Supporting Information

for

Co-crystallization of anti-inflammatory pharmaceutical contaminants and rare carboxylic acid-pyridine supramolecular synthon breakdown

Qixuan Zheng, Samantha L. Rood, Daniel K. Unruh, and Kristin M. Hutchins*

Department of Chemistry & Biochemistry, Texas Tech University, 1204 Boston Avenue, Lubbock, Texas 79409, United States.

*Email. kristin.hutchins@ttu.edu

1. Materials and synthesis of the co-crystals

Materials

Mefenamic acid (**1**) and naproxen (**2**) were purchased from Alfa Aesar (Ward Hill, MA, USA). 1,2-Bis(4-pyridyl)ethylene (**a**) and 4,4'-azopyridine (**b**) were purchased from Sigma-Aldrich Chemical (St. Louis, MO, USA). 1,2-Bis(4-pyridyl)ethane (**c**) was purchased from Acros Organics (New Jersey, USA). 1,3-Bis(4-pyridyl)propane (**d**) was purchased from Tokyo Chemical Industry (Kita-ku, Tokyo, Japan). Lastly, toluene and acetone were purchased from Fisher Scientific (Lenexa, KS, USA). All chemicals and solvents were used as received.

Co-crystallizations.

Co-crystals of **1b** were synthesized by dissolving **1** (30mg, 0.1303 mmol) and **b** (23.99 mg, 0.1302 mmol) in toluene. The solution was allowed to evaporate slowly over a period of two days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **1c** were synthesized by dissolving **1** (30mg, 0.1303 mmol) and **c** (23.99mg, 0.1302 mmol) in toluene. The solution was allowed to evaporate slowly over a period of two days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **1d** were synthesized by dissolving **1** (30mg, 0.1303 mmol) and **d** (25.83mg, 0.1303 mmol) in toluene. The solution was allowed to evaporate slowly over a period of two days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **2a** were synthesized by dissolving **2** (40mg, 0.164mmol) and **a** (15 mg, 0.081mmol) in toluene. Slow evaporation of the solution was allowed for a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **2b** were synthesized by dissolving **2** (20mg, 0.083 mmol) and **b** (7.6 mg, 0.041 mmol) in toluene. Slow evaporation of the solution was allowed for a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **2c** were synthesized by dissolving **2** (40mg, 0.164 mmol) and **c** (15.1 mg, 0.082mmol) in toluene. Slow evaporation of the solution was allowed for a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **2d** were synthesized by dissolving **2** (20mg, 0.082 mmol) and **d** (8.2 mg, 0.041 mmol) in acetone. Slow evaporation of the solution was allowed for a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

2. X-ray diffraction information and data tables

X-ray data were collected on a Bruker PLATFORM three circle diffractometer equipped with an APEX II CCD detector and operated at 1350 W (45kV, 30 mA) to generate (graphite monochromated) Mo Kα radiation (λ = 0.71073 Å). Crystal sample and oil were mounted on a MiTiGen cryoloop and kept under a cold nitrogen stream at 100K for throughout the experiment. Intensity data were corrected for Lorentz, polarization, and background effects using the Bruker program APEX 3. A semi-empirical correction for adsorption was applied using the program SADABS[1]. The SHELXL-2014[2], series of programs was used for the solution and refinement of the crystal structure. Hydrogen atoms bound to carbon, nitrogen, and oxygen atoms were located in the difference Fourier map and were geometrically constrained using the appropriate AFIX commands.

Table S1. X-ray data for co-crystals **1b**, **1c**, and **1d**.

compound name	**1b**	**1c**	**1d**
chemical formula	$C_{38}H_{36}N_4O_6$	$C_{40}H_{40}N_2O_6$	$C_{41}H_{42}N_2O_6$
formula mass	644.71	535.42	658.76
crystal system	Monoclinic	Monoclinic	Monoclinic
space group	*P2*$_1$	*C2*	*C2*
a/Å	15.483	38.014	35.567
b/Å	5.745	5.787	5.7333
c/Å	19.668	15.566	33.199
α/°	90	90	90
β/°	110.025	93.646	91.732
γ/°	90	90	90
V/Å^3	1643.5	3418	6767
P_{calc}/g cm^{-3}	1.303	1.253	1.293
T/K	100	100	100
Z	2	4	8
radiation type	Mo Kα	Mo Kα	Mo Kα
absorption coefficient, μ/mm^{-1}	0.089	0.084	0.087
no. of reflections measured	19374	17520	40017
no. of independent reflections	7221	6219	14930
no. of reflection (I>2σ(I))	6035	4854	11453
R_{int}	0.0291	0.0359	0.0383
R_1 ((I>2σ(I))	0.0381	0.0404	0.0447
wR(F^2) (I>2σ(I))	0.0866	0.0865	0.0947
R_1 (all data)	0.0500	0.0583	0.0660
wR(F^2) (all data)	0.0921	0.0949	0.1038
Goodness-of-fit	1.048	1.017	1.039
CCDC deposition number	1864926	1864925	1864927

compound name	**2a**	**2b**	**2c**	**2d**
chemical formula	$C_{21}H_{20}N_2O_2$	$C_{20}H_{19}N_3O_2$	$C_{21}H_{21}N_2O_2$	$C_{28}H_{29}N_3O_2$
formula mass	332.39	333.38	333.40	439.54
crystal system	Triclinic	Triclinic	Triclinic	Monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a/Å	7.8199(14)	7.549(5)	7.450(7)	7.503(3)
b/Å	8.6152(15)	8.736(6)	7.835(7)	7.836(3)
c/Å	12.900(2)	13.095(8)	16.895(16)	20.382(7)
α/°	98.216(2)	100.617(10)	94.30(3)	88.77(9)
β/°	99.515(2)	99.729(9)	93.160(17)	85.38(5)
γ/°	90.024(2)	93.918(9)	117.89(2)	79.99(5)
V/Å^3	848.0(3)	832.2(9)	864.5(14)	1176.1(8)
P_{calc}/g cm^{-3}	1.302	1.330	1.281	1.241
T/K	100	100	100	100
Z	2	2	2	2
radiation type	MoKα	MoKα	MoKα	MoKα
absorption coefficient, μ/mm^{-1}	0.084	0.088	0.283	0.079
no. of reflections measured	9598	9970	15696	4245
no. of independent reflections	3684	3720	3912	4245
no. of reflection (I>2σ(I))	2901	2666	2909	2845
R_{int}	0.0218	0.0320	0.0250	0.0417
R_1 ((I>2σ(I))	0.0421	0.0415	0.0423	0.0523
wR(F^2) (I>2σ(I))	0.1078	0.0958	0.1035	0.1188
R_1 (all data)	0.0561	0.0641	0.0601	0.0929
wR(F^2) (all data)	0.1162	0.1078	0.1143	0.1398
Goodness-of-fit	1.064	1.036	1.052	0.014
CCDC deposition number	1864913	1864915	1864914	1864916

Table S2. X-ray data for co-crystals **2a**, **2b**, **2c**, and **2d**.

3. Single-crystal X-ray structures

For thermal ellipsoid structures, carbon, hydrogen, oxygen, nitrogen, and chlorine atoms are represented by gray, white, red, light blue and light green ellipsoids, respectively.

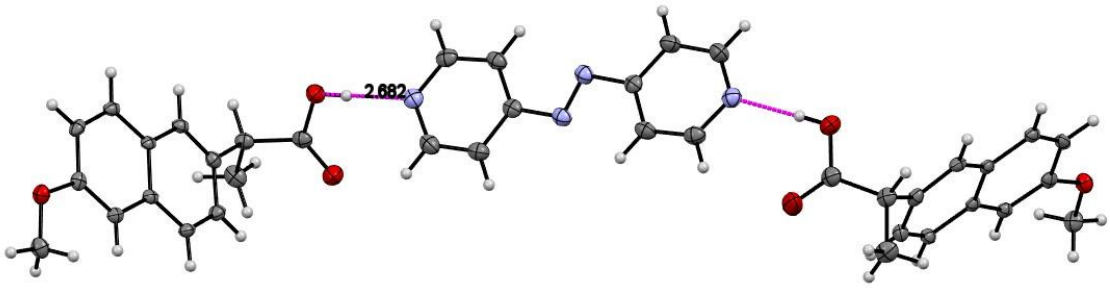

Figure S1. Three-component hydrogen-bonded assembly of co-crystal **1b** with thermal ellipsoids plotted at 50% probability.

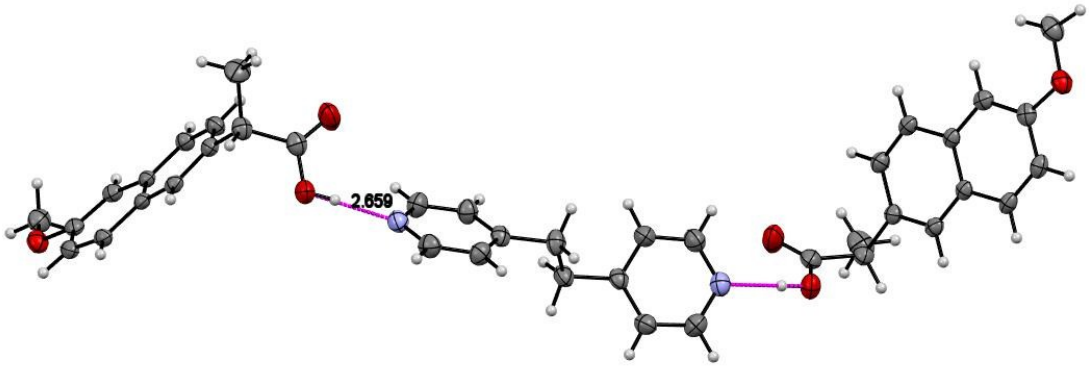

Figure S2. Three-component hydrogen-bonded assembly of co-crystal **1c** with thermal ellipsoids plotted at 50% probability.

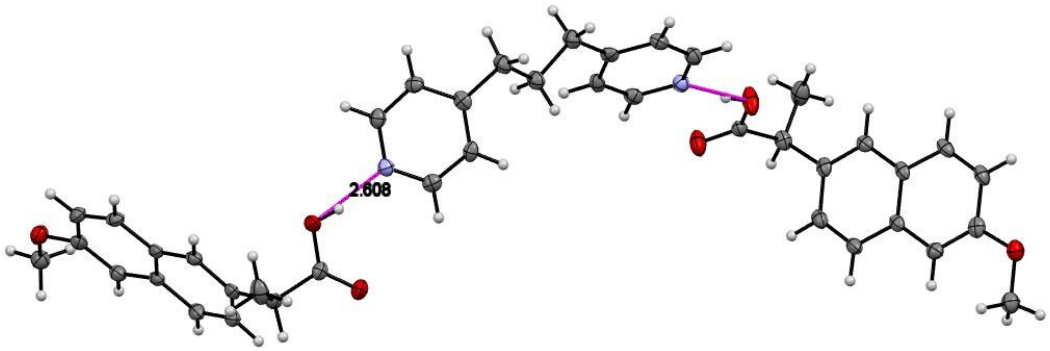

Figure S3. Three-component hydrogen-bonded assembly of co-crystal **1d** with thermal ellipsoids plotted at 50% probability.

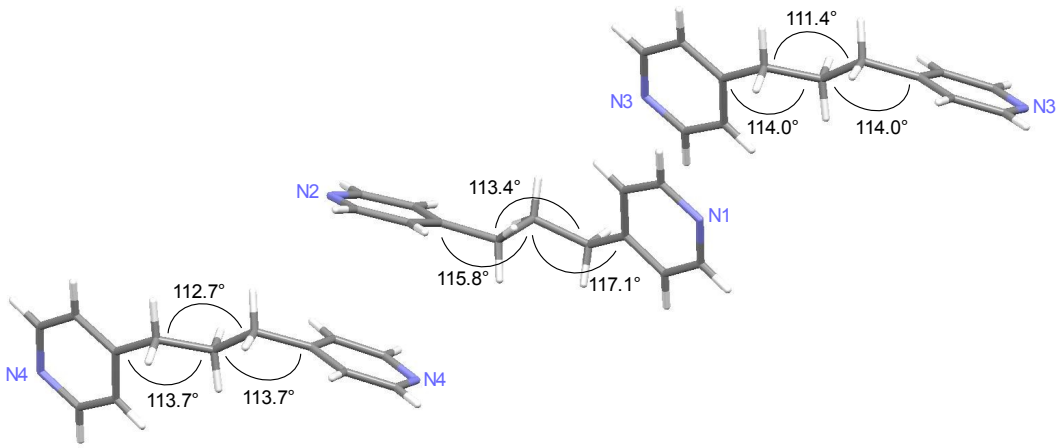

Figure S4. Molecules of **d** in co-crystal **1d** showing bond angles between propane chain and pyridine. Bipyridine containing N1/N2 is unsymmetrical, while the N3 and N4 molecules are symmetrical.

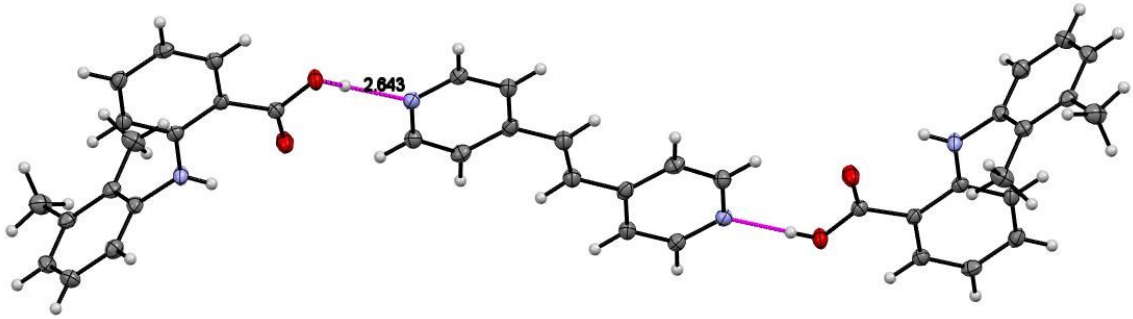

Figure S5. Three-component hydrogen-bonded assembly of co-crystal **2a** with thermal ellipsoids plotted at 50% probability.

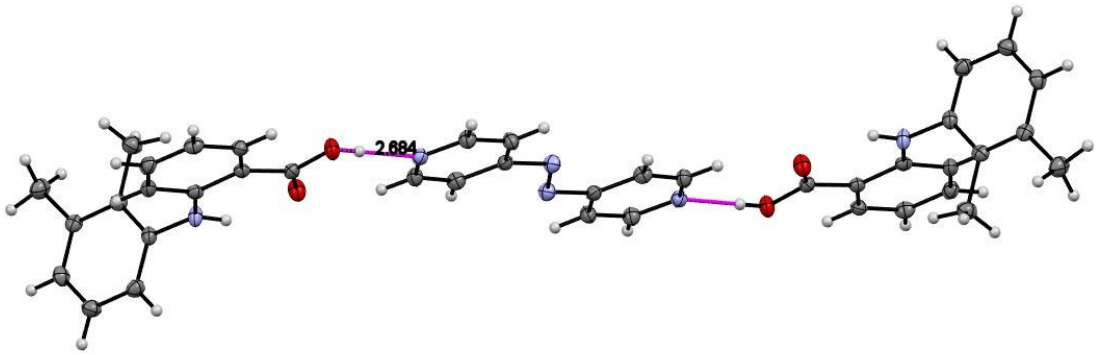

Figure S6. Three-component hydrogen-bonded assembly of co-crystal **2b** with thermal ellipsoids plotted at 50% probability.

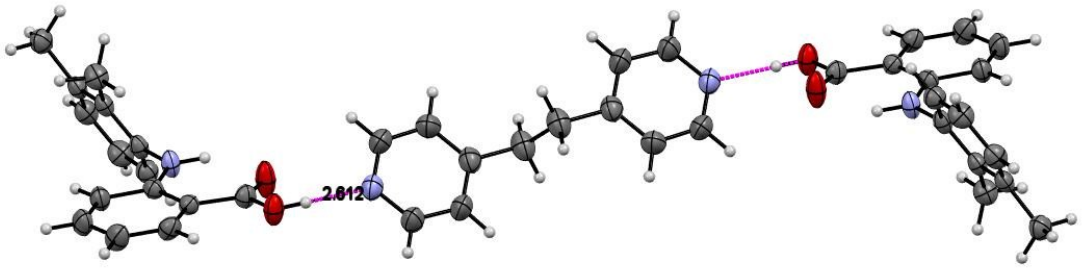

Figure S7. Three-component hydrogen-bonded assembly of co-crystal **2c** with thermal ellipsoids plotted at 50% probability.

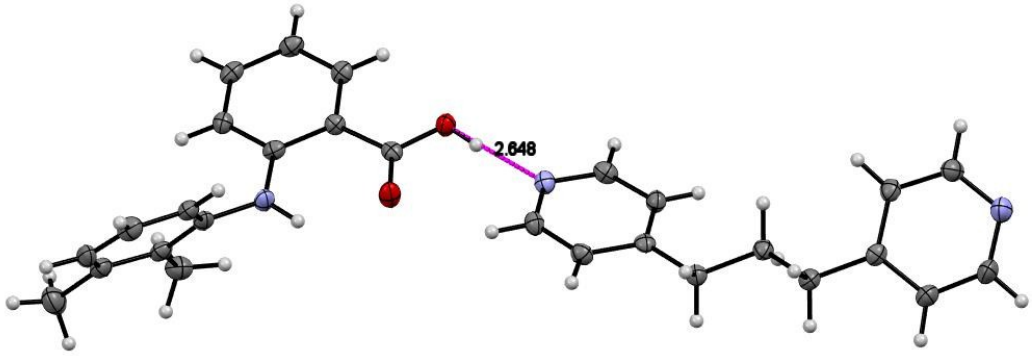

Figure S8. Asymmetric unit of co-crystal **2d** with thermal ellipsoids plotted at 50% probability.

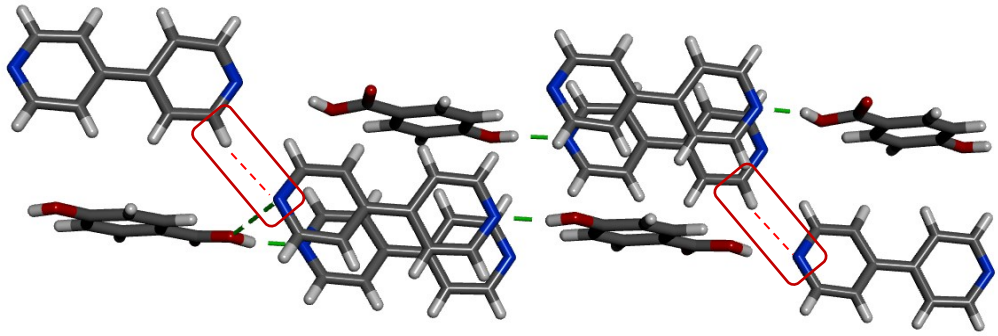

Figure S9. Published co-crystal (CSD refcode EPUQEM)[3] of a bipyridine with a monocarboxylic acid. Pyridine-pyridine interactions highlighted with red dashed lines and boxes.

4. NMR data for co-crystals

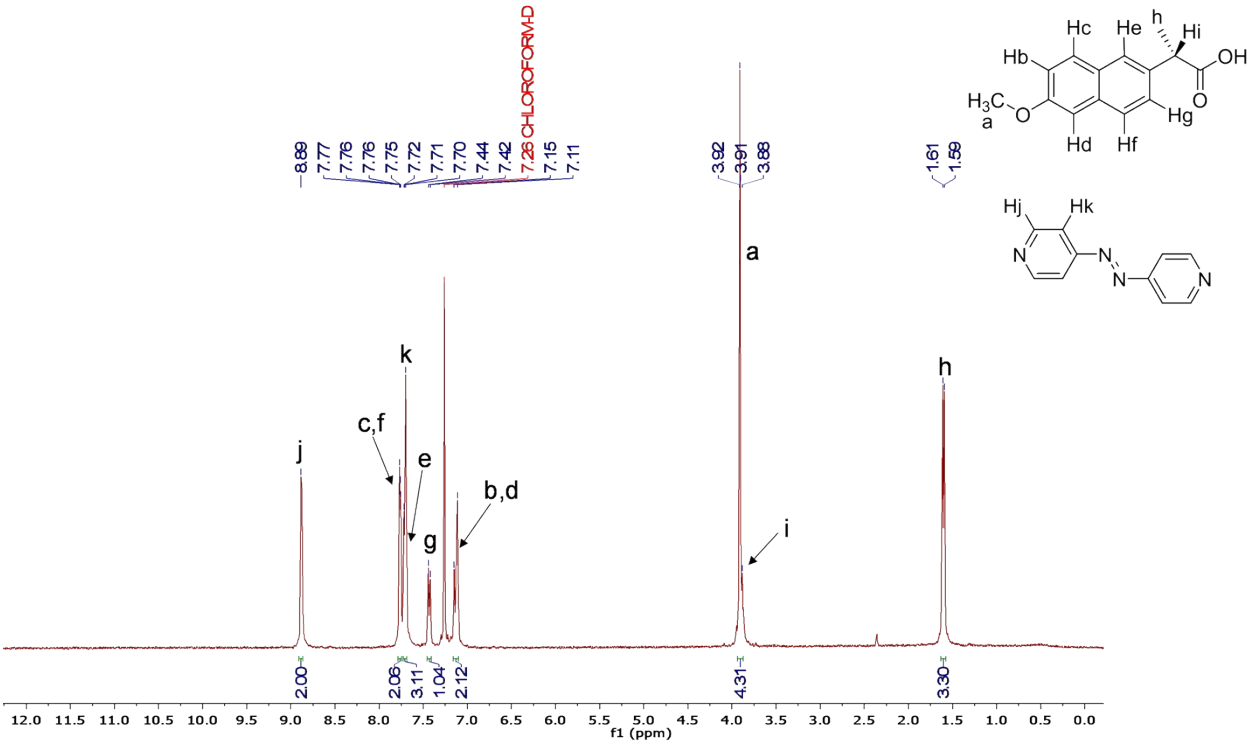

Figure S10. [1]H NMR spectrum of co-crystal **1b**.

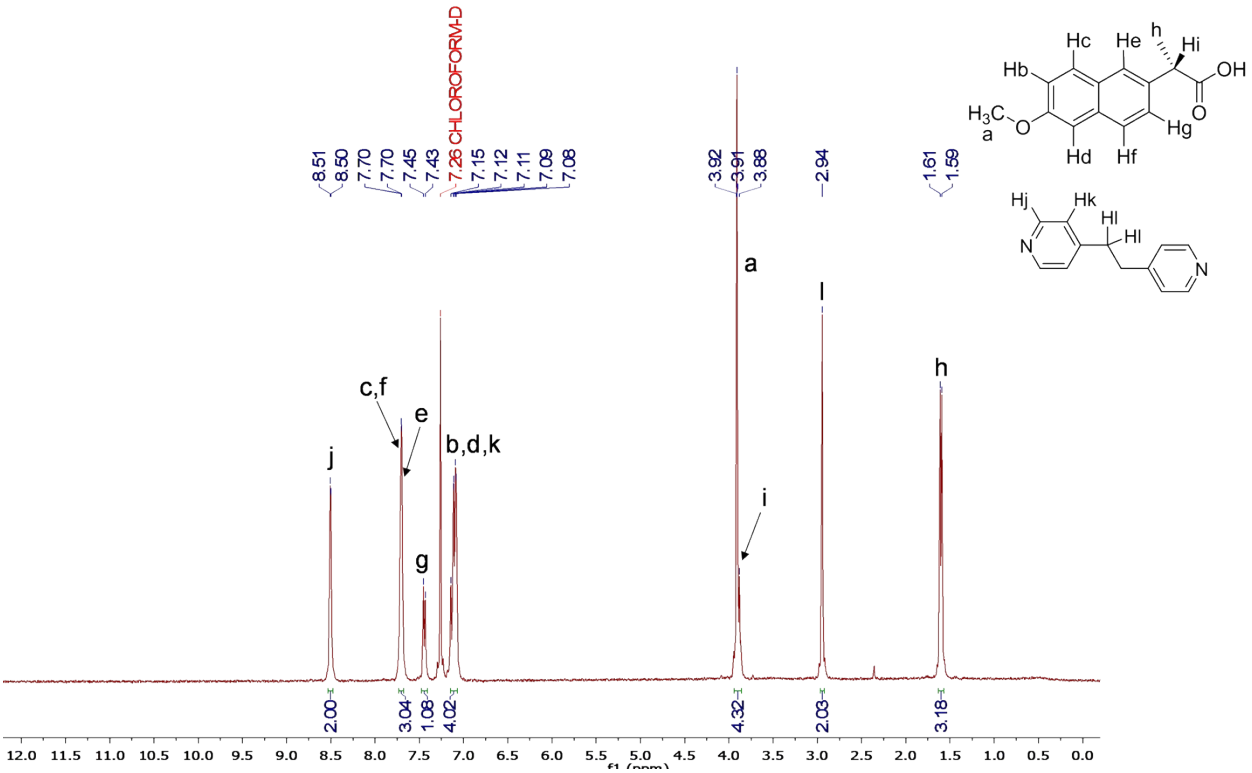

Figure S11. [1]H NMR spectrum of co-crystal **1c.**

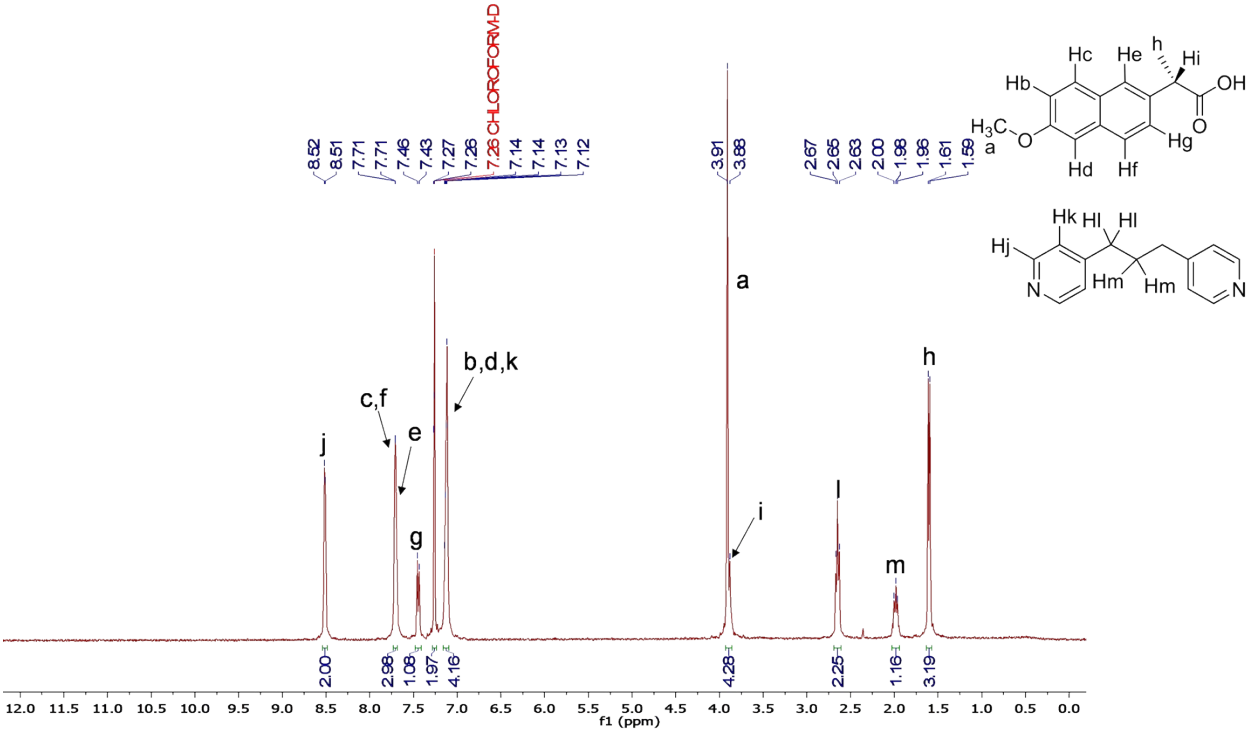

Figure S12. [1]H NMR spectrum of co-crystal **1d**.

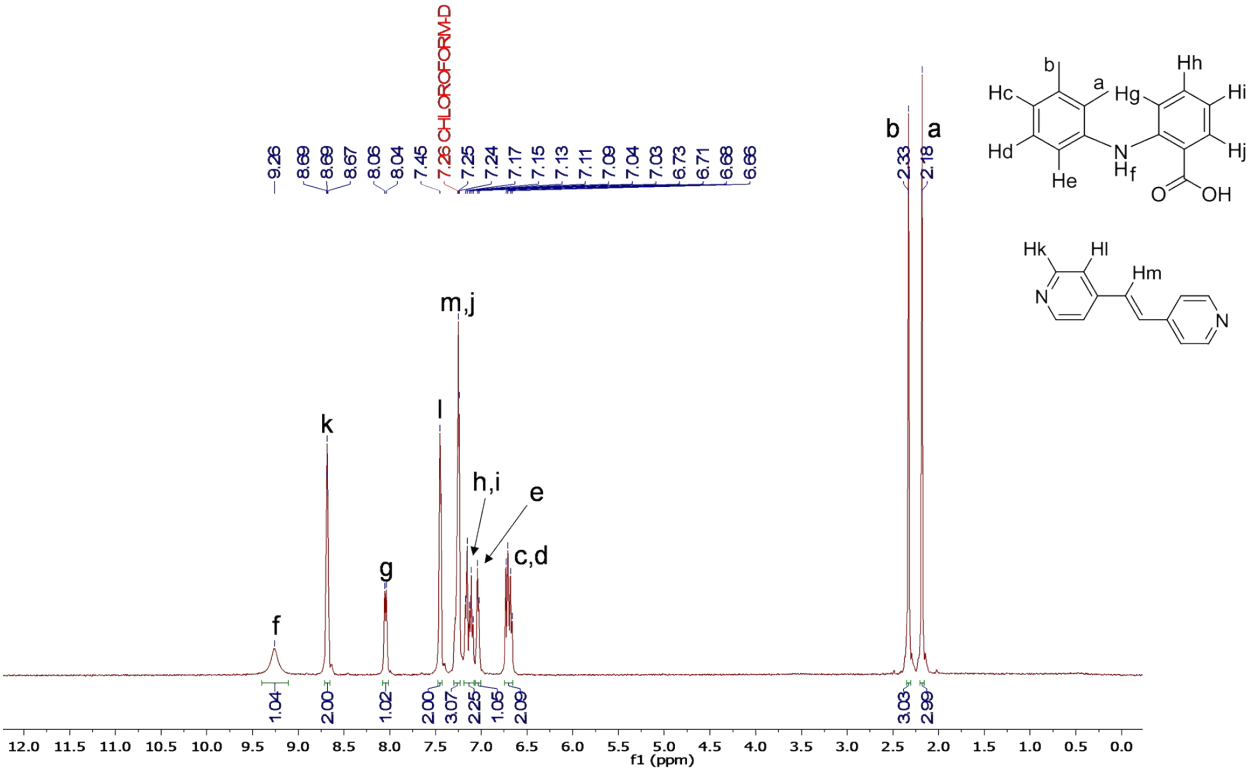

Figure S13. [1]H NMR spectrum of co-crystal **2a**.

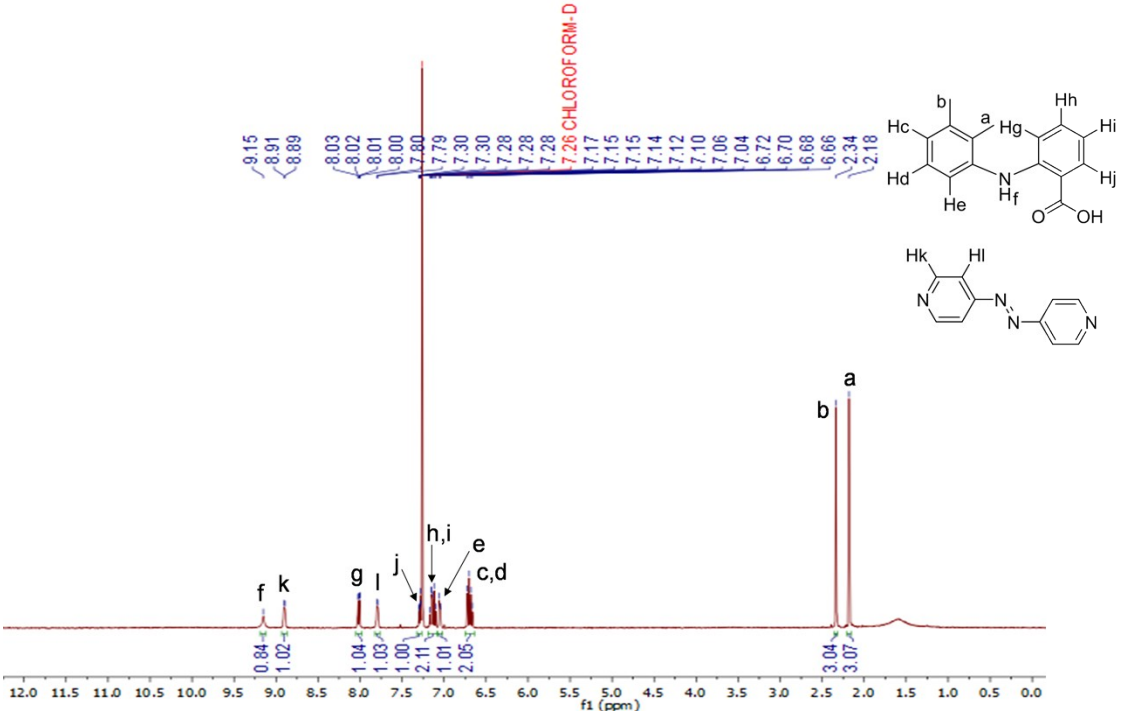

Figure S14. ^{1}H NMR spectrum of co-crystal **2b**.

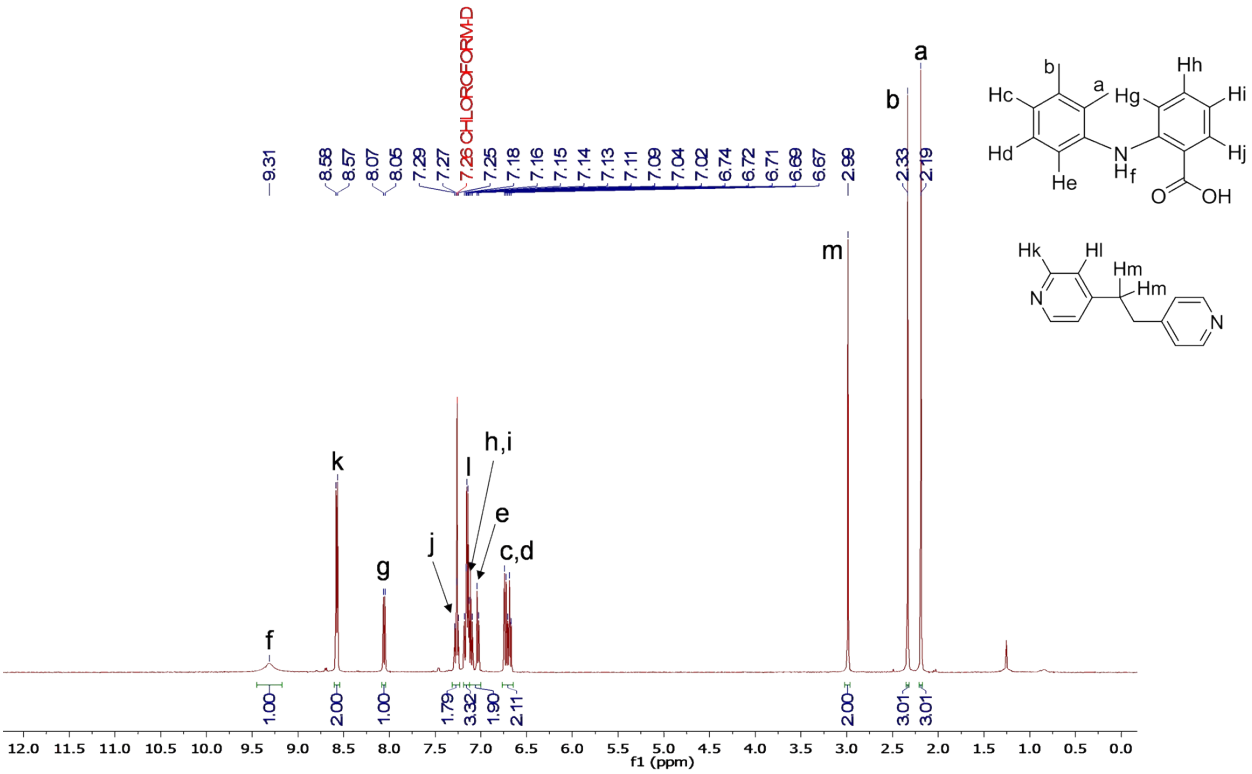

Figure S15. ^{1}H NMR spectrum of co-crystal **2c**.

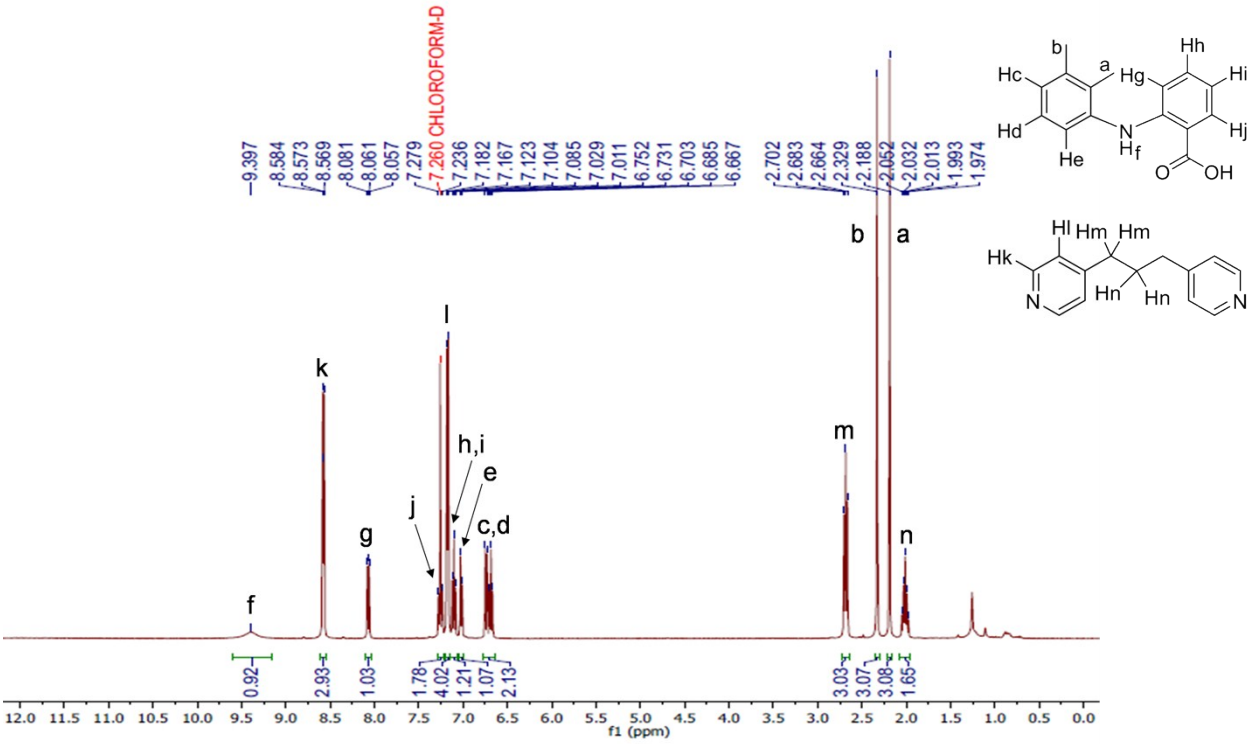

Figure S16. [1]H NMR spectrum of co-crystal **2d.**

5. CSD Search Parameters

We performed a search using the Crystal Packing Feature tool in Mercury.[4] Using a co-crystal of a monocarboxylic acid and a bipyridine, we selected the carboxylic acid group and two nitrogen atoms in the bipyridine to search for the COO-H···N(pyridine) synthon. The search resulted in 1423 hits. We examined bipyridines that exhibited at least one COO-H···N(pyridine) synthon and investigated situations of unused hydrogen bonding capacity.

References

1. Krause *et al.*, (2015) SADABS v 2016/2.

2. G. M. Sheldrick *Acta Crystallogr., Sect. C: Cryst. Struct. Commun*., 2015, **C71**, 3.

3. A. Mukherjee and G. R. Desiraju *Chem*. *Commun*., 2011, **47**, 4090.

4. Mercury CSD 3.10.3