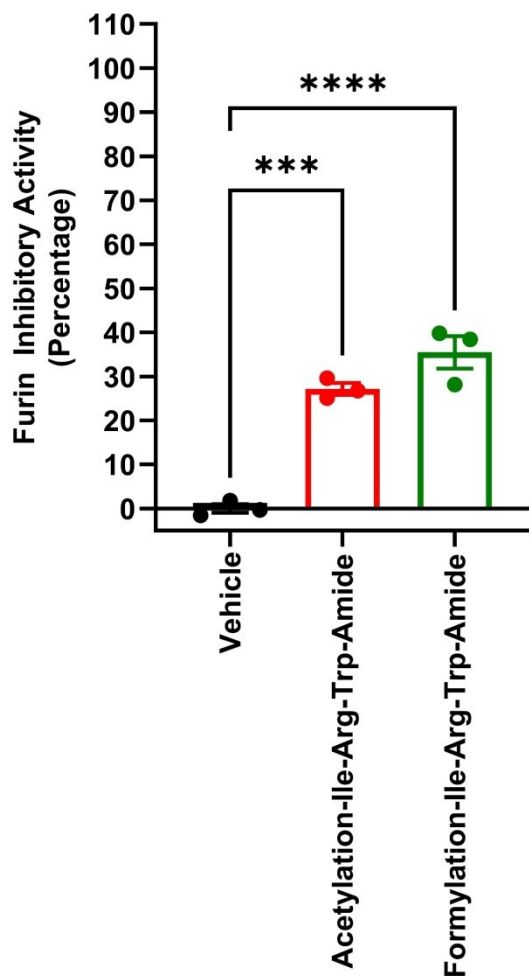
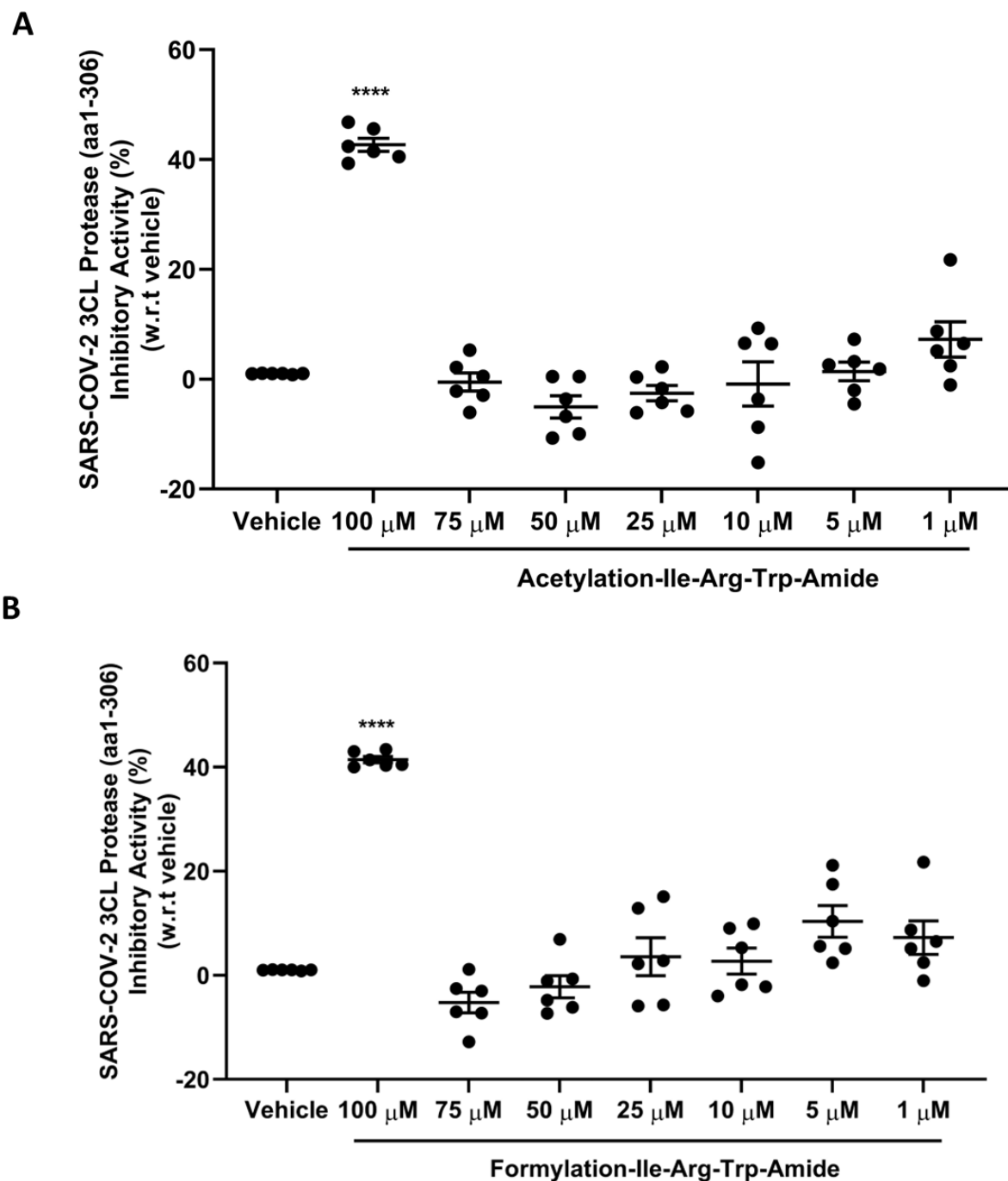


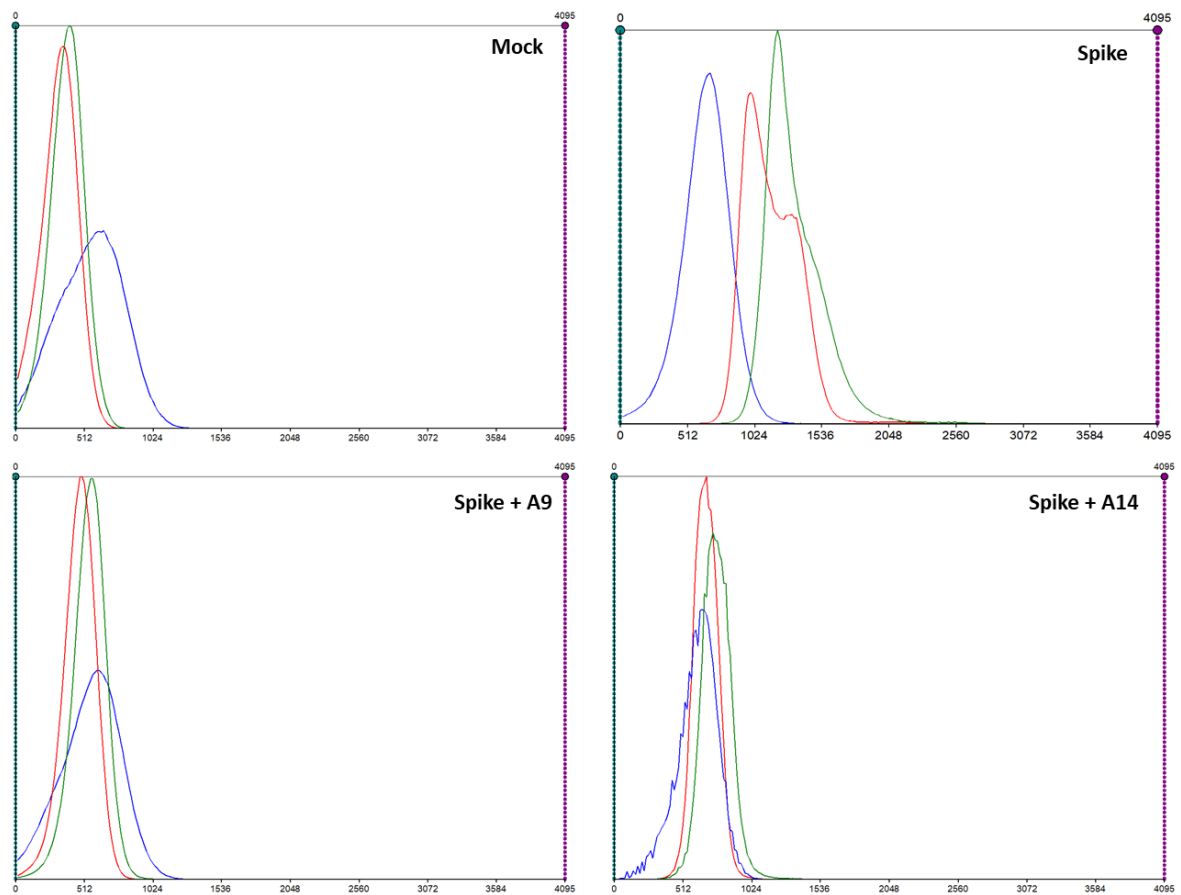
**Figure S1.** Impact of constituent IRW di-peptides on SARS-Cov-2 S1 RBD-ACE2 interaction. An in vitro assay was conducted to assess the possible inhibitory impact of constituent IRW di-peptides (50  $\mu$ M) on SARS-Cov-2 S1 RBD-ACE2 interaction. The results are expressed as percentage inhibition with respect to the vehicle control (nuclease free water). Data expressed as mean  $\pm$  SEM of  $n = 3$ . P values were determined by Analysis by one-way ANOVA followed by Bonferroni's post-hoc test for the vehicle. ns: nonsignificant.



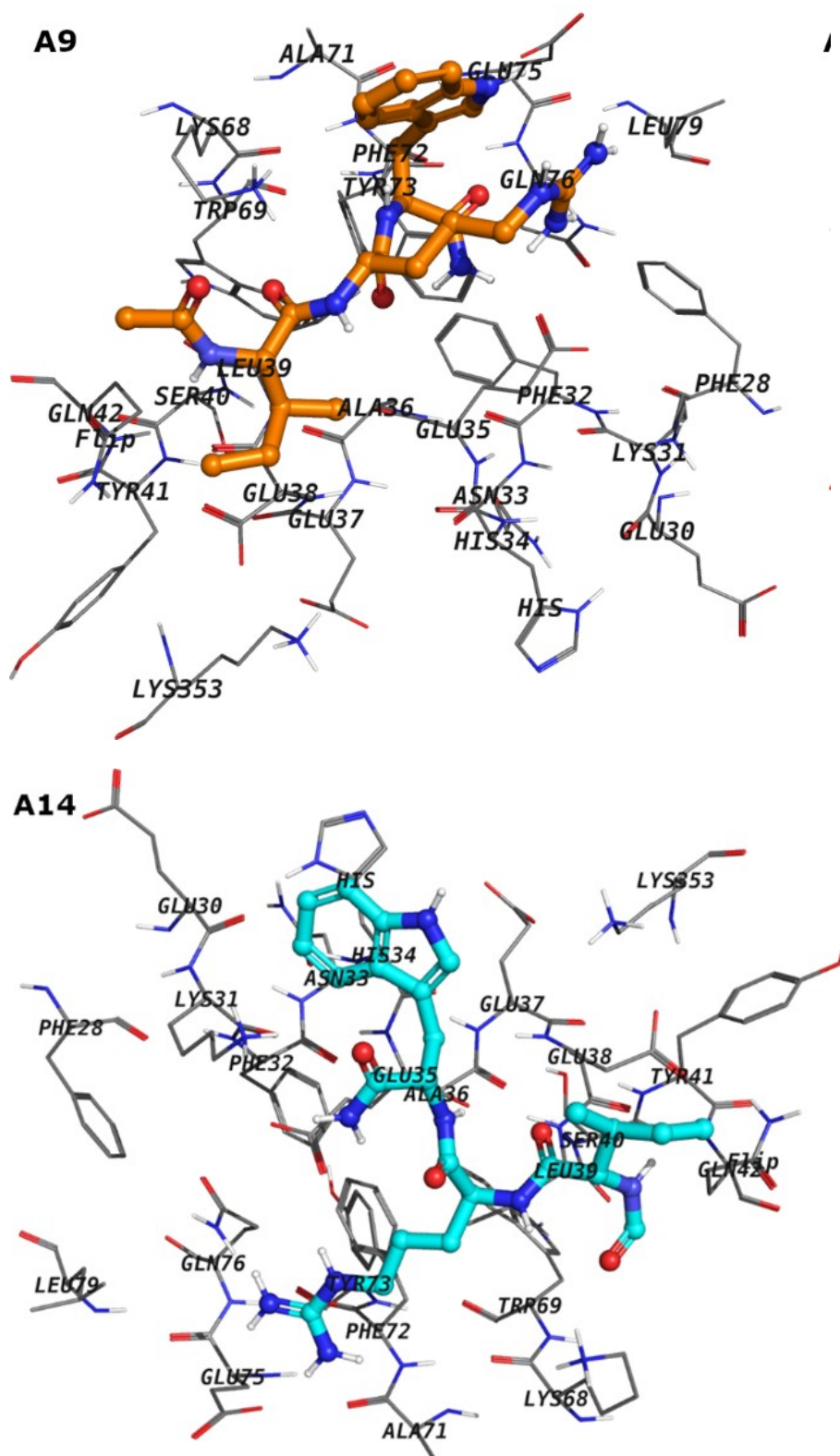
**Figure S2.** Assessment of furin inhibitory potential of peptides A9 (Acetylation-IRW-Amide) and A14 (Formylation IRW-Amide). The results are expressed as the percentage furin inhibitory activity with respect to the vehicle control. Data expressed as mean  $\pm$  SEM of  $n=3$ . P values were determined by Analysis by one-way ANOVA followed by Bonferroni's post-hoc test for vehicle. \*\*\* indicates  $p < 0.001$  and \*\*\*\* indicates  $p < 0.0001$  versus vehicle. The error bar indicates S.D. of the mean value. The assay was conducted at the peptide concentration of 50  $\mu\text{M}$ .  $\mu\text{M}$ : micromolar.



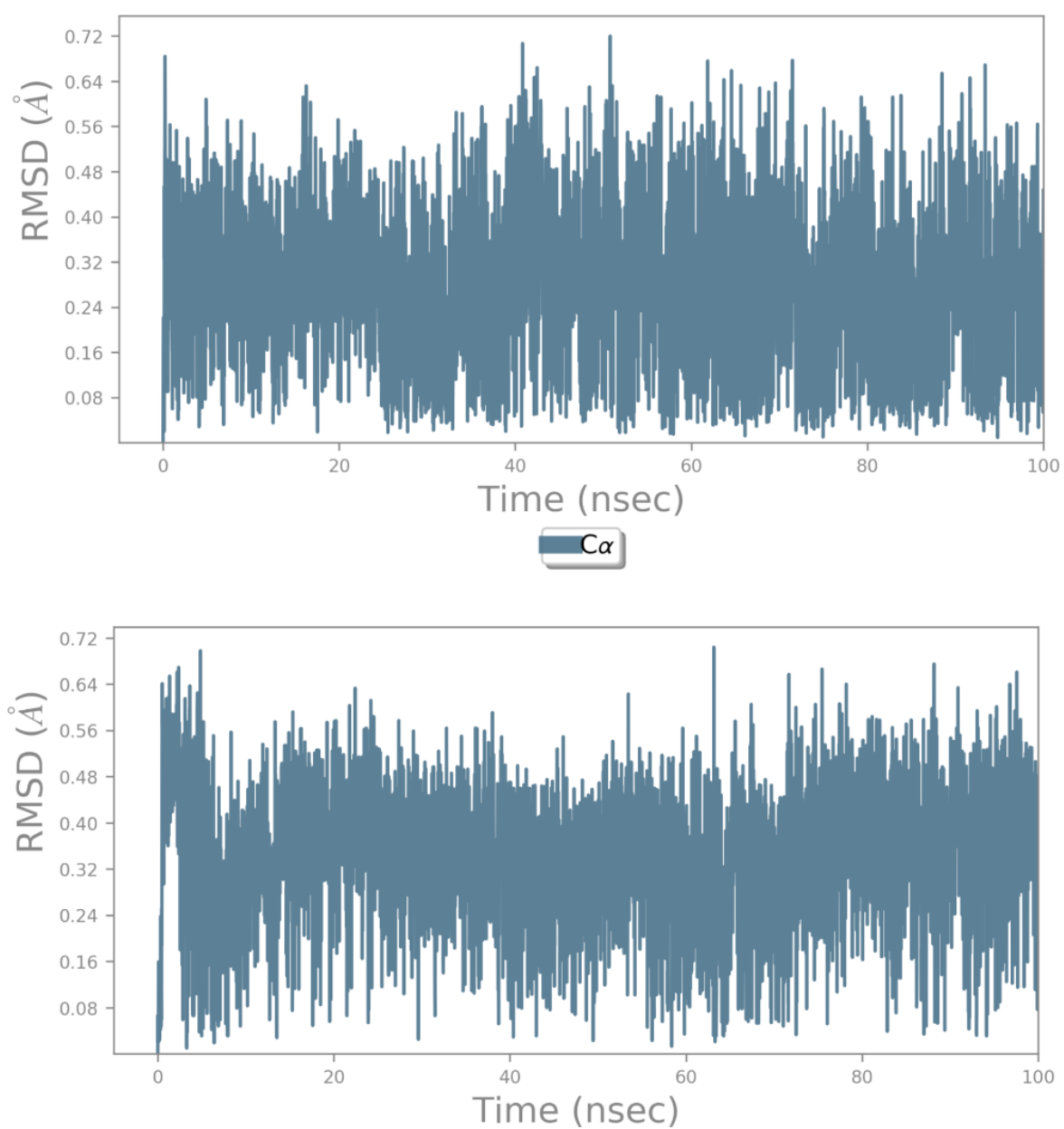
**Figure S3.** Impact of the selected peptides (A) Acetylation-IRW-Amide and (B) Formylation IRW-Amide on SARS-COV-2 3CL Protease (aa1-306) activity at various concentrations. The results are expressed as the percentage on SARS-COV-2 3CL Protease (aa1-306) inhibitory activity with respect to the vehicle control. Data expressed as mean  $\pm$  SEM of  $n = 6$ . P values were determined by Analysis by one-way ANOVA followed by Bonferroni's post-hoc test for vehicle. \*\*\*\* indicates  $p < 0.0001$  versus vehicle. The error bar indicates S.D. of the mean value.  $\mu$ M: micromolar.



**Figure S4.** Histograms indicating florescence microscopy assessment of spike lentivirus inhibition potential of peptides A9 and A14. Histograms representing florescence intensity indicating lentivirus production in 293T-ACE2.TMPRSS2 cells transfected with the Spike lentiviral particles with the ZsGreen backbone in presence of A9 and A14 at 50  $\mu$ M. The experiment was conducted n = 6 times independently.



**Figure S5.** The interaction profile of A9 and A14 with ACE2. The amino acid residues 4 Å around the analogs are shown as lines. A9 and A14 are shown as sticks.



**Figure S6.** The root mean square deviation curves of A9 (Acetylation-IRW-Amide) and A14 (Formylation IRW-Amide) relative to their initial configurations.