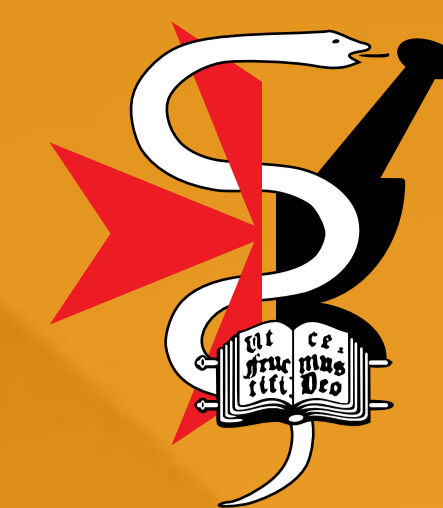


Drug Design of *de novo* designed molecules at the Peroxisome Proliferator Activated Receptor

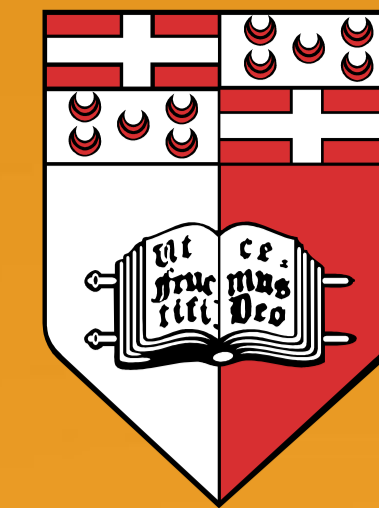
Stephanie Portelli, Claire Shoemake, Lilian M. Azzopardi

Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

email: spor0011@um.edu.mt



Department of Pharmacy



University of Malta

INTRODUCTION

Following rosiglitazone withdrawal¹, newer therapies aiming at the Peroxisome Proliferator Activated Receptor γ (PPAR γ) as treatment for type 2 diabetes acting mainly via partial agonism are being studied. Such partial agonists include selective PPAR γ modulators such as S-26948.²

AIM

To obtain and optimise molecules having a high affinity to PPAR γ , and which are also Lipinski Rule³ compliant.

METHOD

Phase 1

- PDB entries 1FM6, 1FM9 and 3FUR were edited via the initial removal of a dimer, removal of crystallised water molecules at a distance $> 5 \text{ \AA}$, and extraction of ligand.
- S-26948² was constructed *de novo* and docked into 1FM6, 1FM9 and 3FUR using Sybyl-X[®] v1.1,⁴ permitting identification of its 20 highest affinity conformers for each PPAR γ ligand binding pocket (LBP) conformation.
- Binding energies for these conformers were calculated using Sybyl-X[®] v1.1⁴ and ligand binding affinities (pKd) were calculated using SCORE[®] v1.3.⁵
- The best conformers in each case were chosen on the basis of the highest pKd and lowest binding energy.

Phase 2

- The best conformers were edited to create 3 seed structures having the fundamental moieties for partial agonism, and assigned growing sites permitting molecular growth within PPAR γ (Fig.1).
- LBP mapping and analysis for each PPAR γ LBP conformation was carried out using the 'pocket' algorithm of LigBuilder[®] v1.2,⁶ and the three seeds were consequently introduced into the LBPs. Growth of the seeds was enabled, within user-driven parameters in accordance with Lipinski's Rules.³
- A different LBP map was required for the seeds of Conformer number 17, since it exhibited an alternative orientation to that observed by rosiglitazone (Fig.2).

RESULTS

Two conformers were chosen for both PDB 1FM6 and PDB 1FM9, and only one conformer was chosen for PDB 3FUR.

84.3% out of the 1817 novel molecules generated are Lipinski Rule compliant. The pKd of all the molecules ranged from 5.01 to 9.99, while molecular weight ranged from 266 to 600.

The highest pKd recorded for a Lipinski Rule³ compliant molecule was 9.40, while that for a non-Lipinski rule compliant molecule was 9.99.

Moieties which increased pKd were: aliphatic side chains within the acidic region terminating in H-bond acceptors, and terminal cyclic moieties capable of H-bond interactions within the linker and hydrophobic regions.

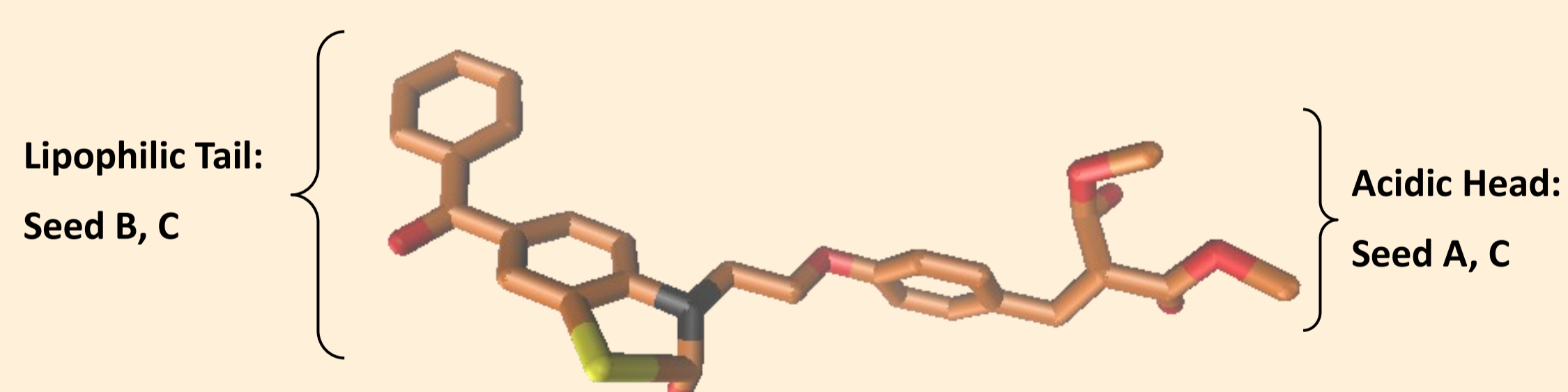


Figure 1: A 3-dimensional representation of S-26948 as rendered in VMD[®] v1.9,⁷ where Carbon atoms are depicted in orange, Oxygen in red, Sulphur in yellow and Nitrogen in black. Moieties chosen for the preparation of seeds are also shown.

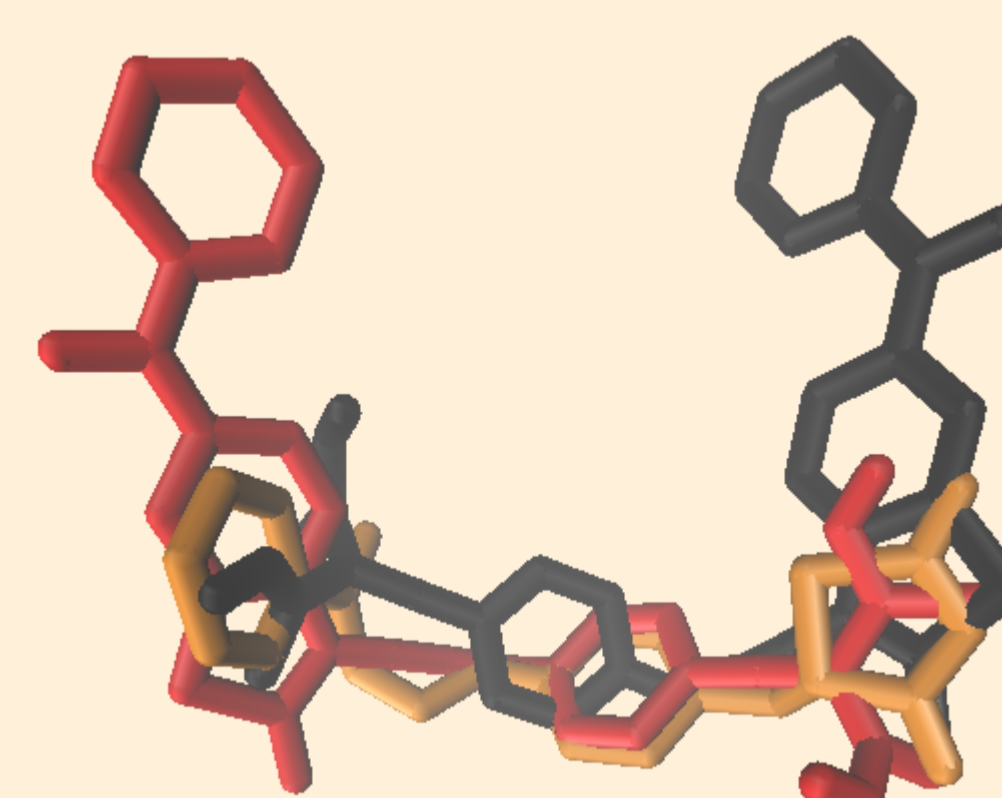


Figure 2: A 3-dimensional representation of S-26948 conformers 9 (red), 17 (black) and Rosiglitazone (orange) as rendered in VMD[®] v1.9,⁷ where the alternative conformation of conformer number 17 to that of Rosiglitazone within the PPAR γ LBP of 1FM6 is evident.

CONCLUSION

The identification of an alternative high affinity orientation, that molecules structurally similar to S-26948 could potentially adopt within the PPAR γ LBP warrants further investigation from a receptor modality point of view. This may, in turn, alter conventional rational drug design approaches at this locus.

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