Supporting Information (SI) for Binding affinity and mechanisms of potential antidepressants targeting human NMDA receptors

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Table S1 The total score and important energy terms of the selected eight drugs after docking with Rosetta3. The energy terms include binding energy, Coulombic electrostatic potential, solvation energy, sidechain-backbone hydrogen bond energy (hbond_bb_sc), attractive and repulsive energies between atoms in different residues.

Conformations	Total score	Bind energy	electrostatic	Solvation energy	hbond_bb_sc	attractive	repulsive
s-ketamine	-144.654	-9.103	-0.499	288.838	-0.190	-588.516	85.782
r-ketamine	-147.176	-8.828	-0.110	289.401	-0.190	-592.509	88.448
ifenprodil	-153.57	-12.687	-1.095	289.735	-0.471	-597.576	91.693
traxoprodil	-153.915	-13.365	-1.479	290.701	-0.677	-600.377	91.680
Ro 25-6981	-152.242	-11.568	0.411	291.098	0.000	-600.546	91.234
Memantine	-146.729	-7.231	-0.406	288.884	-0.190	-588.893	86.600
Dextromethorphan	-150.362	-10.635	-0.063	289.428	-0.190	-594.154	87.531
Lanicemine	-147.129	-8.365	-0.635	289.476	-0.190	-590.556	86.555

Table S2 The hydrogen bond analysis of the selected eight drugs after docking using cpptraj. Acceptor, DonorH, and Donor are the residue and atom name of the atoms involved in the hydrogen bond. AvgDist is the average distance of the bond when present, and AvgAng is the average angle of the bond when present.

Conformations	Acceptor	DonorH	Donor	AvgDist	AvgAng
S-ketamine	SKE_170@O1	ASN_160@HD22	ASN_160@ND2	2.8644	158.146
R-ketamine	LEU_124@O	RKE_170@H9	RKE_170@N1	2.8816	162.275
	RKE_170@N1	ASN_126@HD21	ASN_126@ND2	2.9043	152.594
ifenprodil	LEU_165@O	IF1_170@H27	IF1_170@O2	2.7693	162.539
traxoprodil	TRA_170@O2	TYR_69@HH	TYR_69@OH	2.6340	139.755
Ro 25-6981	VAL_42@O	RO1_170@H29	RO1_170@O2	2.7397	162.840
	LEU_43@O	RO1_170@H29	RO1_170@O2	2.7294	163.301

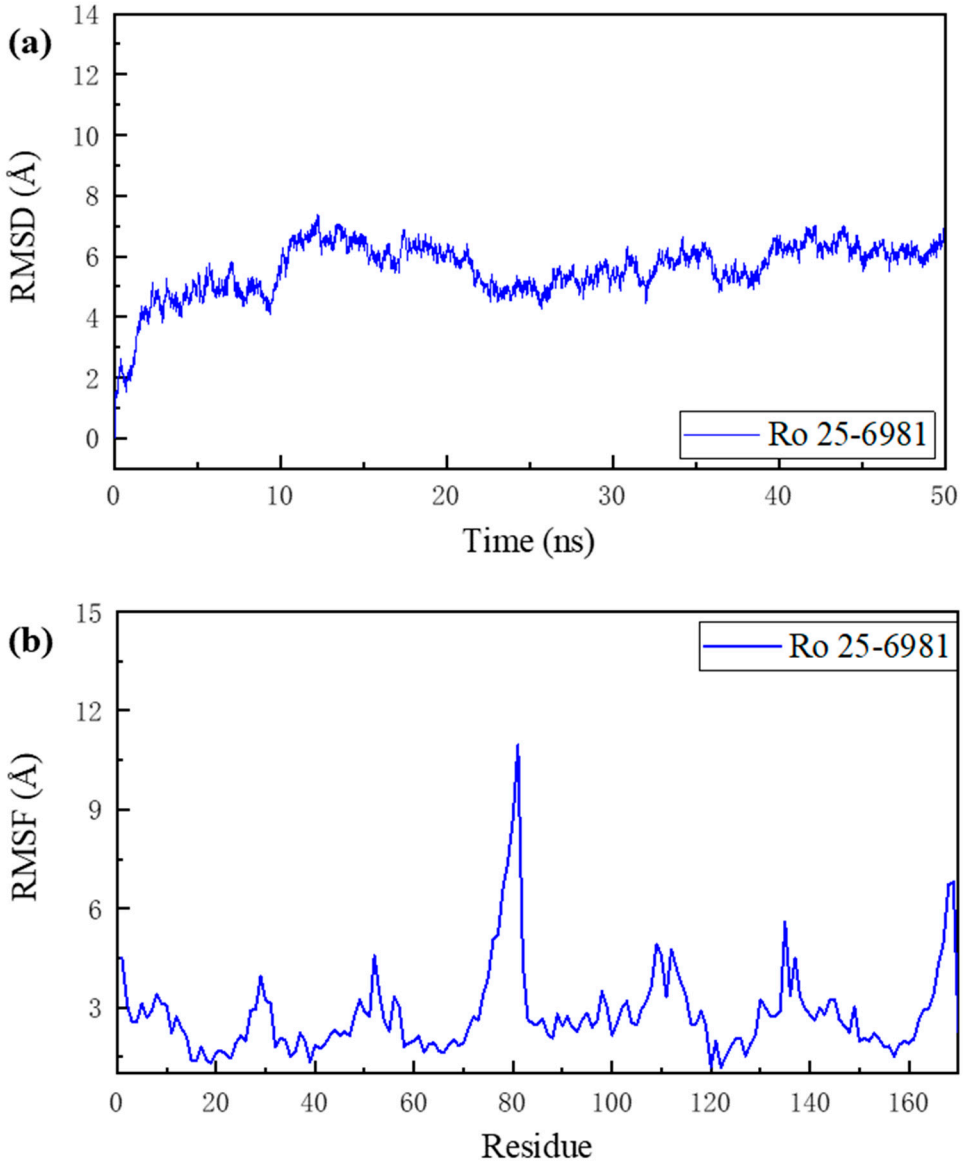

Figure S1 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of s-ketamine and the NMDA receptor complex in a 40-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

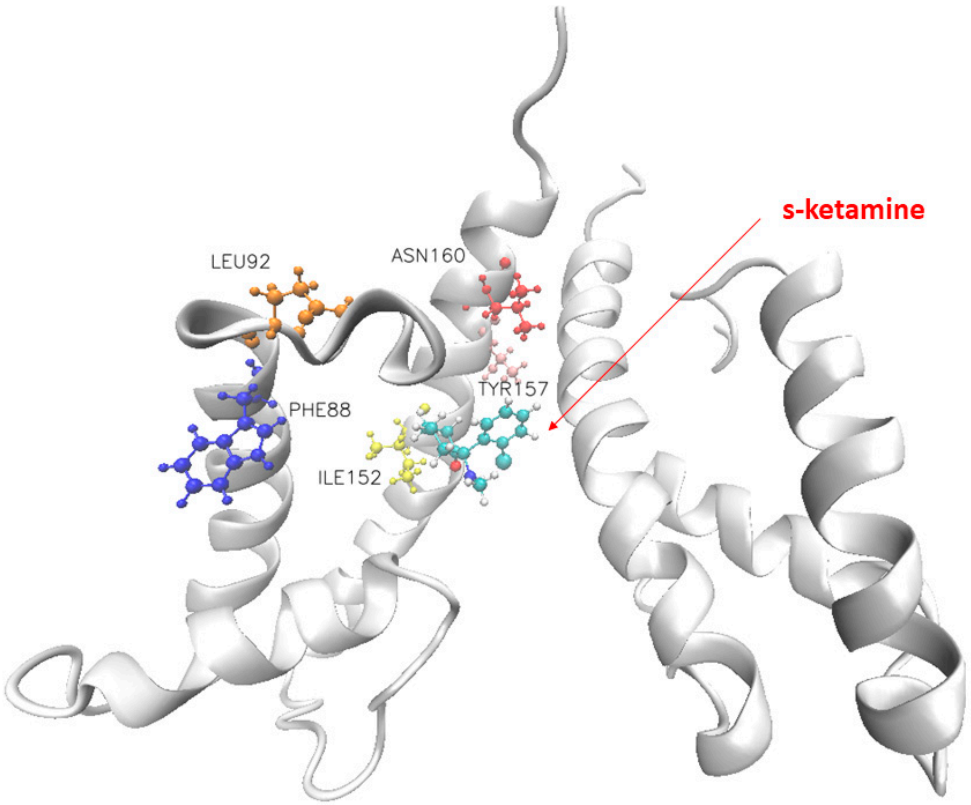

Figure S2 Visualization of the docking conformation of the NMDA receptor and s-ketamine. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to ketamine.

Table S3 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to s-ketamine, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Phe88	-2.19287	-2.04711	-1.12602	1.110792	-0.13053
Asn160	-2.14918	-0.94558	-4.3375	3.318178	-0.18428
Leu92	-1.78956	-1.93294	-0.47498	0.903851	-0.28549
Tyr157	-1.34733	-1.25785	-0.23522	0.212931	-0.06719
Trp93	-1.27813	-1.4686	-0.2309	0.501495	-0.08012
Val96	-0.99227	-0.93196	0.324644	-0.21474	-0.17021
Ile153	-0.8618	-0.76555	0.223871	-0.25334	-0.06678
Ser156	-0.58111	-1.14993	0.636683	0.152842	-0.2207
Trp121	-0.56147	-0.70984	0.034218	0.184792	-0.07064
Gln89	-0.44267	-0.92434	-0.57443	1.113663	-0.05757

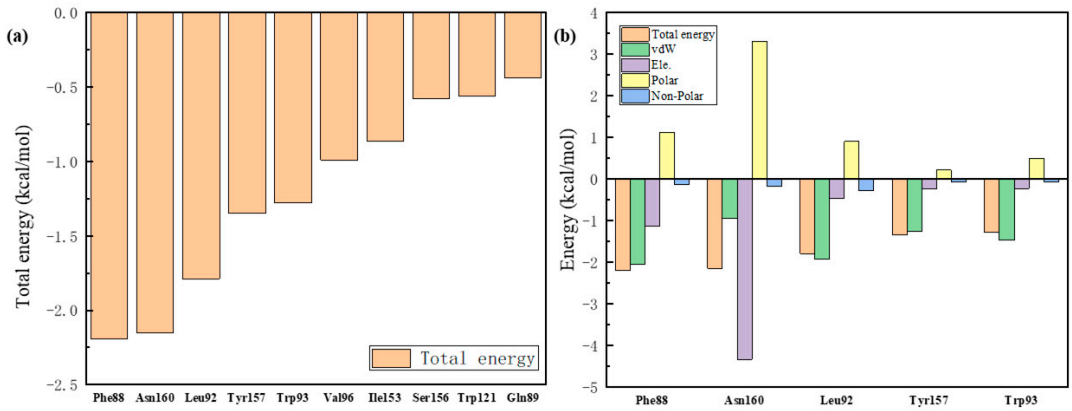

Figure S3 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to s-ketamine. (b) Decomposition of the energy of the five key residues and s-ketamine pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

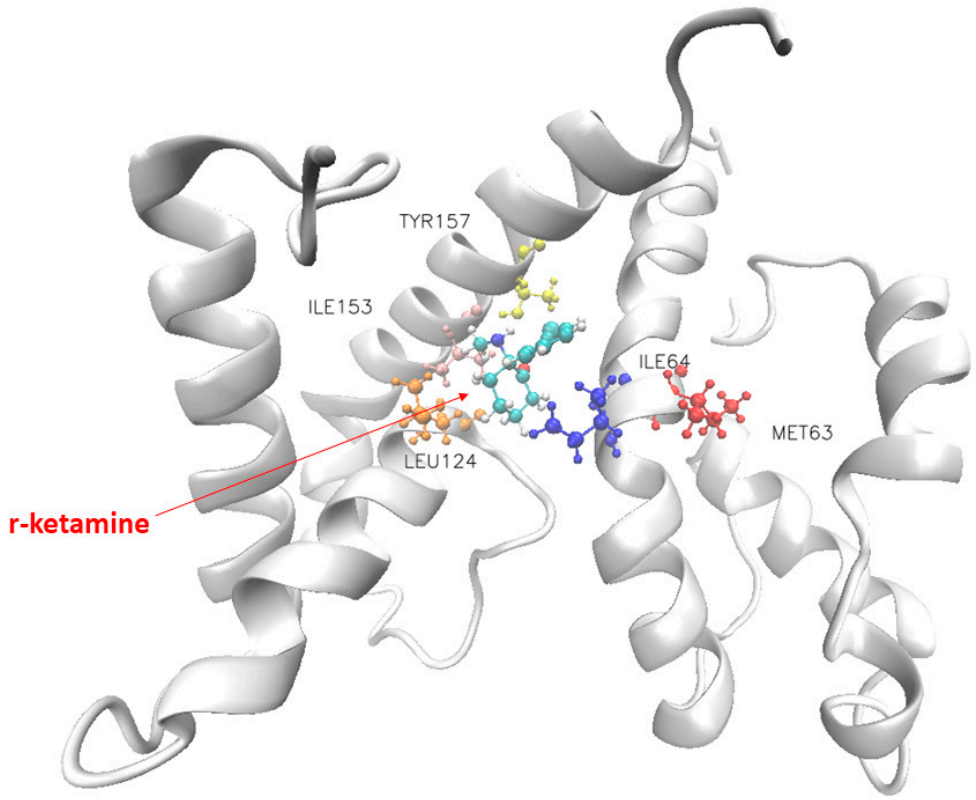

Fig S4 Visualization of the docking conformation of the NMDA receptor and r-ketamine. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to r-ketamine.

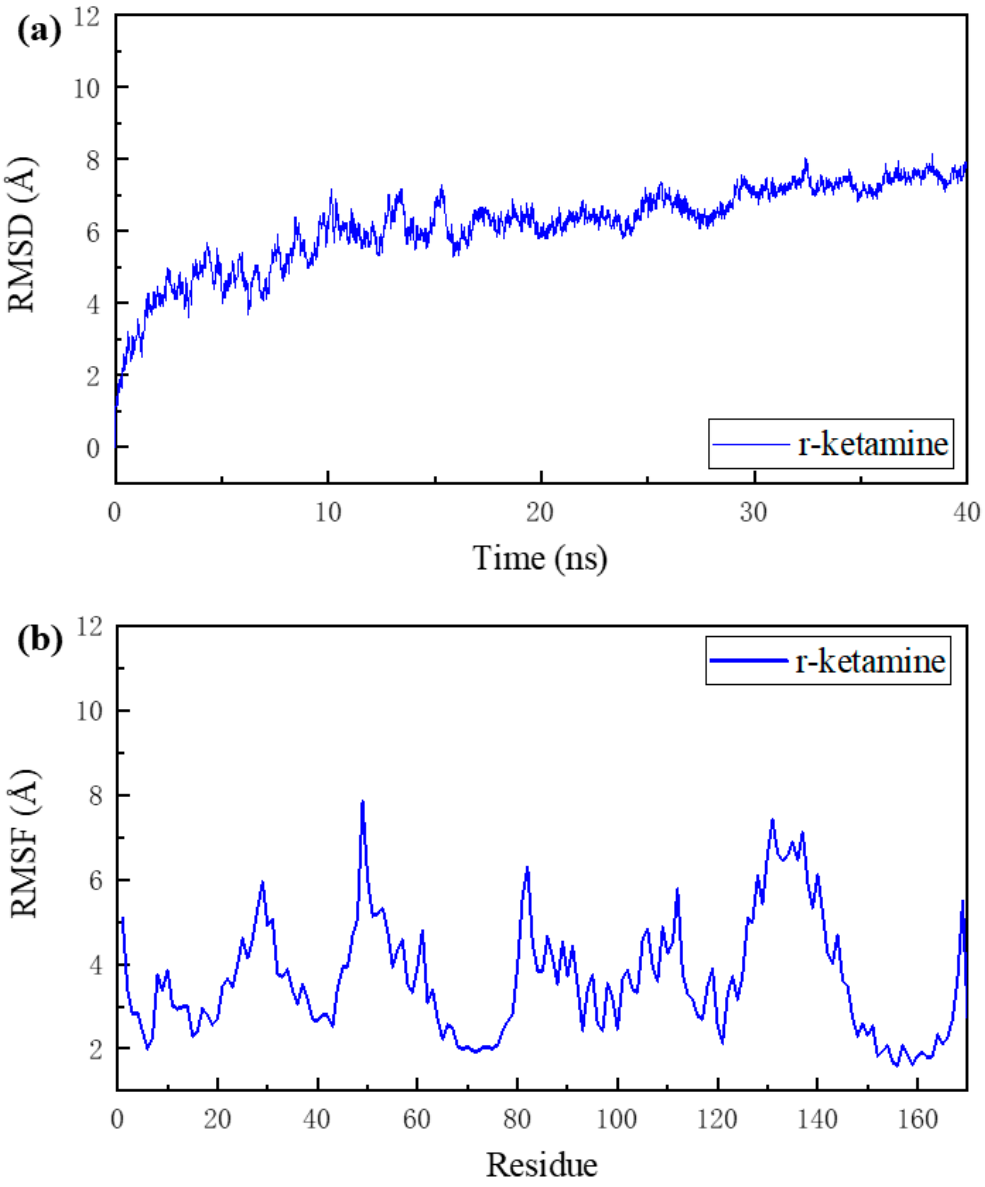

Figure S5 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of r-ketamine and the NMDA receptor complex in a 40-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S4 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to r-ketamine, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Met63	-1.76638	-1.28128	-1.22127	0.824329	-0.08815
Ile64	-1.60067	-1.51763	-0.64395	0.767993	-0.20708
Leu124	-1.37106	-1.48867	-0.72941	1.008282	-0.16127
Ile153	-1.24179	-1.20975	-0.01193	0.119086	-0.13919
Tyr157	-1.11015	-1.32248	-0.07776	0.417628	-0.12753
Val154	-0.95168	-0.93403	-0.12226	0.206771	-0.10216
Trp 146	-0.68055	-0.96497	-0.23216	0.601987	-0.0854
Leu125	-0.65302	-0.72225	0.042748	0.106176	-0.0797
Asn126	-0.61274	-0.3845	-0.82881	0.668924	-0.06835
Phe88	-0.57836	-0.7225	0.032405	0.238734	-0.127

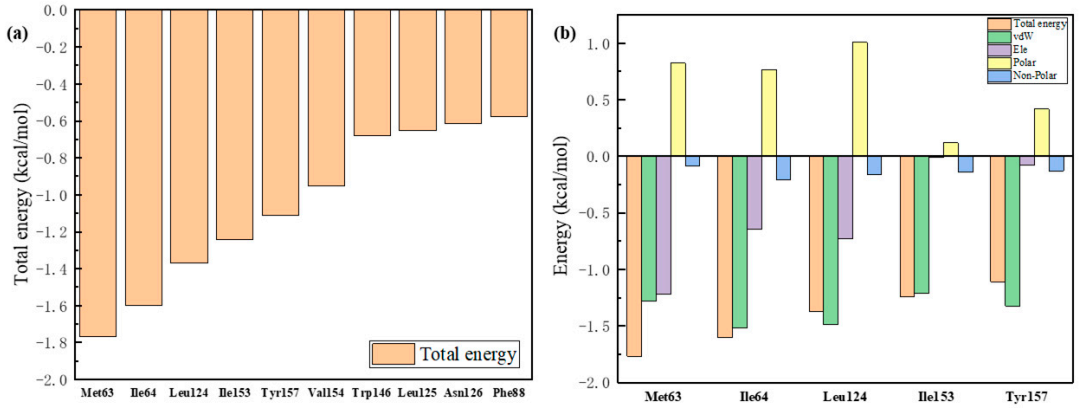

Figure S6 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to r-ketamine. (b) Decomposition of the energy of the five key residues and r-ketamine pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

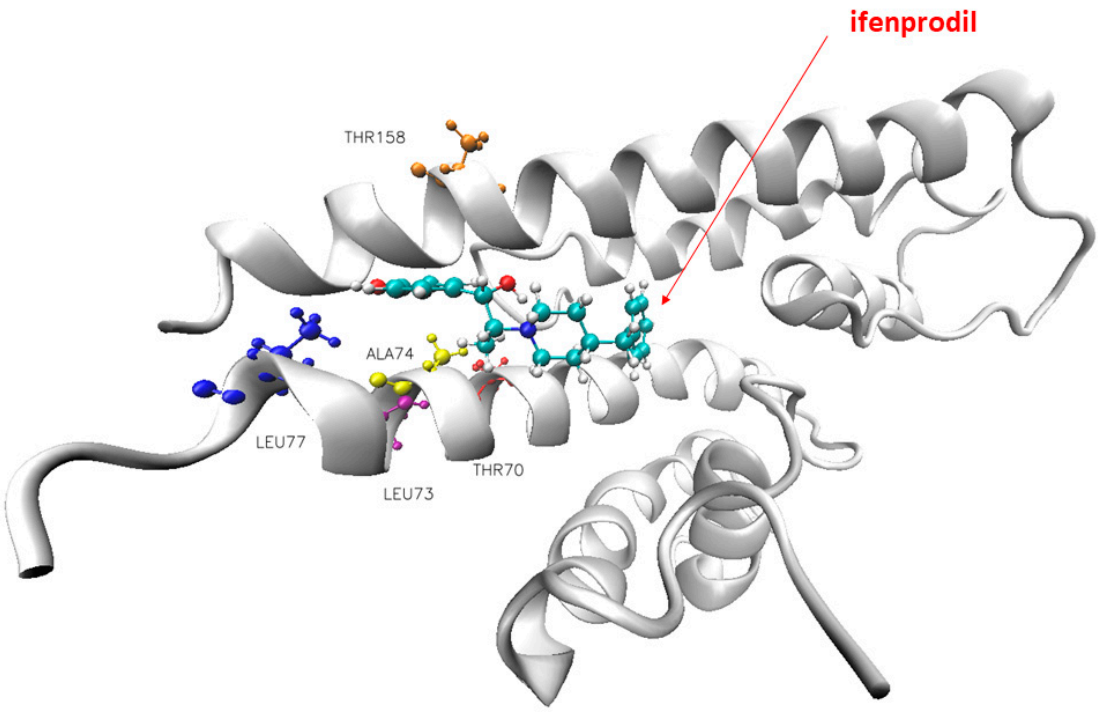

Figure S7 Visualization of the docking conformation of the NMDA receptor and ifenprodil. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to ifenprodil.

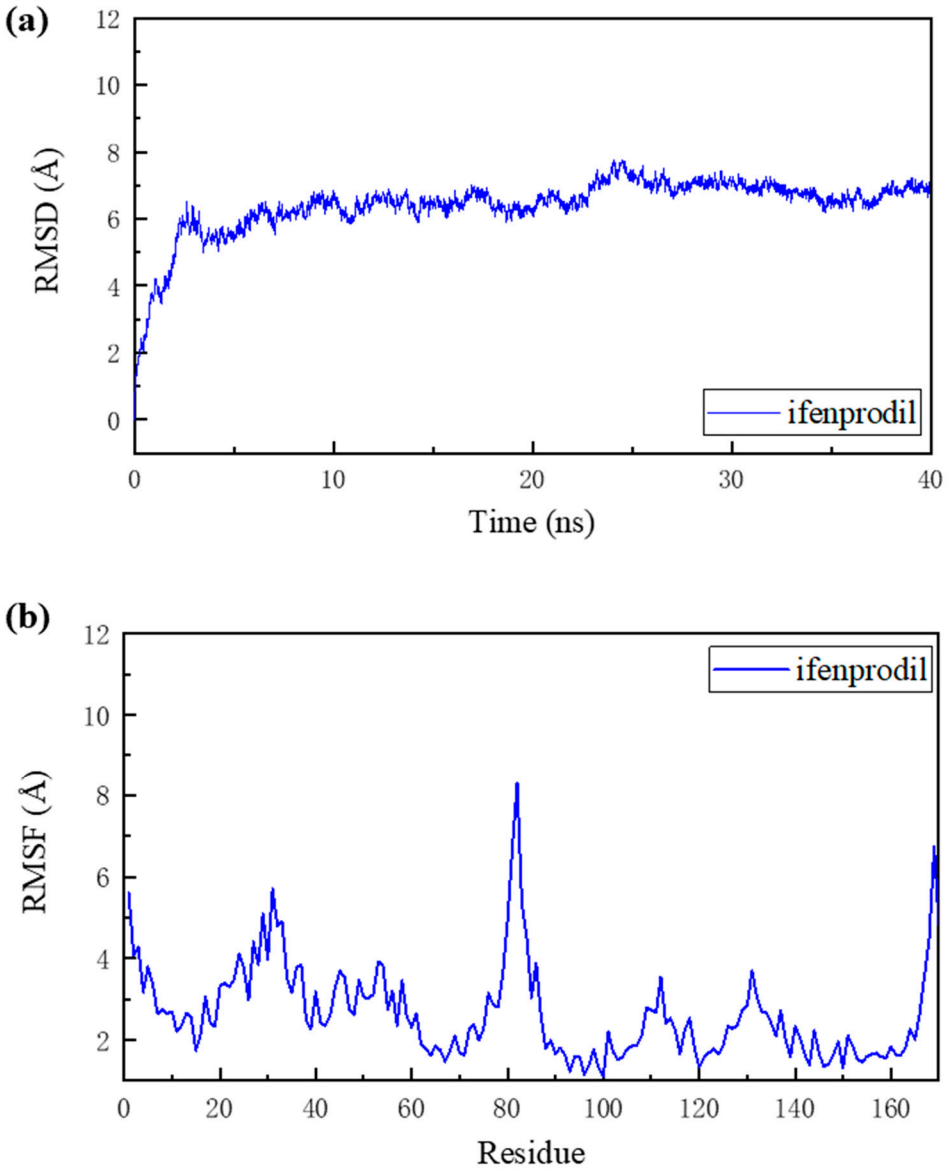

Figure S8 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of ifenprodil and the NMDA receptor complex in a 40-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S5 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to ifenprodil, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Leu77	1.687922	-1.54449	-0.2605	0.427807	-0.31074
Thr70	1.583291	-1.2928	-0.07637	-0.06165	-0.15246
Thr158	1.410215	-1.59881	-0.00882	0.402392	-0.20498
Leu 73	1.375455	-1.14104	0.062973	-0.14098	-0.15641
Ala74	0.991262	-1.04664	-0.01878	0.163475	-0.08931
Ala 162	0.933872	-0.83479	-0.24005	0.309635	-0.16867
Val 154	0.717936	-0.64291	0.175276	-0.17372	-0.07658
Leu 165	0.684936	-0.39705	-0.56417	0.302684	-0.0264
Leu 161	0.64939	-0.49321	-0.06996	-0.06838	-0.01785
Met 151	0.635817	-0.63292	-0.11679	0.241465	-0.12757

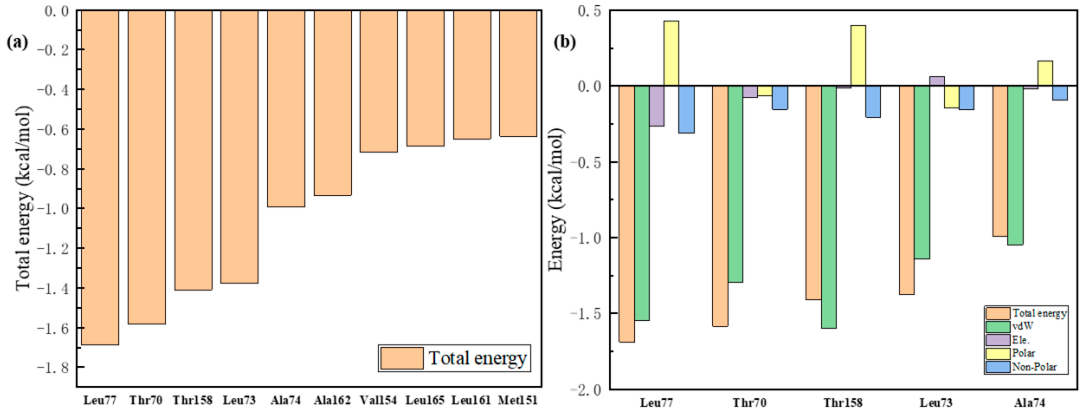

Figure S9 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to ifenprodil. (b) Decomposition of the energy of the five key residues and ifenprodil pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

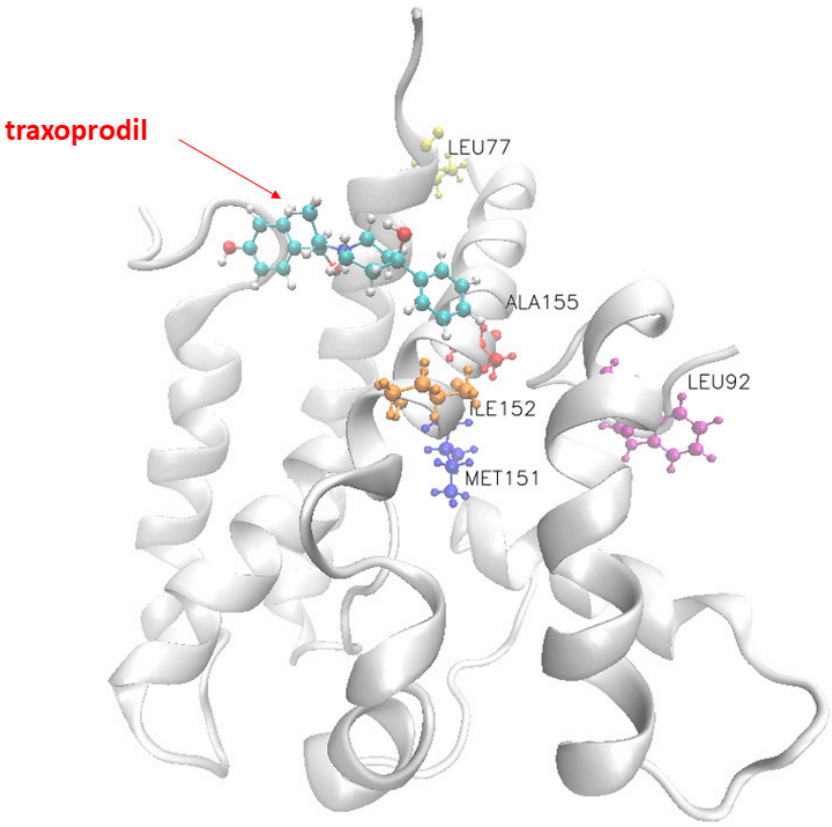

Figure S10 Visualization of the docking conformation of the NMDA receptor and traxprodil. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to traxprodil.

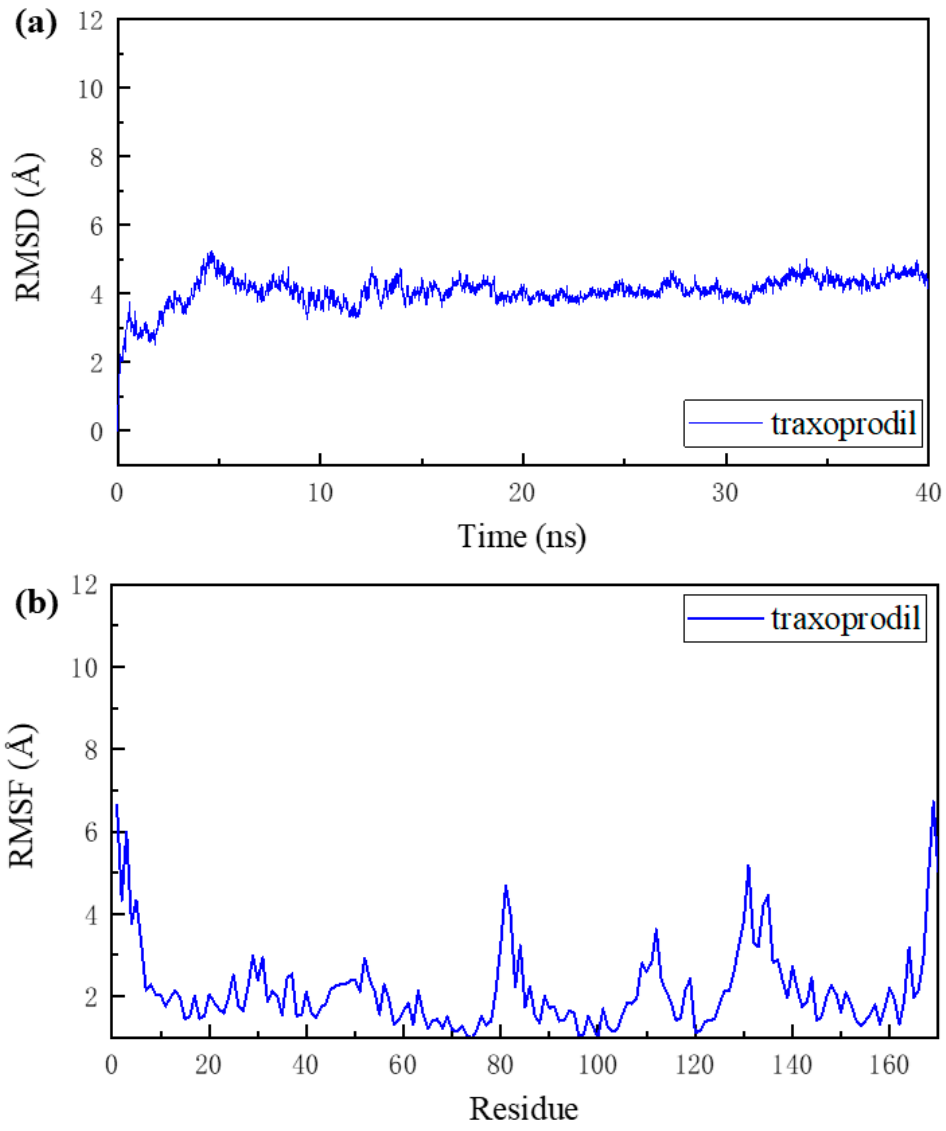

Figure S11 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of traxprodil and the NMDA receptor complex in a 40-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S6 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to traxprodil, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
IleLE 152	1.574005	-1.47964	0.002555	0.161645	-0.25856
Ala 155	1.50332	-1.23123	-0.23519	0.128362	-0.16526
Leu77	1.178284	-1.27187	-0.18614	0.51792	-0.23819
Leu92	0.85404	-0.7672	-0.01114	0.096595	-0.17229
Met 151	0.826756	-0.8536	-0.00697	0.186957	-0.15314
Met4	0.632208	-0.50579	-0.28928	0.237581	-0.07472
Pro6	0.607193	-0.59218	-0.30466	0.362017	-0.07237
Ala 159	0.572672	-0.54884	-0.03852	0.099731	-0.08504
Phe76	0.528461	-0.63222	-0.0879	0.311136	-0.11948
Leu73	0.515525	-0.46042	-0.04371	0.037983	-0.04938

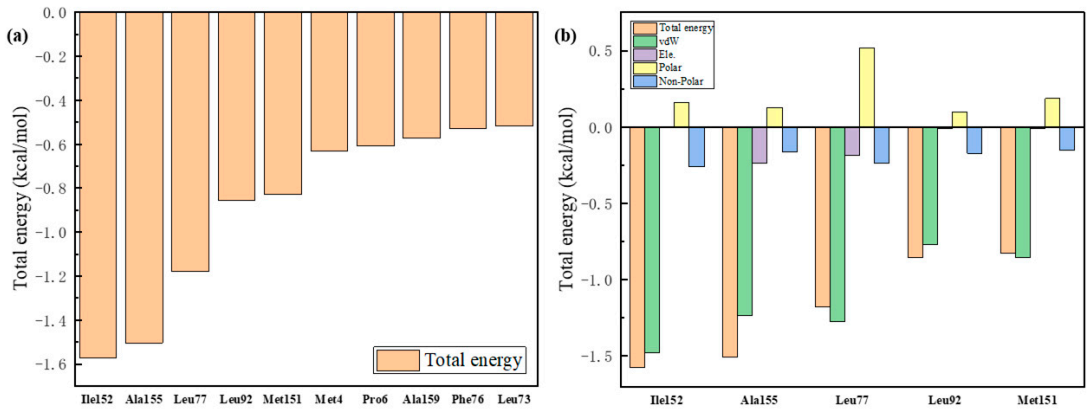

Figure S12 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to traxprodil. (b) Decomposition of the energy of the five key residues and traxprodil pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

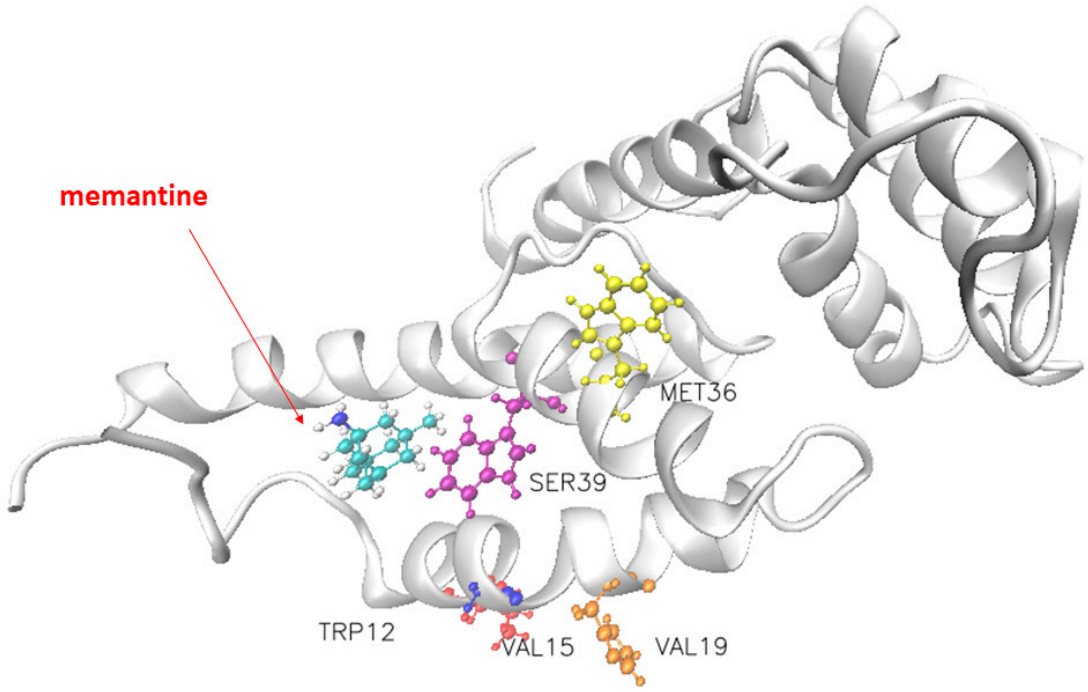

Figure S13 Visualization of the docking conformation of the NMDA receptor and memantine. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to memantine.

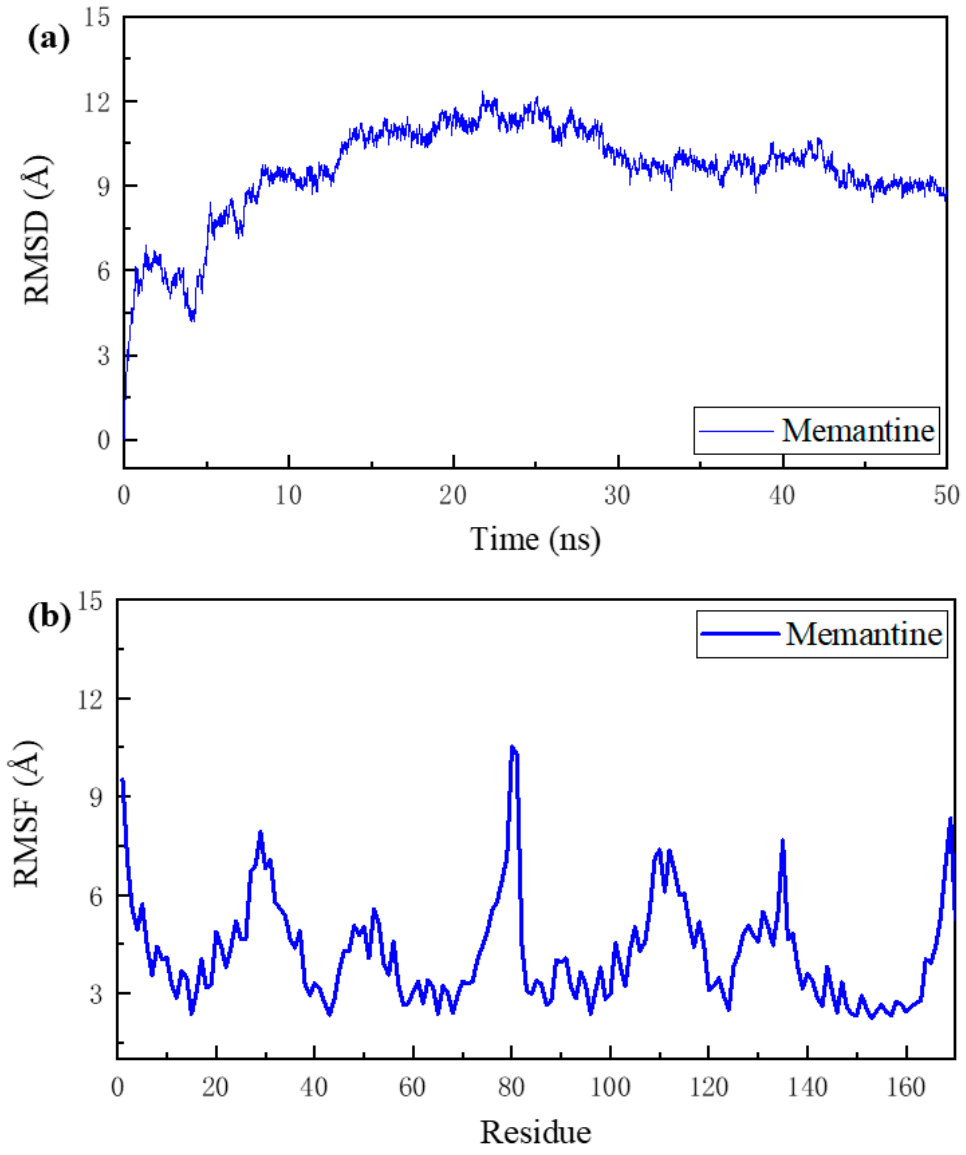

Figure S14 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of memantine and the NMDA receptor complex in a 50-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S7 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to memantine, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar)

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Met36	-1.22973	-1.32584	-0.12447	0.452622	-0.23204
Val15	-1.1356	-0.98899	0.04405	-0.12713	-0.06353
Trp12	-0.95294	-1.6389	-0.16025	1.02093	-0.17472
Val19	-0.93217	-0.7985	0.014264	-0.05241	-0.09551
Trp40	-0.91198	-1.61507	-0.19885	1.071532	-0.16959
Gly16	-0.67071	-0.69202	-0.00529	0.159731	-0.13312
Met4	-0.64472	-0.71532	-0.04542	0.267005	-0.15098
Ser39	-0.42161	-0.50578	0.012915	0.114542	-0.04329
Leu43	-0.31954	-0.30826	0.022955	-0.00696	-0.02728
Leu13	-0.23787	-0.2985	-0.01988	0.110294	-0.02979

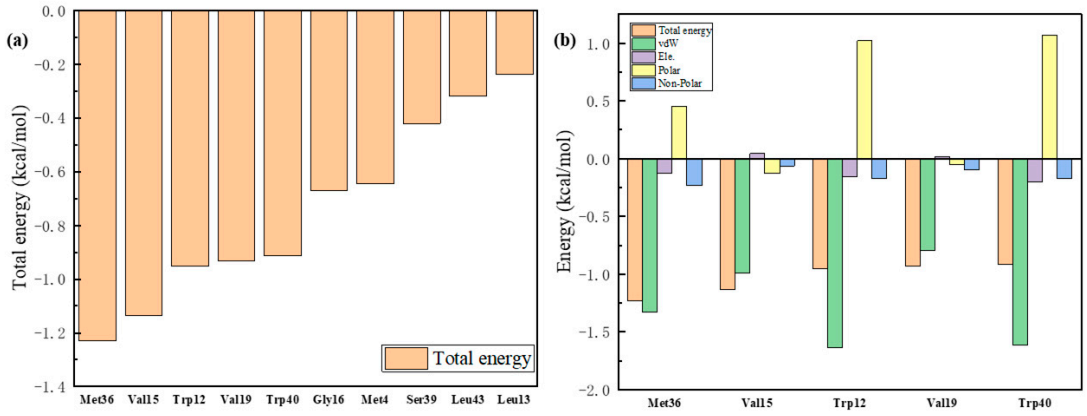

Figure S15 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to memantine. (b) Decomposition of the energy of the five key residues and memantine pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

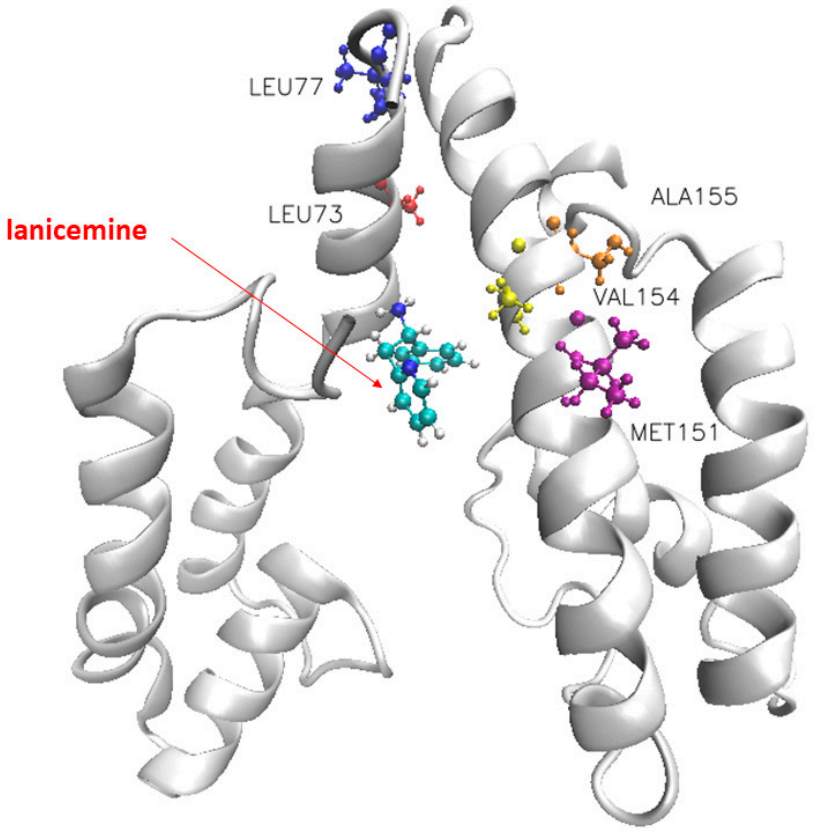

Figure S16 Visualization of the docking conformation of the NMDA receptor and lanicemine. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to lanicemine.

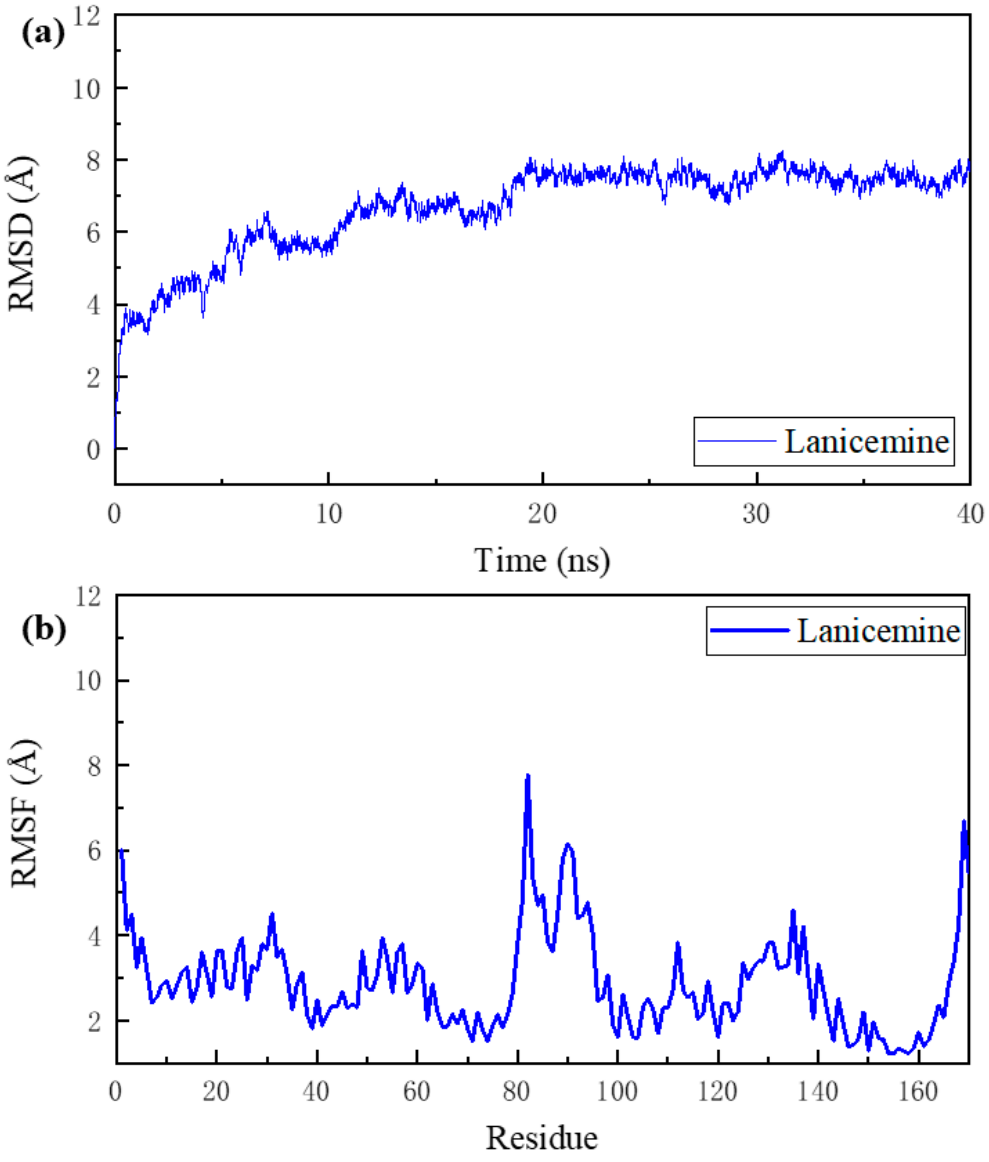

Figure S17 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of lanicemine and the NMDA receptor complex in a 40-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S8 Binding energy and decomposition of top 10 residues with dominant binding contributions of the NMDA receptor to lanicemine, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	Total energy	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Ala155	-1.38505	-1.26383	-0.24229	0.345445	-0.22439
Leu73	-0.74935	-0.66406	0.055282	-0.01769	-0.12289
Met151	-0.72665	-0.75208	-0.01362	0.191402	-0.15235
Leu77	-0.70765	-0.67469	-0.00131	0.137066	-0.16871
Val154	-0.67319	-0.57298	-0.04368	0.009777	-0.0663
Thr158	-0.45623	-0.5595	-0.13422	0.267106	-0.02961
Ile 152	-0.44839	-0.39728	-0.03973	0.052193	-0.06358
Ala159	-0.39072	-0.37716	-0.01477	0.083784	-0.08258
Phe3	-0.38615	-0.46228	-0.09865	0.280917	-0.10614
Thr70	-0.19303	-0.28424	-0.07625	0.191146	-0.02369

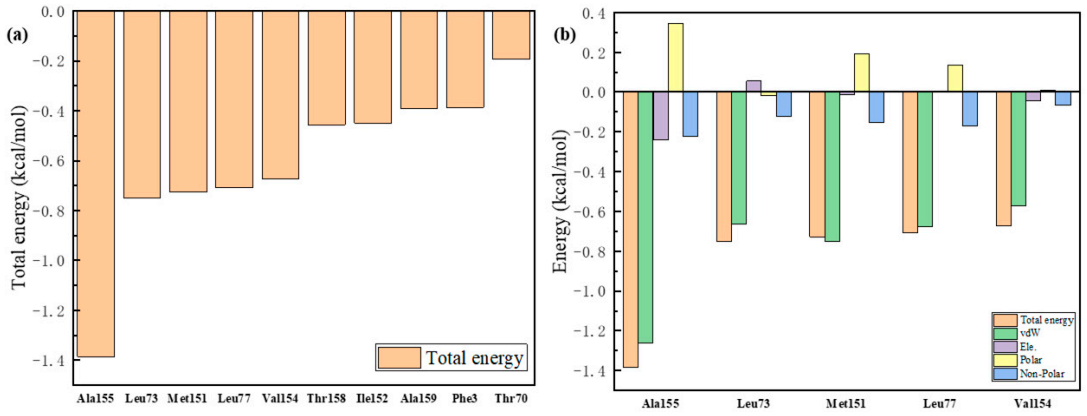

Figure S18 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptors to lanicemine. (b) Decomposition of the energy of the five key residues and lanicemine pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).

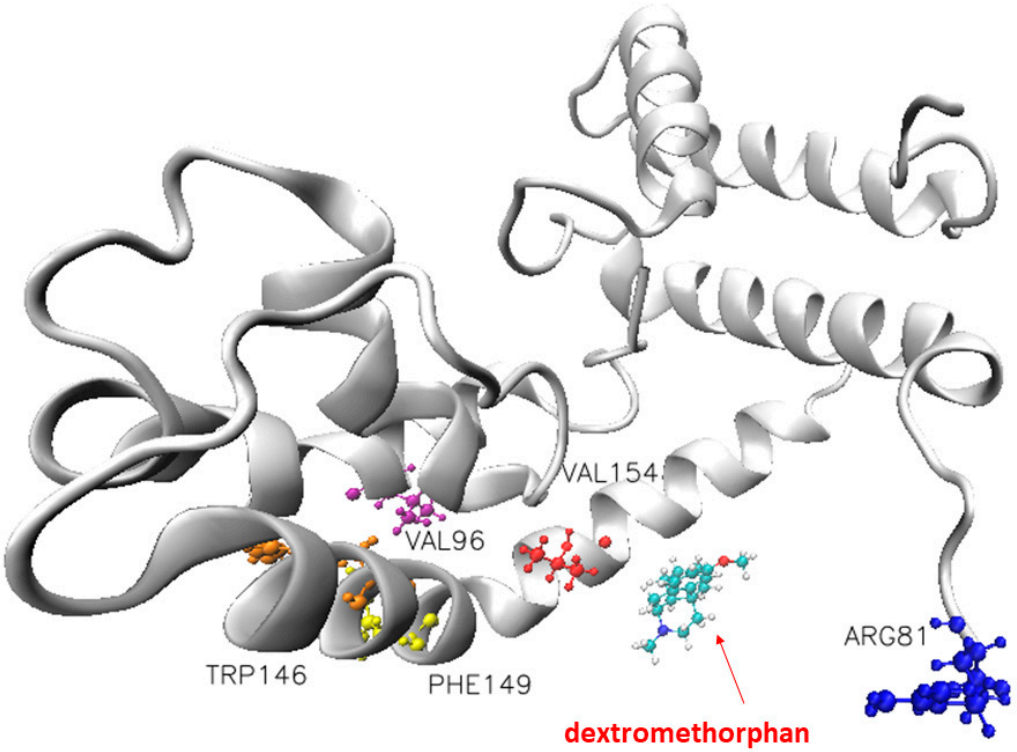

Figure S19 Visualization of the docking conformation of the NMDA receptor and dextromethorphan. The ball-and-stick model shows the binding pocket of five residues in the NMDA receptor with dominant binding contributions to dextromethorphan.

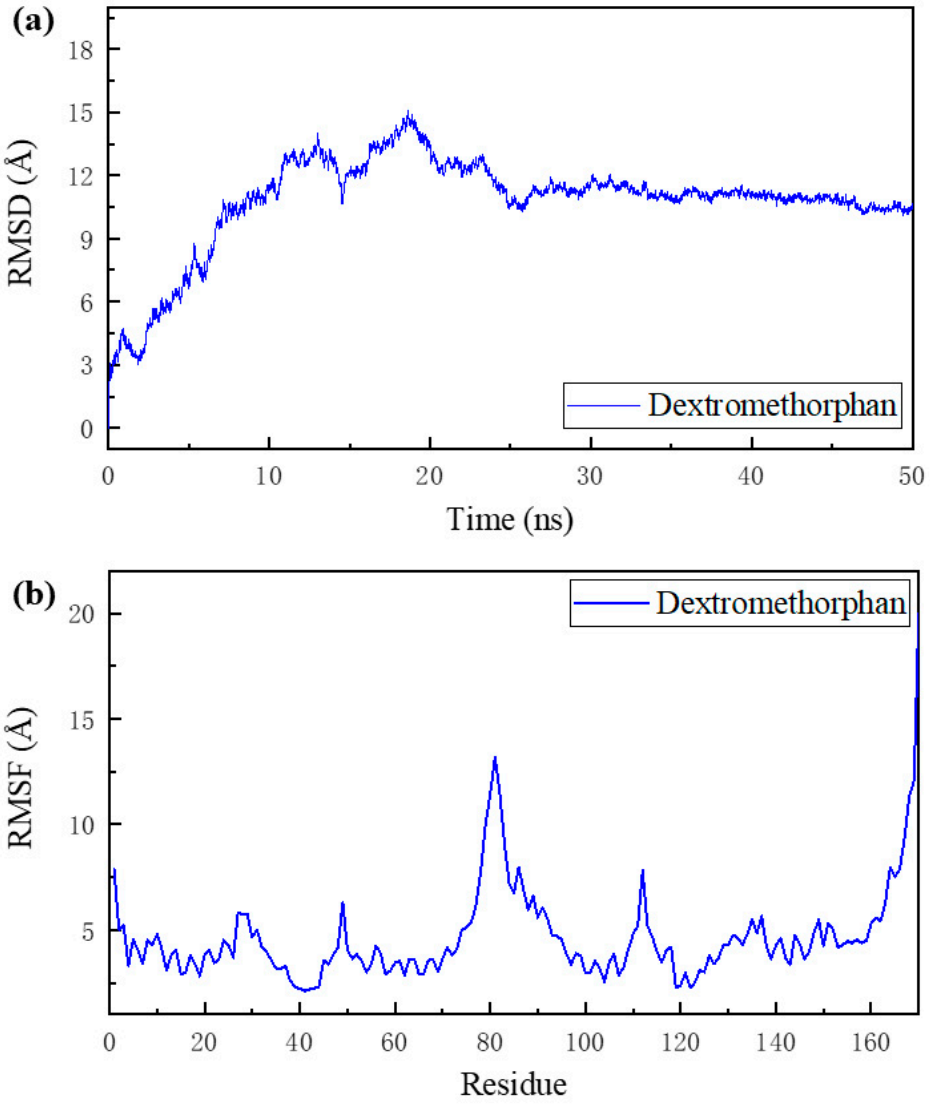

Figure S20 Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) of dextromethorphan and the NMDA receptor complex in a 50-ns simulation MD. (a) The RMSD of all non-hydrogen atoms in the complex. (b) The RMSF of all non-hydrogen atoms in the NMDA receptor throughout the simulation.

Table S9 Binding energy and decomposition of top 10 residues with dominant binding contributions of NMDA receptor to dextromethorphan, including van der Waals energy (vdW), electrostatic energy (Ele), polar solvation energy (Polar) and non-polar solvation energy (Non-polar).

Residue	TOTAL	van der Waals	Electrostatic	Polar Solvation	Non-Polar Solv.
Val96	-0.5848	-0.51287	-0.01389	0.03004	-0.08808
Phe149	-0.54639	-0.74609	0.029353	0.311368	-0.14101
Trp146	-0.34524	-0.61197	-0.03936	0.387806	-0.08171
Arg81	-0.34509	-0.57003	-0.23569	0.556045	-0.09541
Val154	-0.26438	-0.24528	-0.02877	0.041169	-0.0315
Ser99	-0.25508	-0.31555	-0.16573	0.298333	-0.07213
Val100	-0.20423	-0.20154	-0.00052	0.012124	-0.0143
Ile153	-0.17272	-0.14407	-0.02008	0.001572	-0.01013
Val103	-0.15839	-0.13281	-0.00159	-0.00228	-0.02172
Leu77	-0.15532	-0.15283	0.003647	0.022507	-0.02864

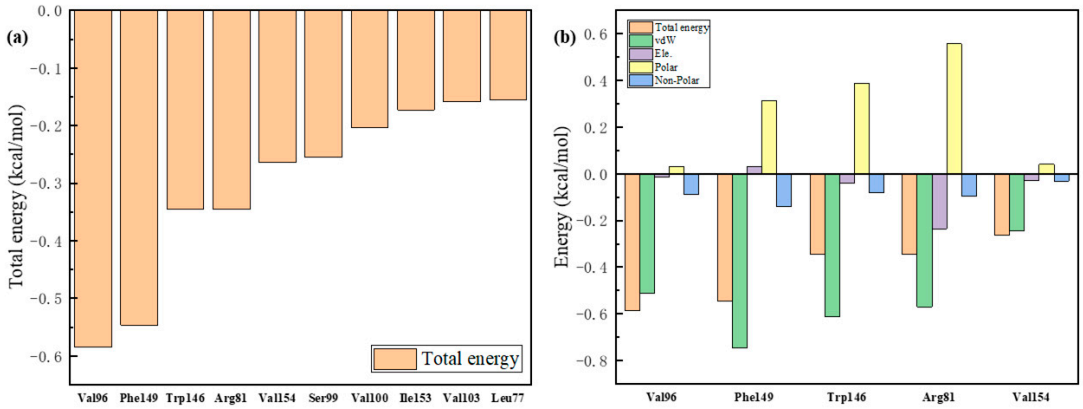

Figure S21 Decomposition of the free energy of binding of key residues. (a) The 10 key residues with dominant binding contributions from the NMDA receptor to dextromethorphan. (b) Decomposition of the energy of the five key residues and dextromethorphan pairs into four energy terms, namely van der Waals interaction (vdW), electrostatic interaction (ele), polar solvation energy (polar), and nonpolar energy (nonpolar).