Acyclovir as an Ionic Liquid Cation or Anion Can Improve Aqueous Solubility

Electronic Supporting Information

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Figures

(a) (b)

Figure S1. [Cho][Acy] **1** in water (a) after mixing for 24 h at room temperature and (b) aliquot taken from (a) after centrifugation and standing for 15 days at room temperature showing phase separation.

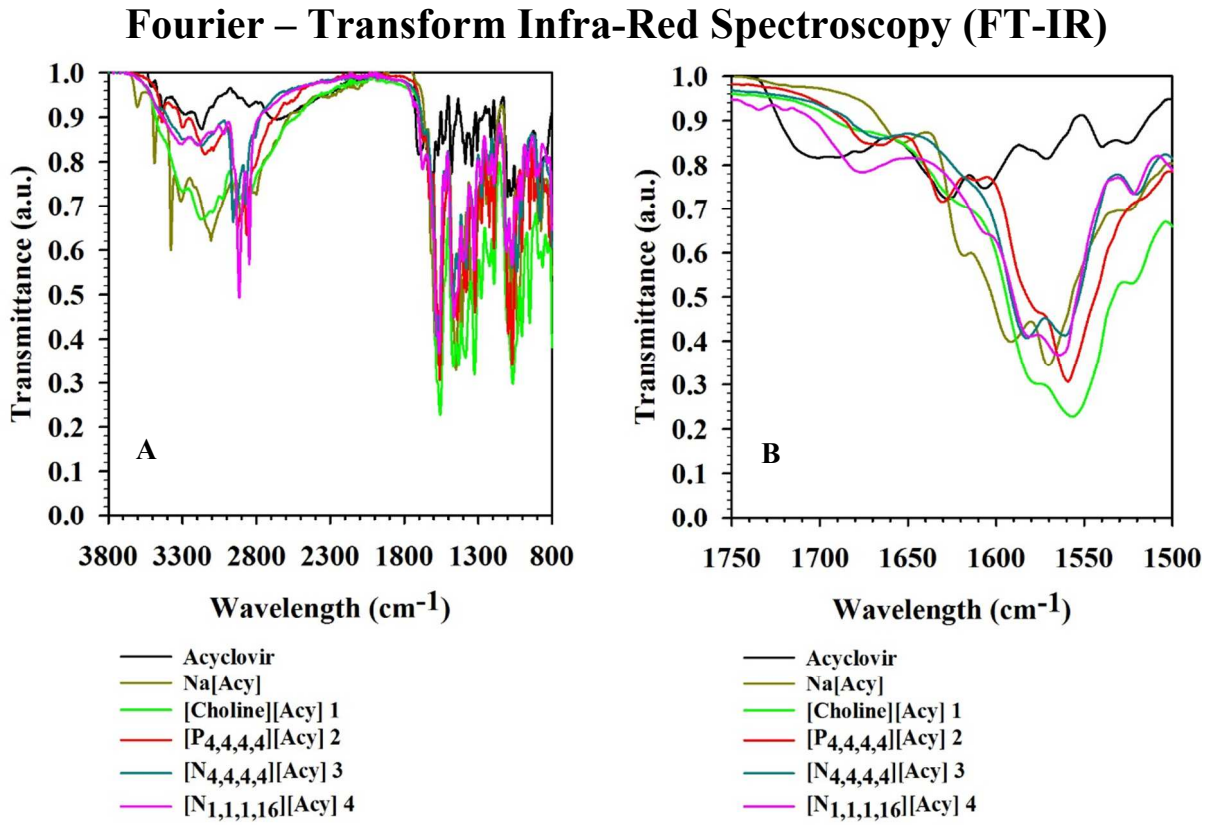

Figure S2. IR spectra (**A** - full spectrum, **B** - expanded region) of acyclovir hydrate (3Acy·2H_2O) black; sodium acyclovirate – dark yellow; [Cho][Acy] **1** – green; [$P_{4,4,4,4}$][Acy] **2** – red; [$N_{4,4,4,4}$][Acy] **3** – dark cyan; and [$N_{1,1,1,16}$][Acy] **4** – pink.

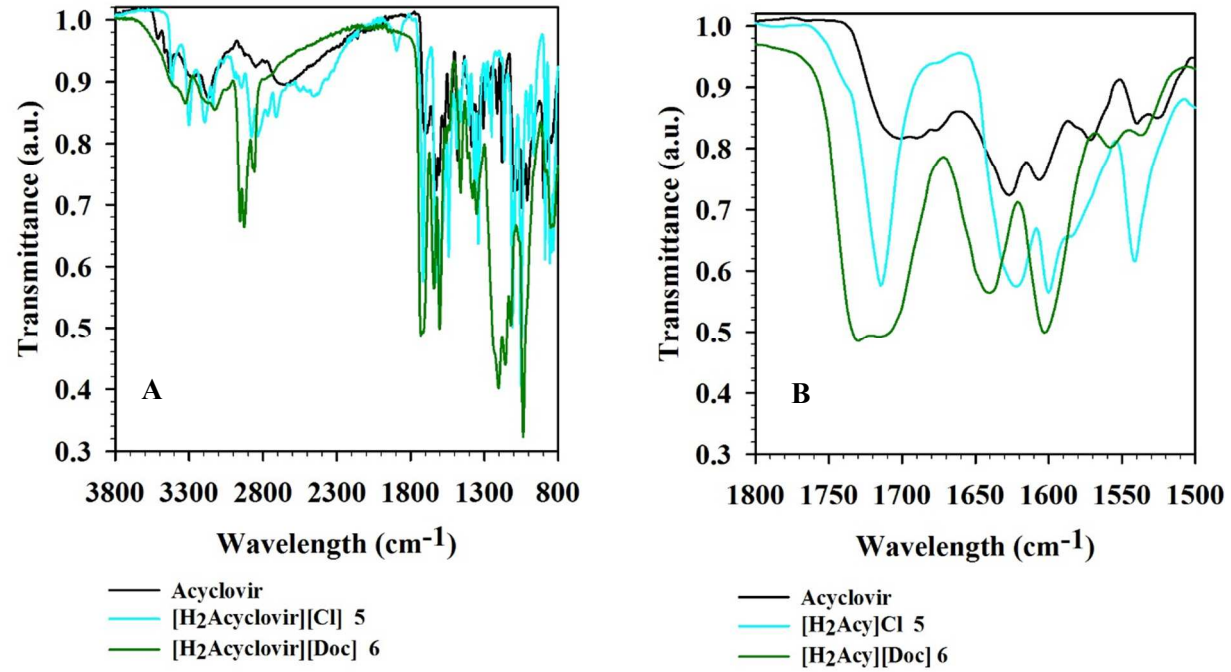

Figure S3. IR spectra (**A** - full spectrum, **B** - expanded region) of acyclovir hydrate (3Acy·2H_2O)– black; [H_2Acy]Cl **5** – cyan; and [H_2Acy][Doc] **6** – dark green.

Structural Description and Analysis of $[P_{4444}][Acy]\cdot HAcy$ (product of disproportionation of $[P_{4444}][Acy]$)

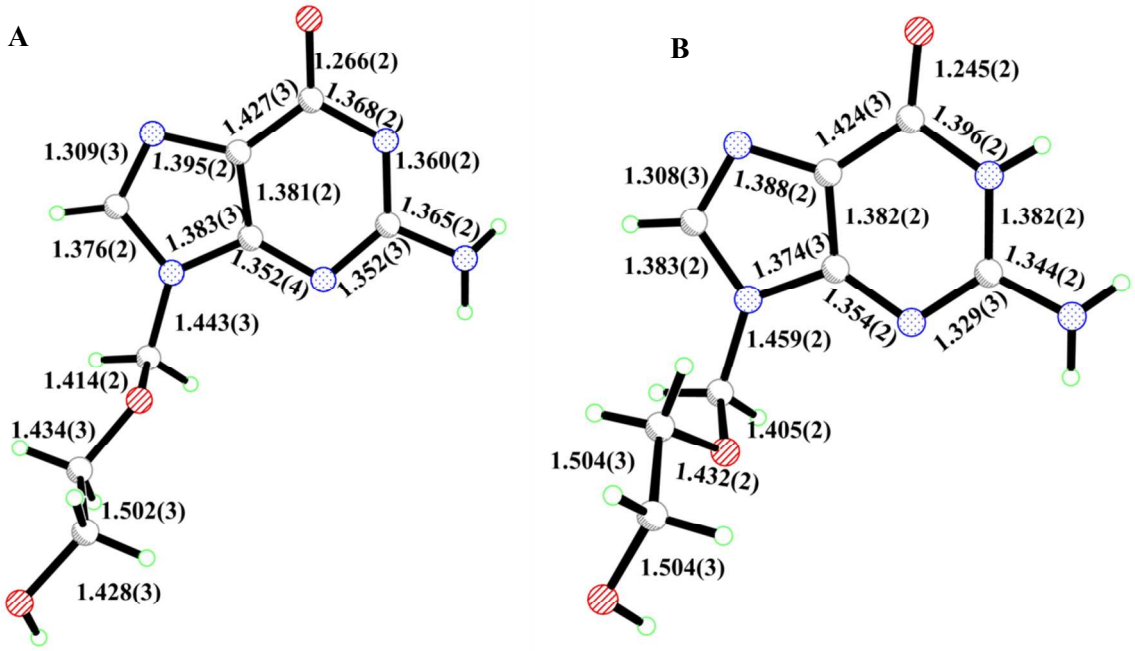

Figure S4. Bond distances (in Å) for $[Acy]^-$ (**A**) and HAcy (**B**).

The $[P_{4444}]^+$ makes short contacts to 3 anions and 1 neutral HAcy molecule. Two of these anions and the HAcy molecule sandwich the cation by stacking above and below it, while the third anion makes short contacts to one of the butyl groups through C-H groups on its ether side chain. The anion makes short contacts to 3 cations, 4 anions, and 2 neutral molecules of acyclovir. The anion donates and receives hydrogen bonds between the –OH group of the side chain and the free nitrogen position on the imidazole ring, which are the shortest hydrogen bonds in the structure. The other two anions interact by either donating or recieving a hydrogen bond from the imidazole C-H group to the alcohol –OH group. Atoms O6, N9, and N10 are all involved in hydrogen bonding to a single complementary HAcy neighbor. The other neighboring HAcy molecule interacts through by donating and receiving hydrogen bonds between the amino group and non-protonated ring nitrogen atoms, forming a symmetric 8-membered hydrogen bonded cycle. The HAcy molecule makes short contacts to 1 cation and 2 anions through the aformentioned interactions as well as 5 other HAcy molecules. Two neighboring HAcy molecules interact to form a chain through hydrogen bonds between the –OH groups and carbonyl oxygen atoms. One neighbor engages in a dimeric interaction where the imidazole C-H group is donated in a weak hydrogen bond to the imidazole N atom. The remaining two HAcy molecules either donate or receive weak hydrogen bonds between C-H groups and the –OH group oxygen atom.

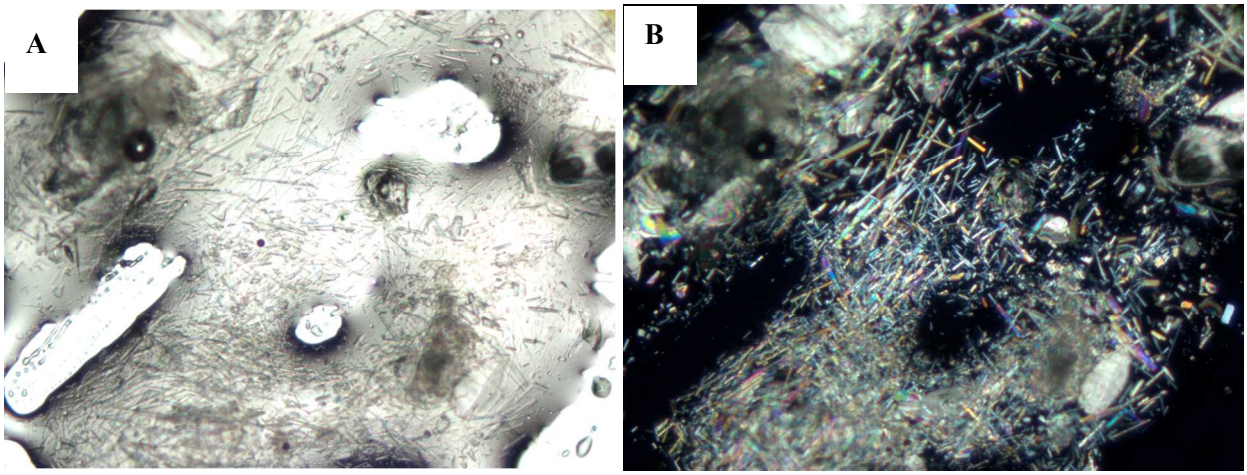

Figure S5. Transmission optical microscope images of $[P_{4,4,4,4}][Acy]$ after crystallization under polarized light without filters (**A**) and under crossed polarizers (**B**).

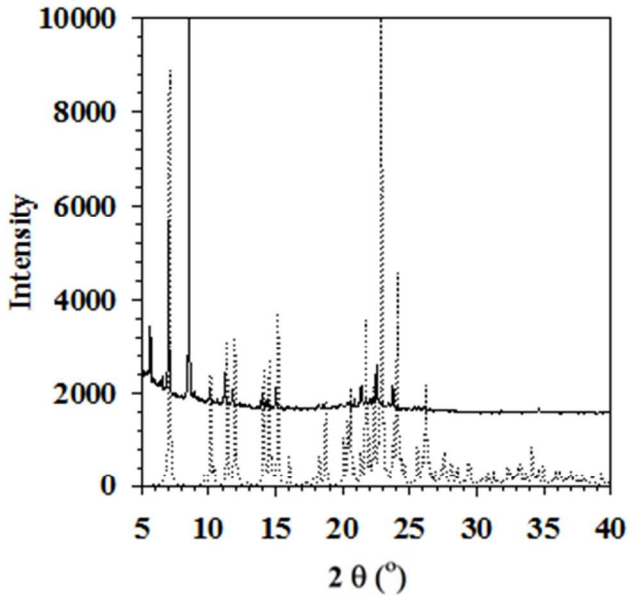

Figure S6. PXRD of $[P_{4,4,4,4}][Acy]$ bulk after crystallization (solid line) *vs.* simulated powder pattern of $[P_{4,4,4,4}][Acy]\cdot HAcy$ (dotted line).

Powder X-Ray Diffraction (pXRD)

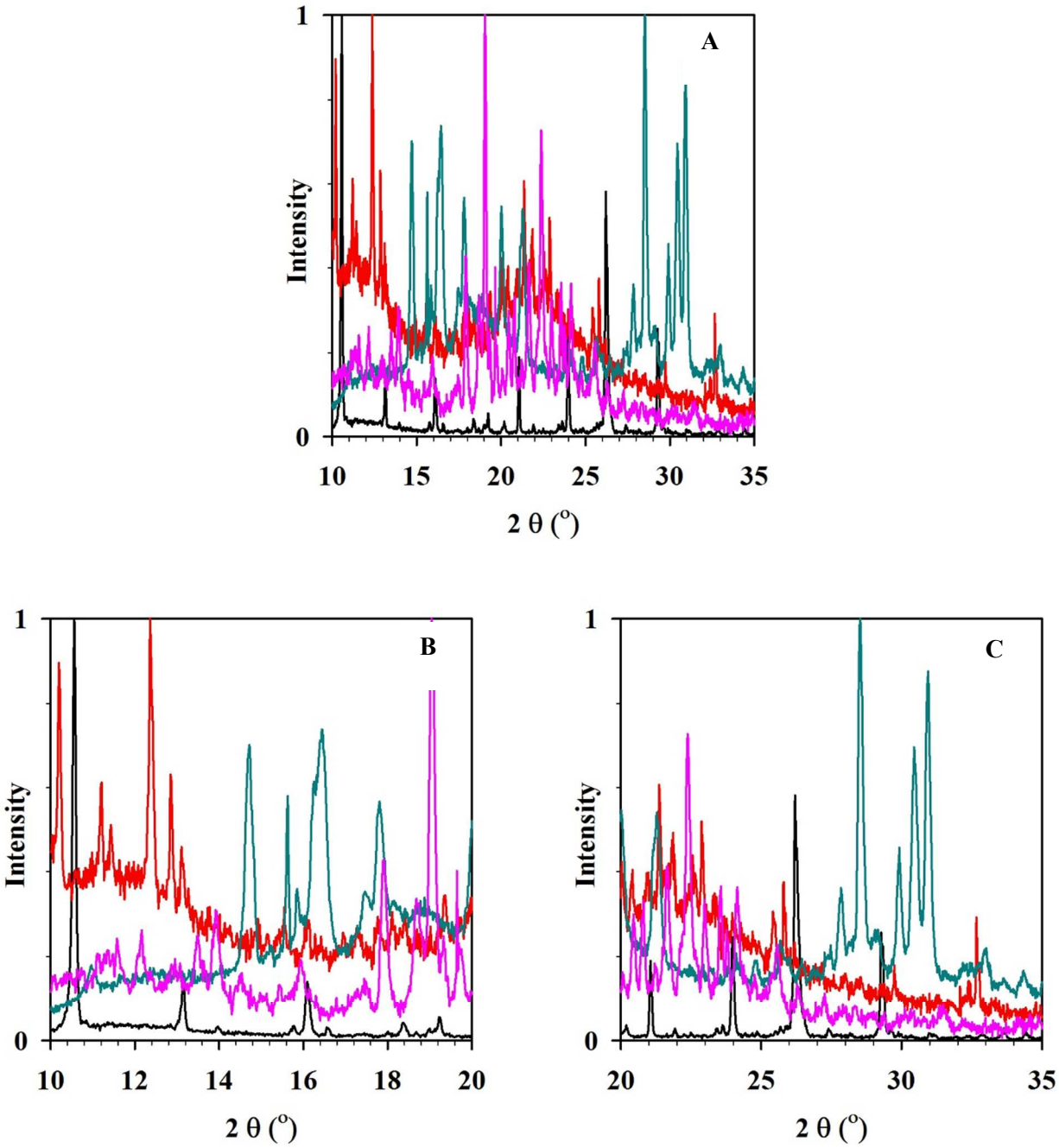

Figure S7. pXRD diffractograms (**A** - full spectrum, **B**, **C** - expanded regions) of acyclovir hydrate 3Acy·2H_2O black; [$P_{4,4,4,4}$][Acy] **2** – red; [$N_{4,4,4,4}$][Acy] **3** – dark cyan; and [$N_{1,1,1,16}$][Acy] **4** – pink.

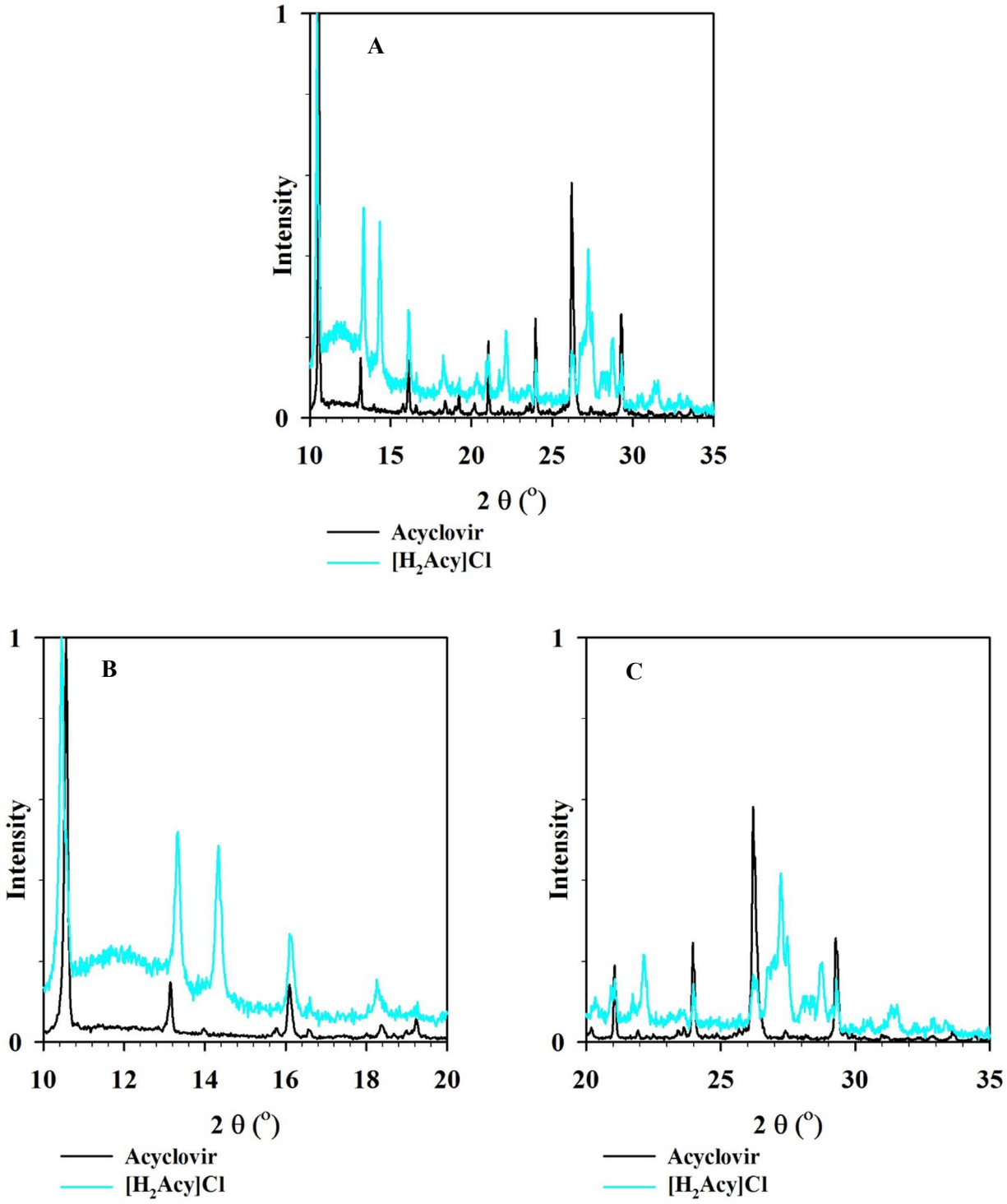

Figure S8. pXRD diffractograms (**A** - full spectrum, **B**, **C** - expanded regions) of acyclovir hydrate ($3Acy \cdot 2H_2O$)-black and $[H_2Acy]Cl$ **5** – cyan.

Thermal Gravimetric Analysis (TGA)

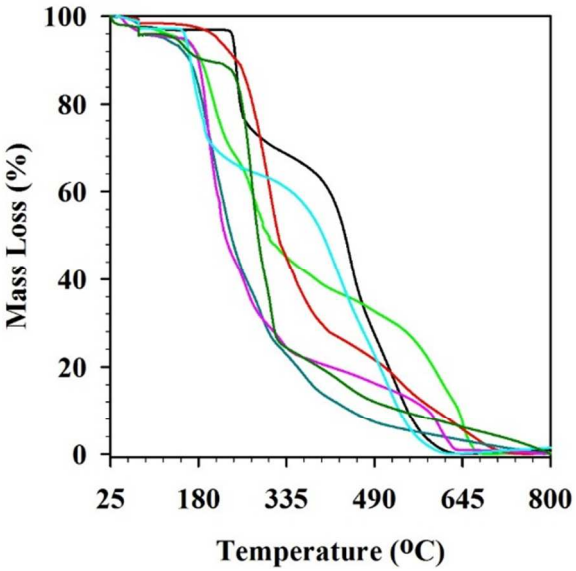

Figure S9. TGA profiles for acyclovir hydrate ($3Acy \cdot 2H_2O$) – black; [Cho][Acyclovir] **1** – green; $[P_{4,4,4,4}]$[Acy] **2 -** red; $[N_{4,4,4,4}]$[Acy] **3** – dark cyan; $[N_{1,1,1,16}]$[Acy] **4** – pink; $[H_2Acy]Cl$ **5** – cyan; and $[H_2Acy]$[Doc] **6** – dark green.

Differential Scanning Calorimetry (DSC)

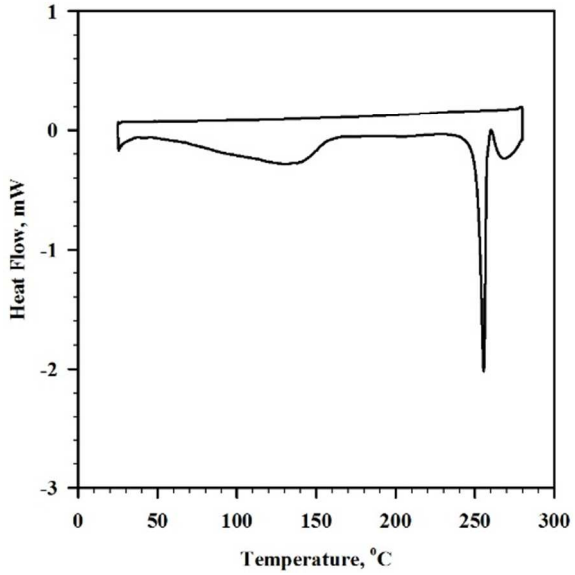

Figure S10. DSC profile for Acyclovir hydrate ($3Acy \cdot 2H_2O$), 1st decomposition cycle.

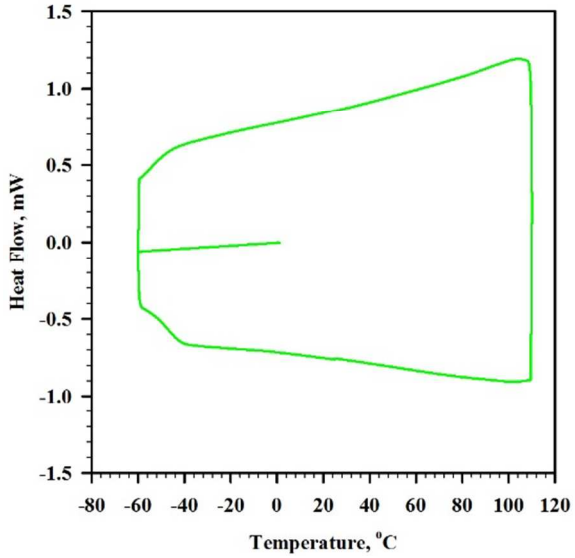

Figure S11. DSC profile for [Cho][Acy] **1**.

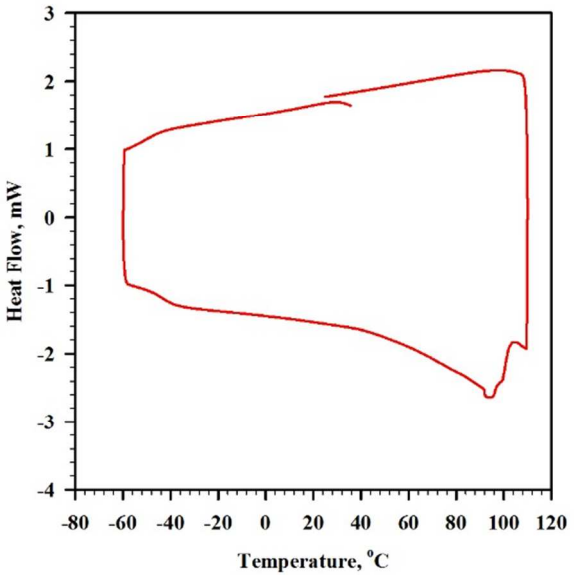

Figure S12. DSC profile for $[P_{4,4,4,4}][Acy]$ **2**, 1st cycle.

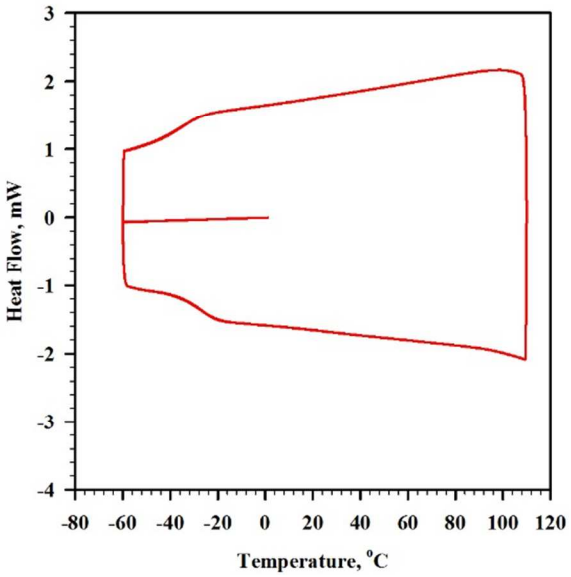

Figure S13. DSC profile for $[P_{4,4,4,4}][Acy]$ **2**, 2nd cycle.

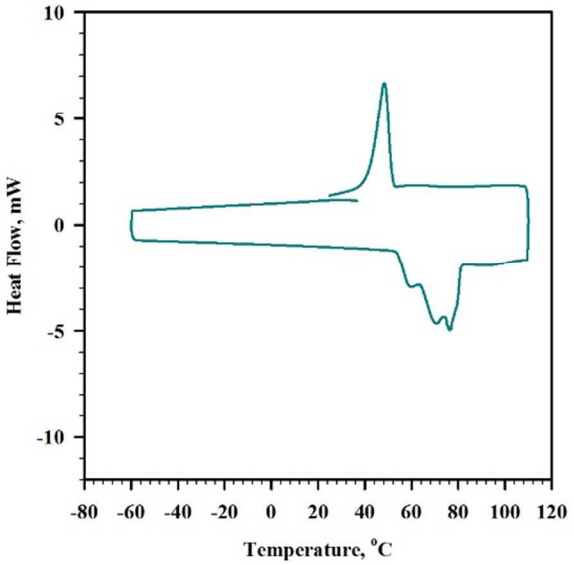

Figure S14. DSC profile for $[N_{4,4,4,4}][Acy]$ **3**, 1st cycle.

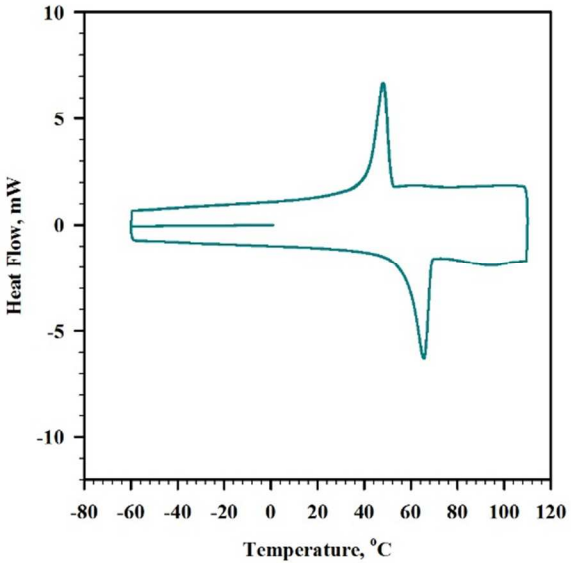

Figure S15. DSC profile for $[N_{4,4,4,4}][Acy]$ **3**, 2nd cycle.

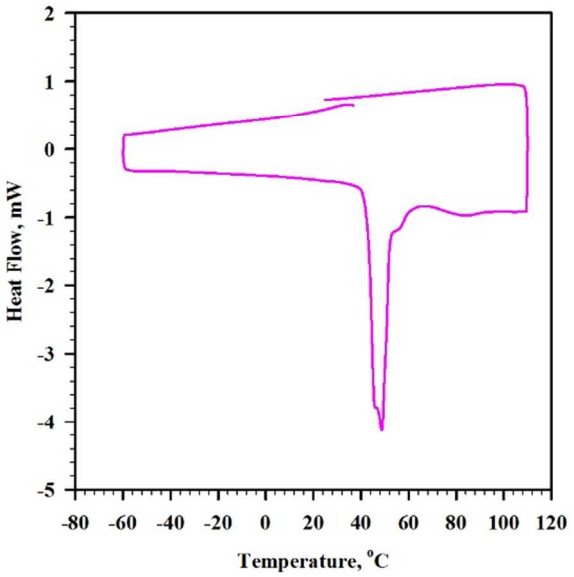

Figure S16. DSC profile for $[N_{1,1,1,16}][Acy]$ **4**, 1st cycle.

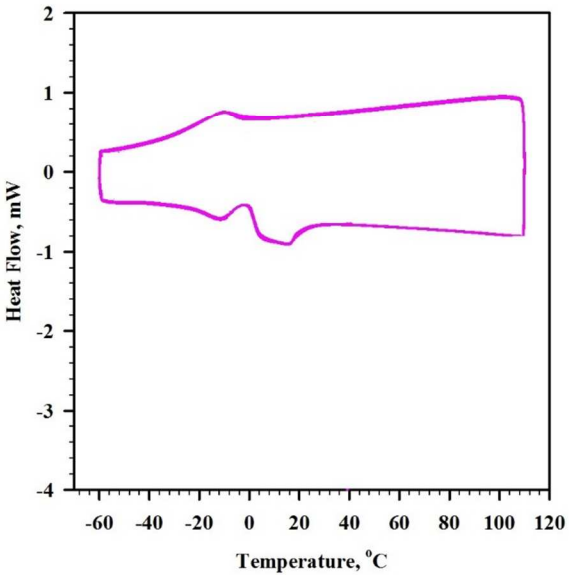

Figure S17. DSC profile for $[N_{1,1,1,16}][Acy]$ **4**, 2nd cycle.

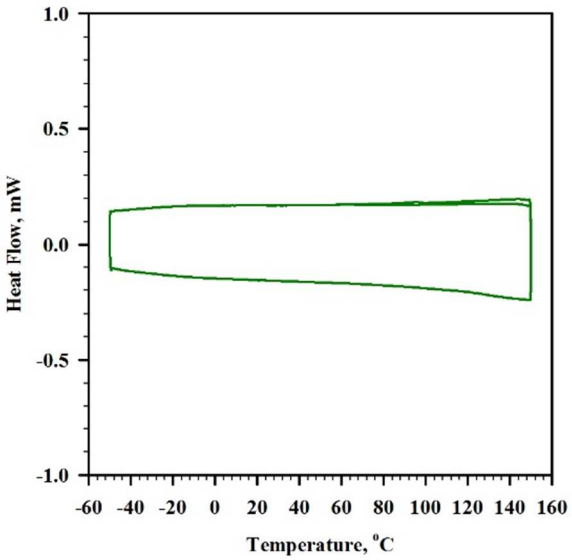

Figure S18. DSC profile for $[H_2Acy][Doc]$ **6**.

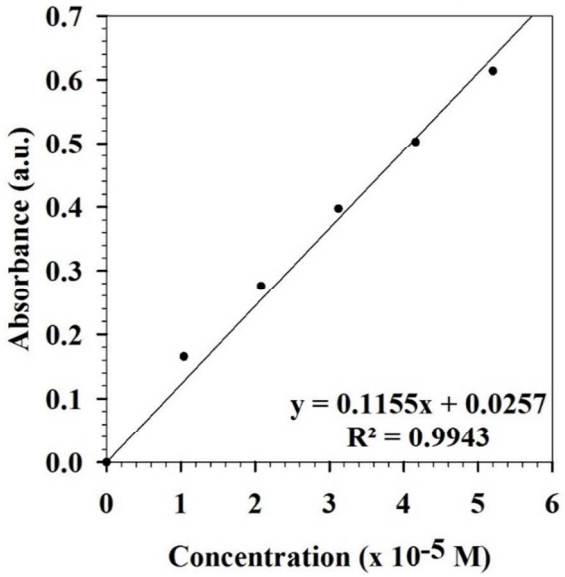

Figure S19. Calibration curve for acyclovir hydrate (3Acy·2H_2O) in water.

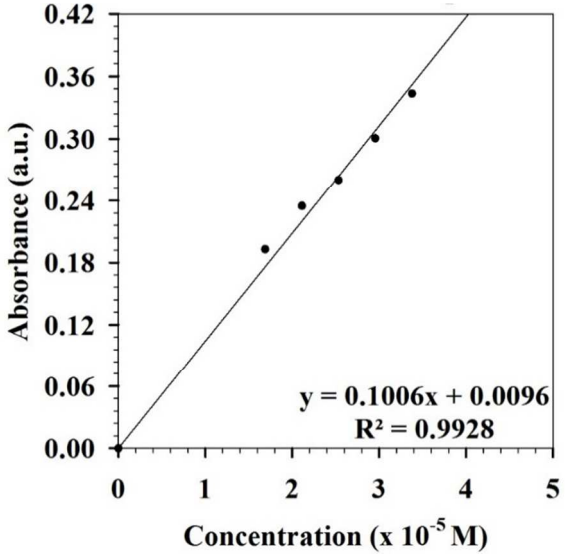

Figure S20. Calibration curve for [Cho][Acy] **1** in water.

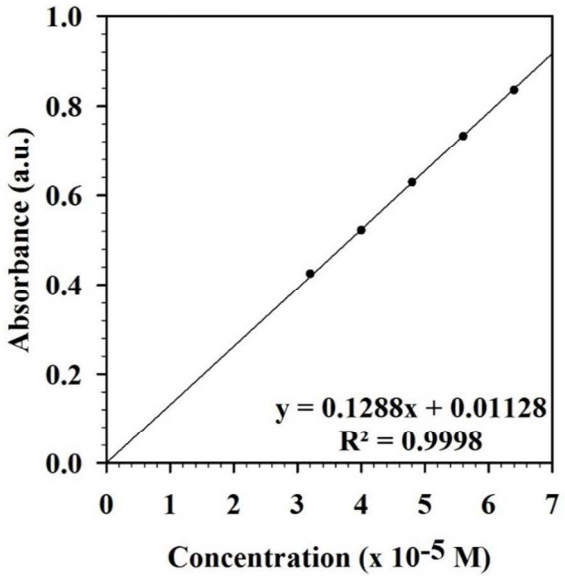

Figure S21. Calibration curve for $[P_{4,4,4,4}][Acy]$ **2** in water.

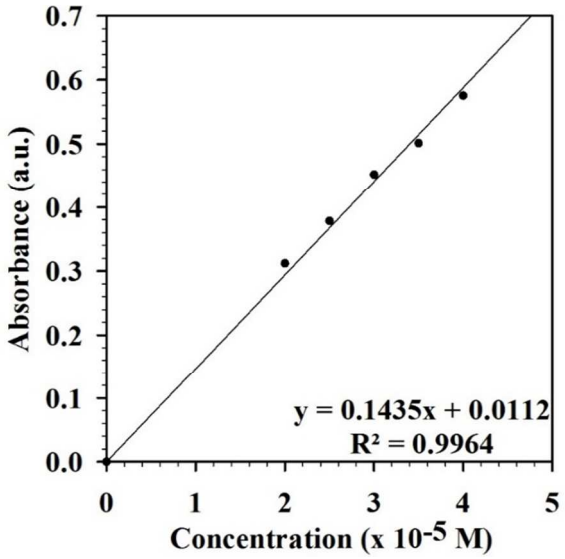

Figure S22. Calibration curve for $[N_{1,1,1,16}][Acy]$ **4** in water.

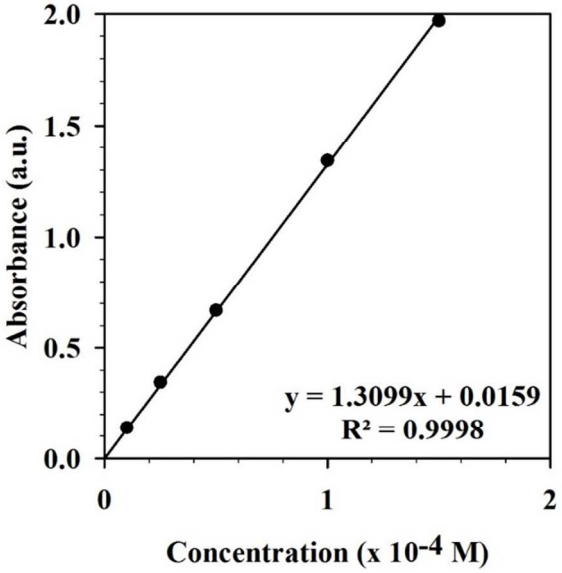

Figure S23. Calibration curve for $[H_2Acy]Cl$ **5** in water.

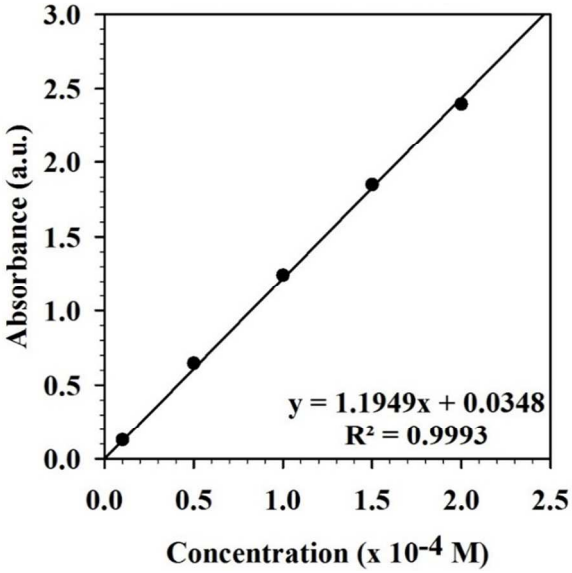

Figure S24. Calibration curve for $[H_2Acy][Doc]$ **6** in water.

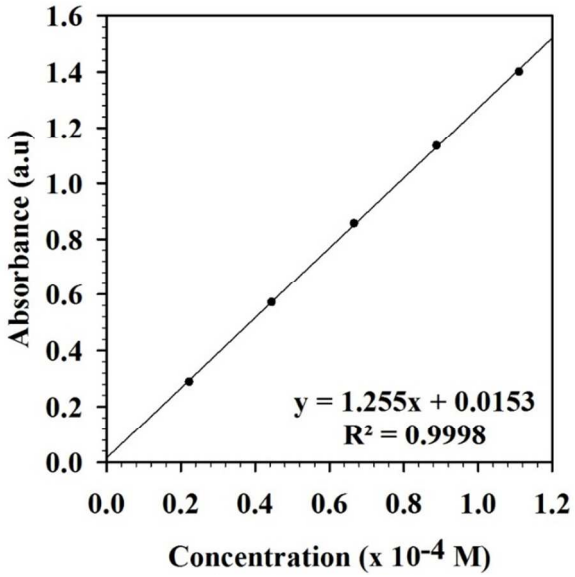

Figure S25. Calibration curve for Acyclovir in PBS buffer.

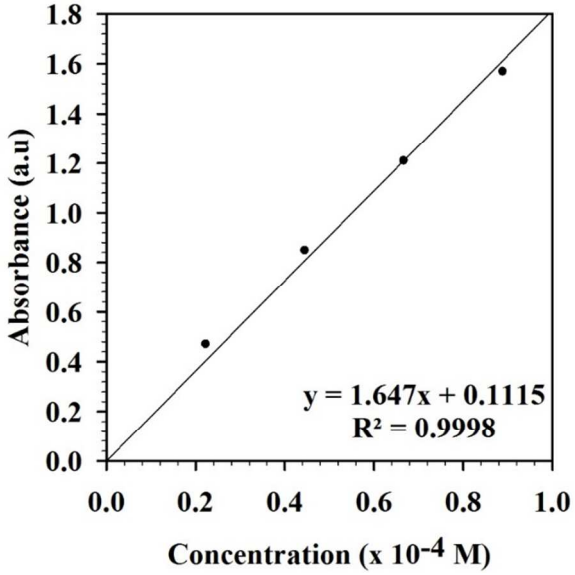

Figure S26. Calibration curve for Acyclovir in SIF buffer.

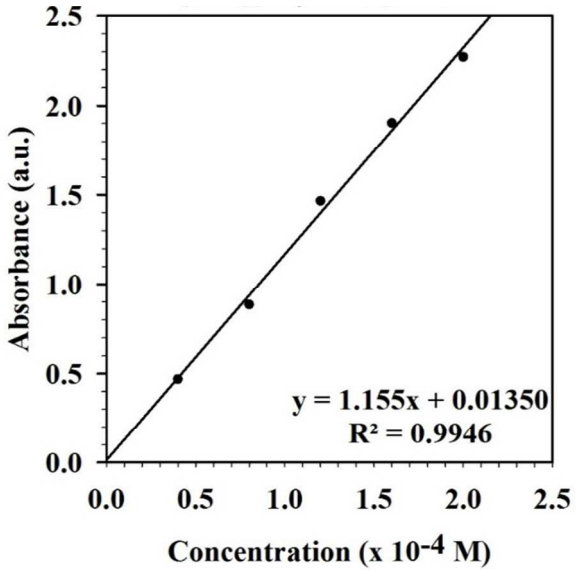

Figure S27. Calibration curve for [Cho][Acy] **1** in PBS buffer.

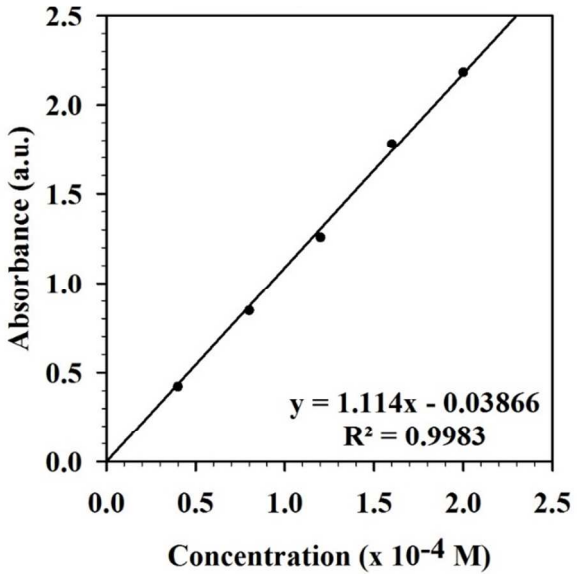

Figure S28. Calibration curve for [Cho][Acy] **1** in SGF buffer.

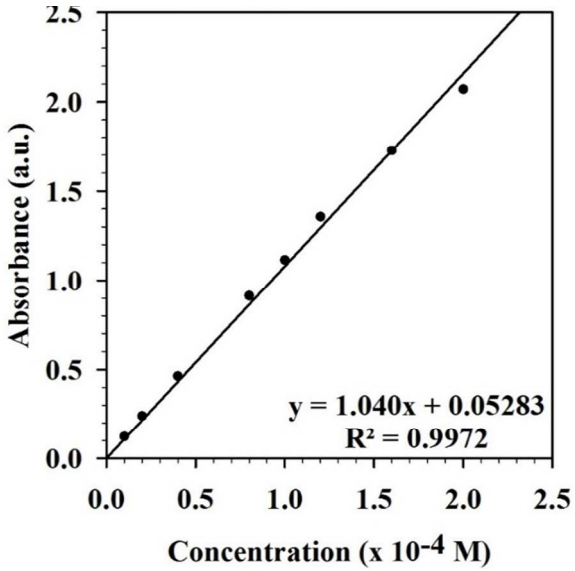

Figure S29. Calibration curve for [Cho][Acy] **1** in SIF buffer.

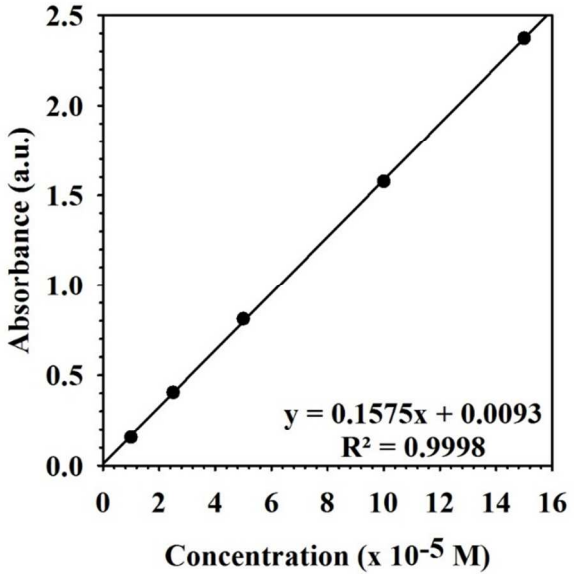

Figure S30. Calibration curve for [H_2Acy]Cl **5** in PBS buffer.

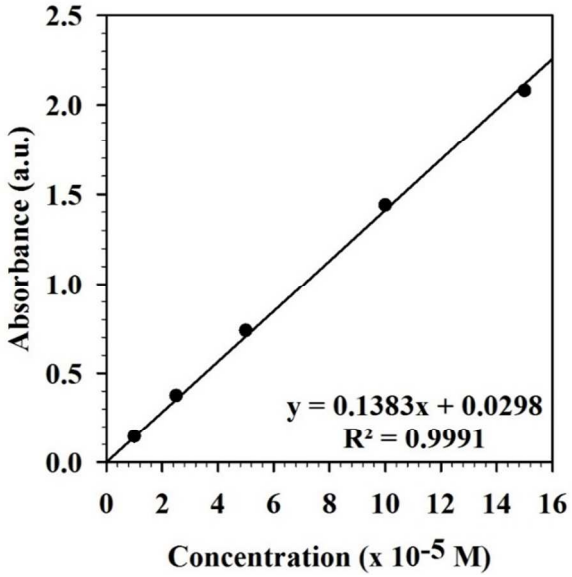

Figure S31. Calibration curve for $[H_2Acy]Cl$ **5** in SGF buffer.

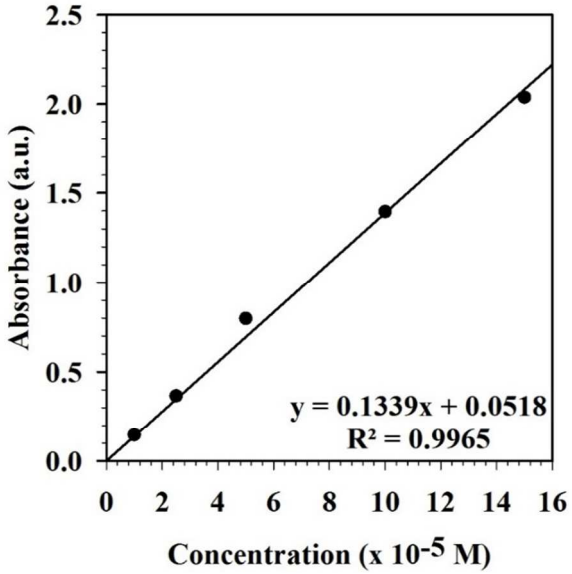

Figure S32. Calibration curve for $[H_2Acy]Cl$ **5** in SIF buffer.