

A

```

MRGPRX4 1 MDPT-----VPEVGTKLTPHNGREET---PCYNOITLSTVLTCLISLVGLTGNVA
MRGPRX2 1 MDPT-----TPAWGTESTTVNGNDCAILLGKETLIPVFLIFHALVGLVGNVF
Mrgpra1 1 MGESSTCAGFLAINTSASPTAPTINPMDNTIPGGINITILIPNLIIIFGLVGLTNGNI
Mrgprb2 1 MSGDFLI---KNLSTSAWKTNETVINGSYIDTSVQVTRNOAMLLSIIISLVGMLNAI

MRGPRX4 48 VLWLLGVRMRNASTYIILNLAADFLFLSFQIIRLPLRLINISHLT---RKILVSVMT
MRGPRX2 51 VLWLLGFRMRNAFSVYVLSLAGADFLFCFOIINCLVYLSNFFCSISINFBSEFTTVMT
Mrgpra1 61 VLWLLGFCHRNAFSVYIILNLAADFLFLGLGHLDISLILINVFYPI--TFLICFYTMM
Mrgprb2 58 VLWFLGIRMTNNAFTVYIILNLAADFLFLCSQFVICLLAFYLFYSIDINIPVLVWVPI

MRGPRX4 104 FPFVFTGLSMLSIAISTERCLSVLWPIWYRCRRPHTLSAVVCVILWGLSLLFSMLEWRFQDF
MRGPRX2 111 CAYLAGLSMLSTVSTERCLSVLWPIWYRCRRPRHLSAVVCVILWALSILLSILECKFCGF
Mrgpra1 119 VLYLAGLSMLSIAISTERCLSVLQPIWYICHRPEHTSIVMCAVWVLSLLCILNSYFCGF
Mrgprb2 118 FAYLSGLSILSTIISTERCLSVLWPIWYRCRRPRHTSAITCFVLWVMSLLIGLEGRACGL

MRGPRX4 164 LFSGAN--SNCETSDFIPVAWLIFLCVVLQVSSIVLVLRILCGSRKMPLTRLYVTITLTV
MRGPRX2 171 LFSDDG--SNCQTFDFITAAWLIFLFLVLCGSSLALLVLRILCGSRGLPLTRLYTITLTV
Mrgpra1 179 LNFQYKNENGCLALSFTTAAVLMFLFVVLCSLALVARIFCGGGQIKLTRLYVTIILSI
Mrgprb2 178 LNSFD--SYWCETFDVITNIWVVFEGVLCGSSITLLVRIFCGSQIFMTRLYVTITLTV

MRGPRX4 223 LVFLLCGLPFGILGALIRHHLNLEVLVCHVYVLCVSLSSLNSSANPIIYFFVGSFRQV-
MRGPRX2 230 LVFLLCGLPFGIQWFLIIVHWKDSVVLVCHIHVSVVLSLSSANPIIYFFVGSFRKQW
Mrgpra1 239 LVFLLCGLPFGIHWFLIRKIKDDFHVFDLGFYLASVVLAINNSCANPIIYFFVGSFRHR-
Mrgprb2 237 LVFLIFGLPFGIYIILYQWISNFYVVEICNFYLEIIFLSCVNSCMNPIIYFLVGSIRHR-

MRGPRX4 282 -QNRRNKKLVLQRALQDKPEVDKGEGLPEEELFSGSKLG-P
MRGPRX2 290 RLQQPILKLLALQRALQDIAEVDHSEGCFRQGTPEMSRSST--V
Mrgpra1 298 -LKHOTLKMVLQNALQDTPETAKIM-----VPMRSRSE-E
Mrgprb2 296 RFRFKPLKLLQRALQDTPEEIQSGNKSSSHPEELETVQSCS

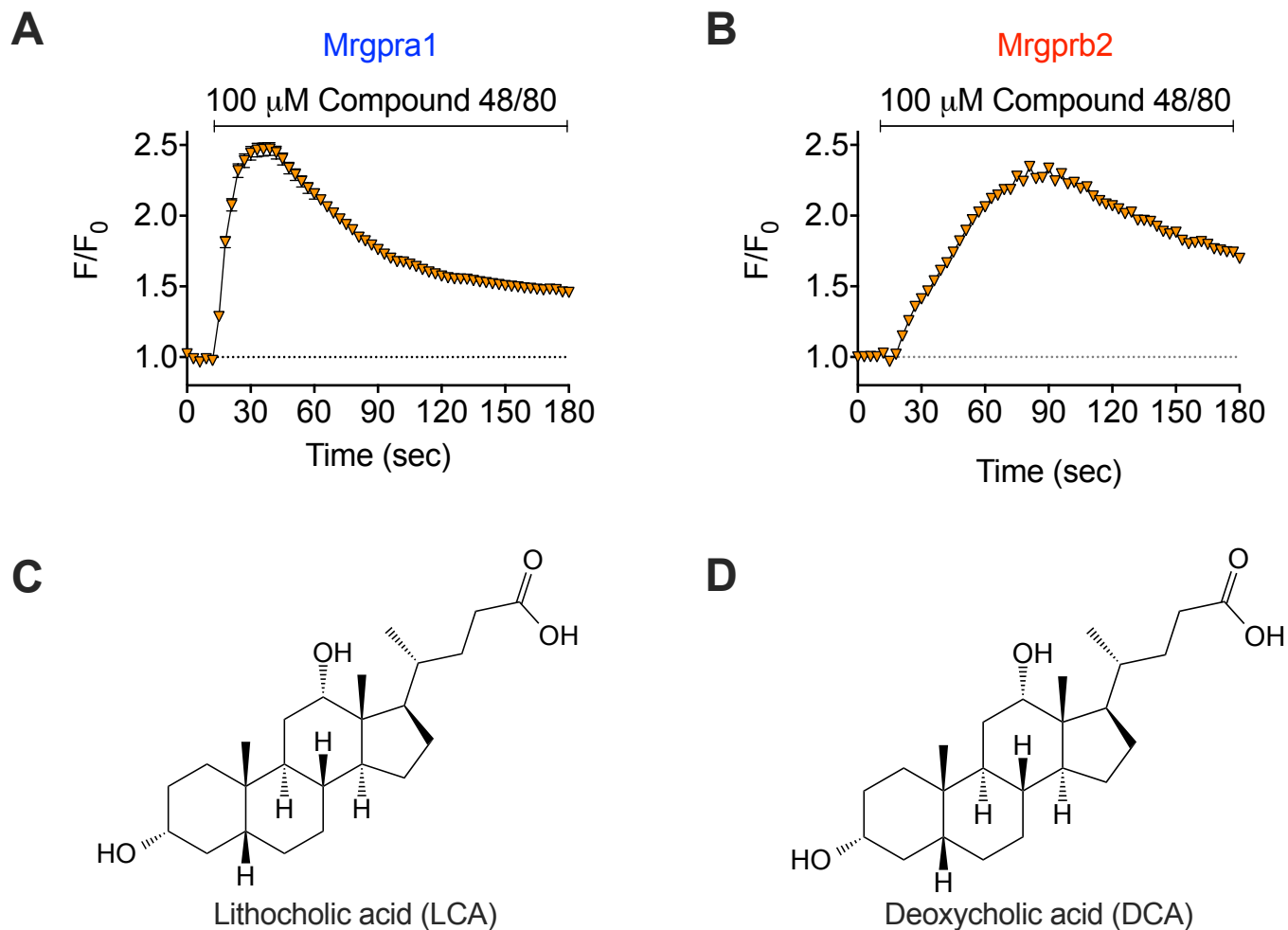
```

B

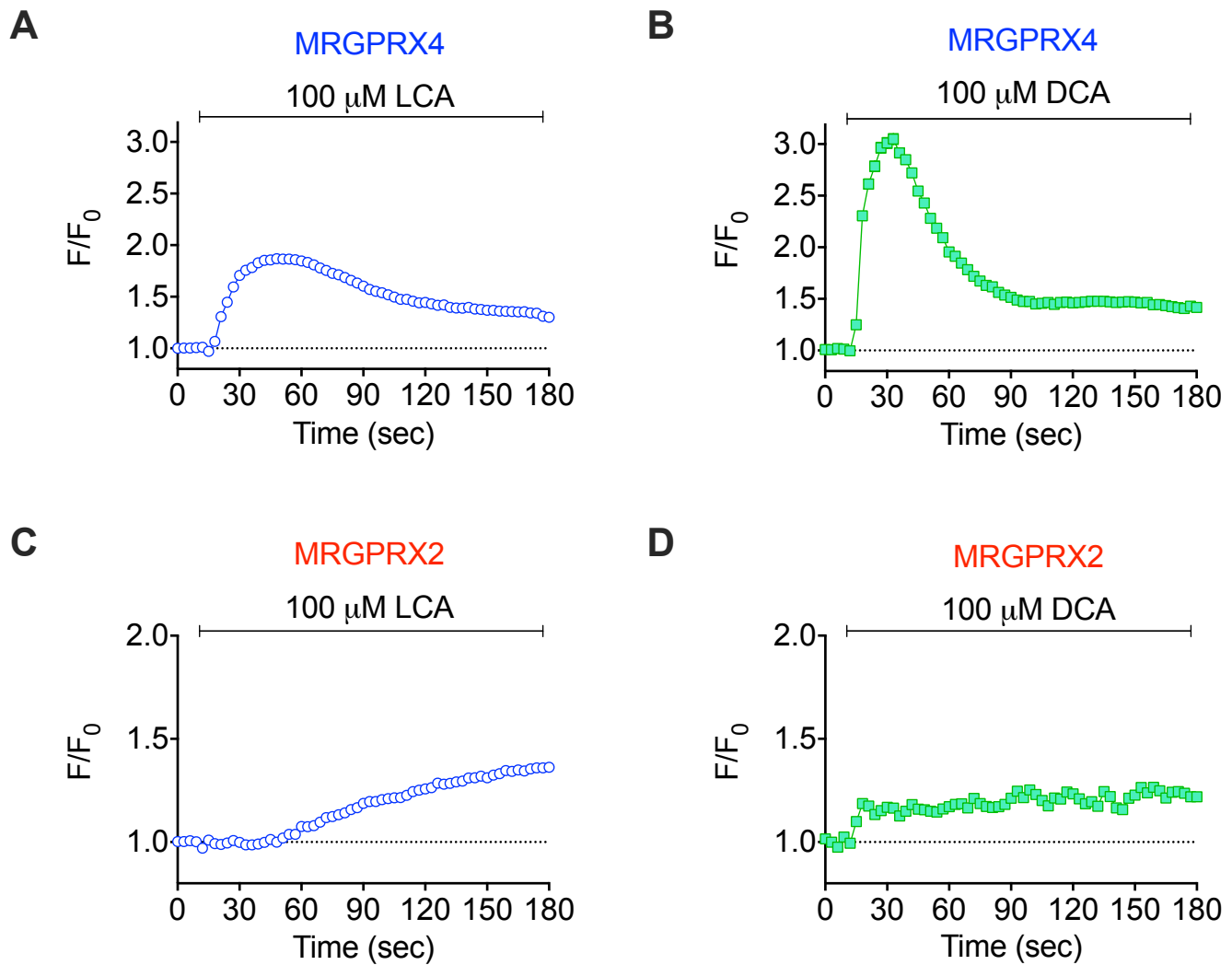
Supplementary Fig. 1. (A) Comparison of the amino acid sequences of human MRGPRX2, human MRGPRX4, mouse Mrgpra1, and mouse Mrgprb2. Identical residues are shaded in black, and conservative substitutions are colored in gray. (B) Phylogenetic tree showing the sequence similarity among human MRGPRX2, human MRGPRX4, mouse Mrgpra1, and mouse Mrgprb2.

TM indicates transmembrane region predicted by TMHMM Server v. 2.0

(<http://www.cbs.dtu.dk/services/TMHMM/>)



Supplementary Fig. 2. (A) HEK293T cells transiently expressing Mrgpra1 were treated with compound 48/80 (100 μ M), which led to an increase in intracellular calcium levels (n = 3794 cells). (B) HEK293T cells transiently expressing Mrgprb2 were treated with compound 48/80 (100 μ M), which led to an increase in intracellular calcium levels. (n = 2216 cells) (C, D) The molecular stereochemical structure of lithocholic acid (LCA) and deoxycholic acid (DCA).



Supplementary Fig. 3. (A, B) HEK293T cells transiently expressing MRGPRX4 were treated with lithocholic acid (LCA; 100 μ M, n = 1788 cells) and deoxycholic acid (DCA; 100 μ M, n = 3331 cells) (C, D) HEK293T cells transiently expressing MRGPRX2 were treated with LCA (100 μ M, n = 2491 cells) and DCA (100 μ M, n = 3932 cells).