**Supplementary file 1A. RosettaScripts XML file (.xml)**

<ROSETTASCRIPTS>

 <SCOREFXNS>

 <hard\_symm weights=beta\_cst symmetric=1>

 <Reweight scoretype=coordinate\_constraint weight=0.5 />

 <Reweight scoretype=aa\_composition weight=1.0 />

 </hard\_symm>

 <soft\_symm weights=beta\_nov15\_soft symmetric=1>

 <Reweight scoretype=aa\_composition weight=1.0 />

 </soft\_symm>

 <up\_ele weights=beta\_cst symmetric=1>

 <Reweight scoretype=fa\_elec weight=1.4 />

 <Reweight scoretype=hbond\_sc weight=2.0 />

 <Reweight scoretype=aa\_composition weight=1.0 />

 </up\_ele>

 <hard\_symm\_cart weights=beta\_cart symmetric=1 />

 </SCOREFXNS>

 <RESIDUE\_SELECTORS>

 <Index name=res1to16\_65to72 resnums=1-16,65-72 />

 <Not name=notres1to16\_65to72 selector=res1to16\_65to72 />

 <Index name=res67\_68\_71 resnums=67,68,71 />

 </RESIDUE\_SELECTORS>

 <TASKOPERATIONS>

 <OperateOnResidueSubset name=near\_junction selector=notres1to16\_65to72 >

 <PreventRepackingRLT/>

 </OperateOnResidueSubset>

 <OperateOnResidueSubset name=mba\_binding\_res selector=res67\_68\_71 >

 <RestrictToRepackingRLT/>

 </OperateOnResidueSubset>

 <ReadResfile name=re

 <LayerDesign name=all\_layers layer=Nterm\_core\_boundary\_surface\_Cterm make\_pymol\_script=0 use\_sidechain\_neighbors=True core=4 >

 <core>

 <Helix append="M"/>

 </core>

 <boundary>

 </boundary>

 <surface>

 </surface>

 </LayerDesign>

 <LayerDesign name=select\_core layer=core make\_pymol\_script=0 use\_sidechain\_neighbors=True core=4 />

 <LayerDesign name=select\_boundary layer=boundary make\_pymol\_script=0 use\_sidechain\_neighbors=True core=4 />

 <LayerDesign name=select\_surface layer=Nterm\_surface\_Cterm make\_pymol\_script=0 use\_sidechain\_neighbors=True core=4 />

 <LimitAromaChi2 name=arochi />

 <ExtraRotamersGeneric name=ex1\_ex2 ex1=1 ex2=1/>

 <ExtraRotamersGeneric name=ex1 ex1=1/>

 </TASKOPERATIONS>

 <FILTERS>

 <Geometry name=geom confidence=0 />

 </FILTERS>

 <MOVERS>

 <SetupForSymmetry name=setup\_symm definition="/work/sboyken/Rosetta/main/database/symmetry/cyclic/C3\_Z.sym"/>

 <FastDesign name=fdes scorefxn=hard\_symm repeats=1 task\_operations=near\_junction,mba\_binding\_res,resin,all\_layers,arochi,ex1 >

 <MoveMap >

 <Span begin=1 end=16 chi=1 bb=1 />

 </MoveMap>

 </FastDesign>

 </MOVERS>

 <PROTOCOLS>

 <Add mover=setup\_symm/>

 <Add mover=fdes />

 <Add filter=geom />

 </PROTOCOLS>

</ROSETTASCRIPTS>

**Supplementary file 1B. Parameter constraint file for amantadine (.cst)**

AtomPair N1 1B N1 1D HARMONIC 0.00 0.01

AtomPair N1 1B N1 1F HARMONIC 0.00 0.01

AtomPair C1 1B C1 1D HARMONIC 0.00 0.01

AtomPair C1 1B C1 1F HARMONIC 0.00 0.01

AtomPair C2 1B C2 1D HARMONIC 2.60 0.01

AtomPair C2 1B C2 1F HARMONIC 2.60 0.01

AtomPair H5 1B H5 1D HARMONIC 2.50 0.01

AtomPair H5 1B H5 1F HARMONIC 2.50 0.01

AtomPair C4 1B C4 1D HARMONIC 2.50 0.01

AtomPair C4 1B C4 1F HARMONIC 2.50 0.01

AtomPair H1 1B N1 1B HARMONIC 1.02 0.01

AtomPair H1 1B C1 1B HARMONIC 2.05 0.01

AtomPair H1 1B C3 1B HARMONIC 2.70 0.01

AtomPair H1 1B H3 1B HARMONIC 2.70 0.01

AtomPair H1 1B H4 1B HARMONIC 3.04 0.01

AtomPair H1 1B C2 1B HARMONIC 4.14 0.01

AtomPair H1 1B H2 1B HARMONIC 4.81 0.01

AtomPair H1 1B C4 1B HARMONIC 4.47 0.01

AtomPair H1 1B H5 1B HARMONIC 5.54 0.01

AtomPair H1 1B H6 1B HARMONIC 4.37 0.01

AtomPair N1 1B C1 1B HARMONIC 1.48 0.01

AtomPair N1 1B C3 1B HARMONIC 2.50 0.01

AtomPair N1 1B H3 1B HARMONIC 2.74 0.01

AtomPair N1 1B H4 1B HARMONIC 2.74 0.01

AtomPair N1 1B C2 1B HARMONIC 3.87 0.01

AtomPair N1 1B H2 1B HARMONIC 4.66 0.01

AtomPair N1 1B C4 1B HARMONIC 4.36 0.01

AtomPair N1 1B H5 1B HARMONIC 5.37 0.01

AtomPair N1 1B H6 1B HARMONIC 4.50 0.01

AtomPair C1 1B C3 1B HARMONIC 1.57 0.01

AtomPair C1 1B H3 1B HARMONIC 2.17 0.01

AtomPair C1 1B H4 1B HARMONIC 2.17 0.01

AtomPair C1 1B C2 1B HARMONIC 2.56 0.01

AtomPair C1 1B H2 1B HARMONIC 3.49 0.01

AtomPair C1 1B C4 1B HARMONIC 3.01 0.01

AtomPair C1 1B H5 1B HARMONIC 3.97 0.01

AtomPair C1 1B H6 1B HARMONIC 3.36 0.01

AtomPair C3 1B H3 1B HARMONIC 1.07 0.01

AtomPair C3 1B H4 1B HARMONIC 1.07 0.01

AtomPair C3 1B C2 1B HARMONIC 1.56 0.01

AtomPair C3 1B H2 1B HARMONIC 2.17 0.01

AtomPair C3 1B C4 1B HARMONIC 2.55 0.01

AtomPair C3 1B H5 1B HARMONIC 3.48 0.01

AtomPair C3 1B H6 1B HARMONIC 2.77 0.01

AtomPair H3 1B H4 1B HARMONIC 1.75 0.01

AtomPair H3 1B C2 1B HARMONIC 2.17 0.01

AtomPair H3 1B H2 1B HARMONIC 2.49 0.01

AtomPair H3 1B C4 1B HARMONIC 2.76 0.01

AtomPair H3 1B H5 1B HARMONIC 3.74 0.01

AtomPair H3 1B H6 1B HARMONIC 2.55 0.01

AtomPair H4 1B C2 1B HARMONIC 2.16 0.01

AtomPair H4 1B H2 1B HARMONIC 2.48 0.01

AtomPair H4 1B C4 1B HARMONIC 3.48 0.01

AtomPair H4 1B H5 1B HARMONIC 4.30 0.01

AtomPair H4 1B H6 1B HARMONIC 3.74 0.01

AtomPair C2 1B H2 1B HARMONIC 1.07 0.01

AtomPair C2 1B C4 1B HARMONIC 1.56 0.01

AtomPair C2 1B H5 1B HARMONIC 2.17 0.01

AtomPair C2 1B H6 1B HARMONIC 2.17 0.01

AtomPair C4 1B H5 1B HARMONIC 1.07 0.01

AtomPair C4 1B H6 1B HARMONIC 1.07 0.01

AtomPair H5 1B H6 1B HARMONIC 1.75 0.01

**Supplementary file 1C. Parameter definition file for amantadine (.params)**

NAME AMA

IO\_STRING AMA Z

TYPE LIGAND

AA UNK

ATOM C3 CH2 X -0.00

ATOM C1 VIRT VIRT -0.01

ATOM N1 VIRT VIRT 0.22

ATOM H1 Hpol X 0.20

ATOM C2 CH1 X -0.04

ATOM C4 CH2 X -0.05

ATOM H5 Hapo X 0.03

ATOM H6 Hapo X 0.03

ATOM H2 Hapo X 0.03

ATOM H3 Hapo X 0.03

ATOM H4 Hapo X 0.03

BOND\_TYPE N1 C1 1

BOND\_TYPE N1 H1 1

BOND\_TYPE C1 C3 1

BOND\_TYPE C2 C3 1

BOND\_TYPE C2 C4 1

BOND\_TYPE C2 H2 1

BOND\_TYPE C3 H3 1

BOND\_TYPE C3 H4 1

BOND\_TYPE C4 H5 1

BOND\_TYPE C4 H6 1

CHI 1 C3 C1 N1 H1

PROTON\_CHI 1 SAMPLES 3 60 -60 180 EXTRA 1 20

CHI 2 C2 C3 C1 N1

CHI 3 C1 C3 C2 C4

NBR\_ATOM C3

NBR\_RADIUS 4.061247

ICOOR\_INTERNAL C3 0.000000 0.000000 0.000000 C3 C1 N1

ICOOR\_INTERNAL C1 0.000000 179.999999 1.566251 C3 C1 N1

ICOOR\_INTERNAL N1 0.000000 69.171297 1.475135 C1 C3 N1

ICOOR\_INTERNAL H1 -59.992968 70.501815 1.019861 N1 C1 C3

ICOOR\_INTERNAL C2 -179.913313 69.987429 1.563477 C3 C1 N1

ICOOR\_INTERNAL C4 -60.077215 70.557006 1.562665 C2 C3 C1

ICOOR\_INTERNAL H5 179.932145 70.486499 1.069869 C4 C2 C3

ICOOR\_INTERNAL H6 120.004104 70.545223 1.070033 C4 C2 H5

ICOOR\_INTERNAL H2 -120.058942 70.607612 1.069608 C2 C3 C4

ICOOR\_INTERNAL H3 -120.092430 70.622215 1.069827 C3 C1 C2

ICOOR\_INTERNAL H4 -120.198575 70.836634 1.069942 C3 C1 H3

**Supplementary file 1D. Restype file (in.res)**

ALLAAxc

START

1 A PIKAA SDTN

8 A PIKAA Y