Supporting Information

Table 1. List of receptor type-specific distance constraints for the distance geometry refinement of the model of the active conformation of MC4R.

H-bond distance constraints (2.9 Å) in MC4R

H-Donors		H-Acceptors		H-Donors		H-Acceptors	
Residues	**Atoms**	**Residues**	**Atoms**	**Residues**	**Atoms**	**Residues**	**Atoms**
Leu31	N	Asn120	Oδ1	Ser139	Oγ	Ala135	O
Lyz33	Nζ	Asp113	Oδ1	Ser142	Oγ	Cys138	O
Tyr35	Oη	Ser28	O	Arg147*	Nη1	Tyr302	Oη
Tyr35	Oη	Leu31	O	Arg147*	Nη2	Tyr212	Oη
Ser36	Oγ	Ala114	O	Thr150	Oγ1	Asp146	O
Ser47	Oγ	Glu49	Oε1	Arg165*	Nη1	Asp146	Oδ1
Thr53	Oγ1	Glu49	O	Ser171	Oγ	Gly167	O
Ser58	Oγ	Ser295	O	Trp174	Nε1	Ser85	Oγ
Asn62	Nδ2	Ser58	Oγ	Thr178	Oγ1	Trp174	O
Asn72	Nδ2	Ala68	O	Ser188	Oγ	Phe184	O
Lys73	Nζ	Ala70	O	Ser190	Oγ	Tyr268	Oη
Tyr80	Oη	Glu308	Oε2	Ser191	N	Asp189	Oδ2
Ser94	Oγ	Asp90	O	Thr203	Oγ1	Ile198	O
Ser96	Oγ	Ile125	O	Ser210	Oγ	Ala206	O
Asn97	Nδ2	Glu100	Oε1	His222*	Nδ1	Asn240	Oδ1
Thr101	Oγ1	Asn97	O	Arg236*	Nη2	Leu229	O
Thr105	Oγ1	Thr101	O	Asn240*	Nδ2	Ala219	O
Thr109	Oγ1	Ile103	O	Thr248	Oγ1	Ala244	O
Thr112	Oγ1	Ser116	O	Thr270	Oγ1	Ile266	O
Ser116	Oγ	Glu42	Oε2	Ser282	Oγ	Gln43	Oε1
Asn120	N	Asn108	Oδ1	Asn285	Nδ2	Phe45	O
Asn120	Nδ2	Thr110	Oγ1	Asn284	Nδ2	Met281	O
Ile121	N	Asn108	Oδ1	Asn294*	Nδ2	Ser136	Oγ
Asn123	Nδ2	Glu29	Oε2	Ser295	Oγ	Met292	O
Ser127	Oγ	Asn123	O	Arg305*	Nη2	Thr246	Oγ1
Ser131	Oγ	Ser127	O	Arg310	Nη1	Leu304	O
Ser136	Oγ	Asp298	Oδ2	Thr312	Oγ1	Gly308	Oδ

* H-bonds present only in the active conformation of MC4R

Residues	Atoms	Residues	Atoms	Distances (Å)
Disulfide bond constraints for MC4R				
Cys40	Cβ	Cys279	Cβ	4.20
Cys40	Cβ	Cys279	Sγ	3.05
Cys40	Sγ	Cys279	Gβ	3.05
Cys40	Sγ	Cys279	Sγ	2.04
Cys271	Cβ	Cys277	Cβ	4.20
Cys271	Cβ	Cys277	Sγ	3.05
Cys271	Sγ	Cys277	Gβ	3.05
Cys271	Sγ	Cys277	Sγ	2.04
H-bonds between NDP-MSH and MC4R				
NDP-MSH		**MC4R**		
Residues	**Atoms**	**Residues**	**Atoms**	**Distances (Å)**
Ser1	Oγ	Asp37	Oδ2	2.90
Tyr2	Oη	Thr118	Oγ1	2.90
Ser3	Oγ	Glu42	Oε1	2.90
Glu5	Oε1	His264	Nδ1	2.90
His6	Nδ1	Glu100	Oε2	2.90
D-Phe7	N	Asp126	Oδ1	2.90
Arg8	Nε	Asp126	Oδ1	2.90
Arg8	Nη1	Asp122	Oδ1	2.90
Arg8	Nη1	Thr118	Oγ1	2.90
Trp9	O	His264	Nε2	2.90
Gly10	O	Tyr268	Oη	2.90
Lys11	Nζ	Asp189	Oδ1	2.90
Additional constraints in NDP-MSH				
Glu5	O	Arg8	N	2.90
Nle4	Cβ	Gly10	Cβ	4.50
Asp5	Cβ	Gly10	Cβ	7.50