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4s0v_OX2 : AKRARNISIVIIWIVSCIIMTPQAIVMECSTVNKT-----TLFTVCDERWGGEIYPK--MYHICFFLVTPMPLCLMVLAYLQFRKWCQRQIDIRARRKTARMLMVLLVFAICYLEISTLN : 232
4u15_ACM3 : TKRAGVMIGLAWVLSFVLWAPAILFVQYFVGKRT-----VPPGECFIQFLSEP-----TITFGTAIAAFYMPVTIMTILYWRKYKETEKMNDAYLIKEKAAQTLSAIILAFITITWTFYNTMV : 231
4xnv_P2Y1 : KKNACISISLVVWLVVVAISPILFYSGTGVRK-----NKTITCYDITTSDEYLRSYFIYSMCTTVAMCVPLVLIILGCYGLIVRAIYKMKKEEPLRKRKSIYLVIIIVLTVFAVSYIEFHVMMK : 235
4xt1_CX3CL : VKQACLFSIFWVIFAVIIAIPHFVVVT-----KKDNQCMTDYDYLEVSYPIILNVELMIGAVIPLSVISYCYRISRIAVS---QSRHKGRIVRVLIIVLVLEIIFWLEIYHHTL : 220
4yay_AT1R : MLVAKVTCIIIIWLAGLASLPAIHRNVFFIEN-----TNIITVCAFHYESQNSTLPIGLGLTKNIIIGLFLFIIILTSYTLWKAKKAYEINKPRNDDIFKIIMAVLFFSFWIEHQIFT : 236
4z35_LPA1 : NRRVVVIVVIVVITIAIVMGAIPSVGWNCI-----CDIENCSNMAPLYSDS-----YLVFWAIFNLVTFVVMVVLVAHIFGYADLYLRNRDTMMSLLKTVVIVLGAFTICWTEGLVLL : 225

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4.50
5.50
6.60

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60          *          280          *          300          *          320          *          340          *          360
FFAR1_HUMA : VASFLYPNLGGSRWKLGLITGAWSVVLPVLTGYLGRGPGLKTVCAARTQGGKSQK----- : 300
FFAR2_HUMA : LVGYHQKRSF-WWRSIAVVFSSLNASIDPLLFFYSSSVVRAFGRLQVLRNQGSLLGRRGKDTAEGTNEEDRQVGGEGMPSSDFTTE----- : 330
FFAR3_HUMA : VVGYICGESP-AWRIYVTLSTLNSCVDPFVYFYSSSGQADFHELLRLRCLGWQWQOQESSMELKEQKGGEEQRADRPAPERKTSSEHSQCGGTGGQVACAES : 346
2rh1_ADRB2 : IVHVIQDNRK-EVYIILLNWIGYVNSGFNPLIYC-RSPDFRFAEQELLCLRSSSLKAYGNGYSSNGTGEQSG----- : 303
2z73_rho : LLAQFGPLTP-YAAQLPVMFAKASAIHNPVIYVSVSHPKFREAISQTFPWVCCQFDDKETEDDKDAETEIPAGESSDAAPSADAAQMKE----- : 320
3odu_CXCR4 : SIDSFENTVH-KWISITETAFFHCCLNPLIYAFLGAKFKTSAQHALTSGRPL----- : 282
3pb1_D3 : VLNTHCQTSF-ELYSATTWIGYVNSALNPVIYITTFNIEFRKAFKILKILSCGRPLE----- : 277
3rze_H1 : MVIAFCCKNE-HLMFTIWIIGYINSTLNPLIYPLCNENFKKTKRILHIRSGEN----- : 284
3uon_ACM2 : IINTFCAPPN-TVWTIGYWICYINSTINPACYALCNATFKKTFKHLLMCHYKNIGA----- : 285
3v2y_S1P : LLDVGCKDIL-FRAEYFLVAVLNSGTNPLIYTLNKEMRAFIRIMGRPLEVLFQGPHHHHHHHHHHYKDDDDK----- : 300
3vw7_PAR1 : IAHYSFLSAY-FAYLLCVCVSSISCCIDPLIYYASSECCQRYVYSILCCKESSDPSCYHHHHHHHHHH----- : 303
4bvn_ADRB1 : IVNVFNRPDK-WLFVAFNWIGYANSAMNPIILC-RSPDFRKAFAKRLAFPRKADRRLHHHHHH----- : 296
4dk1_OPRM : IIKALITYPE-TTFQTVSWIGYNSCLNPLIYAFLDENFKRCFRFCPIPTSSIEQP----- : 289
4ea3_OPRX : LAQGLGVQPS-SETAVCTAIGYVNSCLNPLIYAFLDENFKACFRKFCASALGRPLEVLFQGPHHHHHHHHHH----- : 305
4eiy_A2A : CFTFFCPDPL-WLMYLAIVSHTNSVNVNPIYAYRIRERFRQTERKIIRSHVLRQOEPFKAHHHHHHHHHH----- : 305
4grv_NTSR1 : LMFYISDEQ-WFYMLTNAIAYASSAINPLIYNLVSANFRQVFLSTLACLCPGWRHRRKAHHHHHHHHHHGG----- : 304
4iar_5HT1B : IVMPICKDHL-AIFDFFTWIGYLNSLNPLIYITMSNEDFKQAFHKLIRFKCTS----- : 278
4ib4_5HT2B : IITLVLCDSLQ-MLLEIFVWIGYVSSGVNPLVYITLNFNKTFRDAFGRYITCNYRATKSVGRPLE----- : 292
4mbs_CCR5 : ILLNTFSNRDL-QAMQVTEIGMTHCCINPLIYAFVGEFFRNYLLVVFQKHIARFCKCCSIFQQEAPERASSVYTRSTGEQEI SVGLGR----- : 320
4n6h_OPRD : IVWTLVDIVV-AALHLCIAGYANSSLNPLIYAFLDENFKRCFRQLCRKPCG----- : 284
4phu_FFA1 : VASFLYPNLG-SWRKLGLITGAWSVVLPVLTGYLGRGPGLKTVCAARTQGGKSQKAENLYFQGHHHHHHHHH----- : 307
4pxz_P2Y12 : IPYTLSTQTLF-YVKESTLWITSLNACLNPLIYFFLCKSFRNSLISMLKCPNSATSLSQDNRRKQDGGDPNEETPMGRP----- : 311
4s0v_OX2 : VLKRVFGMFA-HWFTFSHWVYANSAANPLIYNFLSGKFRFEEKAAFSCCLGVHHHHHHHHHH----- : 295
4u15_ACM3 : LVNTFCDSPK-TYWNLYGWICYINSTVNPVYALCNKTFRTTEKTLLLCQCDKRRKRHHHHHHHH----- : 296
4xnv_P2Y1 : TMNLRADRVY-ATYQVTRGASLNSCVNPLIYFLAGDTFRRLSRATRKASRRSEANLQSKSEMDTLNIIPEFKQNGDTSL----- : 315
4xt1_CX3CL : FVDTLKRSLK-RALILTESAFHCCLNPLIYVFGTKFRQELHCLLAEFRQLFRSDVSWYHSMFSRRSSPSRRETSSDTLSDEVCR----- : 308
4yay_AT1R : FLDVLIQLGD-TAMPITICAYFNCLNPLIYGFGLGKKFRYFLQLLKY----- : 284
4z35_LPA1 : LLDVCCPQVL-AYEKFFLLIAEFNSAMNPLIYSYRDKEMSATFRQILGRPLEVLFQGPHHHHHHHHHHYKDDDDK----- : 300

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7.50

**Additional Figure 7S.** Sequence alignment of the free fatty acid receptors and 25 GPCRs with available crystal structures. The sequence alignment was built using the HHpred server (<http://toolkit.tuebingen.mpg.de/hhpred>). The sequence name starts with the pdb-code and ends with the receptor name.

N	Template	FFA1			FFA2			FFA3		
	PDB_name	probability	E-value	P-value	probability	E-value	P-value	probability	E-value	P-value
1	2rh1_ADRB2	100	4.90E-43	1.40E-47	100	5.00E-44	1.40E-48	100	7.10E-44	2.00E-48
2	2z73_RHODOPSIN	100	9.70E-41	2.70E-45	100	5.20E-42	1.50E-46	100	8.10E-43	2.30E-47
3	3odu_CXCR4	100	5.00E-43	1.40E-47	100	7.00E-43	2.00E-47	100	4.00E-43	1.10E-47
4	3pbl_D3	100	6.80E-42	1.90E-46	100	3.80E-42	1.10E-46	100	1.60E-42	4.60E-47
5	3rze_H1	100	9.70E-43	2.80E-47	100	1.60E-42	4.40E-47	100	2.10E-42	5.90E-47
6	3uon_ACM2	100	4.10E-43	1.10E-47	100	7.40E-43	2.10E-47	100	2.20E-43	6.20E-48
7	3v2y_S1P	100	4.50E-39	1.30E-43	100	1.80E-40	5.10E-45	100	2.90E-40	8.10E-45
8	3vw7_PAR1	100	2.20E-43	6.30E-48	100	3.00E-44	8.50E-49	100	1.60E-44	4.50E-49
9	4bvn_ADRB1	100	3.30E-44	9.40E-49	100	1.00E-44	2.90E-49	100	1.80E-44	5.10E-49
10	4dkl_OPRM	100	2.70E-43	7.70E-48	100	2.80E-43	8.00E-48	100	1.10E-43	3.20E-48
11	4ea3_OPRX	100	4.10E-40	1.20E-44	100	7.60E-41	2.10E-45	100	3.30E-41	9.40E-46
12	4eiy_A2A	100	9.20E-41	2.60E-45	100	6.60E-42	1.90E-46	100	1.30E-41	3.60E-46
13	4grv_NTSR1	100	2.70E-41	7.60E-46	100	4.20E-42	1.20E-46	100	1.10E-42	3.20E-47
14	4iar_5HT1B	100	2.80E-44	7.90E-49	100	4.40E-44	1.20E-48	100	2.20E-44	6.30E-49
15	4ib4_5HT2B	100	1.60E-41	4.60E-46	100	2.00E-41	5.60E-46	100	9.40E-42	2.70E-46
16	4mbs_CCR5	100	2.60E-42	7.50E-47	100	2.10E-43	6.10E-48	100	1.10E-43	3.10E-48
17	4n6h_OPRD	100	4.50E-40	1.30E-44	100	4.10E-40	1.20E-44	100	2.10E-40	6.10E-45
18	4phu_FFA1	100	5.10E-42	1.40E-46	100	7.90E-42	2.20E-46	100	3.30E-42	9.30E-47
19	4pxz_P2Y12	100	5.80E-44	1.60E-48	100	1.40E-44	3.90E-49	100	1.20E-45	3.30E-50
20	4s0v_OX2	100	1.20E-39	3.40E-44	100	2.80E-39	7.80E-44	100	1.40E-39	3.80E-44
21	4u15_ACM3	100	3.40E-42	9.70E-47	100	1.00E-42	2.90E-47	100	7.70E-43	2.20E-47
22	4xnv_P2Y1	100	1.40E-42	3.90E-47	100	3.60E-44	1.00E-48	100	3.00E-44	8.60E-49
23	4xt1_CX3CL	100	2.50E-39	7.10E-44	100	2.70E-41	7.50E-46	100	2.60E-42	7.30E-47
24	4yay_AT1R	100	6.20E-40	1.70E-44	100	1.30E-40	3.60E-45	100	5.00E-41	1.40E-45
25	4z35_LPA1	100	1.20E-38	3.30E-43	100	2.1E-40	5.9E-45	100	1.20E-40	3.40E-45

**Additional Table 2S.** HHpred server (<http://toolkit.tuebingen.mpg.de/hhpred>) predictions of a homologous relationship. Probability represents a homologous relationship; E-value is the average expected number of non-homologous proteins with a score higher than the one obtained for the database match. An E-value <<< 1 indicates statistical significance; and P-values is the area under the extreme value distribution. Receptor templates are shown with a pdb code and receptor name. The calculated values indicate a strong homologous relationship.