

SUPPORTING INFORMATION

Inhibition of N-type calcium ion channels by tricyclic antidepressants – experimental and theoretical justification for their use for neuropathic pain

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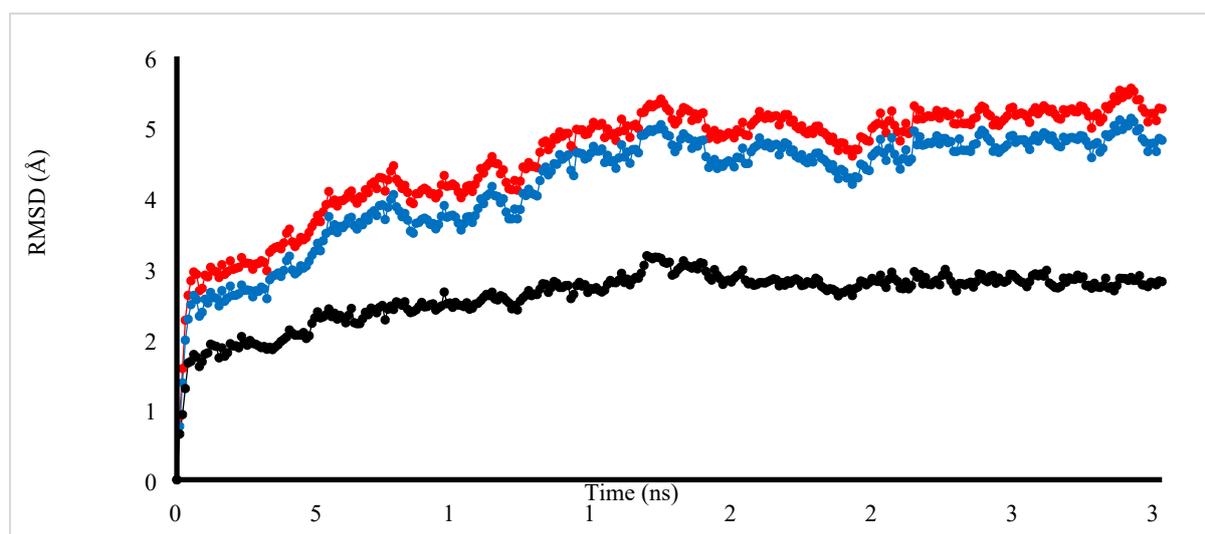


Fig. S1. Root-mean-square deviation of Ca_v2.2 over the first equilibration simulation, which employed solvation with 0.15 M NaCl. Red: Non-hydrogen RMSD; Blue: protein backbone RMSD; Black: transmembrane backbone RMSD.

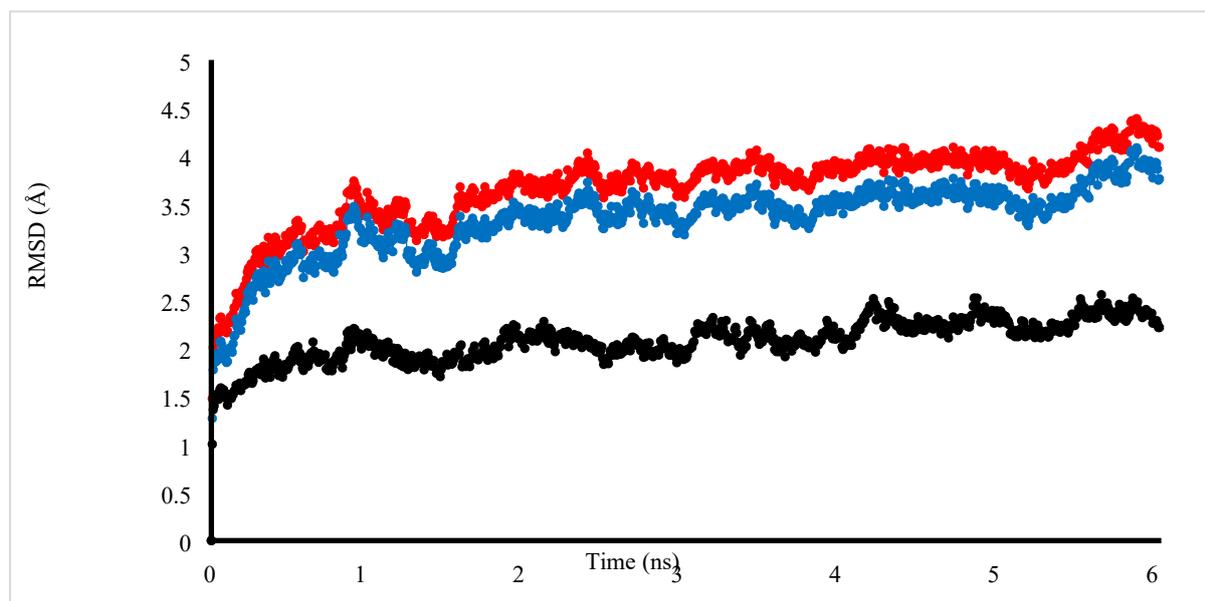


Fig. S2. Root-mean-square deviation of Ca_v2.2 over the second equilibration simulation, which employed solvation with 0.15 M CaCl₂. Red: Non-hydrogen RMSD; Blue: protein backbone RMSD; Black: Transmembrane backbone RMSD.

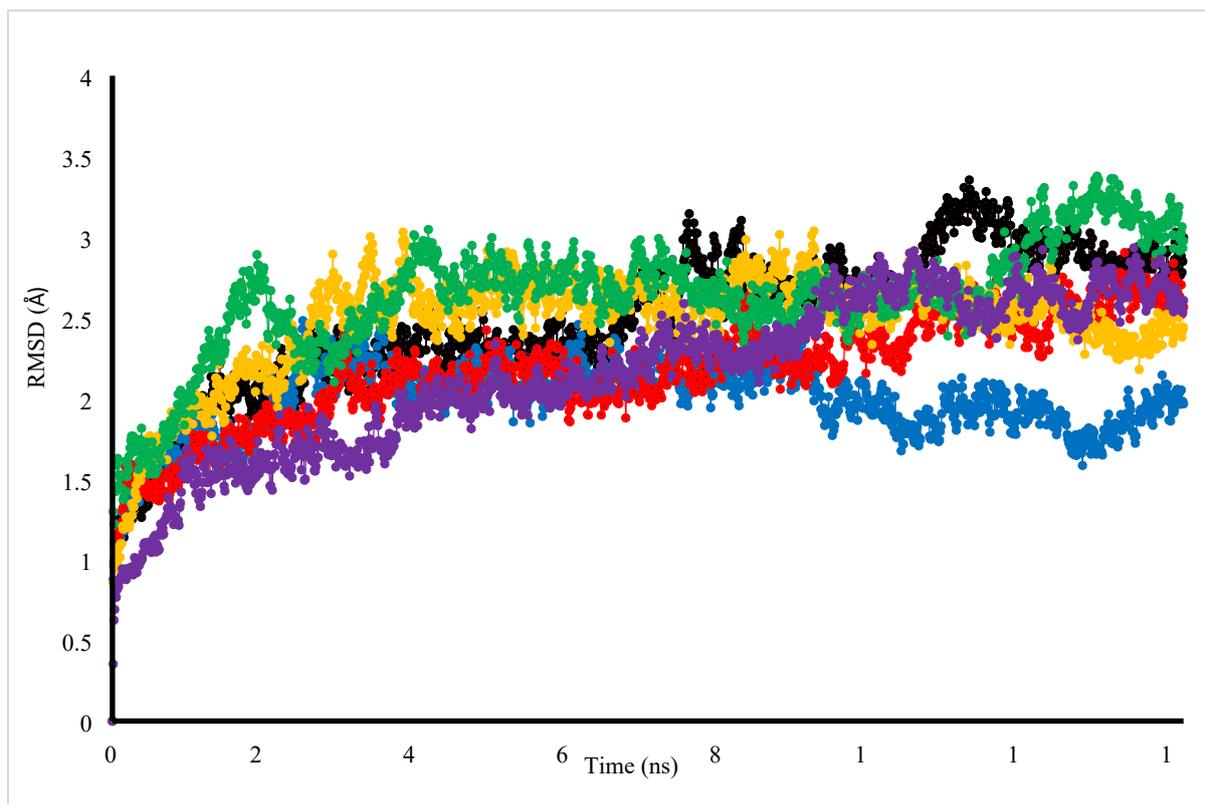
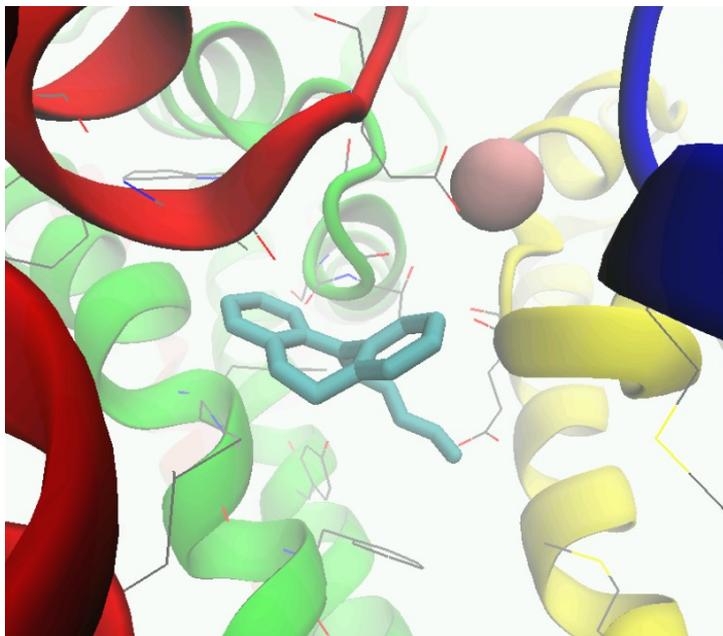


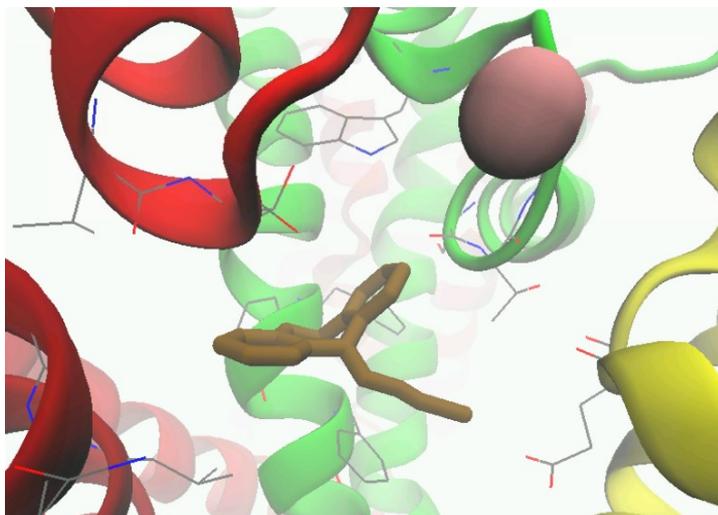
Fig S3. Backbone RMSD of transmembrane residues of $\text{Ca}_v2.2$ containing docked TCAs. Black: RMSD with no ligand; Yellow: RMSD with nortriptyline (**5**); Blue: RMSD with maprotiline (**10**); Purple: RMSD with amitriptyline (**3**); Red: RMSD with desipramine (**2**); Green: RMSD with trimipramine (**6**).

Fig S4. Images of nortriptyline's main poses observed during MD calculations, showing coordinating residues.

Cluster 1



Cluster 2



Cluster 3

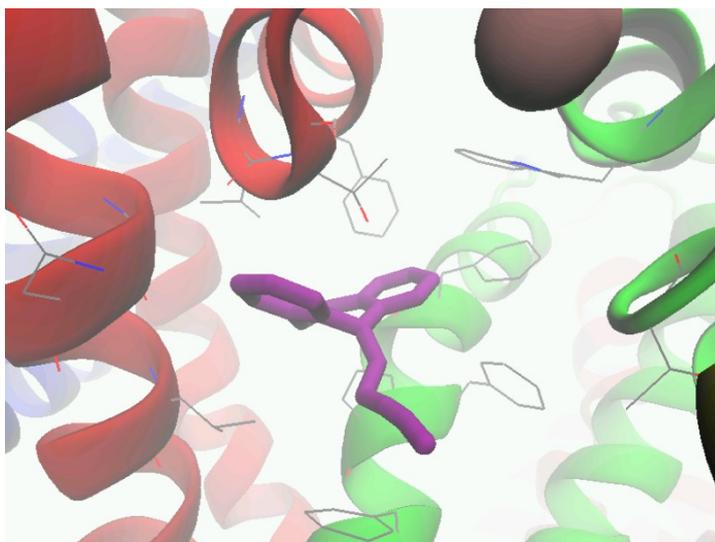
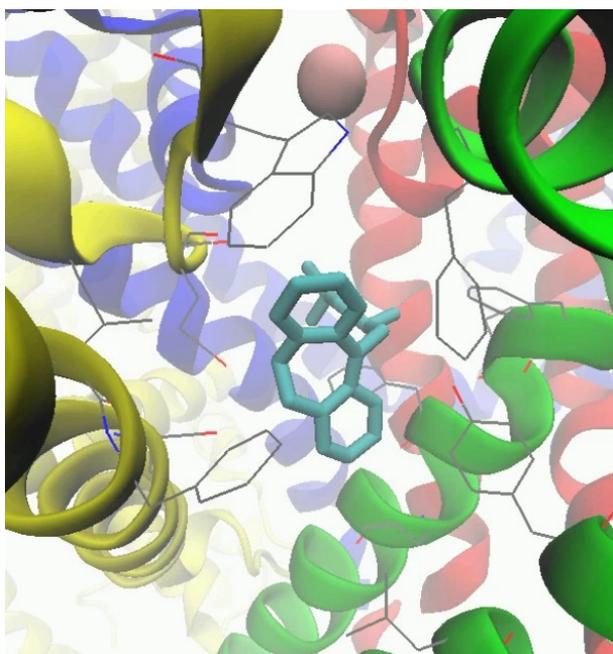
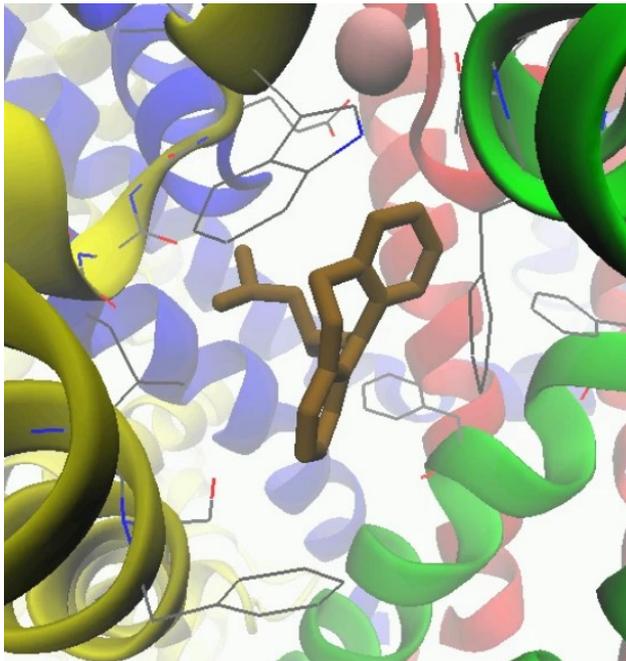


Fig S5. Images of trimipramine's main poses observed during MD calculations, showing coordinating residues.

Cluster 1



Cluster 2



Cluster 3

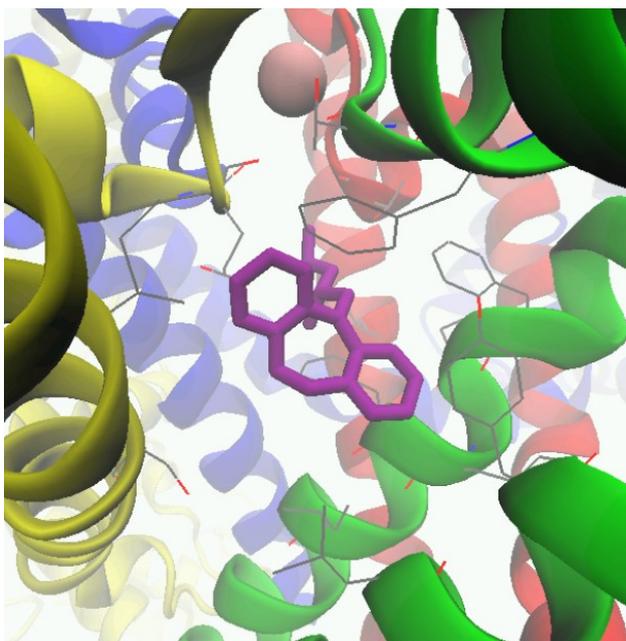


Table S1. Main binding modes of nortriptyline observed during molecular dynamics simulation, with coordinating residues listed.

Cluster	Total Frames	Time Interval (ns)	Residues within 4 Å																
			<i>Phe</i> ¹⁴⁰⁰	<i>Phe</i> ¹⁴⁰³	<i>Pro</i> ¹⁴⁰⁴	<i>Phe</i> ¹⁴⁰⁷	<i>Phe</i> ¹⁴⁰⁰	<i>Thr</i> ¹³⁶³	<i>Phe</i> ⁷⁰⁰	<i>Trp</i> ¹³⁶⁷	<i>Ser</i> ¹³⁶²	<i>Phe</i> ⁶⁵⁷	<i>Thr</i> ⁶⁶¹	<i>Leu</i> ⁶⁶⁰	<i>Gly</i> ⁶⁹⁶	<i>Asn</i> ⁶⁹⁷	<i>Leu</i> ⁷⁰⁰	<i>Met</i> ³¹³	<i>Glu</i> ¹⁶⁵⁵
1 (cyan)	631	7-86	-	x	x	x	x	x	-	x	x	x	x	-	-	-	x	x	x
2 (ochre)	243	101-145	-	x	x	x	-	x	-	x	-	-	x	x	x	x	x	x	x
3 (magenta)	161	87-99	x	-	x	x	-	x	x	-	-	-	x	x	x	x	x	x	x

Table S2. Main binding modes of trimipramine observed during molecular dynamics simulation, with coordinating residues listed.

Cluster	Total Frames	Time Intervals (ns)	Residues within 4 Å																			
			<i>Leu</i> ¹²⁸⁶	<i>Tyr</i> ¹²⁸⁹	<i>Phe</i> ¹³⁵⁹	<i>Thr</i> ¹³⁶³	<i>Phe</i> ¹⁴⁰³	<i>Phe</i> ¹⁴⁰⁶	<i>Phe</i> ¹⁴⁰⁷	<i>Thr</i> ¹⁶⁵³	<i>Gly</i> ¹⁶⁵⁴	<i>Ile</i> ¹⁴¹⁰	<i>Ser</i> ¹⁶⁹⁶	<i>Ile</i> ¹⁶⁹²	<i>Glu</i> ¹⁶⁵⁵	<i>Ala</i> ¹⁶⁵⁶	<i>Trp</i> ¹⁶⁵⁷	<i>Leu</i> ⁷⁰⁰	<i>Met</i> ³¹³	<i>Val</i> ¹⁶⁸⁹	<i>Phe</i> ¹⁶⁹³	<i>Ile</i> ¹⁶⁹²
1 (cyan)	758	29-96; 120-133	x	x	x	-	x	x	x	-	-	x	x	x	x	x	x	-	-	-	x	-
2 (ochre)	196	98-119; 133-144	-	x	x	x	x	-	x	x	x	-	-	-	x	-	x	-	-	x	x	x
3 (magenta)	185	7-29	x	x	x	x	x	x	x	-	-	x	x	x	x	-	-	-	-	-	x	-