Supplementary Information.

Supplementary Figure 1. Amino acid sequence of ten $TRPM_{PZQ}$ orthologs that were functionally profiled in this study. Binding pocket residues are highlighted in yellow (trematode consensus) with amino acid variation from the trematode consensus color coded as per Table 1.

Supplementary Figure 2. Metadynamics simulations of (*R*)-PZQ complexed with *Sm*.TRPM[D1677E]$_{PZQ}$. *Left*, representative free energy plot resulting from metadynamics simulations of (R)-PZQ complexed with *Sm*.TRPM[D1677E]$_{PZQ}$. The x-axis is the collective variable (CV), set as the distance between the center of mass of (*R*)-PZQ and the center of mass of D1677 (in Å). The y-axis shows the free energy of that interaction (in kcal/mol). The red box encloses the relative minima of the simulation. *Right*, the associated binding pose of (*R*)-PZQ within *Sm*.TRPM[D1677E]$_{PZQ}$ from the boxed frame on the left.

Supplementary Figure 3. A Comparison of the Binding Pose of (*R*)-PZQ in *Sm*.$TRPM_{PZQ}$ to the binding pose of icilin and Cryosim-3 in *Hs*.TRPM8. (A&B) The overlay of ribbon structures of *Sm*.$TRPM_{PZQ}$ and *Hs*.TRPM8 (PDB: 6NR3, panel A) and the overlay of ribbon structures of *Sm*.$TRPM_{PZQ}$ and the agonist bound, open state of *Hs*.TRPM8 (PDB: 8E4L, panel B) are shown. Both show good alignment of the secondary structure of the VSLD. **(C&D)** The binding pose of (*R*)-PZQ (pink) in the VSLD of *Sm*.$TRPM_{PZQ}$ superimposed on the binding poses of (**C**) icilin (green, from PDB 6NR3) in *Hs.*TRPM8 and (**D**) Cryosim-3 (green, from PDB 8E4L) in *Hs*.TRPM8 is depicted. D1677 (*Sm*.$TRPM_{PZQ}$) is anchored outside the binding pocket (pink) whereas E1003 (*Hs*.TRPM8) projects into the binding pocket (green). **(E&F)** The binding pose of (*R*)-PZQ (pink) in the VSLD of *Sm*.TRPM[D1677E]$_{PZQ}$ (from metadynamics, Figure **6**) superimposed on the binding pose of (**E**) icilin (green, from PDB 6NR3) in *Hs*.TRPM8 and (**F**) Cryosim-3 (green, from PDB 8E4L) in *Hs*.TRPM8 is depicted. Residues E1677 (*Sm*.TRPM[D1677E]$_{PZQ}$, pink) and E1003 (*Hs*.TRPM8, green) both project into the binding pocket. Notably, (*R*)-PZQ, icilin, and Cryosim-3 all present in similar 'vertical' binding poses in the presence of the TRP domain glutamic acid.

Supplementary Table 1. Amino acid identity between functionally profiled $TRPM_{PZQ}$ orthologs. Sequences were aligned and analyzed as detailed in the Methods. Species are abbreviated as: Sm (*Schistosoma mansoni*), Sh (*Schistosoma haematobium*), Sj (*Schistosoma japonicum*), Cs (*Clonorchis sinensis*), Ov (*Opisthorchis viverrini*), Ec (*Echinostoma caproni*), Fh (*Fasciola hepatica*), Fg (*Fasciola gigantica*), Ml (*Macrostomum lignano*), Eg (*Echinococcus granulosus*), Mc (*Mesocestoides corti*). Identity is color-mapped >80% (green), >60% (yellow), >40% (blue) and >20% (red).

Supplementary Table 2. $TRPM_{PZQ}$ binding pocket comparison. This table lists the identities of twenty-three residues predicted to comprise the PZQ binding pocket in $TRPM_{PZQ}$ orthologs across 46 different flatworm species as well as human TRPM2 and TRPM8. These species comprise 43 parasitic flatworms and 3 free-living flatworm (*Rhabditophora*) representatives. The identity of the 23 residues lining the binding pocket in *Schistosoma mansoni* $TRPM_{PZQ}$ (*Sm*.$TRPM_{PZQ}$) are used as reference for comparison (top row of table). Grey bars represent missing sequence information from published genomes. The consensus sequence is well conserved, with just three loci of variation across all examined parasitic flatworm sequences (highlighted by shading). These loci are (i) in the S1 helix (green, N1388 in *Sm*.$TRPM_{PZQ}$), (ii) in the cytoplasmic loop between S4 and S5 (pink, T1518 in *Sm*.$TRPM_{PZQ}$) and (iii) at the distal end of the TRP helix (orange, D1677 in *Sm*.$TRPM_{PZQ}$). Further positions of variation present in free-living platyhelminths and human TRPM channels are shown in black. For each species, the related BioProject IDs and gene identifiers are as follows. Orthologs that are functionally profiled

in this study are bolded. Gene Identifiers (Wormbase, BioProject ID) and Genbank (GB) accession numbers for available sequences are as follows: *Schistosoma mansoni* (PRJEA36577, Smp_246790.5); *Schistosoma haematobium* (PRJNA78265, MS3_0012599.1 partial); *Schistosoma japonicum* (PRJEA34885/PRJNA520774, EWB00_008853); *Schistosoma bovis* (PRJNA451066, DC041_0009326 partial); *Schistosoma curassoni* (PRJEB519, various); *Schistosoma margrebowiei* (PRJEB522, SMRZ_0001736801 partial); *Schistosoma mattheei* (PRJEB523, various); *Schistosoma rodhaini* (PRJEB526, SROB_0000612701 partial); *Trichobilharzia regent* (PRJEB4662, various); *Clonorchis sinensis* (PRJDA72781/PRJNA386618, csin109609); *Opisthorchis felineus* (PRJNA413383, CRM22_004304 partial); *Opisthorchis viverrini* (PRJNA222628, T265_03361); *Paragonimus westermani* (PRJNA454344, DEA37_0005686 partial); *Paragonimus heterotremus* (PRJNA284523, KAF5404912.1; KAF5404913.1 (GB)); *Paragonimus kellicotti* (PRJNA179523, KAF6777619.1 partial (GB)); *Paragonimus miyazakii* (PRJNA245325, KAF7262430.1 (GB)); *Dicrocoelium dendriticum* (PRJEB3954, various); *Atriophallophorus winterbourne* (PRJNA636673, maker-jcf7180000220132-snap-gene-0.1; maker-agouti_scaf_1481-snap-gene-0.0); *Echinostoma caproni* (PRJEB1207, ECPE_0000226901); *Fasciola gigantica* (PRJNA230515, FGIG_00826); *Fasciola hepatica* (PRJEB25283/PRJNA179522, THD26109.1 (GB)); *Fasciolopsis buski* (PRJNA284521, KAA0184185.1 (GB)); *Gyrodactylus salaris* (PRJNA244375, maker-scf7180006953457-snap-gene-0.79-mRNA-1 partial); *Gyrodactylus bullartarudis* (PRJNA532341, various); *Protopolystoma xenopodis* (PRJEB1201, PXEA_0002869701-mRNA-1 partial); *Echinococcus canadensis* (PRJEB8992, EcG7_04348; EcG7_07443); *Echinococcus granulosus* (PRJEB121/PRJNA182977, EgrG_000986600); *Echinococcus multilocularis* (PRJEB122, EmuJ_000986600); *Echinococcus oligarthrus* (PRJEB31222, various); *Hydatigera taeniaeformis* (PRJEB534, various); *Taenia asiatica* (PRJEB532/PRJNA299871, TASs00007g01845); *Taenia multiceps* (PRJNA307624, Tm1G005541); *Taenia saginata* (PRJNA71493, TSAs00047g06173); *Taenia solium* (PRJNA170813, TsM_000444100 partial); *Hymenolepis diminuta* (PRJEB30942/PRJEB507, various); *Hymenolepis microstoma* (PRJEB124, HmN_000757100.2); *Rodentolepsis nana* (PRJEB508, various); *Mesocestoides corti* (PRJEB510, MCU_009642-RA partial); *Moniezia expansa* (PRJNA668441, JADFDV010000093.1); *Schistocephalus solidus* (PRJEB527, SSLN_0001491701 partial); *Spirometra erinaceieuropaei* (PRJEB1202, VZI00796.1 partial (GB)); *Dibothriocephalus latus* (PRJEB1206, various); *Sparganum proliferum* (PRJEB35374, VZI30146.1 (GB)).

Supplementary Figure 1.

>*Sh*.TRPM$_{PZQ}$ (2195)

MTEQIPFQRTSTIKHRISRTGSIGQDHNNNNNNNNNNNTTGNMMITSGINNSGIQHQQSSIRRPSIMQKY
MGEIEFTGLNQTARFCKLNSDTPDSVLRDILKRKWGLKPPTLIITVFGTDFEKKRKLKMIFKKGLWKAAE
SGCWIVTGGFHLGVMKLTGEAVRDYTDAYGGNRMMAFGVASWDCVTKNEILEAALHEGTAVYQSEEDEEE
EAEDSEPILIDPLSQSGLKSVRSDIEERALDPNHNFFVLVDDGTTDQLKGKEAELRARFERCISLWNCAS
SPQEQTTTATSPQSGPISSTTHLQQQQQQQQPQNGISTPSNINNNVNSVGLQRQGSTMGGQVSTTSGPQT
SATSIGKNSGITGGSTSNSALSKGASEPIVSNQPISTVSVTRGAKDKLTTESSLKPAKSGKSVGSEEEIL
VPMCGLVVGGDRFTLRQVYCSMIRNRCPIVVTKGTSGAADVLAFGLDAANKMASEEVVDDKDQVPLEARL
ESIIEEFLGDLHPDYTNYTDEVNMLCEIINDYTNLVSVFDMEEDSDLDGYVISSLLASAGTTVTSDQINL
EQLEITLTLNRADIAREKIFLENKKWKKGQLNDYMYQALMSDRHDFVKLFLEQGFSLEDFLTIYMLEKLY
TDQLKNLNSKVAIFNKMWEYNRSHRTSKVALRDVGKVIKALVGDFYHPLYLSKEFQAKLMPEKRLEGAGT
RAIIRRGATSVEPAEKNHDDGDDNDDDYNDDGDDREYNGDELYGNNIDGYTINSRLPRSSTTMTTVSGEP
LIASTILRSNEKGNTMGTSTITLIGGSRLREGNIPHQYHSIDQMNSSRSHSRNPMITIYDKQQINDITED
INNQSKKSKYLSATRNNDGNRNGHSSRNKHGRRSSSQTNEHDMLIPGQPLIYNATVTNVSRSGHGSRGPY
TSLGPGHFRIAGKAPLAYDTTSMGTTTPIQSPKPAINDTLQFSFDNEHVQRNSVLISPIQNEKSIKPVLF
EDEANNKSSRSCFMSCIQKISSFCSRLFRCNTDSKKSNKGLNVSQEPSGIKGPKEFATLRAMAALAAATA
ATAVADPTKTSPGDLLIPSNFFEPDEEQTKSIQLDRPARELLIWSILAGKLRMAELFWTMEKEPIAAALL
ASILLTSLGNKTDDFTDKEDYRSFAKNFQERAEGVLNECYREDEHRTQLIINHELIYYGRSSVIKLAAEG
QSIKFMAHPCCQDFLTNTWSGNLSTKNSVFRYIMGVVCGLTLPFLIPKVILSKPKAIPTTEGEESSPTSE
QQGSTQNNHTLKYVLTAEDAGKKGVRKTLQARTLEYISQIRDFYMAPVVRFVYNTISYITFLILFSYLLL
VDFRINITVVEYVVIAWVITLFIEEIKQIAWAVLSGISFRTYISDGWNKLDCAGLALYIVGFILRLIVLL
RLRSHEGENFNIQYERYYIVTDPILDPSRICLAISLFTFYIRLMYTFSFHIALGPKLIMIGKMVTNDLIP
FMIILTVIMVGYAVAAQSIAYPNGLFTKENMTLNSEIKHMTFADIIFSMYTTAYFQMFGDFSLDALQGED
RTCQNHMCPTKTSRWLVPIMLGFYVLLTNILMFNLLIAMFSKTYEEIESASTYYWNYQRYQMINDYVHRS
PLAPPIIIVWHFYEAYKAIGNQCASLRNAETAKYNPFCVRFTDVKKEREMVKWEHMKAMDYLREPSTKAT
GKRGVAESRAVVFRGGGGVGPGQGPVMDLKSEMSSVTEGIGMELEKRFKEIDNQFQRFNDVDSRLNDVTQ
LLTNLSEVISNVTETQQRIIRQINELPTCQCNEFTDEVVPVQKSTTTQADSGTAETRKRTKLEVAIQSAL
EAAKDVLRPPTPPPPPPPPPPPRESPVLLAAVVPGSEDDSSGSEEGGDPSADPVIVPQVPDIKTGRVIE
RTLGDHRLWRMAPFNFEKYPGMRMNVPPERMAWTVEYPDYFAYDACEEVLLFPSEESHDGVNFTHGNIVF
TFQHSENLRTINFNQYDSKAKLRRQSLLGRYRLDSTTGAPLNPMGRTGLLGKGLLPRWGPNHSFVLCITR
WTRDTRTGVQVIRSNRGVLQYLALERNKRLCMPWYLTDHTNKCDFDECVPKIISSLVTRRGRAILPEKRV
ERLLKRIEKAEVTQIFKGYLDDQLNADSAWMETVVINLHESESKGAQLPDDILKLLNEPGTEEQCKWVEV
SHSSNLRTSHNYILKNIAELRRAFY

>*Sj*.TRPM$_{PZQ}$(2179)

MTEQIPFHRTSTLKHRASRTSSVIVQDNTIGGVATTNTTAATTTTGSIVVPAGGGGSGLQQQSSVRRPSV
MQKYMGEIEFTGLNQTARFCKLNSDTADSVLRDILKRKWGLKPPTLIITVFGTDFEKKRKLKMIFKKGLW
KAAESGCWIVTGGFHLGIMKLTGEAVRDYTDAYGGNRMMAFGVASWDCVTKNEILEAALHEGTAVYQSEE
DDEEEAEDSEPILVDPLSQAGLKSVRSDVEERALDPNHNFFVLVDDGTTDQLKGKEAELRARFERCISLW
NCASSPQEQNITGTNQQSGAITSTTHLQQPQGVISTSSNINNNVTPGGLQRQGSTMGGQTSTTSGPQTSA
TSIGKGSGTTGGSSSNSALSKVVSEPVVSNQPISATSTTRGAKEKPTTDSSIKQKSGKSVGSEEEILVPM
CGLVVGGDRFTLRQVYCSMIRNRCPIVVTKGTSGAADVIAFGLDAANKMASEEVVDDKDQVPLEARIESI
IEEFLSDLHPDYTNYTDEVNMLCEIINDYTNLVSVFDMEEDSDLDGYVISSLLASAGSTIASDQINLEQL
EITLTLNRADIAREKIFLENKKWKKGQLNDYMYQALMSDRHDFVKLFLEQGFSLEDFLTVYMLEKLYTDQ
LKNLNSKVAIFNKMWEYNRSHRTSKVALRDVGKVIKALVGDFYHPLYLSKEFQTKLMPEKRLEGAGTRAI
IRRGATSVEPNEENRDLPDIDDDGNAIYGDNNDEFIVNYRLPRSSTAITTISGEPLLTSTALHNSEKGGT
AMGTTVPAVKIGTGRKGGNVQHYYDPNERAKSSRSHSRNPFTTTYDKQLTNDINDKLDSQPRSTYLSATR
NNNFNRNGHSGRNRYGHHSSSHSNEHDMLIPGQPLIYNATVTSVNRSGRGSRNVYTSLGPGHFRIAGRAP
LAYDAASVGTTSPVQSPKPGMNDTLRFSFDDDRPQRNSVLISSNLNEKPIKPVLFEDEMINKPSRSCLTS
CFQKISSFCGRLFGRNTGSKKSKKASNLSHEVSGIKGPKEFATLRAMAALAAATAATAVADPTKGTQGDL
IIPPNFFDPDEEQTKSIQLDRPARELLIWSILVGKLRMAELFWTMEKEPIAAALLASILLTSLGNKTDDF
TDKEDYRSFAKNFQERAEGVLNECYREDEHRTQLIINHELIYYGRSSVIKLAAEGQSIKFMAHPCCQDFL
TNTWSGNLSTKNSVFRYIMGVVCGLTLPFLIPKVILSKPKTGPTTEGEESSASSEQQPSTQNDHTLKYLT
SAEDAGKNGVRKTLQARTLEYISQIRDFYMAPVVRFVYNTISYITFLILFSYLLLVDFRINITVVEYIVI
AWVVTLFIEEIKQIAWAVLSGISFRTYISDGWNKLDCAGLALYIVGFILRLIVLLRLGGEKNFDFQHERY
YIVTDPILDPSRICLAISLFTFYIRLMYTFSFHIALGPKLIMIGKMVTNDLIPFMIILTVIMVGYAVAAQ
SIAYPNGLFTKENMTLNSEIKHMTFADIIFSMYTTAYFQMFGDFSLDALQGEDRTCQNHMCPTKTSRWLV
PIMLGFYVLLTNILMFNLLIAMFSKTYEEIESASTYYWNYQRYQMINDYVHRSPLAPPIIIVWHFYEAYK
AIGNQCASLRNAETAKYNPFCVRFTDLKKEREMVKWEHMKAMDYLREPSTKATGKRGVAESRAVVFRGGG
GVGPGQGPVMDLKSEMSSVTEGIGMELEKRFKEIDNQFQRFNDVDSRLNDVTQLLTNLSEVISNVTDTQQ
RIIRQINELPTCQCNELTDEIVPVQKSPTTLQADKGTMETRKRTKLEVAIQSALEAAKDVLRPPTPPPPP
PPPPPPPRESPVLLAAVVPGSEDDSSGSEEGGDPSADPTLVPQVPDSKTGRVIERVLGDHRLWRMAPFNF
EKYPGMRMNVPPERMAWTVEYPDYFAYDACEEVLLFPSEESHDGANFTHGNIIFTFQHSENLRTINFNQY
DSKARLRRQSLLGRYRLDSTTGAPLNPMGRTGLLGKGLLPRWGPNHSFVLCITRWTRDTRTGAQIIRSNR
GVLQYLALERNKRLCMPWYLTDHTNKCDFDECIPKLISNLITRRGRAMLPEKRVERLLKRIEKAEVTQIF
KGYLDDQLNADSSWMETVVINLHESESKGAQFPNDILKLLNEPGTEEQVKWIEVSHSSNLRTSHNYILKN
VAELRRAFY

>*Cs*.TRPM$_{PZQ}$(2172)

MQEQPALQRASTVRRSAYRASMMSPGDSGGIGALAASVGLQQQSSVRRTSVMQRYVGEIEFTGMNQTAKF
CKLDSSTNDMVIRDLLKRKWGLKPPTLIITVFGTDFEKKRKLKMIFKKGLWKAAESGCWIVTGGFHLGIM
KLTGEAVRDYTDAYGGNRMMAFGVASWDCVMKNELLEAALHEGTAVYQSEEDDEEQEESVIALNEPTHDG
EKKTVRTDIEERALDPNHNYFVLVDSGVSDQAKGKEAECRARFERCISQWSGAKIALDQSGAGGAGAVTT
QSGGITSSTHLQVTQGSSQTGSNVTNQSNVTLQREGSASGPAGLQSSTSVNKGSKTTGGSSTTSGIQKPG
TEQIASGQVASGAKQAGEKSLLDLSGKLQKTGKSVGGEEDILVPMCGLVVGGDRFTVRQVYCSVIQNRCP
IVVTKGTSGAADVIAFGLDAASKMATEEAVDDKEPVPLETRIESIIEEFLGDMHPDYTSYTEEVNMLCEI
INDYSNLVTVFDMEEDSDLDGYVISSLLASAGSIVASDQINLEQLEITLTLNRADIAREKIFLENKKWRK
GQLNDYMYQALMSDRHDFVKLFLEQGFSLEEFLTVYMLEKLYTDQLKNMNSKVAIFNKMWEYNRSHRSSK
VALRDVGKVIKALVGDFYHPLYLSKEFHAKLMPEKRLEEPGRGKPYDPDAPFISDEDSFSYSDSSYDNGA
ISPRTLGLRERVRFIDHGEEHERDWLAGVHPPGAGFQNPAFLEQDKTVRVTSRRGATSGEPGRPDGDDSD
GKGGTANGTSEKLDPEERYDQQGIPRSSTTVTTVSGDILLPAKSPKRSVDQRDQSQRRTSREHRRGRSPP
PYEGTTLRQNAYARPVRNGSQKRGQQNDPRYTRRRPSLDNMHDIPIPGQPLVYNAIVPAVNRSAAGYGGT
AYTSLGPGHFRITGRAPLAYDASVESSGIAIPLNRAADENIYVSRDNIHEQPIRPFAPPAHSDVSSFTIG
IRSAGTFEQGGLRGCWRWVTSCCVRILGRSSTKNQGETAIEHQDGMKGREFTTLRAMAALAAATAVTAVA
DPSKAPHTDEEQTKAIQLDRPARELLIWSILVGKLRMAELFWTMEKEPIAAALLASILLTSLGNKTDDFT
DKEDYRSFAKNFQERAEGVLNECYREDEHRTQLIINHELMYYGRSSVIKLAAEGQSIKFMAHPCCQDFLT
NTWNGNLSTKNSVIRYFLGIICGLTIPFLIPKIILAKPKTNPVTEEEETSTTVESANVNHDDAGSLVKEN
AMVRRKSIRKSFRHNTKEFIAQIRDFYMAPVIRFVYNTISYMAFLILFSYLLLVDFKIQISVVEYIVIAW
VVTLLIEEIKQIAWAVLSGISFRTYISDGWNKLDCTGLGLFIVGFVLRMIVLLRIGHGQHLDPMHERFYI
VTDLYLDLSRISLAISLFVFYIRLMYTFSFNIALGPKLIMIGKMVTNDLIPFMIILTVIMVGYAVAAQSI
AYPNGLFTKENMTLGCDVKQMNFTDIIFAMYTTSYFQMFGDFSLDALQGEDRTCQNNMCPTKTSRWLVPI
MLGFYVLLTNILMFNLLIAMFSKTYEEIESASTYYWNYQRYQMINDYVHRSPLVPPIIIFWHFYEAYKAI
GNRCASLRNHENTKHNPFCVRFTDLKKEREMVKWEHMKAMDYLREPSQKGSGKRGAAESRAVVFRGGGGG
PMQGPVMDLKSEMSSVTEGIGMELEKRFKEIDSQFQRFNDVDSRLGEVTQMLTNLSDVVRSVTETQQRIM
KQISELPTCQCNELTDEVIPIPSVEPGAPSTESRKRTKLEIAVQSALEAAKDVLRPPTPPPPPPPPPPPP
RESPVLLAAPIPGSDEDSSGSEEGGDPSADPVKSPDVSDNRTGRVIERNVAEHRLWRIAPFNFEKYPGMR
MNVPPERMAWTTEYPDYFAYDACEEVLLYPSEDAHDGENFTHGNADFAFKLSENLRGINFNQYDPHAKIR
RQSLLGRYRLDPTTGAPLNPMGRTGLLGKGLLPRWGPNHSIVICITRWSRDPRTGNQVTRSNRGVLQYIA
LERTKRLCIPWYLTDHSNRCELDTCVPKVISSFITRRARATLSEKRVDRLLKRLDKAEVTQIFKGYLDDQ
LNADSAWTETVVINIHEGNAKGAYMGDDFLKLFGEPATGEQCKWMEVGQSSNLRTSHNYILKSVAESKRA
FY

>*Ov*.TRPM$_{PZQ}$(2173)

MQDQPALQRASTVRRSAYRASMMSPGDSGGIGALAASVGLQQQSSVRRTSVMQRYVGEIEFTGMNQTAKF
CKLDSSTNDTVIRDLLKRKWGLKPPTLIITVFGTDFEKKRKLKMIFKKGLWKAAESGCWIVTGGFHLGIM
KLTGEAVRDYTDAYGGNRMMAFGVASWDCVMKNELLEAALHEGTAVYQSEEDDEEQEDSVIALNEPTHDG
EKKTVRTDIEERALDPNHNYFVLVDSGVSDQAKGKEAECRARFERCISQWSGAKIALDQSGAGGAGAATT
QSGGITSSTHLQATQSSSQTGSNVTNQSNVTLQREGSASGPAGQQSSTSVNKGSKATGGSSTTSGTQKPG
NEQTAPGQAASGAKQAGEKSLLDLSGKLQKTGKSVGGEEDILVPMCGLVVGGDRFTVRQVYCSVIQNRCP
IVVTKGTSGAADVIAFGLDAASKMATEEVVDDKEPVPLETRIESIIEEFLGDMHPDYTSYTEEVNMLCEI
INDYSNLVTVFDMEEDSDLDGYVISSLLASAGSIVASDQINLEQLEITLTLNRADIAREKIFLENKKWRK
GQLNDYMYQALMSDRHDFVKLFLEQGFSLEEFLTVYMLEKLYTDQLKNMNSKVAIFNKMWEYNRSHRQSS
KVALRDVGKVIKALVGDFYHPLYLSKEFHAKLMPEKRLEEPGPGKPYDPDAPFISDEDSFSYSDNSYDNG
AISPRTLGLRERVRFIDHGEEHERDWLAGVHPPGAGFQNPAFLEQDRTIRVTARRGATSGEPGRPDGDDS
DGKGGAANGTSEKLDLEEKYNQQGIPRSSTTVTTVSGDILLPAKSPKRSADQRDQSQRRTSREHRRGRSP
PPYEGTTLRQNAYARPSRNGSQKRGQQNDPRYTRRRPSLDNMHDIPIPGQPLVYNAIVPAVNRSAAGYGG
TAYTSFGPGHFRITGRAPLAYDASVESSGIAIPLNRAADENVYVSRDNINEQPIRPFAPPAHSDVSSFTI
GIRSAGAFEQGGLRGCWRWVTSCCVRILGRSSSKDRGETGMEHQDGMKGREFTTLRAMAALAAATAVTAV
ADPSKAPHTDEEQTKAIQLDRPARELLIWSILVGKLRMAELFWTMEKEPIAAALLASILLTSLGNKTDDF
TDKEDYRSFAKNFQERAEGVLNECYREDEHRTQLIINHELMYYGRSSVIKLAAEGQSIKFMAHPCCQDFL
TNTWNGNLSTKNSVIRYFLGIICGLTIPFLIPKIILAKPKTNPVTEEEETSTTVESANVNQEDAGSLVKE
NAMVRRKSIRKSFRHNTKEFIAQIRDFYMAPVIRFVYNTISYMAFLILFSYLLLVDFKIQISVVEYIVIA
WVVTLLIEEIKQIAWAVLSGISFRTYISDGWNKLDCTGLGLFIIGFVLRMIVLLRIGHRQHLDPMHERFY
IVTDLYLDLSRISLAISLFVFYIRLMYTFSFNIALGPKLIMIGKMVTNDLIPFMIILTVIMVGYAVAAQS
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IMLGFYVLLTNILMFNLLIAMFSKTYEEIESASTYYWNYQRYQMINDYVHRSPLVPPIIIFWHFYEAYKA
IGNRCASLRNHENTKHNPFCVRFTDLKKEREMVKWEHMKAMDYLREPSQKGSGKRGAAESRAVVFRGGGG
GPMQGPVMDLKSEMSSVTEGIGMELEKRFKEIDSQFQRFNDVDSRLGEVTQMLTNLSDVVRSVTETQQRI
MKQISELPTCQCNELTDEVIPIPSVEPGAPSTESRKRTKLEIAVQSALEAAKDVLRPPTPPPPPPPPPPP
PRESPVLLAAPVPGSDEDSSGSEEGGDPSADPVKSPDVSDNRTGRVIERNVAEHRLWRIAPFNFEKYPGM
RMNVPPERMAWTAEYPDYFAYDACEEVLLYPSEDAHDGENFTHGNIDFAFKLSENLRGISFNQYDPHAKI
RRQSLLGRYRLDPTTGAPLNPMGRTGLLGKGLLPRWGPNHSIVICITRWSRDPRTGNQVTRSNRGVLQYI
ALERTKRLCIPWYLTDHSNRCELDTCVPKVISSFITRRARATLSEKRVDRLLKRLDKAEVTQIFKGYLDD
QLNADSAWTETVVINIHEGNAKGAYMGDDFLKLFSEPATGEQCKWMEVGQSSNLRTSHNYILKSVAESKR
AFY

>*Ec*.TRPM$_{PZQ}$(2260)

MTEQIPFHRTSTVRRTVNRTGSVGPGDSVGVSALAASTALQHQASVRRTSVMQRFVGEIEFTGLNQTAKF
CKLDGSTTDQVIRDLLKRKWGLKPPTLIITVFGTDFEKKRKLKMIFKKGLWKAAESGCWIVTGGFHLGVM
KLTGEAVRDYTDAYGGNRMMAFGVASWDCVTKNEILEAALHEGTAVYQSEEDEEEQDESDRGVAGPGGAT
GNKTVRSDVEERALDPNHNFFILVDSGVSDQAKGKEAELRARFERCISQWSCATPALDQSMGGTGGAGGT
APTSAGITSSTQLQQQTQSGSNLNNQSSTLLQREGSTRVSVAPQPGSGVNLSSSSVGKTQVAPGTVSSTA
LATQRTAAEQISASQGTGMRTAGEKSLPDVSKPQKSGKSVGSEEEVLVPMCGLVVGGDRFTLRQVYCSMI
QNRCPIVVTKGTSGAADVIAFGLDAANKMATEEAVDDKEPVPLENRIESIIEEFLSDMHPDCSNYTEEVN
MLSEIINDYSNLVSVFDMEEDSDLDGYVISSLLASAGSTVASDQINLEQLEITLTLNRADIAREKIFLEN
KKWKKGQLNDYMYHALMSDRHDFVKLFLEQGFSLEEFLTVYMLEKLYTDQLKNLNSKVAIFNKMWEYNRS
HRQSSKVALRDVGKVIKALVGDFYHPLYLSKEFQAKLMPDKQLEGAVRDKLLGSRRSRPSHDSGSQSDST
YSNAGAISPRTLGLKERVRFIDHGDEGSVDGFSDPPGPDSGFQNPAFLELDQQQQHLLYHRYQQEEHEEE
DVEKEESKAEDVIHKWCMFSYGQTARNAIRRGATSGEAGPSDLDEADKSRPETNGKAQRGVKGGPLRQDS
KDSDEFYPSRGLPRSSTTVTTVSGEVLLPASSPSKGAATHEAGFSRGRASRDRTQGGAPPPYDNNGAASA
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SNLSEVVRSVTETQQRIIKQISELPTCQCNELSDEVIPAAPGETGTASREVRKRTKLEIAVQSALEAAKD
VLRPPTPPPPPPPPPPPRESPVLLAAPIPGSEDDSSGSEEGGDPKSDPFTVPDVTDNRTGRVIERVINA
HRLWRIAPFNFEKYPGMRMNVPPEKMAWTTEYPDYFAYDACEEVLLFPNEEAHDGENFTHGNYDFAFTLS
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>*Fh*.TRPM$_{PZQ}$(2146)

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IESASTYYWNYQRYQMINDYVHRSPLVPPIIIFWHFYEAYKAIGDRCASLRNHENIKHNPFCVRFTDVKK
EREMVKWEHMKAMDYLREPSTKASGKRGVAESRAVVFRGGGAGPGQGPVMDLKSEMSSVTEGIGMELEKR
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VSSKEIRKRTKLEIAVQSALEAAKDVLRPPTPPPPPPPPPPPRESPVLLAAPVPAGSEDDSSGSEEGGD
PKADPFAVPEVTDSRTGRVIERVINAHRLWRIAPFNFEKYPGMRMNVPPEKMAWTTEYPDYFAYDACEEV
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>*Fg*.TRPM$_{PZQ}$(2134)

MTEQASIHRTSTVRRTVTRTGSVAPGDSVGASALATSAALQHQASVRRASLMQRFVGEIEFTGLNQTAKF
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NMLCEIISEYSNLVSVFDMEEDSDLDGYVISSLLASAGSTVASDQINLEQLEITLTLNRADIAREKIFLE
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HRTQLIINHELTYYGRSSVIKLAAEGQSIKFMAHPCCQDFLTNTWSGNLSTKNSVIRYFFGIVCGLTIPF
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SDGWNKLDCAGLGLFILGFFLRLTVLLRMDKAEPLSPLHERYHVLTDPFLDVSRTCLAISLFVFYTRLMY
TFSFHIALGPKLIMIGKMVTNDLIPFMIILTVIMLGYAVAAQSIAYPNGLFTKENMTLGSDIKHMNFGDI
IFNMYTTSYFQMFGDFSLDALQGEDPKCQNHMCPTKTSRWLVPIMLGFYVLLTNILMFNLLIAMFSKTYE
EIESASTYYWNYQRYQMINDYVHRSPLVPPIIIFWHFYEAYKAIGDRCASLRNHENIKHNPFCVRFTDVK
KEREMVKWEHMKAMDYLREPSTKASGKRGVAESRAVVFRGGGAGPGQGPVMDLKSEMSSVTEGIGMELEK
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RATLPERRVDRLLKKLDKADVTQIFKGYLDDQLNADSAWTETVVINIHEGGTKGAYLNDTFLKIFSEPNS
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>*Eg*.TRPM$_{PZQ}$(2103)

MTDSGGGGGVGGSLLRQMSTIQHRQSRVGSTVNESSASTAHSPHALLPSASIRRPSQVHRFHGEIEFTGL
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TATANATAASSTQKRTDVEELALDPNHNYFIFAETAKTDHTKGREAGMRARFERCISLWSTSTPEADPPP
SAARLSQSGGVGKTTTISTAEPEEDYATTLKRKSTLRHQASEKTEGRSLSRSSSKFKSGGSGAGGDGSAG
GGGGNNASGEDIRIPMCGLVIGGDRFTLRQVYCSIMQNQCPMVVAKGTSGAADVIAFGLEAATKMETEEI
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FIDFFDEHPKVKYKAASLLKQEKGEAENNPNASASHLLFSFTKDNEVQSSPCFDTADSATPRGMQRSSTR
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KRRISFEKMKEIQVASGRGQYYGNPAFLARQHLAFQSSVTAPLAVDEKYSRPSPRMLRENSVESTYESQH
TQQQSMSEDEEDEEEEDEEAVGFGGNLKRRFIEALRRRTSKDHEGGAHLEGLAPGNLQTLRAVAALAAVA
GGMGGGSTDPEKTAANEEARIKLIQFDRPARELLIWSVLVGKLRMSELFWTMEKEPIAAALLASILLSAL
SNKTDDFTDKEDYKNYSKSFQEKAEGVLNECYREDEHRAQLIINHELAYYGHSSVIKLAAEGQSIKFMAH
PCCQDFLTNTWKGNLSSKNSMFRMMFGLMFGLTMPLFIPKVLLYEPEDKQSEAGEESNDSTEQKDEELSE
DVESRVMVKRSLTTSLQVGAMEFWVKIKDFYMSPIVRFVYHTISYVLFLVLFSYLLLVDFKVRITGVEYI
VLAWVITLFIEEIKQIAWSVLSGISFSTYISDGWNKLDCTGLILYIVGFILRLIVLARLGDSQLNHDTEA
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AFY

>*Mc*.TRPM$_{PZQ}$(2126)

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EKPDLAAVLPMKFHKPQNHNRRPDGGGGGGGGGVVNSRNHREGGCYRDGDQLTKTSTSAYDAANRFKSIT
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SSRPAPLMFRESSIESTYESQHAQQQSISGEEEDEDDDDDDEEEEVGLGGHLKRRLIEVLRRGTAKENES
GHFEGLLPGNLQTLKAVAALAAVAGGMGGGGGPTDPDKTAANEEARIKLIQFDRPARELLIWSVLVGKLR
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>*Ml*.TRPM$_{PZQ}$(2143)

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IFLENKKWKKGNLNEFMYQALMEDRHDFVKLFLEQGFSLEDFLTVYILEKLYTDQLKRLNSKVAIFLQLW
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GSFLQQPQQSEHRQSLQQQQQQQQPQHPGPSPGLEEMAICDYERSPVNFSGKDHARKRDLAIANKISSDS
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SLEFMEAVRAPASGSSGHSGKGANSQQMGSKQHLRQQELSGAAAKATKEEESKLKTINLERPARELLIWS
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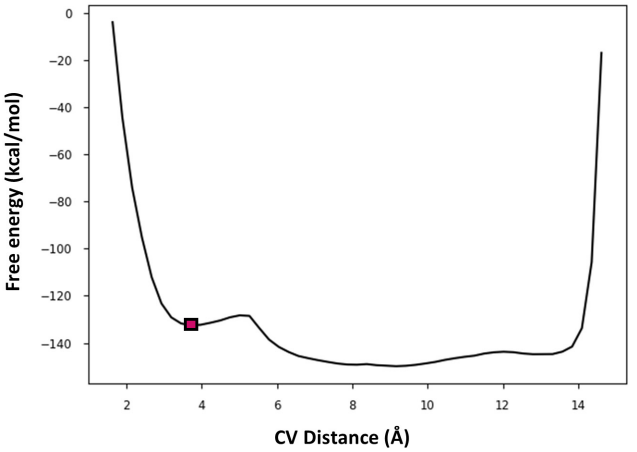
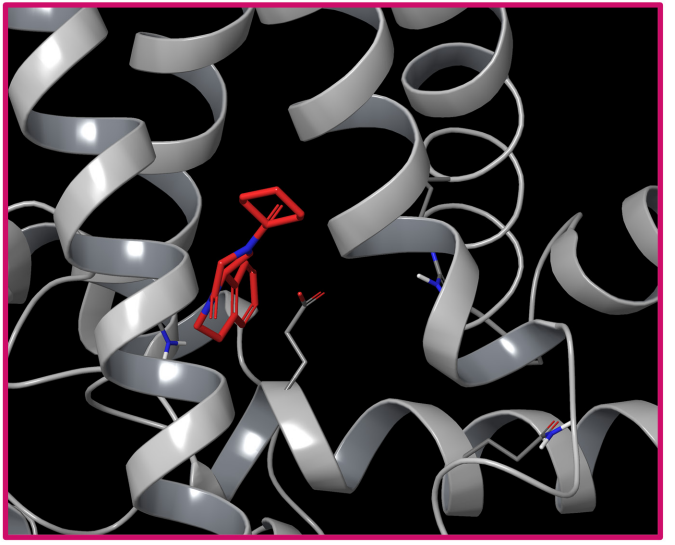
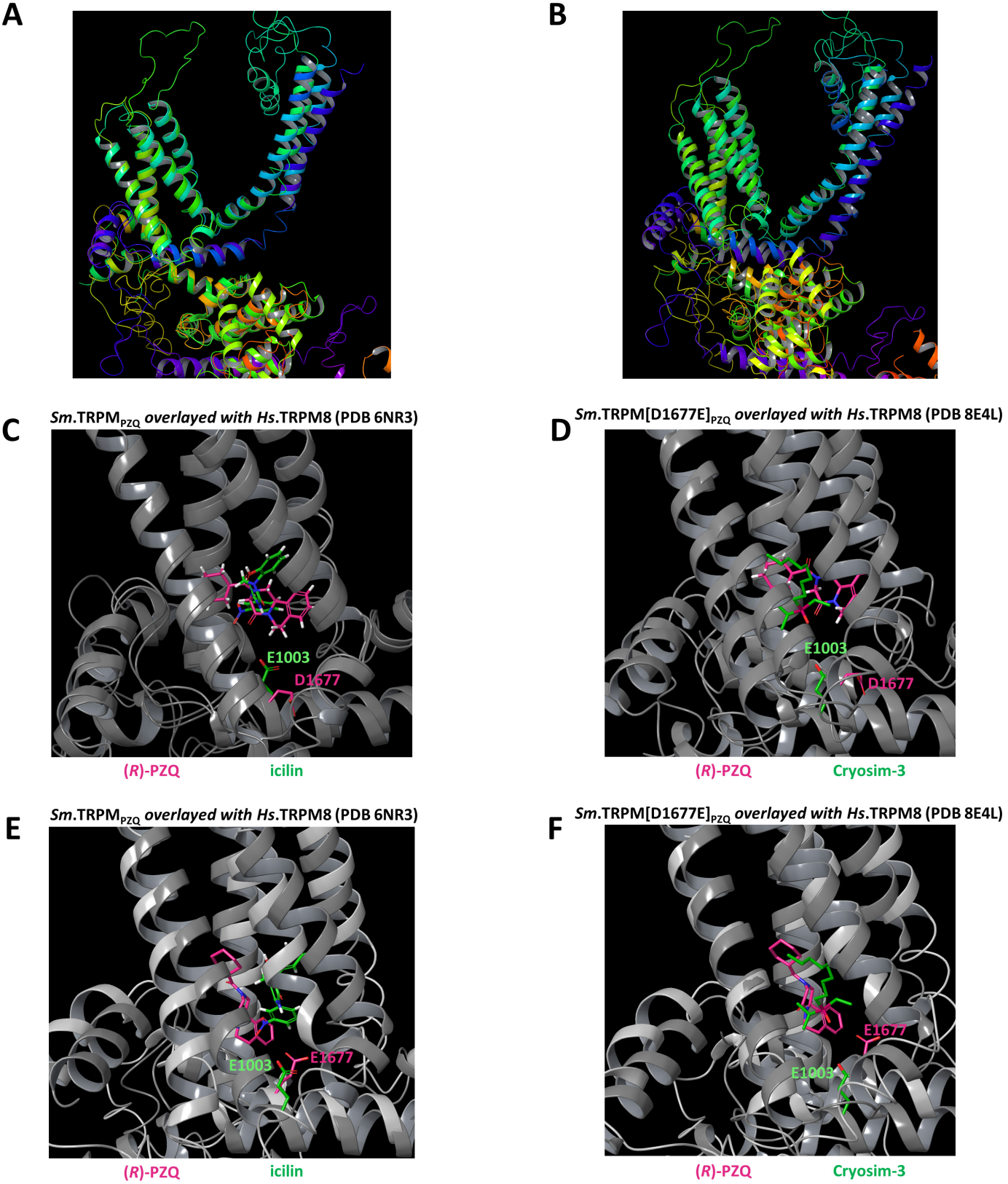
Supplementary Figure 2






A
B
C
Sm.TRPM$_{PZQ}$ *overlayed with Hs*.TRPM8 (PDB 6NR3)
E1003
D1677
(*R*)-PZQ
icilin
D
Sm.TRPM[D1677E]$_{PZQ}$ *overlayed with Hs*.TRPM8 (PDB 8E4L)
E1003
D1677
(*R*)-PZQ
Cryosim-3
E
Sm.TRPM$_{PZQ}$ *overlayed with Hs*.TRPM8 (PDB 6NR3)
E1003
E1677
(*R*)-PZQ
icilin
F
Sm.TRPM[D1677E]$_{PZQ}$ *overlayed with Hs*.TRPM8 (PDB 8E4L)
E1677
E1003
(*R*)-PZQ
Cryosim-3

Supplementary Table 1

	Sm	Sh	Sj	Cs	Ov	Ec	Fh	Fg	Eg	Mc	Ml
Sm		87.1	82.8	67.3	67.3	66.9	64.7	64.3	52.9	53.1	34.3
Sh	87.1		88.0	66.7	66.6	66.0	67.8	67.2	53.5	53.2	34.4
Sj	82.8	88.0		67.6	67.6	66.6	68.6	67.9	53.9	53.6	34.8
Cs	67.3	66.7	67.6		97.9	74.9	72.8	72.0	55.8	56.0	34.7
Ov	67.3	66.6	67.6	97.9		74.6	72.6	71.9	55.9	54.7	34.7
Ec	66.9	66.0	66.6	74.9	74.6		84.1	83.1	54.8	54.5	34.7
Fh	64.7	67.8	68.6	72.8	72.6	84.1		98.0	54.8	54.7	35.3
Fg	64.3	67.2	67.9	72.0	71.9	83.1	98.0		54.5	54.5	35.6
Eg	52.9	53.5	53.9	55.8	55.9	54.8	54.8	54.5		85.8	34.9
Mc	53.1	53.2	53.6	56.0	54.7	54.5	54.7	53.0	85.8		34.9
Ml	34.3	34.4	34.8	34.7	34.7	34.7	35.3	35.6	34.9	34.9	

Supplementary Table 2

Class	Order	Family	Genus & Species	TM1	TM2	TM3	TM4	TRP
TREMATODA	**Strigeidida**	**Schistosomatidae**	**Schistosoma mansoni**	**N T x S Y x x F**	**W x x T L x x E**	**W N x L D**	**F x x R L x Y T**	**D Y x x R x x x x P x x I**
TREMATODA	Strigeidida	Schistosomatidae	**Schistosoma haematobium**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	**Schistosoma japonicum**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Schistosoma bovis	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Schistosoma curassoni	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Schistosoma margrebowiei	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Schistosoma mattheei	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Schistosoma rodhaini	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Strigeidida	Schistosomatidae	Trichobilharzia regenti	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Opisthorchiida	Opisthorchiidae	**Clonorchis sinensis**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Opisthorchiida	Opisthorchiidae	Opisthorchis felineus	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Opisthorchiida	Opisthorchiidae	**Opisthorchis viverrini**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Troglotrematidae	Paragonimus westermani	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Troglotrematidae	Paragonimus heterotremus	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Troglotrematidae	Paragonimus kellicotti	x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Troglotrematidae	Paragonimus miyazakii	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Dicrocoeliidae	Dicrocoelium dendriticum	N T x S Y x x F	W x x T		F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Microphallidae	Atriophallophorus winterbourni	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Echinostomatidae	**Echinostoma caproni**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Fasciolidae	**Fasciola gigantica**	T T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Fasciolidae	**Fasciola hepatica**	T T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
TREMATODA	Plagiorchiida	Fasciolidae	Fasciolopsis buski	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	D Y x x R x x x x P x x I
MONOGENEA	Monopisthocotylea	Gyrodactylidae	Gyrodactylus salaris	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
MONOGENEA	Monopisthocotylea	Gyrodactylidae	Gyrodactylus bullartarudis	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
MONOGENEA	Polyopisthocotylea	Polystomatidae	Protopolystoma xenopodis	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Echinococcus canadensis	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	**Echinococcus granulosus**	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Echinococcus multilocularis	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Echinococcus oligarthrus	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	
CESTODA	Cyclophyllidea	Taeniidae	Hydatigera taeniaeformis	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Taenia asiatica	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Taenia multiceps	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Taenia saginata	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Taeniidae	Taenia solium	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Hymenolepididae	Hymenolepis diminuta	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Hymenolepididae	Hymenolepis microstoma	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Hymenolepididae	Rodentolepsis nana	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Mesocestoididae	**Mesocestoides corti**	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Cyclophyllidea	Anoplocephalidae	Moniezia expansa	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y S	D Y x x R x x x x P x x I
CESTODA	Diphyllobothriidea	Diphyllobothriidae	Schistocephalus solidus	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
CESTODA	Diphyllobothriidea	Diphyllobothriidae	Spirometra erinaceieuropaei	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
CESTODA	Diphyllobothriidea	Diphyllobothriidae	Dibothriocephalus latus	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
CESTODA	Diphyllobothriidea	Diphyllobothriidae	Sparganum proliferum	H T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y T	E Y x x R x x x x P x x I
RHABDITOPHORA	Macrostomida	Macrostomidae	**Macrostomum lignano**	N T x S Y x x F	W x x T L x x E	W N x L D	F x x R L x Y I	E Y x x R x x x x P x x I
RHABDITOPHORA	Dugesiidae	Dugesiidae	Schmidtea mediterranea	N S x S Y x x F	W x x T L x x E	W N x L D	F x x R V x Y I	E F x x K x x x x P x x I
RHABDITOPHORA	Tricladida	Dugesiidae	Dugesia japonica	N A x S Y x x F	W x x T L x x E	W N x L D	F x x R V x Y I	E F x x K x x x x P x x I
Homo sapiens: TRPM2				N I x S Y x x F	W x x S L x x E	W N x L D	F x x R L x H I	E Y x x R x x x x P x x I
Homo sapiens: TRPM8				N V x F Y x x F	F x x V L x x D	W N x M D	F x x R L x H I	E Y x x R x x x x F x x I
				TM1	TM2	TM3	TM4	TRP