

Supporting information for

Novel huperzine A based NMDA antagonists: insights from molecular docking, ADME/T and molecular dynamics simulation studies

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Protein sequence alignment:

| | |
|---------------------|--|
| sp Q05586 5un1_C | KENITDPPRGCVGNTNIWKTGFLFKRVLMSKSYADGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYNGTHVIPNDRKIIWPGGETEKPRGYQST |
| sp Q05586 5un1_C | RLKIVTTHQPPFVYKPTLSIGTCKEFTVNGIPVKKVCTGPNDSPGSPRHIVPQCCYGFCLILLIKLARTNNTYVHLVADGKTGTQQRVNNNSNK RLKIVTTHQPPFVYRPTTSIGTCREYTINGIPIKKVTCNGPDETIIPGR--TVPQCCYGFCLILLIKLARENDITYVHLVADGKTGTQQRVNNNSNA |
| sp Q05586 5un1_C | KEWNGMGLISQADMIVAPITNNRQYVFSKPKKQGITLWKKIIPRSTLSENPQFQSTLWLLVGLSHVAVVMLYLLRISPFGRKVNSE AAWNGMGLISQADMIVAPITNNRQYVFSKPKKQGITLWKKIIPRSTLSENPQFQSTLWLLVGLSHVAVVMLYLLRISPFGR----- |
| sp Q05586 5un1_C | EEEEDALTISSAMWFSWGLVNSGICEGAPRSTSRARLLGMVWAGFAMILIVASVTANLAAFLVDRPERRITGINDPRLRNPSDKFIYATVKQSSVDTY ---EDALTISSAMWFSRWLVNSGLCEGAPRSTSRARLLGMVWAGFAMILIVASVTANLAAFLVRRPERRITGINDPRLRNPSDKFIYATVKQSSVDTY |
| sp Q05586 5un1_C | RRQVELSTYRHMKHNYSAAEAQAVRNKIHAFIWSAVLIERASQKCLAVTTGELFERSGFGGRKISPWQONSISLIKSHNGMEDIKTN RRQVELSTYRHMKHNYSAAEAQAVRNKIHAFIWSAVLIERASQKCLAVTTGELFERSGFGGRKISPWQONSISLIKSHNGMEDIKTN |
| sp Q05586 5un1_C | RYQICDSRSNAPATITENNAGVFYMLVAGGIVAGIFLIFELIAYKRHKDPRKQ-MQLAAAVNVWRKNLQDRKSGRAEPDPKPKATFRATISTLASS RYQICDSRSNAPATITENNAGVFYMLVAGGIVAGIFLIFELIAYKSRAEPRKMKGLEVLQ----- |

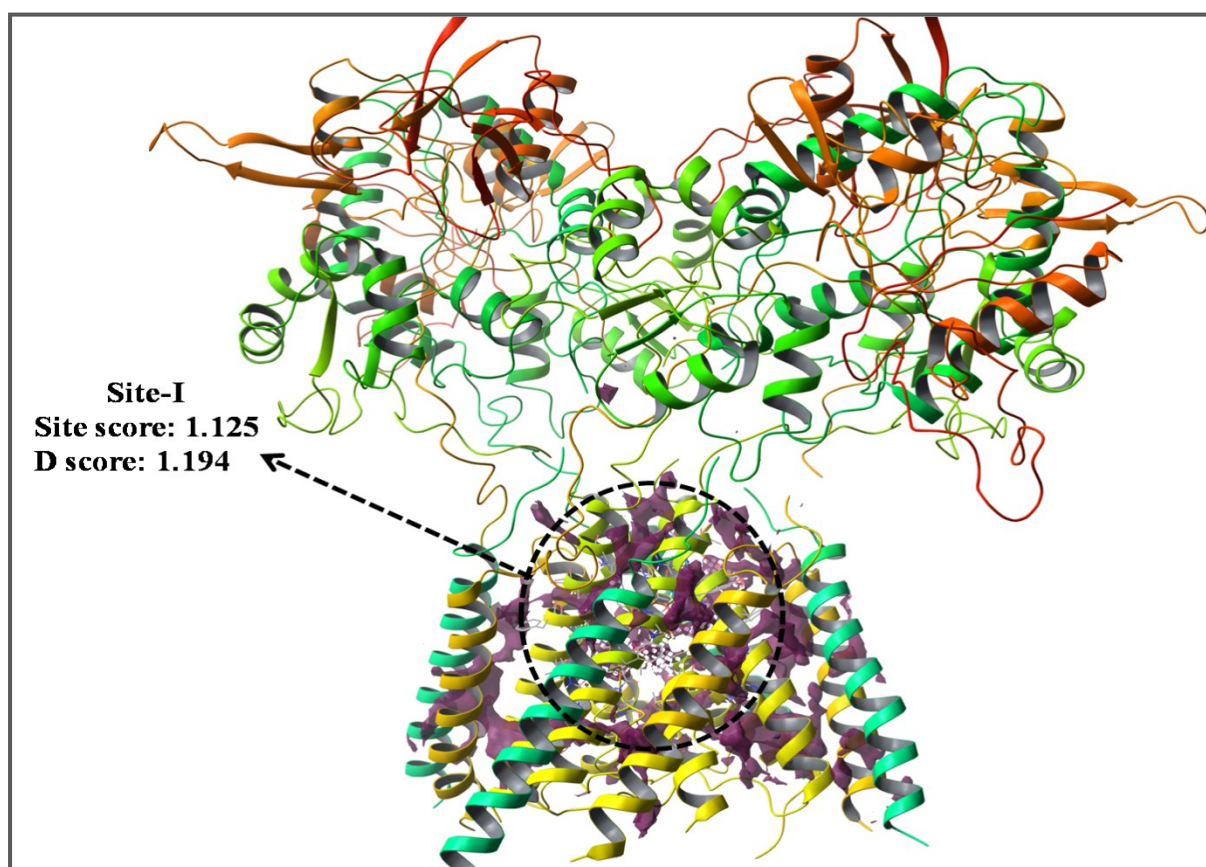
Figure S1. Sequence alignment of GluN1 from *Homo sapiens* (UniProt Q05586) and *Xenopus laevis* (PDB ID: 5UN1).

| | |
|---------------------|--|
| sp Q13224 5un1_D | ETEEQEDELISVTEEAFFVIVSMDPISGTCVRNTPCOKRVTNKTIDEPGYLRKCKGICDILIKKSKSKKFTYLYLVNNGKHGKKNGTWN -----EHLISVTEEAFFVIVDMDPISGTCVRNTPCRKQRFENRTEGGNYLRKCKGICDILIKKAKTKFTYLYLVNNGKHGKKNGVWN |
| sp Q13224 5un1_D | GLIGVVMKRAYMAVGSITNERSFVVDSPPIETGLSVMVSRNGTSPSAPFTFFSADVVWMMFVMLLIVSAVAVFVEFTSPYGTNRCLADGRE GLIGVVTKRAYMAVGSITNERSFVVDSPPIETGLSVMVSRNGTSPSAPFTFFSADVVWMMFVMLLIVSAVAVFVEFTSPYGTNRCLADGRE |
| sp Q13224 5un1_D | PGGPSITIGKALWLLWGLVNNVSPQNPKGTTSKIMVSVWAEFAVIFLASITANLAAFMQEEYVQVSGLSKKIQRPNDSESPRRTGTENGSTER ~GPSITIGKALWLLWGLVNNVSLPQNPKGTTSKIMVSVWAEFAVIFLASITANLAAFMQRRYVQVSGLSKKIQRPNDSESPRRTGTENGSTER |
| sp Q13224 5un1_D | NTRNNLADHAYMCKENQRGDIALISIKTGGIDAFIYDAAVLNVMAGRDEGCKLVTIGSGKVFASTIGTGLAQKISGWRQVQLALIQLFSGGMEEL NTRNNLADHAYMCKENQRSQIALISIKSGKIDAFIYDAAVLNVMAGRDEGCKLVTIGSGKVFASTIGTGLAQKISGWRQVQLALIQLFSGGMEEL |
| sp Q13224 5un1_D | EALWITGICHNPKNEVMSSQITLNNMAGVFYMLAAMALSITFIMCHLFWQFRHCFMGVCSGKPGMVFSISRGIYSCHIGVAIEERQSVMNSPTATM EALWITGICHNPKNEVMSSQITLNNMAGVFYMLAAMALSITFIMCHLFWQFRHCFMGVCSGKPGMVFSISRGIYSCHIGVAIEERQSVMNSPTATM |

Figure S2. Sequence alignment of GluN2B from *Homo sapiens* (UniProt Q13224) and *Xenopus laevis* (PDB ID: 5UN1).

Binding site evaluation:**Table S1.** Average SiteMap values across NMDA receptor

| S. No | Site name | Site score | D score | Size | Hydrophobic | Volume |
|----------|---------------|--------------|--------------|-------------|--------------|-----------------|
| 1 | Site-I | 1.125 | 1.194 | 2211 | 1.920 | 4920.335 |
| 2 | Site-II | 1.038 | 1.037 | 488 | 0.590 | 1299.970 |
| 3 | Site-III | 1.122 | 1.150 | 342 | 1.585 | 648.613 |
| 4 | Site-IV | 1.057 | 1.102 | 333 | 1.101 | 1005.333 |
| 5 | Site-V | 1.111 | 1.159 | 316 | 1.666 | 728.189 |

**Figure S3.** Site points (white spheres) and SiteMap surface (maroon colour contour) for Site-I binding site of NMDA receptor.

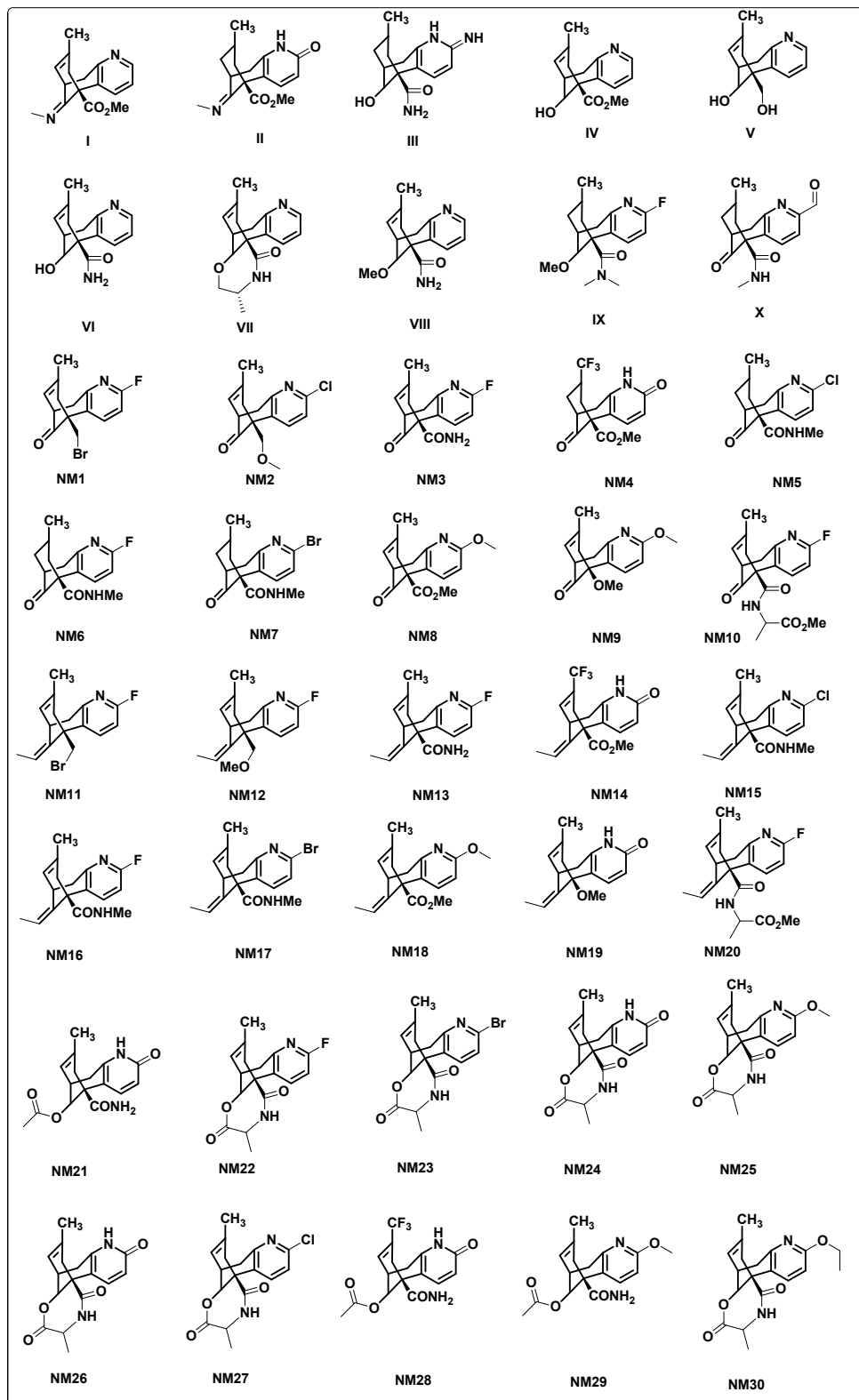
Derivatized compounds of Huperzine A:

Figure S4. The derivatized compounds of Huperzine A.

Molecular docking protocol validation:

The docking protocol was validated by redocking of the bound ligand MK-801 in the active site of NMDA receptor using GLIDE module of Schrödinger software. The bound and docked conformations of MK-801 (RMSD 0.0806 Å) showed similar interactions and binding pose at the binding site. This analysis establishes the acceptability of docking protocol and thus can be extended to dock investigated molecules in the active site of NMDA receptor.

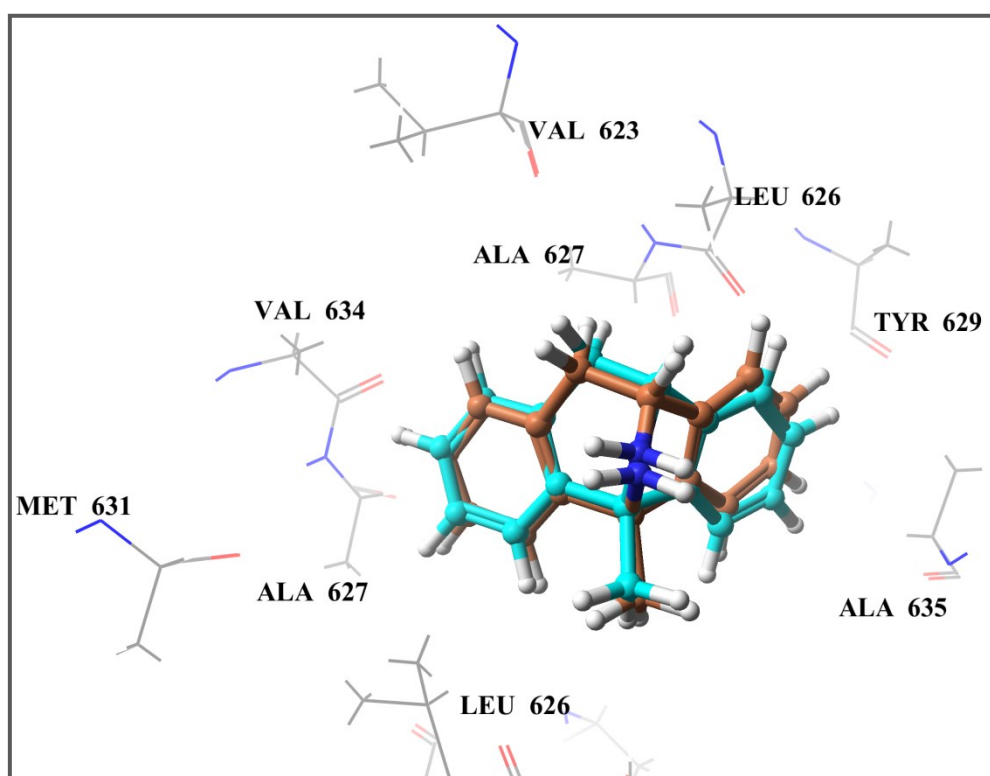
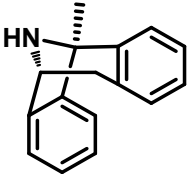
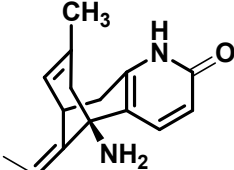
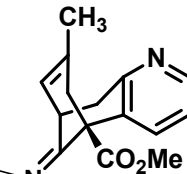
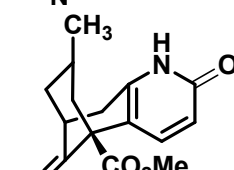
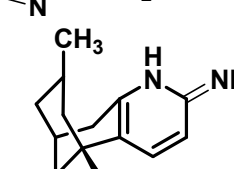
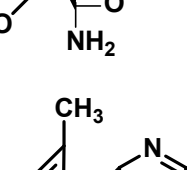
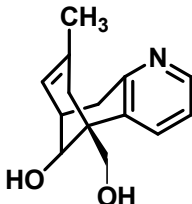
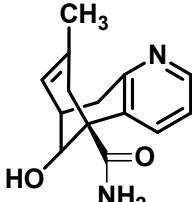
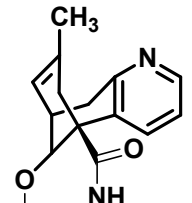
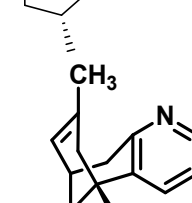
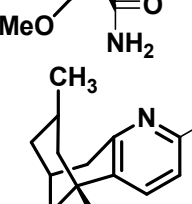
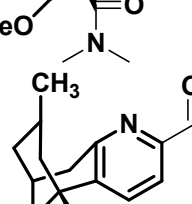
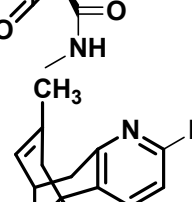
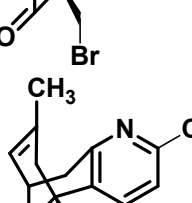
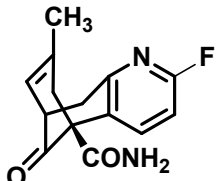
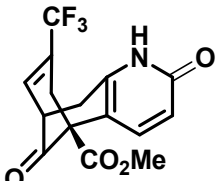
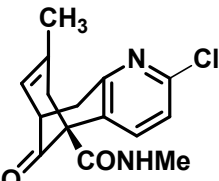
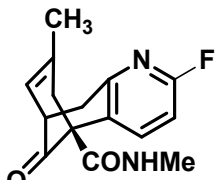
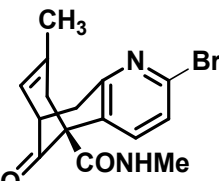
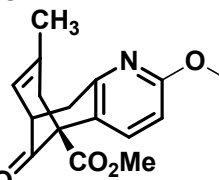
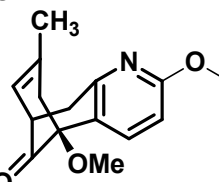
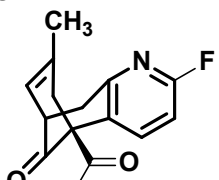
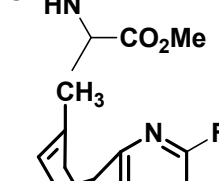


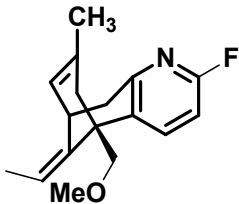
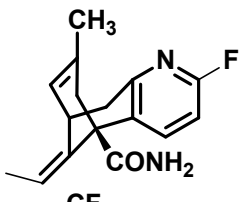
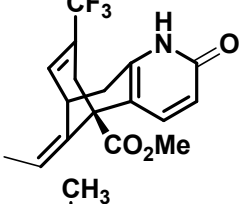
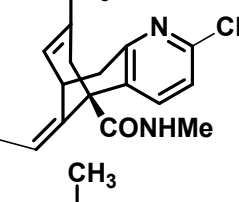
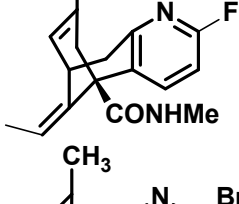
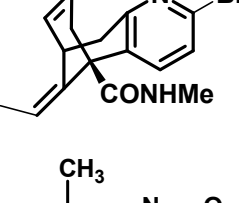
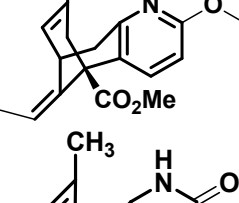
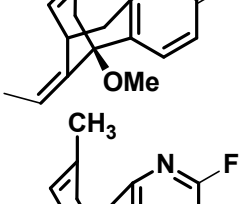
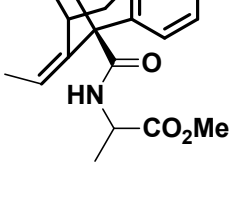
Figure S5 . Superimposition of bound co-crystal (cyan colour) and docked conformation of co-crystal (burnt orange colour) in the binding site of NMDA receptor (PDB ID: 5UN1).

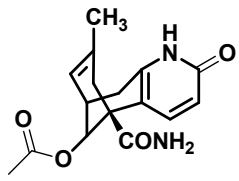
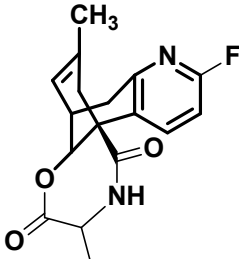
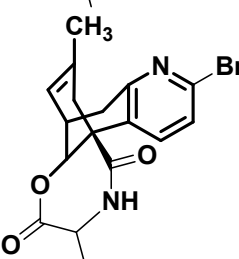
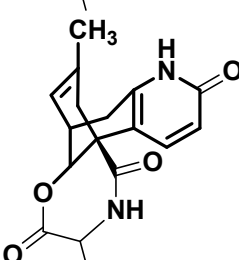
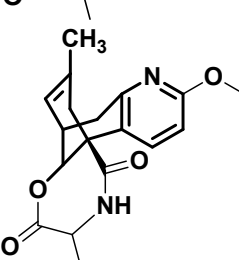
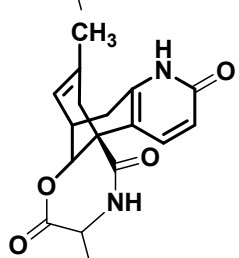
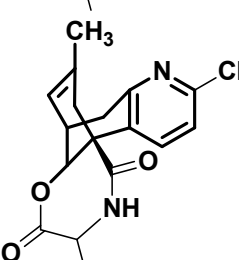
Molecular docking analysis:**Table S2.** GLIDE docking results for designed Huperzine A analogues at active site of NMDA receptor (PDB ID: 5UN1).

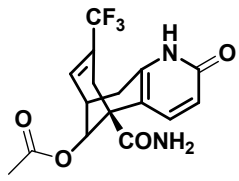
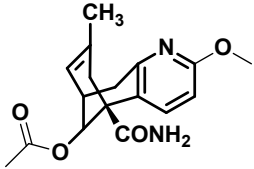
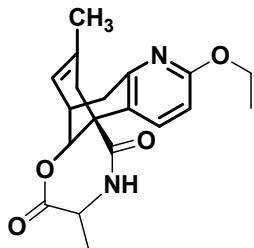
| S. no | Ligand name | Ligand structure | Docking score | Interactions | |
|-------|-------------|---|---------------|---|----------|
| | | | | Hydrophobic | H- bonds |
| 1 | MK-801 |  | -7.365 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val623(D), Leu626(D), Ala627(D) | - |
| 2 | Huperzine A |  | -6.970 | Met631(A), Val634(A), Ala635(A), Phe597(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) | - |
| 3 | I |  | -7.006 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Val623(D), Leu626(D), Ala627(D) | - |
| 4 | II |  | -6.684 | Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Ala630(C), Met631(C), Val634(C), Ala635(C), Tyr637(C), Phe597(D), Leu626(D), Ala627(D) | - |
| 5 | III |  | -6.903 | Met631(A), Val634(A), Ala635(A), Phe597(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Val623(D), Leu626(D), Ala627(D) | - |
| 6 | IV |  | -6.546 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | - |

| | | | | | |
|----|------|---|--------|---|-----------|
| 7 | V |  | -6.289 | Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | Thr630(D) |
| 8 | VI |  | -6.614 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Val623(D), Leu626(D), Ala627(D) | - |
| 9 | VII |  | -6.761 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | - |
| 10 | VIII |  | -6.960 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | - |
| 11 | IX |  | -6.441 | Met631(A), Val634(A), Ala635(A), Phe597(B), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | - |
| 12 | X |  | -7.311 | Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Ala630(C), Met631(C), Val634(C), Ala635(C), Phe597(D), Leu626(D), Ala627(D) | - |
| 13 | NM1 |  | -7.173 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Ala622(D), Val623(D), Leu626(D), Ala627(D) | |
| 14 | NM2 |  | -6.612 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |

| | | | | | |
|----|------|---|--------|---|-----------|
| 15 | NM3 |  | -7.365 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val623(D), Leu626(D), Ala627(D) | |
| 16 | NM4 |  | -7.148 | Val634(A), Ala635(A), Leu626(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 17 | NM5 |  | -7.102 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) | |
| 18 | NM6 |  | -7.298 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) | |
| 19 | NM7 |  | -7.011 | Met631(A), Val634(A), Ala635(A), Phe597(B), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Val623(D), Leu626(D), Ala627(D) | Leu626(B) |
| 20 | NM8 |  | -6.495 | Met631(A), Val634(A), Ala635(A), Phe597(B), Leu626(B), Ala627(B), Met631(C), Val634(C), Ala635(C), Leu626(D), Ala627(D) | |
| 21 | NM9 |  | -6.246 | Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Ala630(C), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 22 | NM10 |  | -7.304 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 23 | NM11 |  | -5.721 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Ala622(D), Val623(D), Leu626(D), Ala627(D) | |

| | | | | |
|----|------|---|--------|---|
| 24 | NM12 |  | -7.331 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) |
| 25 | NM13 |  | -7.193 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) |
| 26 | NM14 |  | -7.475 | Met631(A), Val634(A), Ala635(A), Phe597(B), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Val623(D), Leu626(D), Ala627(D) |
| 27 | NM15 |  | -7.388 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D), Ala631(D) |
| 28 | NM16 |  | -7.542 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Val623(D), Leu626(D), Ala627(D) |
| 29 | NM17 |  | -7.178 | Met631(A), Val634(A), Ala635(A), Phe597(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) |
| 30 | NM18 |  | -6.404 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Ala630(C), Met631(C), Val634(C), Ala635(C), Phe597(D), Val623(D), Leu626(D), Ala627(D) |
| 31 | NM19 |  | -6.839 | Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) |
| 32 | NM20 |  | -7.722 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) |

| | | | | | |
|----|------|---|--------|---|-----------|
| 33 | NM21 |  | -7.123 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Tyr629(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 34 | NM22 |  | -7.558 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 35 | NM23 |  | -7.036 | Met631(A), Val634(A), Ala635(A), Leu626(B), Tyr629(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 36 | NM24 |  | -7.386 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala622(D), Val623(D), Leu626(D), Ala627(D) | Leu626(B) |
| 37 | NM25 |  | -7.273 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Ala619(D), Leu595(D), Ala622(D), Val623(D), Leu626(D), Ala627(D) | |
| 38 | NM26 |  | -7.208 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Ala627(B), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |
| 39 | NM27 |  | -7.365 | Met631(A), Val634(A), Ala635(A), Leu626(B), Tyr629(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) | |

| | | | | |
|----|------|---|--------|---|
| 40 | NM28 |  | -7.830 | Val634(A), Phe597(B), Val623(B), Leu626(B), Val634(C), Val623(D), Leu626(D), Ala627(D) |
| 41 | NM29 |  | -7.324 | Met631(A), Val634(A), Ala635(A), Val623(B), Leu626(B), Tyr629(B), Met631(C), Val634(C), Ala635(C), Val623(D), Leu626(D), Ala627(D) |
| 42 | NM30 |  | -7.152 | Leu605(A), Met631(A), Val634(A), Ala635(A), Leu626(B), Ala627(B), Tyr629(B), Val634(C), Ala635(C), Ala619(D), Leu595(D), Ala622(D), Val623(D), Leu626(D), Ala627(D) |

Molecular dynamics simulation:

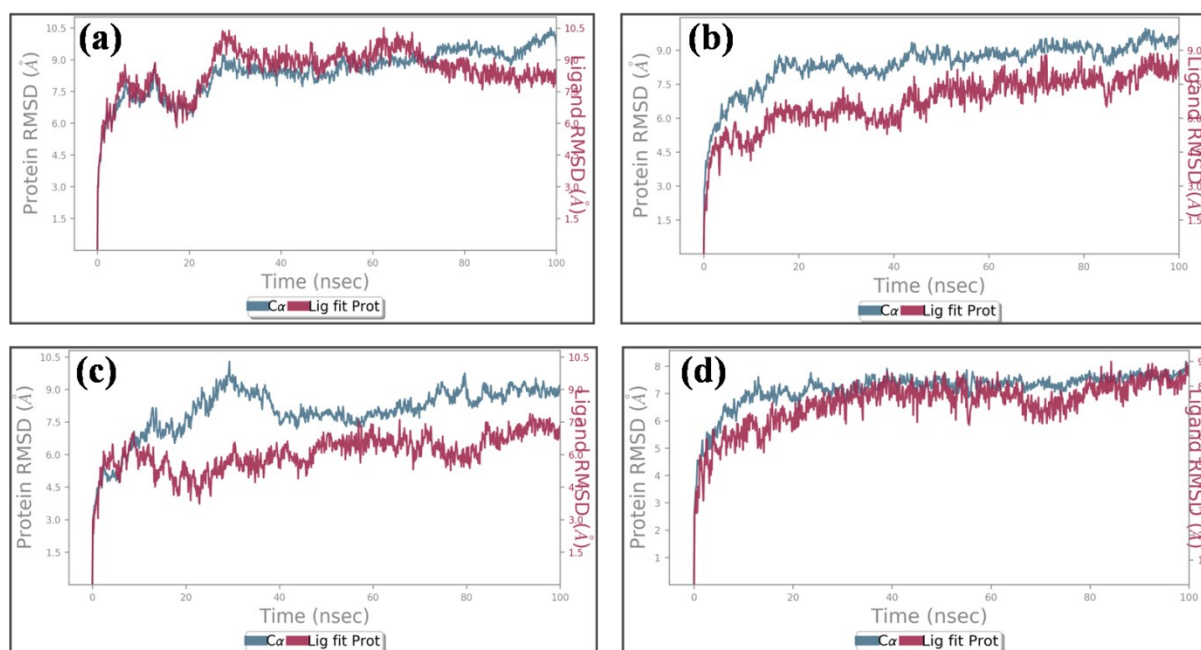


Figure S6. Average RMSD of C-alphas of protein and ligand complexes (a) NM14-5UN1, (b) NM16-5UN1, (c) NM20-5UN1 and (d) NM22-5UN1 during molecular dynamics simulation (100 ns).

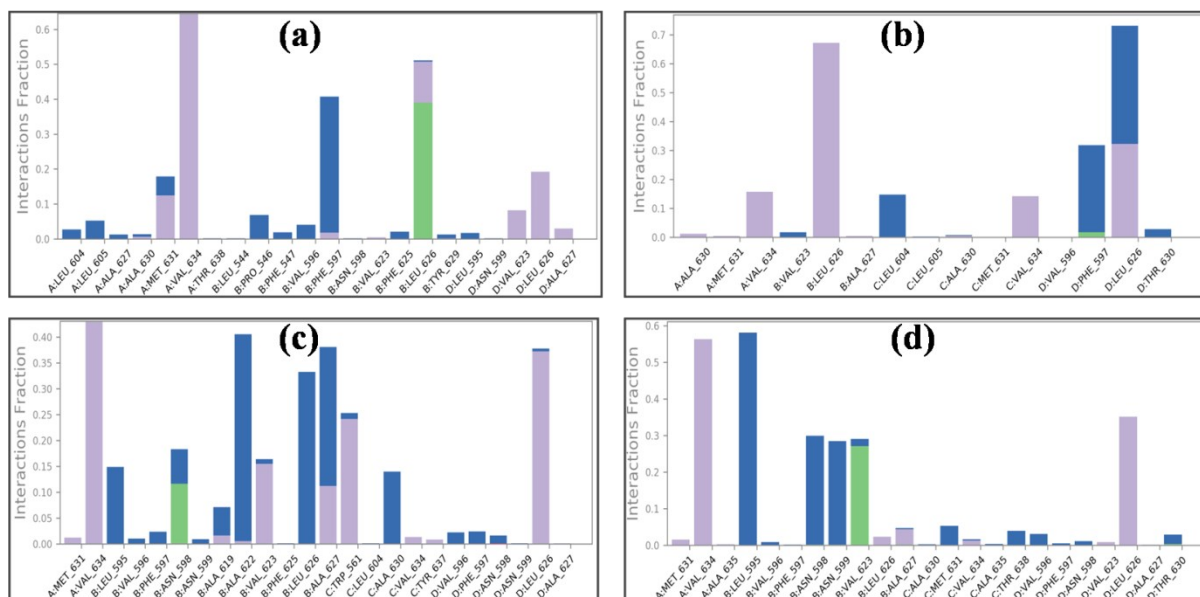


Figure S7. Bar-chart representation of protein-ligand contacts of (a) NM14-5UN1, (b) NM16-5UN1, (c) NM20-5UN1 and (d) NM22-5UN1 complexes during molecular dynamics simulation.

Simulation quality analysis:

Table S3. Thermodynamic properties of NM28-5UN1 complex observed during molecular dynamics simulation.

| Properties | Time duration | Average | Standard deviation | Slope (ps ⁻¹) |
|-----------------------------|---------------|-------------|--------------------|---------------------------|
| Total energy (kcal/mol) | 0ps | -553039.708 | 490.896 | -0.002 |
| | 100ps | -553039.643 | 142.450 | -0.002 |
| | 1000ps | -553039.564 | 103.576 | -0.002 |
| | 10000ps | -553035.673 | 95.499 | -0.003 |
| | 50000ps | -553039.666 | 75.035 | -0.002 |
| Potential energy (kcal/mol) | 0ps | -673674.854 | 411.323 | -0.002 |
| | 100ps | -673674.836 | 129.568 | -0.002 |
| | 1000ps | -673674.774 | 102.579 | -0.002 |
| | 10000ps | -673670.487 | 95.859 | -0.003 |
| | 50000ps | -673674.816 | 75.081 | -0.002 |
| Temperature | 0ps | 298.742 | 0.838 | 0.000 |

| | | | | |
|-------------------------------|---------|-------------|----------|--------|
| (K) | 100ps | 298.741 | 0.145 | 0.000 |
| | 1000ps | 298.740 | 0.047 | 0.000 |
| | 10000ps | 298.739 | 0.013 | 0.000 |
| | 50000ps | 298.740 | 0.005 | 0.000 |
| Pressure (bar) | 0ps | 1.402 | 62.664 | 0.000 |
| | 100ps | 1.400 | 6.996 | 0.000 |
| | 1000ps | 1.362 | 2.272 | 0.000 |
| | 10000ps | 1.359 | 1.075 | 0.000 |
| | 50000ps | 1.393 | 0.699 | 0.000 |
| Volume (Å³) | 0ps | 2002998.364 | 2049.943 | -0.006 |
| | 100ps | 2002998.083 | 479.333 | -0.006 |
| | 1000ps | 2002995.069 | 345.851 | -0.006 |
| | 10000ps | 2002990.303 | 290.735 | -0.008 |
| | 50000ps | 2002998.555 | 213.145 | -0.006 |

Table S4. Thermodynamic properties of MK-801-5UN1 complex observed during molecular dynamics simulation.

| Properties | Time duration | Average | Standard deviation | Slope (ps⁻¹) |
|------------------------------------|----------------------|----------------|---------------------------|--------------------------------|
| Total energy (kcal/mol) | 0ps | -552851.770 | 495.571 | -0.002 |
| | 100ps | -552851.703 | 148.515 | -0.002 |
| | 1000ps | -552850.964 | 111.829 | -0.003 |
| | 10000ps | -552845.658 | 104.093 | -0.003 |
| | 50000ps | -552851.732 | 72.174 | -0.002 |
| Potential energy (kcal/mol) | 0ps | -673548.262 | 416.462 | -0.003 |
| | 100ps | -673548.153 | 137.449 | -0.003 |
| | 1000ps | -673547.412 | 111.276 | -0.003 |
| | 10000ps | -673541.869 | 105.255 | -0.003 |
| | 50000ps | -673548.225 | 74.052 | -0.002 |
| Temperature (K) | 0ps | 298.746 | 0.841 | 0.000 |
| | 100ps | 298.744 | 0.145 | 0.000 |
| | 1000ps | 298.744 | 0.044 | 0.000 |
| | 10000ps | 298.743 | 0.016 | 0.000 |
| | 50000ps | 298.745 | 0.009 | 0.000 |
| Pressure (bar) | 0ps | 1.121 | 62.977 | 0.000 |
| | 100ps | 1.116 | 6.844 | 0.000 |
| | 1000ps | 1.127 | 2.148 | 0.000 |
| | 10000ps | 1.041 | 0.845 | -0.000 |
| | 50000ps | 1.113 | 0.370 | 0.000 |
| Volume (Å³) | 0ps | 2004076.296 | 2077.442 | -0.010 |
| | 100ps | 2004076.806 | 566.144 | -0.010 |
| | 1000ps | 2004080.431 | 456.372 | -0.010 |
| | 10000ps | 2004094.839 | 438.579 | -0.012 |
| | 50000ps | 2004076.464 | 298.533 | -0.008 |

Table S5. Thermodynamic properties of HupA-5UN1 complex observed during molecular dynamics simulation.

| Properties | Time duration | Average | Standard deviation | Slope (ps ⁻¹) |
|------------------------------------|---------------|-------------|--------------------|---------------------------|
| Total energy (kcal/mol) | 0ps | -552862.922 | 491.736 | -0.003 |
| | 100ps | -552862.841 | 147.724 | -0.003 |
| | 1000ps | -552861.736 | 109.590 | -0.003 |
| | 10000ps | -552855.143 | 97.376 | -0.003 |
| | 50000ps | -552862.894 | 90.088 | -0.003 |
| Potential energy (kcal/mol) | 0ps | -673542.711 | 413.991 | -0.003 |
| | 100ps | -673542.623 | 134.380 | -0.003 |
| | 1000ps | -673541.715 | 108.047 | -0.003 |
| | 10000ps | -673535.021 | 97.891 | -0.003 |
| | 50000ps | -673542.684 | 90.341 | -0.003 |
| Temperature (K) | 0ps | 298.742 | 0.839 | 0.000 |
| | 100ps | 298.741 | 0.147 | 0.000 |
| | 1000ps | 298.741 | 0.041 | 0.000 |
| | 10000ps | 298.740 | 0.015 | 0.000 |
| | 50000ps | 298.741 | 0.006 | 0.000 |
| Pressure (bar) | 0ps | 0.927 | 62.715 | 0.000 |
| | 100ps | 0.922 | 7.325 | 0.000 |
| | 1000ps | 0.919 | 2.541 | 0.000 |
| | 10000ps | 0.917 | 1.109 | 0.000 |
| | 50000ps | 0.919 | 0.783 | 0.000 |
| Volume (Å³) | 0ps | 2003742.042 | 2031.195 | -0.005 |
| | 100ps | 2003741.933 | 480.800 | -0.005 |
| | 1000ps | 2003743.950 | 351.596 | -0.005 |
| | 10000ps | 2003744.956 | 288.420 | -0.007 |
| | 50000ps | 2003742.215 | 151.515 | -0.004 |

Table S6: RMSD values of free protein (5UN1) with that of the bound proteins.

| S. No. | Ligand-Protein Complex ID | RMSD value (Å) |
|--------|---------------------------|----------------|
| 1 | Co-crystal (MK-801)/ 5UN1 | 2.2654 |
| 2 | HupA/5UN1 | 3.8548 |
| 3 | NM14/5UN1 | 3.7380 |
| 4 | NM16/5UN1 | 3.4747 |
| 5 | NM20/5UN1 | 3.5872 |
| 6 | NM22/5UN1 | 3.8196 |
| 7 | NM28/5UN1 | 3.7960 |

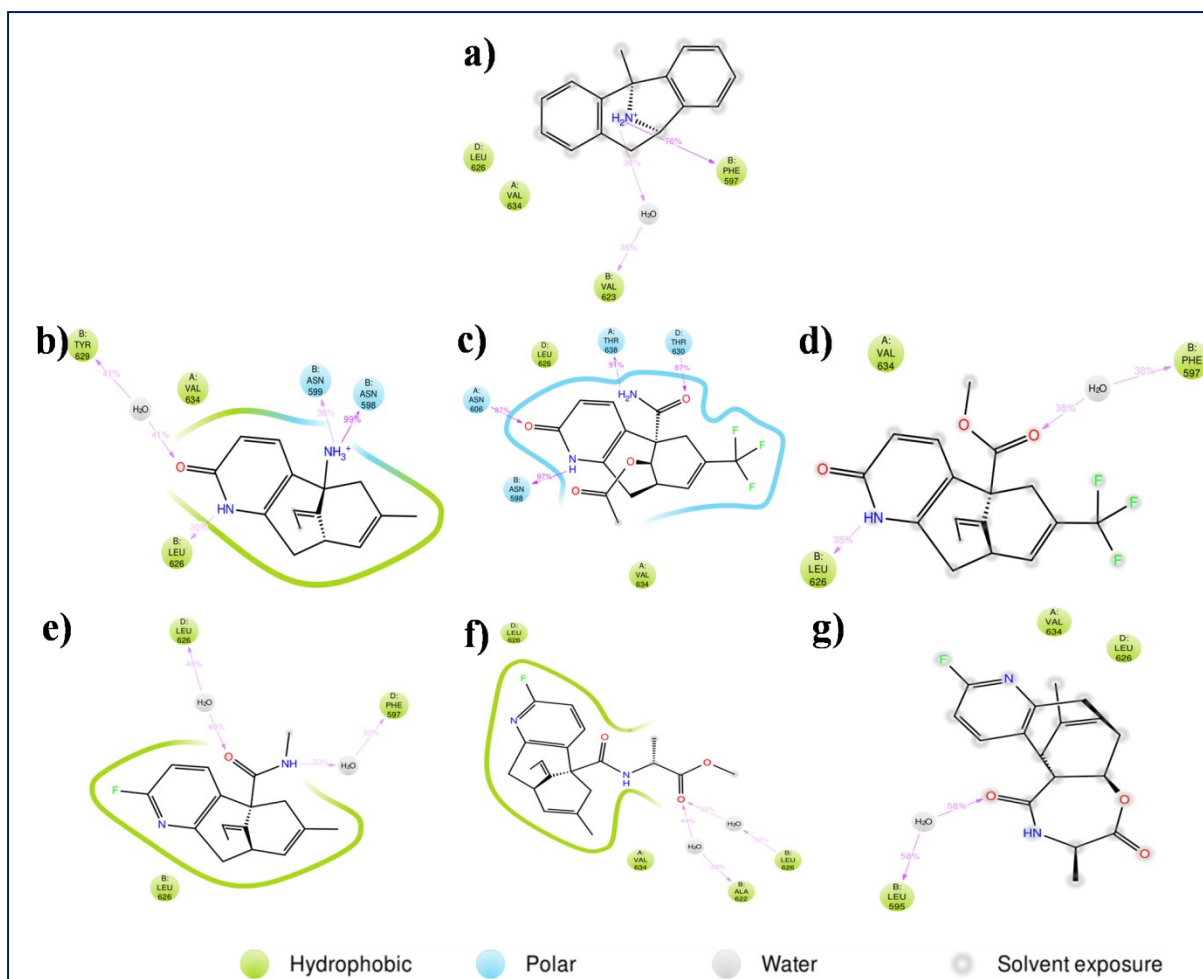


Figure S8. Simulation Interactions Diagram (SID) of compound co-crystal (a), HupA (b), NM28 (c), NM14 (d), NM16 (e), NM20(f) and NM22 (g) with NMDA receptor.