Supplemental data

Ligand-receptor interactions in machine learning-assisted GCGR and GLP-1R drug discovery

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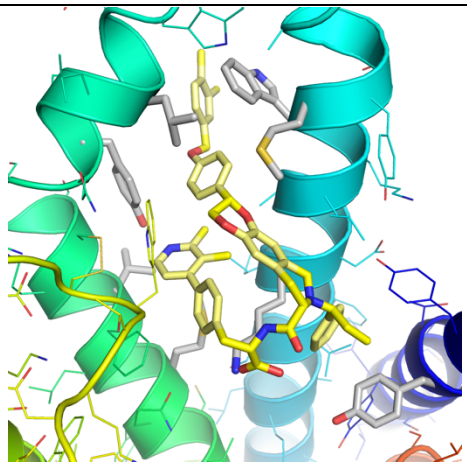
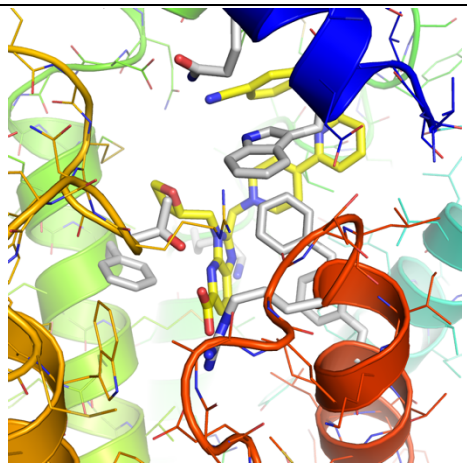
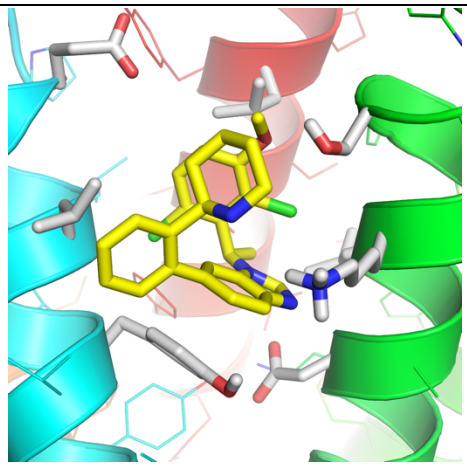
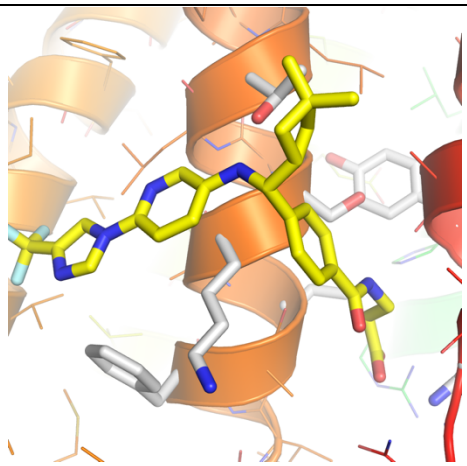
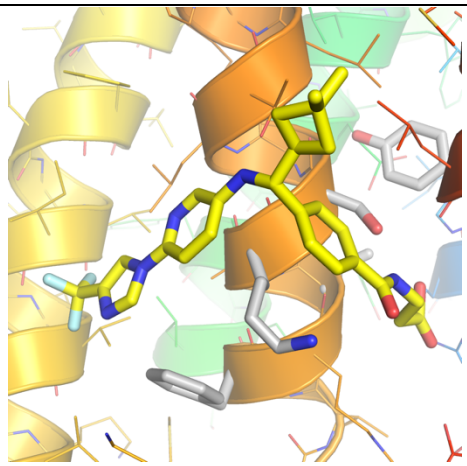
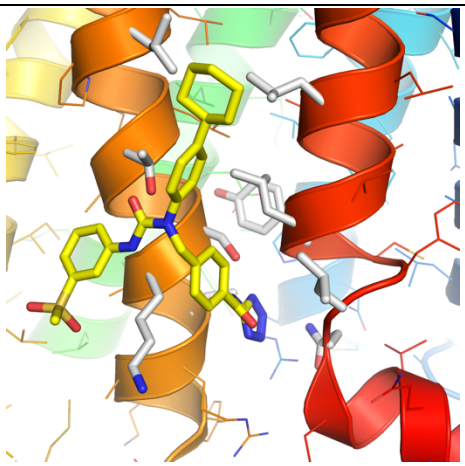
This file includes Table S1 and Figures S1-S7 and that corresponds to the main manuscript text.

Tables

Table S1. Flexible residues (grey) selected in binding sites 1-4 of GLP-1R and in the binding site 4 of GCGR with PDB ligands (yellow).

Receptor	Binding site	PDB id	Residues kept as flexible during molecular docking
GLP-1R	1	6ORV	
	2	7C2E	

3	6VCB	
4 (I)	6LN2	
4 (II)	5VEW	

GCGR	4	5XEZ	

Figures

Figure S1. Distribution of ChEMBL datasets – Daylight/Tanimoto coefficients vs. pEC50 (GLP-1R – left) and pIC50 (GCGR - right). GLP-1R dataset splits into two groups – one dissimilar to the site 1 ligands and another – similar to the site 1 ligands. The latter group demonstrates high pEC50. In the case of GCGR, ligands formed four clusters with decreasing number of members. Ligands similar to the binding site 4 ligand demonstrated rather high pIC50, though not the best possible.

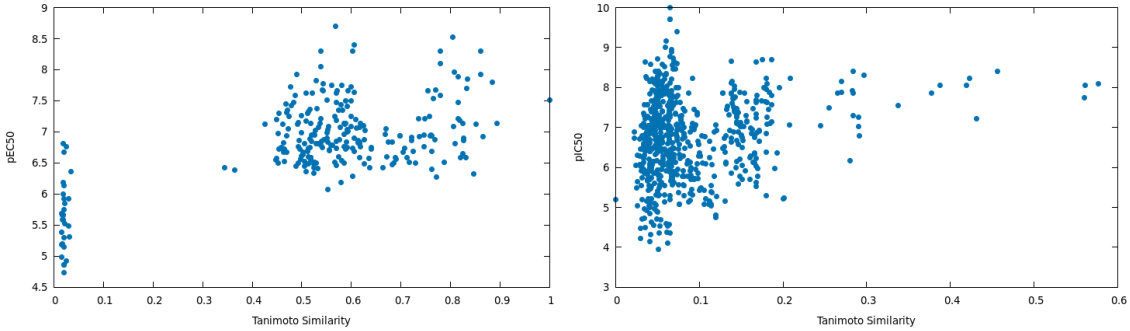


Figure S2. AlogP of the GLP-1R ligand set vs. Autodock VINA binding energy. Here, the binding site 1 from 6ORV was used in molecular docking. Autodock VINA scores (ligand binding energies) reflected the compound lipophilicity. Site 1 of GLP-1R demonstrated high affinity for lipophilic ligands.

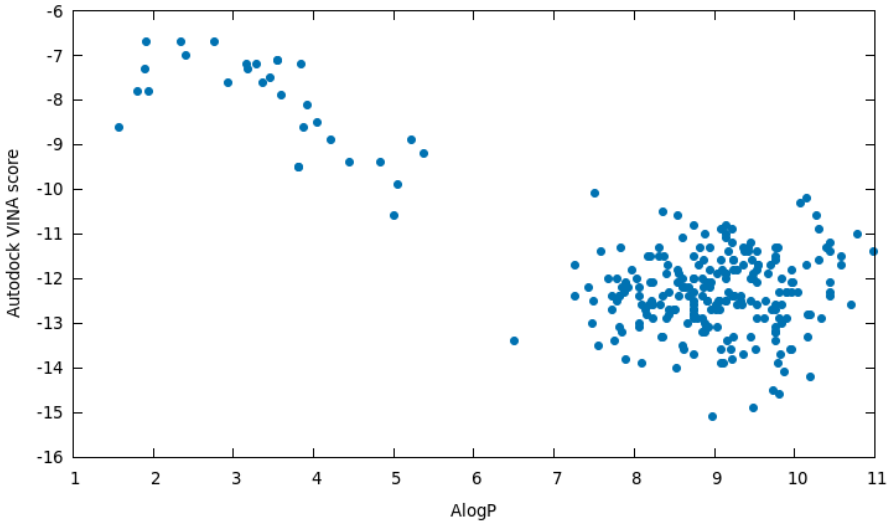


Figure S3. Results of docking of GLP-1R actives to all possible binding sites. Compounds similar to the binding site 1 ligand were scored better by Autodock VINA than the 'other' compounds in all cases. Results for docking to the binding site 1 are presented in the main manuscript. Inverse correlation coefficients were in the range of 0.4-0.6.

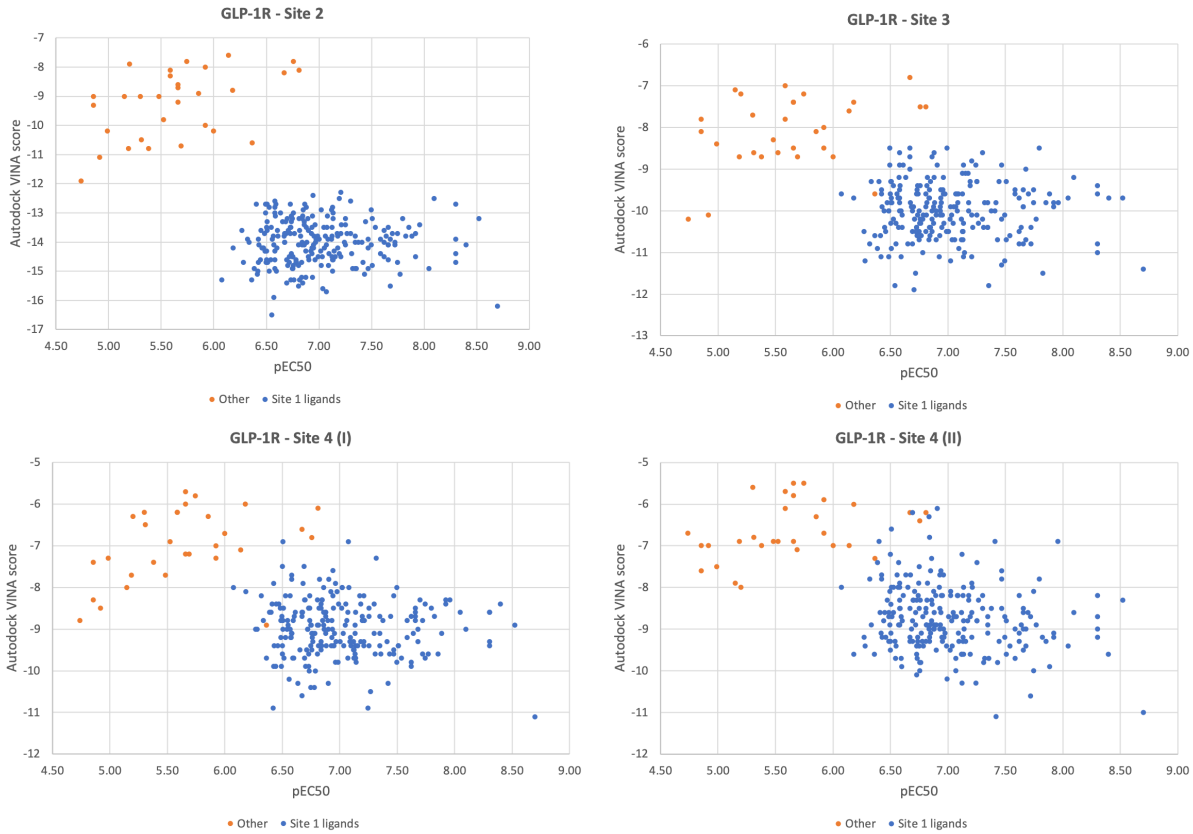


Figure S4. Autocorrelation plots of true vs. predicted values of EC50 (GLP1R) and true vs. predicted values of IC50 (GCGR).

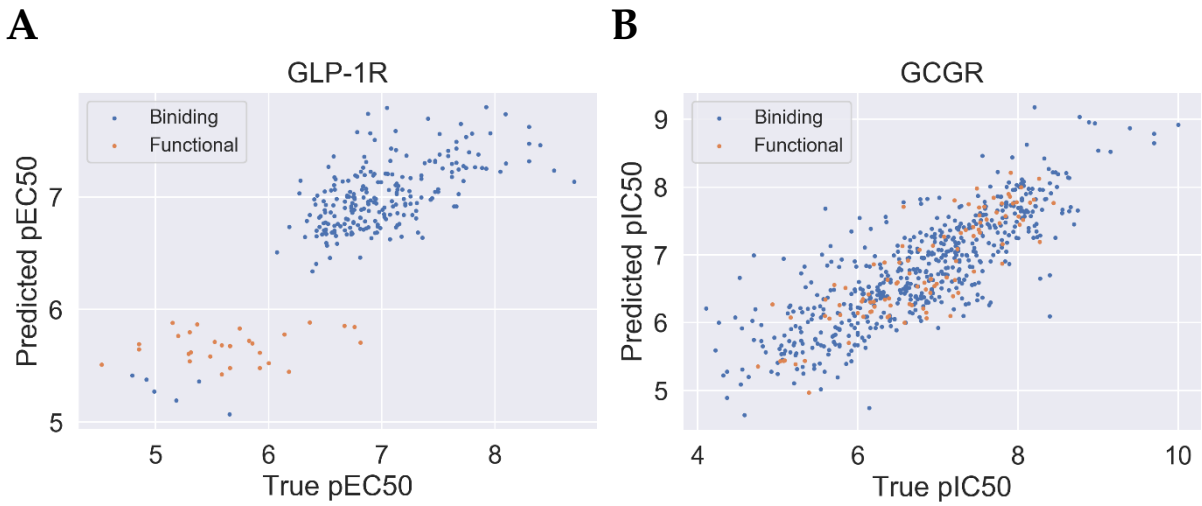


Figure S5. Multidimensional scaling embedding (MDS) for the relative similarity of ligand structures in GLP-1R dataset (A) and GCGR dataset (B). 'True pEC50/IC50' means in this case 'Experimental pEC50/pIC50'.

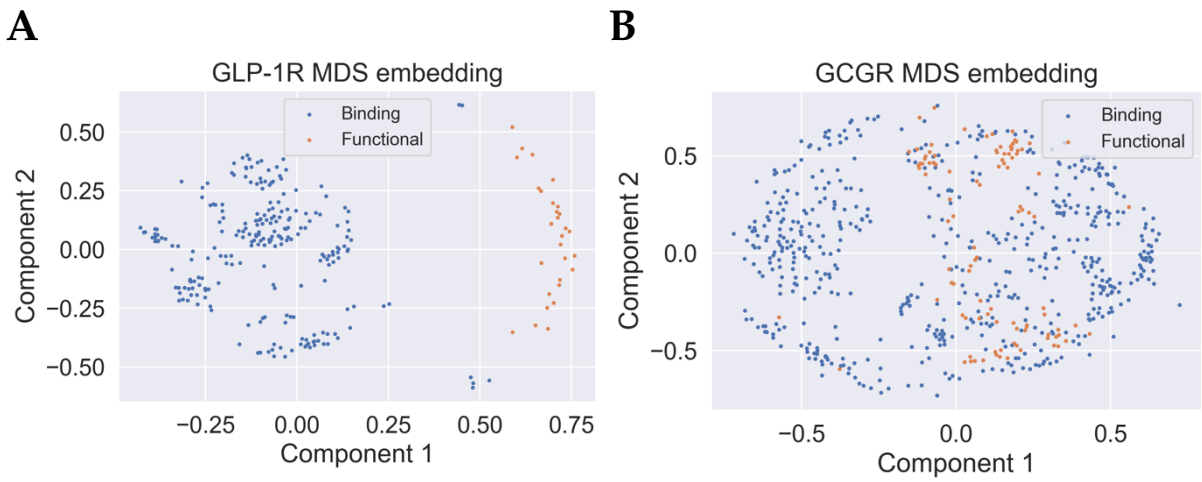


Figure S6. Compounds derived from the CMAUP database with confirmed activity for GCGR. Although both compounds are dissimilar to any of PDB ligands, compound NPC471603 (left) from *Mammea siamensis* could be modified to fit the V-shape of known NAMs. Molecular weight and shape of compound NPC62792 (right) from *Trigonostemon reidioides* - suggest that it would rather bind to the orthosteric site, if to any.

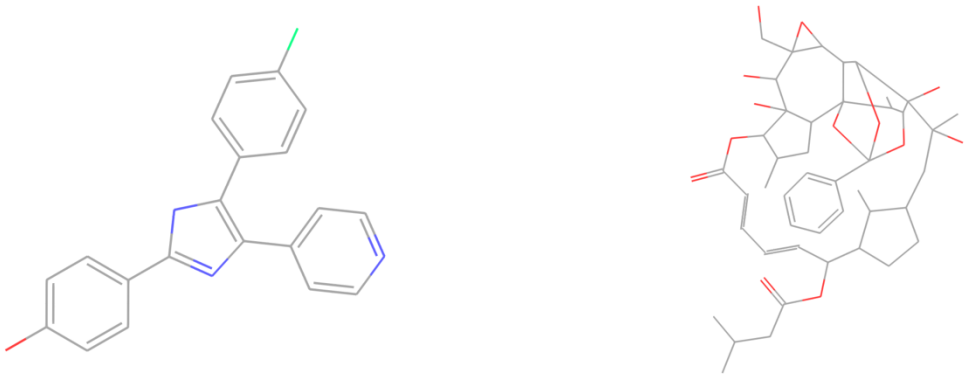
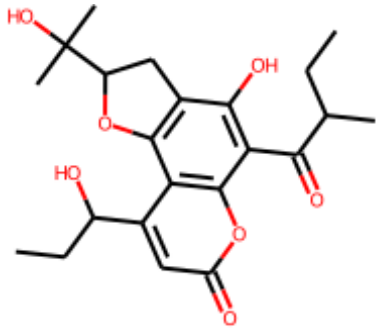


Figure S7. A distinct compound found with our model in *Mammea siamensis* extract for GLP-1R. This compound is not similar to any of GLP-1R actives that bind to sites 1-4.



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