

## Appendix A.

### A.1. Sequences used in alignment to predict TM regions of LPA<sub>2</sub>

>sp|Q9HBW0|EDG4\_HUMAN Lysophosphatidic acid receptor Edg-4 (LPA receptor 2) (LPA-2) - Homo sapiens (Human).

>sp|Q9UBY5|EDG7\_HUMAN Lysophosphatidic acid receptor Edg-7 (LPA receptor 3) (LPA-3) - Homo sapiens (Human).

>sp|Q92633|EDG2\_HUMAN Lysophosphatidic acid receptor Edg-2 (LPA receptor 1) (LPA-1) - Homo sapiens (Human).

>sp|Q61130|EDG2\_MOUSE Lysophosphatidic acid receptor Edg-2 (LPA receptor 1) (LPA-1) (Rec1.3) (VZG-1) - Mus musculus (Mouse), and Rattus norvegicus (Rat).

>sp|Q9EQ31|EDG7\_MOUSE Lysophosphatidic acid receptor Edg-7 (LPA receptor 3) (LPA-3) - Mus musculus (Mouse).

>sp|Q9JL06|EDG4\_MOUSE Lysophosphatidic acid receptor Edg-4 (LPA receptor 2) (LPA-2) - Mus musculus (Mouse).

>tr|Q9DC35 Endothelial differentiation sphingolipid G-protein-coupled receptor 1 (Hypothetical protein) - Mus musculus (Mouse).

>sp|P21453|EDG1\_HUMAN Probable G protein-coupled receptor Edg-1 - Homo sapiens (Human).

>sp|Q99500|EDG3\_HUMAN Sphingosine 1-phosphate receptor Edg-3 (S1P receptor Edg-3) (Endothelial differentiation G-protein-coupled receptor 3) - Homo sapiens (Human).

>tr|Q8BP20 Endothelial differentiation - Mus musculus (Mouse).

>sp|O95136|EDG5\_HUMAN Sphingosine 1-phosphate receptor Edg-5 (S1P receptor Edg-5) (Endothelial differentiation G-protein coupled receptor 5) - Homo sapiens (Human).

>tr|Q8C3Q7 Endothelial differentiation - Mus musculus (Mouse).

>tr|Q9Z0L1|G protein-coupled receptor precursor - Mus musculus (Mouse).

>sp|P47746|CB1R\_MOUSE Cannabinoid receptor 1 (CB1) (CB-R) (Brain-type cannabinoid receptor) - Mus musculus (Mouse).

>sp|P21554|CB1R\_HUMAN Cannabinoid receptor 1 (CB1) (CB-R) (CANN6) - Homo sapiens (Human).

>sp|P33032|MC5R\_HUMAN Melanocortin-5 receptor (MC5-R) (MC-2) - Homo sapiens (Human).

>tr|Q9EQM7|Melanocortin-4 receptor - Mus musculus (Mouse).

>sp|P32245|MC4R\_HUMAN Melanocortin-4 receptor (MC4-R) - Homo sapiens (Human).

>sp|P41968|MC3R\_HUMAN Melanocortin-3 receptor (MC3-R) - Homo sapiens (Human).

## A.2. Alignment for predicting the TM region of LPA<sub>2</sub>

CLUSTAL W (1.74) multiple sequence alignment

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sp|Q9HBW0|EDG4_HUMAN  -----
sp|Q9UBY5|EDG7_HUMAN  -----
sp|Q92633|EDG2_HUMAN  -----
sp|Q61130|EDG2_MOUSE  -----
sp|Q9EQ31|EDG7_MOUSE  -----
sp|Q9JL06|EDG4_MOUSE  -----
tr|Q9DC35              -----
sp|P21453|EDG1_HUMAN  -----
sp|Q99500|EDG3_HUMAN  -----
tr|Q8BP20              -----
sp|O95136|EDG5_HUMAN  -----
tr|Q8C3Q7              -----
tr|Q9Z0L1              -----
sp|P47746|CB1R_MOUSE  MKSILDGLADTTFRITITD
sp|P21554|CB1R_HUMAN  MKSILDGLADTTFRITITD
sp|P33032|MC5R_HUMAN  -----
tr|Q9EQM7              -----
sp|P32245|MC4R_HUMAN  -----
sp|P41968|MC3R_HUMAN  -----MSIQKTYLEGDFVFPVSSSS

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sp|Q9HBW0|EDG4_HUMAN  -----MVIMG--QCYYNETIGFF
sp|Q9UBY5|EDG7_HUMAN  -----MN--ECHYDKHMDFF
sp|Q92633|EDG2_HUMAN  AISTSIPVISIQPQFTAMNE
sp|Q61130|EDG2_MOUSE  AASTSSPVISIQPQFTAMNE
sp|Q9EQ31|EDG7_MOUSE  -----MN--ECHYDKRMDFF
sp|Q9JL06|EDG4_MOUSE  -----MG--QCYYNETIGFF
tr|Q9DC35              -MVSTSIPEVKALRSSVS--
sp|P21453|EDG1_HUMAN  -MGPTSVPLVKahrssvs--
sp|Q99500|EDG3_HUMAN  -----MATALPPRLQ--PVR
tr|Q8BP20              -----MATTHAQGHQ--PVL
sp|O95136|EDG5_HUMAN  -----MGLYS--EYLNPNKV
tr|Q8C3Q7              -----MGGLYS--EYLNPEKV
tr|Q9Z0L1              -MNISTWSTLVTPEschrla
sp|P47746|CB1R_MOUSE  KMTAGDNSPLVPAGDTNTE
sp|P21554|CB1R_HUMAN  KMTAGDNPQLVPA-DQVNI
sp|P33032|MC5R_HUMAN  -----MNSSPHLHFLDLN
tr|Q9EQM7              -----MNSTHHGMYTSLHLWN
sp|P32245|MC4R_HUMAN  -----MVNSTHRGMHTSLHL
sp|P41968|MC3R_HUMAN  LRTLLEPQLGSALLTAMN

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sp|Q9HBW0|EDG4_HUMAN  DVVVVALGLTIVSVLVLLTN
sp|Q9UBY5|EDG7_HUMAN  LVIVLCVGTFFCLFIFFSNS
sp|Q92633|EDG2_HUMAN  SKLVMGLGITVCFIFIMLAN
sp|Q61130|EDG2_MOUSE  SKLVMGLGITVCFIFIMLAN
sp|Q9EQ31|EDG7_MOUSE  LVIVLCVGTFFCLFIFFSNS
sp|Q9JL06|EDG4_MOUSE  DVVVVALGLTIVSVLVLLTN
tr|Q9DC35              IKLTSVVFILICCFIILEN
sp|P21453|EDG1_HUMAN  IKLTSVVFILICCFIILEN
sp|Q99500|EDG3_HUMAN  STLTTLVFLVICSFIVLEN
tr|Q8BP20              TLITTLVFLVICSFIVLEN
sp|O95136|EDG5_HUMAN  RQVASAFIVILCCAIIVEN
tr|Q8C3Q7              RKVASAFIILCCAIIVEN
tr|Q9Z0L1              LGMLRGPSVAAGLVLENAM
sp|P47746|CB1R_MOUSE  QLAIAVLSLTLGTFTVLEN
sp|P21554|CB1R_HUMAN  QLAIAVLSLTLGTFTVLEN
sp|P33032|MC5R_HUMAN  QLAIAVLSLTLGTFTVLEN
tr|Q9EQM7              LFVSPEVFTLGVISLLENIL
sp|P32245|MC4R_HUMAN  LFVSPEVFTLGVISLLENIL
sp|P41968|MC3R_HUMAN  VFIKPEVFLSLGIVSLENIL

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sp|Q9HBW0|EDG4_HUMAN HTGPRT-----ARLSLEGWFLRQGLDTSLTASVATLLAIAVERHRSVMA-VQLHSRL
sp|Q9UBY5|EDG7_HUMAN NTGPVS-----KTLTVNRWFLRQGLDSSLTASLTNLLVIAVERHMSIMR-MRVHSNL
sp|Q92633|EDG2_HUMAN NTGPNT-----RRLTVSTWLLRQGLIDTSLTASVANLLAIAIERHITVFR-MQLHTRM
sp|Q61130|EDG2_MOUSE NTGPNT-----RRLTVSTWLLRQGLIDTSLTASVANLLAIAIERHITVFR-MQLHTRM
sp|Q9EQ31|EDG7_MOUSE NTGPVS-----KTLTVNRWFLRQGLDTSLTASLTNLLVIAVERHMSIMR-MRVHSNL
sp|Q9JL06|EDG4_MOUSE HTGPPH-----CQALHQRLVPATGPAGHPHGVSHTAGIAVERHRSVMA-VQLHSRL
tr|Q9DC35|          LSGATT-----YKLTPAQWFLREGSMFVALSASFVSLLAIAIERHITMVK-MKLHNGS
sp|P21453|EDG1_HUMAN LSGATT-----YKLTPAQWFLREGSMFVALSASFVSLLAIAIERHITMVK-MKLHNGS
sp|Q99500|EDG3_HUMAN MSGKKT-----FSLSPVWFLREGSMFVALGASTCSLLAIAIERHITMVK-MRPYDAN
tr|Q8BP20|          MSGRKT-----FRLSPTVWFLREGSMFVALGASTCSLLAIAIERHITMVK-MRPYDAN
sp|O95136|EDG5_HUMAN LSGSVT-----LRLTPVQWFLREGSAFITLSASFVSLLAIAIERHVAIAK-VKLYGSD
tr|Q8C3Q7|          LSGHVT-----LSLTPVQWFLREGSAFITLSASFVSLLAIAIERQVALAK-VKLYGSD
tr|Q9Z0L1|          LSGTRT-----FQLSPVHWFLREGLLFMALAASTFSLFTAGERFATMVR-VAESGAT
sp|P47746|CB1R_MOUSE DFHVFH-----RKDSRNVFLFKLGGVTASFTASVGSFLFTAIDRYISIHRLAYKRIV
sp|P21554|CB1R_HUMAN DFHVFH-----RKDSRNVFLFKLGGVTASFTASVGSFLFTAIDRYISIHRLAYKRIV
sp|P33032|MC5R_HUMAN TIYLLNNKHLVIADAFVRHIDNVFDSMICISVVAMCSLLAIAVDRYVTIFALRYHHIM
tr|Q9EQM7|          VITLLN-STDTDAQSFVFNIDNVIDSVICSSLLASICSLLSIAVDRYVTIFALQYHNIM
sp|P32245|MC4R_HUMAN IITLLN-STDTDAQSFVFNIDNVIDSVICSSLLASICSLLSIAVDRYVTIFALQYHNIM
sp|P41968|MC3R_HUMAN MIAIVHSDYLTFFEDQFIQHMDNIFDSMICISLVASICNLLAIAVDRYVTIFALRYHSIM

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sp|Q9HBW0|EDG4_HUMAN PRGRVVMVIVGVVAALGLGLLPAHSWHCLCALDRCSRMAPLLSRYSYLAVALSSLLVFL
sp|Q9UBY5|EDG7_HUMAN TKKRVTLILLVWVIAIAIFMGAVPTLGNWCLCNISACSSLAPIYSRSLVFWFVSNLMAFL
sp|Q92633|EDG2_HUMAN SNRRVVVVVIVVWMAIVMGAIPSVGWNICIDIENCSNMAPLYSDSYLVFWAIFNLVTFV
sp|Q61130|EDG2_MOUSE SNRRVVVVVIVVWMAIVMGAIPSVGWNICIDIENCSNMAPLYSDSYLVFWAIFNLVTFV
sp|Q9EQ31|EDG7_MOUSE TKKRVTLILLVWVIAIAIFMGAVPTLGNWCLCNISACSSLAPIYSRSLVFWFVSNLMAFL
sp|Q9JL06|EDG4_MOUSE PRGRVVTIVGVVAAALGLGLLPAHFHWHCLCDLDCSRMVPLFSRYSYLAVALSSLLVFL
tr|Q9DC35|          NSSRSFLLISACWVIVSLILGGLPIMGWNCISSLSSCSTVPLPLYHKKYILFCTVFTLLLL
sp|P21453|EDG1_HUMAN NNFRLLFLLISACWVIVSLILGGLPIMGWNCISSLSSCSTVPLPLYHKKYILFCTVFTLLLL
sp|Q99500|EDG3_HUMAN KRHRVFLIGMCWLIASFGLGALPILGWNCLENLPCDSTILPLYSKKYIAFLSIFTAILV
tr|Q8BP20|          KKHRVFLIGMCWLIASFGLGALPILGWNCLENLPCDSTILPLYSKKYIAFLSIFTAILV
sp|O95136|EDG5_HUMAN KSCRMLLIGASWVIVSLILGGLPILGWNCLEACSTVPLPLYAKHYVLCVVTIFSVILL
tr|Q8C3Q7|          KSCRMLLIGASWVIVSLILGGLPILGWNCLEACSTVPLPLYAKHYVLCVVTIFSVILL
tr|Q9Z0L1|          KTSRVYGCIGLWLLAAILGGLPLLGWNCVCAFPKCSLLPLYSKGYVLFVCFVVFALILV
sp|P47746|CB1R_MOUSE TRPKAVVAFCLMWTIAIVIAVPLLGWNCCKLQSVCSDFIPFLIDETVYLMFWIGVTSVLLL
sp|P21554|CB1R_HUMAN TRPKAVVAFCLMWTIAIVIAVPLLGWNCCKLQSVCSDFIPFLIDETVYLMFWIGVTSVLLL
sp|P33032|MC5R_HUMAN TARRSGAIIAGIWAFCFGCGIVFIIYS-----ESTVILCLISMFFAMLF
tr|Q9EQM7|          TVRRVGIISCIWAACVSGVLFIIYS-----DSSAVIICLISMFFTMLV
sp|P32245|MC4R_HUMAN TVKRVGIISCIWAACVSGVLFIIYS-----DSSAVIICLITMFFTMLA
sp|P41968|MC3R_HUMAN TVRKALTLIVAIWVCCGVCVVFIIVYS-----ESKMVIVCLITMFFAMLL

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sp|Q9HBW0|EDG4_HUMAN LMVAVYTRIFFYVRRRVERMAEHVSCH-----P--RYRETTLSLVKTVVIV
sp|Q9UBY5|EDG7_HUMAN IMVVVYLRIYVYVRRKTNVLSPTS-----I--SRRRTPMKLMKTVMTV
sp|Q92633|EDG2_HUMAN VMVVLYAHIFGYVRQRTMRSRHSRSGP-----R--RNRDTMMSLLKTVVIV
sp|Q61130|EDG2_MOUSE VMVVLYAHIFGYVRQRTMRSRHSRSGP-----R--RNRDTMMSLLKTVVIV
sp|Q9EQ31|EDG7_MOUSE IMVAVYVRIYMYVRRKTNVLSPTS-----I--SRRRAPMKLMKTVMTV
sp|Q9JL06|EDG4_MOUSE LMVAVYTRIFFYVRRRVERMAEHVSCH-----P--RYRETTLSLVKTVVIV
tr|Q9DC35|          SIVILYCRIYSLVTRRSRRLTFRKNIS-----KASRSSEKSLALLKTVIIV
sp|P21453|EDG1_HUMAN SIVILYCRIYSLVTRRSRRLTFRKNIS-----KASRSSE-NVALLKTVIIV
sp|Q99500|EDG3_HUMAN TIVILYARIYFLVKSSSRKRVANHNN-----SERSMALLRTVVIV
tr|Q8BP20|          TIVILYARIYCLVKSSSRVANHNN-----SERSMALLRTVVIV
sp|O95136|EDG5_HUMAN AIVALYVRIYCVVRSRSHADMAAPQ-----TLALLKTVTIV
tr|Q8C3Q7|          AIVALYVRIYFVVRSSHADVAGPQ-----TLALLKTVTIV
tr|Q9Z0L1|          AILSLYGAIFRVVRANGQKSPRPP-----ARRKSRLLNTVLMVI
sp|P47746|CB1R_MOUSE FIVYAYMYILWKAHSHAVRMIQRGTQKSIIIHTSEDGKVVQVTRPDQARMDIRLAKTLVLI
sp|P21554|CB1R_HUMAN FIVYAYMYILWKAHSHAVRMIQRGTQKSIIIHTSEDGKVVQVTRPDQARMDIRLAKTLVLI
sp|P33032|MC5R_HUMAN LLVSLYIHMFLRLARTHKRIALPGAS-----SARQRTSMQGAVTVMTL
tr|Q9EQM7|          LMASLYVHMFLMARLHIKRIAVLPGTG-----TIRQGTNMKGAITLTIL
sp|P32245|MC4R_HUMAN LMASLYVHMFLMARLHIKRIAVLPGTG-----AIRQGANMKGAITLTIL
sp|P41968|MC3R_HUMAN LMGTLYVHMFLFARLHVKRIALPPADG-----VAPQOHSCKMGAVTITIL

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sp|Q9HBW0|EDG4_HUMAN  LGAFVVCWTPGQVVLVLLDGLGCES----CNVLAVEKYFLLLAEANSLVNAAVYSCRDAEM
sp|Q9UBY5|EDG7_HUMAN  LGAFVVCWTPGLVVLVLLDGLNCRQ----CGVQHVKRWFLLLALLNSVVPNPIIYSYKDEDM
sp|Q92633|EDG2_HUMAN  LGAFIICWTPGLVVLVLLD-VCCPQ----CDVLAYEKFLLLAEFNSAMNPIIYSYRDKEM
sp|Q61130|EDG2_MOUSE  LGAFIVCWTPGLVVLVLLD-VCCPQ----CDVLAYEKFLLLAEFNSAMNPIIYSYRDKEM
sp|Q9EQ31|EDG7_MOUSE  LGAFVVCWTPGQVVLVLLDGLNCKQ----CNVQHVKRWFLLLALLNSVMNPIIYSYKDEDM
sp|Q9JL06|EDG4_MOUSE  LGAFVVCWTPGQVVLVLLDGLDCKT----CNVLAVEKYFLLLAEANSLVNAVYSCRDAEM
tr|Q9DC35|              LSVFIACWAPLFIILLLD-VGCKAK--TCDILYKAEYFLVLAVLNSGTNPIIYTLTNKEM
sp|P21453|EDG1_HUMAN  LSVFIACWAPLFIILLLD-VGCKVK--TCDILFRAEYFLVLAVLNSGTNPIIYTLTNKEM
sp|Q99500|EDG3_HUMAN  VSVFIACWSPLFIIFLID-VACRVQ--ACPILFKAQWFIVLAVLNSAMNPIIYTLASKEM
tr|Q8BP20|              VSVFIACWSPLFIIFLID-VACRAK--ECSILFKSQWFIMLAVLNSAMNPIIYTLASKEM
sp|O95136|EDG5_HUMAN  LGVFIICWLPAPFILLLD-YACPVH--SCPILYKAHYFFAVSTLNSLLNPVIYTWRSRDL
tr|Q8C3Q7|              LGVFIICWLPAPFILLLD-STCPVR--ACPVLKHAHYFFAFATLNSLLNPVIYTWRSRDL
tr|Q9Z0L1|              LVAFVVCWGPLFGLLLADIFGSNVW--AQEYLRGMDWILALAVFNSAINPLIYSFRSREV
sp|P47746|CB1R_MOUSE  LVVLIICWGPLLAIMVYDVFGKMN---KLIKTVFAFCSMLCLLNSTVNPPIIYALRSKDL
sp|P21554|CB1R_HUMAN  LVVLIICWGPLLAIMVYDVFGKMN---KLIKTVFAFCSMLCLLNSTVNPPIIYALRSKDL
sp|P33032|MC5R_HUMAN  LGVFTVCWAPFHLHLTLM-LSCPQNYCSRFSHFNMYLILIMCNSVMDPLIYAFRSQEM
tr|Q9EQM7|              IGVFVVCWAPFHLHLIFY-ISCQPQNYCVCVCFMSHFNLYLILIMCNAVIDPLIYALRSQEL
sp|P32245|MC4R_HUMAN  IGVFVVCWAPFHLHLIFY-ISCQPQNYCVCVCFMSHFNLYLILIMCNSIDPLIYALRSQEL
sp|P41968|MC3R_HUMAN  LGVFIICWAPFHLHLVI-ITCPTNPYCICTAHFNLYLILIMCNSVIDPLIYAFRSLEL
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sp|Q9HBW0|EDG4_HUMAN  -RRTFRLLC-CACLR-----QSTR----ESVHYTSSAQ----GGASTRIMLPENGRHP
sp|Q9UBY5|EDG7_HUMAN  -YGTMKMIC-CFSQE-NPER-RPSRI----PSTVLSRSDT----GSQYIEDSISQGAVC
sp|Q92633|EDG2_HUMAN  -SATFRQILC-CQ-----RSEN----PTGPTEGSDR----SASSLNHTILAGVHS
sp|Q61130|EDG2_MOUSE  -SATFRQILC-CQ-----RSEN----PNGPTEGSDR----SASSLNHTILAGVHS
sp|Q9EQ31|EDG7_MOUSE  -YNTMRKMIC-CALQDSNTER-RPSRN---PSTIHSRSET----GSQYLEDISISQGPVC
sp|Q9JL06|EDG4_MOUSE  -RRTFRLLC-CMLR-----WSSH----KSARYSASQAQ----TGASTRIMLPENGRP
tr|Q9DC35|              RRAFIRIVSC-CKCPNGDSAG-KFKRP--IIPGMEFSSRSKS---DNSSHPQKDDGDNPET
sp|P21453|EDG1_HUMAN  RRAFIRIMSC-CKCPNGDSAG-KFKRP--IIPGMEFSSRSKS---DNSSHPQKDEGDNPET
sp|Q99500|EDG3_HUMAN  RRAFFRLV---CNCLVR-GRG-ARASP--IQPALDPSRSKSSSSNNSHSPVKEDLPHT
tr|Q8BP20|              RRAFFRLV---CGCLVK-GKG-TQASP--MQPALDPSRSKSSSSNNSHSPVKEDLPHT
sp|O95136|EDG5_HUMAN  RREVLRLP----QCWRP-GVG-VQGRRRGGTPGHLLPLRS---SSSLERGMHMPSTPTF
tr|Q8C3Q7|              QRAVLAFLLCCGLWLGLRPGDCLTRITEAHSGASTDSSLRPRDSFRTSRLSFRMREP
tr|Q9Z0L1|              RHAFRSMFPS-CEGTAQPLDN-SMGDSACLHKHANNASVHR--AAESCIKSTVKIAKVT
sp|P47746|CB1R_MOUSE  RHAFRSMFPS-CEGTAQPLDN-SMGDSACLHKHANNASVHR--AAESCIKSTVKIAKVT
sp|P21554|CB1R_HUMAN  RHAFRSMFPS-CEGTAQPLDN-SMGDSACLHKHANNASVHR--AAESCIKSTVKIAKVT
sp|P33032|MC5R_HUMAN  RKTTFKEIIC--CRGFRIACSF-PRRD-----
tr|Q9EQM7|              RKTTFKEIIC--FYPLGGICEL-SSRY-----
sp|P32245|MC4R_HUMAN  RKTTFKEIIC--CYPLGLCDL-SSRY-----
sp|P41968|MC3R_HUMAN  RNTFREILCG-CNGMNLG-----

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sp|Q9HBW0|EDG4_HUMAN  LMDSTL-----
sp|Q9UBY5|EDG7_HUMAN  NKSTS-----
sp|Q92633|EDG2_HUMAN  NDHSVV-----
sp|Q61130|EDG2_MOUSE  NDHSVV-----
sp|Q9EQ31|EDG7_MOUSE  NKNGS-----
sp|Q9JL06|EDG4_MOUSE  LMDSTL-----
tr|Q9DC35|              IMSSGNVNSSS-----
sp|P21453|EDG1_HUMAN  IMSSGNVNSSS-----
sp|Q99500|EDG3_HUMAN  DPSSCIMDKNAALQNGIFCN
tr|Q8BP20|              ATSSCIIDKNRSFQNGVLCK
sp|O95136|EDG5_HUMAN  LEGNTVV-----
tr|Q8C3Q7|              LEGNTVV-----
tr|Q9Z0L1|              LSSISSVRST-----
sp|P47746|CB1R_MOUSE  MSVSTDTSAEAL-----
sp|P21554|CB1R_HUMAN  MSVSTDTSAEAL-----
sp|P33032|MC5R_HUMAN  -----
tr|Q9EQM7|              -----
sp|P32245|MC4R_HUMAN  -----
sp|P41968|MC3R_HUMAN  -----

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## Appendix B.

### B.1. Sequences used in alignment to predict TM regions of S1P<sub>1</sub>

>sp|O08530|EDG1\_MOUSE Sphingosine 1-phosphate receptor Edg-1 (Lysophospholipid receptor B1) - Mus musculus (Mouse).

>sp|Q99500|EDG3\_HUMAN Sphingosine 1-phosphate receptor Edg-3 (S1P receptor Edg-3) (Endothelial differentiation G-protein-coupled receptor 3) - Homo sapiens (Human).

>sp|Q9Z0U9|EDG3\_MOUSE Sphingosine 1-phosphate receptor Edg-3 (S1P receptor Edg-3) (Endothelial differentiation G-protein-coupled receptor 3) (Lysophospholipid receptor B3) - Mus musculus (Mouse).

>sp|O95136|EDG5\_HUMAN Sphingosine 1-phosphate receptor Edg-5 (S1P receptor Edg-5) (Endothelial differentiation G-protein coupled receptor 5) - Homo sapiens (Human).

>sp|O95977|EDG6\_HUMAN Sphingosine 1-phosphate receptor Edg-6 (S1P receptor Edg-6) (Endothelial differentiation G-protein coupled receptor 6) - Homo sapiens (Human).

>sp|Q9Z0L1|EDG6\_MOUSE Sphingosine 1-phosphate receptor Edg-6 (S1P receptor Edg-6) (Endothelial differentiation G-protein coupled receptor 6) (Lysophospholipid receptor C1) - Mus musculus (Mouse).

>sp|Q92633|EDG2\_HUMAN Lysophosphatidic acid receptor Edg-2 (LPA receptor 1) (LPA-1) - Homo sapiens (Human).

>sp|Q8K5E0|EDG7\_RAT Lysophosphatidic acid receptor Edg-7 (LPA receptor 3) (LPA-3) (snGPCR32) - Rattus norvegicus (Rat).

>sp|Q95KH4|EDG4\_MACFA Lysophosphatidic acid receptor Edg-4 (LPA receptor 2) (LPA-2) - Macaca fascicularis (Crab eating macaque) (Cynomolgus monkey).

>sp|Q98894|CB1A\_FUGRU Cannabinoid receptor type 1A - Fugu rubripes (Japanese pufferfish) (Takifugu rubripes).

>sp|P21554|CB1R\_HUMAN Cannabinoid receptor 1 (CB1) (CB-R) (CANN6) - Homo sapiens (Human).

>sp|P46089|GPR3\_HUMAN Probable G protein-coupled receptor  
GPR3 (ACCA orphan receptor) - Homo sapiens (Human).

>sp|P51651|GPR6\_RAT Probable G protein-coupled receptor  
GPR6 (CNL3) - Rattus norvegicus (Rat).

>sp|P46095|GPR6\_HUMAN Probable G protein-coupled receptor  
GPR6 - Homo sapiens (Human).

>sp|P34972|CB2R\_HUMAN Cannabinoid receptor 2 (CB2) (CB-2)  
(CX5) - Homo sapiens (Human).

## B.2. Alignment for predicting the TM region of S1P<sub>1</sub>

CLUSTAL W (1.74) multiple sequence alignment

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unk|VIRT9968|Blast_submission
sp|O08530|EDG1_MOUSE
sp|Q99500|EDG3_HUMAN
sp|Q9Z0U9|EDG3_MOUSE
sp|O95136|EDG5_HUMAN
sp|O95977|EDG6_HUMAN
sp|Q9Z0L1|EDG6_MOUSE
sp|Q92633|EDG2_HUMAN
sp|Q8K5E0|EDG7_RAT
sp|Q95KH4|EDG4_MACFA
sp|Q98894|CB1A_FUGRU
sp|P21554|CB1R_HUMAN
sp|P46089|GPR3_HUMAN
sp|P51651|GPR6_RAT
sp|P46095|GPR6_HUMAN
sp|P34972|CB2R_HUMAN
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MKSVL DGVADTTFRITITSG LQY LGSNDANYDDPLNDAAFK TGFSLQK-PL
MKSILDGLADTTFRITITD LLYVGSNDIQYEDIKGDMA SKLGYFPQKFP L
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-----MNASAAALNESQ
-----MNASAAALNDSQ
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unk|VIRT9968|Blast_submission
sp|O08530|EDG1_MOUSE
sp|Q99500|EDG3_HUMAN
sp|Q9Z0U9|EDG3_MOUSE
sp|O95136|EDG5_HUMAN
sp|O95977|EDG6_HUMAN
sp|Q9Z0L1|EDG6_MOUSE
sp|Q92633|EDG2_HUMAN
sp|Q8K5E0|EDG7_RAT
sp|Q95KH4|EDG4_MACFA
sp|Q98894|CB1A_FUGRU
sp|P21554|CB1R_HUMAN
sp|P46089|GPR3_HUMAN
sp|P51651|GPR6_RAT
sp|P46095|GPR6_HUMAN
sp|P34972|CB2R_HUMAN
-----
-----MGPT--SVPLVKAHRSSVSDYVNYDIIVRHYN-----
-----MVST--SIPEVKALRSSVSDYGYNDIIVRHYN-----
-----MATALPPRLQPVRGNETLREHYQ-----
-----MATTHAQGHQPVLGNDTLREHYD-----
-----MGSLYSEYLNPNKVQEHYN-----
-----MNAT--GTPVAPESCQQLAAGGHSRLIVLHYN-----
-----MNISTWSTLVTPESCHRLAASGHSLIVLHYN-----
-----MAAISTSIIPVISQPQFTAMNEPQCFYNESIAFFYN-----
-----MN--ECHYDKRMDFFYN-----
-----MVTMG--HCYYNETIGFFYN-----
SAFRSNSFPNKVPADEELIFKGI PFFPTNSTDLFGNRNTRDEN--SIQC
TSFRGSPFQEKMTAGDNP--QLVPADQVNIT E FYNKLSSFKENEENIQ C
-----MMWGAGSPLAWLSAGSGNVNVSS-----
VVAVAAEGAAAAATAAGT PDTSEWGPPAASAALGGGGPNGSLE-----
VVVVA AEGAAAAATAAGG PDTGEWGPPAA-AALGAGGGANGSLE-----
-----MEECWVTEIANGSKD-----

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unk|VIRT9968|Blast_submission
sp|O08530|EDG1_MOUSE
sp|Q99500|EDG3_HUMAN
sp|Q9Z0U9|EDG3_MOUSE
sp|O95136|EDG5_HUMAN
sp|O95977|EDG6_HUMAN
sp|Q9Z0L1|EDG6_MOUSE
sp|Q92633|EDG2_HUMAN
sp|Q8K5E0|EDG7_RAT
sp|Q95KH4|EDG4_MACFA
sp|Q98894|CB1A_FUGRU
sp|P21554|CB1R_HUMAN
sp|P46089|GPR3_HUMAN
sp|P51651|GPR6_RAT
sp|P46095|GPR6_HUMAN
sp|P34972|CB2R_HUMAN
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-YTGKLN--ISADKENS I KLT SVVFILICCFI ILENIFVLLTIWTKKFKH
-YTGKLN--IGA EKDHGIKLT SVVFILICCFI ILENIFVLLTIWTKKFKH
-YVGKLAGRLKEASEG-STLTTVLFVLC SFIVLENLMVLI AIWKNNKFH
-YVGKLAGRLRDPPEGGLTITLITLFLVTC SFIVLENLMVLI AIWKNNKFH
-YTKETL---ETQETTSQVASFIVILCCA I VVENLLVLI AVARNKSFH
-HSGRLAGRGGPEDGG-LGALRGLSVAASCLV VLENLLVLA I TSHMRSR
-HSGRLASRGGSEDDGGGLGMLRGP SVAAGCLV VLENAMVLA I AYMRSR
-RSGKHL--ATEWN-TVSKLVMGLGITVC I FIMLANL LVMVA I YVNR RFH
-RSNTDT--ADEWTGTKLVIVLCVGTFFCLF I FFSNSLVIA AVITNRK FH
-NSGKEL--SSHR--PKD VVVVALGLTVSVL VLLTNLLVIA I ASNRRFH
GENFMDMECFMILTSPQQLAVAVLSLTLGTFTVLENLVVLCVIFQSR TLR
GENFMDIECFMVLNPSQQLA IAVLSLTLGTFTVLENLLVLCVILHSRSLR
-VGPAEGPTGPAAPLPSKAWDVVLCISGTLV SCENALVVA I IVGTPAFR
-LSSQLPAGPSG LLLSAVNPWDVLLCVSGT V IAGENALVVA I IASTPALR
-LSSQLSAGPPGLLLPAVNPWDVLLCVSGT V IAGENALVVA I IASTPALR
GLDSNPMKDYMILSGPQKTAVAVLCTLLG LLSALENVA VLYLILSSHQLR

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unk|VIRT9968|Blast_submission
sp|O08530|EDG1_MOUSE
sp|Q99500|EDG3_HUMAN
sp|Q9Z0U9|EDG3_MOUSE
sp|O95136|EDG5_HUMAN
sp|O95977|EDG6_HUMAN
sp|Q9Z0L1|EDG6_MOUSE
sp|Q92633|EDG2_HUMAN
sp|Q8K5E0|EDG7_RAT
sp|Q95KH4|EDG4_MACFA
sp|Q98894|CB1A_FUGRU
sp|P21554|CB1R_HUMAN
sp|P46089|GPR3_HUMAN
-----
R-PMYYFIGNLALSDLLAGVAYTANLLLSGATTYKLT PAQWFLREGSMFV
R-PMYYFIGNLALSDLLAGVAYTANLLLSGATTYKLT PAQWFLREGSMFV
N-RMYFFIGNLALCDLLAGIAYKVNILMSGKTFSLSP TVWFLREGSMFV
N-RMYFFIGNLALCDLLAGIAYKVNILMSGKTFSLSP TVWFLREGSMFV
S-AMYLFLGNLAASDLLAGVAVFVANTLLSGSVTLRLTPVQWFAREGSAFI
R-WVYYCLVNIITLSDLLTGAAYLANVLLSGARTFRLAPAQWFLREGGLFT
R-WVYYCLLNITLSDLLTGLAYVNVVLLSGTRTFQLSPVHWFVREGGLFM
F-PIYYL MANLAADFFAGL AYFLMFNTGPNTRRLTVSTWLLRQGLIDT
F-PFYLLANLAADFFAGIAYVFLMFNTGPNTRRLTVSTWLLRQGLIDT
Q-PIYYLGNLAADLFAVAYLFLMFHTGPR TARLSLEGWFLRQGLIDT
CRPSYHF I GSLAVADLLGSVIFVYSFLDFHVFHKKDSPNVF LKLGAVTA
CRPSYHF I GSLAVADLLGSVIFVYSFIDFHVFHKKDSRNVFLKLGAVTA
A-PMFLLVGS LAVADLLAGL G---LVLHFAAVFCIGSAEMSLVLVGLAM

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sp|P51651|GPR6_RAT      T-PMFVLVGLATADLLAGCG---LILHFVFOYVVPSETVSLLMVGFVLA
sp|P46095|GPR6_HUMAN   T-PMFVLVGLATADLLAGCG---LILHFVFOYVLPSETVSLLTGKGFVLA
sp|P34972|CB2R_HUMAN   RKPSYLFIGSLAGADFLASVVFACSFVNFHVPHGVDSKAVFLFKIGSVTM
      :  :  .: .*: : .      :      :      *

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unk|VIRT9968|Blast_submission
sp|008530|EDG1_MOUSE   ALSASVFSLLAIAIERYITMLK-MKLHNGSNFRLLISACWVISLILG
sp|Q99500|EDG3_HUMAN   ALSASVFSLLAIAIERYITMLK-MKLHNGSNFRLLISACWVISLILG
sp|Q92009|EDG3_MOUSE   ALGASTCSLLAIAIERHLMIK-MRPYDANKRHRVFLIGMCWLIATFLG
sp|Q95136|EDG5_HUMAN   ALGASTCSLLAIAIERHLMIK-MRPYDANKRHRVFLIGMCWLIATFLG
sp|O95977|EDG6_HUMAN   TLSASVFSLLAIAIERHVAIAK-VKLYGSDKSCRMILLIGASWLISLVLG
sp|Q920L1|EDG6_MOUSE   ALAASFLLFTAGERFATMVRPVAESGATKTSRVYGFIGLCWLLAALLG
sp|Q92633|EDG2_HUMAN   ALAASFLLFTAGERFATMVR-VAESGATKTSRVYGCIGLCWLLAAILG
sp|Q8K5E0|EDG7_RAT     SLTASVANLLAIAIERHITVFR-MQLHTRMSNRRVVVVIVVITWMAIVMG
sp|Q95KH4|EDG4_MACFA   SLTASVATLLAIAVERRRSVMA-VQLHSRSLPRGRVVMIVGVVAALFGLG
sp|Q98894|CB1A_FUGRU   SFTASVGSFLFTAIDRYISIHRLAYRRIVTRTKAVIAFCMMWTISIIIA
sp|P21554|CB1R_HUMAN   SFTASVGSFLFTAIDRYISIHRLAYKRIVTRPKAVVAFCLMWTIAIVIA
sp|P46089|GPR3_HUMAN   AFTASIGSLLAIVDRYLSLYNALTYSETTVTRTYVMLALVWGGALGLG
sp|P51651|GPR6_RAT     SFAASVSSLLAIVDRYLSLYNALTYYSRRTLLGVHLLAATWTVSLGLG
sp|P46095|GPR6_HUMAN   SFAASVSSLLAIVDRYLSLYNALTYYSRRTLLGVHLLAATWTVSLGLG
sp|P34972|CB2R_HUMAN   TFTAASVGSLLTAIDRYLCLRYPPSYKALLTRGRALVTLGIMWVLSALVS
      : : * .*: : : *      :      * : : .

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unk|VIRT9968|Blast_submission
sp|008530|EDG1_MOUSE   GLPIMGWNCISALSSCSTVLPPLYHKHYILFCTVFTVTLTLLSIVILYCRIY
sp|Q99500|EDG3_HUMAN   GLPSMGWNCISSLSSCSTVLPPLYHKHYILFCTVFTVTLTLLSIVILYCRIY
sp|Q92009|EDG3_MOUSE   ALPILGWNCIHLNLPDCSTILPLYSKKYIAFCISIFTAILVTIVILYARIY
sp|O95136|EDG5_HUMAN   ALPILGWNCLENFPDCSTILPLYSKKYIAFLISIFTAILVTIVILYARIY
sp|O95977|EDG6_HUMAN   GLPILGWNCGLHLEACSTVLPPLYAKHYVLCVVTIFSIILLAIIVALYVRIY
sp|Q920L1|EDG6_MOUSE   MLPILLGWNCLEAFDRCSLLPLYSKRYILFCLVIFAGVLATIMGLYGAIF
sp|Q92633|EDG2_HUMAN   LLPLLGNWCVCAFPRCSLLPLYSKGYVLFVCFVVFALILVALLSLYGAIF
sp|Q8K5E0|EDG7_RAT     AIPSVGWNCICDIENCSNMAPLYSDSYLVFWAIFNLVTFVVMVLYAHIF
sp|Q95KH4|EDG4_MACFA   AVPTLGNWNCLEISACSSLAITYRSYLIFFWTVSNLLAFFIMVVVYVRIY
sp|Q98894|CB1A_FUGRU   LLPASHWHCLCALDRCSRMAPLLSRSYLAVALSLLVFLLMVAVYTRIF
sp|P21554|CB1R_HUMAN   VLPLLGNWNCRLNSVCSDFPLIDENYLMFWIGVTVSVLVFIIYAYIIL
sp|P46089|GPR3_HUMAN   VLPLLGNWNCLEKQSVCSDFPHIDETYLFWIGVTVSVLFFFVYAYMYIL
sp|P51651|GPR6_RAT     LLPVLAWNCLDGLTTCGVVYP-LSKNHLVVLAIAFFMVFIMQLQYQAIC
sp|P46095|GPR6_HUMAN   LLPVLGNWNCADRASCVVVRP-LTRSHVALLSTFFVVFIMLHLYVRIC
sp|P34972|CB2R_HUMAN   LLPVLGNWNCLEAERACVVVRP-LARSHVALLSAAFMMVFIMLHLYVRIC
      YLPLMGWTCPP--RPCSELPPLIPNDYLLSWLLFIAFLFSGIITYYGHVL
      : * . * * * . : * : :      . : : * :

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unk|VIRT9968|Blast_submission
sp|008530|EDG1_MOUSE   SLVTRSRRLTFRKNIS-----KASRSSE-NVALLKTVIIV
sp|Q99500|EDG3_HUMAN   SLVTRSRRLTFRKNIS-----KASRSSEKSLALLKTVIIV
sp|Q92009|EDG3_MOUSE   FLVKSSSRKVANHNN-----SERSMALLRTVVIV
sp|O95136|EDG5_HUMAN   CLVKSSSRVANHN-----SERSMALLRTVVIV
sp|O95977|EDG6_HUMAN   CVVRSSHADMAAPQ-----TLALLKTVTIV
sp|Q920L1|EDG6_MOUSE   RLVAASGQKAPRA-----ARRKARLLKTVLMI
sp|Q92633|EDG2_HUMAN   RVVRANGQKSRPP-----ARRKSRLLNTVLM
sp|Q8K5E0|EDG7_RAT     GYVQRTRMRSRHSSGP-----R--RNRDTMMSLLKTVIV
sp|Q95KH4|EDG4_MACFA   MYVKKRTNVLSPHTSGS-----I--SRRRAPMKLMKTVMTV
sp|Q98894|CB1A_FUGRU   FVYVRRVQRMMAEHVSC-----P--RYRETTLSLVKTVVVI
sp|P21554|CB1R_HUMAN   WKAHSHAVRMLSRTSQKSLVVSAGETKVQVTRPEQTRMDIRLAKTLVLI
sp|P46089|GPR3_HUMAN   WKAHSHAVRMLSRGTQKSIIIHTSEGDGVQVTRPDQARMDIRLAKTLVLI
sp|P51651|GPR6_RAT     RIVCRHAQQIALQRHLL-----PA-SHYVATRKGIATLAVV
sp|P46095|GPR6_HUMAN   QVVWRHAHQIALQQHCL-----AP-PHLAATRKGVTGLAVV
sp|P34972|CB2R_HUMAN   QVVWRHAHQIALQQHCL-----AP-PHLAATRKGVTGLAVV
      WKAHQHVASLSGHQDRQ-----VPGMARMLDVRLLAKTLGLV
      .
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unk|VIRT9968|Blast_submission
sp|008530|EDG1_MOUSE   LSVFIACWAPLFIILLLLDVG-CKVKTCDILFRAEYFLVLAVALNSGTNP
sp|Q99500|EDG3_HUMAN   LSVFIACWAPLFIILLLLDVG-CKAKTCDILYKAEYFLVLAVALNSGTNP
sp|Q92009|EDG3_MOUSE   VSVFIACWSPFLIFLIDVA-CRVQACPILFKAQWFIIVLAVLNSAMNPVI
sp|O95136|EDG5_HUMAN   VSVFIACWSPFLIFLIDVA-CRAKECSILFKSQWFIMLAVLNSAMNPVI
sp|O95977|EDG6_HUMAN   LGFVIVCWLPAPFISILLDYA-CPVHSCPILYKAHYFFAVSTLNSLNPVI
sp|Q920L1|EDG6_MOUSE   LLAFLVCWGPLFGLLLADVFGSNLWAEYLRGMDWILALAVLNSAVNPII
sp|Q92633|EDG2_HUMAN   LVAFVVCWGPLFGLLLADIFGNSVWAEYLRGMDWILALAVLNSAINPLI
sp|Q8K5E0|EDG7_RAT     LGAFIICWTPGLVLLLDG---VCCPQCDVLAYEKFFLLAEFNSAMNPII
sp|Q95KH4|EDG4_MACFA   LGAFVVCWTPGLVLLLDG---LNCKQCNVQHVVRWFLLLALLNSVMNPII
sp|Q98894|CB1A_FUGRU   LGAFVVCWTPGQVLLLDG---LGCKSCNVLAVEKYFLLAEANSLVNAAV
sp|P21554|CB1R_HUMAN   LAVLVICWGPLLAIMVYDL---FWKMDNIIKTVFAFCMSLCLLNSTVNP
sp|P46089|GPR3_HUMAN   LVVLIICWGPLLAIMVYDV---FGKMNKLIKTVFAFCMSLCLLNSTVNP
sp|P51651|GPR6_RAT     LGAFVVCWTPGQVLLLDG---DAHSPPPLYTYLTLTPATYNSMINPII
      LGTFGASWLPFAIYCVVG-----SQEDPAIYTYATLTPATYNSMINPII

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sp|P46095|GPR6_HUMAN          LGTFGASWLPFAIYCVVG-----SHEDPAVYTYATLLPATYNSMINPII
sp|P34972|CB2R_HUMAN          LAVLLICWFPVLALMAHSLA--TTLSDQVKKAFACFCSMLCLINSMVNPVI
                               :.: .* * . . ** *.:
unk|VIRT9968|Blast_submission YTLTNKEMRRAFRIRIM---SCCKCPGSDSAGKFKRPIIA-GMEFSRSKS-
sp|O08530|EDG1_MOUSE          YTLTNKEMRRAFRIRIV---SCCKCPNGDSAGKFKRPIIP-GMEFSRSKS-
sp|Q99500|EDG3_HUMAN          YTLASKEMRRAFFRLV---CNCLVRG---RGARASPIQP-ALDPSRSKSS
sp|Q9Z0U9|EDG3_MOUSE          YTLASKEMRRAFFRLV---CGCLVKG---KGTQASPMQP-ALDPSRSKSS
sp|O95136|EDG5_HUMAN          YTWRSRDLRREVLRP----LQCWRPGVGQGRRRGGTPGHLLPLRSSSS
sp|O95977|EDG6_HUMAN          YSFRSREVCRAVLSFLC--CGCLRLGMRGPGDCLARAVEAHSGASTTDSS
sp|Q9Z0L1|EDG6_MOUSE          YSFRSREVQRAVLAFLC--CGCLWLGLRGP GDCLTRITEAHSGASTTDSS
sp|Q92633|EDG2_HUMAN          YSYRDKEMSATFRQILC--CQRSEN-----PTGPTEGSDRSA
sp|Q8K5E0|EDG7_RAT            YSYKDEDMYNTMRKMIC--CAPHDSN----AERHPSRIPSTIHSRSDTGS
sp|Q95KH4|EDG4_MACFA          YSCRDAEMRRTFRRLLC--CACLRRS----TR-----ESAHYTSSAQGG
sp|Q98894|CB1A_FUGRU          YALRSRDLRHAFLLSSC---HACRGSAAQQLDNSL--ESDCQNRNVN--ISA
sp|P21554|CB1R_HUMAN          YALRSKDLRHAFRSMF---PSCFETAQPLDNSMG--DSDCLHKHANNAASV
sp|P46089|GPR3_HUMAN          YAFRNQDVQKVLWAVC---CCSSS-----KIPFRSRSPSDV
sp|P51651|GPR6_RAT            YAFRNQEIQRALWLLF---CGCFQS-----KVPFRSRSPSEV
sp|P46095|GPR6_HUMAN          YAFRNQEIQRALWLLF---CGCFQS-----KVPFRSRSPSEV
sp|P34972|CB2R_HUMAN          YALRSGEIRSSAHHCLAHWKKCVRG-----LGSEAKEEAPRSS
                               *: . .:

unk|VIRT9968|Blast_submission --DNSSHQKDEGDNPETIMSSGNVNSSS-----
sp|O08530|EDG1_MOUSE          --DNSSHQKDDGDNPETIMSSGNVNSSS-----
sp|Q99500|EDG3_HUMAN          SSNNSSHSPKVKEDLPHPTAPSSCIMDKNAALQNGIFCN
sp|Q9Z0U9|EDG3_MOUSE          SSNNSSHSPKVKEDLPRVATSSCIIDKNRSFQNGVLCK
sp|O95136|EDG5_HUMAN          -LERGMHMPTS---PTFLEGNTVV-----
sp|O95977|EDG6_HUMAN          LRPRDSFRGRSRLSFRMREPLSSISSVRSI-----
sp|Q9Z0L1|EDG6_MOUSE          LRPRDSFRTRSRLSFRMREPLSSISSVRST-----
sp|Q92633|EDG2_HUMAN          SSLNHTILAGV-----HSNDHSV-----
sp|Q8K5E0|EDG7_RAT            QYLEDSISQGG-----VCNKSS-----
sp|Q95KH4|EDG4_MACFA          ASTRIMLPENG-----HPLMDSL-----
sp|Q98894|CB1A_FUGRU          NRAAESCVKTTVKIAKVTMSVSTETSAEAV-----
sp|P21554|CB1R_HUMAN          HRAAESCISKSTVKIAKVTMSVSTETSAEAL-----
sp|P46089|GPR3_HUMAN          -----
sp|P51651|GPR6_RAT            -----
sp|P46095|GPR6_HUMAN          -----
sp|P34972|CB2R_HUMAN          VTETEADGKITPWPDSRDLDLSDC-----

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