Article

Cocrystals based on 4,4′-bipyridine: Influence of Crystal Packing on Melting Point

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List of Figures

List of tables

Elemental Analysis (EA), FTIR-ATR and ^{1}H NMR Spectroscopies

The phase purity of the bulk samples of the two cocrystals was confirmed by PXRD (Figure S1). The EA of cocrystals **1** and **2** agree with the proposed formula. In the FTIR-ATR spectra of **1** and **2**, the ν(O-H) bands were shifted to lower wavenumber values (2597-2165 (**1**) and 2583-2166 (**2**) cm^{-1}) respect to the free carboxylic acids, probably due to the formation of the strong acid-pyridine heterosynthon. The broad bands present in both spectra between 1980-1771 (**1**) and 2029-1787 (**2**) cm^{-1} are attributed to the acid-pyridine H-bond, supporting the presence of the heterosynthon [1,2]. Furthermore, the C=O stretching band at 1699 (**1**) and 1688 (**2**) cm^{-1} also remarks that the proton is bonded to the carboxylate moiety and consequently supports the cocrystal formation [2]. The specific assignation of other signals is provided in the Experimental Section and the Supporting Information (Figures S2-S3).

The ^{1}H NMR spectra of **1** and **2** have been recorded in dmso-d_6 solution. Both show two signals attributed to the aromatic protons from the 4,4′-bipy molecules between 8.73 and 7.82 ppm, while each cocrystal presents the signals of their corresponding carboxylic acids (**1**: HPip; **2**: HCinn). The molar relation between the carboxylic acids and the 4,4′-bipy ligand indicates the presence of binary multicomponent solids with different acid:4,4′-bipy (1:1 (**1**) and 2:1 (**2**)) molar ratios. Further ^{1}H NMR details are provided in the Experimental Section and the Supporting Information (Figures S4-S5).

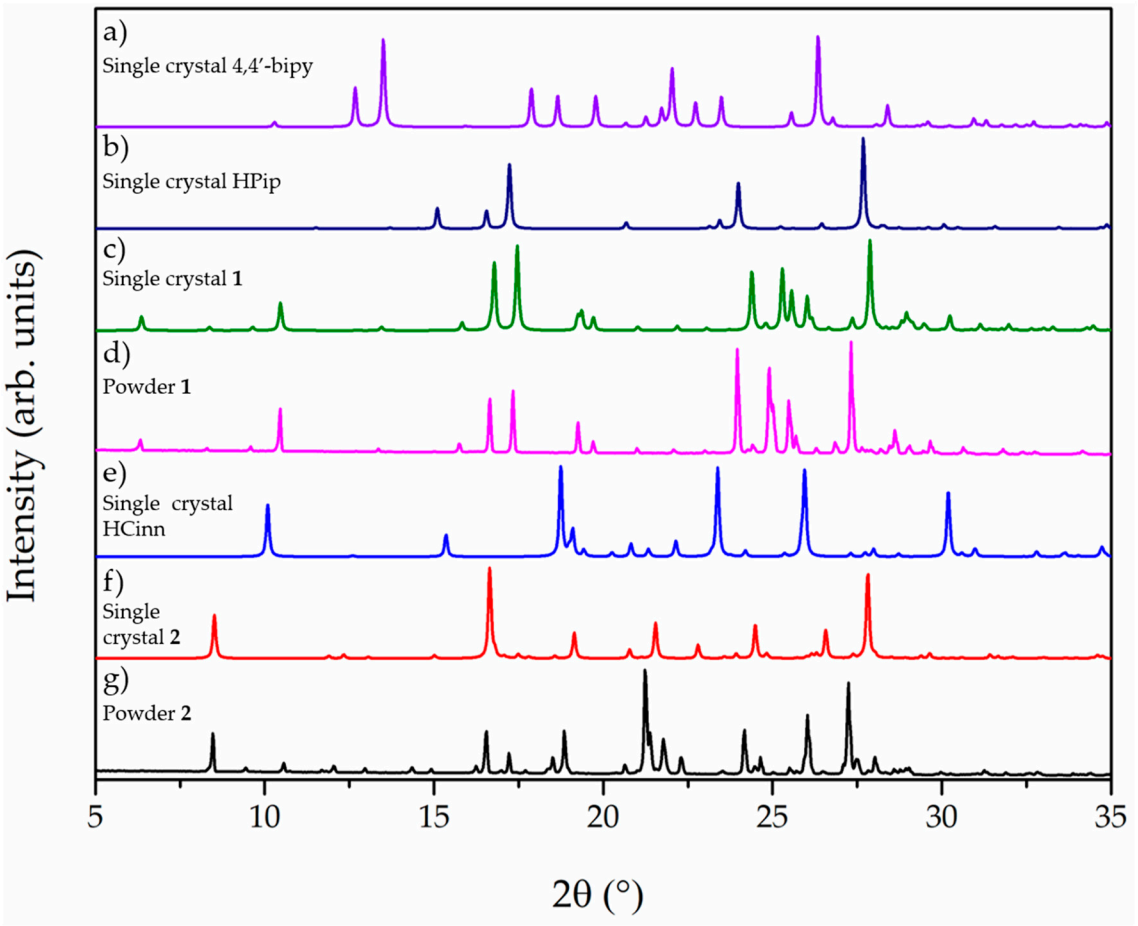

Figure S2. XRD patterns from single crystals collected data of (a) 4,4′-bipy at 200 K, (b) HPip at 298 K (c), cocrystal **1** at 100 K and (d) powder XRD pattern at 298 K of cocrystal **1**. XRD patterns from single crystals collected data at 100 K of (e) HCinn, (f) cocrystal **2** and (g) powder XRD pattern at 298 K of cocrystal **2**.

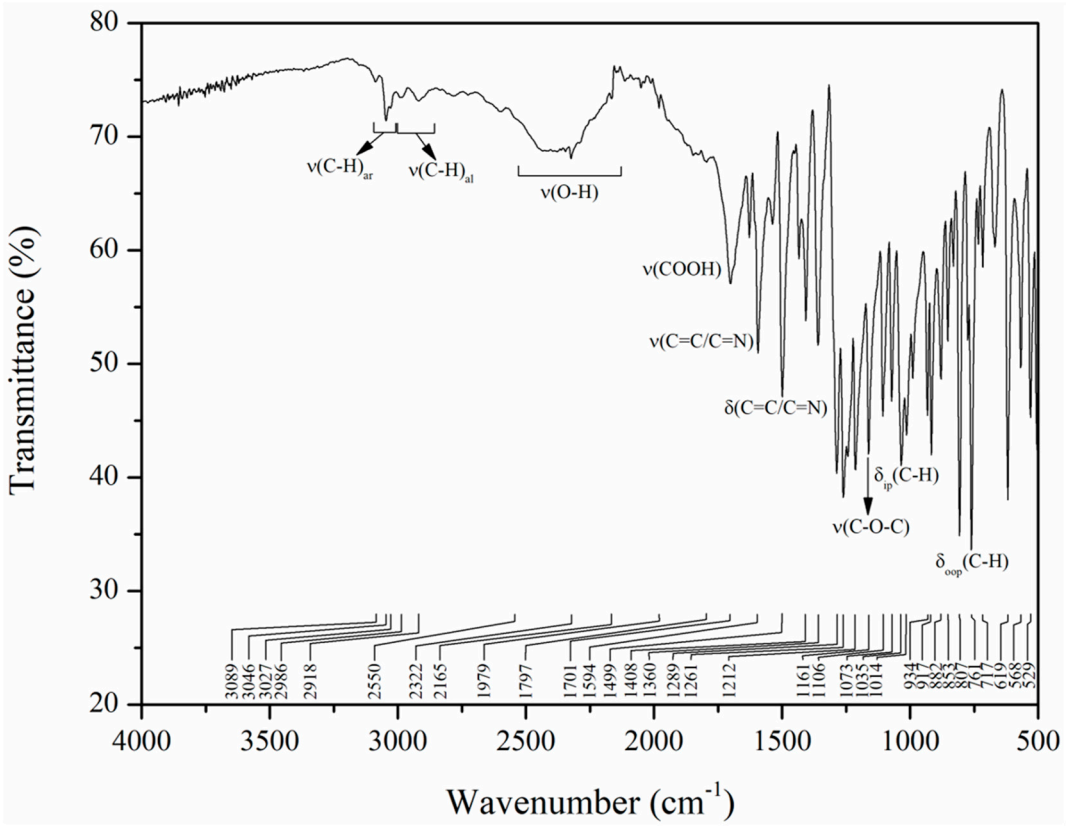

Figure 2. FTIR-ATR spectrum of cocrystal (HPip)(4,4′-bipy) (**1**).

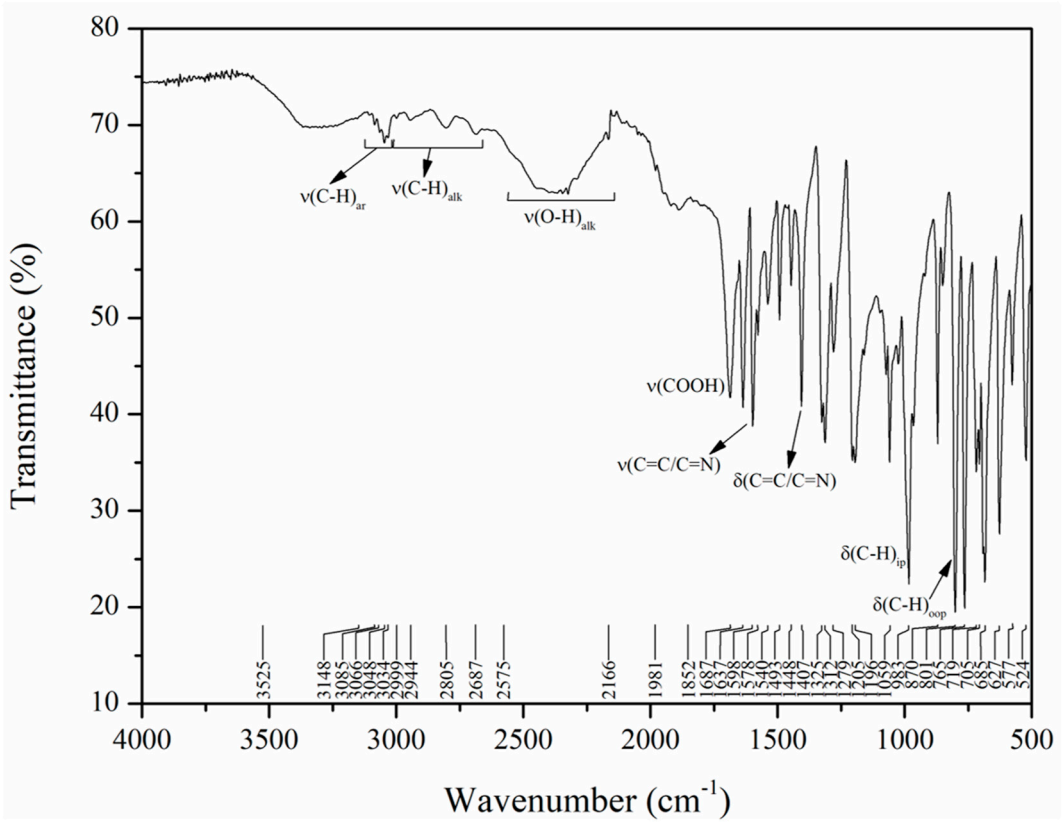

Figure S3. FTIR-ATR spectrum of cocrystal $(HCinn)_2$(4,4′-bipy) (**2**).

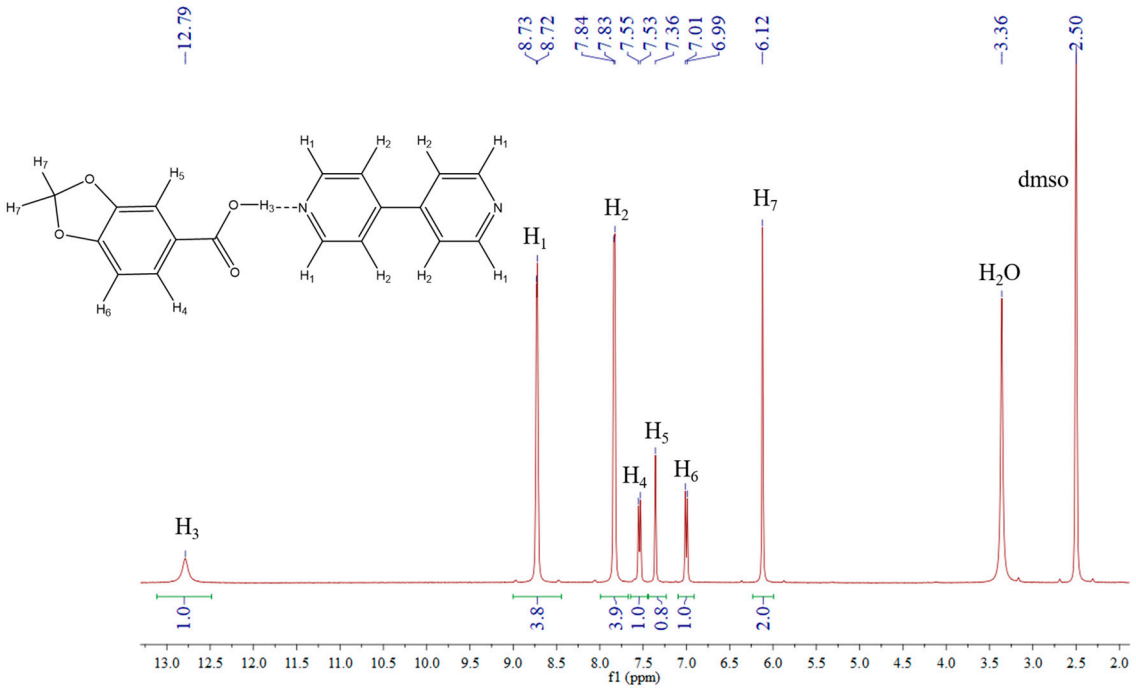

Figure S4. ^{1}H NMR spectrum of cocrystal (HPip)(4,4′-bipy) (**1**).

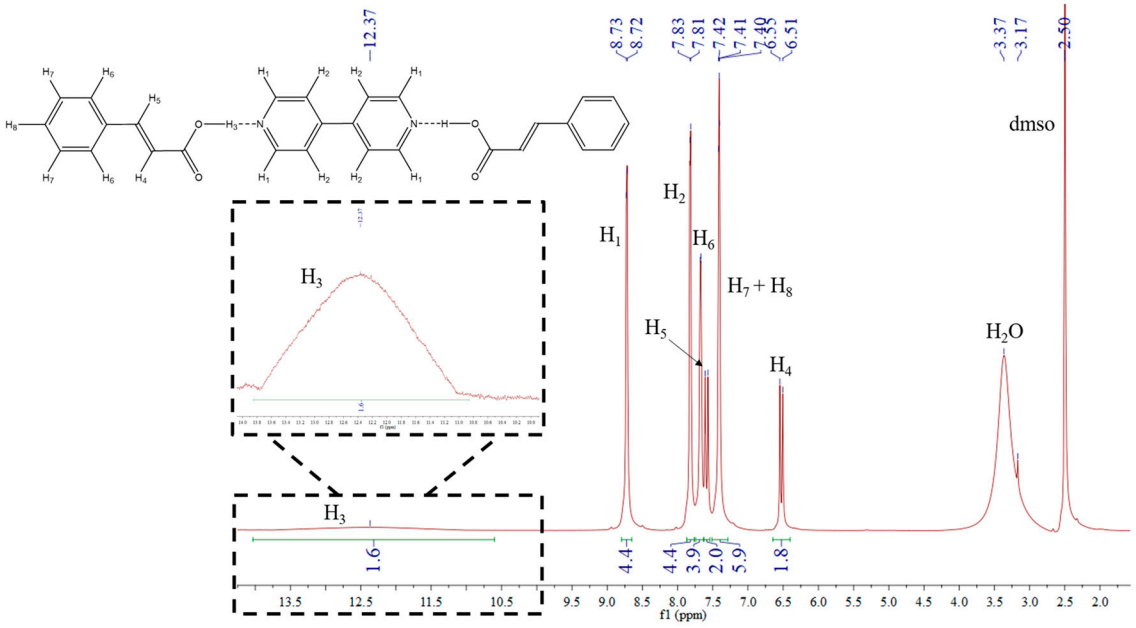

Figure S5. ^{1}H NMR spectrum of cocrystal (HCinn)$_2$(4,4′-bipy) (**2**).

References

1. Mukherjee, A.; Tothadi, S.; Chakraborty, S.; Ganguly, S.; Desiraju, G.R. Synthon identification in co-crystals and polymorphs with IR spectroscopy. Primary amides as a case study. *CrystEngComm* **2013**, *15*, 4640–4654, doi:10.1039/c3ce40286j.
2. Karagianni, A.; Malamatari, M.; Kachrimanis, K. Pharmaceutical cocrystals: New solid phase modification approaches for the formulation of APIs. *Pharmaceutics* **2018**, *10*, 1–30, doi:10.3390/pharmaceutics10010018.

Hirshfeld Surface Analysis

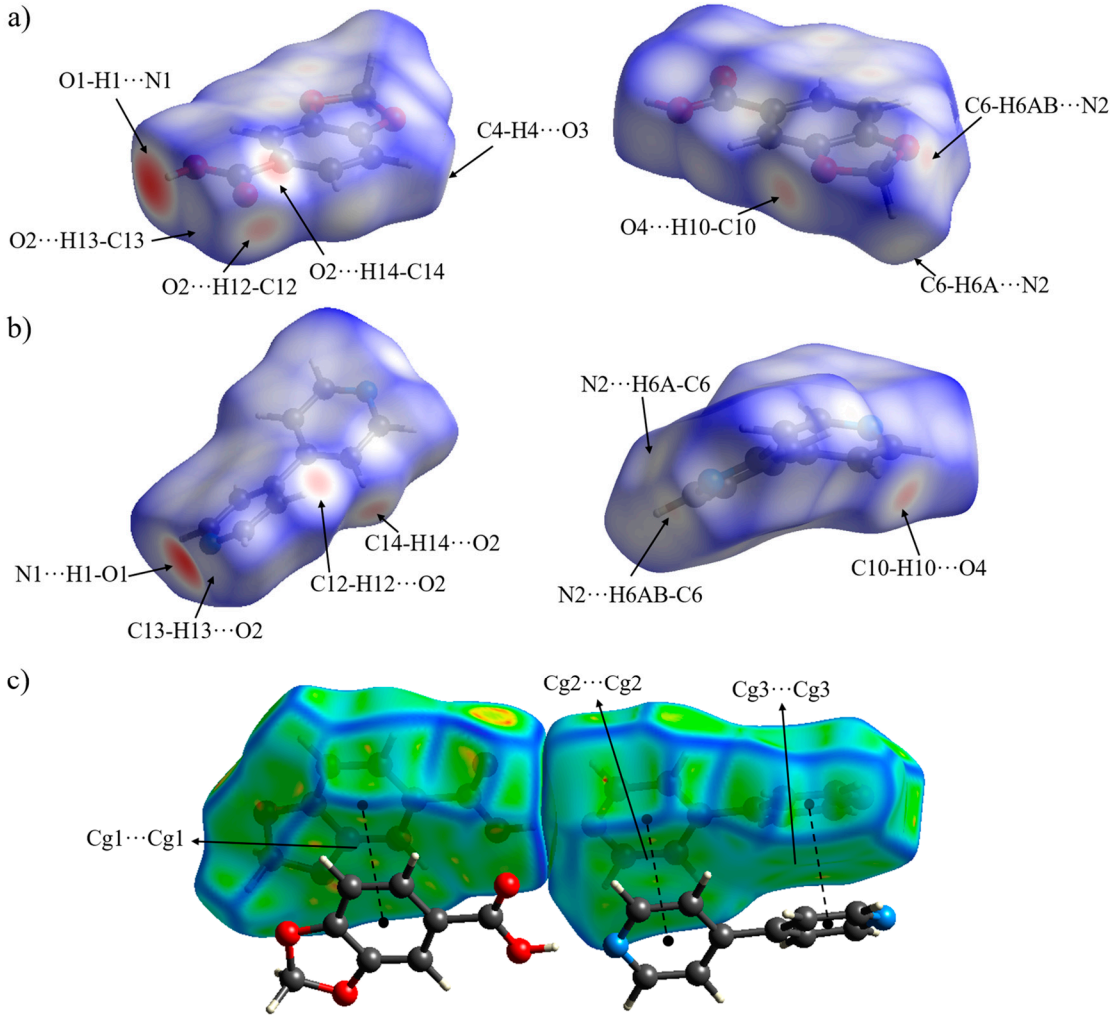

Figure S6. Hirshfeld surfaces mapped with d_{norm} of (**a**) HPip and (**b**) 4,4′-bipy molecules highlighting the intermolecular interactions present in the crystal packing of cocrystal **1**. (**c**) Curvedness representation of **1** showing the planar regions of both molecules which are attributed to the presence of π·· π interactions.

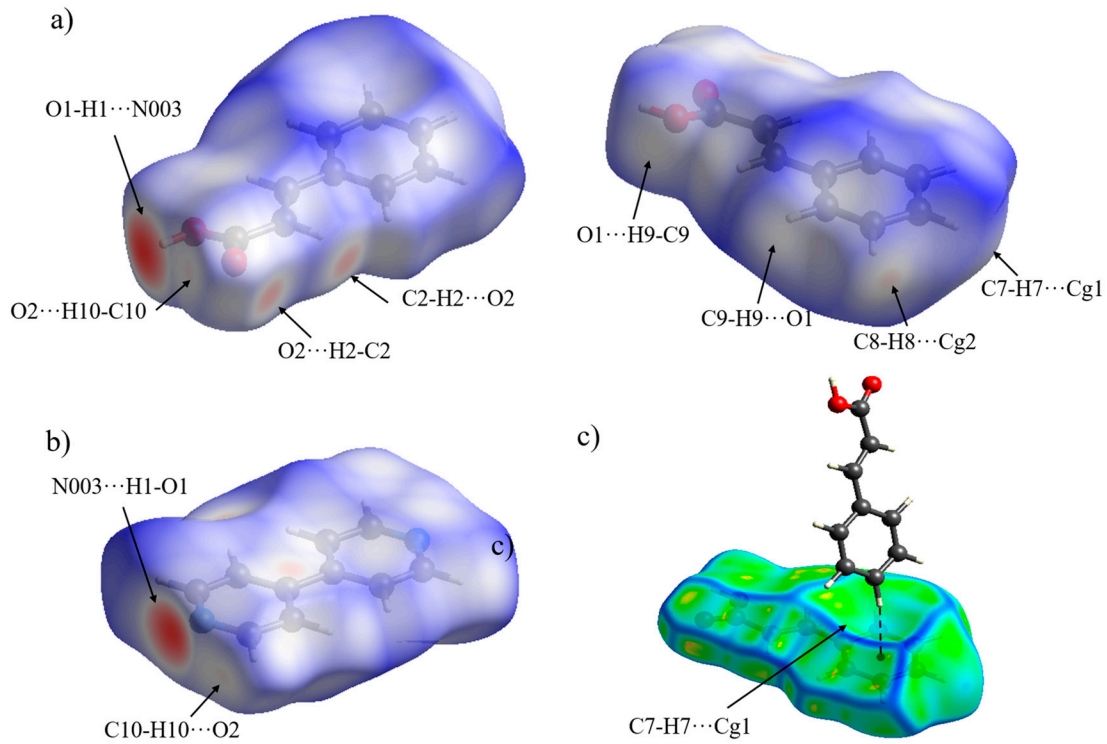

Figure S7. Hirshfeld surfaces mapped with d_{norm} of (**a**) HCinn and (**b**) 4,4′-bipy molecules highlighting the intermolecular interactions present in the crystal packing of cocrystal **2**. (**c**) Curvedness representation of **2** showing the planar region of HCinn attributable to a C-H···π interaction.

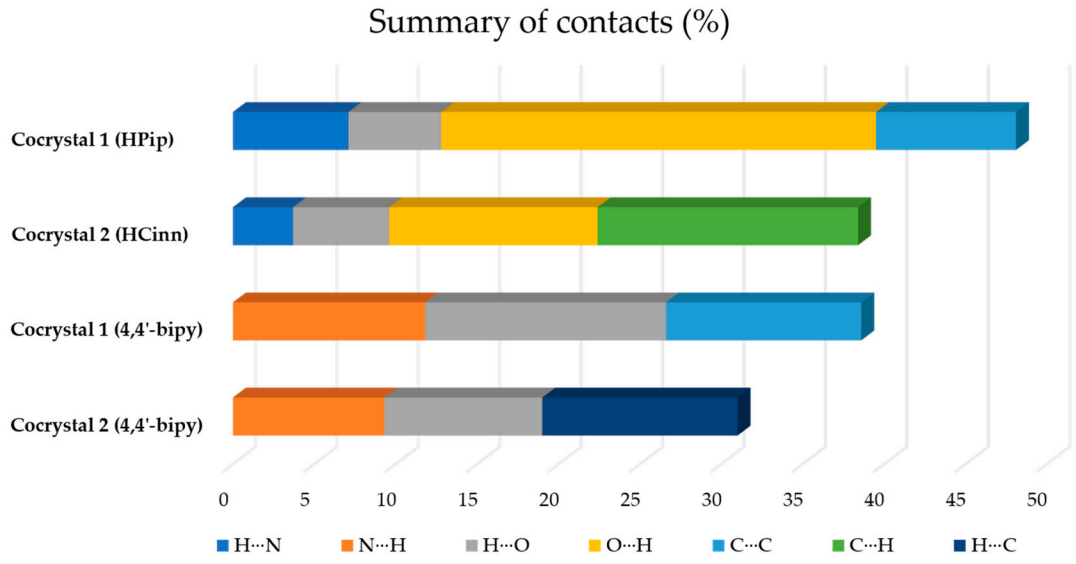

Figure S8. Percentage contribution to the Hirshfeld surface for the different molecules of cocrystals **1** and **2**.

Energy Frameworks

Table S4. Associated total energy values of the individual intermolecular interactions of cocrystal **1** and **2**. It should be noted that for some interactions, the energy value encompasses two interactions of the same type.

Interaction	Total energy (KJ/mol)	Number of interactions encompassed in each associated total energy value
Cocrystal **1**		
O1-H1···N003	−46.1 (Heterosynthon)	1
C13-H13···O2		
C4-H4···O3	−10.8	2
C6-H6AB···N2	−13.5	1
C12-H12···O2	−16.2	1
C14-H14···O2	−15.1	1
C10-H10···O4	−13.1	1
C6-H6A···N2	−8.8	1
Cg1···Cg1	−25.8	1
Cg2···Cg2	−23.4	1
Cg3···Cg3		
Cocrystal **2**		
O1-H1···N003	−48.9 (Heterosynthon)	1
C10-H10···O2		
C2-H2···O2	−26.1	2
C9-H9···O1	−11.8	1
C7-H7···Cg1	−10.8	1

Table 2. Contribution energies (electrostatic, E_{ele}; polarization, E_{pol}; dispersion, E_{dis}; repulsion, E_{rep}), total energies (E_{tot}) and lattice energies (E_{lat}) of the crystal structures of the starting materials and cocrystals **1** and **2**. All the values have been obtained using CrystalExplorer 17.5 from the corresponding .cif files.

Structure (CCDC)	Molecules	E_{ele} (KJ/mol)	E_{pol} (KJ/mol)	E_{dis} (KJ/mol)	E_{rep} (KJ/mol)	E_{tot} (KJ/mol)	E_{latt} (KJ/mol)
4.4′-bipy (131130)	4.4′-bipy$_1$	−82.8	−16.2	−178.2	87.8	−189.4	−93.8
	4.4′-bipy$_2$	−80.1	−16.3	−183.0	93.5	−185.9	
HPip (608427)	HPip$_1$	−189.6	−39.6	−176.8	163.7	−242.3	−121.2
HCinn (1547787)	HCinn$_1$	−187.1	−37.2	−179.2	172.3	−231.2	−115.6
1 (2058460)	HPip	−163.8	−27.2	−198.9	171.5	−218.2	−225.4
	4.4′-bipy	−164.2	−28.4	−201.8	161.9	−232.5	
2 (2058461)	HCinn	−156.2	−27.8	−172.1	145.3	−210.8	−333.7
	4.4′-bipy	−224.5	−41.6	−202.8	223.1	−245.8	

Table S5. Associated total energy values of the individual intermolecular interactions of the crystal structures of HPip, HCinn and 4,4′-bipy ligands. It should be noted that for some interactions, the energy value encompasses two interactions of the same type.

Interaction	Total energy (KJ/mol)	Number of interactions encompassed in each associated total energy value
HPip (CCDC 608427)		
O3-H3B···O4	−84.5	2
C3-H3A···O3	−6.3	1
C4-H4A···O4	−11.6	2
Cg1···Cg1	−35.6	1
Cg1 = C2 C3 C4 C5 C7 C8		
HCinn (CCDC 1547787)		
O1-H1···O2	−79.7	2
C5-H5···O2	−20.7	1
C6-H6···O1	−3.6	1
C7-H7···Cg1	−9.5	1
Cg1 = C4 C5 C6 C7 C8 C9		
4,4′-bipy (CCDC 131130)		
C12-H12···N21	−18.1	1
C16-H16A···N21		1
C12-H12A···N21A	−20.1	1
C16-H16···N21A		1
C22-H22···N11	−17.2	1
C22A-H22A···N11A		1
C26-H26···N11A	−17.2	1
C26A-H26A···N11		1
Cg1···Cg1	−18.0	1
Cg2···Cg2	−16.7	1
Cg1 = N11 C11 C12 C13 C15 C16; Cg2 = N21A C21A C22A C25A C26A		

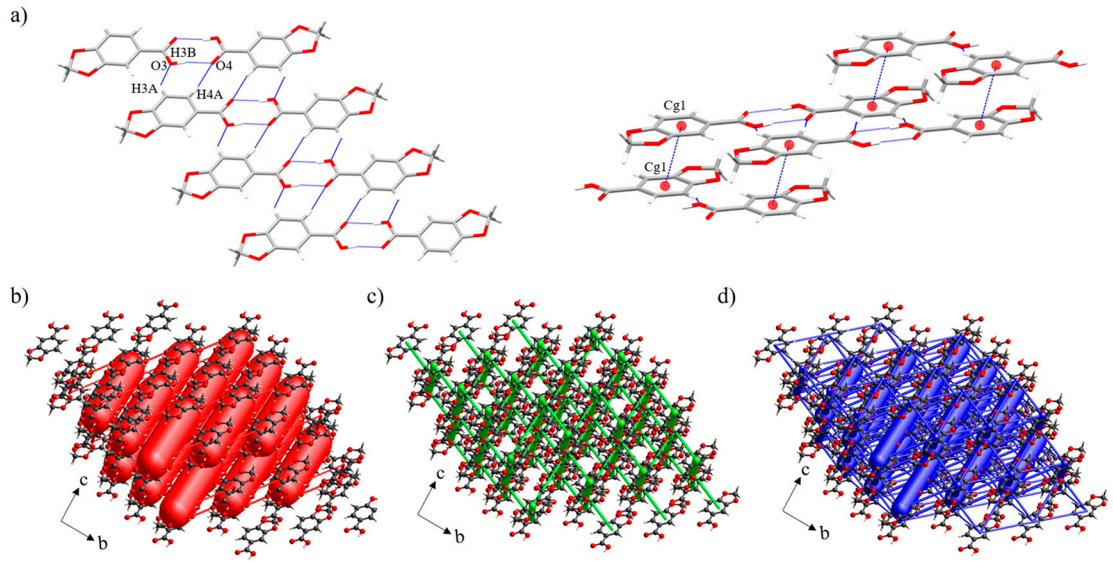

Figure S9. (**a**) Intermolecular interactions which assemble the HPip crystal structure. Energy frameworks representing (**b**) E_{ele} (**c**) E_{dis} and (**d**) E_{tot} contribution energies for HPip crystal structure. All the frameworks use the same energy cylinder scale factor of 150 and an energy cut-off of 6.00 KJ/mol within a 3×3×3 unit cell. Cg1 = C2 C3 C4 C5 C7 C8.

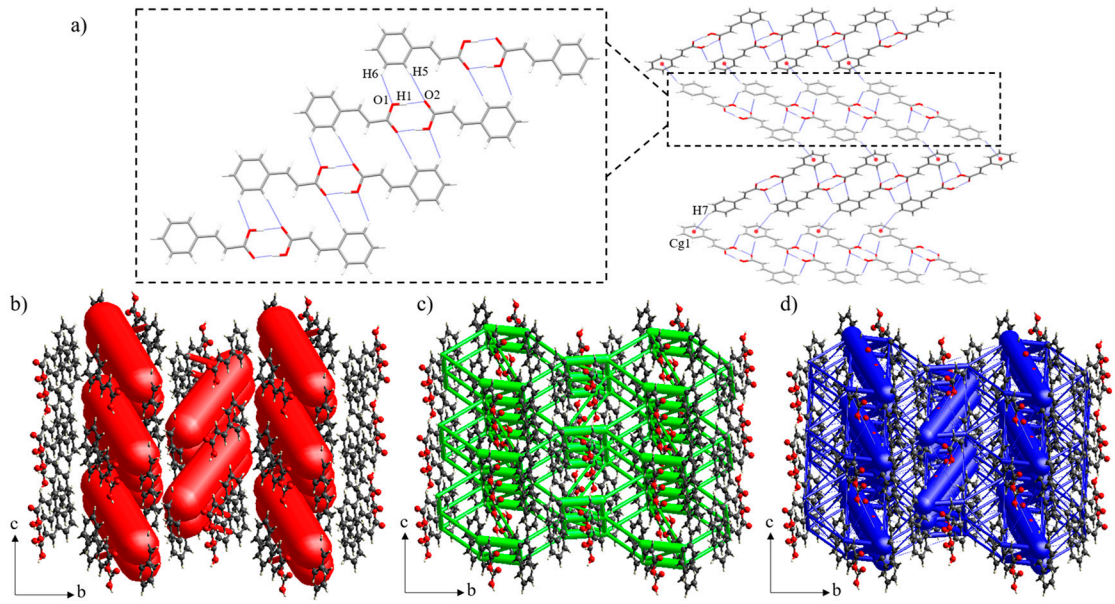

Figure S10. (**a**) Intermolecular interactions which assemble the HCinn crystal structure. Energy frameworks representing (**b**) E_{ele} (**c**) E_{dis} and (**d**) E_{tot} contribution energies for HCinn crystal structure. All the frameworks use the same energy cylinder scale factor of 150 and an energy cut-off of 6.00 KJ/mol within a 2×2×2 unit cell. Cg1 = C4 C5 C6 C7 C8 C9.

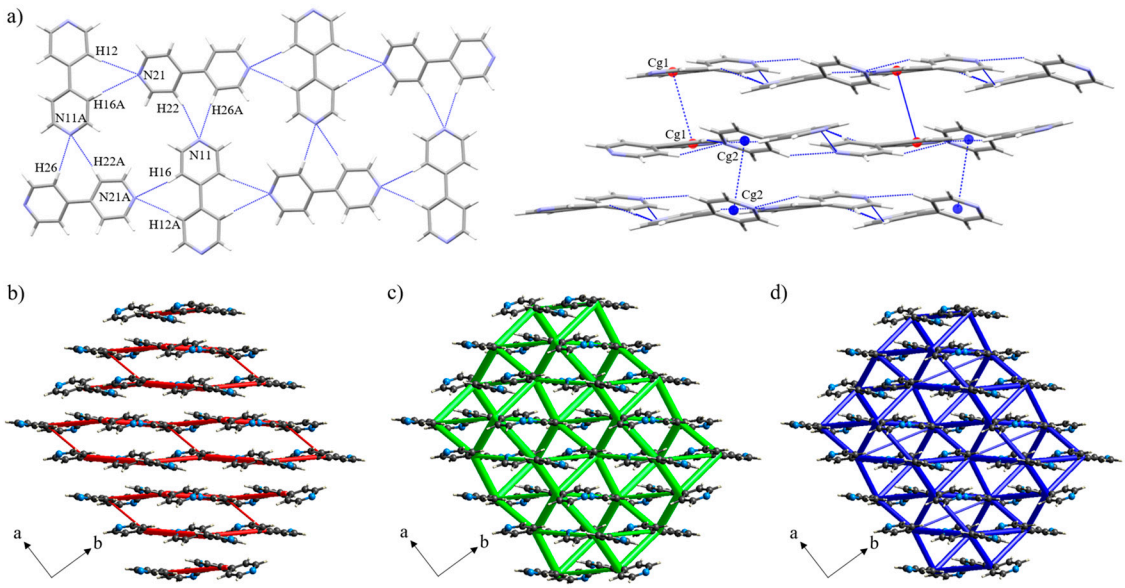

Figure S11. (**a**) Intermolecular interactions which assemble the 4,4′-bipy crystal structure. Energy frameworks representing (**b**) E_{ele} (**c**) E_{dis} and (**d**) E_{tot} contribution energies for 4,4′-bipy crystal structure. All the frameworks use the same energy cylinder scale factor of 150 and an energy cut-off of 6.00 KJ/mol within a 2×2×2 unit cell. Cg1 = N11 C11 C12 C13 C15 C16; Cg2 = N21A C21A C22A C25A C26A