*Girly Tony et al. / Journal of Pharmacy Research 2014,8(2),136-138*

**Research Article**
**ISSN: 0974-6943**

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# Molecular docking studies: 1, 3-thiazine and 1,3-oxazine dervatives

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**Received on:17-12-2013; Revised on: 08-01-2014; Accepted on:19-01-2014**

## ABSTRACT

Some novel derivatives of 1, 3 thiazines and 1, 3 oxazines were synthesized from five different chalcones with thiobenzamide and benzamide respectively. The synthesized five 1,3 thiazines and 1,3 oxazines derivatives were subjected to molecular docking docking studies against cytochrome p450 14 alpha sterol demethylase from *mycobacterium tuberculosis* using Argus Lab software .The results indicated that the chalcone derivatives of 1,3 thiazines (ligand binding energy varies from -12.135kcal/molto-14.2547 kcal/mol) shows considerable anti-fungal activity than the chalcone derivatives of 1,3 0xazines (ligand binding energy varies from -11.3042kcal/mol to -13.0389kcal/mol) against cytochrome p450 alpha sterol demethylase from *Mycobacterium tuberculosis*. Out of 10 derivatives, 3a (Methyl substituted 1, 3 thiazine) possess best ligand pose energy (-13.9505kcal/mol) and have one hydrogen bond .This study suggested that 1, 3 thiazine derivatives could be a potent antifungal activity than 1, 3 oxazine derivatives.

**Key words**: Oxazine, Thiazine, Argus Lab, Anti-fungal activity

## INTRODUCTION

Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in many natural products such as vitamins, hormones, antibiotics etc.1,3thiazines-nitrogen and sulfur and 1,3 oxazine contains- nitrogen and oxygen in their six membered hetero cyclic ring(N-C-S,N-C-Olinkage). The heterocyclic compounds which contain nitrogen, sulphurand oxygen possess an enormous significance in the field of medicinal chemistry. Thiazine and oxazine derivatives possess various biological activities such as anti-tubercular, anti-fungal, anti-bacterial, analgesic, anti-inflammatory, anti-cancer etc. Different chalcone derivatives are used as the starting material for the synthesis of thiazines and oxazines.

Cytochrome P-450-14-Alpha Sterol Demethylase is an enzyme that is needed for the demathylation of lanosterol, an intermediate in egosterol biosynthesis. Thiazine and oxazine derivatives block ergosterol synthesis by inhibiting the enzyme Cytochrome P-450-14-Alpha Sterol Demethylase, causing its depletion and accumulation of lanosterol and some other 14-methysterols. Such sterols alter membrane fluidity with concomitant reduction in the activity of membrane associated enzymes, increased permeability, and inhibition of cell growth and replication. The crystal structure of CYP51 a soluble orthologue from mycobacterium tuberculosis (MTCYP51) is available until now[1,2,3,4].

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In the present work involves the synthesis of chalcones by using aryl aldehyde and aryl ketone( Claisen-Schimdt condensation reaction)[5]. Then the chalcones are treated with thiobenzamide for 1,3 thiazine and benzamide for 1,3 oxazine. Molecular docking studies against Cytochrome P-450-14-Alpha Sterol Demethylase demethylase from *Mycobacterium tuberculosis* (PDB ID: 1H5Z) were done to compare the antifungal activities of synthesized 1,3-thiazine and 1,3-oxazine derivatives.

## MATERIALS AND METHODS

All the solvents and chemicals reagents were collected from MERCK, CHEMCO and NICE 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 etc.

## GENERAL PROCEDURE[6,7]:

### Step1-General Procedure for synthesis of chalcone

Chalcones are synthesized by reacting eqimolar amounts of aryl aldehyde and aryl ketones in the presence of sodium hydroxide and ethanol .Shake it thoroughly and kept it in the shaker for 2 to 3 hour. After that it taken from the shaker and keep it for 12 hours in the refrigerator, filter it using whatmann filter paper and dried.

### Step2- Synthesis of 1, 3-Thiazine and 1, 3-Oxazine derivatives[8]

Chalcone (0.01mol) was added to a solution of thiobenzamide (0.01mol) in dry dichloromethane (25ml) at room temperature .to this solution was added boron trifluride diethyl ether (1.2 mol).the reaction mixture

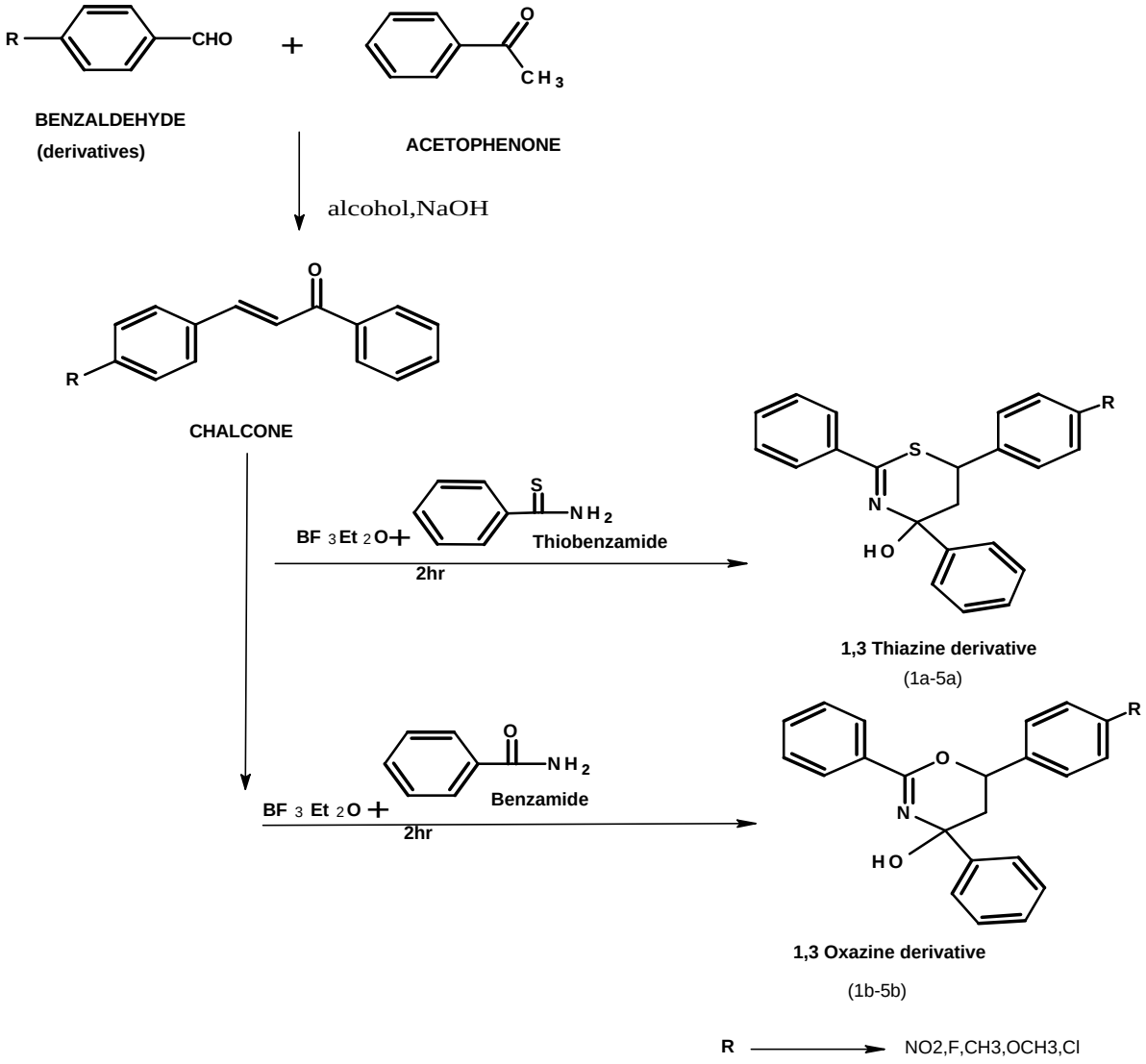


**Table 1:Physical data of synthesized 1,3thiazines and 1,3 oxazines**

| Compound Code | R | Molecular formula | Molecular weight | M.P ($^0$C) | % yield | $R_f$ value |
|---|---|---|---|---|---|---|
| 1a | $NO_2$ | $C_{22}H_{18}N_2SO_3$ | 390 | 153 | 73 | 0.581 |
| 1b | $NO_2$ | $C_{22}H_{18}N_2O_4$ | 374 | 91 | 74 | 0.687 |
| 2a | F | $C_{22}H_{18}NSOF$ | 363 | 82 | 54 | 0.555 |
| 2b | F | $C_{22}H_{18}NO_2F$ | 347 | 77 | 51 | 0.587 |
| 3a | $CH_3$ | $C_{23}H_{21}NOS$ | 359 | 82 | 65 | 0.644 |
| 3b | $CH_3$ | $C_{23}H_{21}NO_2$ | 343 | 93 | 68 | 0.694 |
| 4a | $OCH_3$ | $C_{23}H_{21}NO_2S$ | 375 | 73 | 53 | 0.569 |
| 4b | $OCH_3$ | $C_{23}H_{21}NO_3$ | 359 | 65 | 58 | 0.582 |
| 5a | Cl | $C_{22}H_{18}NOSCl$ | 382 | 81 | 51 | 0.680 |
| 5b | Cl | $C_{22}H_{20}NO_2Cl$ | 366 | 110 | 57 | 0.722 |

was stirred for 2 hr., quenched with saturated sodium carbonate solution (50 ml) and extracted with dichloromethane .The extract were dried (sodium sulphate unhydrous) and evaporated to dryness.Recrystallised from ether .Incase of oxazine, benzamide is used instead of thiobenzaldehyde.

**Molecular docking studies**

Docking is used to predict the binding orientation of small moleculedrug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. The structure of the protein cytochrome p 450 14 alpha demethylase with the PDB ID: 1H5Z was retrieved from the Protein Data Bank. The possible binding sites of the proteins were searched using Computed Atlas of Surface Topography of proteins (CASTp).The inhibitor (synthesized thiazines and oxazines) and target protein was geometrically optimized and docked using the docking engine Argus Dock (http:www.arguslab .com). Argus lab consists of user interface that supports Open GL graphics display of molecule structures and runs quantum mechanical calculation using the Argus compute server[9].

**RESULTAND DISCUSSION**

In the present work totally 10 compounds were synthesized in single scheme .Step 1 involves the formation of chalcones from aryl alde-

**Table: 2 Summery of binding energy of all synthesized 1,3-thiazine and 1,3-oxazine derivatives against the target cytochrome p 450 14 alpha demethylase (PDB ID 1H5Z)**

| Compound Code | Number of conformation | Binding energy | Hydrogen bonds |
|---|---|---|---|
| 1a | 140 | -12.894 | Nil |
| 1b | 140 | -11.3042 | Nil |
| 2a | 140 | -13.7455 | Nil |
| 2b | 140 | -11.7056 | Nil |
| 3a | 140 | -13.9505 | 1 |
| 3b | 140 | -12.4285 | 1 |
| 4a | 140 | -12.135 | 1 |
| 4b | 140 | -12.154 | 1 |
| 5a | 140 | -14.2547 | Nil |
| 5b | 140 | -13.0389 | nil |

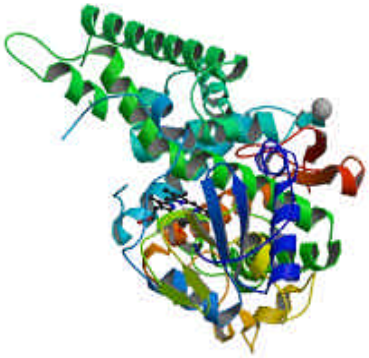

**Fig: 1 Structure of 1H5Z (PDB ID )**

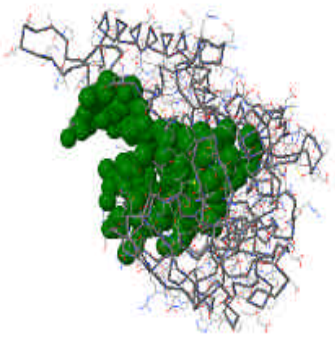

**Fig : 2 Binding sites of PDB ID: 1H5Zfrom CASTp**

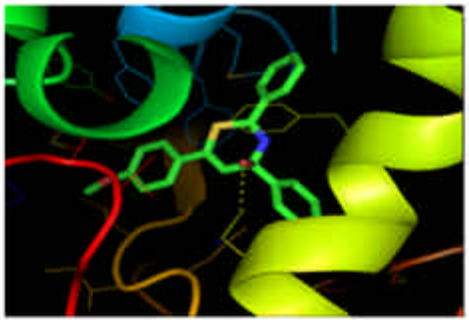

**Fig 3: Docking comples of PDB ID: 1H5Z with 3a**

hyde and aryl ketone(Claisen Schmidt condensation).The step 1 product(chalcone) reacted with thiobenzamide(thiazine) and benzamide(oxazine) in presents of boron trifluride diethyl ether undergo cyclization to form 1,3-thiazine and 1,3-oxazine. Molecular docking studies were carried out for the synthesized compounds against cytochrome p 450 14 alpha demethylase protein by using Argus Lab software which gives an insight in to the binding modes for the various inhibitors. Out of 10 inhibitors analyzed 3a has showed binding energy of -13.95 with 1 hydrogen bond against the target protein.

## CONCLUSION

Five different derivatives of were synthesized from chalcones and thiobenzamide (thiazine) and benzamide (oxazine). The synthesized compounds were checked for their anti-fungal activity by molecular docking studies against cytochrome p 450 14 alpha demethylase by using Argus lab. The best drug was selected, depended upon the binding energy and hydrogen bonds are formed.All the synthesised 1,3 thiazines and 1,3 oxazines derivatives were having considerable antifungal activity. From the above results it would be concluded that 1,3-thiazines possess more active antifungal acivity than 1,3-oxazines.

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**Source of support: Nil, Conflict of interest: None Declared**