities on gram negative (*E. coli*) bacteria This study suggested that 1,3-thiazine derivatives possess more antimicrobial activities on gram negative (*E. coli*) bacteria than gram positive bacteria (*S.aureus*).

Keywords: 1, 3 Thiazine; Molecular Docking; Antimicrobial Activities; Thiourea; Phenyl Thiourea

Introduction

The heterocyclic compounds which contain nitrogen, sulphur and oxygen possess a huge significance within the field of medicinal chemistry. Thiazines are very useful units within the fields of medicinal and pharmaceutical chemistry and are reported to exhibit a spread of biological activities [1]. A large number of thiazine derivatives also exhibited various biological activities such as antimicrobial [2], anti-inflammatory [3], antioxidant, antipyretic, antitumor [4], calcium channel modulators [5]. 1, 3-thiazine derivatives and their evaluation as potential antimicrobial agents [6]. Literature review reveals that chalcones exhibited various biological and pharmacological activities such as antimicrobial [7], antifungal [8], analgesic [9], anti-platelet [10], insecticidal [8], anti-malarial [11], antiviral [7] activities. The reaction of thiourea and phenyl thiourea with α, β-unsaturated ketones results in 1, 3 thiazine derivatives [12]. Different chalcone derivatives are used as the starting material for the synthesis of 1, 3 thiazine derivatives. Based on the careful analysis of literature survey, the well focused and biologically potent 1, 3 thiazines derivatives were synthesized via three stages of reaction.

In the present work involves the synthesis of chalcones by using aryl aldehyde and 2-Hydroxy-3-nitro-5-chloroacetophenone. Then the chalcones are treated with thiourea and phenyl thiourea to give 1, 3 thiazine derivatives. Molecular docking studies against *E.coli* Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID-4 AMV) and crystal structure of peptide deformylase from *Staphylococcus aureus* complex with actinonin (PDB ID-1Q1Y) were done to compare the antimicrobial activities of synthesized 1, 3-thiazine derivatives.

Materials and Methods

All the solvents and chemical reagents were collected from P.C Chem. pharmaceutical. The melting points of the organic compounds were determined by open capillary tube method and are uncorrected. The solubility of the synthesized compounds was tested in various solvents like water, ethanol, chloroform, benzene, hexane etc.

General procedure

Preparation of 2-hydroxy-3-nitro-5-chloroacetophenone (2a)

2-Hydroxy-5-chloroacetophenone (3g) was dissolved in glacial acetic acid (3ml). Nitric acid was added drop wise with constant stirring to this reaction mixture. The temperature of the reaction mixture was maintained below 0°C. The mixture was allowed to

stand for 1hour. It was poured into ice cold water with stirring. A yellow solid then obtained was filtered, dried and crystallized from ethanol.

Preparation of 2-hydroxy-3-nitro- 5-chlorochalcones (3a-e)

2-Hydroxy-3-nitro-5-chloroacetophenone (2a), (0.1M) was dissolved in ethanol (50 ml) and derivatives of benzaldehyde (0.1M) were added to the above solution and the mixture was heated to boiling. Aq. sodium hydroxide solution (40%, 40 ml) was added drop wise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hour and kept overnight. It was then acidified by hydrochloric acid solution (50%). The solid separated was filtered and washed with sodium bicarbonate (10%) followed by water. The crude product was crystallized from ethanol acetic acid mixture (3a-e).

Preparation of 4-(2-hydroxy-3-nitro-5-chlorophenyl)-6-(aryl)-2-imino- 3,6 dihydro-1, 3-thiazines (4a-e)

2-Hydroxy-3-nitro-5-chlorochalcone (3a-e), (0.01M) and thiourea (0.01M) were dissolved in ethanol (25 ml).To this aq. KOH solution (0.02M) was added (prepared from KOH in small amount of distilled water). The reaction mixture was refluxed for 2.5 hours, cooled, diluted with water and acidified with 1:1 HCl. The product was filtered, dried and crystallized from ethanol (4a-e).

Preparation of 4-(2-hydroxy-3-nitro-5-chlorophenyl)-6-(aryl)-2-iminophenyl- 3, 6 dihydro-1, 3-thiazine (5a-e)

2-hydroxy-3-nitro-5-chlorochalcone (4a-e), (0.01M) dissolved in ethanol (25 ml) were added to phenylthiourea (0.01M).To this aq. KOH solution (0.02M) was added. The reaction mixture was refluxed for 2.5 hours, cooled, diluted with water and acidified with concentrate HCl. The product was filtered, dried and crystallized from ethanol (5a-e). (Scheme: Synthesis of 1, 3 Tiazine derivatives)

Characterization of the compounds

The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of final compounds was checked by TLC on silica gel G plate using hexane and ethyl acetate visualized in iodine chamber.

Compound Code	R	Molecular formula	Molecular weight	M.P(^{0}C)	% yield	R_f value
4a	Cl	$C_{16}H_{11}Cl_2N_3O_3S$	396.25	120	76	0.55
4b	Br	$C_{16}H_{11}BrClN_3O_3S$	440.70	145	68	0.58
4c	OCH_3	$C_{17}H_{14}ClN_3O_4S$	391.83	102	58	0.68
4d	NO_2	$C_{16}H_{11}ClN_4O_5$	406.01	138	70	0.64
4e	OH	$C_{16}H_{12}ClN_3O_4S$	377.02	132	51	0.72
5a	Cl	$C_{22}H_{15}Cl_2N_3O_3S$	472.34	110	74	0.69
5b	Br	$C_{22}H_{15}BrClN_3O_3S$	516.79	157	75	0.49
5c	OCH_3	$C_{23}H_{18}ClN_3O_4S$	467.92	142	54	0.51
5d	NO_2	$C_{22}H_{15}ClN_4O_5S$	482.90	138	60	0.35
5e	OH	$C_{22}H_{16}ClN_3O_4S$	453.90	140	65	0.55

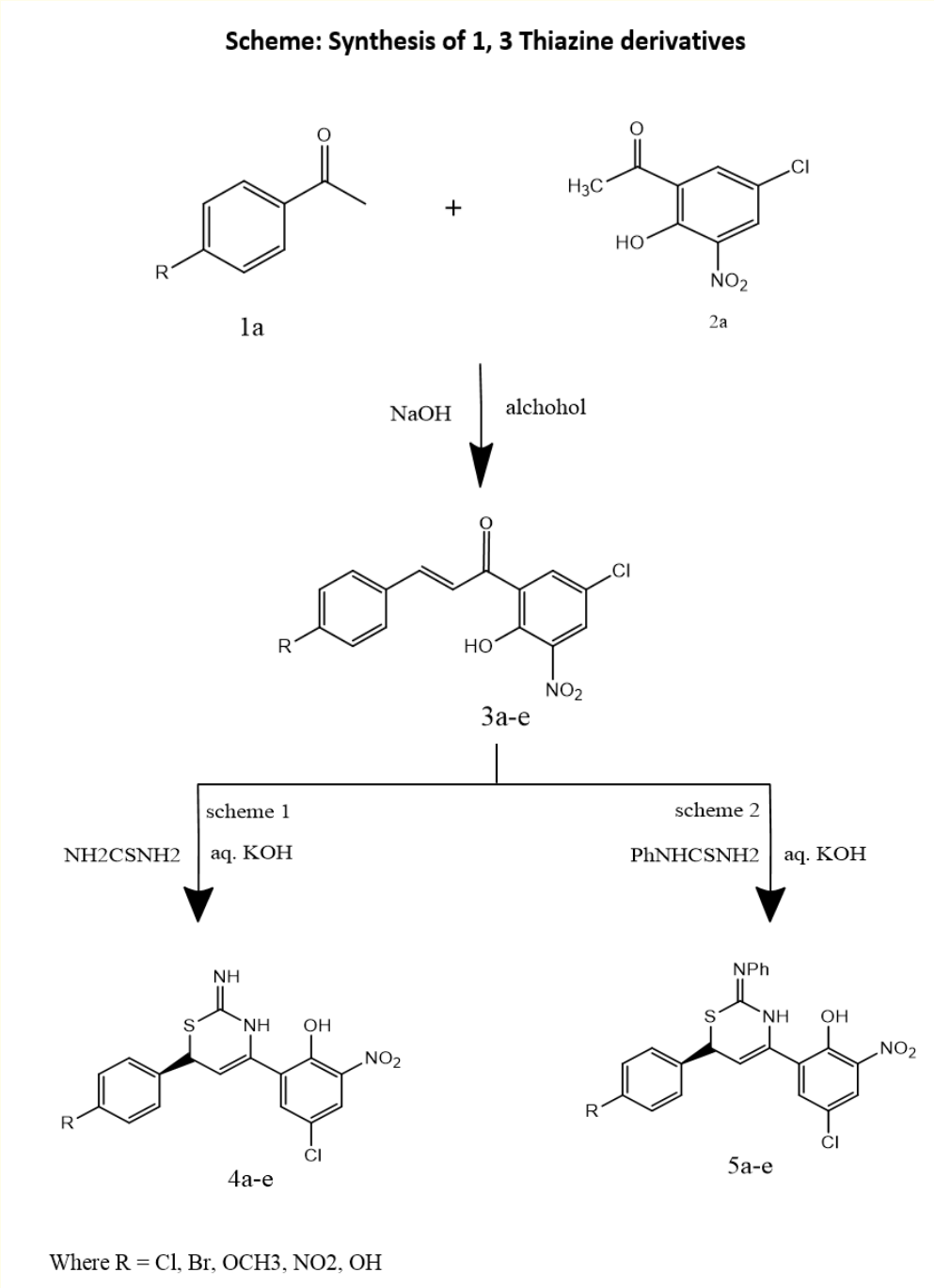
Table 1: Physical data of synthesized 1,3 thiazine derivatives.

Molecular docking studies

Docking is employed to predict the binding orientation of small molecule drug candidates to their protein targets so as to successively predict the affinity and activity of the tiny molecule. The structure of the protein *E.coli* Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID-4 AMV) and Crystal structure of Peptide deformylase from *Staphylococcus aureus* Complex with Actinonin (PDB ID- 1Q1Y) was retrieved from the RCSB (research Collaboratory for structure bioinformatics) Protein Data Bank. The binding site of protein was defined by selecting all atoms within 10Å, which was found by redocking the native ligand at the active site and docked using Molegro Virtual Docker. Molegro Virtual Docker is an excellent, non-commercial docking program that is widely used. Molegro Virtual Docker 6.0 developed by CLC drug discovery Workbench.

Results and Discussion

In the present work totally 10 compounds were synthesized in two scheme.Step 1 involves the formation of chalcones from 2-Hydroxy-3-nitro-5-chloroacetophenone.The step 1 product (chalcone) reacted with thiourea or phenyl thiourea in presence of potassium hydroxide undergo cyclization to form 1,3-thiazine derivatives. Molecular docking studies were carried out for the syn-



Scheme: Synthesis of 1, 3 Tiazine derivatives

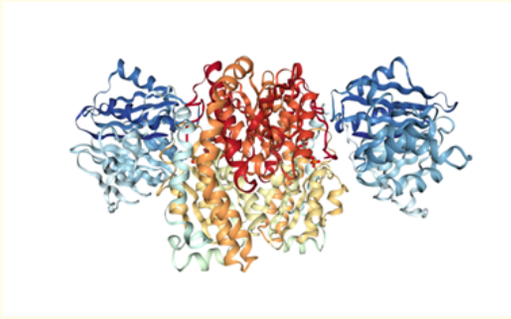


Figure 1: Structure of 4AMV (PDB ID).

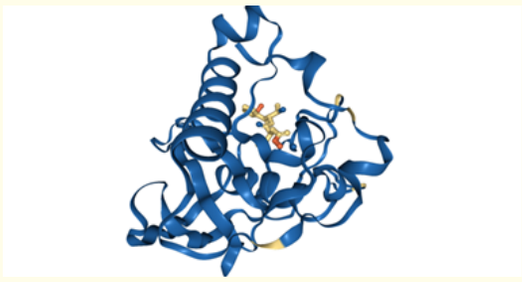


Figure 2: Structure of 1Q1Y (PDB ID).

thesized compounds against *E.coli* Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID-4 AMV) and Crystal structure of Peptide deformylase from *Staphylococcus aureus* Complex with Actinonin (PDB ID-1Q1Y) by using Molegro Virtual Docker software which gives an insight in to the binding modes for the various inhibitors. Out of 10 inhibitors analyzed 5a has showed Mol Dock Score of -110.723 for *E.coli* and 5d has showed Mol Dock Score of -96.683 for *S.aureus*. Then all ten derivatives of 1, 3 thiazine were screened for their antimicrobial activity against gram positive bacteria viz. *S. aureus* and gram negative bacteria viz. *E. coli* species at conc. of 1000 µm azithromycin as a standard. DMF was used as a solvent control using agar plate techniques. The zone of inhibition formed were measured in mm and shown in table 4.

Compound code	MolDock Score	Rerank Score	HBond
4a	-86.7749	-67.5634	-6.83585
4b	-88.8064	-74.5592	-6.18152
4c	-93.706	-76.7804	-3.95941
4d	-86.8956	-58.2635	-9.75651
4e	-106.654	-81.0678	-12.0967
5a	-110.723	-78.4613	-5.48575
5b	-82.4321	19.6867	-6.4191
5c	-86.7144	19.3956	-6.50447
5d	-88.6181	10.7845	-6.41836
5e	-81.9273	19.5981	-6.47967

Table 2: Summary of docking score of all synthesized 1,3-thiazine derivatives against the target E. coli Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID: 4 AMV).

Compound code	Mol Dock Score	Rerank Score	HBond
4a	-83.9601	-66.2623	-4.97171
4b	-84.5862	-66.6038	-4.37323
4c	-87.6422	-70.5666	-6.48139
4d	-85.0538	-69.3519	-4.87202
4e	-83.252	-66.2025	-3.71184
5a	-87.4778	-66.6463	-7.1557
5b	-92.1642	-75.5591	-4.89751
5c	-95.4961	-77.3788	-3.69138
5d	-96.5073	-80.1216	-4.02885
5e	-94.7954	-78.3154	-5.3336

Table 3: Summary of docking score of all synthesized 1,3-thiazine derivatives against the target Crystal structure of Peptide deformylase from Staphylococcus Aureus Complex with Actinonin (PDB ID:1Q1Y).

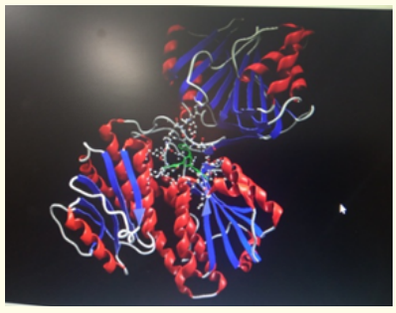


Figure 3: Docking complex of 5a with 4AMV.

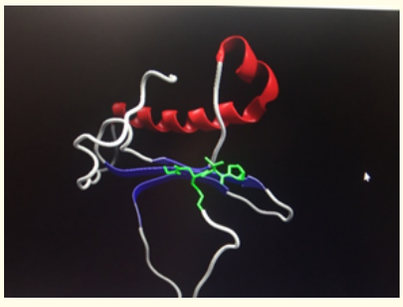


Figure 4: Docking complex of 1Q1Y with 5d.

Compound Code	Zone of inhibition (mm)	
	E. coli	*S. aureus*
4a	17	16
4b	20	17
4c	23	19
4d	19	17
4e	25	15
5a	26	19
5b	17	18
5c	19	19
5d	20	21
5e	17	21

Table 4: Antimicrobial activities of all synthesized 1, 3 thiazine derivatives.

Conclusion

Ten different 1, 3 Thiazine derivatives were synthesized from chalcones and thiourea or phenyl thiourea. The synthesized compounds were checked for their antimicrobial activity by molecular docking studies against *E.coli* Glucosamine-6 P Synthase in Complex with Fructose-6 P (PDB ID-4 AMV) and Crystal structure of Peptide deformylase from *Staphylococcus aureus* Complex with Actinonin (PDB ID-1Q1Y) by using Molegro Virtual Docker software. Then *in-vitro* evaluation of antimicrobial activity of all synthesized 1, 3-Thiazine derivatives were performed and all having considerable antimicrobial activity. From the above results it would be concluded that 1, 3-thiazines derivatives possess more antimicrobialactivities on gram negative (*E. coli*) bacteria than gram positive bacteria (*S.aureus*).

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