Supporting Information

Structure-Activity Investigations and Optimisations of Non-metabolite Agonists for the Succinate Receptor 1

Elisabeth Rexen Ulven[†], Mette Traulsen[‡], Matjaz Brvar[†], Michael Lückmann[§], Line Ø. Bielefeldt[†], Lisa K. I. Jensen[†], Thue W. Schwartz[‡,§], Thomas M. Frimurer[‡]*

[†]Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

[‡]NNF Center for Basic Metabolic Research, Section for Metabolic Receptology, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen, Denmark

[§]Laboratory for Molecular Pharmacology, Department of Biomedical Research, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen, Denmark

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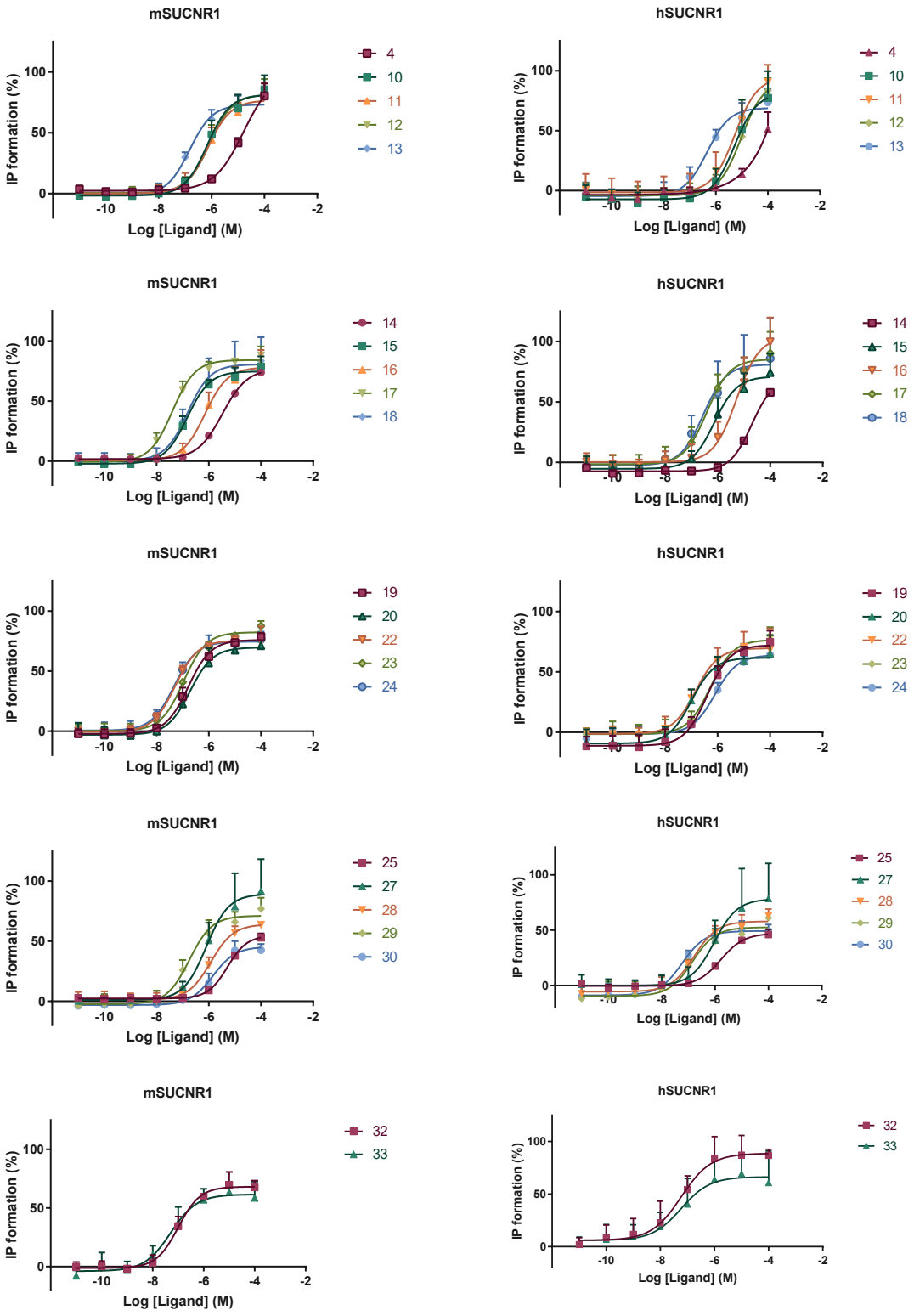

Figure S1: Dose-response curves of active compounds on mSUCNR1 and hSUCNR1.

Table S1: Training set used for ALiBERO optimisation and small-scale virtual ligand screening evaluation of receptor pocket ensembles. Compounds were divided into active (1) and inactive (0) based on an EC_{50} threshold of 10 μM.

Structure (smiles)	Cmpd ID	Active
C(C([O-])=O)[C@H](C([O-])=O)NC(COc1ccc(cc1[Cl])[Cl])=O	(*R*)-184	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(COc1ccc(cc1[Cl])[Cl])=O	(*S*)-184	1
C(C([O-])=O)[C@H](C([O-])=O)NC(c1ccc(c2ccc(cc2)F)o1)=O	(*R*)-130	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccc(cc2)F)o1)=O	3	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(o1)[Br])=O	4	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccccc1[Cl])=O	5	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c1)I)=O	6	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(cc1)[Br])=O	7	0
C(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)c1ccc(cc1)[Br]	8	0
C(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)c1ccc(cc1)c1ccc(cc1)F	9	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccccc2)o1)=O	10	1
Cc1ccccc1c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	11	1
Cc1cccc(c1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	12	1
Cc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	13	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2cccc(CO)c2)o1)=O	14	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccc(cc2)O)o1)=O	15	1
COc1ccccc1c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	16	1
COc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	17	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccc(cc2)C(F)(F)F)o1)=O	18	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccc(C#N)cc2)o1)=O	19	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(c2ccc(cc2)OC(F)(F)F)o1)=O	20	1
CCOc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	21	1
CC(C)Oc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	22	1
CC1(COC1)COc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1	23	1
CS(CCCOc1ccc(cc1)c1ccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)o1)(=O)=O	24	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c1)c1ccc(cc1)F)=O	25	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(cc1)c1ccc(cc1)F)=O	26	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c2ccc(cc2)F)n1)=O	27	1
COc1ccc(cc1)c1cccc(c1)C(N[C@@H](CC([O-])=O)C([O-])=O)=O	28	1
COc1ccc(cc1)c1cccc(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)n1	29	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c1)c1ccc(cc1)OC(F)(F)F)=O	30	1
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c2ccc(cc2)OC(F)(F)F)n1)=O	31	1
C(C([O-])=O)[C@H](C([O-])=O)NC(c1ccc(o1)[Br])=O	TUG-1623	0
Cc1c(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)c(c2ccccc2)no1	TUG-1639	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cc2ccccc2[nH]1)=O	TUG-1640	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(c1)Oc1ccccc1)=O	TUG-1641	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(cc1)Oc1ccccc1)=O	TUG-1642	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccc(nc1)[Cl])=O	TUG-1646	0

C(C([O-])=O)[C@@H](C([O-])=O)NC(c1ccnc(c1)[Cl])=O	TUG-1647	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccc(n1)[Br])=O	TUG-1648	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(c1cccnc1[Cl])=O	TUG-1649	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(/C=C/c1ccc(cc1[Cl])[Cl])=O	TUG-1652	0
C(C(N[C@@H](CC([O-])=O)C([O-])=O)=O)c1c[nH]c2ccccc12	TUG-1658	0
C(Cc1ccccc1)C(N[C@@H](CC([O-])=O)C([O-])=O)=O	TUG-1674	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(COc1ccc(cc1)OC(F)(F)F)=O	TUG-1675	0
Cc1ccc(cc1)OCC(N[C@@H](CC([O-])=O)C([O-])=O)=O	TUG-1677	0
C(C([O-])=O)[C@@H](C([O-])=O)NC(COc1ccccc1C#N)=O	TUG-1678	0
C(C([O-])=O)[C@@H](C([O-])=O)OC(c1ccc(c2ccc(cc2)F)o1)=O	TUG-1679	0

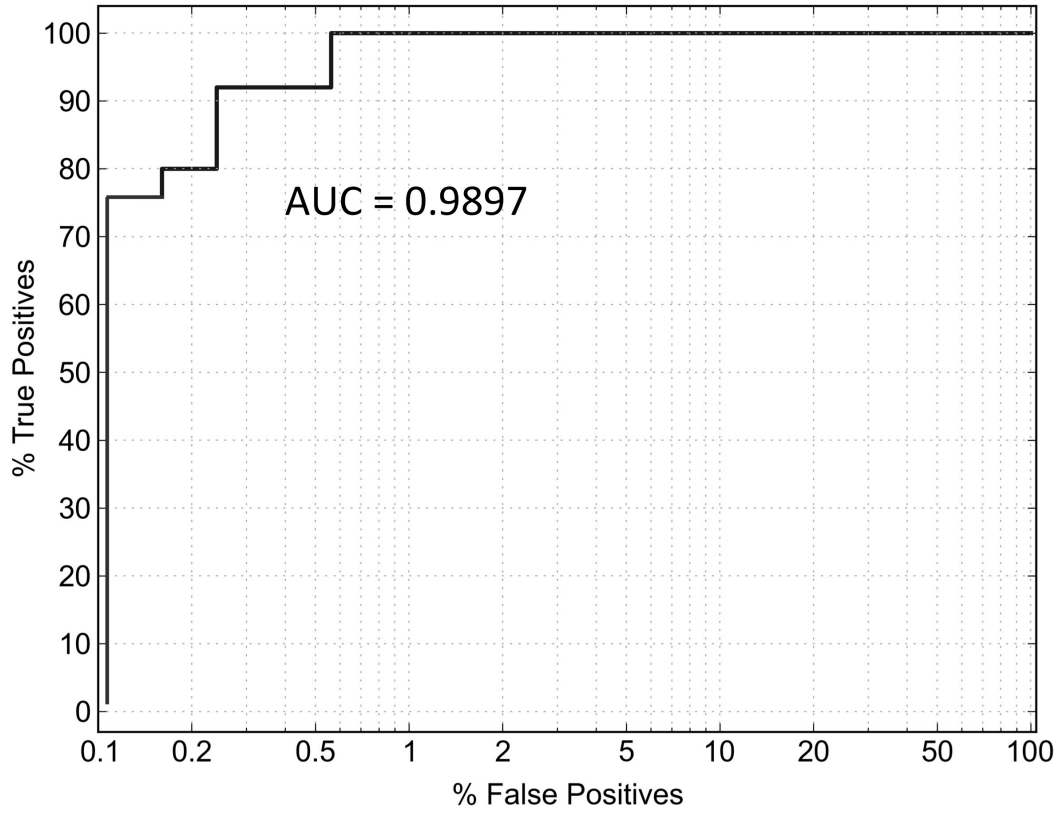

Figure S2: Model validation of the ALiBERO-optimised SUCNR1 models by a large-scale virtual ligand screening. The ROC-curve and area under the curve (AUC) value is shown for the combined performance of the best-performing receptor ensemble of generation 10 of the ALiBERO refinement. A ligand test set consisting of 25 actives and 1247 decoy molecules, that were derived from a similarity search based on the active compound **3** was used.