SUPPLEMENTARY MATERIALS

Complexation: An Interesting Pathway for Combining Two APIs at the Solid State

Fucheng Leng, Oleksii Shemchuk, Koen Robeyns and Tom Leyssens *

Institute of Condensed Matter and Nanosciences, Université catholique de Louvain, 1 Place Louis Pasteur, B-1348 Louvain-La-Neuve, Belgium.
Correspondence: tom.leyssens@uclouvain.be

Contents

1. Preparation method

Crystal	Single crystal preparation	Bulk preparation
$Zn(IBU)_2(NC)$,	Zinc acetate, Ibu, NC dissolved by methanol in 1:2:1, then evaporation	Slurrying $Zn(IBU)_2$ and NC in 1:1 ratio with ethyl acetate as solvent
$Zn(PABA)_2(INC)_2 \cdot 0.5H_2O$	Zinc acetate, PABA, INC dissolved by methanol in 1:2:2, then evaporation	
$Zn(PABA)(Ac)(MN)_2 \cdot H_2O$	Zinc acetate, PABA, MN dissolved by methanol in 1:1:2, then evaporation	
$Zn(PABA)_2(NC)_2$	Zinc acetate, PABA, NC dissolved by methanol in 1:2:2, then evaporation	
$Zn(PABA)_2(INZ) \cdot CH_3OH$	Zinc acetate, PABA, INZ dissolved by methanol in 1:2:1, then evaporation	
$Zn(IBU)_2(INC)$	$Zn(IBU)_2$, INC dissolved by methanol in 1:1, then evaporation	Slurrying $Zn(IBU)_2$ and INC in 1:1 ratio with methanol as solvent
$Zn(ASP)_2(MN)_2$	$Zn(ASP)_2$, MN dissolved by methanol in 1:2, then evaporation	
$Zn(ASP)_2(INC)$	$Zn(ASP)_2$, INC dissolve by methanol in 1:1, then evaporation	
$Zn(PABA)_2(MN)_2 \cdot H_2O$	$Zn(PABA)_2$, MN dissolve by methanol in 1:2, then evaporation	
$Zn(IBU)_2(AMI)$	$Zn(IBU)_2$, AMI dissolved by methanol in 1:4, then evaporation and cool in fridge	Slurrying $Zn(IBU)_2$ and AMI in 1:1 ratio with isopropanol as solvent
$Zn(IBU)_2(INC)_2(H_2O)_2$	$Zn(IBU)_2$, INC dissolved by methanol/H_2O mixed solvent(7:3) in 1:2, then evaporation	Slurrying $Zn(IBU)_2$ and INC in 1:2 ratio with water as solvent
$Zn(IBU)_2(INZ)$	$Zn(IBU)_2$, INZ dissolved by methanol/H_2O mixed solvent(7:3) in 1:1, then evaporation	Slurrying $Zn(IBU)_2$ and INZ in 1:1 ratio with water as solvent
$Zn(PABA)_2(AMI)_2$	stoichiometric quantities of Zinc acetate, Ibu, NC dissolve in methanol than evaporation	

2. Crystallographic data.

Table S1a. Crystal data and structure refinement for the investigated structures. CCDC 2194913-2194925 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.

Identification code	**$Zn(IBU)_2(NC)$**	**$Zn(IBU)_2(INC)_2(H_2O)_2$**	**$Zn(IBU)_2(INZ)$**	**$Zn(PABA)_2(INC)_2\cdot(H_2O)_{0.5}$**	**$Zn(IBU)_2(INC)$**	**$Zn(PABA)_2(AMI)_2$**	**$Zn_2(ASP)_4(INC)_2$**
Empirical formula	$C_{64}\ H_{80}\ N_4\ O_{10}\ Zn_2$	$C_{38}\ H_{50}\ N_4\ O_8\ Zn$	$C_{32}\ H_{42}\ N_3\ O_5\ Zn$	$C_{52}\ H_{50}\ N_{12}\ O_{13}\ Zn_2$	$C_{38}\ H_{46}\ N_4\ O_6\ Zn$	$C_{62}\ H_{82}\ N_6\ O_8\ Zn_2$	$C_{30}\ H_{26}\ N_4\ O_{10}\ Zn$
Formula weight	1196.06	756.19	614.05	1181.78	720.16	1170.07	667.92
Temperature (K)	297(2)	297(2)	297(2)	297(2)	297(2)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*P*-1	*P*-1	$P2_1/c$	*I*2/*a*	*I*2/*a*	*P*-1	$P2_1/c$
Unit cell dimensions (Å,°)	a = 10.8461(8)	a = 5.5047(5)	a = 5.49695(15)	a = 22.7349(13)	a = 20.7691(13)	a = 10.7578(13)	a = 19.2090(10)
	b = 11.1730(14)	b = 10.9599(6)	b = 15.4850(5)	b = 11.6737(6)	b = 5.4155(3)	b = 11.2000(9)	b = 8.4481(6)
	c = 15.667(2)	c = 16.9517(16)	c = 36.8845(9)	c = 20.3594(11)	c = 33.352(2)	c = 14.613(2)	c = 19.0056(12)
	α= 109.991(12)	α= 72.152(7)	α= 90	α= 90	α= 90	α= 84.364(10)	α= 90
	β= 95.467(9)	β= 86.676(8)	β= 89.950(3)	β= 90.019(5)	β= 105.757(6)	β= 75.219(12)	β= 94.578(5)
	γ = 111.284(10)	γ = 89.379(6)	γ = 90	γ = 90	γ = 90	γ = 65.014(11)	γ = 90
Volume ($Å^3$)	1609.5(4)	971.83(14)	3139.61(15)	5403.4(5)	3610.3(4)	1543.0(4)	3074.4(3)
Z	1	1	4	4	4	1	4
Density (calc.) (g/cm^3)	1.234	1.292	1.299	1.453	1.325	1.259	1.443
Absorption coeff. (mm^{-1})	0.802	0.686	0.825	0.963	0.731	0.834	0.862
F(000)	632	400	1300	2440	1520	620	1376
Crystal size (mm^3)	0.50x 0.07 x 0.05	0.20x 0.10 x 0.06	0.30x 0.18 x 0.01	0.80x 0.10 x 0.04	0.15x 0.05 x 0.03	0.15x 0.15 x 0.10	0.50x 0.50 x 0.05
Theta range for data collection (°)	3.280 to 25.255	3.639 to 25.246	3.059 to 25.254	3.205 to 26.148	2.538 to 26.034	3.255 to 25.514	2.640 to 25.417
Reflections collected	19056	14375	5682	17451	12341	18613	5552
Independent reflections	5803 [R(int) = 0.0682]	3521 [R(int) = 0.0633]	5682 [R(int) = ?]	5357 [R(int) = 0.0415]	3559 [R(int) = 0.0480]	5740 [R(int) = 0.0560]	5552 [R(int) = ?]
Completeness to θ=25.242° (%)	99.7	99.8	99.6	99.6	99.8	99.7	99.8
Absorption correction	Semi-empirical from equivalents						
Max. and min. transmission	1.00000 and 0.46090	1.00000 and 0.87178	1.00000 and 0.07930	1.00000 and 0.87119	1.00000 and 0.88261	1.00000 and 0.84376	1.00000 and 0.72332
Refinement method	Full-matrix least-squares on F^2						
Data / restraints / parameters	5803 / 317 / 548	3521 / 127 / 278	5682 / 52 / 407	5357 / 1 / 360	3559 / 46 / 255	5740 / 197 / 450	5552 / 0 / 410
Goodness-of-fit on F^2	1.095	1.058	1.059	1.051	1.038	1.033	1.097
Final R indices [I>2s(I)]	R1 = 0.0636, wR2 = 0.1546	R1 = 0.0552, wR2 = 0.1423	R1 = 0.0359, wR2 = 0.1003	R1 = 0.0368, wR2 = 0.0959	R1 = 0.0439, wR2 = 0.0986	R1 = 0.0559, wR2 = 0.1429	R1 = 0.0640, wR2 = 0.1686

R indices (all data)	R1 = 0.0815, wR2 = 0.1645	R1 = 0.0639, wR2 = 0.1494	R1 = 0.0392, wR2 = 0.1028	R1 = 0.0454, wR2=0.1011	R1 = 0.0611, wR2 = 0.1055	R1 = 0.0699, wR2 = 0.1520	R1 = 0.0732, wR2 = 0.1753
Δρ (max,min)(e.Å^{-3})	1.113, -0.562	1.319, -0.434	0.338, -0.325	0.481, -0.238	0.375, -0.325	0.865, -0.817	1.101, -0.488

Table S1b. Crystal data and structure refinement for the investigated structures.

Identification code	**Zn(IBU)$_2$(AMI)**	**Zn(PABA)$_2$(NIC)$_2$**	**Zn(PABA)(Ac)(MN)$_2$·H$_2$O**	**Zn(PABA)$_2$(MN)$_2$·H$_2$O**	**Zn(PABA)$_2$(INZ)·CH$_3$OH**	**Zn(PABA)$_2$(AMI)$_2$**
Empirical formula	C_{62} H_{82} N_6 O_8 Zn_2	C_{26} H_{24} N_6 O_6 Zn	C_{32} H_{32} N_4 O_{12} Zn_2	C_{28} H_{28} N_4 O_9 Zn	C_{21} H_{23} N_5 O_6 Zn	C_{24} H_{26} N_8 O_4 Zn
Formula weight	1170.07	581.88	795.35	629.91	506.81	555.90
Temperature (K)	297(2)	297(2)	297(2)	297(2)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*P*-1	*C*2/*c*	*P*2$_1$/*n*	*P*2/*c*	*P*-1	*P*2$_1$/*c*
Unit cell dimensions (Å,°)	a = 10.7578(13)	a = 27.119(2)	a = 10.5805(10)	a = 15.2611(14)	a = 9.6899(17)	a = 10.0747(10)
	b = 11.2000(9)	b = 5.8028(5)	b = 12.6078(14)	b = 16.2486(11)	b = 10.4485(7)	b = 19.0081(18)
	c = 14.613(2)	c = 16.6168(15)	c = 13.0496(15)	c = 11.2437(7)	c = 12.2345(16)	c = 13.0252(13)
	α= 84.364(10)	α= 90	α= 90	α= 90	α= 70.702(10)	α= 90
	β= 75.219(12)	β= 97.624(8)	β= 107.058(12)	β= 103.123(8)	β= 88.709(12)	β= 103.795(11)
	γ = 65.014(11)	γ = 90	γ = 90	γ = 90	γ = 73.166(11)	γ = 90
Volume (Å^3)	1543.0(4)	2591.8(4)	1664.2(3)	2715.3(4)	1115.3(3)	2422.4(4)
Z	1	4	2	4	2	4
Density (calc.) (g/cm^3)	1.259	1.491	1.587	1.541	1.509	1.524
Absorption coeff. (mm^{-1})	0.834	1.001	1.511	0.968	1.149	1.063
F(000)	620	1200	816	1304	524	1152
Crystal size (mm^3)	0.15x 0.15 x 0.10	0.30x 0.10 x 0.08	0.30x 0.30 x 0.25	0.30x 0.28 x 0.10	0.50x 0.10 x 0.04	0.20x 0.20 x 0.15
Theta range for data collection (°)	3.255 to 25.514	3.068 to 26.195	2.721 to 26.206	2.398 to 25.772	2.586 to 26.185	2.681 to 26.324
Reflections collected	18613	8735	9950	7886	15465	15722
Independent reflections	5740 [R(int) = 0.0560]	2582 [R(int) = 0.0448]	3308 [R(int) = 0.0271]	7886 [R(int) = ?]	4324 [R(int) = 0.0269]	4878 [R(int) = 0.0371]
Completeness to θ=25.242° (%)	99.7	99.7	99.6	99.7	97.7	99.7
Absorption correction	Semi-empirical from equivalents					
Max. and min. transmission	1.00000 and 0.84376	1.00000 and 0.88234	1.00000 and 0.94940	1.00000 and 0.81152	1.00000 and 0.75799	1.00000 and 0.44842
Refinement method	Full-matrix least-squares on F^2					
Data / restraints / parameters	5740 / 197 / 450	2582 / 0 / 177	3308 / 0 / 231	7886 / 0 / 385	4324 / 0 / 300	4878 / 0 / 334
Goodness-of-fit on F^2	1.033	1.072	1.034	1.050	1.046	1.026
Final R indices [I>2s(I)]	R1 = 0.0559, wR2 = 0.1429	R1 = 0.0350, wR2 = 0.0826	R1 = 0.0290, wR2 = 0.0759	R1 = 0.0602, wR2 = 0.1538	R1 = 0.0370, wR2 = 0.1020	R1 = 0.0405, wR2 = 0.0989
R indices (all data)	R1 = 0.0699, wR2 = 0.1520	R1 = 0.0420, wR2 = 0.0857	R1 = 0.0326, wR2 = 0.0781	R1 = 0.0750, wR2 = 0.1608	R1 = 0.0385, wR2 = 0.1034	R1 = 0.0504, wR2 = 0.1049
Δρ (max,min)(e.Å^{-3})	0.865, -0.817	0.284, -0.181	0.338, -0.244	0.623, -0.585	0.750, -0.532	0.461, -0.411

3. Crystal structures.

3.1 Complexes of $Zn(IBU)_2$

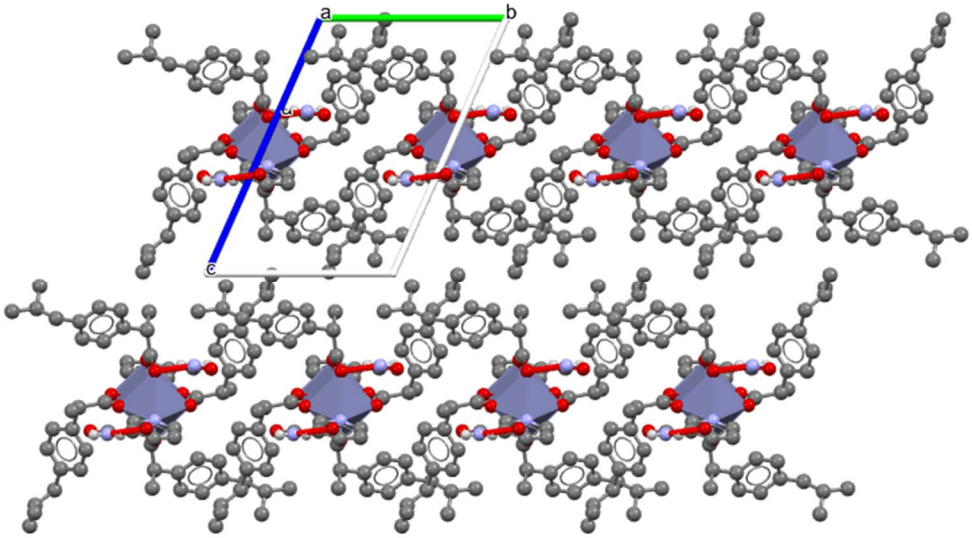

Figure S1. Crystal packing of $Zn(IBU)_2(NC)$; view along crystallographic a-axis. H_{CH} are omitted for clarity.

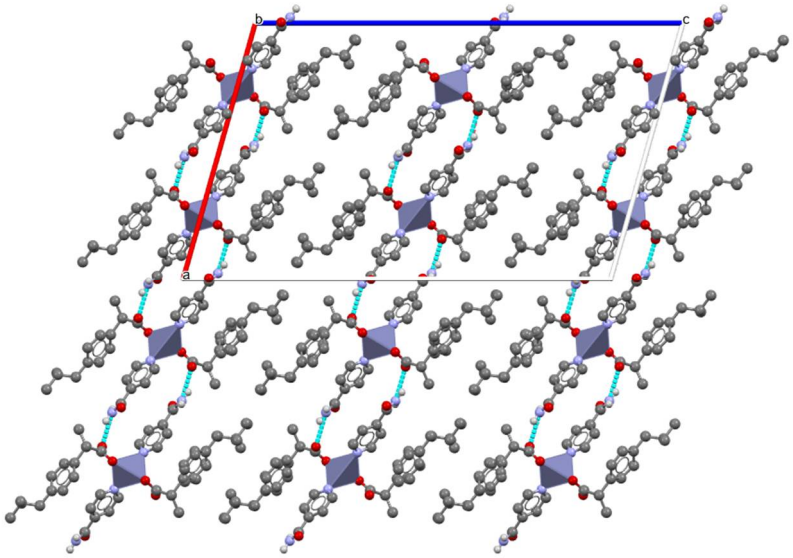

Figure S2. Crystal packing of $Zn(IBU)_2(INC)_2$; view along crystallographic b-axis. H_{CH} are omitted for clarity.

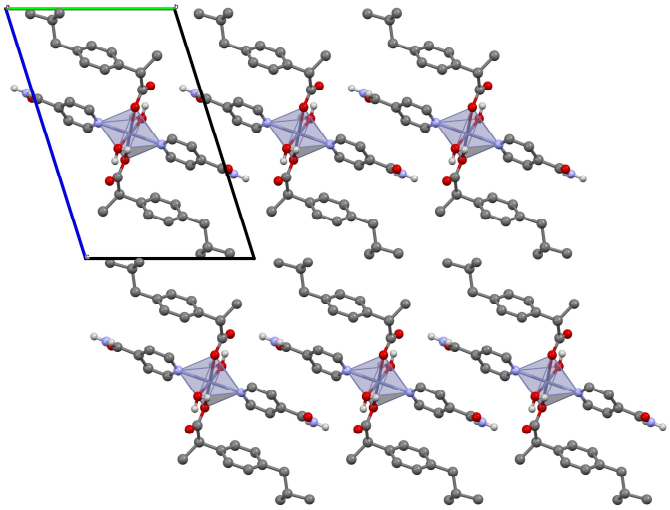

Figure S3. Crystal packing of $Zn(IBU)_2(INC)_2(H_2O)_2$; view along crystallographic b-axis. H_{CH} omitted for clarity.

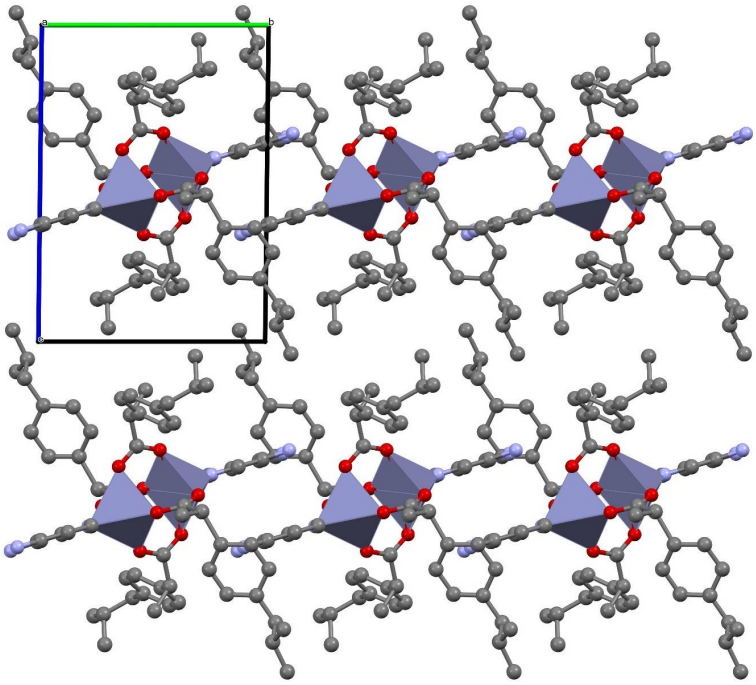

Figure S4. Crystal packing of $Zn(IBU)_2(AMI)$; view down crystallographic a-axis. Hydrogen atoms omitted for clarity.

3.2 Complexes of $Zn(PABA)_2$

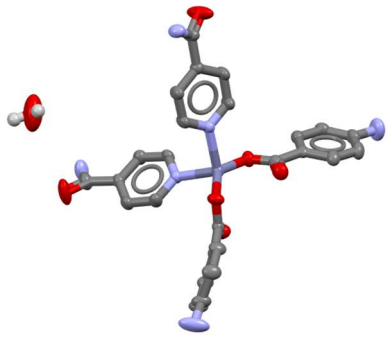

Figure S5. Tetragonal coordination structure in $Zn(PABA)_2(INC)_2 \cdot 0.5H_2O$. Hydrogen atoms are omitted for clarity.

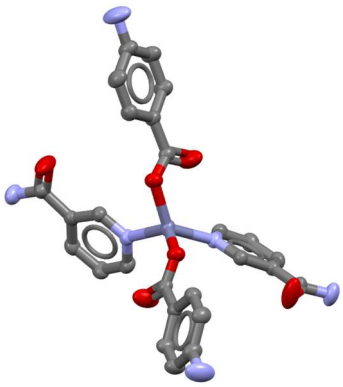

Figure S6. Tetragonal coordination structure in $Zn(PABA)_2(NC)_2$. Hydrogen atoms are omitted for clarity.

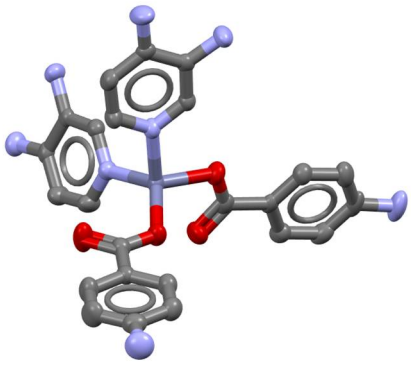

Figure S7. Tetragonal coordination structure in $Zn(PABA)_2(AMI)_2$. Hydrogen atoms are omitted for clarity.

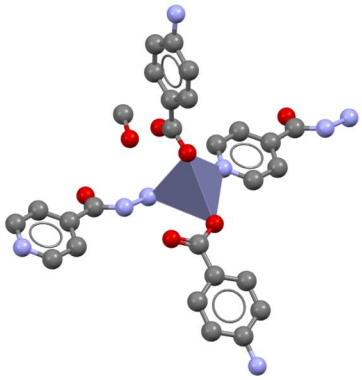

Figure S8. Tetragonal coordination structure in $Zn(PABA)_2(INZ)\cdot CH_3OH$. Hydrogen atoms omitted for clarity.

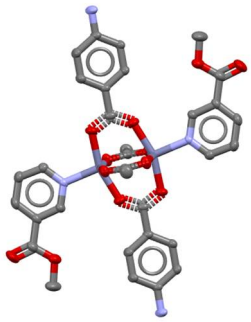

Figure S9. Paddle-wheel coordination structure in $Zn(PABA)(Ac)(MN)\cdot H_2O$. Hydrogen atoms are omitted for clarity.

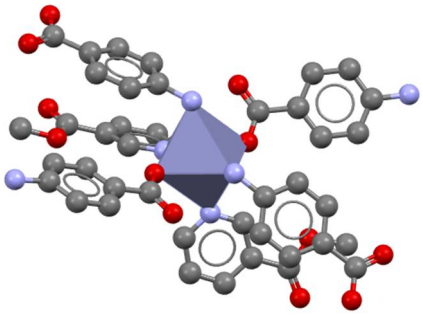

Figure S10. Octahedral coordination structure in $Zn(PABA)_2(MN)_2\cdot H_2O$. Hydrogen atoms omitted for clarity.

3.3 Complexes of $Zn(ASP)_2$

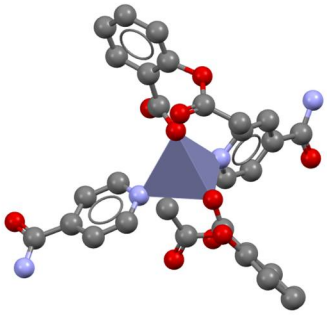

Figure S11. tetragonal coordination structure in Zn $(ASP)_2(INC)_2$. Hydrogen atoms omitted for clarity.

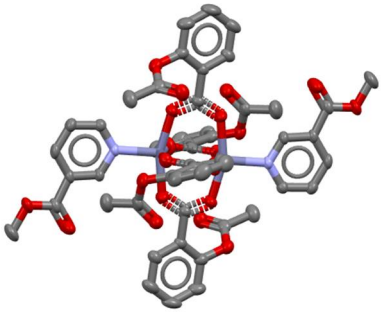

Figure S12. Paddle-wheel coordination structure in $Zn(ASP)_2(MN)$. Hydrogen atoms omitted for clarity.

3. Thermal analyses.

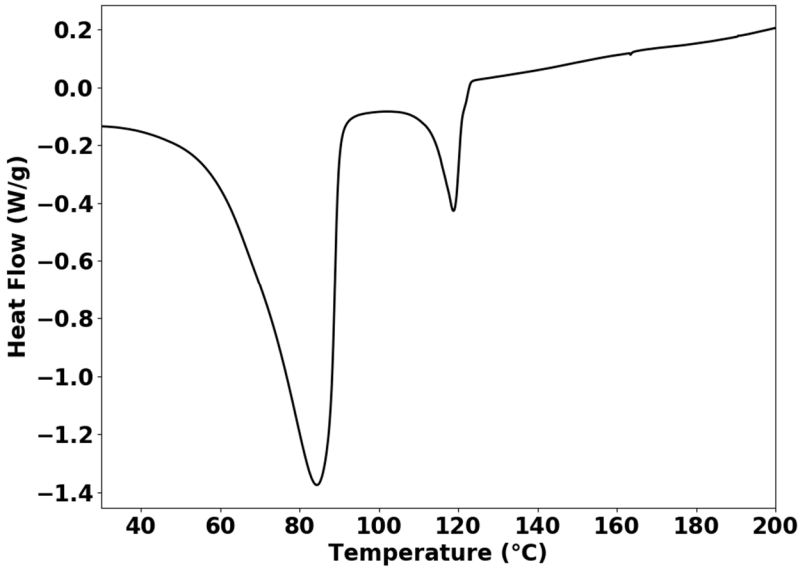

Figure S13. DSC thermogram of $Zn(IBU)_2(H_2O)_2$.

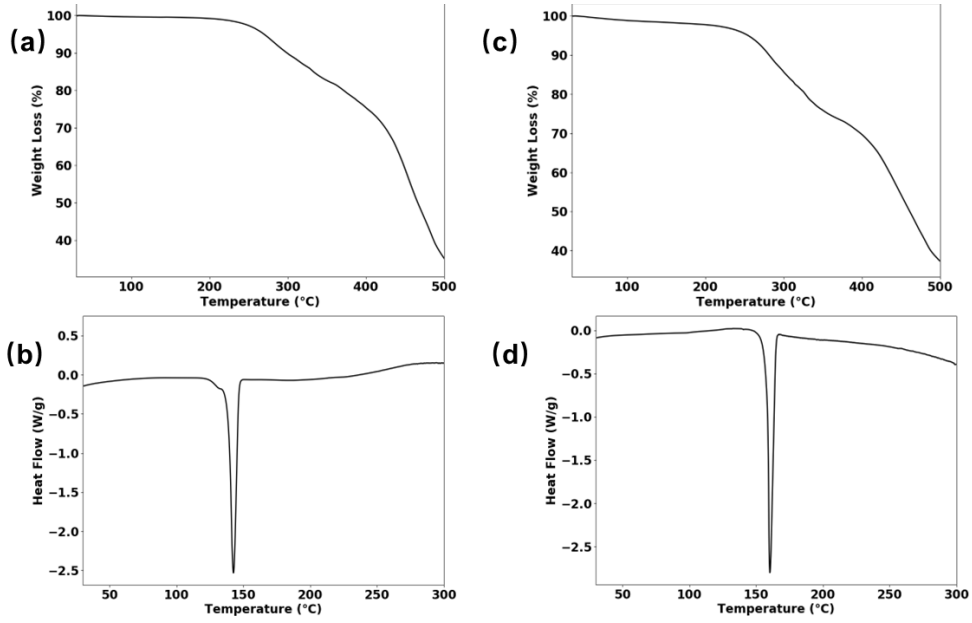

Figure S14 TGA and DSC thermograms of $Zn(IBU)_2(AMI)$ (**a** and **b**) and of $Zn(IBU)_2(AMI)_2$ (**c** and **d**).

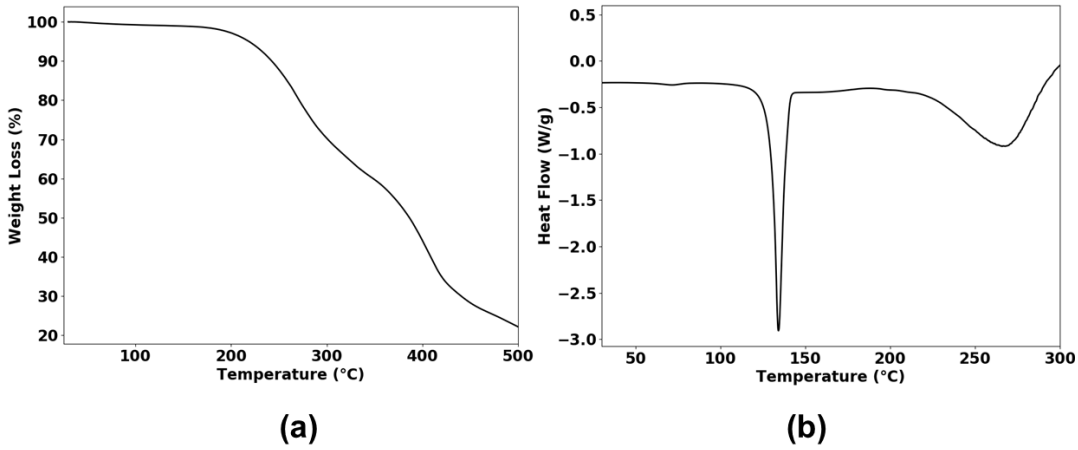

Figure S15. TGA (**a**) and DSC (**b**) thermograms of $Zn(IBU)_2(NC)$.

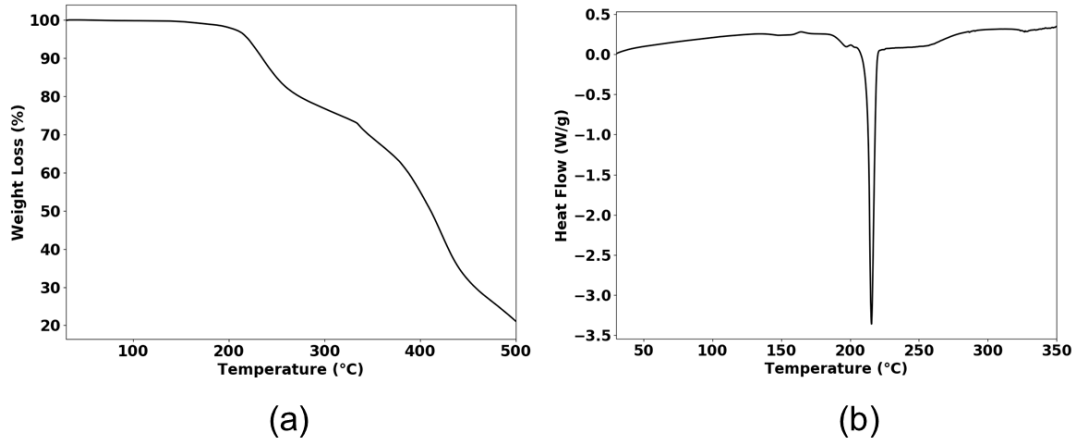

Figure S16. TGA (**a**) and DSC (**b**) thermograms of $Zn(IBU)_2(INZ)$.

4. PXRD patterns

4.1 The comparison of experimental and simulated PXRD patterns of Zn(IBU)$_2$-PD complexes.

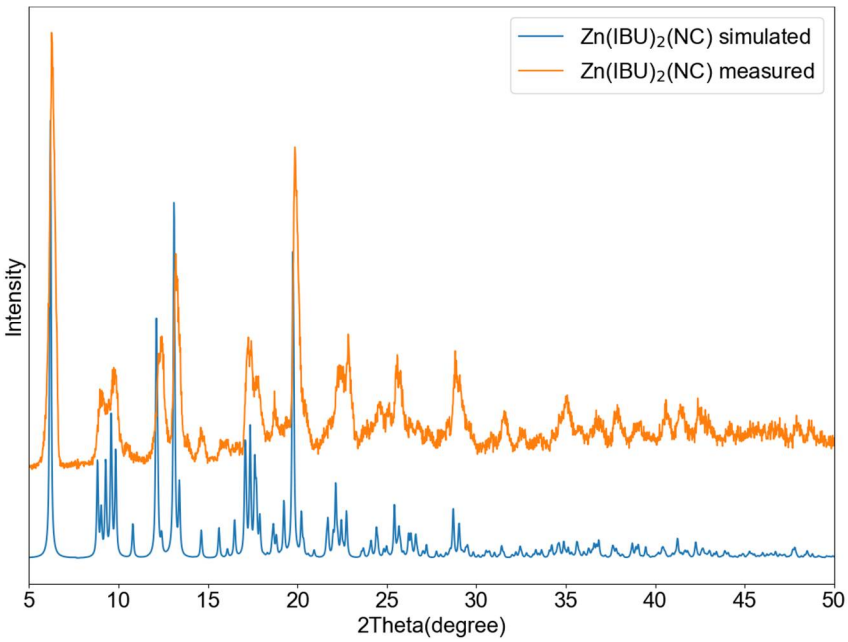

Figure S17. Comparison between the experimental (obtained by slurry in acetonitrile) and calculated PXRD patterns for Zn(IBU)$_2$(NC).

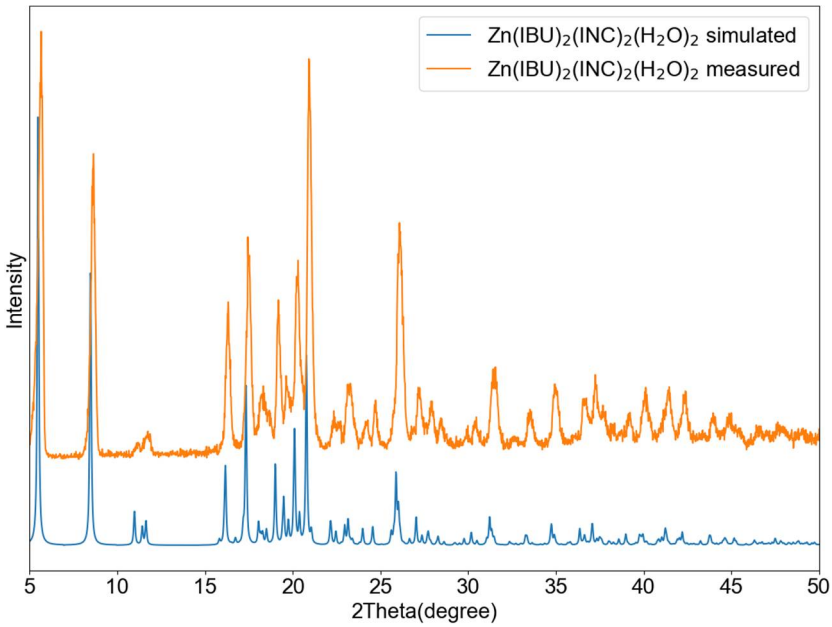

Figure S18. Comparison between the experimental (obtained by slurry in H_2O) and calculated PXRD patterns for Zn(IBU)$_2$(INC)$_2$(H_2O)$_2$.

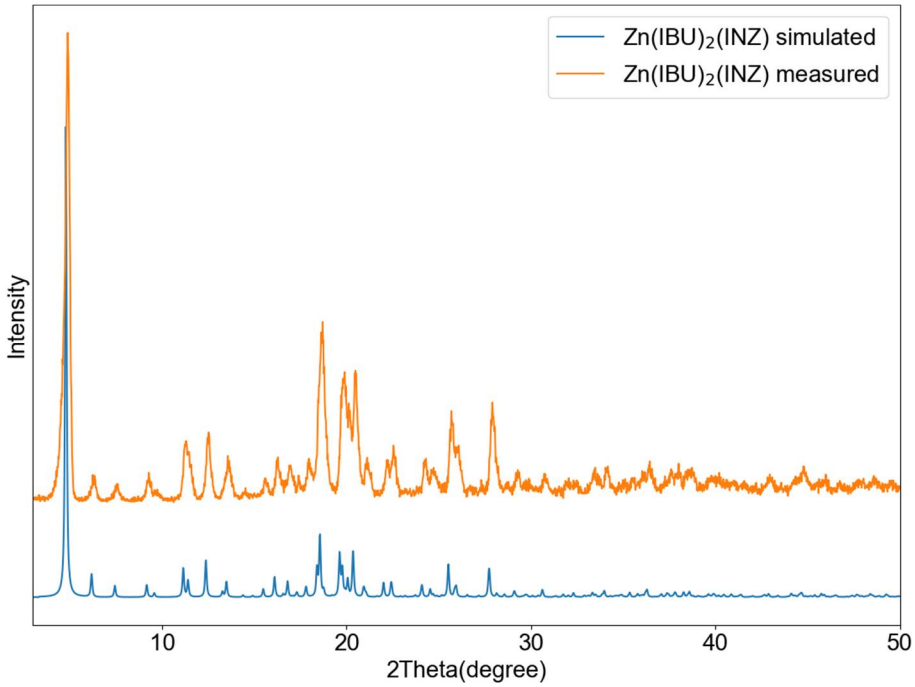

Figure S19. Comparison between the experimental (obtained by slurry in H_2O) and calculated PXRD patterns for $Zn(IBU)_2(INZ)$.

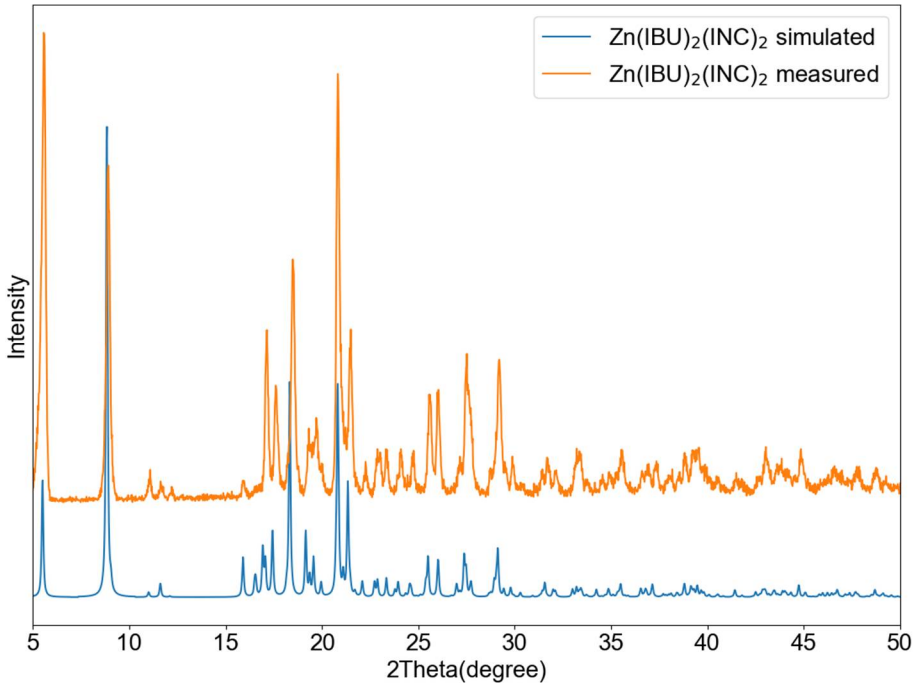

Figure S20. Comparison between the experimental (obtained by slurry in H_2O) and simulated PXRD patterns for $Zn(IBU)_2(INC)_2$.

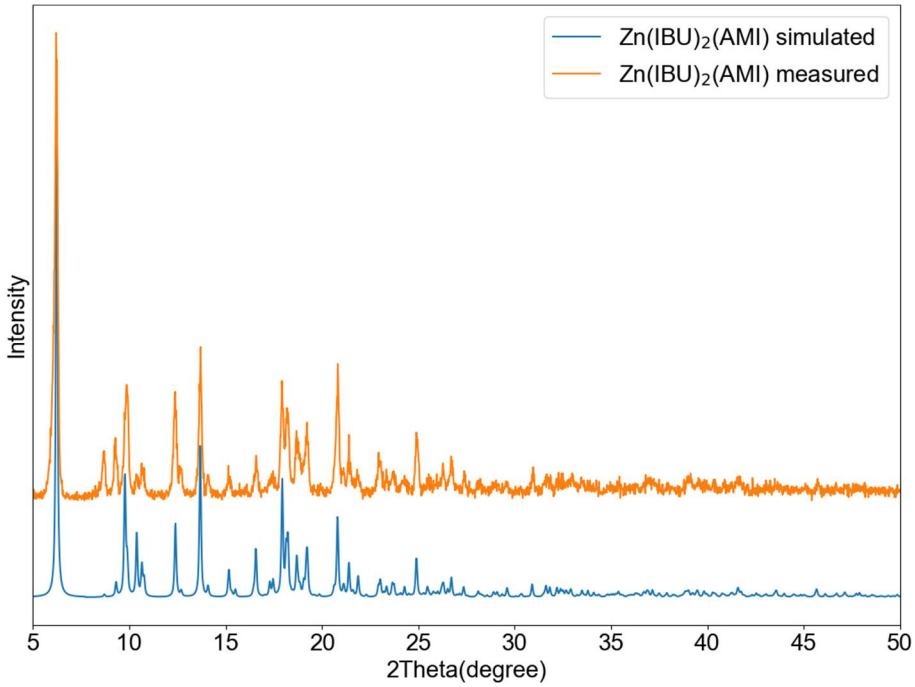

Figure S21. Comparison between the experimental (obtained by slurry in H_2O) and simulated PXRD patterns for $Zn(IBU)_2(AMI)$.

4.2 Mechanochemical screening results

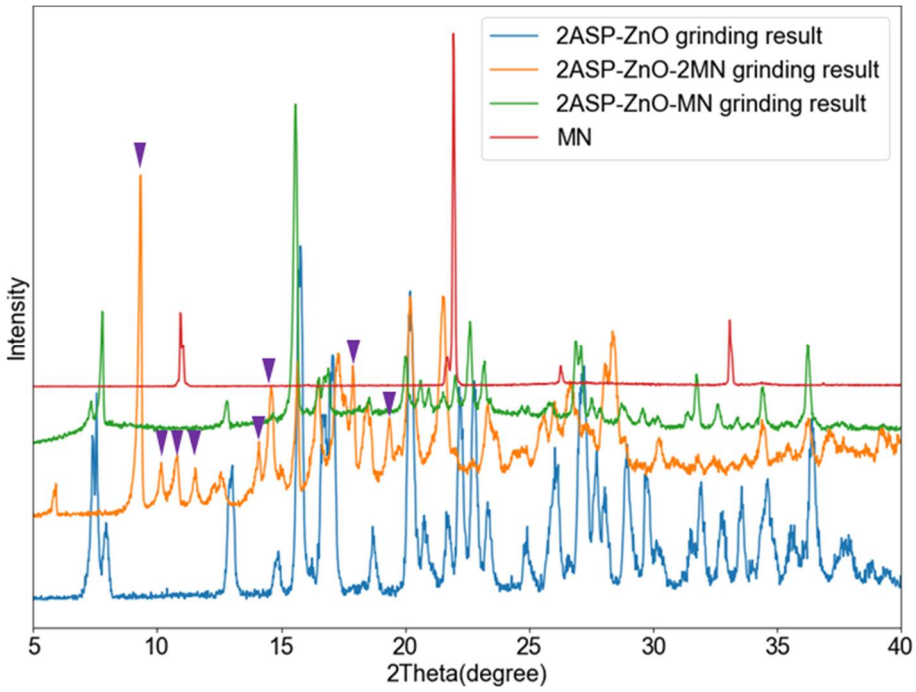

Figure S22. Comparison of PXRD patterns for MN (red), ASP-ZnO grinding result in 2:1 (blue) as well as ASP-ZnO-MN three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

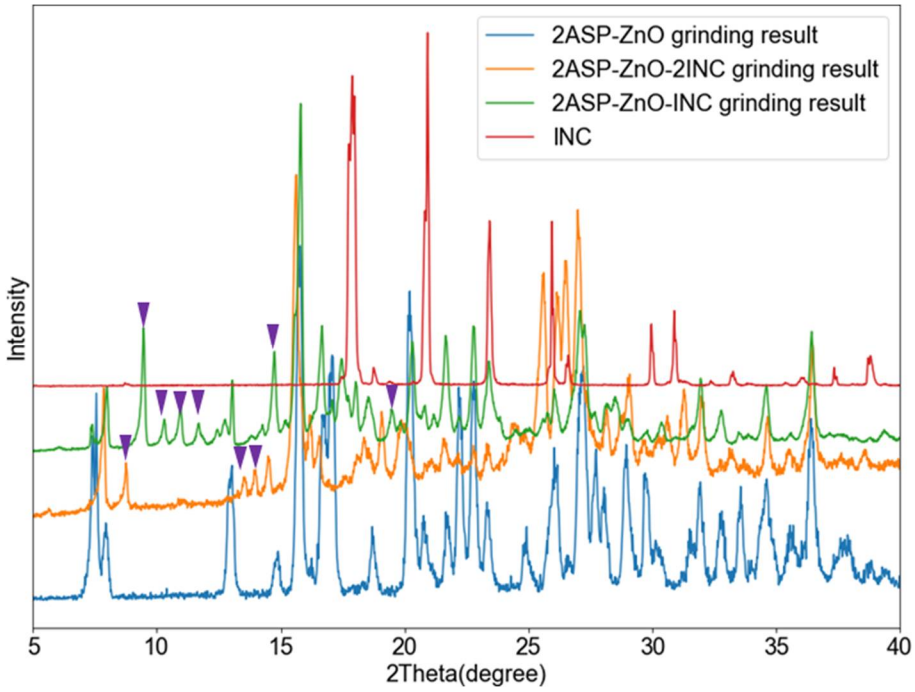

Figure S23. Comparison of PXRD patterns for INC (red), ASP-ZnO grinding result in 2:1 (blue) as well as ASP-ZnO-INC three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

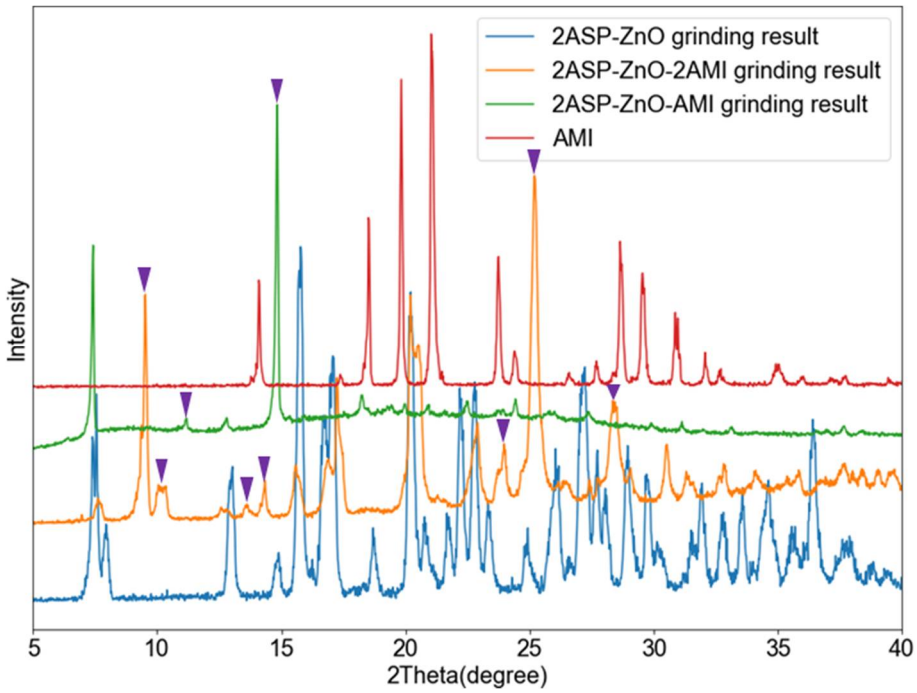

Figure S24. Comparison of PXRD patterns for AMI (red), ASP-ZnO grinding result in 2:1 (blue) and ASP-ZnO-AMI three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

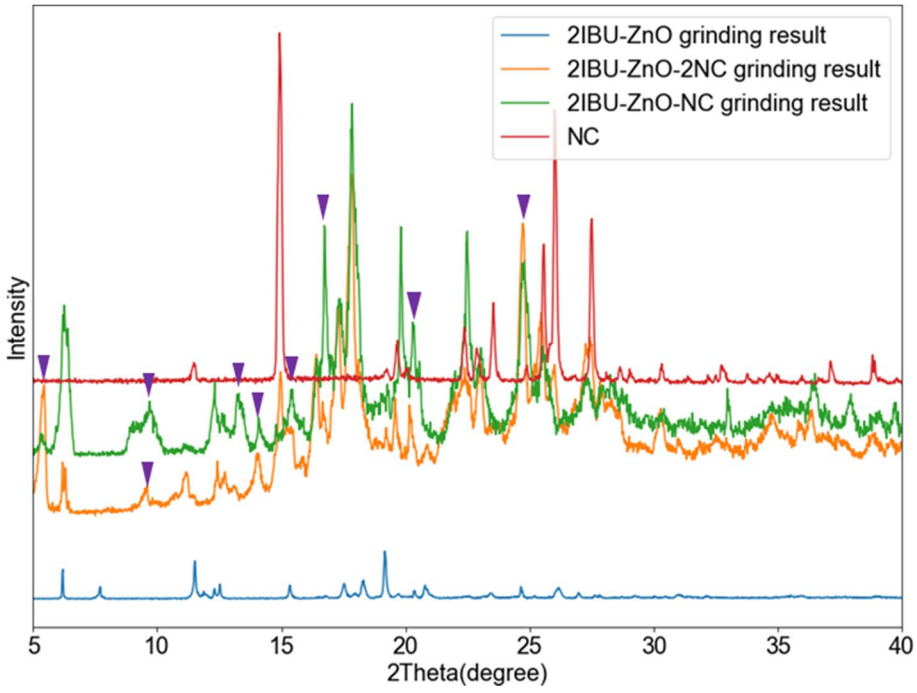

Figure S25. Comparison of PXRD patterns for NC (red), IBU-ZnO grinding result in 2:1 (blue) and IBU-ZnO-NC three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

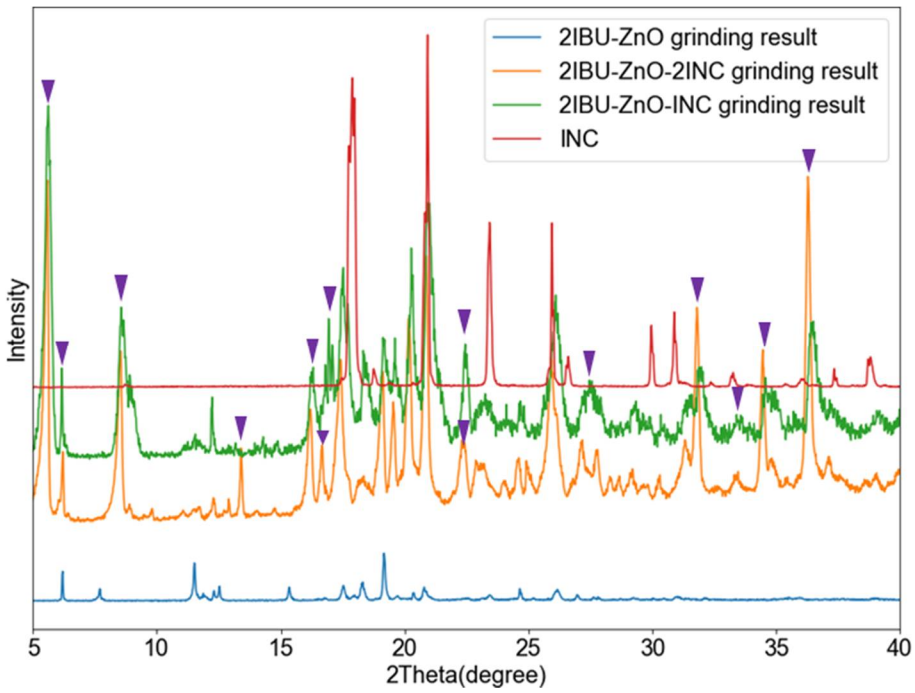

Figure S26. Comparison of PXRD patterns for INC (red), IBU-ZnO grinding result in 2:1 (blue) and IBU-ZnO-INC three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

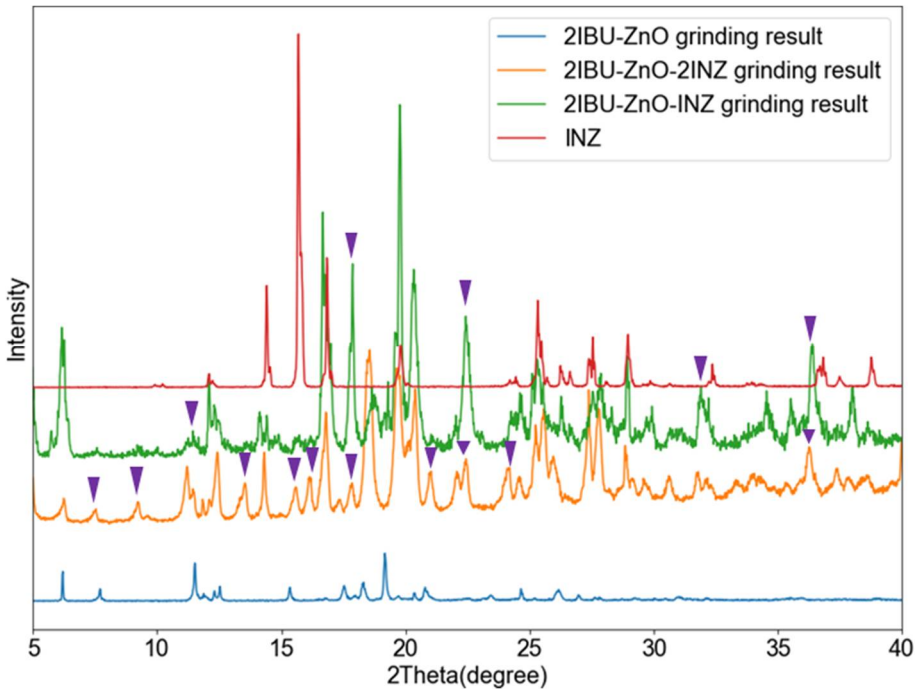

Figure S27. Comparison of PXRD patterns for INZ (red), IBU-ZnO grinding result in 2:1 (blue) and IBU-ZnO-INZ three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

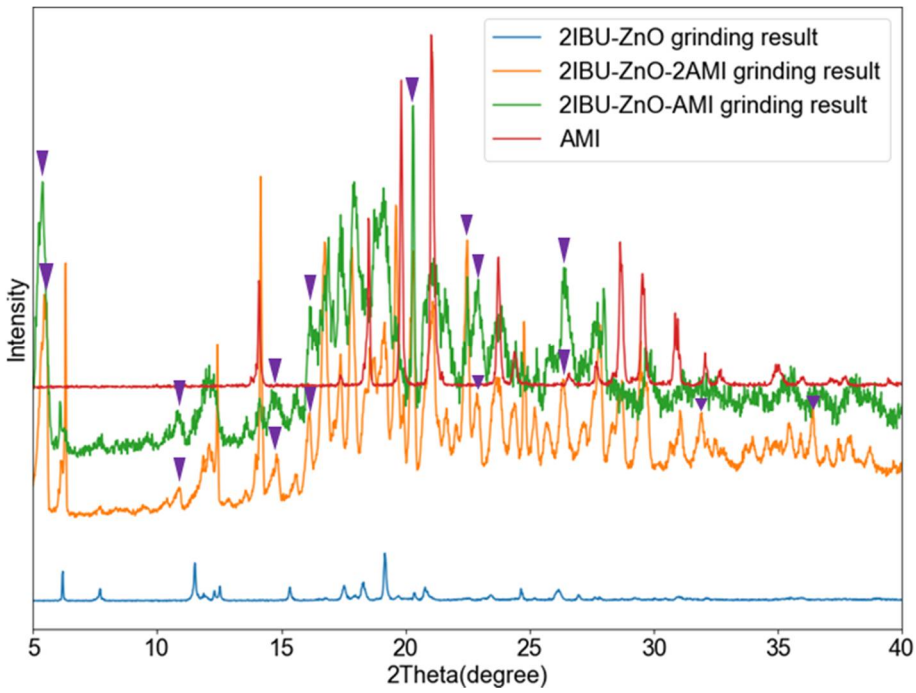

Figure S28. Comparison of PXRD patterns for AMI (red), IBU-ZnO grinding result in 2:1 (blue) and IBU-ZnO-AMI three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

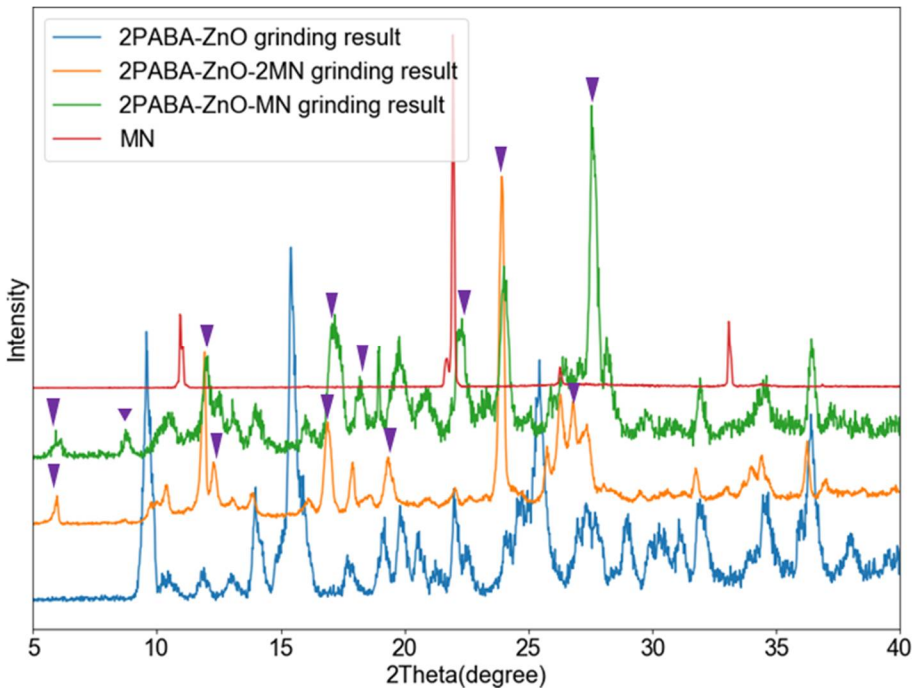

Figure S29. Comparison of PXRD patterns for MN (red), PABA-ZnO grinding result in 2:1 (blue) and PABA-ZnO-MN three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

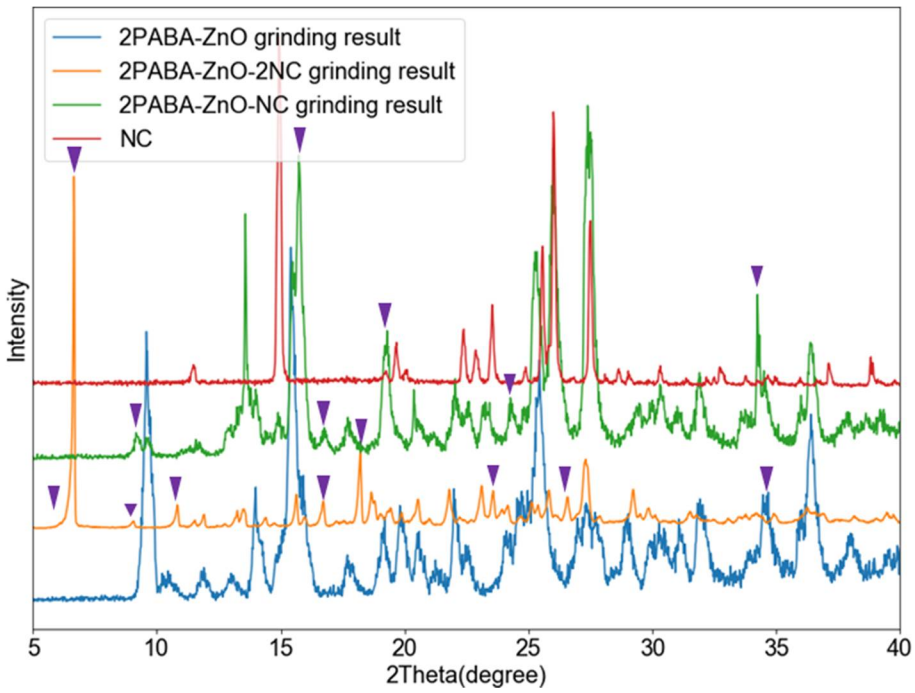

Figure S30. Comparison of PXRD patterns for NC (red), PABA-ZnO grinding result in 2:1 (blue) as well as PABA-ZnO-NC three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

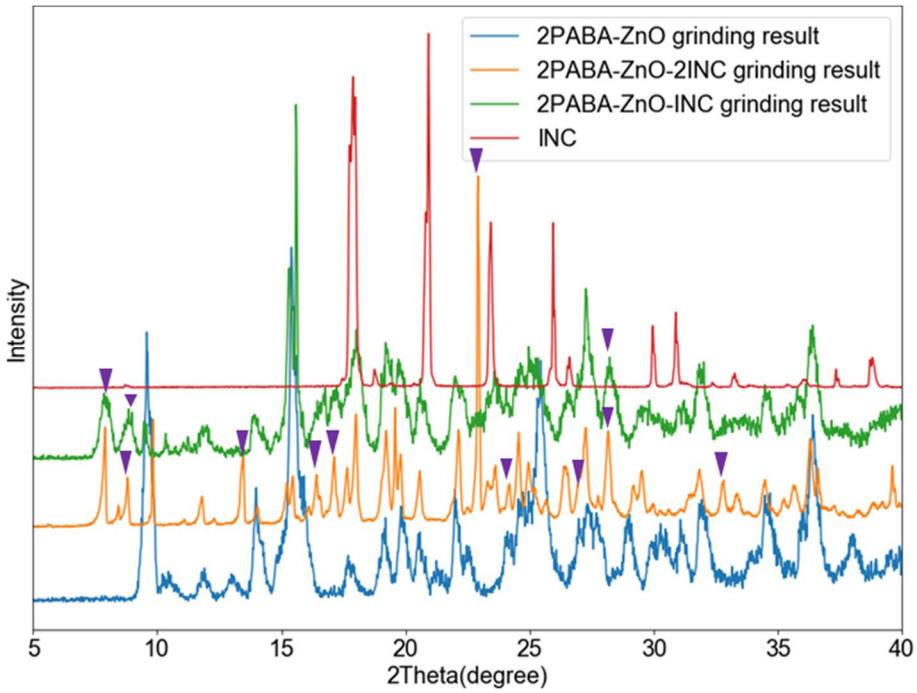

Figure S31. Comparison of PXRD patterns for INC (red), PABA-ZnO grinding result in 2:1 (blue) as well as PABA-ZnO-INC three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

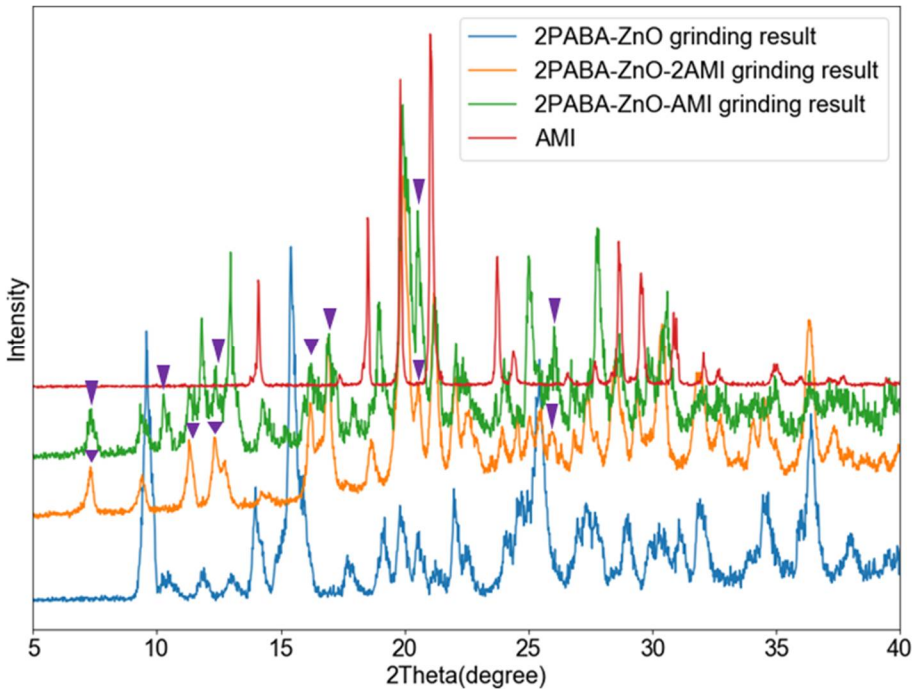

Figure S32. Comparison of PXRD patterns for AMI (red), PABA-ZnO grinding result in 2:1 (blue) as well as PABA-ZnO-AMI three-component grinding results in 2:1:1 (green) and 2:1:2 (orange) ratios.

4.1 VT-PXRD

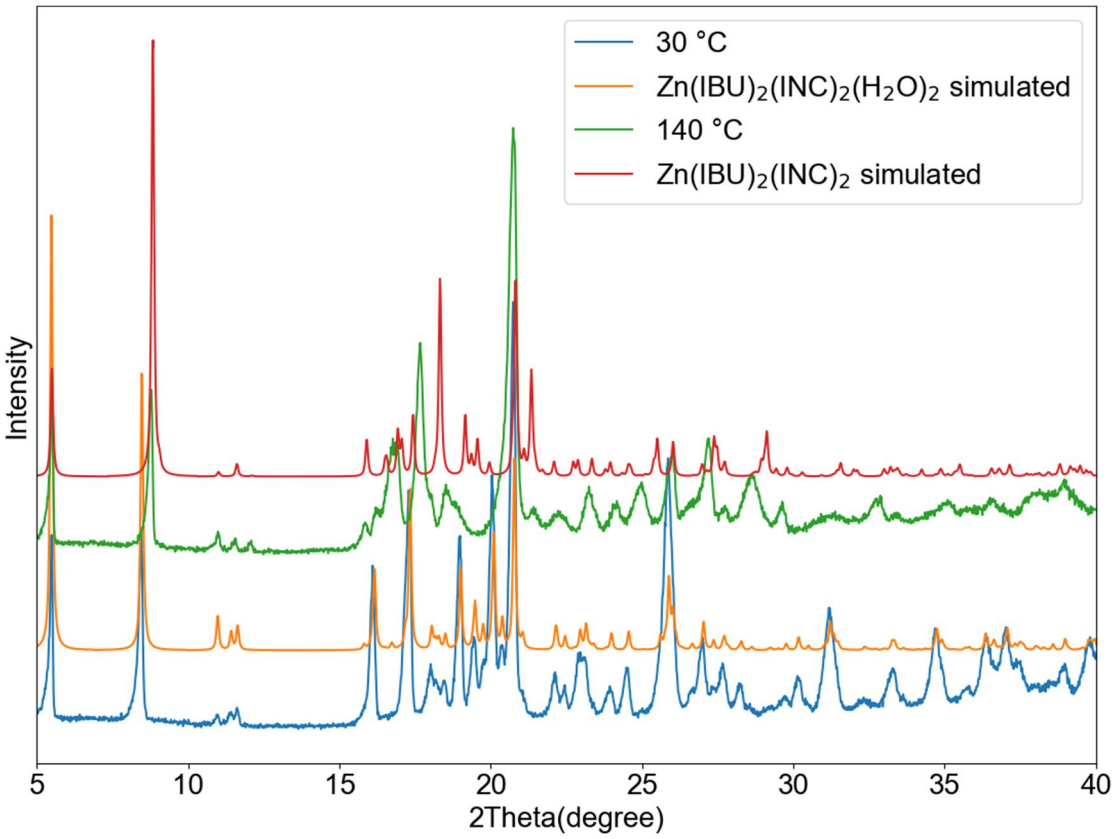

Figure S33. VT-PXRD analyses of $Zn(IBU)_2(INC)_2(H_2O)_2$ taken at 30 °C (blue) and 140 (green). The simulated PXRD patterns of the hydrated (orange) and the anhydrous (red) complexes are given for comparison.

5. Binary cocrystal screen

A binary cocrystal screen was performed between the organic compounds through methanol liquid assisted grinding. Most binary combinations also lead to cocrystal formation. However, this is not the case for eg. Aspirin-methylnocotinate.

	Aspirin (ASP)	**Ibuprofen (IBU)**	**4-aminobenzoic acid (PABA)**
Methylnicotinate (MN)	liquid	liquid	yes
Nicotinamide (NC)	yes	yes	yes
Isonicotinamide (INC)	yes	yes	yes
Isoniazid (INZ)	yes	no	yes
Amifampridine (AMI)	salt	liquid	yes