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Supplementary Materials: Improving Nefiracetam Dissolution and Solubility Behavior Using a Cocrystallization Approach

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Cocrystal Screening

Coformer List

Table S1. List of the coformers screened during the cocrystal screening. Suspected cocrystals (orange), Confirmed cocrystals (green) and no cocrystal (black).

COFORMERS SCREENED		
(L)-3-phenyllactic acid	(DL)-3-phenyllactic acid	(L)-ascorbic acid
(S)-2-phenylbutyric acid	(RS)-2-phenylbutyric acid	(RS)-2-phenoxypropionic acid
(RS)-2-phenoxypropionic acid	(RS)-2-phenoxypropionic acid	(RS)-oxiracetam
(S)-oxiracetam	(RS)-phenylsuccinic acid	(RS)-tropic acid
1H-pyrazole-3,5-dicarboxylic acid monohydrate	1-hydroxy-2-napthoic acid	2,2-dimethylsuccinic acid
2,3-dihydroxybenzoic acid	2,4-dihydroxy benzoic acid	2,5-dihydroxybenzoic acid
2-aminobenzoic acid	2-benzoylbenzoic acid	2-hydroxy-1-napthoic acid
2-ketoglutaric acid	2-pyrrolidone-5-carboxylic acid	3,4-dihydroxybenzoic acid
3,5-dihydroxybenzoic acid	3-aminobenzamide	3-hydroxy-2-napthoic acid
3-hydroxybenzoic acid	3-methylbutanamide	3-nitrobenzoic acid
(RS)-3-phenylbutyric acid	4,4-bipyridine	4-aminobenzamide
4-aminobenzoic acid	4-aminomethylbenzoic acid	4-dimethylbenzoic acid
4-hydroxybenzoic acid	4-nitrobenzoic acid	5-aminoisophthalic acid
5-bromoisophthalic acid	5-cyano-1,3-benzenedicarboxylic acid	5-hydroxisophtalic acid
5-methoxyisophthalic acid	5-methylisophthalic acid	5-nitroisophtalic acid
6-hydroxy-2-napthoic acid	7-(2-hydroxyethyl)theophylline	7-(2-hydroxypropyll)theophylline
acetaminophen	acetoacetamide	acetylsalicylic acid
adipic acid	alanine (DL)	alanine (L)
aniracetam	anthranilamide	arginine (L)
asparagine (L)	aspartame	aspartic acid (DL)
aspartic acid (L)	benzenesulfonic acid	benzoic acid
calcium chloride	Caffeine	camphoric acid (D)
carphedon	carbamazepine	cholic acid
citraconic acid	citric acid	cysteine (L)
diphylline	(D)-mannitol	(D)-sorbitol
erythorbic acid	ethyl gallate	etiracetam
ferulic acid	flurbiprofen (RS)	fructose
fumaric acid	gallic acid	glucose
glutamine (L)	glutaric acid	glycine
lycolic acid	histidine (DL)	ibuprofen (RS)
isoleucine (DL)	isonicotinamide	isophtalic acid
ketoprofen (RS)	leucine (L)	leviteracetam
lysine (L)	maleic acid	malic acid
malonic acid	Maltol	mesaconic acid

methionine (L)	methyl-3,4,5-trihydroxybenzoate	magnesium chloride
myo-inositol	naproxen (RS)	nicotinamide
nicotinic acid	oxalic acid	pamoic acid
p-coumaric acid	phenylalanine (DL)	phenylsulfoxide
phtalic acid	piracetam	pramiracetam
proline (DL)	proline (L)	pyridine-2,6-dicarboxylic acid
saccharin	salicylic acid	salicylic acid
serine (DL)	serine (L)	sorbic acid
stearic acid	succinic acid	sucrose
tartaric acid	theophylline	thiomalic acid
threonine (L)	trimellitic acid	trimesic acid
tryptophane (DL)	tryptophane (L)	tyrosine (L)
urea	valine (L)	xanthine
zinc chloride		

PXRD patterns

Suspected Cocrystals

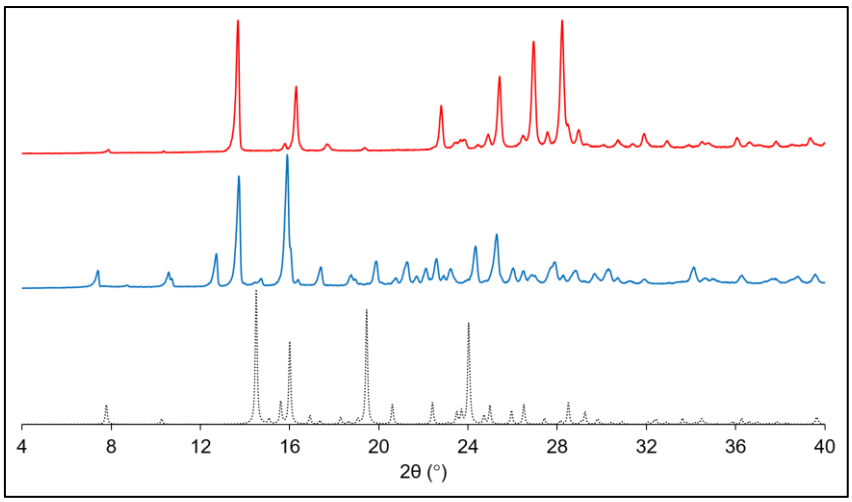

Figure S1. Experimental diffraction patterns of the 1:1 Nefiracetam-**2,4-dihydroxybenzoic acid** ground product (blue), the 2,4-dihydroxybenzoic acid coformer (red) and Nefiracetam simulated diffraction pattern (dashed black).

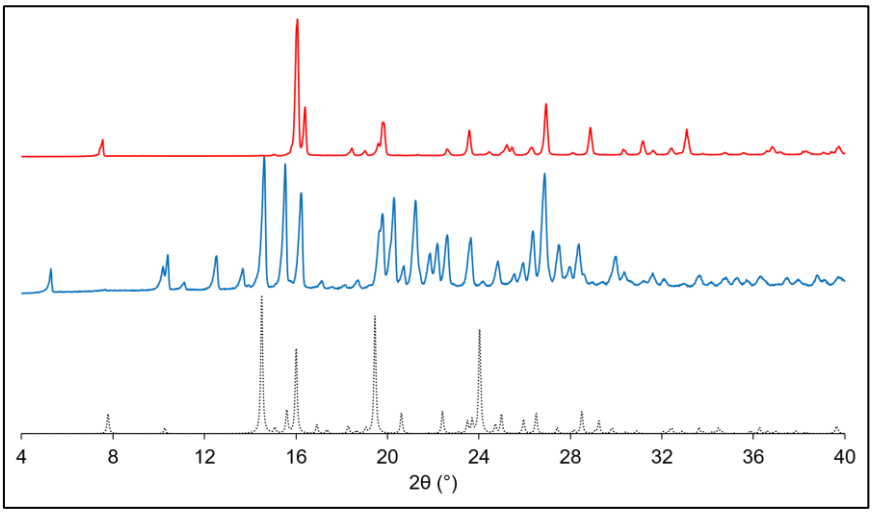

Figure S2. Experimental diffraction patterns of the 1:1 Nefiracetam-**2,5-dihydroxybenzoic acid** ground product (blue), the 2,5-dihydroxybenzoic acid coformer (red) and Nefiracetam simulated diffraction pattern (dashed black).

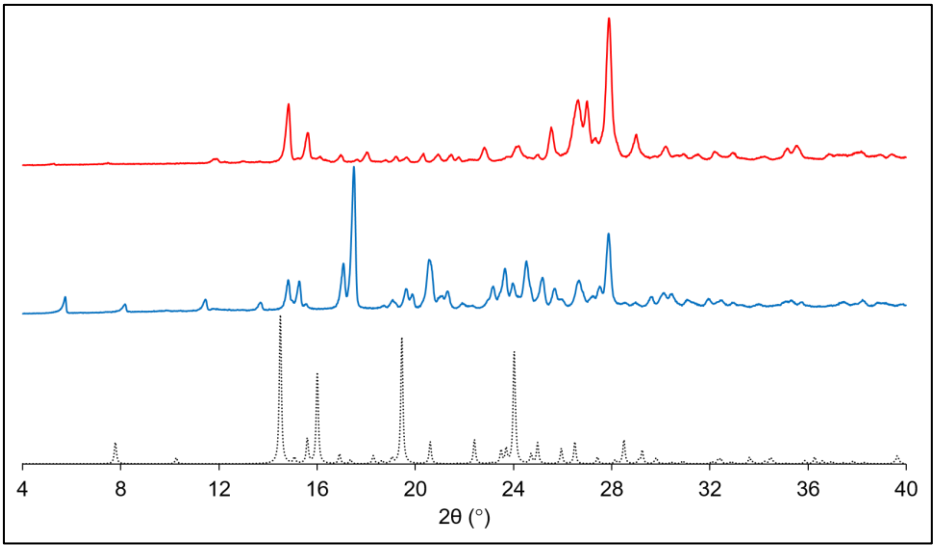

Figure S3. Experimental diffraction patterns of the 1:1 Nefiracetam-**3,4-dihydroxybenzoic acid** ground product (blue), the 3,4-dihydroxybenzoic acid coformer (red) and Nefiracetam simulated diffraction pattern (dashed black).

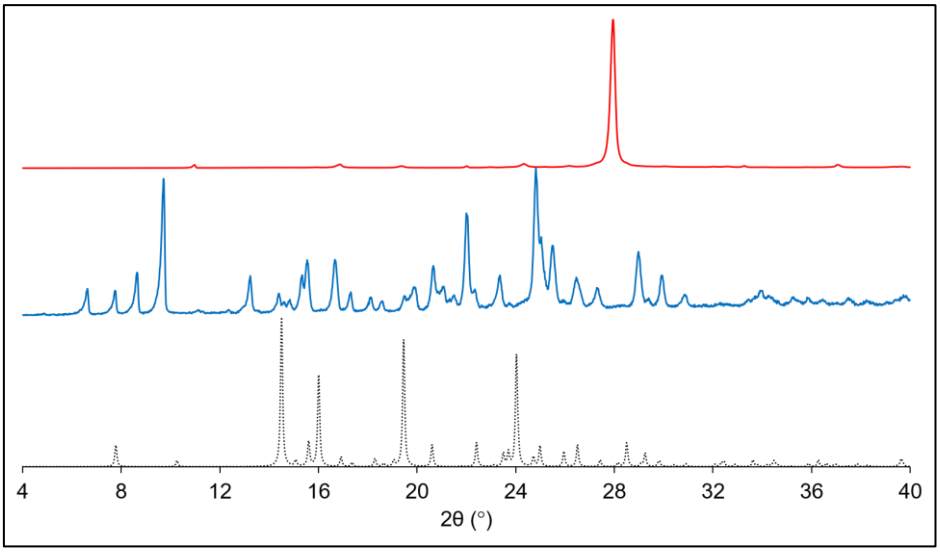

Figure S4. Experimental diffraction patterns of the 1:1 Nefiracetam-**pyridine-2,6-dicarboxylic acid** ground product (blue), the pyridine-2,6-dicarboxilic acid coformer (red) and Nefiracetam simulated diffraction pattern (dashed black).

Confirmed Cocrystals

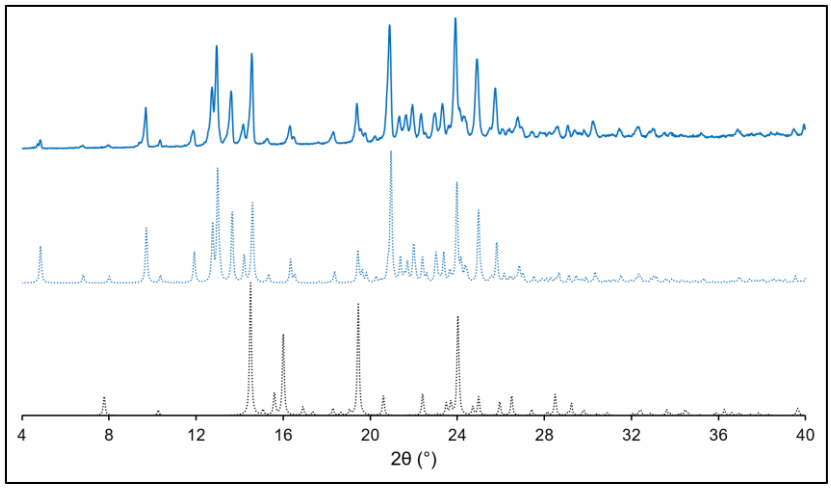

Figure S5. Simulated diffraction patterns (dashed line) of 1:1 **Nefiracetam-5-hydroxyisophthalic acid** cocrystal (blue) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

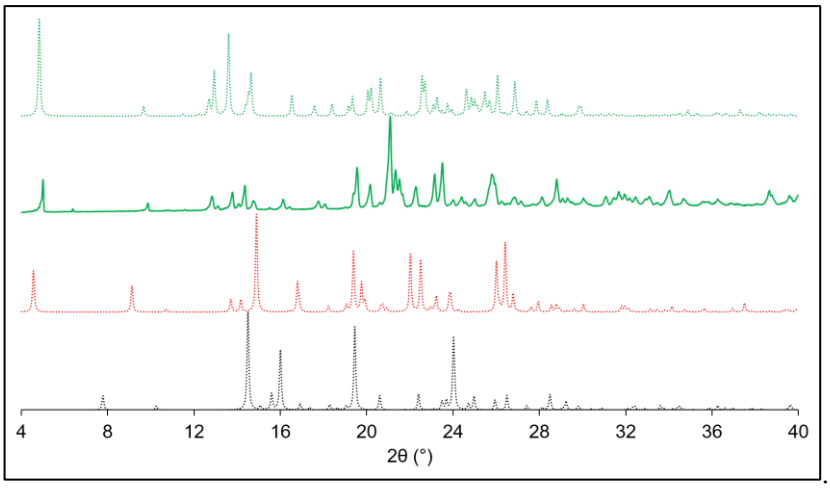

Figure S6. Simulated diffraction patterns (dashed line) of 1:1 **Nefiracetam-5-nitroisophthalic acid FI** cocrystal (green) and **FII** (red) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

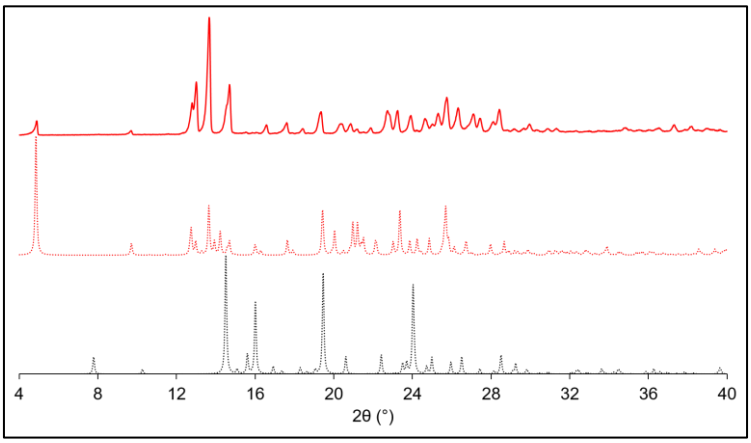

Figure S7. Simulated diffraction patterns (dashed line) of **Nefiracetam-5-bromoisophthalic acid** (red) and comparison with the experimental one (red full line) and the simulated diffractogram of Nefiracetam **FI** (black).

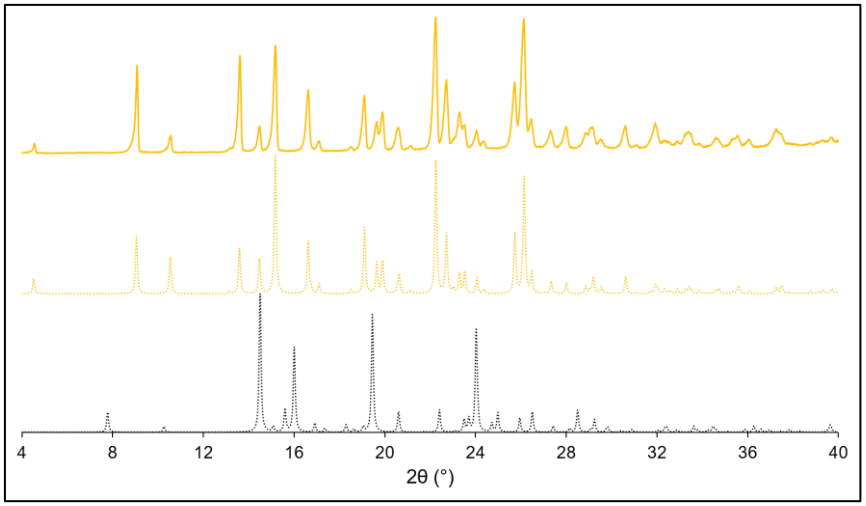

Figure S8. Simulated diffraction patterns (dashed line) of **Nefiracetam-5-cyano-1,3-benzenedicarboxylic acid** (orange) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam **FI** (black).

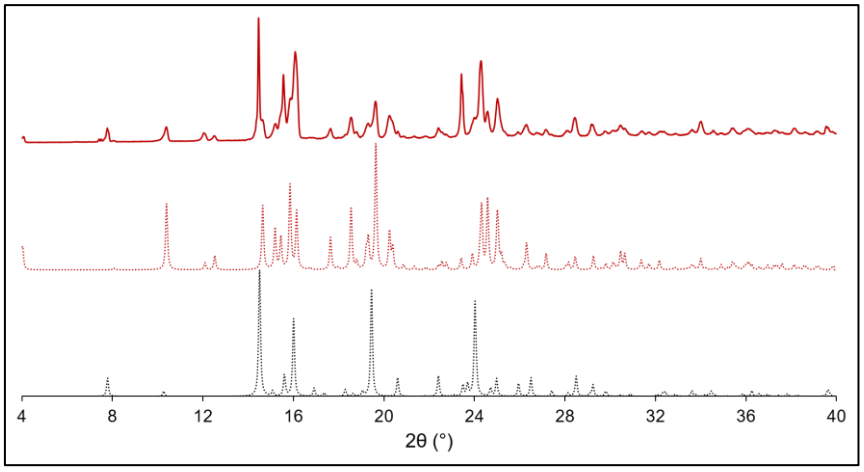

Figure S9. Simulated diffraction patterns (dashed line) of **Nefiracetam-2-benzylbenzoic acid** (dark red) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

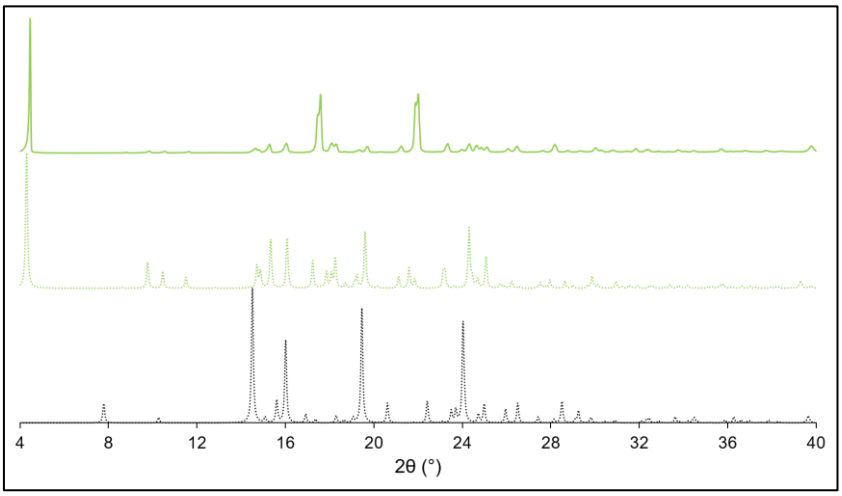

Figure S10. Simulated diffraction patterns (dashed line) of **Nefiracetam-2-phenylbutyric acid** cocrystal solid solution (light green) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

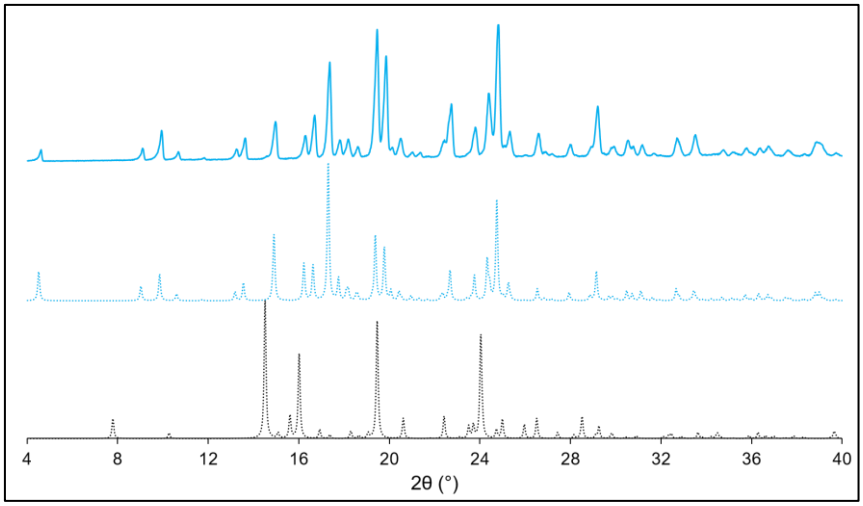

Figure S11. Simulated diffraction patterns (dashed line) of **Nefiracetam-(DL)-3-phenyllactic acid** racemic cocrystal (light blue) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

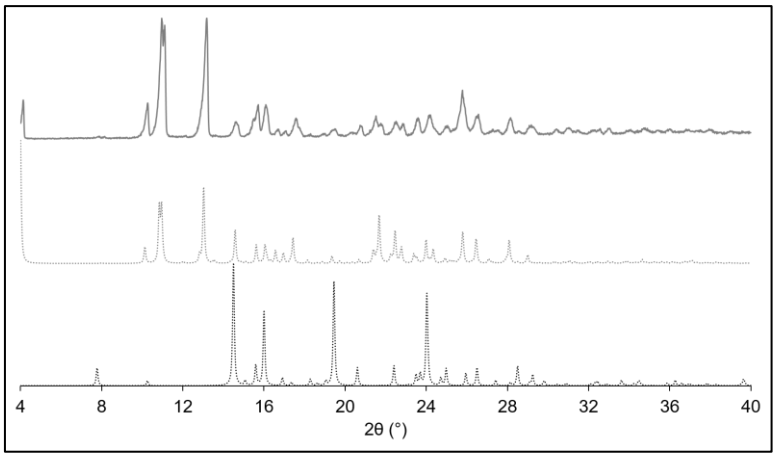

Figure S12. Simulated diffraction patterns (dashed line) of **4:1:1 Nefiracetam-3,4,5-trihydroxybenzoic acid (gallic acid)** cocrystal hydrate (grey) and comparison with the experimental one (full line) and the simulated diffractogram of Nefiracetam FI (black).

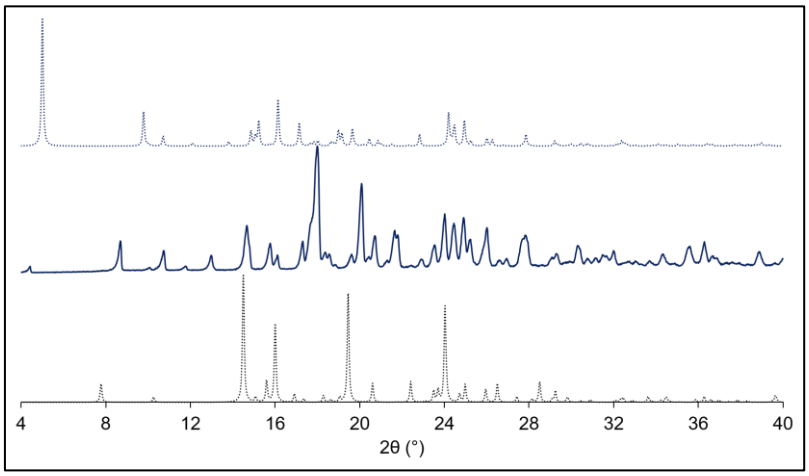

Figure S13. Simulated diffraction patterns (dashed line) of **2:1 Nefiracetam-(RS)-phenylsuccinic acid** racemic cocrystal (dark blue) and comparison with the ground product (full line) and the simulated diffractogram of Nefiracetam FI (black).

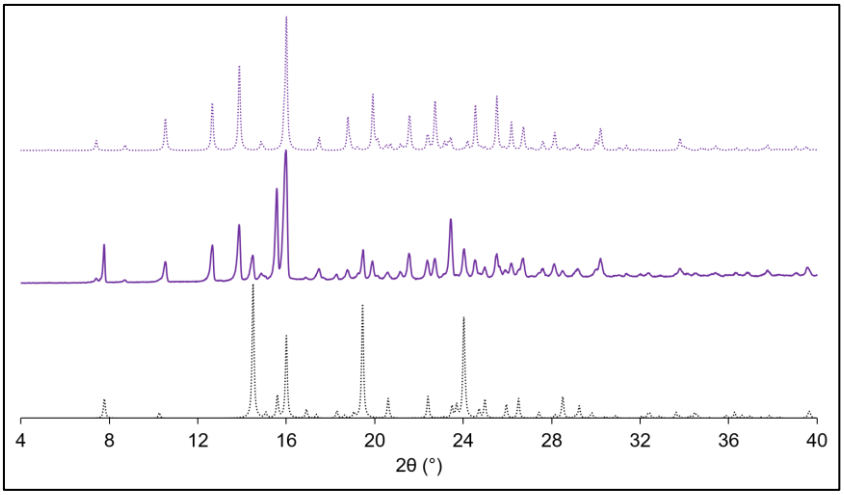

Figure S14. Simulated diffraction patterns (dashed line) of **1:1 Nefiracetam-4-hydrobenzoic acid** cocrystal (purple) and comparison with the ground product (full line) and the simulated diffractogram of Nefiracetam FI (black).

DSC curves

Suspected Cocrystals

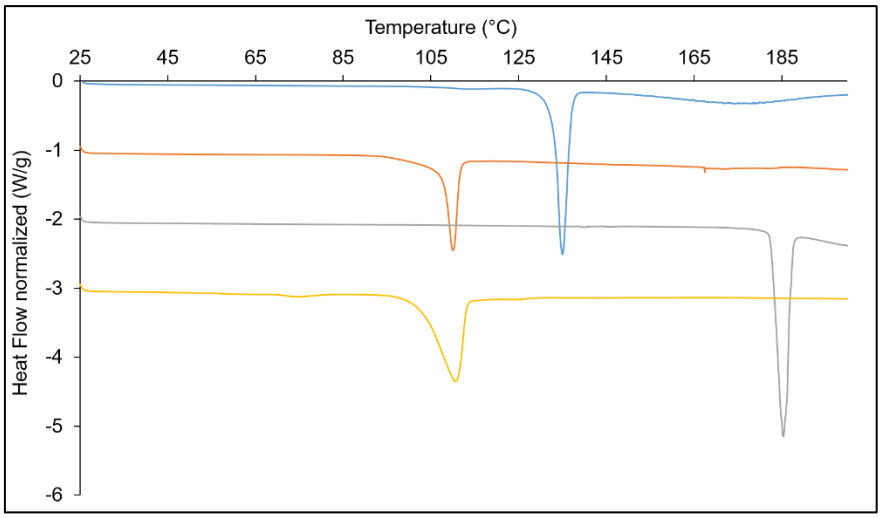

Figure S15. DSC curves of 1:1 Nefiracetam-**2,4-dihydroxybenzoic acid** (bleu), 1:1 Nefiracetam-**2,5-dihydroxybenzoic acid** (orange), 1:1 Nefiracetam-**pyridine-2,6-dicarboxylic acid** (grey) and 1:1 Nefiracetam-**3,4-dihydroxybenzoic acid** (gold) ground products.

Confirmed Cocrystals

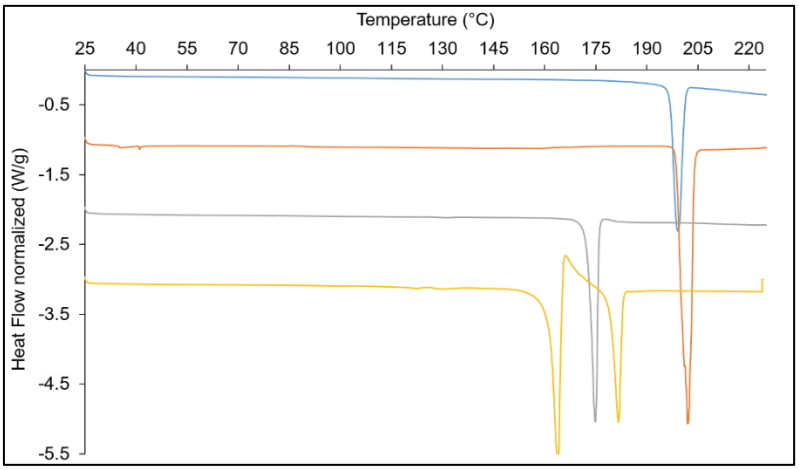

Figure S16. DSC curves of 1:1 Nefiracetam-5-hydroxyisophthalic acid (blue), 1:1 Nefiracetam-5-bromoisophthalic acid (orange), 1:1 Nefiracetam-5-nitroisophthalic acid FI (grey) and 1:1 Nefiracetam-5-cyano-1,3-benzendicarboxylic acid (gold) cocrystals.

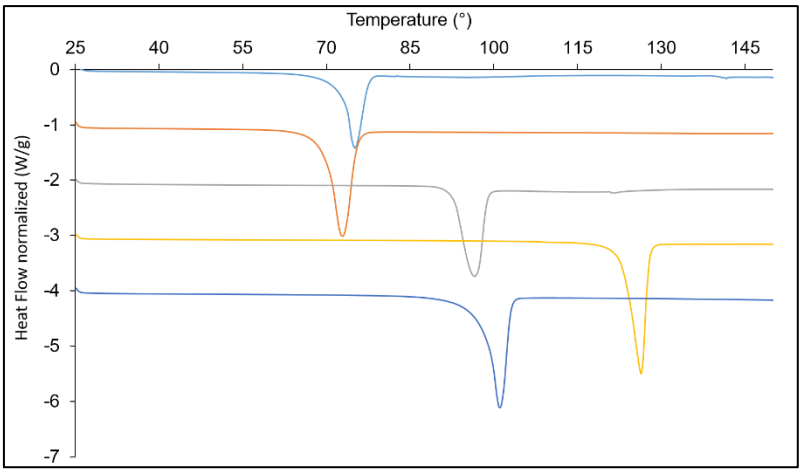

Figure S17. DSC curves of 1:1 Nefiracetam-(RS)-2-phenylbutyric acid (blue), 1:1 Nefiracetam-(DL)-3-phenyllactic acid (orange), and 1:1 Nefiracetam-2-benzoylbenzoic acid (grey), 1:1-Nefiracetam-4-hydroxybenzoic acid (gold) and 2:1 Nefiracetam-(RS)-phenylsuccinic acid (darker blue) cocrystals.

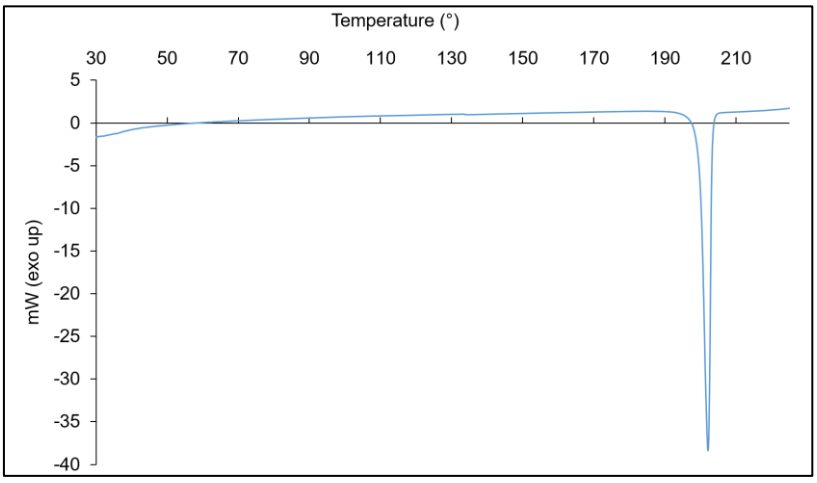

Figure S18. DSC curve of **the 1:1 Nefiracetam-5-nitroisophthalic acid FII cocrystal**. The measurement was occasionally performed on measurements were performed from 30°C to 225°C at a scanning rate of 5°C.min^{-1} on a "Mettler Toledo DSC821e".

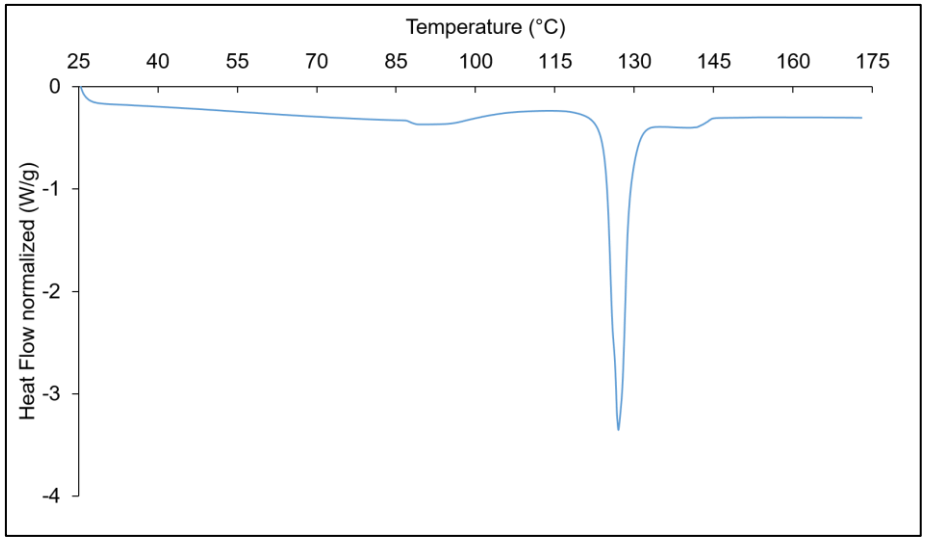

Figure S19. DSC curve of **4:1:1 Nefiracetam-gallic acid-water cocrystal hydrate**. Upon heating, the cocrystal decomposes into a mixture Nefiracetam and amorphous phase.

Cocrystal Form Screening (NCA, NOA and NZC)

2:1 Nefiracetam-Citric Acid Cocrystal (NCA)

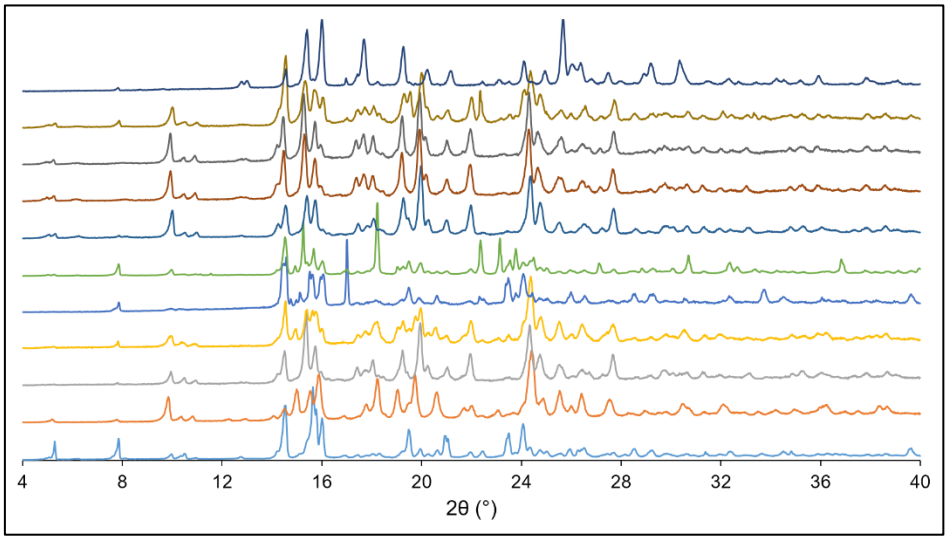

Figure S20. XRPD pattern on powders retrieved from the **NCA** form screening through **LAG** with different solvents. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: ethyl acetate; **6**: ethanol; **7**: 2-propanol; **8**: methyl acetate; **9**: methanol; **10**: tetrahydrofuran; **11**: water.

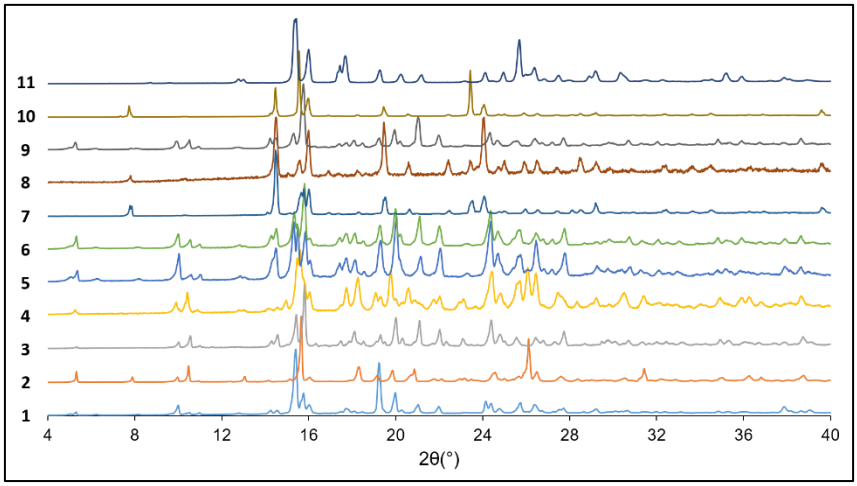

Figure S21. XRPD pattern on powders retrieved from the **NCA** form screening through **slurry crystallization** in different solvents. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: diethyl ether; **6**: ethyl acetate; **7**: ethanol; **8**: 2-propanol; **9**: methyl acetate; **10**: tetrahydrofuran; **11**: water.

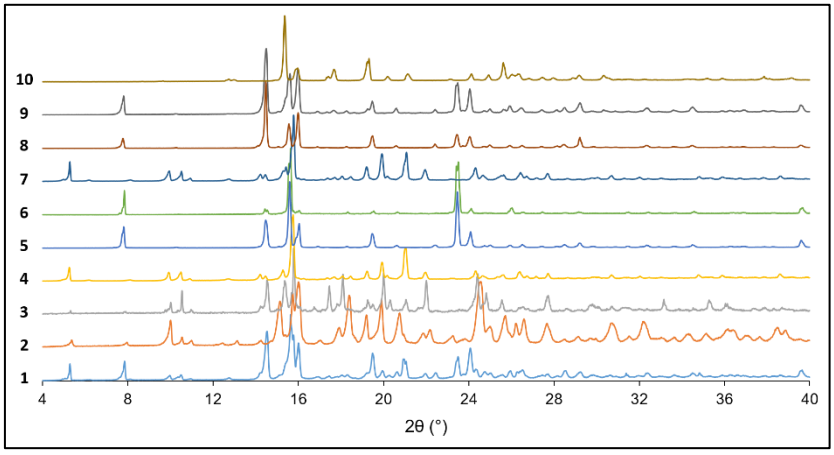

Figure S22. XRPD pattern on powders retrieved from the **NCA** form screening through **cooling crystallization** indifferent solvents. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: ethyl acetate; **5**: ethanol; **6**: 2-propanol; **7**: methyl acetate; **8**: methanol; **9**: tetrahydrofuran; **10**: water.

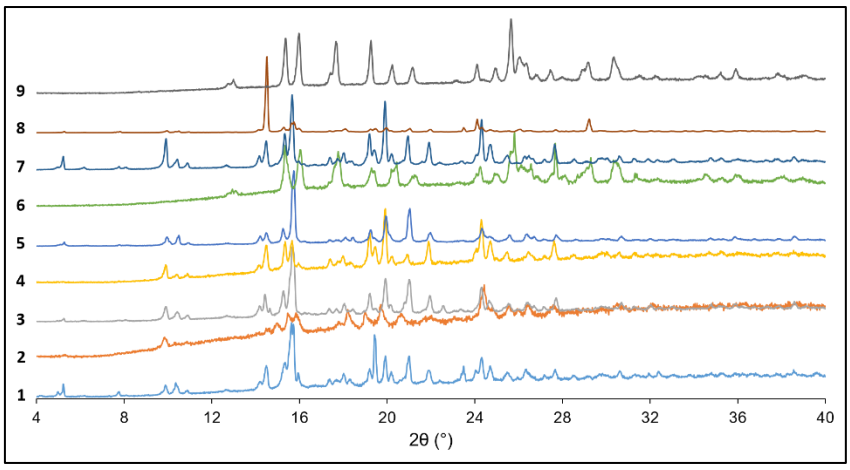

Figure S23. XRPD pattern on powders retrieved from the **NCA** form screening through **slow evaporation** in different solvents at room temperature. **1**: acetone; **2**: acetonitrile; **3**: ethyl acetate; **3**: ethanol; **5**: methyl acetate; **6**: methanol; **7**: 2-propanol; **8**: tetrahydrofuran; **9**: water.

2:1 Nefiracetam-Oxalic Acid Cocrystal (NOA)

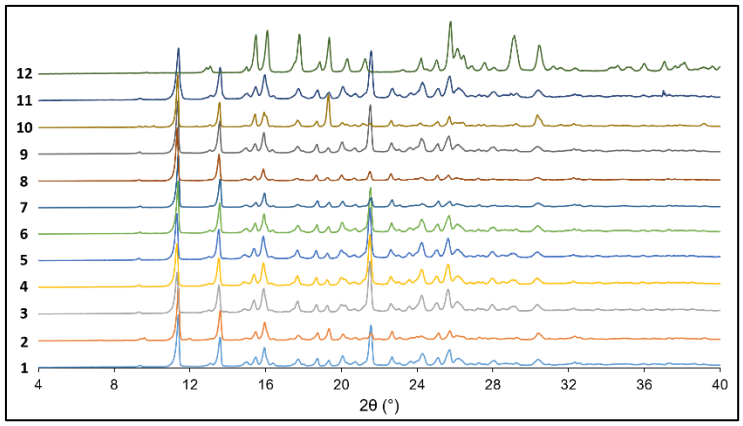

Figure S24. XRPD pattern on powders retrieved from the **NOA** form screening through **LAG** with different solvents. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: diethyl ether; **6**: ethyl acetate; **7**: ethanol; **8**: 2-propanol; **9**: methyl acetate; **10**: methanol; **11**: tetrahydrofuran; **12**: water.

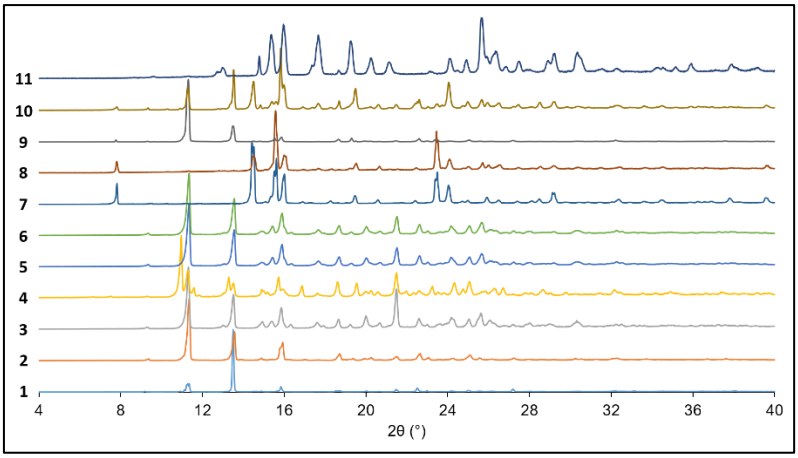

Figure S25. XRPD pattern on powders retrieved from the **NOA** form screening through **slurry crystallization** in different solvents at 25°C. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: diethyl ether; **6**: ethyl acetate; **7**: ethanol; **8**: 2-propanol; **9**: methyl acetate; **10**: tetrahydrofuran; **11**: water.

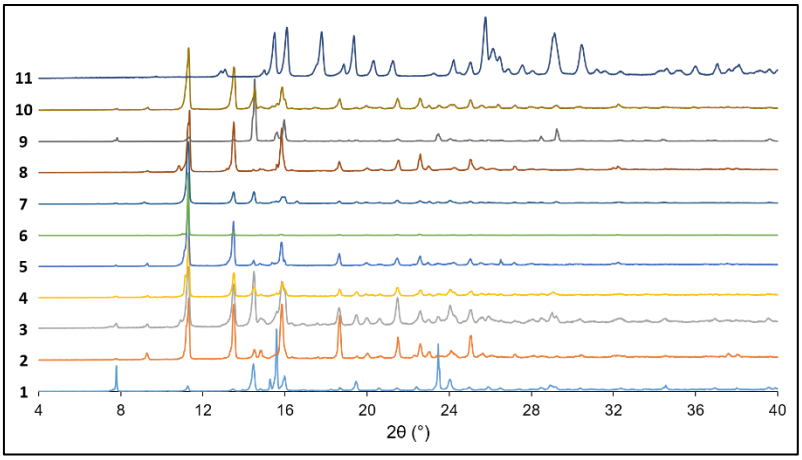

Figure S26. XRPD pattern on powders retrieved from the **NOA** form screening through **evaporative crystallization** in different solvents at room temperature. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: ethyl acetate; **6**: ethanol; **7:** 2-propanol; **8**: methyl acetate; **9**: methanol; **10**: tetrahydrofuran; **11**: water.

1:1 Nefiracetam-Zinc Chloride Ionic Cocrystal (NZC)

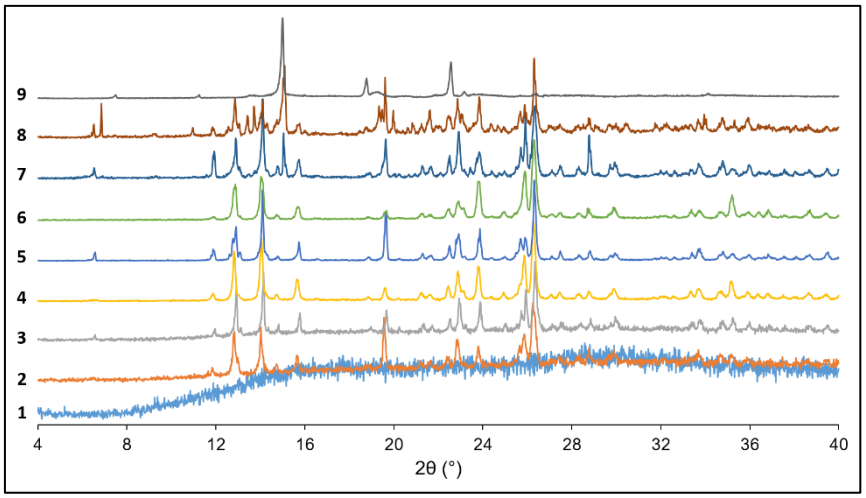

Figure S27. XRPD pattern on powders retrieved from the **NZC** stoichiometry screening through **slurry crystallization** in acetonitrile at 25°C. **1**: 100% ZC; **2**: ZC 89%-11% N; **3**: ZC 81%-19% N; **4**: ZC 70%-30% N; **5**: ZC 57%-43% N; **6**: ZC 48%-52% N; **7**: ZC 46%-54% N; **8**: ZC 30%-70% N; **9**: ZC 19%-81% N. Percent are given in molar ratio with N = Nefiracetam and ZC = zinc chloride.

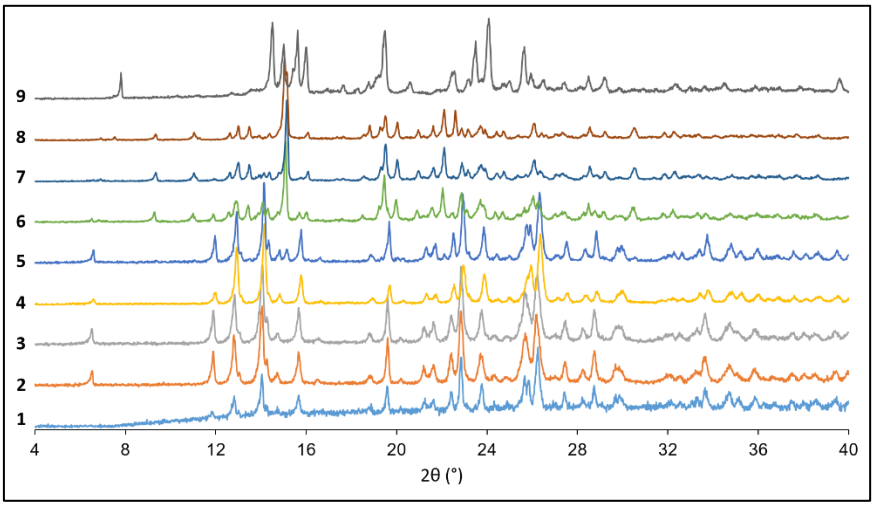

Figure S28. XRPD pattern on powders retrieved from the **NZC** stoichiometry screening through slurry crystallization in ethyl acetate at 25°C. **1**: ZC 89%-11% N; **2**: ZC 80%-20% N; **3**: ZC 68%-32% N; **4**: ZC 59%-41% N; **5**: ZC 50%-50% N; **6**: ZC 39%-61% N; **7**: ZC 37%-63% N; **8**: ZC 31%-69% N; **9**: ZC 10%-90% N. Percent are given in molar ratio with N = Nefiracetam and ZC = zinc chloride.

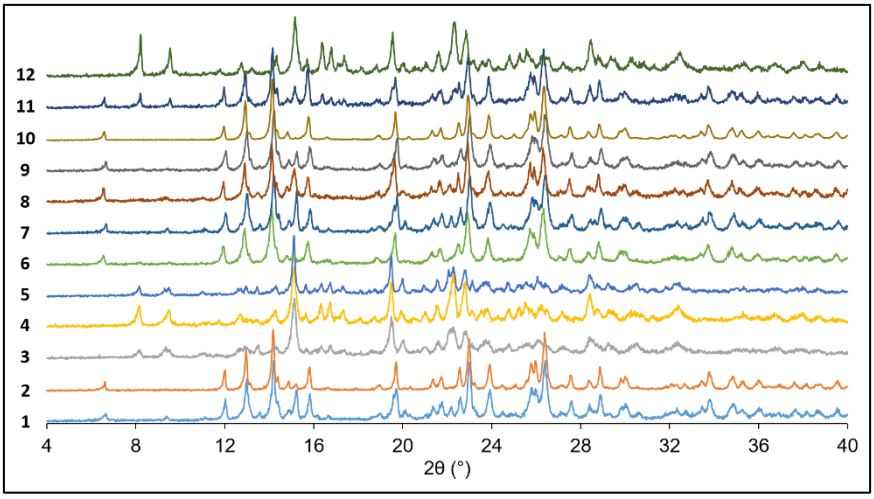

Figure S29. XRPD pattern on powders retrieved from the **NZC** form screening through LAG with different solvents. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: diethyl ether; **6**: ethyl acetate; **7**: ethanol; **8**: methyl acetate; **9**: 2-propanol; **10**: methanol; **11**: tetrahydrofuran ; **12**: water.

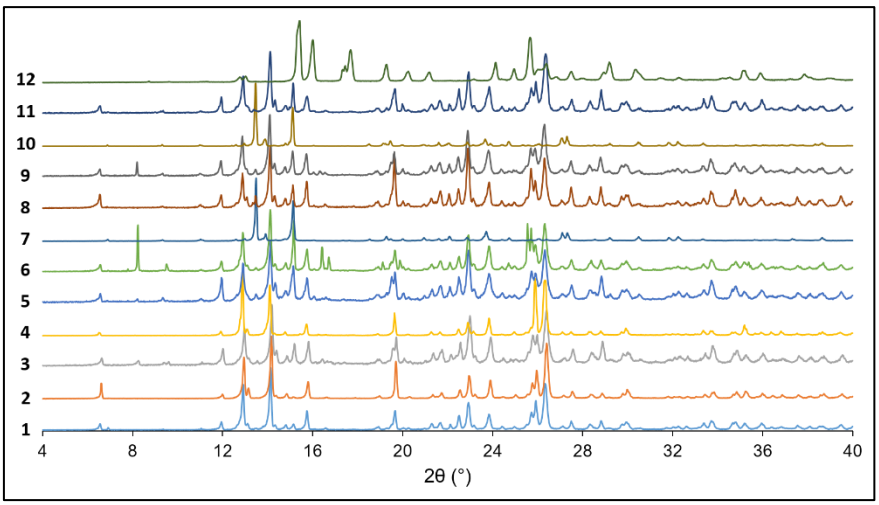

Figure S30. XRPD pattern on powders retrieved from the **NZC** form screening through **slurry crystallization** with different solvents at 25°C. **1**: acetone; **2**: acetonitrile; **3**: chloroform; **4**: dichloromethane; **5**: diethyl ether; **6**: ethyl acetate; **7**: ethanol; **8**: 2-propanol; **9**: methyl acetate; **10**: methanol; **11**: tetrahydrofuran; **12**: water.

Crystal Packing and Crystallographic Tables (other structures)

CCDC 2010261-2010276 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

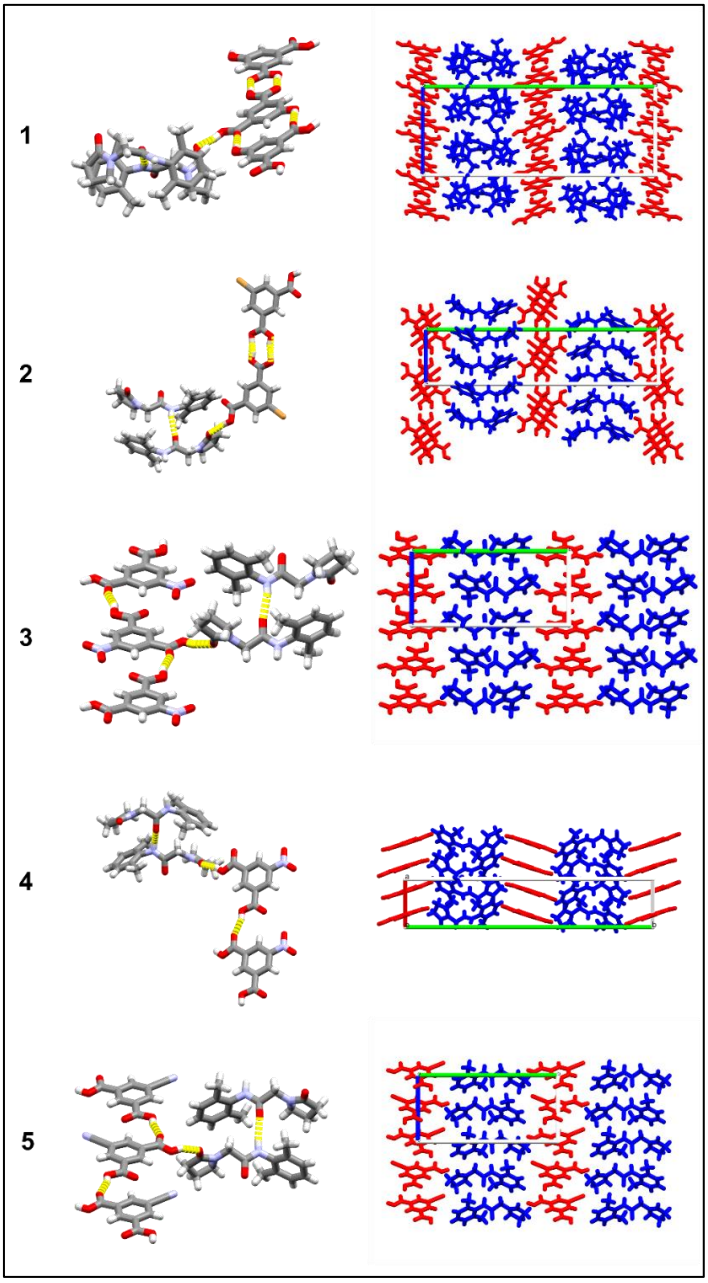

Figure S31. (left) Main intermolecular interactions and (right) crystal packing of **1**: 1:1 Nefiracetam-5-hydroxyisophthalic acid, **2**: 1:1 Nefiracetam-5-bromoisophthalic acid, **3**: 1:1 Nefiracetam-5-nitroisophthalic acid FII, **4**: 1:1 Nefiracetam-5-nitroisophthalic acid FI and **5**: 1:1 Nefiracetam-5-cyano-1,3-benzenedicarboxylic acid cocrystals. The Nefiracetam molecules and coformers are respectively colored in blue and red in the crystal lattices. Yellow contact sticks are used to highlight the intermolecular hydrogen bonds.

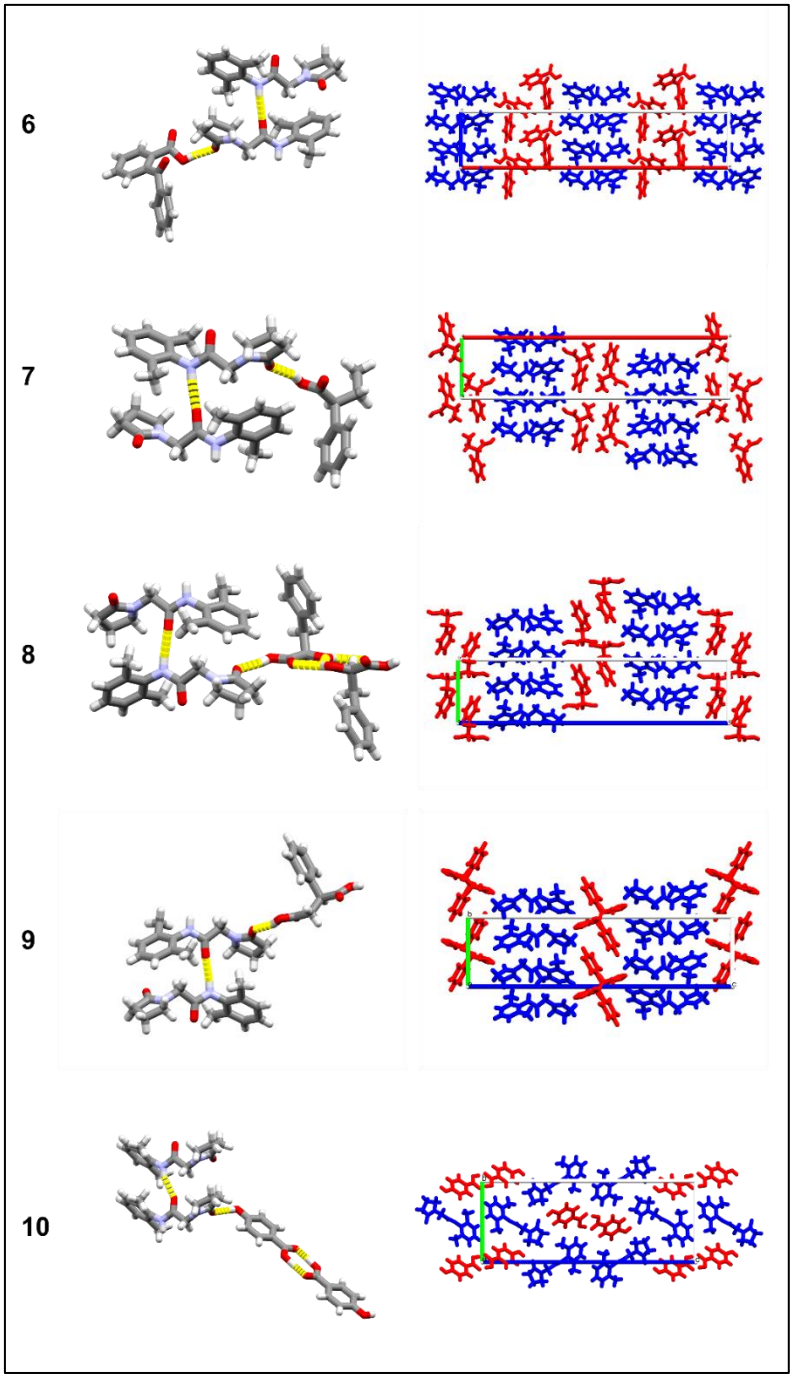

Figure S32. (left) Main intermolecular interactions and (right) crystal packing of **6**: 1:1 Nefiracetam-2-benzoyl benzoic acid, **7**: Nefiracetam-(RS)-2-phenylbutyric acid and **8**: Nefiracetam-(DL)-3-phenyllactic acid (solid solution), **9**: 2:1 Nefiracetam-(RS)-phenylsuccinic acid (racemic) and **10**: 1:1 Nefiracetam-4-hydroxybenzoic acid cocrystals. The Nefiracetam molecules and coformers are respectively colored in blue and red in the crystal lattices. Yellow contact sticks are used to highlight the intermolecular hydrogen bonds. The cocrystal structure of 2:1 Nefiracetam-(RS)-phenylsuccinic acid exhibits an inversion centre on each phenylsuccinic acid molecule.

Table S2. Main crystallographic data of **NCA**, **NCA1**, **NOA**, **NZC** and **NZCW** and refinement parameters.

Compound	**NCA**	**NCA1**	**NOA**	**NZC**	**NZCW**
Empirical formula	$C_{68}H_{87}N_8O_{22}$	$C_{34}H_{43}N_{24}O_{11}$	$C_{30}H_{38}N_4O_8$	$C_{14}H_{18}Cl_2N_2O_2Zn$	$C_{14}H_{20}Cl_2N_2O_3Zn$
Formula weight ($g.mol^{-1}$)	1368.45	683.72	582.84	382.57	400.59
Temperature (K)	297(2)	297(2)	100(2)	100(2)	297(2)
Wavelength (Å)	1.54184	1.54184	0.798	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P*-1	*P*21/*c*	*P*2$_1$	*C*2/*c*	*P*2$_1$/*c*
a, b, c (Å)	6.1877(2),18.7399(4),35.3540(11)	6.439(3),35.361(9),9.782(3)	88.4663(5),15.4852(9),23.4755(11)	14.9275(3),7.66202(16),27.3619(6)	8.8632(3),18.2415(8),22.1746(12)
α, β, γ (°)	74.626(3), 87.939(3), 82.248(2)	90, 97.68(3). 90	90, 99.903(6), 90	90, 97.3147(19), 90	90, 101.353(5), 90
Volume ($Å^3$)	3916.7(2)	2207.3(13)	3031.8(3)	3104.06(11)	3515.0(3)
Z	2	2	4	8	8
Density ($g.cm^{-3}$)	1.160	1.029	1.276	1.637	1.514
Absorption coefficient (mm^{-1})	0.727	0.645	0.120	1.931	1.713
F(000)	1454	726	1240	1568	1648
Crystal size (mm^3)	0.500 x 0.385 x 0.039	Crystallized on **NCA**	0.50 x 0.04 x 0.02	0.490 x 0.280 x 0.280	0.45 x 0.30 x 0.07
Theta range for data collection (°)	6.493 to 66.601	8.182 to 58.930	1.777 to 28.729	2.751 to 32.666	3.025 to 25.688
Reflections collected	13586	14428	24245	10307	31528
Completeness to θ = 25.242°	98.8 % (to theta = 66.601°)	99%	98.1 % (to 28.607°)	100.0 %	99.7 %
Max. and min. transmission	1.000 and 0.836	1.000 and 0.836	1.000 and 0.747	0.701 and 0.582	1.000 and 0.428
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	13586 / 451 / 972	3125 / 30 / 282	24245 / 1 / 767	5151 / 0 / 196	6638 / 0 / 407
Goodness-of-fit on F^2	1.086	1.087	1.091	1.105	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0747, wR2 = 0.1703	R1 = 0.0969, wR2 = 0.1878	R1 = 0.0806, wR2 = 0.2053	R1 = 0.0258, wR2 = 0.0577	R1 = 0.0351, wR2 = 0.0846
R indices (all data)	R1 = 0.0849, wR2 = 0.1777	R1 = 0.1688, wR2 = 0.2275	R1 = 0.0976, wR2 = 0.2213	R1 = 0.0295, wR2 = 0.0590	R1 = 0.0447, wR2 = 0.0891
$\Delta\rho$ (max, min) ($e.Å^{-3}$)	0.498 and -0.274	0.238 and -0.201	0.312 and -0.2451	0.427 and -0.395	0.541 and -0.411

Table S3. Main crystallographic data and refinement parameters of all cocrystal structures (part 1) not presented in the main manuscript.

Compound	1:1 Nefiracetam-5-nitroisophthalic acid FI	1:1 Nefiracetam-5-nitroisophthalic acid FII	1:1 Nefiracetam-5-bromoisophthalic acid	1:1 Nefiracetam-5-hydroxyisophthalic acid
Empirical formula	$C_{22}H_{23}N_3O_8$	$C_{22}H_{23}N_3O_8$	$C_{22}H_{23}BrN_2O_6$	$C_{22}H_{24}N_2O_7$
Formula weight ($g.mol^{-1}$)	457.43	457.43	491.33	428.43
Temperature (K)	297(2)	295(2)	297(2)	297(2)
Wavelength (Å)	1.54184	1.54184	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	Pc	$P2_1/c$	$P2_1/c$
a, b, c (Å)	7.87163(18),36.5803(6),8.70817(18)	6.33727(5),19.36454(12), 9.28378(8)	7.5009(5), 6.4477(18), 9.2134(5)	8.7567(4), 36.4005(17), 14.2304(6)
α, β, γ (°)	90, 115.254(3), 90	90, 99.8062(8), 90	90, 112.191 (8), 90	90, 102.985(4), 90
Volume ($Å^3$)	2267.84(9)	1122.644(14)	2332.3(3)	4419.9(3)
Z	4	2	4	8
Density ($g.cm^{-3}$)	1.340	1.353	1.399	1.288
Absorption coefficient (mm^{-1})	0.872	0.881	1.801	0.0997
F(000)	960	480	1008	1808
Crystal size (mm^3)	0.572 x 0.423 x 0.239	0.450 x 0.330 x 0.047	0.45 x 0.30 x 0.10	0.50 x 0.50 x 0.40
θ range for data collection (°)	4.836 to 67.118	2.282 to 67.115	3.439 to 25.790	2.918 to 26.267
Reflections collected	11946	24140	10325	31147
Completeness (%)	98.6 % (to theta = 67.118°)	99.5 (to theta = 67.115°)	96.8 (to theta = 25.242°)	99.0 (to theta = 25.242°)
Max. and min. transmission	1.000 and 0.918	0.960 and 0.763	1.000 and 0.705	1.000 and 0.873
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4012 / 147 / 441	3871 / 2 / 306	4295 / 5 / 320	8765 / 0 / 571
Goodness-of-fit on F^2	1.088	0.950	1.082	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1153	R1 = 0.0295, wR2 = 0.0885	R1 = 0.0515, wR2 = 0.1367	R1 = 0.0516, wR2 = 0.1404
R indices (all data)	R1 = 0.0510, wR2 = 0.1191	R1 = 0.0298, wR2 = 0.0892	R1 = 0.0767, wR2 = 0.1536	R1 = 0.0613, wR2 = 0.1477
Δρ (max, min) ($e.Å^{-3}$)	0.216 and -0.172	0.149 and -0.146	0.354 and -0.426	0.262 and -0.187

Table S4. Main crystallographic data and refinement parameters of all cocrystal structures (part 2) not presented in the main manuscript.

Compound	1:1 Nefiracetam-5-cyano-1,3-benzenedicarboxylic	Nefiracetam-(RS)-2-phenylbutyric acid	1:1 Nefiracetam-2-benzoylbenzoic acid	1:1 Nefiracetam-(RS)-3-phenyllactic acid
Empirical formula	$C_{23}H_{23}N_3O_6$	$C_{24}H_{30}N_2O_4$	$C_{28}H_{28}N_2O_5$	$C_{23}H_{28}N_2O_5$
Formula weight ($g.mol^{-1}$)	437.44	410.50	472.52	412.47
Temperature (K)	297(2)	297(2) K	297(2)	297(2) K

Wavelength (Å)	0.71073	0.71073 Å	0.71073	0.71073 Å
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	*Pc*	$P2_12_12$	*Pca*21	$P2_12_12_1$
a, b, c (Å)	6.1863(3), 19.5370(8), 9.3910(4)	41.158(2), 9.2846(6), 6.0202(4)	43.8966(14),6.04575(19),9.2293(3)	6.0151(5), 9.2249(6), 39.209(2)
α, β, γ (°)	90, 98.507, 90	90, 90, 90	90, 90, 90	90, 90, 90
Volume ($Å^3$)	1122.52(8)	2300.5(3)	2449.33(13)	2175.6(3) $Å^3$
Z	2	4	4	4
Density ($g.cm^{-3}$)	1.294	1.185 Mg/m^3	1.281	1.259 Mg/m^3
Absorption coefficient (mm^{-1})	0.095	0.081 mm^{-1}	0.088	0.089 mm^{-1}
F(000)	460	880	1000	880
Crystal size (mm^3)	0.35 x 0.28 x 0.09	0.490 x 0.301 x 0.148	0.28 x 0.19 x 0.02	0.410 x 0.270 x 0.085
Theta range for data collection (°)	3.026 to 25.243	2.249 to 25.679°	3.402 to 25.265	2.268 to 25.247°.
Reflections collected	7577	6688	19309	5814
Completeness (%)	94.9 (to theta = 25.242°)	99.5 %	99.2 (to theta = 25.242°)	99.0 %
Max. and min. transmission	1.00000 and 0.85329	0.959 and 0.871	1.00000 and 0.88720	0.975 and 0.923
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	7577 / 2 / 294	4063 / 81 / 360	4399 / 1 / 318	3606 / 0 / 275
Goodness-of-fit on F^2	1.040	1.082	1.077	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0404, wR2 = 0.1028	R1 = 0.0667, wR2 = 0.1123	R1 = 0.0442, wR2 = 0.1051	R1 = 0.0619, wR2 = 0.1027
R indices (all data)	R1 = 0.0589, wR2 = 0.1084	R1 = 0.1118, wR2 = 0.1320	R1 = 0.0514, wR2 = 0.1093	R1 = 0.0915, wR2 = 0.1211
Δρ (max, min) ($e.Å^{-3}$)	0.135 and -0.110	0.148 and -0.148	0.188 and -0.161	0.164 and -0.166

Table S5. Main crystallographic data and refinement parameters of all cocrystal structures (part 3) not presented in the main manuscript.

Compound	2:1 Nefiracetam-(RS)-phenylsuccinic acid	1:1 Nefiracetam-4-hydroxybenzoic acid	4:1:1 Nefiracetam-gallic acid-water
Empirical formula	$C_{76}H_{92}N_8O_{16}$	$C_{21}H_{24}N_2O_5$	$C_{64}H_{80}N_8O_{14}$
Formula weight ($g.mol^{-1}$)	1373.57	384.42	1185.36
Temperature (K)	293(2)	295(2)	293(2)
Wavelength (Å)	1.54184	1.54184	0.71073
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/n$	*P*-1
a, b, c (Å)	5.98623(16), 9.3427(2), 35.3554(9)	4.7571(2), 12.7544(5), 33.4306(15)	8.3372(5), 8.8647(12), 22.302(2)
α, β, γ (°)	90, 94.247(3), 90	90, 91.108(4), 90	87.663(10), 81.860 (7), 79.777(8)
Volume ($Å^3$)	1971.91(9)	2027.99(15)	1605.5(3)
Z	1	4	1
Density ($g.cm^3$)	1.157	1.259	1.226
Absorption coefficient (mm^{-1})	0.666	0.744	0.087
F(000)	732	816	632
Crystal size (mm^3)	0.533 x 0.333 x 0.270	0.480 x 0.350 x 0.240	0.55 x 0.10 x 0.06
θ range for data collection (°)	5.017 to 66.872°	2.644 to 67.194	2.902 to 25.090°

Reflections collected	11005	5363	16276
Completeness (%)	98.0 % (to theta = 66.872°)	98.4 % (to theta = 67.194°)	98.9% (to theta = 25.090°)
Max. and min. transmission	1.000 and 0.918	1.000 and 0.938	1.000 and 0.765
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3431 / 62 / 273	5363 / 0 / 264	5650 / 75 / 437
Goodness-of-fit on F^2	1.088	1.093	1.096
Final R indices [I>2sigma(I)]	R1 = 0.0799, wR2 = 0.1873	R1 = 0.0439, wR2 = 0.1385	R1 = 0.0666, wR2 = 0.1601
R indices (all data)	R1 = 0.0830, wR2 = 0.1889	R1 = 0.0547, wR2 = 0.1423	R1 = 0.0985, wR2 = 0.1765
Largest diff. peak and hole (e.$Å^{-3}$)	0.623 and -0.351	0.176 and -0.152	0.261 and -0.330

DVS and Moisture Exposure

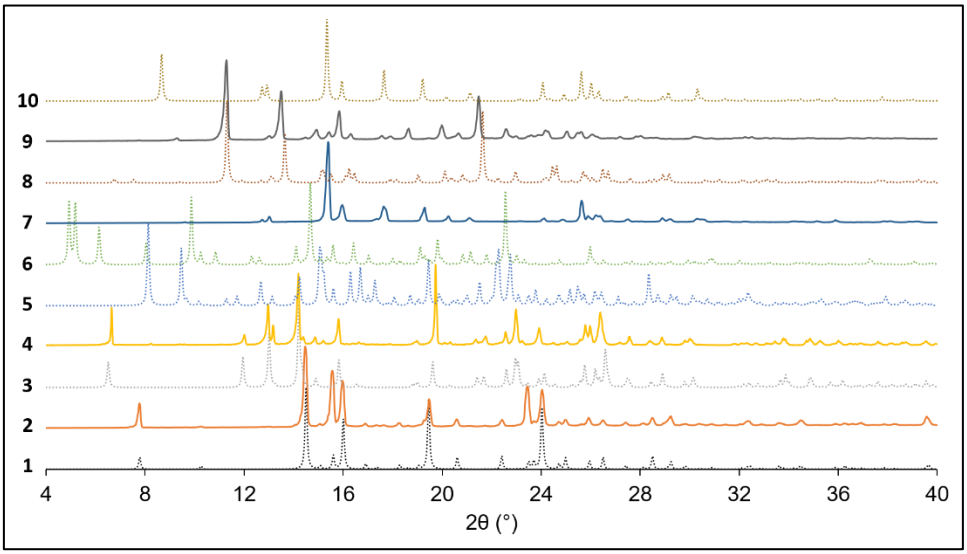

Figure S33. XRPD pattern of **1**: Nefiracetam FI (simulated), **2**: Nefiracetam after 7 days at 100%RH exposure, **3**: **NZC** (simulated), **4**: **NZC** (30 days at 100%RH), **5**: **NZCW** (simulated), **6**: **NCA** (simulated), **7**: **NCA** (30 days at 100%RH), **8**: **NOA** (simulated), **9**: **NOA** (30 days at 100%RH) and **10**: Nefiracetam monohydrate (simulated).

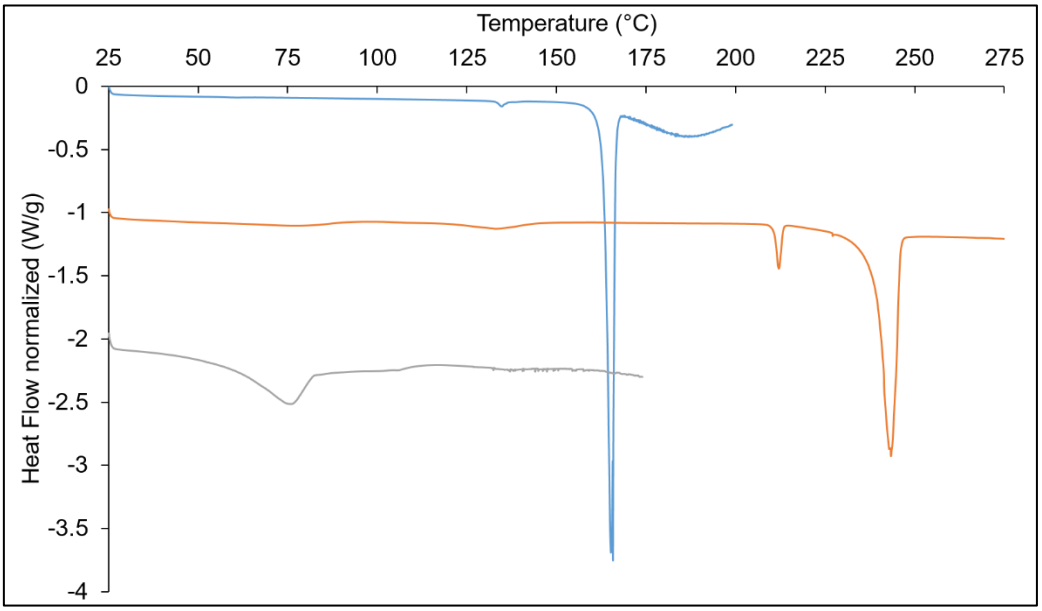

Figure S34. DSC curve of **NOA** (blue), **NZC** (orange) and **NCA** (grey) after 30 days under 100% RH exposure.

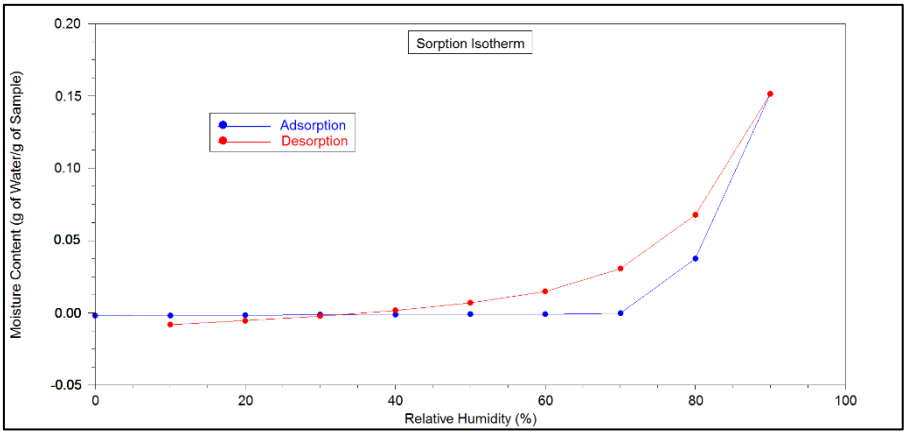

Figure S35. Sorption Isotherm (adsorption and desorption) of **NCA** at 25°C.

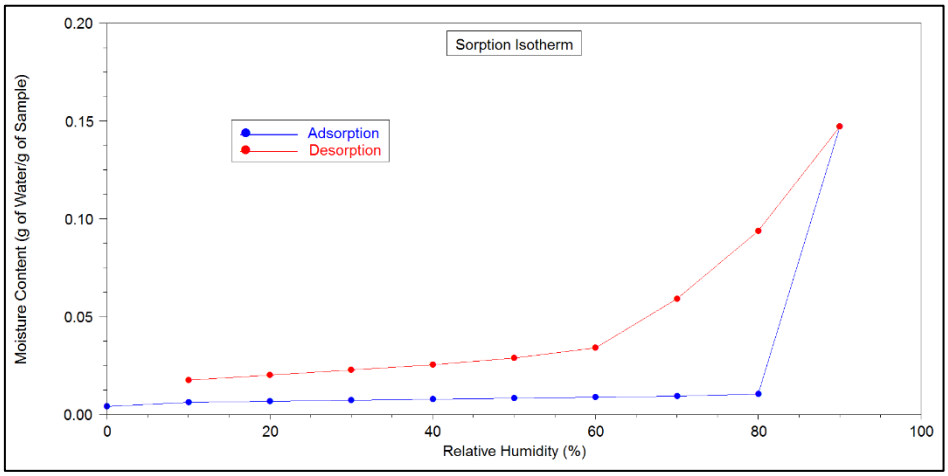

Figure S36. Sorption Isotherm (adsorption and desorption) of **NZC** at 25°C.

Dissolution Experiments

Calibration lines (HPLC and UVS)

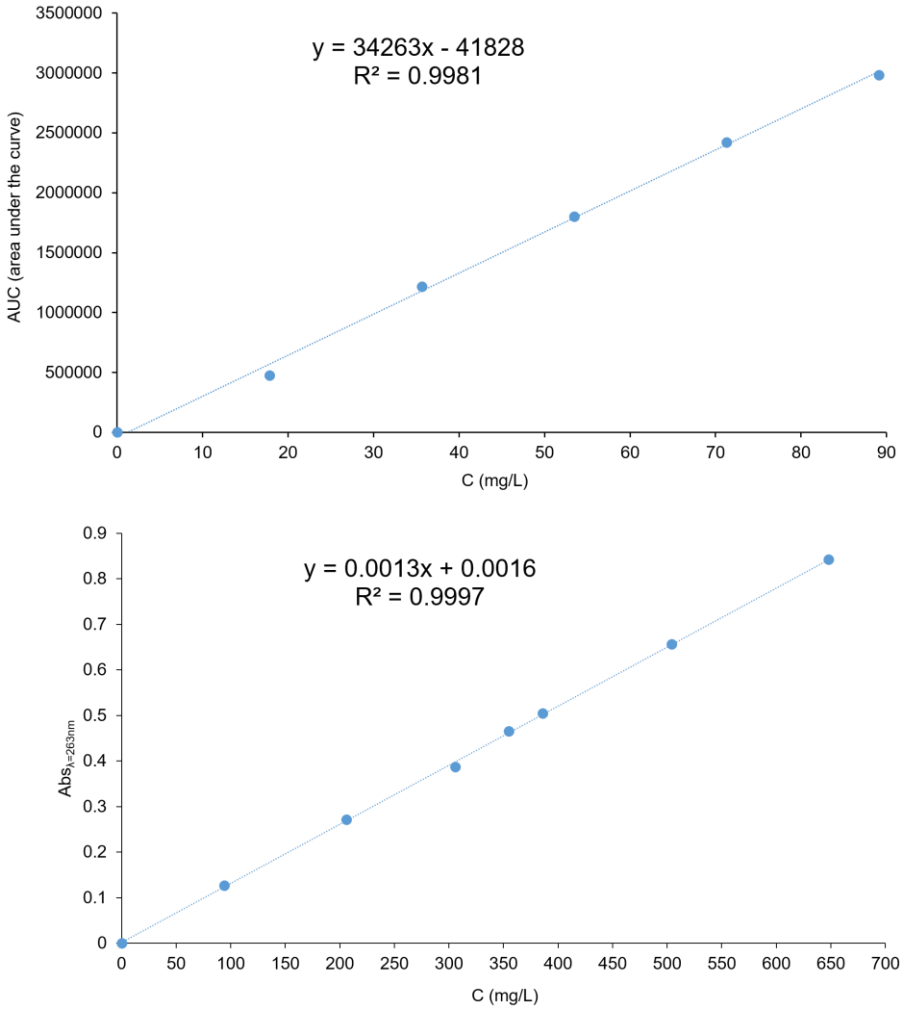

Figure S37. (top) Calibration line used to dose Nefiracetam in solution via HPLC during the dissolution experiments of **NCA** and **NOA** in EtOH and MeCN at 18°C. (below) Calibration line used to dose Nefiracetam in solution via UV spectroscopy during the dissolution experiments of **NZC** in EtOH and MeCN at 18°C.

HPLC data

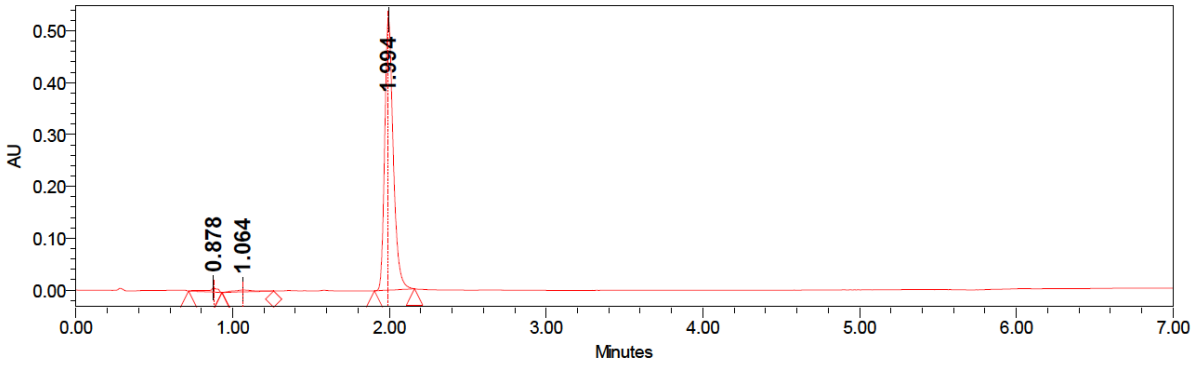

Figure S38. Typical HPLC chromatogram obtained during the quantitative analysis of Nefiracetam from the dissolution experiments.

Table S6. Summary of the data used to build the dissolution curves of **Nefiracetam** in EtOH and MeCN at 18°C under 100 rpm.

NEFIRACETAM	**ACETONITRILE**			**ETHANOL**		
Sampling time (min)	Dilution factor	Retention time (min)	AUC	Dilution factor	Retention time (min)	AUC
0	0	0	0	0	0	0
0.08333333	2000	2.014	412097	2500	2.022	599373
0.16666667						
0.25						
0.33333333	2000	1.994	1123353	2500	2.003	891775
0.41666667						
0.5	2000	1.994	1221140			
0.58333333				2500	2.001	1430751
0.66666667	2000	1.993	1360187			
0.75						
0.83333333				2500	2.001	1660412
1	2000	1.998	1290697		2.030	1803989
1.5	2000	1.999	1443300			
2	2000	1.998	1233092	2000	1.994	1903925
2.5	2000	1.998	1361664			
3	2000	2.000	1021522			
3.5						
4	2000	1.998	1401631	2000	1.996	1810678
4.5						
5	2000	1.998	1258620	2000	1.994	2058476
6				2000	1.994	1975186
7				2000	1.992	1797448
8				2000	1.994	1975222
9				2000	1.996	1688667
10	2000	1.996	1402725	2000	1.994	1994076
11				2000	1.994	1781480
12				2000	1.995	2119195
12.5				2000	1.994	1980331
13						
14				2000	1.995	2200488
15	2000	1.998	1333962	2000	1.995	2191115
30	2000	1.997	1364834	2000	1.992	1746601
45						
60	2000	2.001	1438496	2000	1.995	1775440
120				2000	1.994	1653944
180	2000	2.000	1257201			
240						
1440	2500	1.998	1141196	4000	2.039	1030530
1440	2500	2.027	1233540	4000	2.007	1052120
1440	2500	2.000	1181260	4000	2.007	1052120

Table S7. Summary of the data used to build the dissolution curves of **NCA** in EtOH and MeCN at 18°C under 100 rpm.

NCA	**ACETONITRILE**			**ETHANOL**		
Sampling time (min)	Dilution factor	Retention time (min)	AUC	Dilution factor	Retention time (min)	AUC
0	0	0	0	0	0	0
0.08333333						
0.16666667	2000	2.024	463252			
0.25				4000	2.063	273133
0.33333333						
0.41666667						
0.5	2000	1.991	537961	4000	2.030	314596
0.58333333						
0.66666667						
0.75	2000	1.991	621607	4000	2.025	327294
0.83333333	2000	1.991	640564			
1				4000	2.028	402443
1.5	2000	1.990	1016079	4000	2.030	767192
2	2000	1.990	1038334	4000	2.030	1303657
2.5	2000	1.990	864520	4000	2.029	1256000
3	2000	1.991	1046076	4000	2.031	1279776
3.5	2000	1.989	1059647	4000	2.029	1366063
4	2000	1.991	1038926	4000	2.040	1292413
4.5	2000	1.991	1109477	4000	2.030	1463559
5	2000	1.991	1171218	4000	2.031	1462498
6	2000	1.990	1083436			
7	2000	1.991	1170866	4000	2.031	1351450
8	2000	1.989	1166090	4000	2.031	1400703
9	2500	1.993	914513	4000	2.029	1330640
10	2500	1.992	873151	4000	2.033	1038031
11						
12						
12.5	2500	1.991	945260			
13						
14						
15	2500	1.994	886622	5000	2.032	1207073
30	2500	1.997			2.028	1134123
45						
60	2500	1.996	1002506	5000	2.029	1198447
120	2500	1.998	1003643	5000	2.031	1293977
180						
240				5000	2.030	1247780
1440	2500	1.998	1063223	4000	2.040	1596102
1440	2500	1.997	1046565	4000	2.008	1558081
1440	2500	1.999	1034129	4000	2.008	1664379

Table S8. Summary of the data used to build the dissolution curves of **NOA** in EtOH and MeCN at 18°C under 100 rpm.

NOA	**ACETONITRILE**			**ETHANOL**		
Sampling time (min)	**Dilution factor**	**Retention time (min)**	**AUC**	Dilution factor	Retention time (min)	AUC
0	0	0	0	0	0	0
0.08333333						
0.16666667				2500	2.035	695955
0.25	2000	2.147	479717			
0.33333333						
0.41666667				2500	2.003	577502
0.5	2000	2.111	603500			
0.58333333						
0.66666667						
0.75	2000	2.108	773451	2500	2.006	2140568
0.83333333						
1	2000	2.106	785345	2500	2.003	596136
1.5	2000	2.107	692512	2500	2.004	826694
2	2000	2.105	822251	2500	2.005	905026
2.5	2000	2.104	872370	2500	2.004	2202520
3	2000	2.102	708751	2500	2.003	533911
3.5	2000	2.103	848988	2500	1.999	2307427
4	2000	2.099	796181			
4.5	2000	2.098	818237	2500	1.994	2394271
5	2000	2.096	861858	2500	2.000	2233971
6	2000	2.097	853860	2500	1.998	2359543
7	2000	2.095	851519	2500	1.998	2233371
8	2500	2.093	823877	2500	1.998	2211001
9	2500	2.094	661151	2500	1.997	2221166
10					1.998	2276022
11						
12						
12.5				2500	1.998	2268118
13						
14						
15	2500	2.091	667857	2500	1.998	2290064
30	2500	2.092	651070	2500	1.994	2399600
45						
60	2500	2.092	723930	2500	1.997	2360694
120	2500	2.090	652198	4000	1.997	2496967
180						
240	2500	2.089	645758			
1440	2500	2.085	682654	4000	1.997	1534584
1440	2500	2.007	688118	4000	2.000	1500012
1440	2500	2.003	681328	4000	1.998	1508041

UVS data

Table S9. Summary of the data used to build the dissolution curves of **NZC** in EtOH and MeCN at 18°C under 100 rpm.

NZC	**ACETONITRILE**			**ETHANOL**		
Sampling time (min)	**Dilution factor**	**Retention time (min)**	**Abs_{263}**	Dilution factor	Retention time (min)	Abs_{263}
0		-			-	
0.08333333		-			-	
0.16666667	250	-	0.0278	250	-	0.1135
0.25		-			-	
0.33333333		-			-	
0.41666667	250	-	0.0278	250	-	0.1350
0.5		-			-	
0.58333333		-			-	
0.66666667		-		250	-	0.1608
0.75		-			-	
0.83333333	250	-	0.0314		-	
1		-		250	-	0.1359
1.5	250	-	0.033	250	-	0.1544
2	250	-	0.0331	250	-	0.1036
2.5	250	-	0.0337	250	-	0.1237
3		-		250	-	0.1036
3.5	250	-	0.0341	250	-	0.1310
4	250	-	0.0376	250	-	0.1310
4.5	250	-	0.0374	250	-	0.1207
5	250	-	0.0342	250	-	0.1859
6	250	-	0.0328		-	
7	250	-	0.0331	250	-	0.1517
8	250	-	0.0333	250	-	0.1494
9	250	-	0.0326	250	-	0.1652
10	250	-	0.0337	250	-	0.1669
11		-			-	
12		-			-	
12.5	250	-	0.0337		-	
13		-			-	
14		-			-	
15	250	-	0.0337	250	-	0.1451
30		-			-	
45		-			-	
60	250	-	0.0333		-	
120	250	-	0.0333		-	
180		-			-	
240		-			-	
1440	250	-	0.0342	250	-	0.2590
1440	250	-	0.0334	250	-	0.2573
1440	250	-	0.035	250	-	0.2549