Supporting Information (SI) for

Conserved Residues Control Activation of Mammalian G Protein-Coupled Odorant Receptors

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	TM1		
mOB256-3/1-315			
mOP256-31/1-312			
moR250-51/1-512			
FOR-1//1-32/	MDOSGKVSEFVLLGFPAPAPLKVLLFFLSLLAIVLVLTE		
hOR2W1/1-320	MDQSNYSSLHGFILLGFSNHPKMEMILSGVVAIFYLITLVG		
hOR7D4/1-312	MEAENLTELSKFLLLGLSDDPELQPVLFGLFLSMYLVTVLG		
hOR1D2/1-312	MDGGNQSEGSEFLLLGMSESPEQQRILFWMFLSMYLVTVVG		
bRHO/1-348	MNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEPWQFSMLAAYMFLLIMLGFPI		
hBeta2/1-305	DEVWVVGMGIVMSLIVLAIVFG		
hCXCB1/1-296	PCMLETET-INKYVVIIAYALVFLLSLLG		
hCXCR4/1-359	DECISIONSTREMASCOVOSMEEDCEDEENANENKIELDEUVSIELTGUUG		
$h_{22}/1_{-225}$			
11aza/ 1-525	.0		
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mOR256-3/1-315	NISIILVSRLDPQLDS-PMIFFVSNLSLDLCITTSTVPQMLVNLRGPEKTISIGG		
mOR256-31/1-312	NTAIILASLLDPHLHT-PMYFFLRNLSFLDLCYTTSIVPQMLVNLWGPEKTISSVG		
rOR-17/1-327	NMLIIIAIRN HPTLHK- PMYFFLANMSFLEIWYVTVTIPKMLAGFI GSKENHGQLIS FEA		
hOR2W1/1-320	NTAIILASLLDSQLHT-PMYFFLRNLSFLDLCFTTSIIPQMLVNLWGPDKTISYVG		
hOR7D4/1-312	NLLIILAVSS DSHLHT- PMYFFLSNLSFVDICFISTTVPKMLVSIQ ARSKDIS YMG		
hOR1D2/1-312	NVLIILAISS DSRLHT- PVYFFLANLSFTDLFFVTNTIPKMLVNLQ SHNKAIS YAG		
bRHO/1-348	NFLTLYVTVO HKKLRT- PLNYILLNLAVADLFMVFGGFTTTLYTSL HGYFVFG PTG		
hBeta2/1-305	NVLVITAIAKFERLOT-VTNYFITSLACADLVMGLAVVPFGAAHILMKMWTFGNFW		
hCXCB1/1-296	NSLVMLVILYSBYGRS-VTDVYLINLALADLLF-ALTLPIWAASKVNGWIFGTFI		
hCXCB4/1 - 359	NGLVILVMGYOKKIRS-MTDKYRLHLSVADLLF-VITLPFWAVDAVANWYFGNFI		
ha2A/1-325	NVLVCWAVWLNSNLON-VTNYFVVSAAAADTLVGVLATPFATATSTGFCAACHG		
114211, 2 323			
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mOR256-3/1-315	CVAQLYIFLALGSTECILLAIMAFDRFAAICRPLHYPIIMNQKRCIHMATGTWISGFANS		
mOR256-31/1-312	CIVQLYVYMWLGSIECLLLAVMSYDRFTAICKPLHYFVIMNPRLCVKMIVMVWGISLANS		
rOR-i7/1-327	CMTQLYFFLGLGCTECVLLAVMAYDRYVAICHPLHYPVIVSSRLCVQMAAGSWAGGFGIS		
hOR2W1/1-320	CIIQLYVYMWLGSVECLLLAVMSYDRFTAICKPLHYFVVMNPHLCLKMIIMIWSISLANS		
hOR7D4/1-312	CLTQVYFLMMFAGMDTFLLAVMAYDRFVAICHPLHYTVIMNPCLCGLLVLASWFIIFWFS		
hOR1D2/1-312	CLTOLYFIVSIVALDNLILAVMAYDRYVAICCPLHYTTAMS PKLCILLLSLCWVLSVLYG		
bRHO/1-348	CNLEGFFATLGGEIALWSLVVLAIERYVVVCKPMSNFR-FGENHAIMGVAFTWVMALACA		
hBeta2/1-305	CEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYOSLLTKNKARVIILMVWIVSGLTS		
hCXCR1/1-296			
hCXCR4/1-250	CRAINING AND RECEIVED A FILL A THANKING ADDRESS IN A RECEIVED AT I THE		
hcACK4/1-339			
naza/1-325	CLFIACEVLVLTASSIFSLLAIAIDRIIAIRIPLKINGLVTGIRARGIIAICMVLSFAIG		
	TM5 & 2		
mOR256-3/1-315	LVQSTLTVVAPRCGQRVIDHFFCEVPALLKLACTDTSVNEAELNVLGALLLLVPLS		
mOR256-31/1-312	VILCTLTVNLPRCGHNILDHFLCELPAMVRIACVDTTKVELSVFALGIVIVLTPLI		
rOR-i7/1-327	MVKVFLISRLSYCGPNTINHFFCDVSPLLNLSCTDMSTAELTDFVLAIFILLGPLS		
hOR2W1/1-320	VVLCTLTLNLPTCGNNILDHFLCELPALVKIACVDTTTVEMSVFALGIIIVLTPLI		
hOR7D4/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA		
hOR7D4/1-312 hOR1D2/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLLMTRVTFCGSRKIHYIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRIHYIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSRYIFEGMCSGIDYPHEETNNESFVIMEVVHFIPLI		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLMTRVTFCGSRKIHYIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGWSRYIPEGMQCS		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR1/1-296	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLLMTRVTFCGSRKIHYIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGWSRYIPEGMQCSGGIDYYTPHEETNNESFVIYWFVVHFIIPLT FLPIQMHWYRATHQEAI-NCYAETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFROAYHPNNSSP-VCYEVLGMDTAKWRWVLRILPHTFGFI-VPLF		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSRVIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFI FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVHV LPFFFRQAYHPNNSP-VCYEVLGNDTAKWRMVLRLPHFFGFI-VDFF IPFFFRQAYHPNNSEADBV		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359 ba2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLMTRVTFCGSRKIHYIFCEMYVLLRMACSNIQINHTVLTATCCFIFLIPFG APPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFIIPLI FLFQHMWYRATHQEAI-NCXAEETCCDFFT		
hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSKVIFEGMQCSCGIDYYTPHEETNNESFVIVMEVVHFIPLI FLFIQMHWYRATHQEAI-NCVAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDIMVVVFQFUMVGLILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYMVYFNFFACVLVPLI		
hOR7D4/1-312 hOR1D2/1-312 bRH0/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSRVIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRLPHFFGFI-VPLF IPFFFRAVSEADDR-Y-ICUEVLGNDLWVVYPQPCHTWQCILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYMVYFNFFACVLVPLL TMG 4		
hoR7D4/1-312 hOR1D2/1-312 bRH0/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFPVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLTATGCFIFLIPFG APPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHFIPLI FLIQMHWRATHQBAI-NCXAEETCCDFFT		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-3/1-315	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGNSKVIFEGMQCSCGIDYYPHEETNNESFVIYMFVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHNNSSP-V		
hoR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR4/1-296 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-315 rOPa:7(1-327	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATICFIFLIPG APPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMVVHFIPLI FIPIQHWWRATHQBAI-NCYAEETCCDFFT		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-3/1-312 roR-i7/1-327 bop201/1-320	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSKVIFEGMCGCGIDYYTPHEETINSEFVIYMEVVHFIPLI FLFIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCJRVYRMTVLIHHTFGFI-VPLF IDFFIFANVSEADDR-Y-ICDRFYPNDLWVVFQFQHHWVGLILPGI LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFMYMVYFNFFACVLVPLL TM6 & LILGTYVFIAQAVLKLRSAESRRAFNTCASHLLVVSLFYFFAIS LILGSYYAIKTVLMKSK		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-312 rOR-i7/1-327 hOR2W1/1-320 bOP7D4/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGNSKVIPEGMCSCGIDYYPHEETNNESFVIYMFVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VDLP IPFFFANVSEADDR-Y-ICDRFYPNDLWVVVPPQPHTMVCILLPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYMVYFNFFACVLVPLL TMG & CONTONNESPL		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-31/1-312 rOR-i7/1-327 hoR2W1/1-312 hoR7D4/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATCCFIFLIPFG APPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESFVIYMFVVHIIPLI FIPIQHMWYRATHQEAI-NCYAEETCCDFFTNGAYAIASSIVSFYVPLV LPFFLFQAYHNNSSP-VCYEVLGNDTAKWRMVLRLPHTFGFI-VPLF IPDFIFANVSEADDR-Y-ICDRFYPNDLWVVVFQPQHTMVGLILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFMNYMVFNFACVLVPLL TM6 6 LILGTYVFIAQAVLKLRSA		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-31/1-312 rOR-i7/1-327 hOR2W1/1-320 hOR7D4/1-312 hOR1D2/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSKYIFEGMCGGGIDYYPHEETNNESFVIXHVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFLFRQYHNNSSP-V		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-312 rOR-i7/1-327 hOR2W1/1-320 hOR7D4/1-312 bRH0/1-348	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGNSKVIFEGMCGCGIDYYTPHEETNESFVIYMVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VPLP IPPFIFANVSEADDR-Y-ICDRFYPNDLWVVYPQPCHIWGCILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYMVYFNFFACVLVPLL TMG 6 LILGTYVFIAQAVLKLRSA		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-296 hcXCR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-31/1-312 roR-i7/1-327 hoR7D4/1-312 hoR7D4/1-312 bRH0/1-348 hBeta2/1-305	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGWSKYIFEGMCGGIDYYTPHEETNNESFVIYMEVVHFIPLI FLFIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDLWVVFQFQHHWVGLILPGI LTPFLFNQYHPNNSSP-VCDRFYPNDLWVVFQFQHHWVGLILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFNYMVYFNFFACVLVPLL LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFNYMVYFNFFACVLVPLL LILSYSYIAKTVLNKSK		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-31/1-312 rOR-i7/1-327 hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hCXCR1/1-296	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGNSKIPEGMCGCGIDYYPHEETNNESFVIXMFVVHFIPLI FLPIQHHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHNNSSP-VCYEVLGNDTAKYRMVLRILPHTFGFI-VPLF IPFFFANVSEADDR-Y-ICDRFYPNDLWVVYPPCPHTWCLILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYWYFNFFACVLVPLL STMG & SCORE LILGSTYFIAQAVLKIRSA		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-31/1-312 rOR-i7/1-327 hOR7D4/1-312 hOR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGRSKIPEGMQCSCGIDYYTPHEETNESFVIYMVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRLPHTFGFI-VDLF IPDFIFANVSEADDR-Y-ICDRFYPNDLWVVVFQPCHTWQCILPGGI LTMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPNNYMYFNFFACVLVPLL TMG &		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-31/1-312 rOR-i7/1-327 hOR2W1/1-320 hOR7D4/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGMSKYIFEGMCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG FLPIQMHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFLFRQYHNNSSP-VCYEVLGNDTAKWRMVLRILPHFFGFI-VPLF IPFFFRAVSEADDR-Y-ICDRFYPHDNQAYAIASSIVSFYVPLV LIFFYLFRQYHNNSSEDDR-Y		
horTp4/1-312 horID2/1-312 brH0/1-348 hBeta2/1-305 hCXCR4/1-296 hCXCR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-3/1-312 rOR-i7/1-327 hOrZp1/1-320 hOrTp4/1-312 bRH0/1-348 hBeta2/1-305 hCXCR4/1-296 hCXCR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPGA APPLVGNSKIPEGMCGGIDYYTPHEETNNESFVIYMVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFIFQAYHNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGI-VDLP IDPFIFANVSEADDR-Y-ICDRFYPNDLWVVPPQPHTWUKILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVUPMNYMVYFNFFACVLVPLL VTMG 4 LILGTYVFIAQAVLKLRSA		
hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-31/1-312 rOR-i7/1-327 hOR7D4/1-312 hOR1D2/1-312 bOR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGMSKVIPEGMCGCGIDYYTPHEETINSFSTVJKMVVRIPIPLI FLFIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VPLF IPFFIFAVYHPNNSSP-V		
horTp4/1-312 horID2/1-312 brH0/1-348 hBeta2/1-305 hcXcR1/1-296 hcXcR4/1-359 ha2A/1-325 moR256-3/1-315 moR256-31/1-312 roR-i7/1-327 horTp4/1-312 horID2/1-312 bRH0/1-348 hBeta2/1-305 hcXcR1/1-296 hcXcR4/1-359 ha2A/1-325	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCFIFLIPFG APPLVGNSKIPEGMCGGIDYYPHEETNNESFVIXMFVVHFIPLI FLPIQMHWYRATHQEAI-NCYAEFTCCDFFTNQAYAIASSIVSFYVPLV LPFFIPRQAYHNNSSP-VCYEVLGNDTAKWRMVLRLPHHFGFI-VPLF IPFFIPAVSEADDR-Y-ICDRFYPNDLWVVPPQPHTWQCILPGI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPMNYMVYFNFFACVLVPLL LILSYGYIKATVLNKSK		
horTp4/1-312 horIp2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mor256-3/1-315 mor256-31/1-312 roR-i7/1-327 horTp1/1-320 horTp4/1-312 horIp2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 mor256-3/1-315 mor256-3/1-315	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGWSKYIFEGMCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG FLPIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VPLF IPFFIFAVYBEADQR-Y-ICDRFYPNDLWVVFQFQHIWVGLIPFG LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFPNYMVYFNFFACVLVPLL TMG &		
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hoR7D4/1-312 hoR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-312 rOR-i7/1-327 hOR7D4/1-312 hOR1D2/1-312 bRH0/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-315 mOR256-3/1-312 rOR-i7/1-327 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312 hOR7D4/1-312	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGWSKYIFEGMCGGCIDYYTPHEETNNESFVIYMEVVHFIPLI FLFIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VPLF IPFFIFAVUSEADDR-Y-ICDRYPNDLWVVFQPCHLWGLLIPFI LTPMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPENYMVYFNFFACVLVPLL LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVPENYMVYFNFFACVLVPLL LILSYSYIAKTVLMKSK		
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horTp4/1-312 horID2/1-312 bRHO/1-348 hBeta2/1-305 hcXCR1/1-296 hcXCR4/1-359 ha2A/1-325 mor256-3/1-315 mor256-3/1-312 roR-i7/1-327 horZp1/1-320 horTp4/1-312 horID2/1-312 bRHO/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 mor256-3/1-315 mor256-3/1-312 bRHO/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 mor256-3/1-312 bRHO/1-348 hBeta2/1-305 hcXCR4/1-359 ha2A/1-325 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315 mor256-3/1-315	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGWSKYIFEGMCGGIDYYTPHEETNNESFVIYMEVVHFIPLI FLFIQMHWYRATHQEAI-NCYAEETCCDFFTNQAYAIASSIVSFYVPLV LPFFLFQAYHPNNSSP-VCYEVLGNDLWVVFQPCMUWQLLPFI LIFYLGWINVSEADDR-Y-ICDRYPNDLWVVFQPCMUWQLLPFI LIFYLGWINVSEADDR-Y-ICDRYPNDLWVVFQPCMUWQLLPFI LIFYLGWINVSEADDR-Y-I		
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hoR7D4/1-312 hoR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR1/1-296 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-312 rOR-i7/1-327 hOR2M1/1-320 hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348 hBeta2/1-305 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 mOR256-3/1-315 mOR256-3/1-312 bRHO/1-348 hBeta2/1-305 hCXCR4/1-359 ha2A/1-325 mOR256-3/1-315 hCXCR4/1-320 hOR7D4/1-312 hOR1D2/1-312 bRHO/1-348	LVHILLMKRLTFSTGTEIPHFFCEPAQVLKVACSNTLLNNIVLYVATALLGVFVA LIHTLMTRVTFCGSRKIHVIFCEMYVLLRMACSNIQINHTVLIATGCTIFLIPFG APPLVGWSKYIFEGMCGGIDYYTPHEETNNSSTVSFVYPLV LPFFLFQAYHPNNSSP-VCYEVLGNDTAKWRMVLRILPHTFGFI-VPLF IPFIFAVSVEADDA-Y-ICDRYPHDLWVVFOPCHLWGLLPHT LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFDNYMVYFNFFACVLVPLL LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFDNYMVYFNFFACVLVPLL LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFDNYMVYFNFFACVLVPLL LTFMLGWNNCGQPKEGK-AHSQGCG-EGQVACLFEDVVFDNYMVYFNFFACVLVPLL VTGASYMAITGAVMRIFSA		
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Figure S1. Alignment of MOR256-3 with several human and mouse OR sequences and the GPCR sequences used as templates for homology modeling. Transmembrane (TM) domains are highlighted in gray and the TM number is indicated. The most highly conserved residue in ORs is used as number '50' in the Ballesteros-Weinstein numbering. This residue is boxed for each TM.

Residue number	Human OR residue - conservation	Mouse OR residue - conservation
108 ^{3.36}	G - 47%	G - 44%
108 ^{3.36}	G/A/V/S/T - 88%	G/A/V/S/T - 85%
121 ^{3.49}	D-98%	D-99%
$122^{3.50}$	R - 88%	R – 97%
234 ^{6.30}	R/K-75%	R/K - 77%
252 ^{6.48}	Y/F - 93%	Y/F - 92%

Table S1. Most represented residue conservation within human and mouse OR sequences



Figure S2. Logo representation of the human and mouse OR conservation. The size of the letter is proportional to the residue conservation. A star (*) highlights the residue used for the Ballesteros-Weinstein numbering within each transmembrane domain. This representation was obtained with Jalview software (http://www.jalview.org/).



Figure S3. The dose-response curves for *wt* and mutant MOR256-3. Mutant ORs showed decreased (blue), increased (red), or unchanged (gray) responses to odorant. G203A mutation (in yellow) altered ligand selectivity. Each mutant OR was tested on the same plate as the *wt* (three repeats for each OR) and all activities were normalized to the maximum *wt* response to 1-octanol at 300μ M. Two-way ANOVA tests (concentration and OR type) were performed for each mutant and *wt* pair (ns = not significantly different, * p < 0.05, ** p< 0.01, and *** p< 0.001 for OR type).



Figure S4. Basal activity of mOR256-31 mutants, normalized to the *wt***.** The data are represented as mean \pm s.e.m. (n = 15, 5, and 4 for wt, G108A, and G108L, respectively).



Figure S5. Expression level of mOR256-3 *wt* and mutants, expressed as ratio of Rho+/GFP+ cells. Each data point is averaged from 3-5 plates (mean ± s.e.m.).



Figure S6. OR structure Root Mean Square deviation as a function of time (expressed in ns) computed for all the molecular dynamic simulations using the first frame of the production period (a) or the structure taken from Modeller (b) as a reference. The RMSD (in Å) is computed during the 200 ns of each molecular dynamics simulation on the CA atoms of the bundle (from residue 19 to 309 on each system: *wt*, G108A and G108L).

General Methods and Materials

Site-Directed Mutagenesis

The coding sequences of MOR256-3 and 256-31 were amplified from genomic DNA of C57BL/6 mice and subcloned into the pcDNA3.1/TOPO vector (Invitrogen) with an N-terminal tag of the first 20 amino acids of rhodopsin. Site-directed mutants were constructed using the Quikchange site-directed mutagenesis kit (Agilent Technologies). The sequences of all plasmid constructions were verified by both forward and reverse sequencing (DNA sequencing core facility, University of Pennsylvania).

Evaluation of OR surface expression

Live-cell immunostaining is used to evaluate OR surface expression.¹ Hana3A cells were cotransfected with the receptor and GFP plasmids 24 hours before the staining. The transfected Hana3A cells were incubated with the primary antibody solution (mouse anti-rhodopsin, Rho 4D2, Abcam) on ice for 1 h. After rinsing the cells for three times, the secondary antibody solution (Alexa Fluor 568conjucated anti-mouse IgG) was added onto the cells, and incubated for 45 min on ice. At the end of the incubation, the cells were fixed with 2% Paraformaldehyde, and mounted with vectashield mounting medium (Vector Laboratories, Inc.). The ratio of Rho⁺ cells/GFP⁺ cells is used to evaluate the surface expression of each OR construct.

Luciferase assay in Hana3A cells

The Dual-Glo Luciferase Assay (Promega) was used to determine the activities of firefly and Renilla luciferase in Hana3A cells ¹. Firefly luciferase, driven by a cAMP response element promoter (CRE-Luc; Stratagene), was used to determine OR activation levels. Renilla luciferase, driven by a constitutively active SV40 promoter (pRLSV40; Promega), functioned as an internal control for transfection efficiency and cell viability. Hana3A cells stably expressing RTP1L, RTP2, REEP1, and $G_{\Box off}$ were plated on poly-D-lysine-coated 96-well plates (Nalge Nunc) and incubated overnight in minimum essential medium eagle (Sigma) with 10% FBS at 37°C and5%CO₂. The following day, cells were transfected using Lipofectamine 2000 (Invitrogen). For each 96-well plate, 1 µg pRL-SV40, 1 µg CRE-Luc, 1 µg mouse RTP1s, and 6 µg of receptor plasmid DNA were transfected. After transfection (24 h), medium was replaced with 25 µl of odorant solution diluted in CD293 chemically defined medium (Invitrogen), and cells were further incubated for 4 h at 37°C and 5% CO₂. The manufacturer's protocols were followed to measure firefly luciferase and Renilla luciferase activities. A Wallac Victor 1420 plate reader (Perkin-Elmer) was used to measure luminescence. Data were analyzed using Microsoft Excel and GraphPad Prism. Normalized activity was further calculated using the following formula: [Luc/RLuc(N)-Luc/RLuc(lowest)]/[Luc/RLuc(highest)-Luc/RLuc(lowest)],

where Luc/RLuc(N) = luminescence of firefly luciferase divided by luminescence of Renilla luciferase in a certain well; Luc/RLuc(lowest) = lowest firefly luminescence divided by Renilla luminescence of a plate or set of plates; Luc/RLuc(highest) = highest firefly luminescence divided by Renilla luminescence of a plate. To facilitate comparison between OR responses from multiple plates, the Rho-tag empty vector and *wt* MOR256-3 were always included as negative and positive control, respectively. The basal activity of an OR was averaged from four wells in the absence of odorants and further corrected by subtracting that of the control empty vector. An odorant-induced activity was averaged from at least three wells and further corrected by subtracting the basal activity of that receptor. All odorant-induced activities were normalized to *wt* MOR256-3 response to 300 μ M 1octanol. Both basal activity and odorant-induced responses were corrected for the surface expression ratio (Rho+/GFP+ when Hana3A cells were co-transfected with a Rho-tagged OR and GFP) normalized to that of *wt*.

Molecular modeling

Model building. The protocol follows a previously published method². Sequences of MOR256-3, -8, -17, -22 and -31, I7 (olfr2), mOR-EG (olfr73), and S25 (olfr480) are aligned with 396 human ORs³ and nine sequences of X-ray elucidated GPCRs: bovine rhodopsin (PDB: 1U19)⁴, human beta 2 adrenergic (PDB: 2RH1)⁵, turkey beta 1 adrenergic (PDB: 2VT4)⁶, human chemokine receptors CXCR4 (PDB: 3ODU)⁷ and CXCR1 (PDB: 2LNL)⁸, human dopamine receptor D3 (PDB: 3PBL)⁹, human adenosine a2A receptor (PDB: 2YDV)¹⁰, human histamine H1 receptor (PDB: 3RZE)¹¹ and muscarinic acetylcholine receptor M2 (PDB: 3UON)¹². Highly conserved motifs in ORs are considered as constraints for the alignment: GN in helix 1, PMYFFLXXLSXXD in helix 2, MAYDRYXAICXPLXY in helix 3, SYXXI in helix 5, KAFSTCASH in helix 6, LNPXIY in helix 7 and a pair of conserved cysteines $97^{3.25}$ - $179^{4.80}$ which constitute a known disulfide bridge between the beginning of helix 3 and the extracellular loop 2. Four experimental GPCR structures (1U19, 3ODU, 2YDV and 2LNL) are selected as templates to build MOR256-3 and its G108A and G108L mutants by homology modeling with Modeller.¹³ The N-terminal structure is omitted to avoid perturbing the modeling protocol. Five models are obtained and the one fulfilling several constraints (binding cavity sufficiently large, no large folded structure in extra-cellular loops, all TMs folded as α -helices, a small α -helix structure between TM3 and TM4) is kept for further molecular dynamics simulations.

Molecular dynamics simulations. The *wt*, G108A and G108L mutants are embedded in a model membrane made-up of POPC lipids solvated by TIP3P water molecules using Maestro.¹⁴ The total system is made up of ~48,650 atoms in a periodic box of 91*89*98 Å³.

Molecular dynamics simulations are performed with sander and pmemd.cuda modules of AMBER12 with the ff03 force-field for the protein and the gaff.lipid for the membrane. Hydrogen atoms bond are constrained by SHAKE algorithm and long-range electrostatics interactions are handled with Particle

Mesh Ewald (PME). The cutoff for non-bonded interactions is set at 8 Å. Temperature and pressure are maintained constant with a Langevin thermostat with a collision frequency of 2 ps^{-1} . In addition, a weak coupling anisotropic algorithm with a relaxation time of 1 ps^{-1} is applied. Snapshots are saved every 20 ps.

Two energy minimizations are performed during 10,000 steps with the 5,000 first steps using a conjugate gradient algorithm. The first one is run with a restraint of 200 kcal.mol⁻¹ applied on all atoms of the membrane and water and the second one with the same restraint on all atoms of the receptor. This last constraint is kept for the heating phase of 20 ps (NTP, 100K to 310K, Langevin thermostat with collision frequency of 5 ps⁻¹) and equilibration of 15 ns (NTP, 310K). Restraints are then reduced by 5 kcal.mol⁻¹Å⁻² and another cycle of minimization-equilibration is performed. The systems (*wt*, G108A and G108L mutants) are replicated four times and 200 ns-long production molecular dynamics are performed after an equilibration period of 50 ns.

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