INTRODUCTION

This is a rational drug design study aiming to identify lead molecules capable of successfully interacting with more than one Peroxisome Proliferator Activated Receptor (PPAR) subtype in order to simultaneously manage more than one PPAR mediated condition. The PPARs are nuclear receptors involved in the regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, protein), and tumorigenesis of higher organisms.

This study stems from the loss of the glitazone hypoglycaemics (full PPAR agonists) from the market due to their unacceptable side effect profile, and from the realisation that full PPAR agonism could not be separated from this adverse effect spectrum. It uses the PPARγ partial agonist angiotensin receptor blocker telmisartan (pdb ID 3VN2) and an experimental fibrate PPARα agonist GW590735 (pdb ID 2P54) to probe these respective PPAR Ligand Binding Pockets (PPAR-LBP).

METHOD

The small molecules telmisartan and GW590735 were extracted from the LBP of their cognate receptors such that in silico binding affinity (pKi) could be quantified in XScore®46. These values were established as baselines for comparison for each receptor subtype.

The extracted small molecules telmisartan and GW590735 were docked into their non-cognate counterparts, conformational analysis (Graph 1) performed in each case and affinity of the optimal conformation for their non-cognate LBP quantified in XScore®46.

These optimal conformations were used in parallel processes:

1. The first was a virtual screening exercise, using the molecular database Vcite®2, in which they were used as query molecules for the identification of spatially and electronically analogous structures capable of forging similar or enhanced interactions within the non-cognate LPBs. This process yielded molecular cohorts for each query molecule ranked in order of similarity to the query.

RESULTS

The Virtual Screening exercise yielded 1000 molecules for each submitted query (n=2). The de novo generated molecular cohorts (n=5) consisted of 200 molecules each. Subsequent to filtering the generated cohorts from both approaches for Lipinski Rule compliance, molecules were ranked according to binding affinity (pKi) and logP values.

- 10 molecules from each molecular cohort (n=2) were chosen from the structures generated from the virtual screening exercise
- 5 molecules from each cohort (n=5) were chosen from the de novo generated structures

PosaView® was used to generate 2D topology maps depicting the interactions of the template structures telmisartan and GW590735 in their cognate receptors and of the representative chosen molecules from both approaches as shown in figures 2, 3 and 4.

Figure 2 below shows the critical interactions forged by telmisartan and GW590735 with their cognate receptors

CONCLUSION

A comparison of the physicochemical parameters and critical interactions of the molecules identified in this study to those of the lead molecules towards the PPARα and PPARγ LPBs indicates that the ligand protein contacts that seem significant for dual agonism are:

- Hydrophobic contacts with Met364 in the PPARγ receptor and with Cys282 and Met364 in the PPARα receptor
- Hydrophilic contact with Tyr282 in the PPARγ receptor

Preliminary results consequently suggest that further optimisation of these molecules could have significant clinical impact, with dual PPARα/γ agonists having the potential of simultaneously managing type 2 diabetes mellitus and hypertriglyceridaemia. The added antiprerenal effect of the telmisartan scaffold increases the breadth of the potential effect of derivatives of this molecule to the management of the highly prevalent metabolic syndrome.

REFERENCES