Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.


# *Supporting Information*

# *Accelerated Molecular Dynamics Simulation Analysis of MSI-594 in a Lipid Bilayer*

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**Table S1.** Details of accelerated molecular dynamics (aMD) parameters in the presence of MSI-594.

| Systems | Unbiased MD | Threshold Energy (Kcal/mol) | AlphaD (dihedral) | aMD | System grid (Å) | | |
|---|---|---|---|---|---|---|---|
| | | | | | X | Y | Z |
| POPC | 10ns | -22708.31 | 19.2 | 50ns | 50 | 50 | 90 |
| POPG | 10ns | -35817.26 | 19.2 | 50ns | 54 | 60 | 90 |
| POPE | 10ns | -23362.13 | 19.2 | 50ns | 50 | 50 | 90 |
| POPS | 10ns | -28808.86 | 19.2 | 50ns | 55 | 58 | 90 |
| POPC-POPG (7:3) | 10ns | -20950.49 | 19.2 | 50ns | 58 | 60 | 90 |
| POPC-POPS (7:3) | 10ns | -22730.56 | 19.2 | 50ns | 60 | 60 | 95 |
| POPG-POPE (1:3) | 10ns | -18592.60 | 19.2 | 50ns | 55 | 55 | 90 |
| POPG-POPE (3:1) | 10ns | -20431.05 | 19.2 | 50ns | 55 | 55 | 90 |

**Note:** The values of Threshold Energy (Kcal/mol) and dihedral AlphaD values were cumulatively obtained from unbiased all-atom simulations. The corresponding values were further used in Equation (2) (main text) for accelerated molecular dynamics (aMD).

**Table S2.** Details of accelerated molecular dynamics (aMD) parameters in the absence of MSI-594.

| Systems | Unbiased MD | Threshold Energy (Kcal/mol) | aMD | System grid (Å) | | |
|---|---|---|---|---|---|---|
| | | | | X | Y | Z |
| POPC | 5ns | -21444.67 | 15ns | 60 | 60 | 80 |
| POPG | 5ns | -16263.76 | 15ns | 48 | 48 | 80 |
| POPE | 5ns | -14530.45 | 15ns | 48 | 48 | 80 |
| POPS | 5ns | -23305.8 | 15ns | 48 | 48 | 80 |
| POPC-POPG (7:3) | 5ns | -22276.56 | 15ns | 50 | 50 | 80 |
| POPC-POPS (7:3) | 5ns | -24111.94 | 15ns | 50 | 50 | 80 |
| POPG-POPE (1:3) | 5ns | -15166.37 | 15ns | 48 | 48 | 80 |
| POPG-POPE (3:1) | 5ns | -16968.09 | 15ns | 48 | 48 | 80 |

**Note:** Threshold Energy (Kcal/mol) values were cumulatively obtained from unbiased all-atom simulations. The corresponding values were further used in Equation (2) (main text) for accelerated molecular dynamics (aMD).

**Table S3.** Details of area per lipid and membrane thickness estimation for different model systems

| Model Systems | Area Per Lipid (Å$^2$) | | Membrane Thickness (Å) | |
|---|---|---|---|---|
| | **In presence of MSI-594** ± Standard deviation | **In absence of MSI-594** ± Standard deviation | **In presence of MSI-594** ± Standard deviation | **In absence of MSI-594** ± Standard deviation |
| POPC-POPG (7:3) | POPC 72.40 ± 2.70<br>POPG 74.26 ± 6.32<br>Average 72.96 ± 2.67 | POPC 65.21 ± 1.75<br>POPG 56.97 ± 2.69<br>Average 62.74 ± 1.20 | 36.04 ± 0.87 | 39.77 ± 0.58 |
| POPC-POPS (7:3) | POPC 72.39 ± 3.14<br>POPS 62.94 ± 4.64<br>Average 71.05 ± 1.89 | POPC 63.32 ± 1.62<br>POPS 56.71 ± 2.29<br>Average 61.33 ± 1.38 | 37.01 ± 0.82 | 40.39 ± 0.70 |
| POPG- POPE (1:3) | POPE 65.86 ± 2.11<br>POPG 73.79 ± 4.75<br>Average 67.84 ± 1.72 | POPG 59.52 ± 1.51<br>POPE 54.80 ± 3.77<br>Average 58.34 ± 1.33 | 38.11 ± 0.82 | 41.65 ± 0.78 |
| POPG-POPE (3:1) | POPE 71.95 ± 6.68<br>POPG 71.54 ± 2.58<br>Average 71.65 ± 1.81 | POPG 66.71 ± 2.34<br>POPE 60.75 ± 3.91<br>Average 65.22 ± 1.99 | 36.11 ± 1.29 | 38.31 ± 1.04 |
| POPC | 74.34 ± 2.14 | 63.63 ± 1.21 | 36.48 ± 0.87 | 39.46 ± 0.63 |
| POPS | 68.71 ± 1.35 | 60.58 ± 1.08 | 37.99 ± 0.65 | 40.78 ± 0.58 |
| POPG | 73.72[a] ± 2.18 | 65.49 ± 2.97 | 36.25 [a] ± 0.89 | 38.36 ± 0.72 |
| POPE | 66.92 [a] ± 1.74 | 56.37 ± 2.62 | 38.31 [a] ± 0.78 | 42.58 ± 0.88 |

[a]Simulation for 30 ns

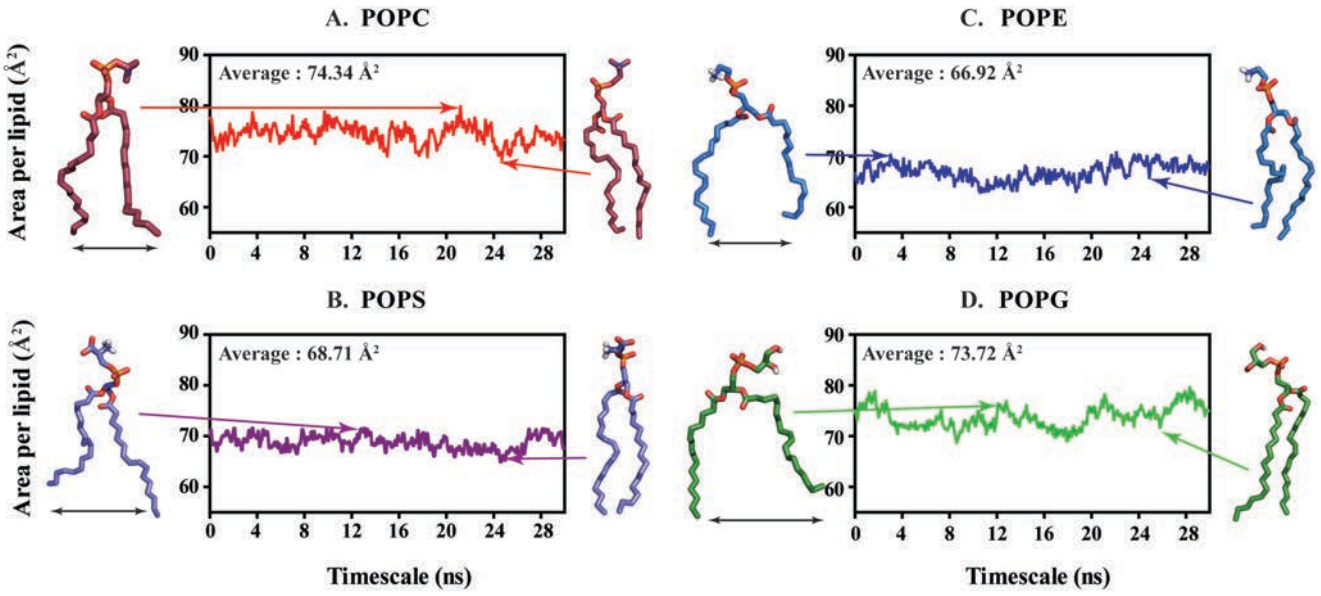


**Figure S1**. Area per lipid estimated for homogenous bilayer systems. (A) POPC, (B) POPS, (C) POPE and (D) POPG. POPC, POPS, POPG and POPE are represented by red, purple, green and blue colour respectively.

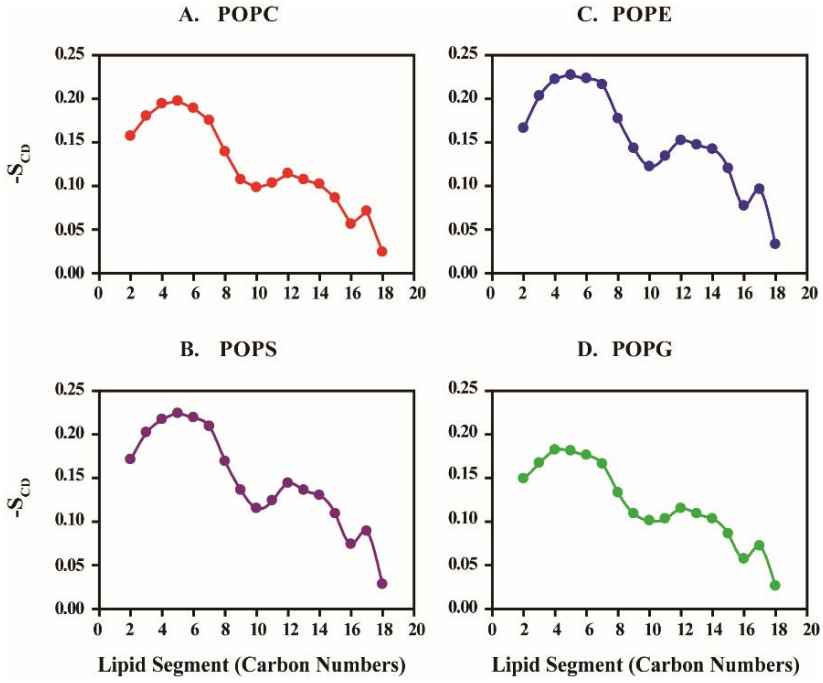


**Figure S2.** Lipid order parameter ($-S_{CD}$) is measured on the basis of POPC, POPS, POPG and POPE lipid fragments in (A) POPC, (B) POPS, (C) POPE and (D) POPG homogenous systems. POPC, POPS, POPG and POPE are represented with red, purple, green and blue respectively.

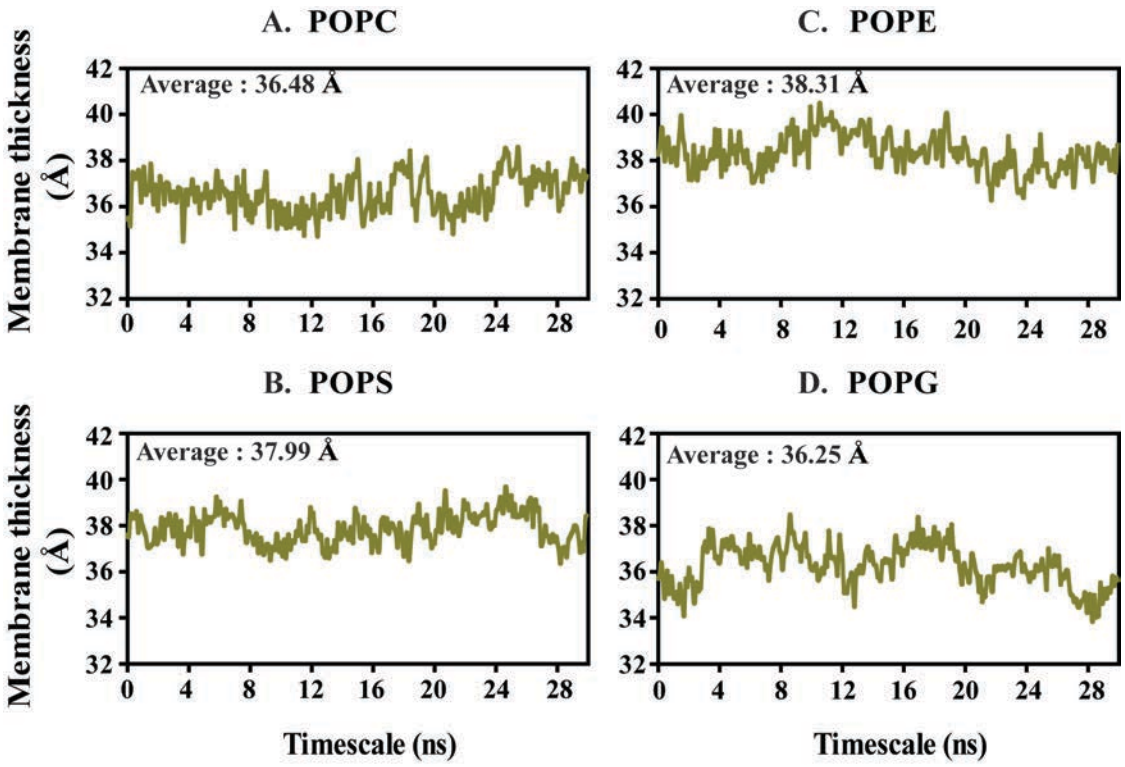


**Figure S3.** Average membrane thickness is computed with respect to simulation time for (A) POPC, (B) POPS, (C) POPE and (D) POPG bilayer systems.

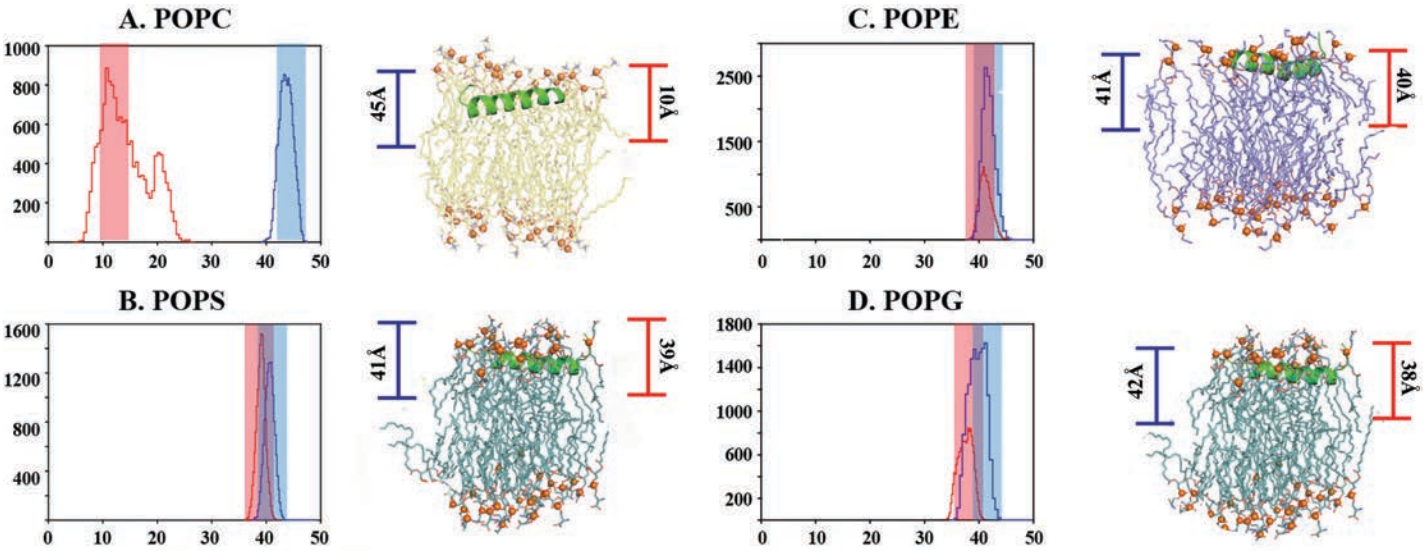


**Figure S4.** The maximum number of MSI-594 configurations present at a particular distance from the centre of bilayer is plotted by histogram analysis and representative snapshots are given from simulation trajectory for (A) POPC, (B) POPS, (C) POPE and (D) POPG bilayer systems. [Blue colour represents the distance between center of bilayer and the residue with maximum bend angle; Red colour represents the distance between center of bilayer and Gly12 residue.]

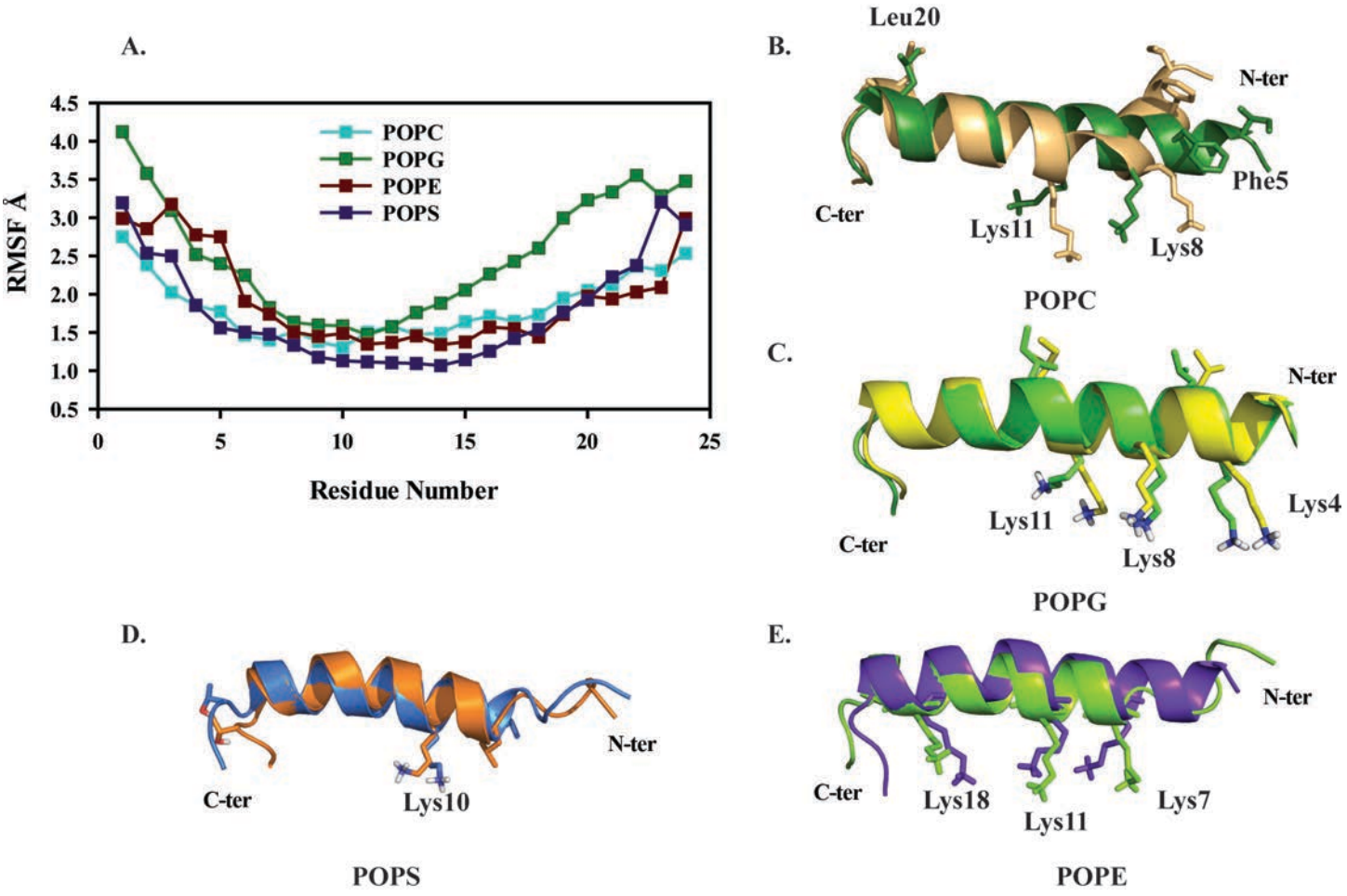


**Figure S5.** RMSF of Cα carbon atoms of MSI-594 in (A) homogenous lipid environments and (B-E) superimposition of MSI-594 conformations from starting and end-point simulation timescale. The side chains of residues that show significant differences are highlighted in stick representations.

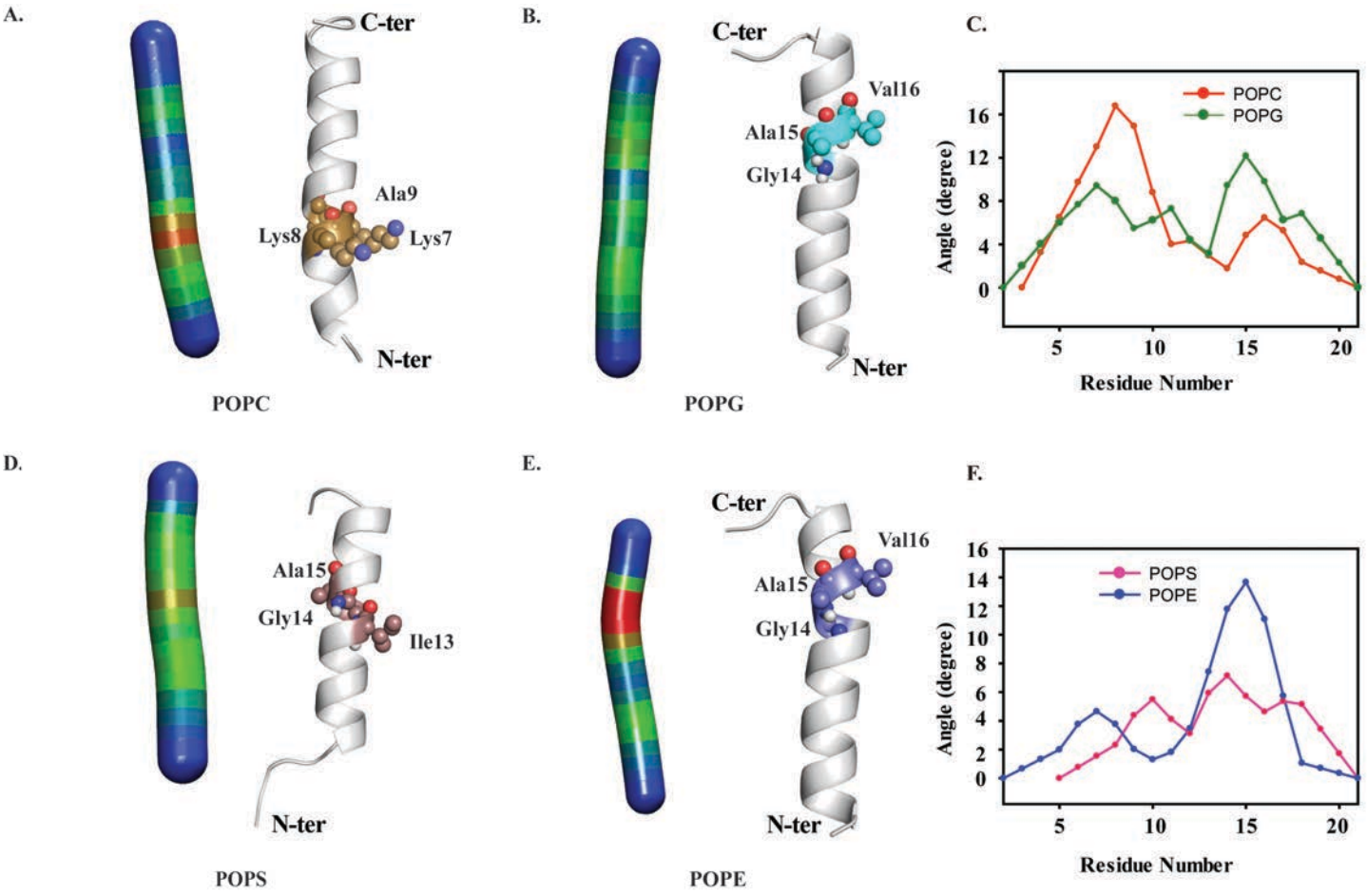


**Figure S6.** Heat map for the helix bend angle and the residues involved along with the degree of angle plot against the residue (C, F) are shown for (A) POPC, (B) POPS, (D) POPE and (E) POPG homogenous lipid systems.

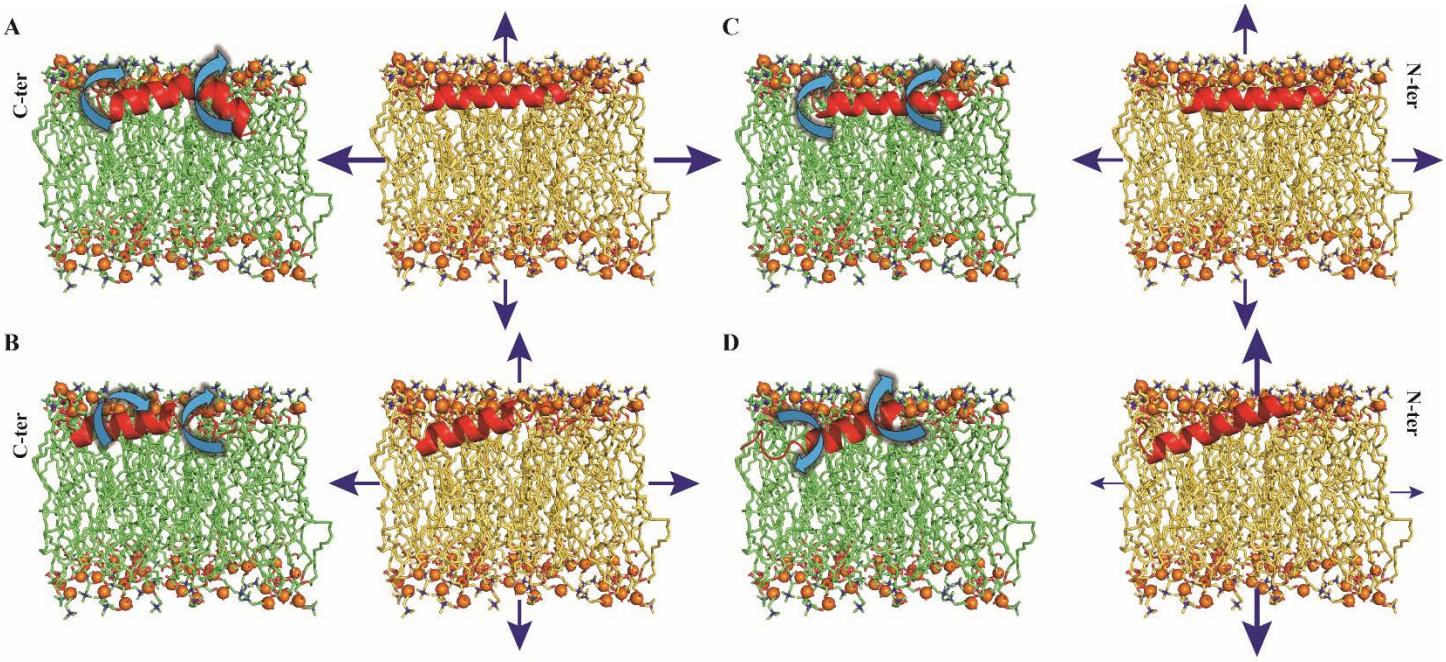


**Figure S7:** Structural models indicating the relative dynamicity of MSI-594 (in green acyl chain) and membrane system (in yellow acyl chain). The structural drift for C-ter, G-I-G middle section, and N-ter is shown with curved arrow, which corresponds to relative dynamicity of MSI-594 from aMD. The membrane thickness (vertical arrows) and average change in area (horizontal arrows) reflect the perturbation of membrane system. The thickness of arrow is indicative of their extent of perturbation. The model represents (A) POPC, (B) POPS, (C) POPG, and (D) POPE.

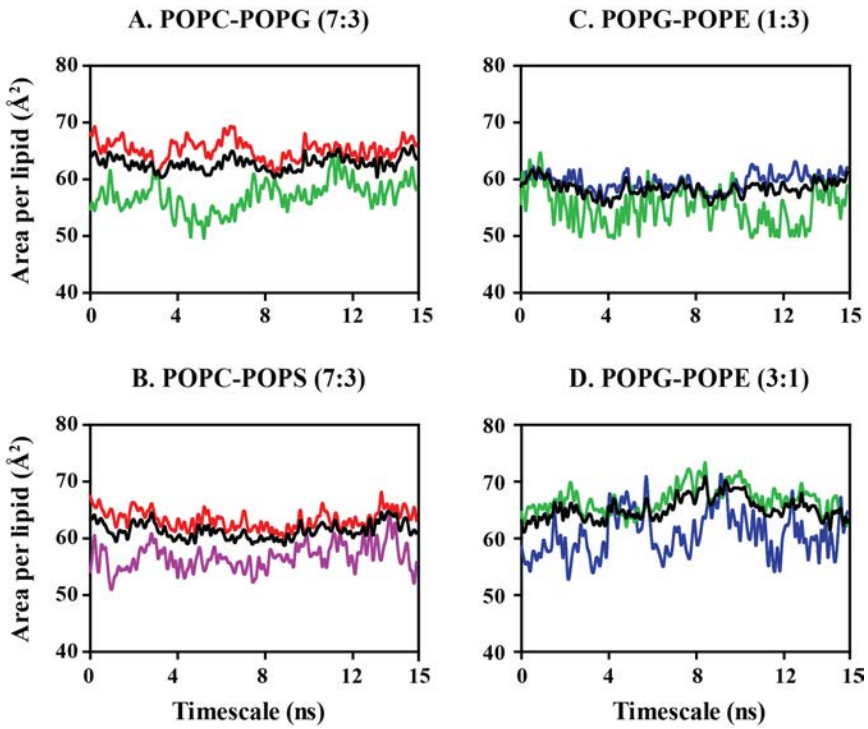


**Figure S8**. Area per lipid estimation for heterogeneous bilayer systems. (A) POPC-POPG (7:3), (B) POPC-POPS (7:3), (C) POPG-POPE (1:3) and (D) POPG-POPE (3:1) in the absence of MSI-594. POPC, POPS, POPG and POPE are represented by red, purple, green and blue colour, respectively.

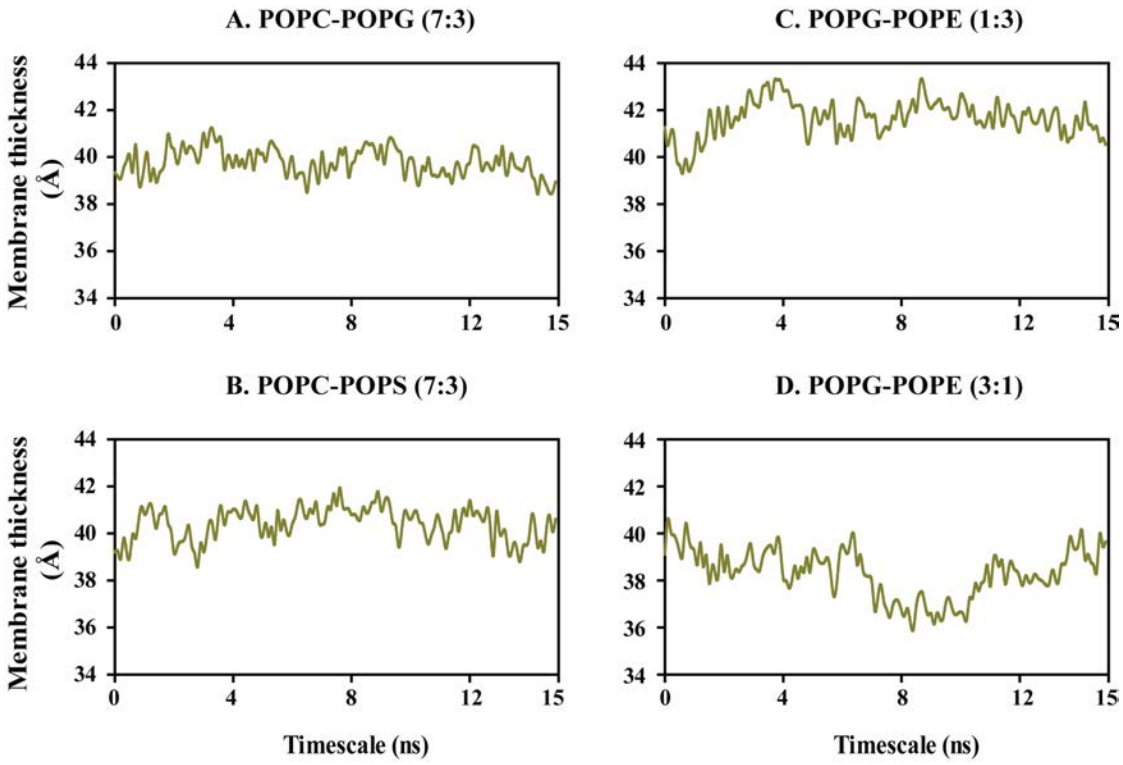


**Figure S9.** Average membrane thickness is computed with respect to simulation time for (A) POPC-POPG (7:3), (B) POPC-POPS (7:3), (C) POPG-POPE (1:3) and (D) POPG-POPE (3:1) bilayer systems in the absence of MSI-594.

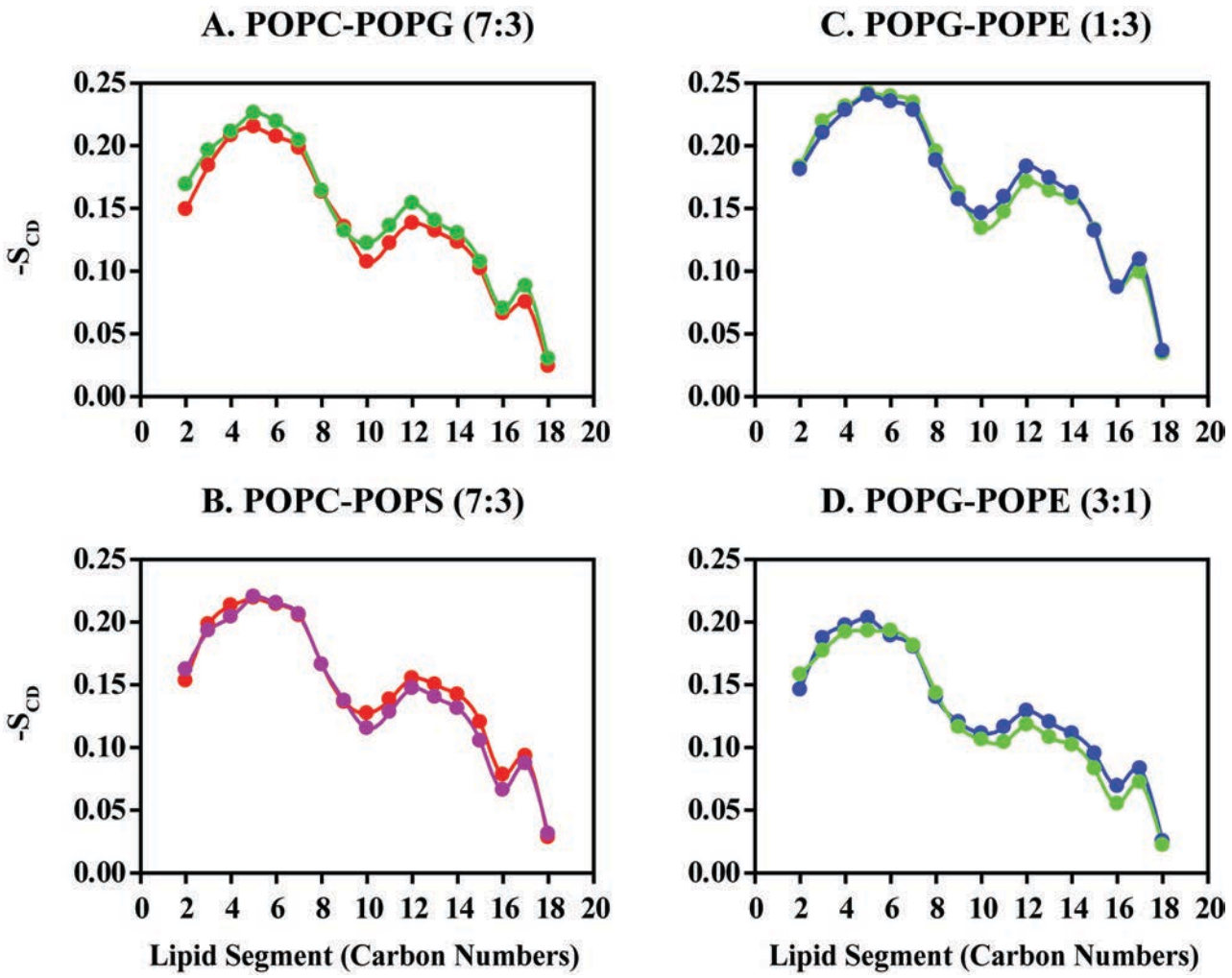


**Figure S10.** Lipid order parameter ($-S_{CD}$) is measured on the basis of POPC, POPS, POPG and POPE lipid fragments in (A) POPC-POPG (7:3), (B) POPC-POPS (7:3), (C) POPG-POPE (1:3) and (D) POPG-POPE (3:1) in the absence of MSI-594. POPC, POPS, POPG and POPE are represented with red, purple, green and blue, respectively.