In silico design of potent agonists for human PPAR γ

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KEY POINTS

- Peroxisome proliferator-activated receptor (PPAR γ) acts as a key regulator on adipocyte differentiation and glucose homeostasis.
- PPAR γ has been down regulated in type 2 diabetes.
- *In silico* screening was carried out to find potent agonists for human PPARγ.
- Structural analog search and interaction studies were performed to design an "ideal drug" by using the existing activators which have some adverse effects like fluid retention and worsen congestive heart failure.

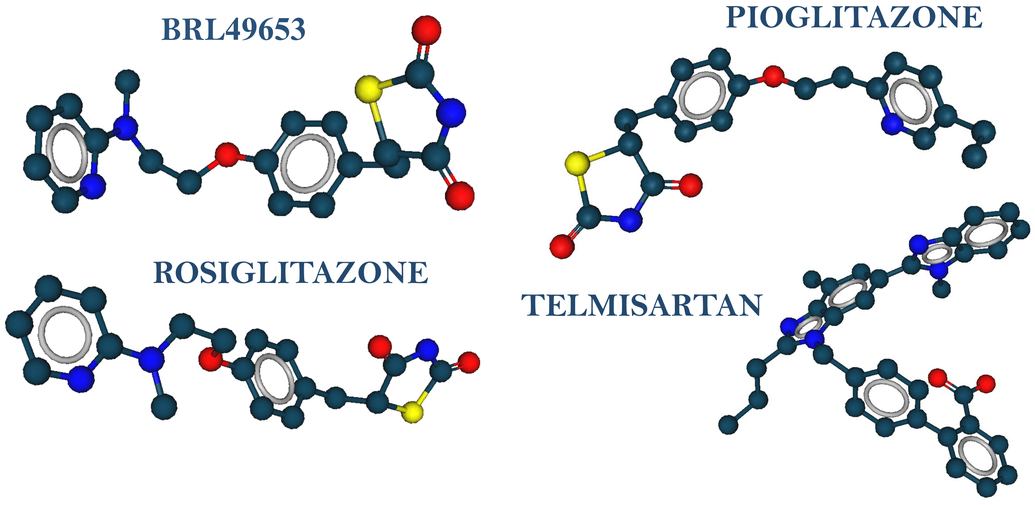


Figure 1:The existing activators of PPAR γ.

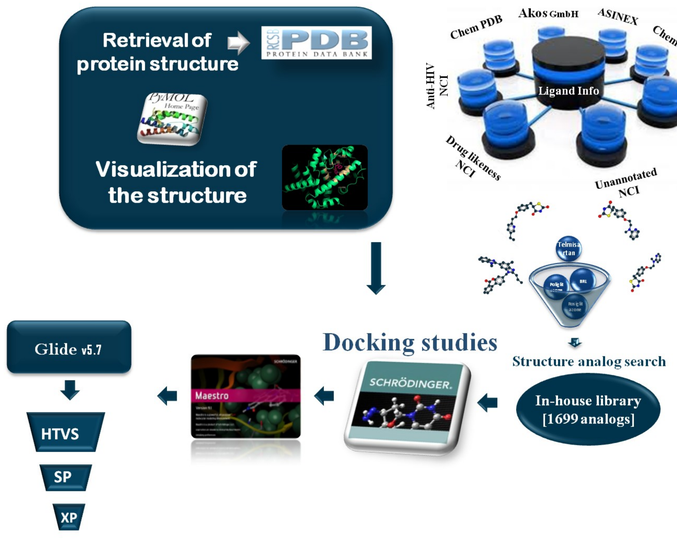
Ligand binding sites

Ile 281, Phe 282, Gly 284, Cys 285, Ser 289, His 323, Ile 326, Tyr 327, Leu 330, Ile 341, Met 348, Met 364, His 449, Leu 453, Leu 469, Tyr 473, HOH 18, HOH 36, HOH 58 and HOH 92

- BRL 49653

Figure 2: The co-crystal structure of human PPAR γ [1ZGY] with BRL49653.

WORKFLOW



RESULTS AND DISCUSSION

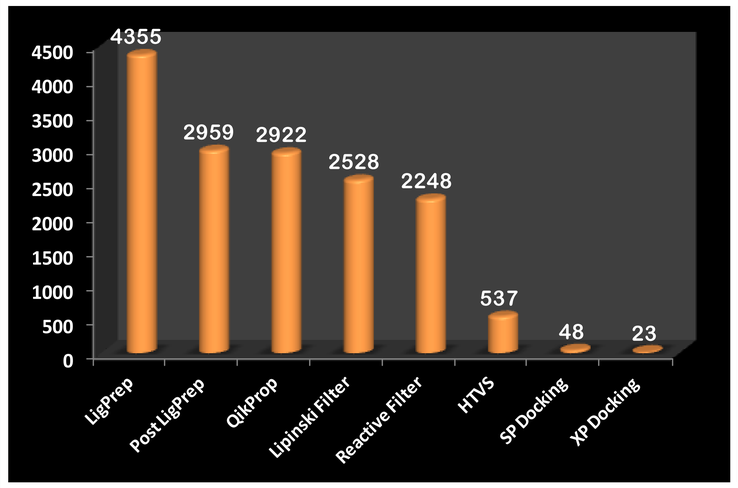
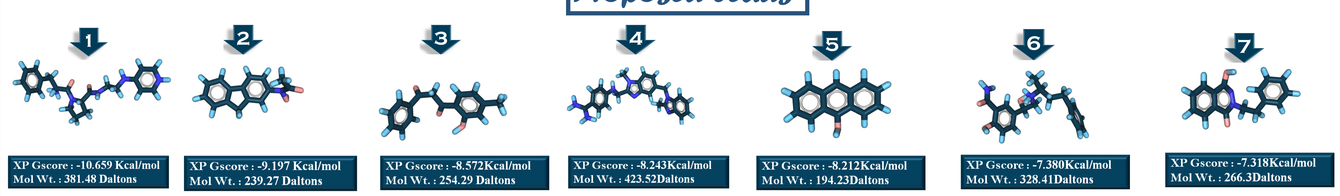


Figure 3: Graphical representation of filtered compounds.

Figure 4: Comparative docking scores of leads and existing inhibitor.

Proposed leads



XP Gscore : -10.659 Kcal/mol
Mol Wt. : 381.48 Daltons

XP Gscore : -9.197 Kcal/mol
Mol Wt. : 239.27 Daltons

XP Gscore : -8.572Kcal/mol
Mol Wt. : 254.29 Daltons

XP Gscore : -8.243Kcal/mol
Mol Wt. : 423.52Daltons

XP Gscore : -8.212Kcal/mol
Mol Wt. : 194.23Daltons

XP Gscore : -7.380Kcal/mol
Mol Wt. : 328.41Daltons

XP Gscore : -7.318Kcal/mol
Mol Wt. : 266.3Daltons

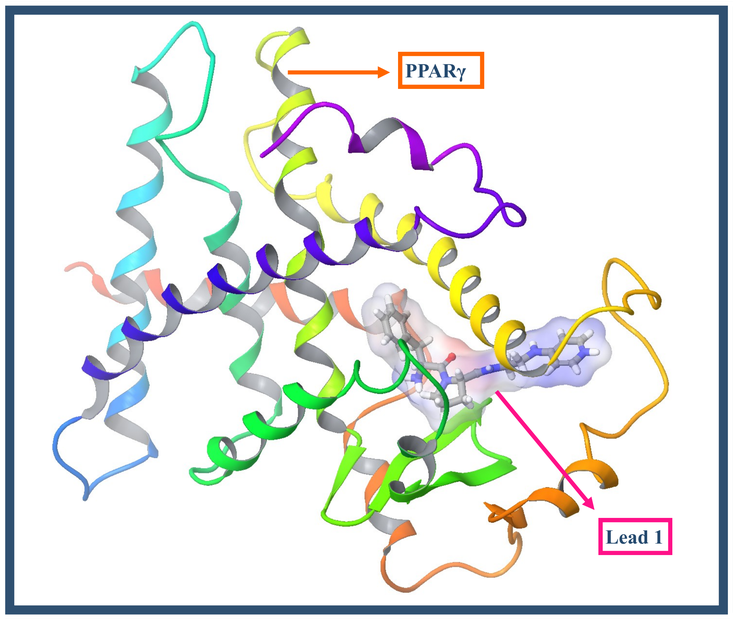
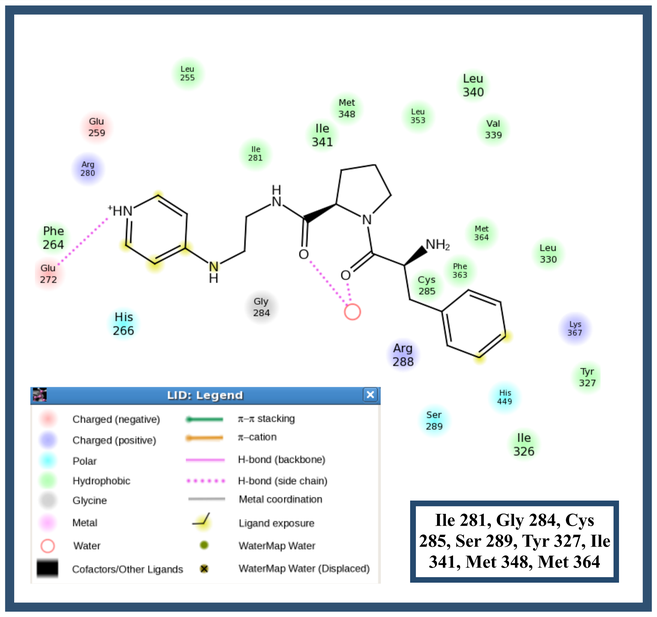


Figure 5: The docking complex of lead 1 and human PPAR γ.



Ile 281, Gly 284, Cys 285, Ser 289, Tyr 327, Ile 341, Met 348, Met 364

Figure 6: The residues involved in van der Waal and H-bond interactions with lead 1– PPARγ docking complex.

CONCLUSION

- Binding orientations, binding affinity and binding interactions of the existing activators were compared with the obtained thirteen leads.
- Seven leads were proposed having good docking score, interactions and pharmacological properties than existing activators.
- Hence, these seven leads can be suggested as novel therapeutics in the treatment of type2 diabetes if tested in animal models.

ACKNOWLEDGEMENT

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