Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Minimalist helical mimics resemble a variety of secondary structures

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A. QMD And Matching Procedures

Quenched Molecular Dynamics (QMD)

NAMD[1] was used for the molecular simulations performed in this work. Explicit atom representations were used throughout the study. The protein structure files (PSF) for all the peptidomimetics were built using Discovery Studio 2.5 (Accelrys Inc) using the CHARMm force field.[2]

Quenched molecular dynamics simulations were performed using the CHARMm force field as implemented in Discovery Studio 2.5. All four molecules were modeled as neutral compounds in a dielectric continuum of 80 (simulating H_2O). Thus, the starting conformers were minimized using 3000 steps of conjugate gradient. The minimized structures were then subjected to heating, equilibration, and dynamics simulation. Throughout, the equations of motions were integrated using the Verlet algorithm with a time step 1 fs. Each peptidomimetic was heated to 1000 K over 10 ps and equilibrated for another 10 ps at 1000 K, then molecular dynamics runs were performed for a total time of 600 ps with trajectories saved every 1 ps. The resulting 600 structures were thoroughly minimized using 1000 steps of SD followed by 3000 steps of conjugate gradient. Structures with energies less than 3.0 kcal mol^{-1} relative to the global minimum were selected for further analysis.

The VMD[2] package was used to display, overlay, and classify the selected structures into conformational groups. The best clustering was obtained using a grouping method based on calculation of RMS deviation of a subset of atoms, in this study these were the Cα - and Cβ- atoms. Thus, threshold cutoff values 0.3 Å were selected to obtain families with reasonable homogeneity. The lowest energy conformation from each family was considered to be a typical representative of the family as a whole.

Procedure for Overlays

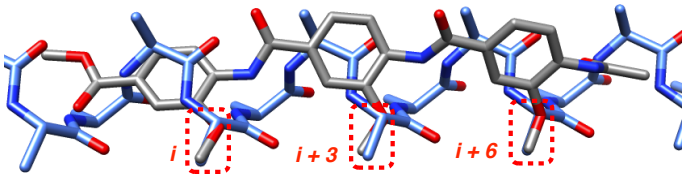
Standard template for overlays with 3_{10}-helix, α-helix, π-helix, and β-strand were obtained from Discovery Studio 2.5.[3] Parallel β-sheet, anti-parallel β-sheet and sheet/turn/sheet templates were obtained by modified β-sheet builder (http://www-lbit.iro.umontreal.ca/bBuilder/index.html).[4]

After minimization in the QMD process, the conformers were grouped into families base on their Cα - Cβ coordinates. The process of systematically matching preferred conformers with secondary structures was performed in the following way. All the conformers within 3.0 kcal/mol were considered to be “preferred”. Each of these was overlaid on ideal secondary structures using an in house generated algorithm that compared Cα - Cβ coordinates of the side chains which generates a list of structures ranked in terms of the RMSD for the overlay process.

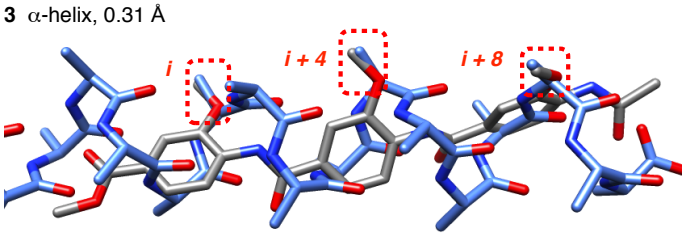
B. Overlay Data For Mimics 3, 3', 6, 6', 8, 8' on Ideal Secondary Structures

Figures 5 and 6 in the text graph overlay data for most of the mimics on the text; the ones for which this data were not provided are **3, 3', 6, 6', 8, 8'**, and these are shown in Figure S1.

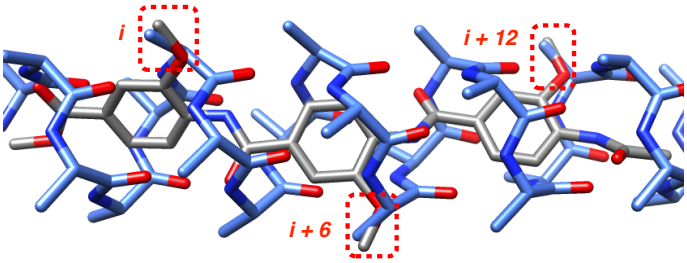
3 3_{10}-helix, RMSD = 0.30 Å



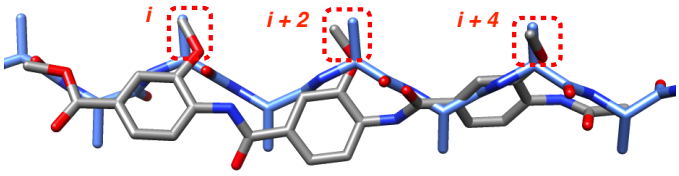
3 α-helix, 0.31 Å



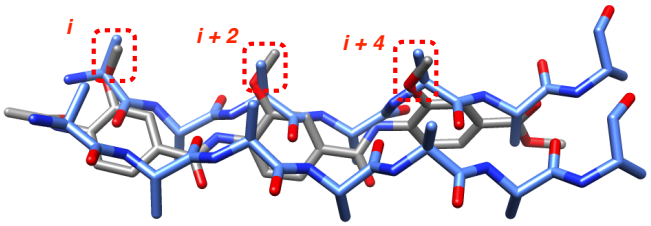
3 π-helix, 0.47 Å



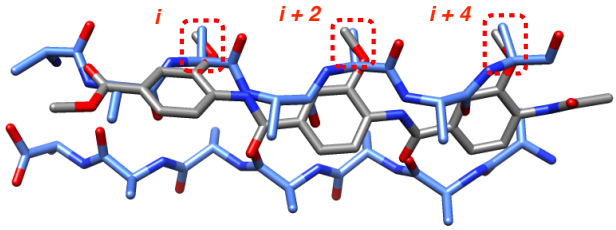
3 β-strand, 0.70 Å



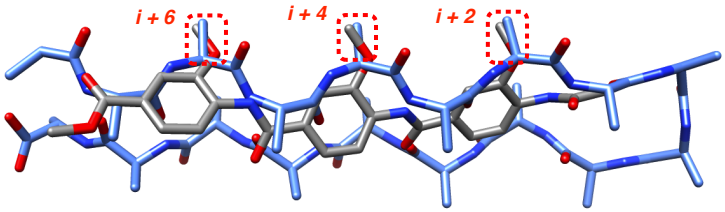
3 parallel β-sheet, 0.58 Å



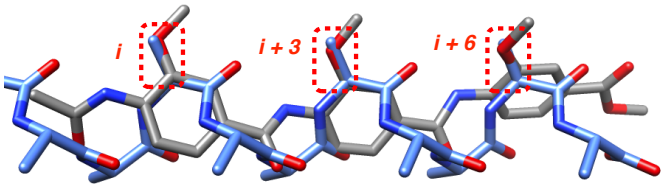
3 antiparallel β-sheet, 0.43 Å



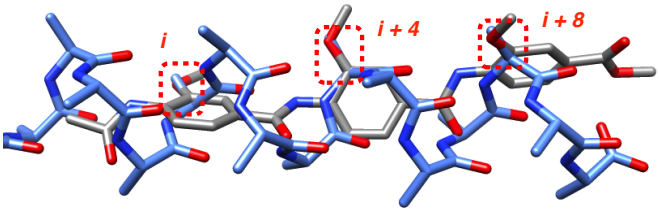
3 sheet-turn-sheet, 0.43 Å



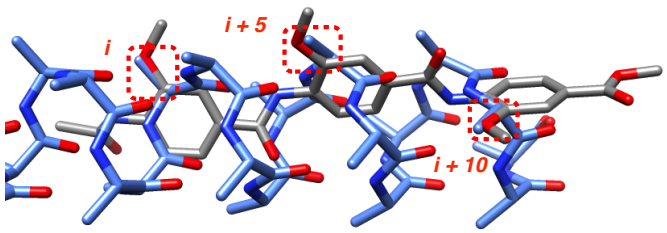
3' 3_{10}-helix, RMSD = 0.33 Å



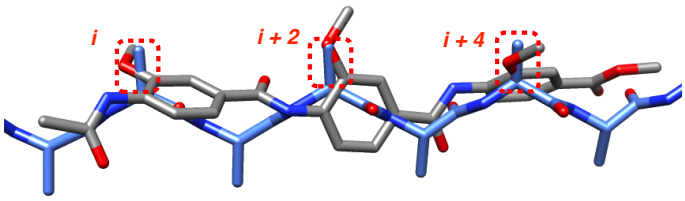
3' α-helix, 0.25 Å



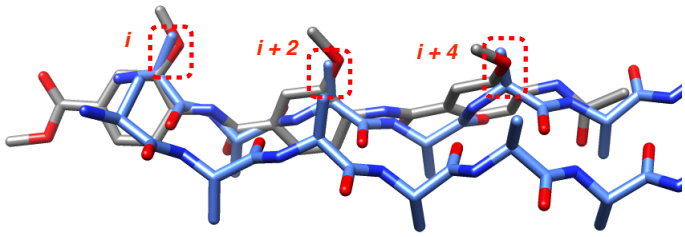
3' π-helix, 0.36 Å



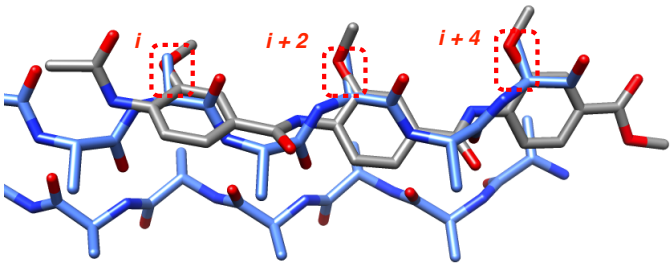
3' β-strand, 0.66 Å



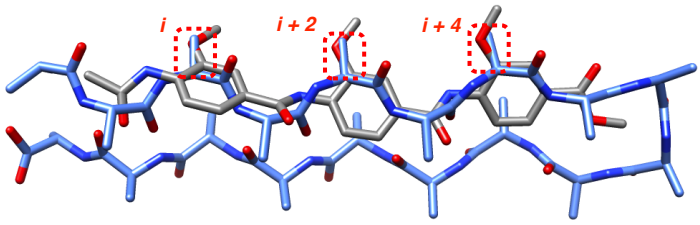
3' parallel β-sheet, 0.41 Å



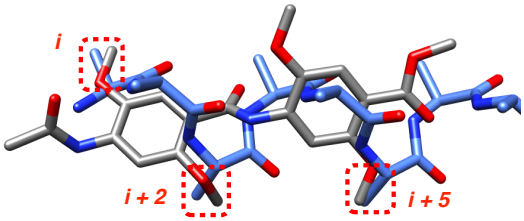
3' antiparallel β-sheet, 0.39 Å



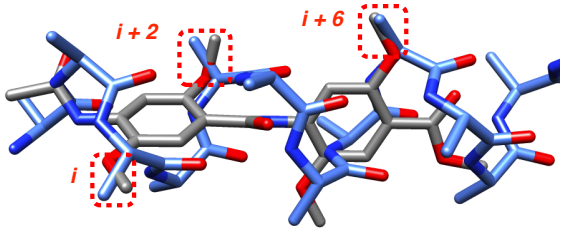
3' sheet-turn-sheet, 0.40 Å



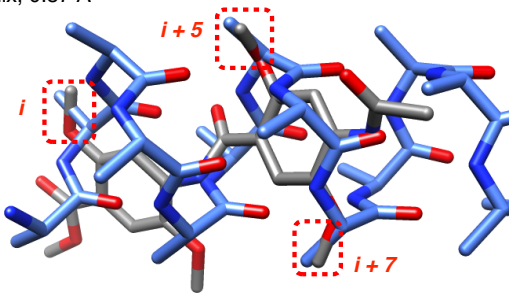
6 3_{10}-helix, RMSD = 0.60 Å



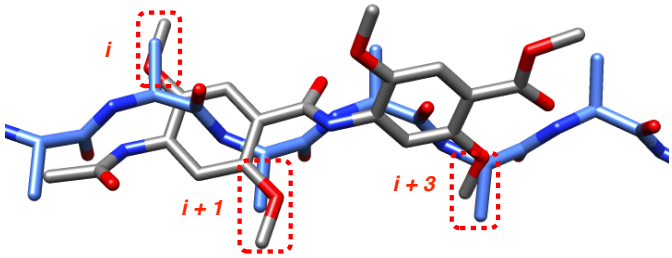
6 α-helix, 0.61 Å



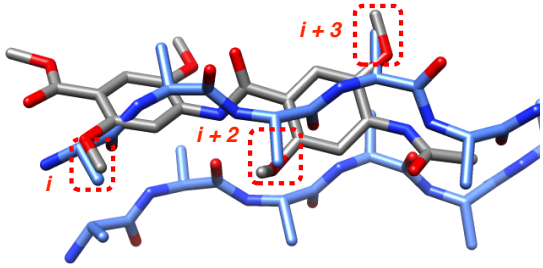
6 π-helix, 0.57 Å



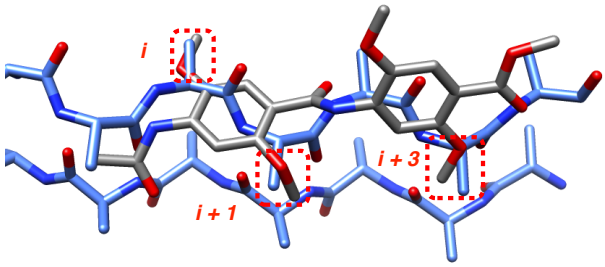
6 β-strand, 0.96 Å



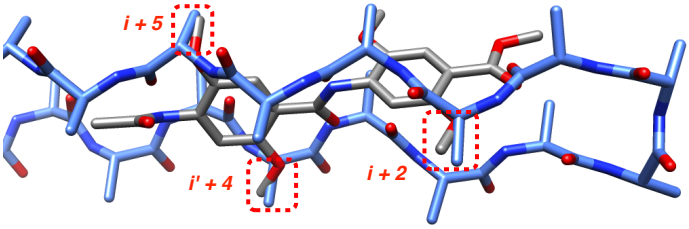
6 parallel β-sheet, 0.93 Å



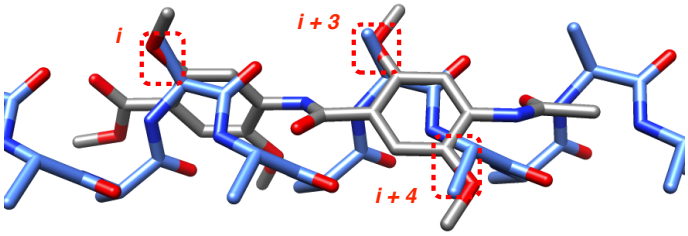
6 antiparallel β-sheet, 0.90 Å



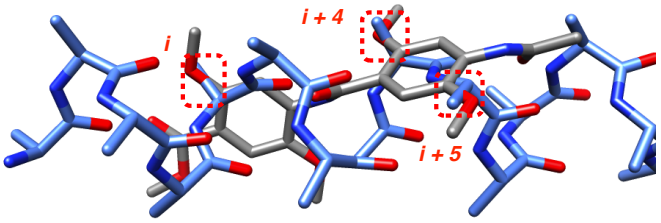
6 sheet-turn-sheet, 0.51 Å



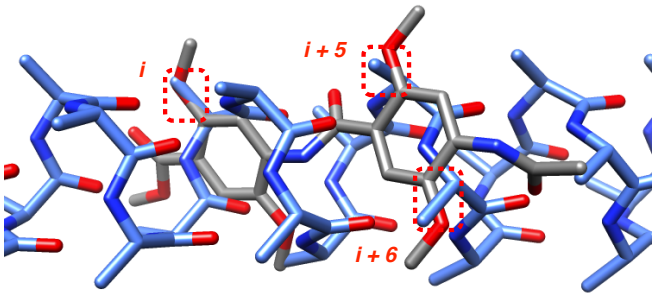
6' 3_{10}-helix, RMSD = 0.59 Å



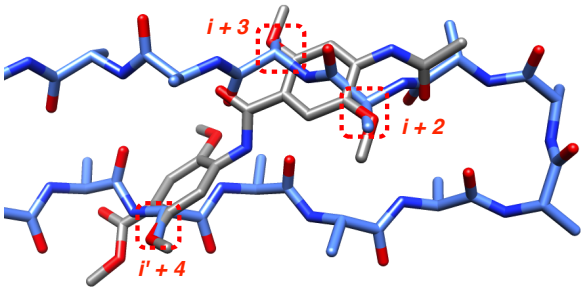
6' α-helix, 0.66 Å



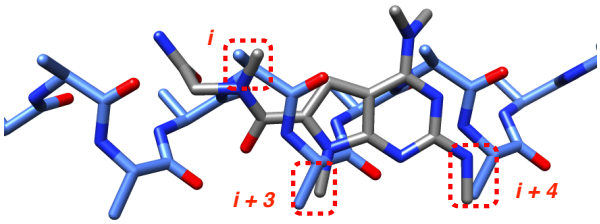
6' π-helix, 0.70 Å



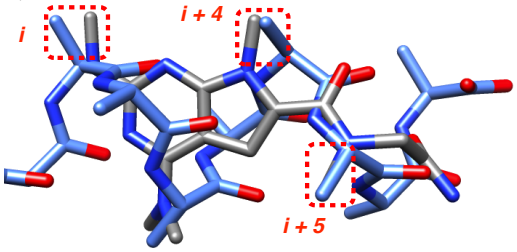
6' sheet-turn-sheet, 0.53 Å



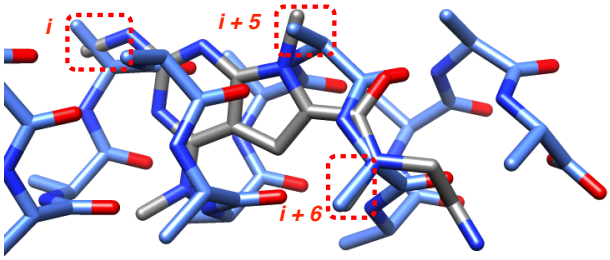
8 3_{10}-helix, RMSD = 0.74 Å



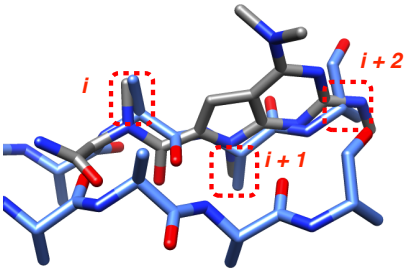
8 α-helix, 0.80 Å



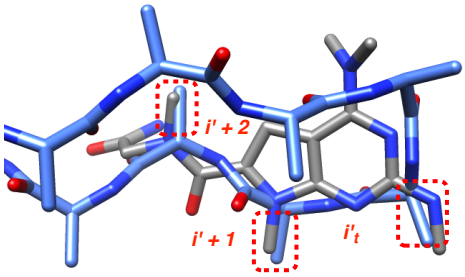
8 π-helix, 0.85 Å



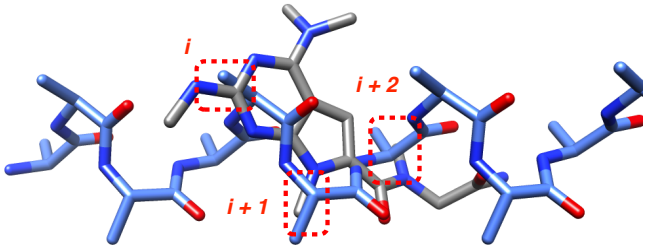
8 parallel β-sheet, 0.61 Å



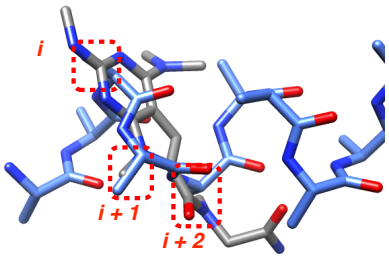
8 sheet-turn-sheet, 0.61 Å



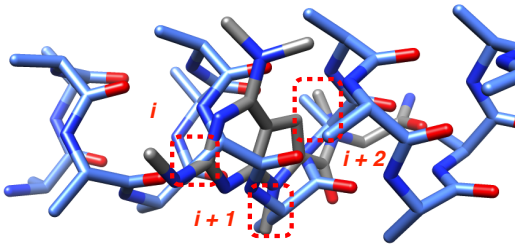
8' 3_{10}-helix, RMSD = 0.99 Å



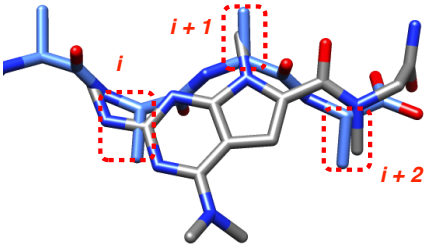
8' α-helix, 0.79 Å



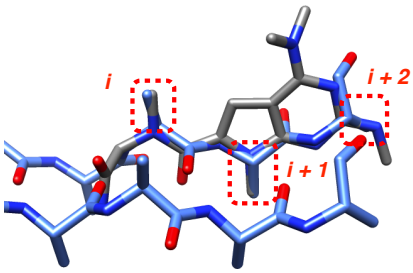
8' π-helix, 0.71 Å



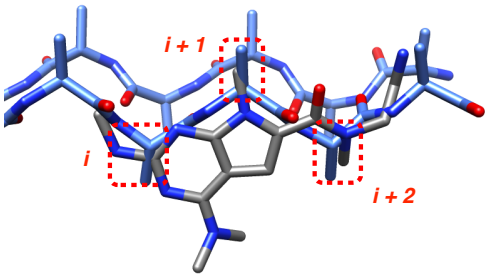
8' β-strand, 0.88 Å



8' parallel β-sheet, 0.40 Å



8' antiparallel β-sheet, 0.95 Å



8' sheet-turn-sheet, 0.40 Å

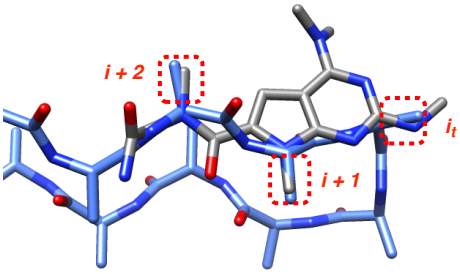


Figure S1. Overlays of mimics **1** – **10** on ideal helical structures.

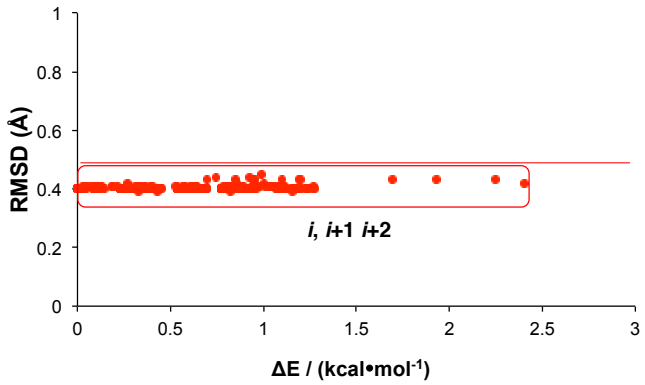
C. Scatter Plots of RMSD Values of Conformers *vs* ΔE For Helical Mimic 1-10

Figure 7 in the text gives illustrative scatter plots for **3'** on all three helical types, and **9** on a parallel β-sheet.

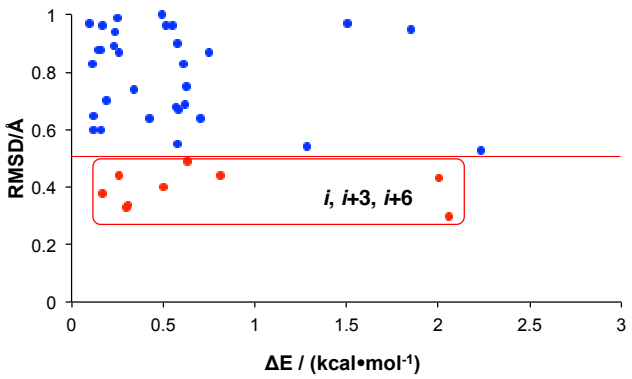
Totally, seven elements of secondary structure were considered for mimics **1** – **10**, and the "revised assignment" structures **3'**, **6'**, and **8'**. Consequently, 7 x 13 dot plots are possible. The most interesting of these are for cases where a conformer was shown to fit a selected secondary structure with an RMSD value of 0.5 Å or less. Figure S2 contains a comprehensive set of those dot plots.

3_{10}-helix

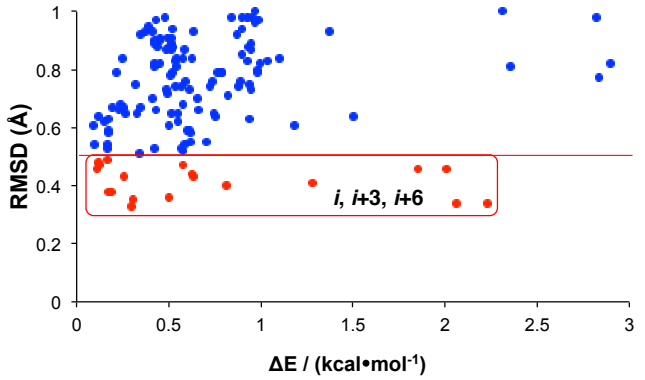
2



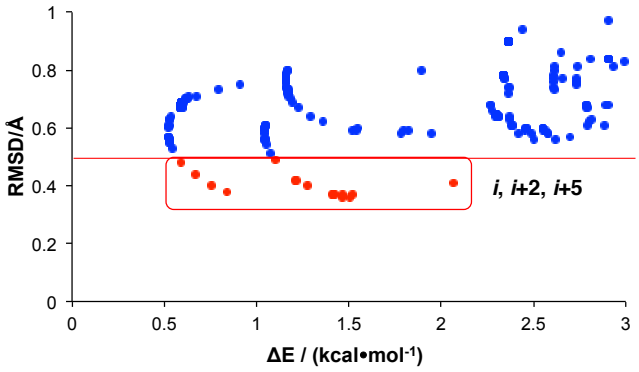
3



3' (revised using bonds adjacent to scaffold)

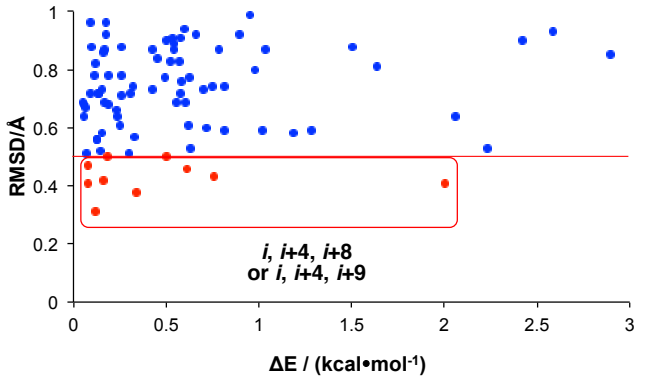


4

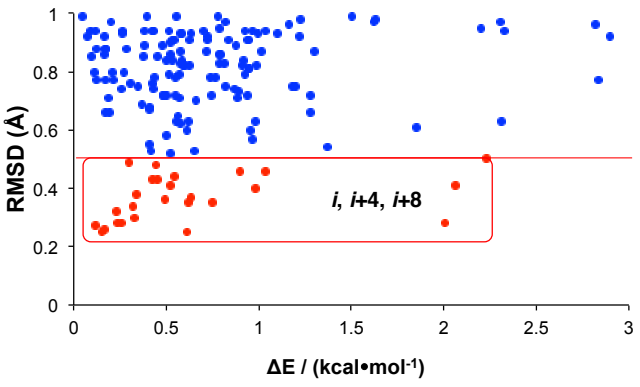


α-helix

3

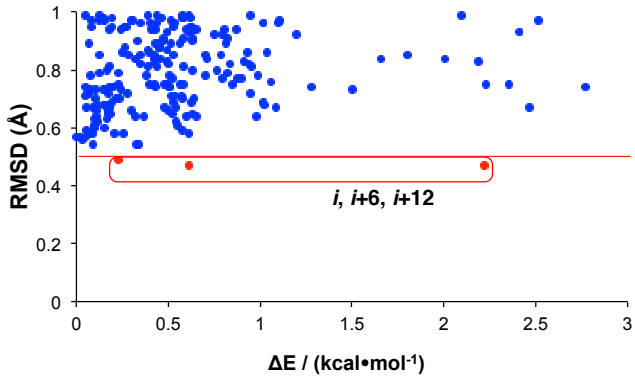


3' (revised using bonds adjacent to scaffold)

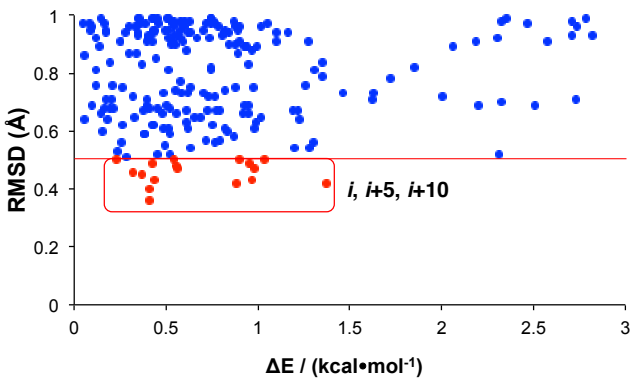


π-helix

3

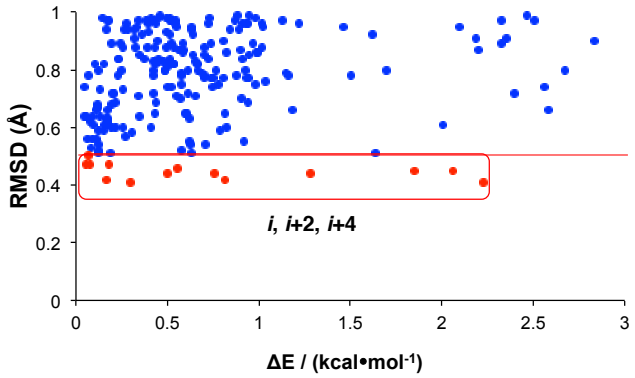


3' (revised using bonds adjacent to scaffold)

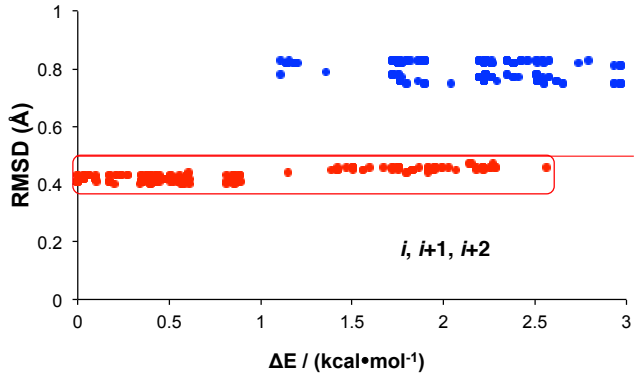


parallel β-sheet

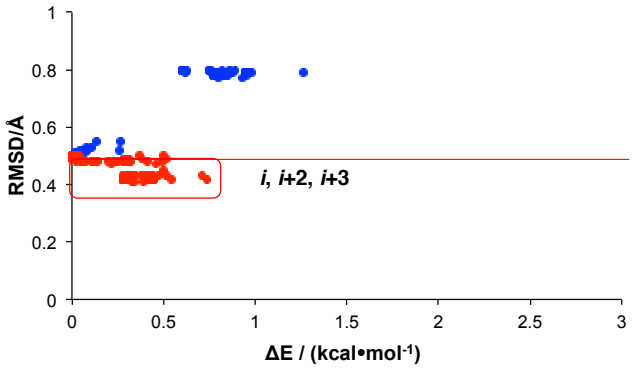
3' (revised using bonds adjacent to scaffold)



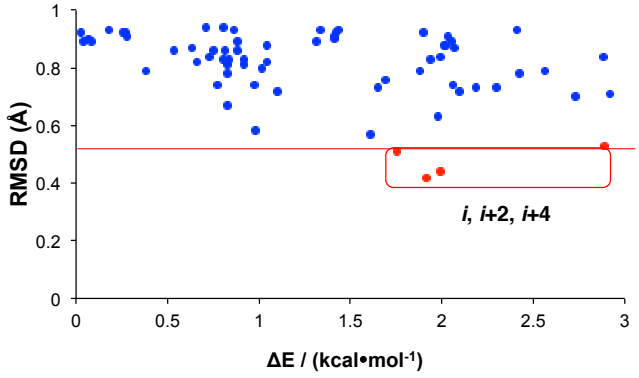
8' (revised using bonds adjacent to scaffold)



9

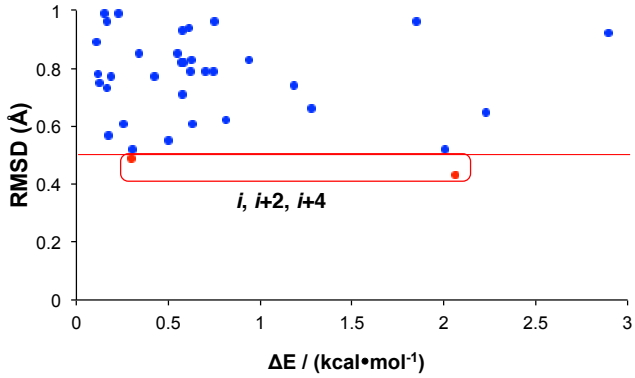


10

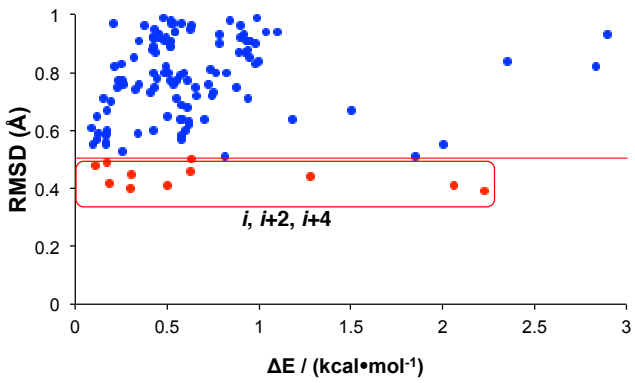


anti-parallel β-sheet

3

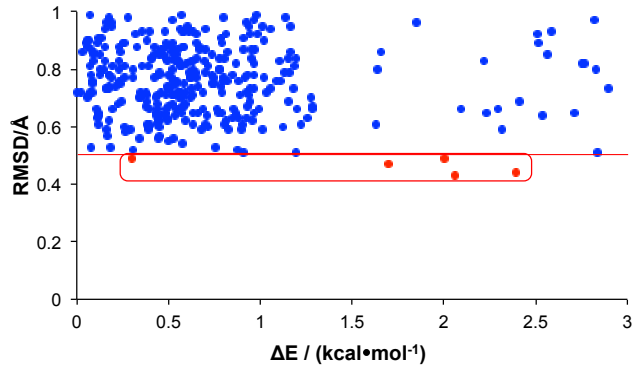


3' (revised using bonds adjacent to scaffold)

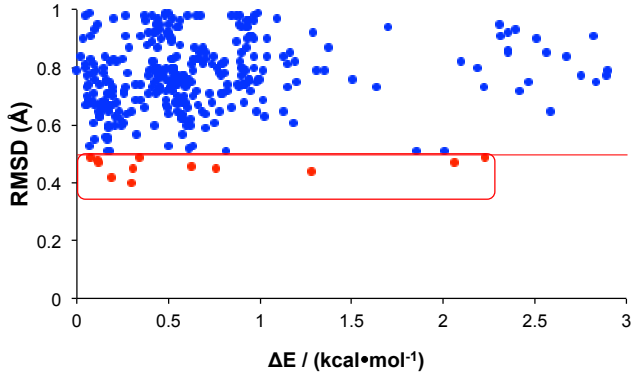


sheet-turn-sheet

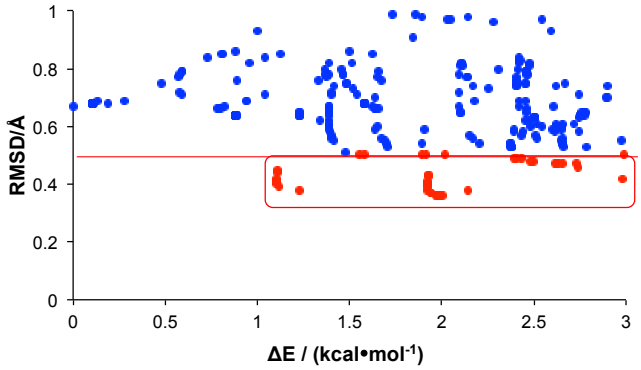
3



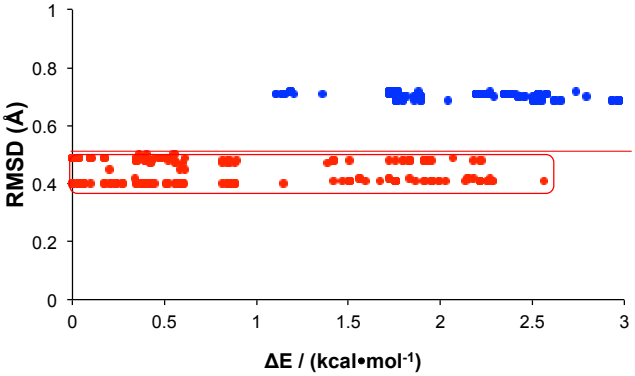
3' (revised using bonds adjacent to scaffold)



7



8' (revised using bonds adjacent to scaffold)



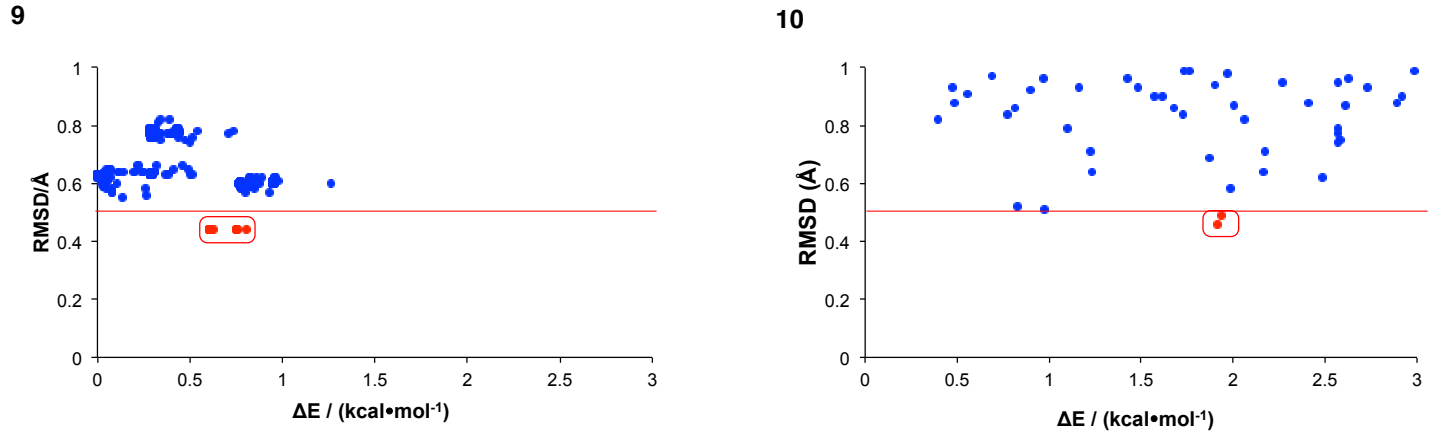


Figure S2. Scatter plots of RMSD values of conformers *vs* energies relative to the lowest energy conformer detected (ΔE) indicate how well each mimic populates the featured overlay states.

D. Graphics Of The Best Fitting Mimics On The PPIs Featured In Table 5

This section shows overlays of the best fitting conformers and best helical mimics for helical components in p53/MDM2 (**8'**), smMLCK/calmodulin (**3'**), and BakBH3/Bcl-x_L (**3**). Surprisingly, Smith β-sheet mimic **9** overlaid on BakBH3/Bcl-x_L and that overlay is shown in Figure S6.

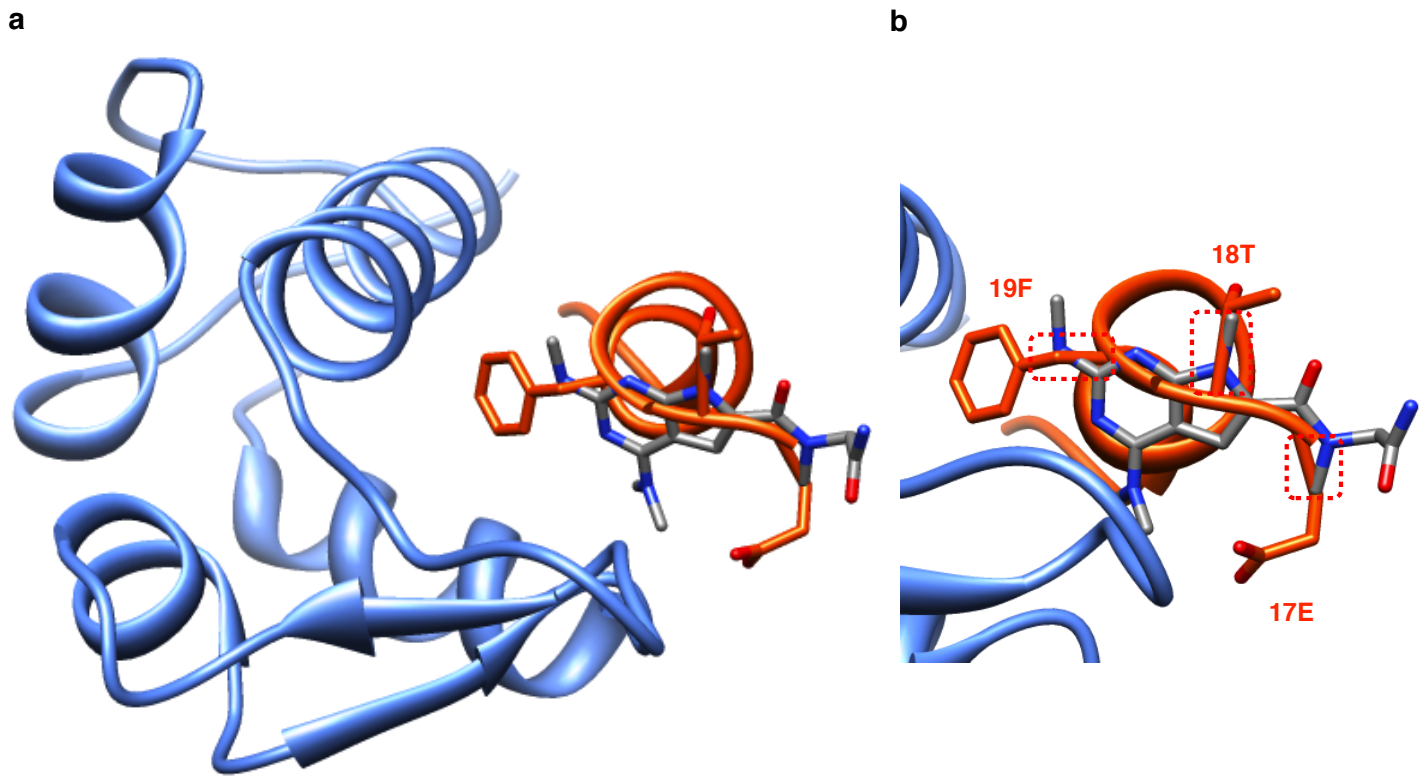


Figure S3. p53/MDM2

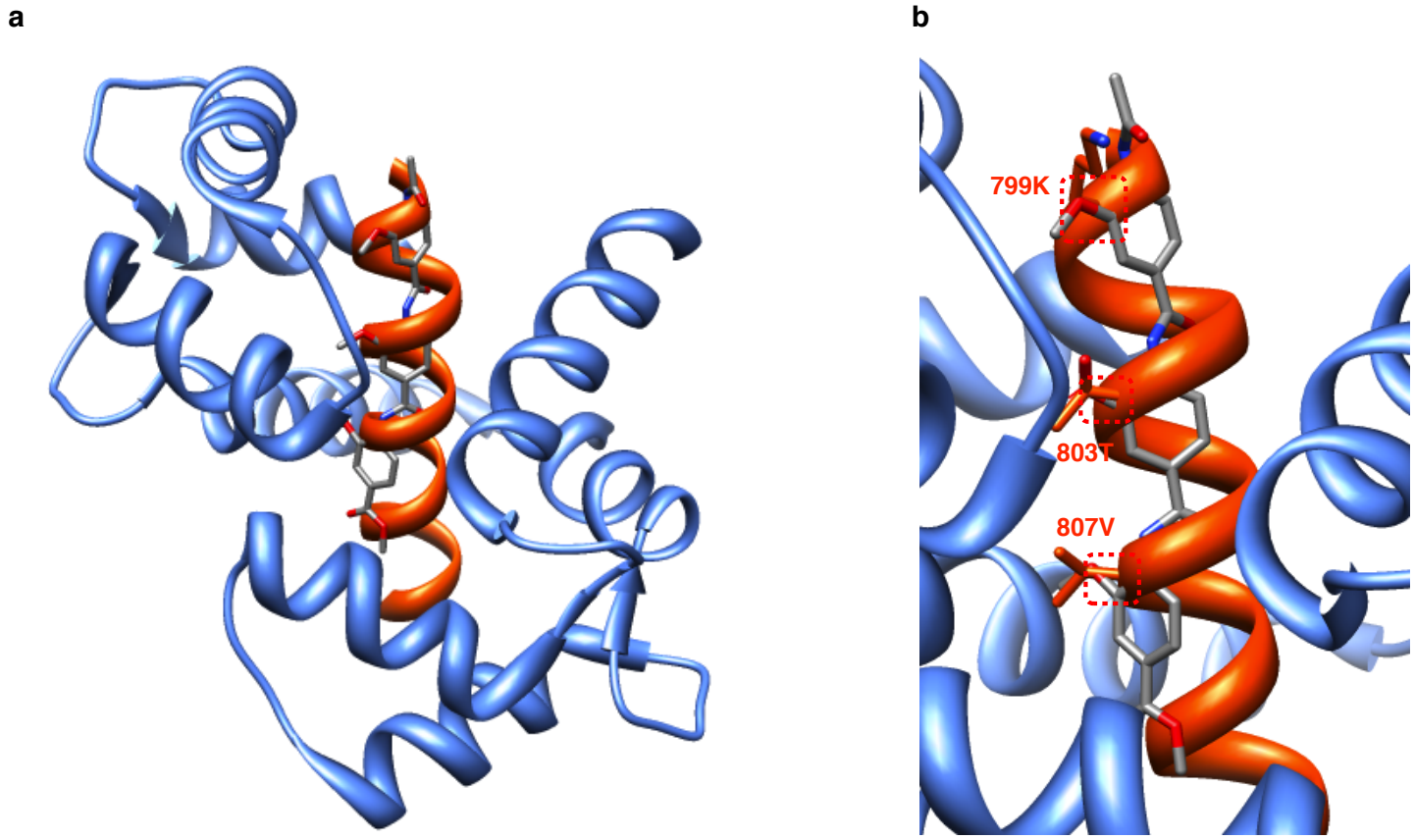


Figure S4. smMLCK/calmodulin

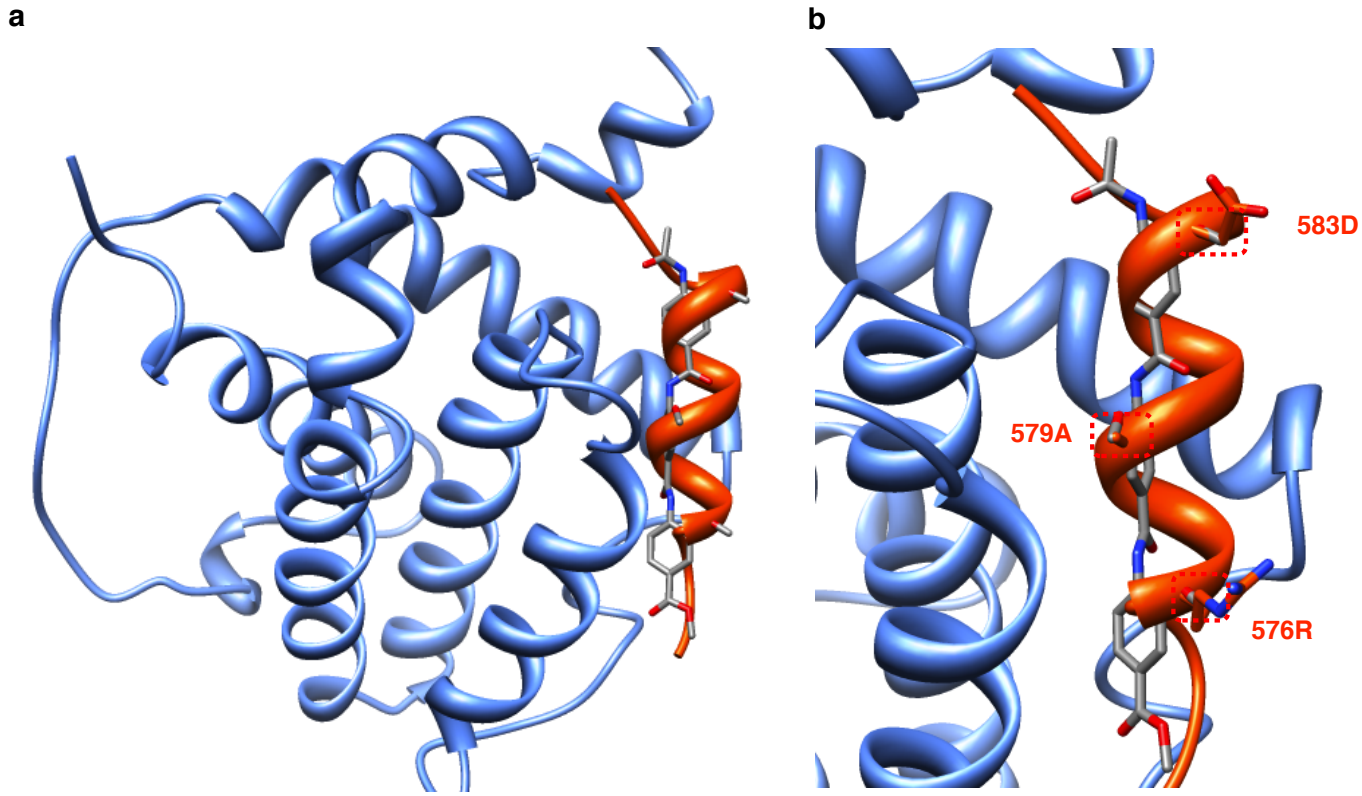


Figure S5. BakBH3/Bcl-x_L

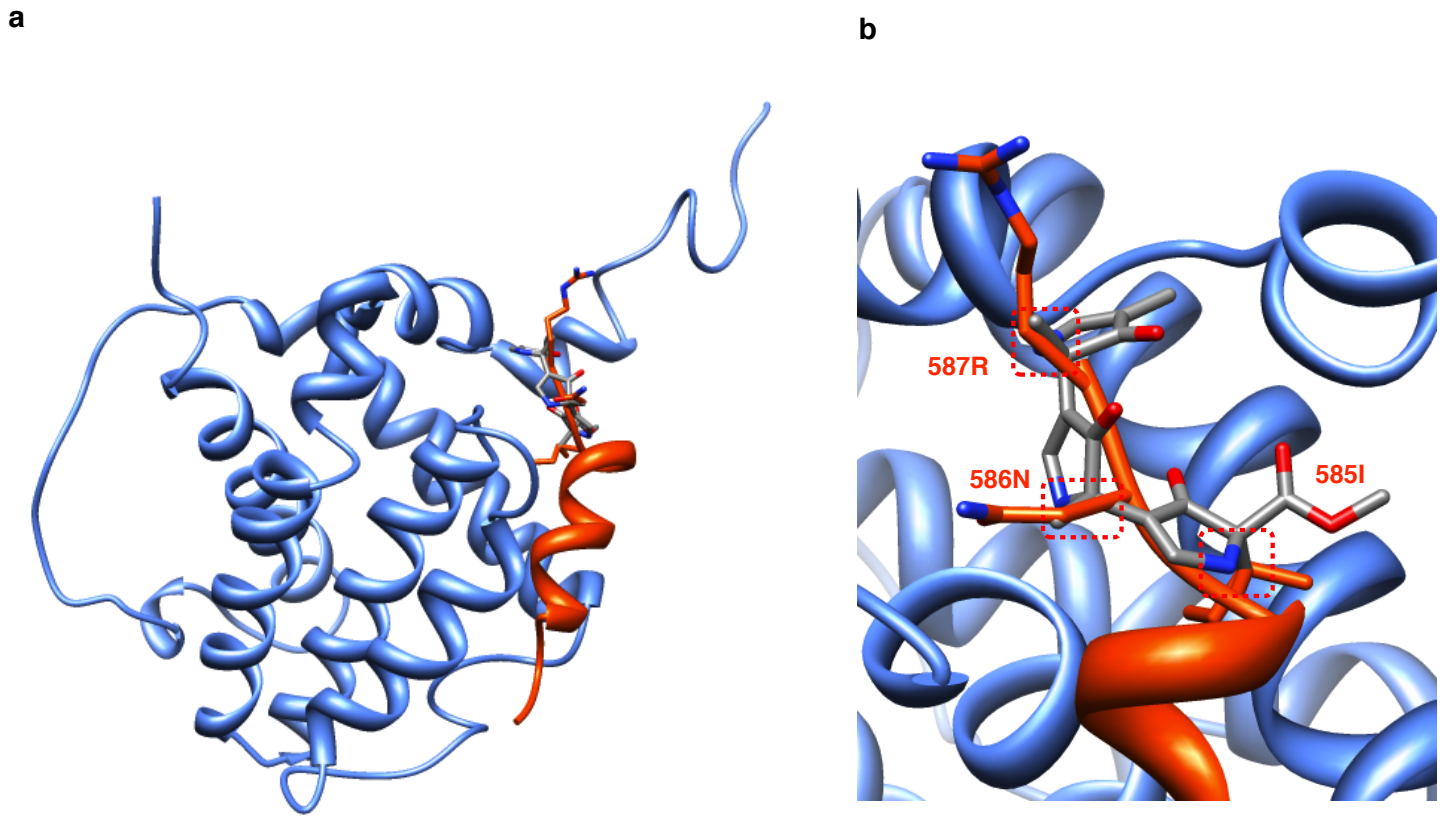


Figure S6. mimic 9 matching with BakBH3/Bcl-x_L

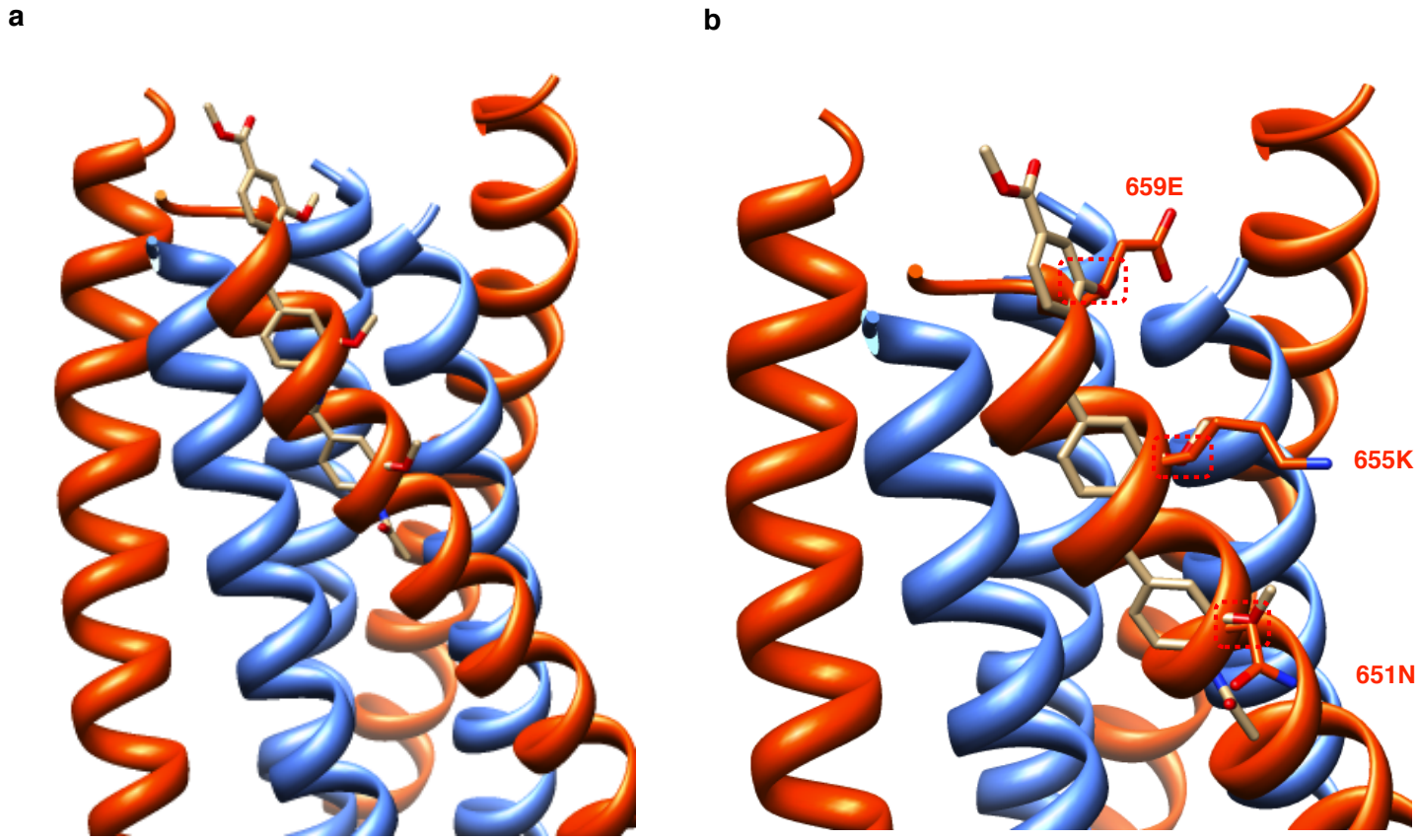


Figure S7. mimic 3' matching with g41 C-terminus helix

E. Sequence Correspondence For Preferred Mimic Conformations Overlaid on PPI Components

Table S1 shows sequence correspondence for preferred mimic conformations overlaid on four PPI components.

Table S1. Sequence correspondences for preferred mimic conformations overlaid on four PPI components

	p53/MDM2[a]	smMLCK/calmodulin[b]	BakBH3/Bcl-x_L[c]	gp41 *C*-/*N*-helical region[d]
1	29N-28E-26L	803T-805H-808R	580I-583D-585I	637N-640S-642I
2	21D-24K-23W	800W-803T-802K	576R-579A-578L	637N-640S-639T
3	28E-25L-21D	807V-803T-799K	583D-579A-576R	656N-652Q-648E
3'	19F-23W-26L	799K-803T-807V	577Q-581I-585I	651N-655K-659E
4	20S-23W-26L	802K-805H-807V	577Q-580I-583D	637N-640S-642I
5	20S-18T-17E	801Q-803T-806A	580I-581I-584D	637N-639T-642I
6	21D-23W-26L	797R-799K-803T	578L-580I-583D	630E-632D-636N
6'	25L-24K-20S	815S-814S-810I	586N-585I-581I	637N-636N-632D
7	24K-25L-27P	805H-806A-810I	584D-585I-587R	635I-636N-638Y
8	24K-26L-27P	810I-814S-815S	581I-585I-586N	638Y-642I-643H
8'	19F-18T-17E	807V-808R-809A	584D-585I-586N	635I-636N-637N
9	17E-18T-19F	799K-798R-801Q	585I-586N-587R	636N-635I-634E
10	18T-22L-26L	814S-810I-806A	581I-577Q-573Q	642I-638Y-634E

[a] Helical component shown first throughout; PDB identifier, 1YCR. [b]1CDL. [c]1BXL [d]1AIK

F. REFERENCES

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