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Virtual Screening and Design of Some Rhodanine Derivatives as Ppar γ Agonists for Anticancer Activity

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ABSTRACT

PPAR γ (Peroxisome proliferator Activated Receptors gamma) has numerous physiological responses in body upon its activation through different agonists which can be fruitful for treatment of different pathological conditions such as diabetes mellitus, chronic complications of diabetes, cancer, cardiovascular diseases, inflammatory processes etc. The current study focuses mainly on the role of PPAR γ for cancer therapy. Molecular docking is employed as a useful tool for designing suitable agonists which can be the possible pharmacophores for PPAR γ activation. Some rhodanine derivatives are designed using Structural Activity Relationship Studies with molecular docking using V Life MDS Software package version 4.2.

INTRODUCTION

PPAR-gamma is an important molecule for adipocyte differentiation and is over-expressed in adipose tissue. In addition to adipose tissue, PPAR-gamma has also been detected in a wide variety of cancer cells. In cancer cells, PPAR-gamma activation by its high-affinity ligands can inhibit cell proliferation and differentiation. Thus PPAR-gamma is involved not only in lipid metabolism but also in cellular proliferation of cancer cells. Therefore, it is suggested that PPAR-gamma is a possible molecular target for Thiazolidinediones and Rhodanines in cancer treatment. Although a lot of evidence has established that PPAR-gamma activation induces growth arrest in cancer cells, the molecular mechanism of the growth inhibition by PPAR-gamma ligands is not well understood. Some researchers have recently demonstrated that the cyclin-dependent kinase inhibitor may be a crucial molecule in cell growth inhibition by PPAR gamma ligands in human cancer cells. In current research work, rhodanine derivatives are designed using SAR and molecular docking as possible agents for cancer treatment[1,2,3].

Structural activity Relationship of Thiazolidinediones

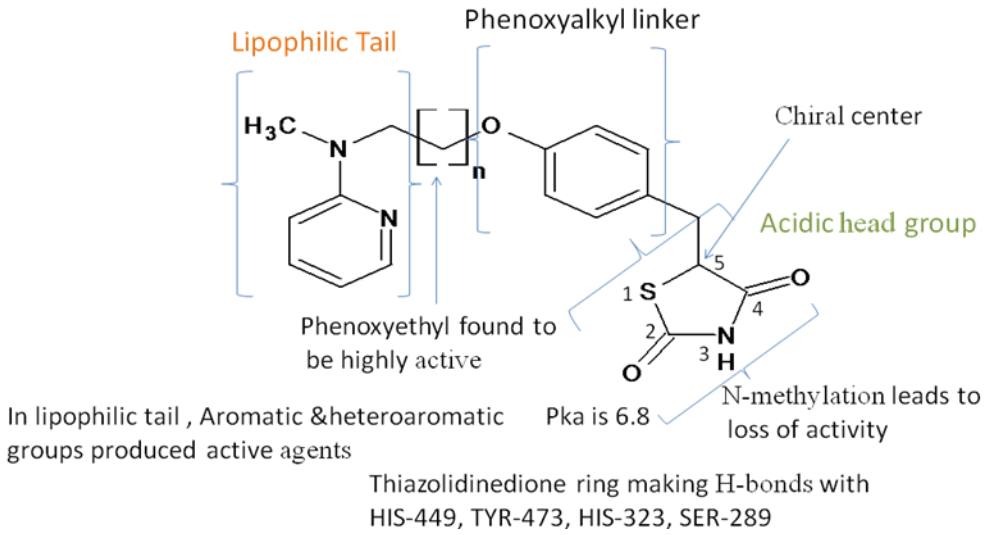


Fig. 1: Structure showing SAR of TZDs

1. Thiazolidinedione can be viewed as being composed of an acidic head group connected to a lipophilic tail by a phenoxyalkyl linker [5].

2. pKa of TZD IS 6.8 partially ionized at physiological pH [5].

3. Removal of acidic function by N-methylation leads to loss of activity. Other acidic heterocyclic groups like oxazolidinediones and particularly α-substituted carboxylic acid can replace thiazolidinedione [5].

4. Substituted carboxylic acids are often highly potent and may not be selective PPARγ agonist [5].

5. Though the majority of TZD-containing glitazones possess a methylene group bridged to the TZD and a phenyl group, it has been shown that compounds with its bioisostere rhodanine ring has also been shown to retain activity to considerable levels [6].

6. Compounds with TZD as an acidic head group shows better activity when compared to its bioisoster rhodanine, indicates that acidic head should be more polar [7, 8.]

7. There is a chiral centre at the 5th position of TZD ring, but this is not configurationally stable under physiological pH. PPAR gamma activity resides in S-enantiomer [5].

8. Compounds with double bond at 5th position of the TZD yields active compounds [6, 7, 8].

9. A phenoxyethyl group (n=2) as the central Phenoxyalkyl linker commonly yields highly active compounds in SAR studies of TZDs [5].

10. Chain length n=1 or inclusion of the phenoxyethyl group into a heterocyclic ring also leads to active compounds [5].

11. The two-carbon acyl linker in the form of amide (-CH_2CONH) which is the common structural moiety in all the compounds appears to be a requirement for the activity [7, 8].

12. An oxygen atom connected to the aromatic ring (hydrophobic trunk) in the form of ether is essential for the activity [8].

13. The incorporation of thioethyloxy linkage with two carbon spacers connecting to triazole derivative and oxadiazole derivative displayed good activities [9].

14. In the lipophilic tail, incorporation of wide variety of mostly aromatic and heteroaromatic groups has produced active agents.

15. Decreasing ring size from six-membered benzene to furan five membered rings found to reduce the activity[5].

16. Increased hydrophobicity and orientation of the substituents of the pyridine moiety shows a more potent activity[5].

MATERIALS AND METHODS

Based on the SAR studies and intensive literature survey, ester derivatives of Rhodanine were designed as anticancer agents. The following are important SAR points[9].

- Thiazolidinedione nucleus is critical for anticancer activity
- Oxygen at second position of thiazolidindione is replaced by isoelectric Sulphur atom show equal activity[5]
- Sulphur atom at the 2nd position of rhodanine nucleus is important for Hydrogen bond formation with the target cells[8,10]
- 5-benzylidene ring at 5th position of is important for anticancer activity probably because of delocalization of electrons[8,10]
- Double bond at 5th position is important for biological activities[8,10]
- Benzyloxy group is present at the second position of the benzylidene ring i.e. an ether group being replaced by ester group in current design[8,10].

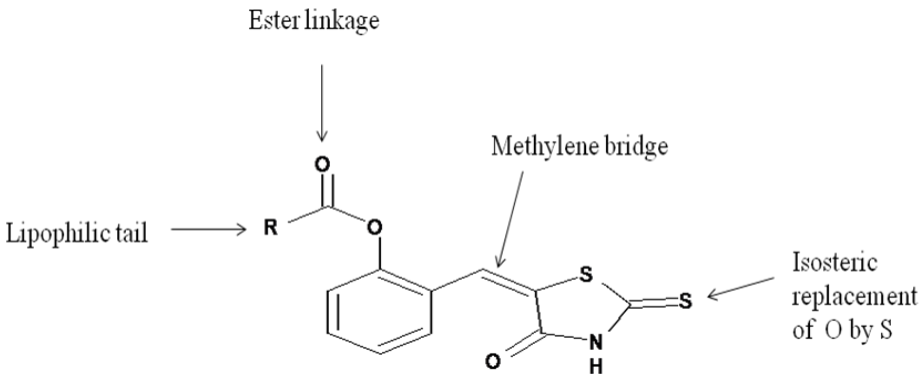


Fig. 2: Proposed structure of Rhodanine derivatives

Hardware and Software

All Docking studies and conformational analysis were performed using the Molecular Design Suite (VLife MDS software package, version 4.2; from VLife Sciences, Pune, India).

Structure Conformation Generation

Structures of compounds were sketched using the 2D structure draw application Vlife2Ddraw and converted to 3D structures. All the structures were minimized and optimized with the Merck Molecular Force Field (MMFF) method taking the root mean square gradient (RMSD) and the iteration limit to 10,000. Conformers for each structure were generated using Monte Carlo by applying MMFF force field method and the least energy conformer was selected for further study**.**

Preparation of protein

The PDB structure 5YCP (www.rcsb.org) was downloaded and energy minimization of the protein complex. All the bound water molecules, ligands and cofactors were removed (pre-process) from the proteins which were taken in pdb format. Incomplete residues were completed and missing residues were added in the protein. The complex obtained was minimized using Merck molecular force field. The minimization was terminated after either the completion of 5,000 steps or after the energy gradient converged below 0.05 kcal/mol.

Preparation of ligands

Structures of the ligands were sketched using built Vlife2Ddraw taken in mol format. Converts it into 3D structure and performs a geometry minimization of the ligands. Merck Molecular Force Fields (MMFF) with default settings were used for the ligand minimization.

Docking methodology

Docking study was performed on VlifeMDS version 4.2 on Lenovo computer, i3 processor with XP operating system. The GRIP-based ligand docking was performed using specific cavity of the receptor 5YCP. The minimum dock score of the complex were measured by PLP scoring function.

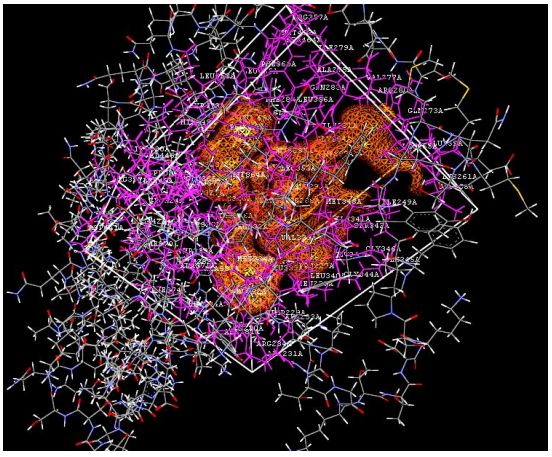
RESULTS AND DISCUSSION

The compounds evaluated *in silico* (docking) to distinguish their hypothetical binding mode using the X-ray crystal structure of 5YCP protein used. To pre-assess the anti-cancer behaviour of designed ligands on structural basis, docking studies were carried out and scoring functions, their binding affinities and the orientation of designed compounds having PPAR agonistic property. The protein-ligand complex was constructed based on the X-ray

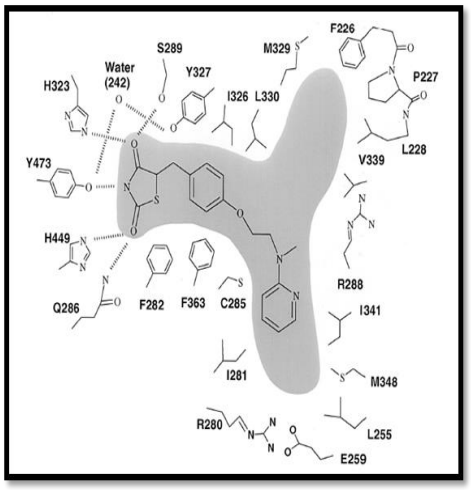
crystallized structure of receptor. The designed compounds built using Vlife2Ddraw converted into 3D structures and energy minimized by using Merck Molecular Force Field (MMFF). Conformers were generated by using Monte Carlo conformational search ring flip method[9].

GRIP implemented in the Molecular design suite (MDS) has been successfully employed to dock inhibitors into the 'Y shape' cavity of the PPAR gamma 5YCP and to well correlate the obtained binding score with anticancer activities of compounds. In this comparative docking experiments of designed compounds with known Rosiglitazone (as a standard) with dock score calculated -8.8. Obtained results were evaluated in terms of docking score in to the Y shape cavity of 5YCP.

The software provides facility of the batch docking of the optimized ligand molecules with the simulated receptor. All ligands are selectively docked against Y shaped cavity of 5YCP. Each molecules takes time for the completion of docking. Molecules that show minimum dock score shows more affinity for PPAR gamma agonism and Dock score shown in Table 1[9]

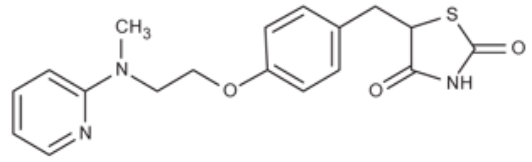
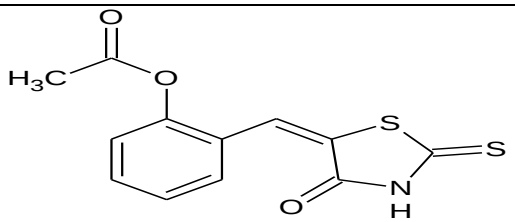
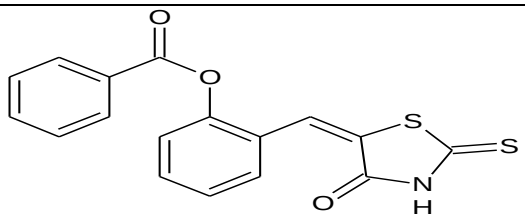
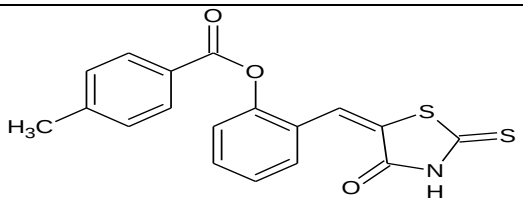
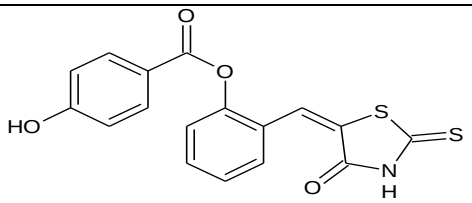
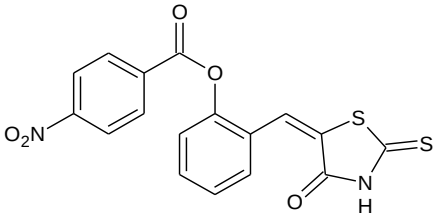


(a) Rosiglitazone docked in Y shape cavity of PPAR literature



(b) Y-shaped cavity as per Fig. 3

Table. 1: Standard rosiglitazone and Newly designed Molecules

No.	Standard Rosiglitazone	Dock Score KCal/mole
1		-44.072427
No.	Newly designed molecules	Dock Score KCal/mole
1		-40.791003
2		-52.518931
3		-40.021477
4		-60.095597
5		-48.459820

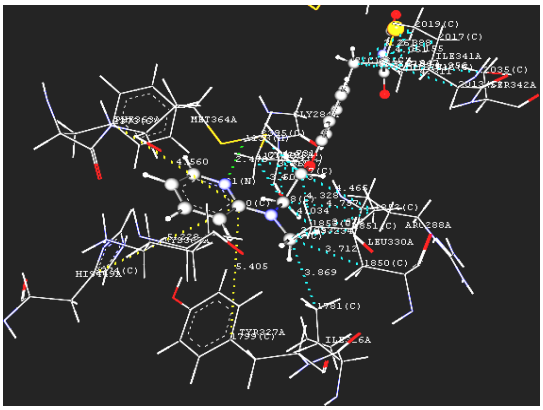


Fig. 4: Rosiglitazone showing H bonding and hydrophobic interactions

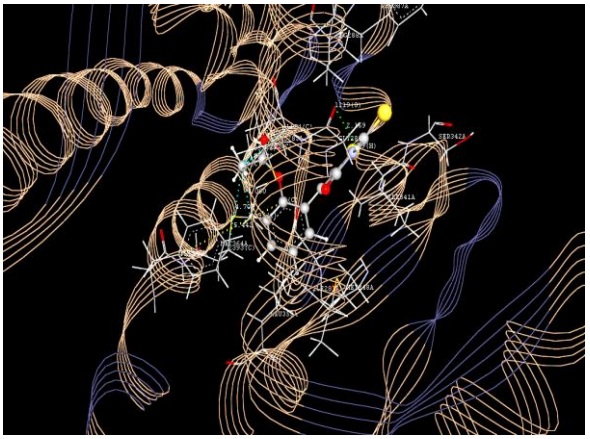


Fig. 5: Compound 1 showing H bonding pi stacking and hydrophobic interactions

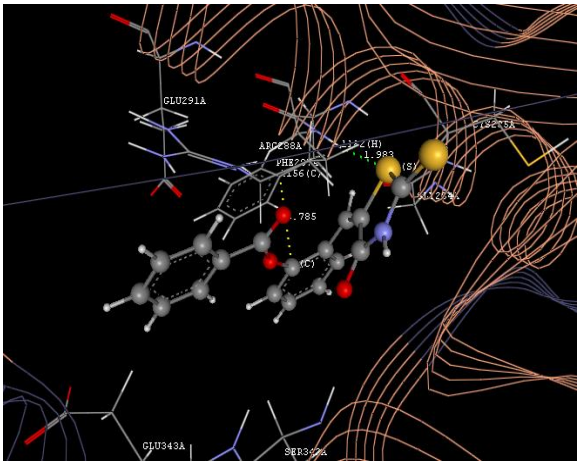


Fig. 6: Compound 2 showing H bonding and hydrophobic interactions

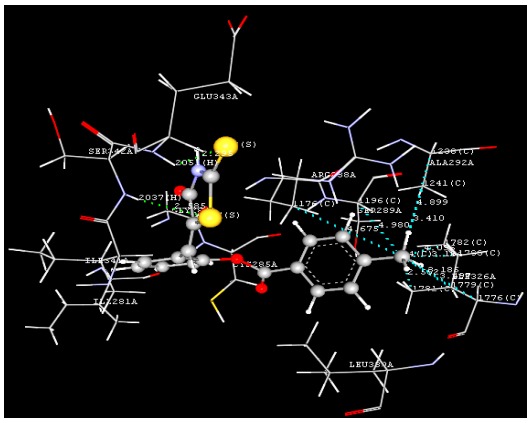


Fig. 7: Compound 3 showing H bonding and hydrophobic interactions

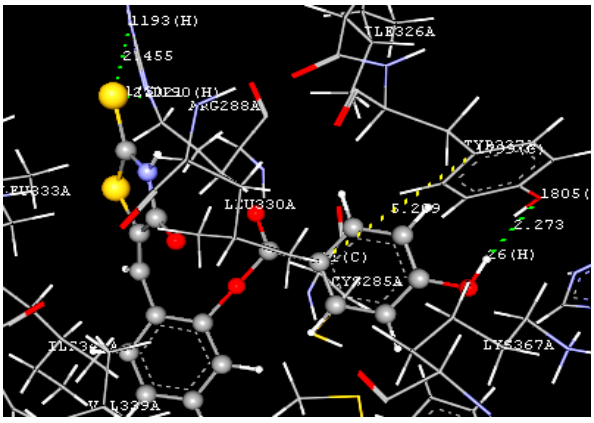


Fig. 8: Compound 4 showing H bonding and hydrophobic interactions

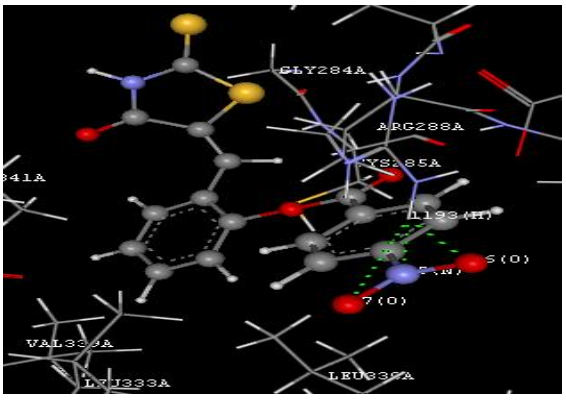


Fig. 9: Compound 5 showing H bonding

CONCLUSION

It is clear after observing the dock score table as shown above, that newly designed rhodanine derivatives are having significant and comparable dock scores when compared to the standard Rosiglitazone, which signifies that the designed molecules are more suitably fitting to the Y-shaped cavity of PPAR γ receptor. It could show PPARγ agonistic activity nearby the standard Rosiglitazone.

Based on the SAR and molecular docking data above mentioned rhodanine derivatives can be synthesized as a possible lead for PPAR γ agonism.

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