Supporting Information for

Phosphatidylinositol-4, 5-biphosphate (PIP_2)-Dependent Thermoring Basis for Cold-Sensing of the Transient Receptor Potential Melastatin-8 (TRPM8) Biothermometer

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The SI includes:

Tables S1, S2, and S3

Table S1 Noncovalent interactions along the PIP_2-dependent minimal gating pathway from Q675 to F1013 in each subunit of closed mTRPV8 with PIP_2 bound at 20 °C (PDB ID, 8E4N)

Noncovalent interaction	Cut-off distance	Linked residues
Salt bridge	3.2-4 Å	R688-PIP_2-R851-PIP_2-**R998-PIP_2-R688,** D781-R1008, D802-R842, **E1004-R1008**
H-bond	<3.9 Å	**Q675-R998, N676-R688,** Y683-N692-R688, E768-Y772, E782-Y793-Q785, Q785-E1004, R862-N990
π–π interaction	2.65–6.5 Å	**W682-Y683-F735, W682-F735, W682-F738, W682-Y1005,** F712-W725, F712-Y726, W725-Y726, **F738-Y1005,** F744-F1013, F748-F752, F748-F839, **F752-F809,** F752-F832, **F752-Y836, F752-F839,** F760-F832, **H761-H765, Y772-F809, W798-H845, F809-F839,** F868-F869, F870-Y981, F874-W877, F874-Y908, W877-F881, F881-Y963, **F996-F1000, Y999-F1000**
cation–π interaction	<6.0 Å	
CH_3/CH–π interaction	2.65-3.01 Å	R851-W994, M878-Y908, Y963-T967
Lone pair–π interaction	3-3.7 Å	Y793-N799, F815-S827

Note: Bold interactions were conserved in both closed and open states.

Table S2 Noncovalent interactions along the PIP_2-dependent minimal gating pathway from Q675 to F1013 in each subunit of closed mTRPM8 with Ca^{2+} and PIP_2 and C3 bound at 20 °C (PDB ID, 8E4M)

Noncovalent interaction	Cut-off distance	Linked residues
Salt bridge	3.2-4 Å	**R688-PIP_2-R998, E782-Ca^{2+}-D802, Q785-Ca^{2+}-N799,** R862-E988, **E1004-R1008**
H-bond		**Q675-R998, N676-R688,** Y683-N692, R688-N692, **Y754-D759, E768-Y772, D802-R842,** H818-N821, R688-PIP_2-S850-PIP_2-R998, R885-S917, Q886-S902
π–π interaction	2.65–6.5 Å	**W682-Y683, W682-F735, W682-F738, W682-Y1005, Y683-F735,** F712-W725, F712-Y726, W725-Y726, **F738-Y1005,** F744-F1013, **Y745-F748,** F748-F839, **F752-F809, F752-Y836, F752-F839, H761-H765, W798-H845,** F869-F870, **F874-W877, F996-F1000, Y999-F1000**
cation–π interaction	<6.0 Å	**F760-R816,** Y1005-R1008
CH_3/CH–π interaction	2.65-3.01 Å	F748-F752, F760-R829, D781-F1013, D835-F839, D866-Y981, F881-T967, R895-W898-S902, **W994-R998**
Lone pair–π interaction	3-3.7 Å	

Note: Bold interactions were conserved in both closed and open states.

Table S3 Noncovalent interactions along the PIP_2-dependent minimal gating pathway from Q675 to F1013 in each subunit of open mTRPM8 with Ca^{2+} and PIP_2 and chemical agents C3 and AITC bound at 20 °C (PDB ID, 8E4L)

Noncovalent interaction	Cut-off distance	Linked residues
Salt bridge	3.2-4 Å	R688-PIP_2-R851-PIP_2-**R998-PIP_2-R688, E782-Ca^{2+}-D802, Q785-Ca^{2+}-N799, E1004-R1008**
H-bond	<3.9 Å	**Q675-R998, N676-R688, Y754-D759, E768-Y772, D781-R784, E782-Y793, D802-R842,** H845-E1004, R851-D991, D866-T982, W877-T967
π–π interaction	2.65–6.5 Å	**W682-Y683, W682-F735, W682-F738, W682-Y1005, Y683-F735**, **F738-Y1005, Y745-F748, F752-F809, F752-Y836, F752-F839,** F760-F832, **H761-H765,** Y772-F809, W786-Y793, **W798-H845,** F807-Y808, F809-F832, F868-F869, F868-F872, **F874-W877,** F874-Y908, W877-F881, F881-Y963, F951-W954, **F996-F1000, Y999-F1000**
cation–π interaction	<6.0 Å	**F760-R816**
CH_3/CH–π interaction	2.65-3.01 Å	Y793-N799, F815-S827, R851-W994, F870-L975, F870-F874, **W994-R998**
Lone pair–π interaction	3-3.7 Å	F735-S739

Note: Bold interactions were conserved in both closed and open states.