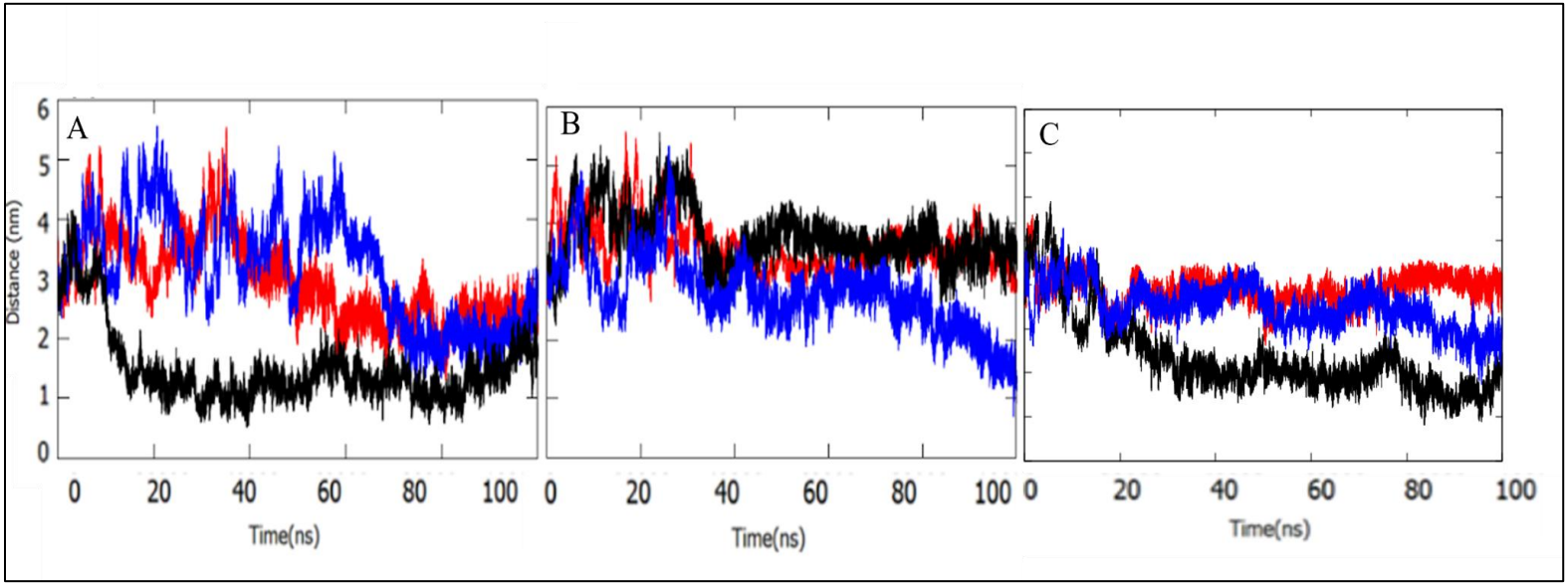
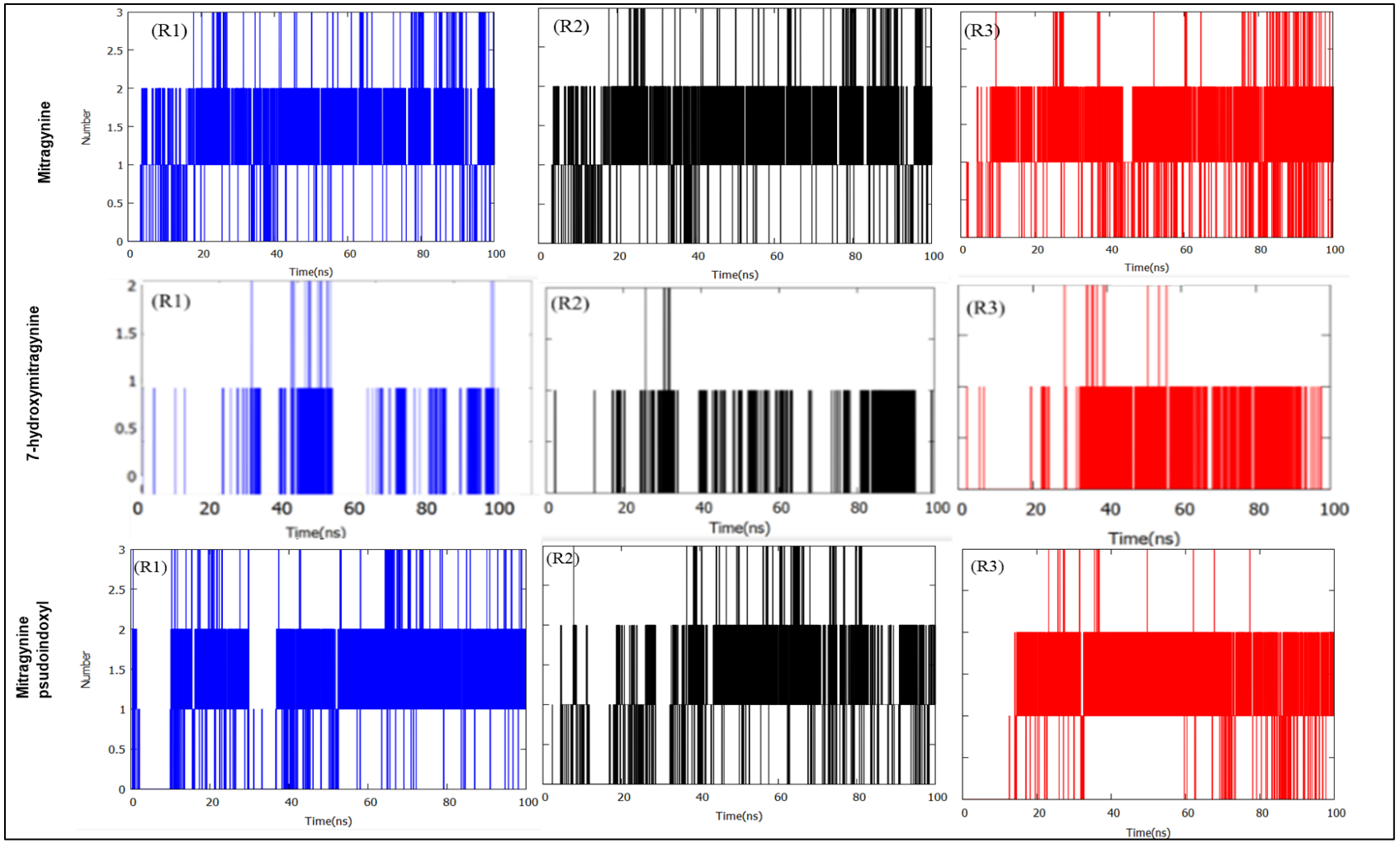
Supplemental Materials



Supplementary Figure 1: Average distance between the alkaloids and the lipid headgroups during the 100 ns MD simulations. (A) Mitragynine, (B) 7-hydroxymitragynine, (C) Mitragynine pseudoindoxyl. Replicate 1 (blue), Replicate 2 (black) and Replicate 3 (red)

Supplementary Table 1: Distance to membrane analysis. The average distance of the compound to the lipid head-group based on the final 50 ns trajectories

Compounds	Distance to membrane
Mitragynine	1.23 nm ± 0.71
7-hydroxymitragynine	3.62 nm ± 0.27
Mitragynine pseudoindoxyl	2.40 nm ± 0.31



Supplementary Figure 2: Analysis hydrogen bond interactions between the alkaloids and lipids. Replicate 1 (blue), Replicate 2 (black), and Replicate 3 (red)

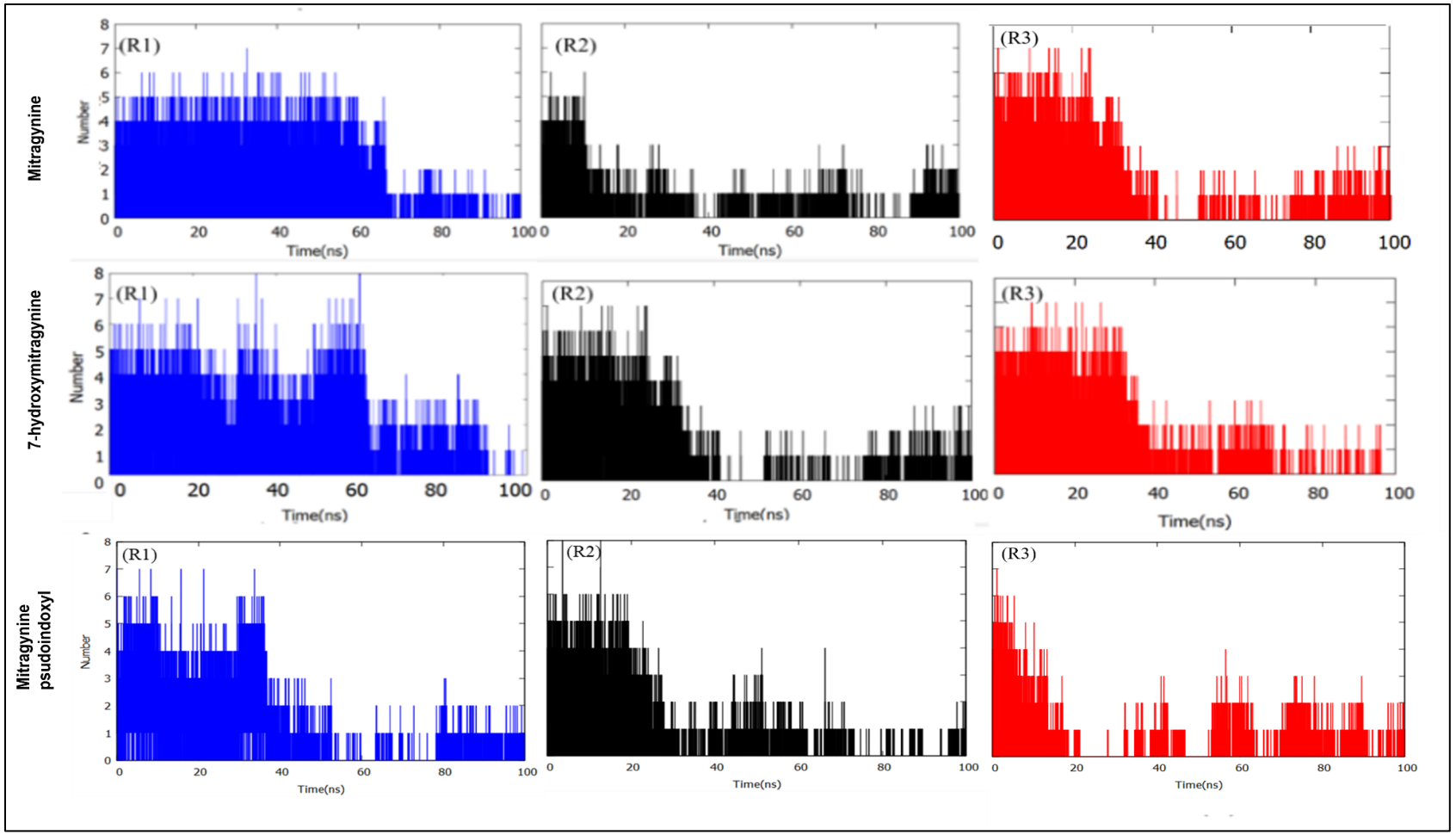


Figure 3: Analysis hydrogen bond interactions between the alkaloids and water molecules. Replicate 1 (blue), Replicate 2 (black), and Replicate 3 (red)

Supplementary Table 2: Solubility of kratom alkaloids mitragynine, 7-hydroxymitragynine and Mitragynine pseudoindoxyl

Compound	Mitragynine	7-hydroxymitragynine	Mitragynine pseudoindoxyl
A. Lipophilicity			
Log $P_{o/w}$ (iLOGP)	3.77	3.87	3.58
Log $P_{o/w}$ (XLOGP3)	3.41	2.27	3.00
Log $P_{o/w}$ (WLOGP)	3.12	1.92	1.91
Log $P_{o/w}$ (MLOGP)	2.02	1.30	1.30
Log$P_{o/w}$ (SILICOS-IT)	3.72	3.10	2.62
Consensus Log $P_{o/w}$	3.21	2.49	2.48
B. Water solubility			
Log *S* (ESOL)	-4.29	-3.59	-4.05
Solubility/Class	2.03e-02 mg/ml ; 5.10e-05 mol/l / Moderately soluble	1.06e-01 mg/ml ; 2.56e-04 mol/l / Soluble	3.68e-02 mg/ml ; 8.87e-05 mol/l / Moderately soluble
Log *S* (Ali)	-4.43	-3.60	-4.28
Solubility/Class	1.48e-02 mg/ml ; 3.72e-05 mol/l / Moderately soluble	1.04e-01 mg/ml ; 2.52e-04 mol/l /Soluble	2.16e-02 mg/ml ; 5.21e-05 mol/l / Moderately soluble
Log *S* (SILICOS-IT)	-5.00	-4.10	-4.58
Solubility/Class	3.95e-03 mg/ml ; 9.91e-06 mol/l / Moderately soluble	3.28e-02 mg/ml ; 7.91e-05 mol/l / Moderately soluble	1.08e-02 mg/ml ; 2.61e-05 mol/l / /Moderately soluble
Log K_p (skin permeation)	-6.31 cm/s	-7.22 cm/s	-6.70 cm/s