Computational exploration of PPARα agonists: integrating ligand- and structure-based modelling for targeted drug discovery

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Introduction

Type 2 diabetes mellitus (T2DM) poses a growing public health challenge, affecting an expanding portion of the global population. Characterized by hyperglycemia due to insulin resistance and/or inadequate insulin production, T2DM can lead to severe complications like nephropathy, retinopathy, and cardiovascular disease. Peroxisome proliferator-activated receptor alpha (PPARα) agonists have emerged as promising **adjunctive treatments**, as they regulate lipid and glucose metabolism by reducing triglycerides, increasing HDL cholesterol, and improving glycemic control. Recent studies suggest that combining PPARα agonists with traditional antidiabetic drugs, such as biguanides or gliptins, may enhance treatment efficacy, especially for patients with concurrent dyslipidemia [1,2]. **We have developed new ligand-based (Q)SAR models and employed existing ones in our platform, ProtoPRED*, combined with structure-based docking with our platform, DockTox**, in order to search for potential PPARα agonists with favorable pharmacokinetic and toxicological properties.**

* https://protopred.protoqsar.com/
** https://chemopredictionsuite.com/DockTox

Workflow and results

97,022 compounds

A dataset of natural compounds was extracted from different sources such as NuBBe (https://nubbe.iq.unesp.br/portal/nubbedb.html) and NPASS (https://bidd.group/NPASS/).

SAR model development

A SAR model has been constructed with a dataset of 2,620 EC_{50} values of PPARα from ChEMBL database (https://www.ebi.ac.uk/chembl/), following a similar approach than the one described in Serrano-Candelas *et a*l. [3], we identified the most representative substructures of the active compounds using SARpy tool [4]. Some of this substructures are represented in Fig. 1.

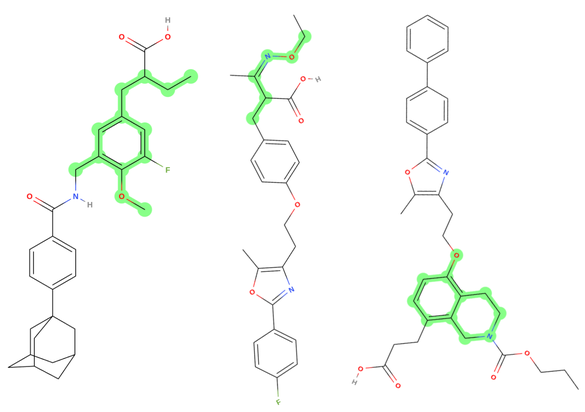

Figure 1. Three substructures (coloured in green) identified as relevant by the SAR analysis.

(Q)SAR

385 compounds selected as candidates presenting positive (Q)SAR predictions

QSAR model development

A QSAR has been developed from a dataset of 2,620 EC_{50} values of PPARα from the ChEMBL database, the obtained model with 20 descriptors presented optimal metrics (Table 1).

Table 1. 10-fold CV metric for the EC_{50} PPARα QSAR model.

	Acc.	Prec.	Sens.	Spec.	AUC
TS (1831 cpds)	0.89 ± 0.01	0.92 ± 0.01	0.92 ± 0.01	0.82 ± 0.02	0.95 ± 0.01
VS (789 cpds)	0.83 ± 0.02	0.88 ± 0.02	0.88 ± 0.01	0.73 ± 0.04	0.89 ± 0.02

TS: Train set; VS: Validation set; Acc: Accuracy; Prec: Precision; Sens: Sensitivity; Spec: Specificity; AUC: Area under the curve.

Docking

Top 5 compounds that presented optimal docking-based predictions

Docking results from DockTox

The 385 selected compounds from the previous step were then subjected to a docking procedure against PPARα binding pocket using online server DockTox. The compounds that presented the top 10 binding energy (Fig. 2) and an interaction fraction of more than 0.4 compared with the reference ligands of the tool (Fig. 3), were selected as best candidates.

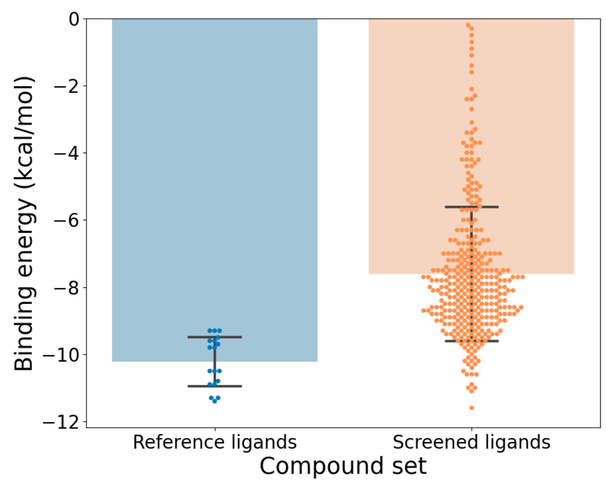

Figure 2. Binding energy distribution of the selected compounds from the (Q)SAR step compared with the reference ligands of PPARα.

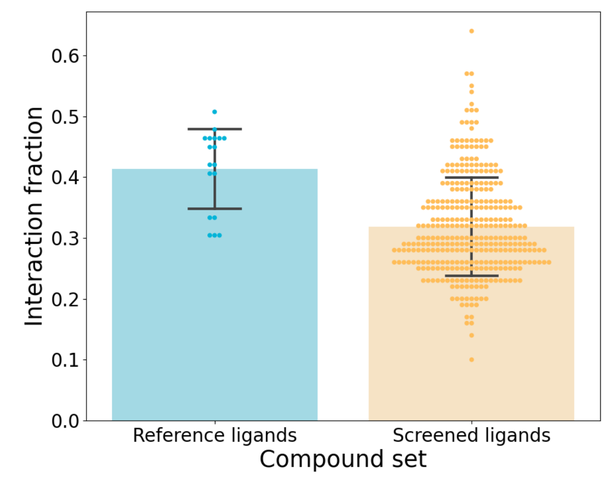

Figure 3. Interaction fraction distribution, which is the fraction of interactions of the studied ligands compared with reference interactions of the protein of the selected compounds from the (Q)SAR step.

ADMET results using ProtoPRED

ADMET

4 compounds presented optimal ADMET predictions

Among the best candidates from previous step, a final last computational study using ProtoPRED was employed for predicting some pharmacokinetic and toxicological parameters (ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicology), showcased in Table 2.

Table 2. ADMET property predictions for the best 5 selected compounds using ProtoADME and ProtoTOX modules from ProtoPRED.

		ID				
		m1	m2	m3	m4	m5
Property	Binding affinity	-11	-10.9	-10.6	-10.6	-10.4
	Interaction fraction	0.41	0.45	0.46	0.42	0.51
	Nº LIPINSKI violations	1/4	1/4	0/4	1/4	1/4
	Human Intestinal Absorption	+	+	+	+	+
	Half-life (h)	18	10	13	19	35
	Acute Oral Toxicity	-	-	-	+	-

Top 5 selected compounds (m1 to m5) presented optimal ADMET metrics except for m4 that was predicted to produce acute toxicity when administered orally. One of the best candidates, compound m1 is represented in Fig. 4.

Candidate compounds

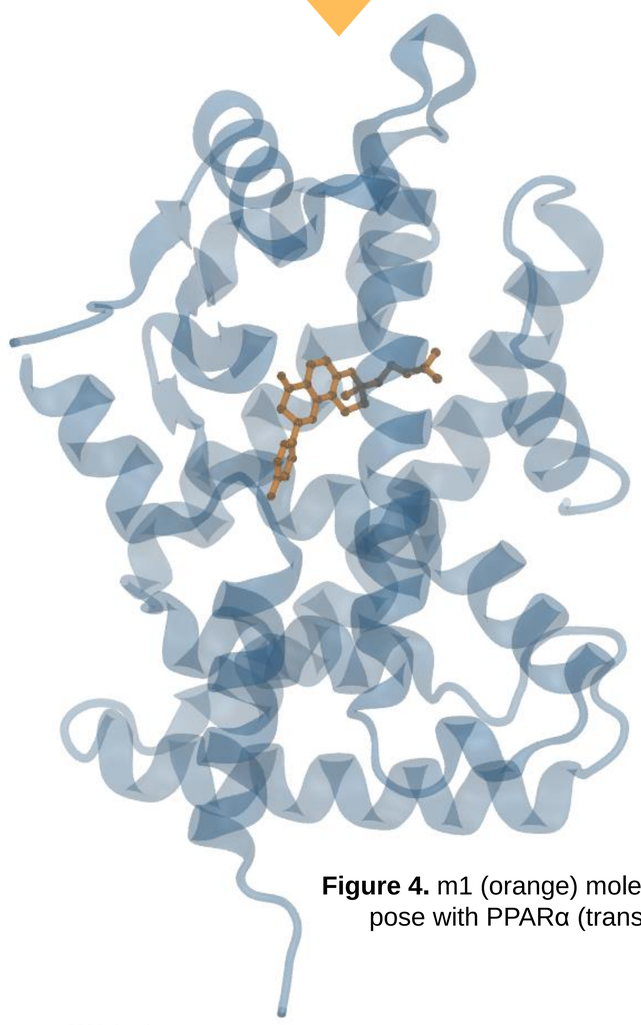

Figure 4. m1 (orange) molecule best binding pose with PPARα (transparent blue).

Conclusions

In conclusion, our study highlights the effectiveness of integrating ligand- and structure-based modelling, to identify and characterize potential PPARα agonists. By systematically screening large compound databases, we efficiently pinpointed candidates with binding affinities and interaction profiles comparable to established agonists. These findings underscore the value of combined computational methods in **accelerating the drug discovery process** and emphasize the potential of *in silico* approaches for identifying promising therapeutic compounds.

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References

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