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# Insilco Screening and Molecular Docking to Identify a Novel Inhibitor for Aldose Reductase

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**Abstract:**

**Background and Objective:**
Diabetes mellitus is a prevailing problem in most of the countries. Aldose Reductase (ALR2) is a target enzyme involved in the treatment of diabetic complications. As the number of currently available drugs used in the treatment of diabetic complications is limited, discovery of new inhibitors for the enzyme Aldose Reductase that can potentially be optimised as drugs would be highly useful.

**Materials and Methods:**
In this study 22 different compounds with thiazole as base were considered. Molinspiration data were obtained and compounds satisfying Lipinski rule of 5 were selected for which target proteins have found using Pharmmapper. Docking of the ligand with protein is done using AutoDock 4.2.

**Results:**
2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole as our best ligand. Aldose Reductase (PDB ID:2DUX) was found to be the best target for this ligand.The best pose was obtained with least energy value from which it can be hypothesized that this compound can be considered as a potential inhibitor of ALR2

**Conclusion:**
A lower Binding energy value -9.22 Kcal/mol was obtained. A Hydrogen bond and a number of electrostatic interactions are found to be present between ligand and protein. Hence this new compound can act as a successful inhibitor for Aldol Reductase.

**Key Words:**2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole, Aldose Reductase, AutoDock, Frog, Molinspiration, Pharmmapper

## INTRODUCTION:

Diabetes mellitus is one of the most common diseases prevailing all over the world. As of 2011 about 366 million people were diagnosed with diabetes globally, and by 2030 this may rise to 552 million [1]. Aldose Reductase is an enzyme involved in the polyol pathway which reduces excess D-glucose into D-sorbitol. During diabetic conditions a significant flux of glucose through polyol pathway are induced to some of the tissues like lens, kidney, retina. The activation of this pathway is determined as a reason for the diabetic complications affecting pathogenic factors. So Aldose Reductase inhibitors offer the possibility of safely preventing progression of long-term diabetic complications. Hence there will be no risk of diabetes mellitus. [2[[3]. Compounds with thiazole as base are working well against pathogenesis of anti-Diabetes. In the current study we use the application of computational tools to identify an ideal molecule which can be developed as an anti-diabetic agent in future.

## MATERIALS AND METHODS:

**Preparationof Ligand Structure:**
Structures of 22 thiazole derivatives were derived from ChemDraw Ultra version 12.0 in SDF and PDB formats. Identified ligands were screened for the rule of Five (Lipinski Rule) using online server, Molinspiration and for ADMET using OSIRIS server. Molinspiration server helps in the calculation of drug likeliness score using sophisticated Bayesian Statistics Method.

**Identification of Potential Target:**
For identification of the target protein the thiazole derivative files converted to SDF format were submitted to Pharmmapper http://59.78.96.61/pharmmapper.

**Protein Molecule Preparation:**
2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl)thiazole was considered as best ligand. Conformers of 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole developed using FROG online server(http://bioserv.rpbs.univ-paris-diderot.fr/services/Frog2/). Crystal structure of human Aldose Reductase complexed with zopolrestat (PDB ID - 2DUX)(http://www.rcsb.org/) was downloaded from Protein Data Bank.Aldose Reductase is a NADPH-dependent oxidoreductase. It involved in catalyzing the reduction of glucose to sorbitol which is the first step in polyol pathway. Aldose Reductase has long been believed to be responsible for pathogenesis in diabetes. The new protein file, the reference ligand file and the thiazole derivatives were used for further docking analysis.

**Docking Analysis:**
Molecular Docking involves computational assessment of most favourable interacting regions between two different molecules[4].For docking study of 2-(1H-pyrazol-1-yl) thiazole derivative and 2DUX protein open source software AutoDock 4.2 is used. Conformers of (1H-pyrazol-1-yl) thiazole derivative made by FROG server(http://bioserv.rpbs.univ-paris-diderot.fr/services/Frog2/) and the most stable conformer is selected for docking. Binding energy was obtained using Auto Dock 4.2

**Results:**

In the current study, the potential target identification for 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole was done. Aldose Reductase was found as a target. Binding efficiency evaluation between Aldose Reductase and 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole was done by using computational approach. For 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole quality binding energies score was shown which illustrate that the ligand has significant affinity towards Aldose Reductase.

**Molinspiration Data Results:**

Molinspiration data results are shown in Table 1. Molinspiration data of 22 compounds are collected and in these 5 compounds are following the Lipinski Rule of 5. According to Lipinski's rule, an orally active drug should not have more than one violation of the following criteria: Hydrogen bond donors should not be more than 5, Hydrogen bond acceptors should not be more than 10 (all nitrogen or oxygen atoms), Molecular mass should be less than 500daltons and log P not greater than 5. [5][6][7]

a ) (Table 1)

**Pharmmapper results:**

Thiazole derivative files in SDF format were submitted to Pharmmapper (http://59.78.96.61/pharmmapper) for the Identification of the target protein. The Pharmmapper server uses the reverse pharmacophore models that are sorted by fit score in descending order [8] [9] .The results are obtained from the Pharmmapper server showed that high fit scores(>4) for three out of five compounds satisfying Lipinski Rule of 5 by Molinspiration. From that we selected 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole as our best ligand. Aldose Reductase (PDB ID:2DUX) was found to be the best target for this ligand. Pharmmapper results are shown in Table 2

b ) (Table 2)

**Docking analysis:**

Docking was performed between Aldose Reductase (PDB ID: 2DUX) and most stable conformer generated by Frog 2 server for 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole (ligand) using Auto Dock 4.2. Binding energy was found to be– 9.22 kcal/mol. The 3D image and 2D image of protein docking is given in Fig.1 and Fig. 2.

## DISCUSSIONS:

2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole is found to be the best ligand for the protein Aldose Reductase. Ligand followed Lipinski Rule of 5 and Pharmmapper results showed that this ligand has Aldose Reductase as its target. The best pose with least Binding Energy was obtained using AutoDock 4.2 which is -9.22 Kcal/mol. Binding energy value indicates that the new ligand can be a successful inhibitor for Aldose Reductase. One Hydrogen bond and many other electrostatic interactions were found between ligand and protein. Hence the new ligand will act as a successful inhibitor for Aldose Reductase.(Fig 3 and 4)

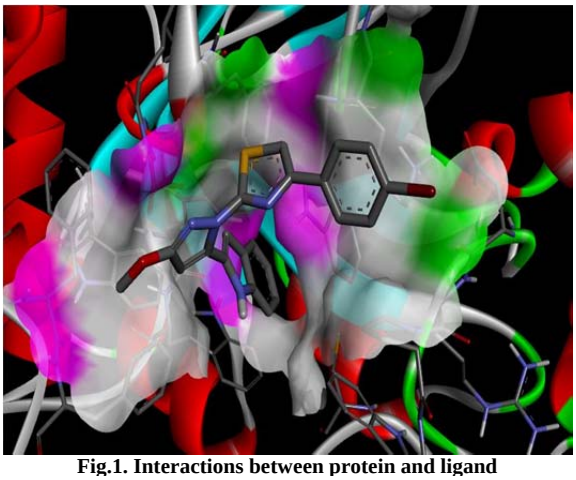

**Fig.1. Interactions between protein and ligand**

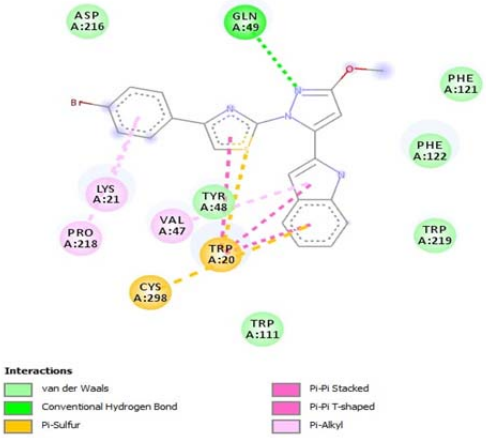


**Fig.2 Interaction of 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole with active site residue of Aldose Reductase**

**Fig.3 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole**

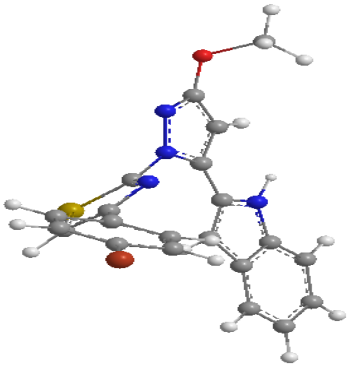

**Fig.4 Selected Conformer (3D) of 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole (Inhibitor for Aldose Reductase)**

**Table 1: Molinspiration data of (1H-pyrazol-1-yl) thiazole derivatives**

| SL NO | COMPOUND NAME | Mi LogP | Mol wt | nOHNH | nON |
|---|---|---|---|---|---|
| 1 | 1-(4-(4-bromophenyl)thiazol-2-yi)-5-(1H-indol-2yl)-1H-parazol-3-amine | 5.00 | 436.34 | 3 | 5 |
| 2 | 1-(4-(4-bromophenyl)thiazol-2-yi)-1H-pyrazol-3amine | 3.23 | 321.20 | 2 | 4 |
| 3 | 1-(4-(4-chlorophenyl)thiazol-2-yi)-5-(1H-indol-2yl)-1H-parazol-3-amine | 4.87 | 391.89 | 3 | 5 |
| 4 | 1-(4-(4-bromophenyl)thiazol-2-yl)-1H-pyrazole-3,5-diamine | 2.83 | 336.22 | 4 | 5 |
| 5 | 1-(4-(4-bromophenyl)thiazol-2-yl)-3-phenyl-1H-pyrazol-5-amine | 4.90 | 397.32 | 2 | 4 |
| 6 | 1-(4-(4-bromophenyl)thiazol-2-yl)-3-nitro-1H-pyrazol-5-amine | 3.31 | 366.20 | 2 | 7 |
| 7 | 5-amino-1-(4-(4-bromophenyl)thiazol-2-yl)-1H-pyrazole-3-carboxamide | 2.29 | 364.23 | 4 | 6 |
| 8 | 4-(2-(5-(1H-indol-2-yl)-3-phenyl-1H-pyrazol-1-yl)thiazol-4-yl)-3-bromobenzoic acid | 6.91 | 541.43 | 2 | 6 |
| 9 | 2-(5-(1H-indol-2-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole | 6.93 | 452.97 | 1 | 4 |
| 10 | 2-(5-(1H-indol-2-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-fluorophenyl)thiazole | 6.42 | 436.51 | 1 | 4 |
| 11 | 2-(5-(1H-indol-2-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-iodophenyl)thiazole | 7.34 | 544.42 | 1 | 4 |
| 12 | 4-(3-(chloromethyl)cyclohexyl)-2-(3-(3-(chloromethyl)cyclohexyl)-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 7.64 | 527.57 | 1 | 4 |
| 13 | 4-(3-(chloromethyl)cyclohexyl)-2-(3-cyclohexyl-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 7.40 | 479.09 | 1 | 4 |
| 14 | 4-cyclohexyl-2-(3-cyclohexyl-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 7.17 | 430.62 | 1 | 4 |
| 15 | 4-(5-chlorocyclopenta-1,3-dien-1-yl)-2-(3-(3-(cyclopenta-1,3-dien-1-yl)cyclohexyl)-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 7.22 | 511.09 | 1 | 4 |
| 16 | 4-(5-chlorocyclopenta-1,3-dien-1-yl)-2-(3-(3-(5-chlorocyclopenta-1,3-dien-1-yl)cyclohexyl)-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 7.54 | 545.54 | 1 | 4 |
| 17 | 4-(cyclopenta-1,3-dien-1-yl)-2-(3-(3-(cyclopenta-1,3-dien-1-yl)cyclohexyl)-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 6.90 | 476.665 | 1 | 4 |
| 18 | 2-(5-(1H-indol-2-yl)-1H-pyrazol-1-yl)-4-(4-bromophenyl)thiazole | 5.39 | 421.32 | 1 | 4 |
| 19 | 4-(4-bromophenyl)-2-(5-phenyl-1H-pyrazol-1-yl)thiazole | 5.29 | 382.29 | 0 | 3 |
| 20 | 1-(4-(4-bromophenyl)thiazol-2-yl)-5-(1H-indol-2-yl)-1H-pyrazol-3-ol | 5.30 | 437.32 | 2 | 5 |
| 21 | 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl)thiazole | 5.57 | 451.35 | 1 | 5 |
| 22 | 4-(4-bromophenyl)-2-(3-chloro-5-(1H-indol-2-yl)-1H-pyrazol-1-yl)thiazole | 5.44 | 406.9 | 1 | 5 |

**Table 2**: **Pharmmapper Results for 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole**

| COMPOUND NAME | TARGET | FITSCORE | FUNCTION | DISEASE | PDB ID |
|---|---|---|---|---|---|
| 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole | Cellular retinoic acid-binding protein 2 | 4.353 | Involved in retinoid binding | NONE | 1CBS |
| | Aldose Reductase | 4.116 | Catalyzes the NADPH-dependent reduction of a wide variety of carbonyl compounds to their corresponding alcohols have broad range of catalytic efficiencies. | In the cells of many tissues, the diabetes and galactosemia, increased the AR activity leads to high levels of sorbitol and galactitol, respectively,. Accumulation of sugar alcohols has been shown to cause osmotic cataracts in the lens. AR is also plays a key role in diabetic complications of three target tissues, such as nerve, kidney and retina. | 2DUX |
| | Heat shock protein HSP 90-alpha | 4.079 | Molecular chaperone. Has ATPase activity (By similarity). | NONE | 1UYH |
| | Molecular chaperone. Has ATPase activity (By similarity). | 4.055 | Involved in phosphatidylcholine transmembrane transporter activity | NONE | 1LN3 |
| | Estrogen receptor beta | 4.026 | Nuclear hormone receptor. Binds estrogens with an affinity similar to that of ESR1, and activates expression of reporter genes containing estrogen response elements (ERE) in an estrogen-dependent manner. Isoform beta-cx lacks ligand binding ability | NONE | INDE |
| | Hepatocyte growth factor receptor | 4.015 | Involved in hepatocyte growth factor activity | NONE | 3F82 |

## CONCLUSION:

The aim of present study was to identify an effective and novel drug for Anti-Diabetes. 22 compounds of thiazole were selected for studies. Their properties were calculated using online tools, MOLINSPIRATION and PHARMMAPPER. Based on these analyses between Aldose Reductase (PDB ID: 2DUX) and 2-(5-(1H-indol-2-yl)-3-methoxy-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole (ligand) were found to be suitable for docking analysis. Docking studies were performed using AUTO DOCK 4.2. From the Auto dock studies the best pose was obtained with least energy value for this compound. A lower Binding energy value -9.22Kcal/mol was obtained. Hence this novel compound can act as a successful inhibitor for Aldose Reductase.

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