Supporting Information: "Co-crystals of Praziquantel: Discovery by Network-Based Link Prediction"

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S1 – Materials

Table S1: Coformers used for the LAG and SE experiments with their CAS-numbers, chemical supplier and purity.

Rank	Coformer	CAS	Supplier	Purity
1	Sebacic acid	111-20-6	Acros Organics	98%
2	Suberic acid	505-48-6	Aldrich	98%
3	Benzoic acid	65-85-0	Sigma-Aldrich	≥ 99.5%
4	Pimelic acid	111-16-0	Sigma-Aldrich	98%
5	Salicylic acid	69-72-7	Alfa-Aesar	99%
6	1,4-Diiodotetrafluorobenzene	392-57-4	Merck	98%
7	4-Hydroxybenzoic acid	99-96-7	Fluka	≥ 99.8%
8	Terephthalic acid	100-21-0	Acros organics	≥ 99%
9	4-Aminobenzoic acid	150-13-0	Sigma-Aldrich	≥ 99%
10	Isophthalic acid	121-91-5	Aldrich	99%
11	Azelaic acid	123-99-9	Sigma-Aldrich	98%
12	4-Aminosalicylic acid	65-49-6	TCI Chemicals	≥ 98%
13	3,5-Dinitrobenzoic acid	99-34-3	Aldrich	97%
14	*trans*-Cinnamic acid	140-10-3	TCI Chemicals	> 98%
15	Hydroquinone	123-31-9	Merck	> 99%
16	3-Hydroxybenzoic acid	99-06-9	Aldrich	99%
17	Anthranilic acid	118-92-3	Sigma-Aldrich	> 98%
18	Phthalic acid	88-99-3	Merck	≥ 99.5%
19	D-(-)-Tartaric acid	147-71-7	Alfa-Aesar	99%
20	Vanillic acid	121-34-6	Sigma-Aldrich	≥ 97%
21	4-Nitrobenzoic acid	62-23-7	Fluorochem	99%
22	2,5-Dihydroxybenzoic acid	490-79-9	Fluorochem	99%
23	2-Fluorobenzoic acid	445-29-4	Merck	97%
24	3,5-Dihydroxybenzoic acid	99-10-5	Fluorochem	recryst. from MeCN
25	3-Nitrobenzoic acid	121-92-6	Sigma-Aldrich	99%
26	4-Nitrophenol	100-02-7	Acros Organics	99%
27	1-Hydroxy-2-naphtoic acid	86-48-6	Aldrich	≥ 97%
28	2,4-Dihydroxybenzoic acid	89-86-1	Aldrich	97%
29	Orcinol	504-15-4	Sigma-Aldrich	97%
30	Dodecanedioic acid	693-23-2	Acros Organics	99%

S2 – Experimental techniques conditions and powder diffraction results

This section contains the experimental techniques used to characterize the phases obtained after single-crystal growth and screening by liquid-assisted grinding (LAG), solvent evaporation (SE) and measurement of saturation temperatures (SAT) (see ter Horst et al. [1]). The conditions used to synthesize the phases obtained after screening are shown in Table S2, and protocols for single crystal growth are reported per structure below. The corresponding powder diffractograms obtained in cases where new patterns emerged are presented in Figures S1-S14. A thorough description of these co-crystal screening methods and their results will be discussed in a future publication.

Powder X-ray diffraction analysis (PXRD)

LAG and SE samples were placed as a thin film of powder on zero-background (557)-silicon wafers and measured with a Panalytical Empyrean diffractometer. The diffractograms were measured in Bragg-Brentano geometry (reflection mode) using monochromatic CuKα radiation from a sealed LFF tube and a PIXcel3D 1x1 detector. A continuous scan was made in the $5° < 2\theta < 30°$ range with a step size of 0.013° and a scan speed of $0.11°.s^{-1}$.

SAT samples were analyzed using a Bruker D8 Advance II diffractometer with Debye–Scherrer transmission from a Cu source radiation (1.541 Å) with an operating voltage of 40kV, current 50mA, Kα1 Johansson monochromator and 1mm anti-divergence slit. A scanning range of 2θ values between 4° and 35° was applied with a scan speed of $0.017°.s^{-1}$.

Single-crystal X-ray diffraction (SC-XRD)

The experimental protocol for growing crystals suitable for SC-XRD are presented in section S3. Reflections were measured on a Bruker D8 Quest diffractometer with sealed tube and Triumph monochromator (λ= 0.71073 Å). Software package used for the intensity integration was Saint (v8.40A, Bruker). Absorption correction was performed with SADABS-2016/2 [2]. The structures were solved with direct methods using SHELXL-2014/5. Least-squares refinement was performed with SHELXL-2018/3 [3] against $|F_0^h|^2$ of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. Hydrogen atoms were placed on calculated positions or located from difference Fourier maps. All calculated hydrogen atoms were refined using a riding model.

Table S2: Solvents used for the LAG, SE and SAT screening methods. For LAG and SE, 50 mg of a 1:1 molar ratio was used. The stoichiometric ratios are expressed as 'mol coformer per mol of PZQ' for the SAT method and were equimolar for LAG and SE. '-[i]': terephthalic, isophthalic and phthalic did not dissolve in the selected solvents. DMF can dissolve these coformers, but its evaporation rate is slow.

Rank	Coformer	Solvent LAG	Solvent SE	Solvent SAT (Ratio)	Figure no.
1	Sebacic acid	MeOH, EtOH	MeOH, EtOH, iPrOH	EtOH (1.42) & AcOEt (0.26)	
2	Suberic acid	MeOH, EtOH	MeOH, EtOH	EtOH (2.08)	
3	Benzoic acid	EtOH	EtOH	EtOH (13.30), MeCN (3.27) & AcOEt (12.88)	
4	Pimelic acid	MeCN	MeCN	MeCN (0.75) & AcOEt (2.36)	S1
5	Salicylic acid	EtOH	EtOH	EtOH (10.59), MeCN (2.17) & AcOEt (9.24)	S2
6	1,4-Diiodotetrafluorobenzene	MeCN	MeCN	EtOH (5.03)	S3
7	4-Hydroxybenzoic acid	MeCN	MeCN	EtOH (8.26) & MeCN (0.93)	S4
8	Terephthalic acid	MeCN	-[i]	-[i]	
9	4-Aminobenzoic acid	MeCN	MeCN	EtOH (3.35), MeCN (1.45) & AcOEt (3.38)	
10	Isophthalic acid	MeCN	-[i]	-[i]	
11	Azelaic acid	EtOH	EtOH	EtOH (4.10) & AcOEt (0.75)	
12	4-Aminosalicylic acid	MeCN	MeCN	MeCN (0.38)	S5
13	3,5-Dinitrobenzoic acid	MeCN	MeCN	MeCN (0.89)	S6
14	*trans*-Cinnamic acid	MeCN	MeCN	EtOH (5.36), MeCN (1.39) & AcOEt (5.45)	
15	Hydroquinone	MeCN	MeCN	MeCN (3.65)	S7
16	3-Hydroxybenzoic acid	EtOH	EtOH	EtOH (7.72) & MeCN (0.94)	
17	Anthranilic acid	MeCN (p.m.), MeOH (-[o])	MeCN, MeOH	EtOH (6.25), MeCN (2.99) & AcOEt (8.74)	
18	Phthalic acid	MeCN	-[i]	-[i]	
19	D-(-)-Tartaric acid	MeCN	MeCN	-[i]	
20	Vanillic acid	EtOH, MeCN	EtOH, MeCN	EtOH (2.05)	S8 (EtOH), S9 (MeCN)
21	4-Nitrobenzoic acid	MeCN	MeCN	MeCN (0.60) & AcOEt (0.58)	
22	2,5-Dihydroxybenzoic acid	Acetone, MeCN	Acetone, MeCN	MeCN (1.41)	S10 (acetone), S11 (MeCN)

Table S2 (continued).

Rank	Coformer	Solvent LAG	Solvent SE	Solvent SAT (Ratio)	Figure no.
23	2-Fluorobenzoic acid	EtOH	EtOH	EtOH (17.45), MeCN (5.26) & AcOEt (12.81)	
24	3,5-Dihydroxybenzoic acid	MeCN	MeCN	MeCN (0.66)	S12
25	3-Nitrobenzoic acid	EtOH	EtOH	MeCN (3.64) & AcOEt (9.68)	
26	4-Nitrophenol	EtOH, MeCN	EtOH	EtOH (32.13) & AcOEt (41.65)	
27	1-Hydroxy-2-naphtoic acid	MeCN	MeCN	AcOEt (0.64)	
28	2,4-Dihydroxybenzoic acid	MeCN	MeCN	EtOH (8.14)	S13
29	Orcinol	EtOH, MeCN (same pat.)	EtOH, MeCN (oil)	Too soluble: viscous liquor formation	S14
30	Dodecanedioic acid	MeCN	EtOH	EtOH (0.92)	

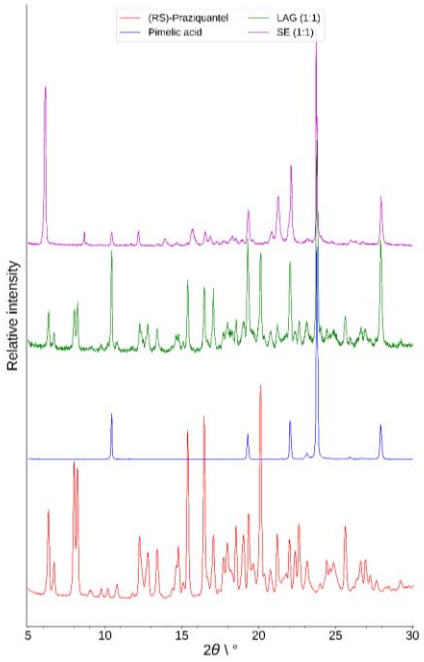


Figure S1: Powder diffractograms for PZQ, pimelic acid and their mixtures acquired after LAG and SE. SAT resulted in a physical mixtures of the coformers both solvents.

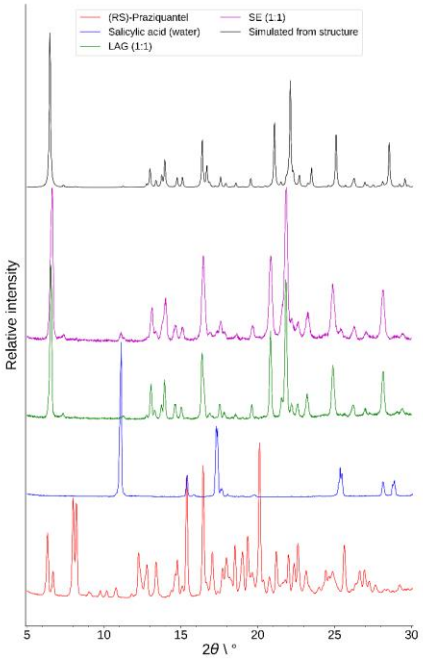


Figure S2: Powder diffractograms for PZQ, salicylic acid and their mixtures acquired after LAG and SE. The simulated powder pattern of its co-crystal hydrate (p1822a) is added for comparison. SAT resulted in a physical mixture for MeCN and AcOEt, and did not crystallize with EtOH.

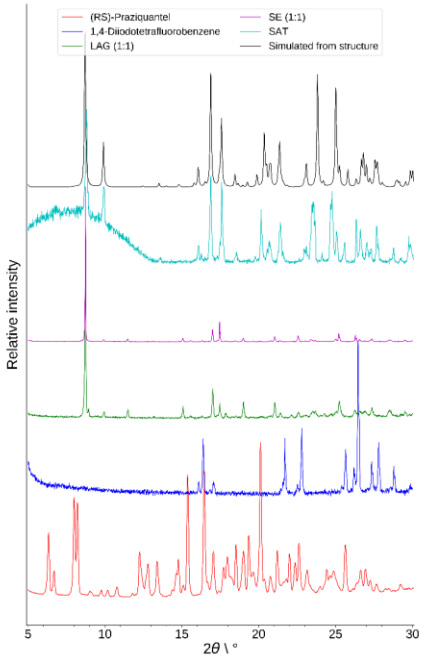


Figure S3: Powder diffractograms for PZQ, 1,4-diiodotetrafluorobenzene and their mixtures acquired after LAG, SE and SAT. The simulated powder pattern of its co-crystal (p2057a) is added for comparison.

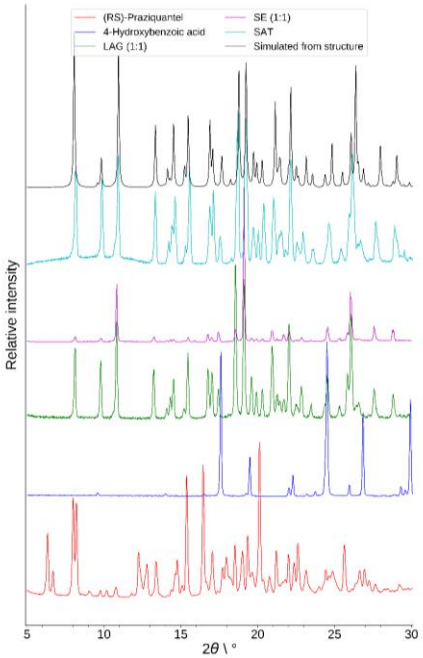


Figure S4: Powder diffractograms for PZQ, 4-hydroxybenzoic acid and their mixtures acquired after LAG, SE (both with MeCN) and SAT (EtOH). The simulated powder pattern of its co-crystal (p1932a) is added for comparison.

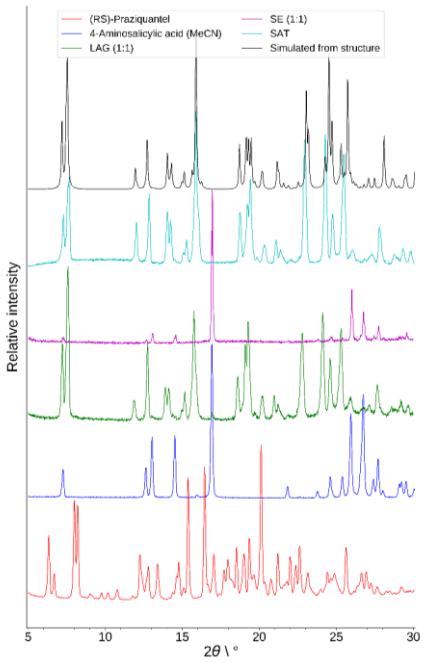


Figure S5: Powder diffractograms for PZQ, 4-aminosalicylic acid and their mixtures acquired after LAG, SE and SAT. The simulated powder pattern of its co-crystal solvate (p2054a) is added for comparison. The SE sample consisted of an oil and 4-aminosalicylic acid crystals (added to figure).

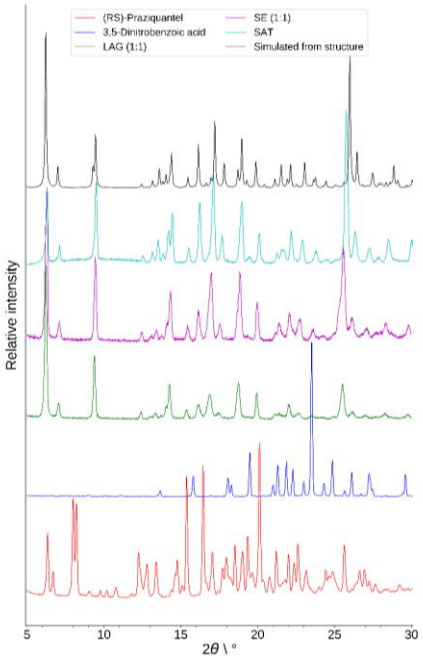


Figure S6: Powder diffractograms for PZQ, 3,5-dinitrobenzoic acid and their mixtures acquired after LAG, SE and SAT. The simulated powder pattern of its co-crystal (p2046a) is added for comparison.

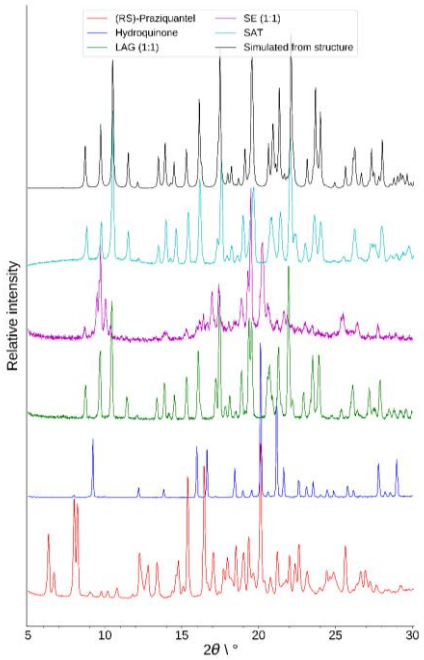


Figure S7: Powder diffractograms for PZQ, hydroquinone and their mixtures acquired after LAG, SE and SAT. The simulated powder pattern of its co-crystal (p1931a) is added for comparison.

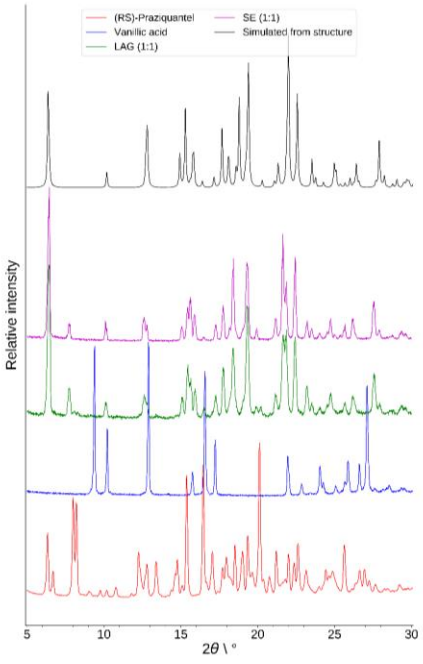


Figure S8: Powder diffractograms for PZQ, vanillic acid and their mixtures acquired after LAG and SE (both with EtOH). The simulated powder pattern of its co-crystal (p2026a) is added for comparison.

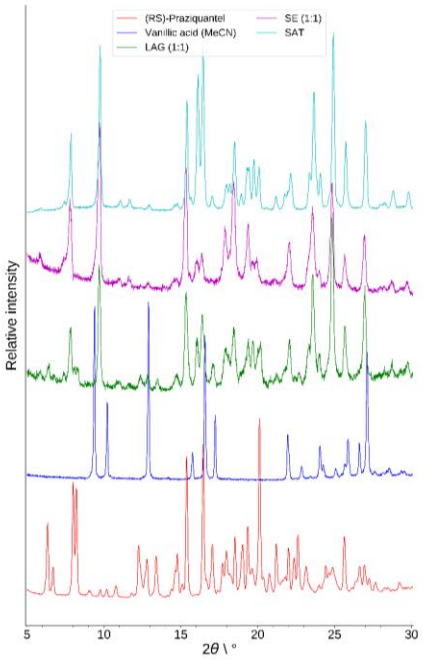


Figure S9: Powder diffractograms for PZQ, vanillic acid and their mixtures acquired after LAG and SE (both with MeCN), and SAT (with EtOH). The results exclude the formation of a co-crystal solvate with either solvents.

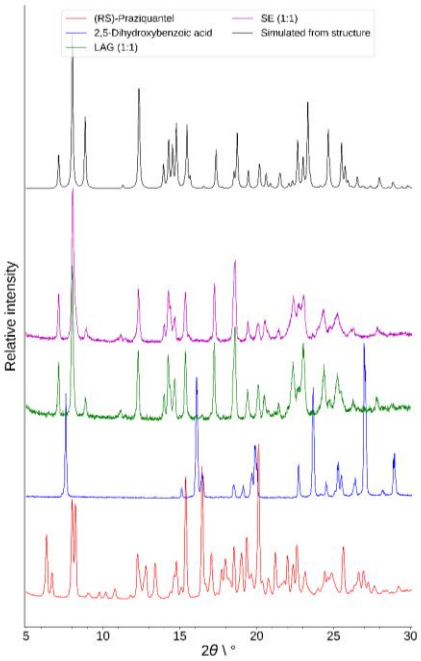


Figure S10: Powder diffractograms for PZQ, 2,5-dihydroxybenzoic acid and their mixtures acquired after LAG and SE (both with acetone). The simulated powder pattern of its co-crystal (p1829a) is added for comparison.

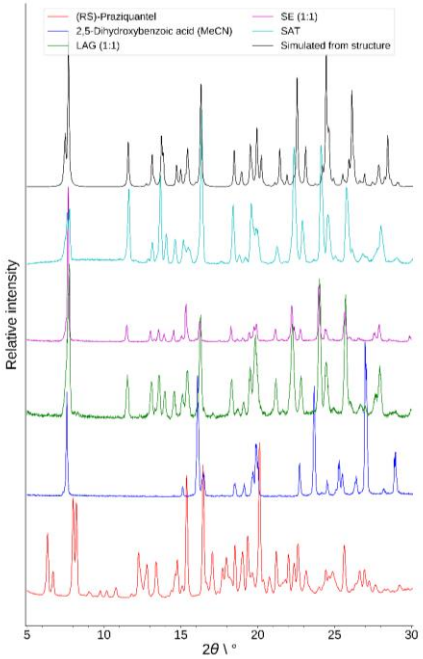


Figure S11: Powder diffractograms for PZQ, 2,5-dihydroxybenzoic acid and their mixtures acquired after LAG, SE and SAT with MeCN. The simulated powder pattern of its co-crystal solvate (p1821a) is added for comparison.

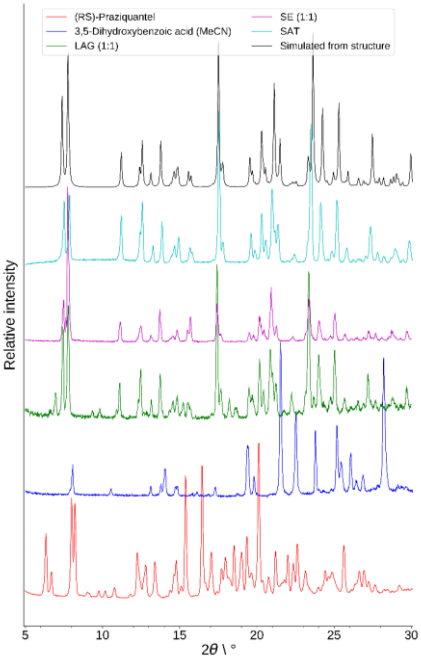


Figure S12: Powder diffractograms for PZQ, 3,5-dihydroxybenzoic acid and their mixtures acquired after LAG, SE, and SAT with MeCN. The simulated powder pattern of its co-crystal solvate (p2044a) is added for comparison.

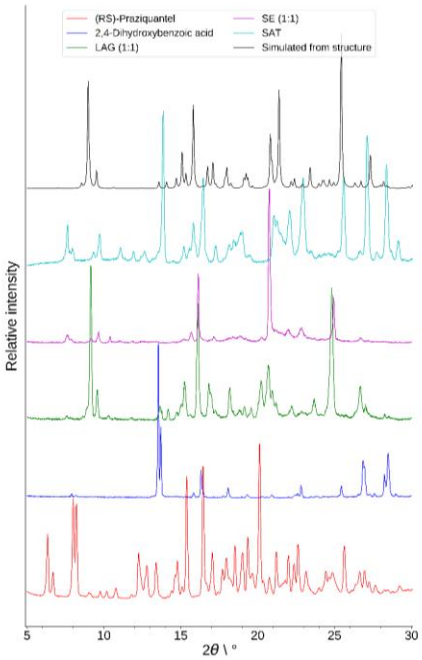


Figure S13: Powder diffractograms for PZQ, 2,4-dihydroxybenzoic acid and their mixtures acquired after LAG and SE (with MeCN), and SAT (with EtOH). The simulated powder pattern of its cocrystal (p2024a) is added for comparison.

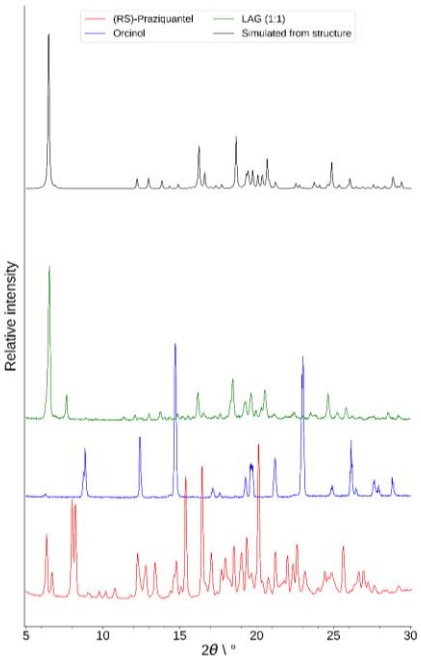


Figure S14: Powder diffractograms for PZQ, orcinol and their mixture acquired after LAG (with EtOH). The simulated powder pattern of its cocrystal (p2040a) is added for comparison.

S3 – Crystallographic data and analysis of the discovered co-crystal structures

The crystal structures of twelve new co-crystals of PZQ were grown, and are classified into four classes based on the hydrogen bonding patterns and packing encountered in the crystal structure:

- Enantiopure chains (**S3.1**);
- Racemic chains (**S3.2**);
- Racemic pairs (**S3.3**);
- Racemic networks (**S3.4**).

The new crystal structures are presented and discussed per class, together with their crystallographic data, experimental procedures for single crystal growth, ORTEP plots and hydrogen bonding interaction details. The latter two were generated using the PLATON-software package (www.platonsoft.nl/platon/).

Below, the CCDC numbers and crystal structure identifiers of the co-crystals are presented together with their corresponding constituents:

CCDC 2054486	p1822a	PZQ, salicylic acid and water
CCDC 2054487	p1821a	PZQ, 2,5-dihydroxybenzoic acid and acetonitrile
CCDC 2054488	p2040a	PZQ and orcinol
CCDC 2054489	p1829a	PZQ and 2,5-dihydroxybenzoic acid
CCDC 2054490	p2026a	PZQ and vanillic acid
CCDC 2054491	p2046a	PZQ and 3,5-dinitrobenzoic acid
CCDC 2054492	p1932a	PZQ and 4-hydroxybenzoic acid
CCDC 2054493	p2054a	PZQ, 4-aminosalicylic acid and acetonitrile
CCDC 2054494	p2024a	PZQ and 2,4-dihydroxybenzoic acid
CCDC 2054495	p2057a	PZQ and 1,4-diiodotetrafluorobenzene
CCDC 2054496	p2044a	PZQ, 3,5-dihydroxybenzoic acid and acetonitrile
CCDC 2054497	p1931a	PZQ and hydroquinone

S3.1 – Enantiopure chains

Table S3: Crystallographic data of the co-crystal structures characterized by the formation of enantiopure chains.

	p1829a	**p1821a**	**p1932a**	**p2054a**	**p2040a**
Crystal data					
Chemical formula	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_4$	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_4 \cdot C_2H_3N$	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_3$	$C_{19}H_{24}N_2O_2 \cdot C_7H_7NO_3 \cdot C_2H_3N$	$C_{19}H_{24}N_2O_2 \cdot C_7H_8O_2$
M_r	466.52	507.57	450.52	506.59	436.53
Crystal system, space group	Monoclinic, *C2/c*	Triclinic, *P-1*	Triclinic, *P-1*	Triclinic, *P-1*	Monoclinic, $P2_1/c$
Temperature (K)	150	150	150	150	150
a, *b*, *c* (Å)	26.1888 (15), 8.2426 (6), 23.2905 (15)	7.9909 (16), 13.488 (3), 14.012 (3)	9.7434 (4), 10.8408 (5), 12.1020 (5)	7.8366 (4), 13.6087 (7), 14.2289 (7)	5.9548 (4), 14.4717 (9), 27.3502 (14)
α, *β*, *γ* (°)	90, 108.777(2), 90	113.666 (6), 105.776 (6), 98.678 (7)	108.0725 (15), 101.9304 (15), 104.1900 (15)	114.6625 (17), 102.0101 (19), 100.0114 (19)	90, 93.596 (2), 90
V (Å^3)	4760.0 (5)	1271.9 (4)	1121.32 (8)	1289.54 (11)	2352.3 (2)
Z	8	2	2	2	4
Radiation type	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα
μ (mm−1)	0.09	0.09	0.09	0.09	0.08
Crystal size	0.60 × 0.48 × 0.41	0.53 × 0.38 × 0.09	0.56 × 0.51 × 0.26	0.57 × 0.21 × 0.08	0.57 × 0.13 × 0.04
Data collection					
Diffractometer	Bruker D8 Quest Apex3				
Absorption correction	Multi-scan SADABS 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10				
T_{min}, T_{max}	0.690, 0.747	0.636, 0.746	0.725, 0.747	0.639, 0.746	0.652, 0.746
No. of measured, independent and observed [I > 2σ(I)] reflections	97359, 9139, 6330	27484, 6327, 4845	78130, 8580, 7621	26145, 6341, 5043	20812, 5644, 3847
R_{int}	0.044	0.034	0.023	0.030	0.044
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.772	0.668	0.770	0.668	0.668
Refinement					
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.057, 0.168, 1.01	0.040, 0.112, 1.03	0.040, 0.122, 1.00	0.051, 0.143, 1.06	0.057, 0.148, 1.01
No. of reflections	9139	6327	8580	6341	5644
No. of parameters	353	344	321	335	324
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.24	0.34, −0.24	0.43, −0.23	0.30, −0.25	0.28, −0.30

p1829a: co-crystal of PZQ and 2,5-dihydroxybenzoic acid (**22**)

An equimolar mixture of 2,5-dihydroxybenzoic acid (35 mg) and PZQ (65 mg) was completely dissolved in minimum amount of a solution containing n-heptane and acetone (approx.70:30 v:v). Colorless block-like crystals were obtained after slow evaporation.

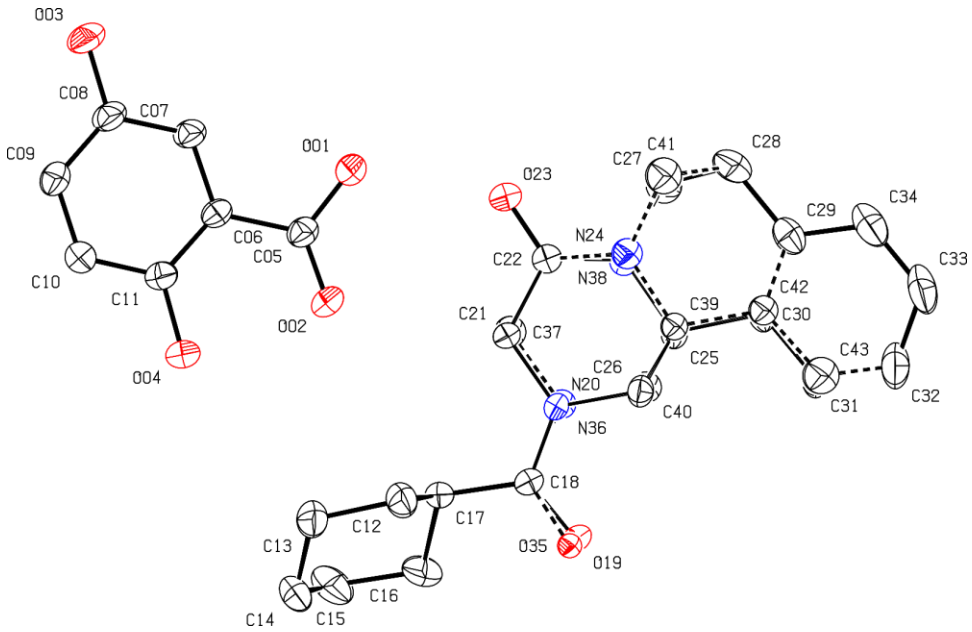


Figure S15: ORTEP plot of the co-crystal containing PZQ and 2,5-dihydroxybenzoic acid (p1829a).

Donor	---	H	....Acceptor	[	ARU	]	D - H	H...A	D...A	D - H...A
O01	--H01		..O23	[	1555.01]		0.89(2)	1.74(2)	2.6146(15)	167.5(19)
O03	--H03		..O19	[	5545.01]		0.91(3)	1.71(3)	2.621(3)	174(2)
O03	--H03		..O35	[	5545.01]		0.91(3)	1.84(4)	2.74(2)	174(2)
O04	--H04		..O02	[	]		0.92(3)	1.76(3)	2.5881(16)	149(2)
C21	--H21B		..O02	[	1555.02]		0.99	2.29	3.0852(19)	137
C26	--H26A		..O19	[	]		0.99	2.32	2.743(3)	104
C26	--H26A		..O35	[	]		0.99	2.45	2.86(2)	105
C26	--H26A		..O03	[	5455.02]		0.99	2.53	3.4090(18)	148
C27	--H27A		..O23	[	]		0.99	2.31	2.744(2)	105
C28	--H28A		..O04	[	4565.02]		0.99	2.47	3.4123(18)	159
C31	--H31		..O03	[	5455.02]		0.95	2.52	3.461(2)	169

p1821a: co-crystal solvate of PZQ, 2,5-dihydroxybenzoic acid and acetonitrile (**22**)

2,5-Dihydroxybenzoic acid (35 mg) and PZQ (65 mg) (1:1 molar ratio) were dissolved in a minimal amount of hot acetonitrile (approx. 60°C). Dissolution was promoted by ultrasound. Colorless plate-like crystals were obtained after slow evaporation.

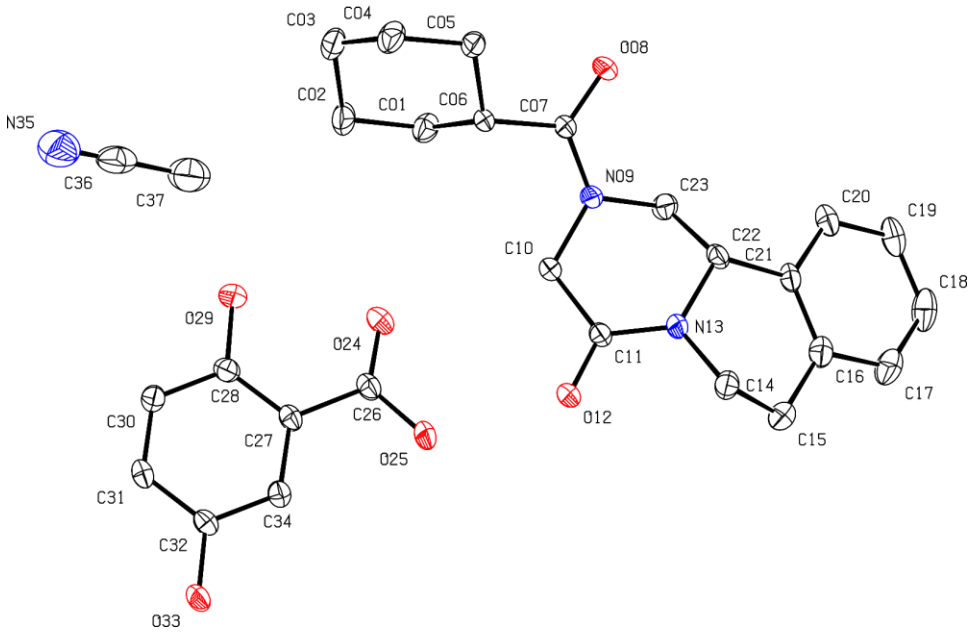


Figure S16: ORTEP plot of the co-crystal solvate containing PZQ, 2,5-dihydroxybenzoic acid and acetonitrile (p1821a).

Donor	--- H	....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O25	--H25	..O12	[1555.01]	0.91(2)	1.74(2)	2.6311(15)	166.3(17)
O29	--H29	..O24	[ ]	0.89(2)	1.78(2)	2.5991(17)	152.7(17)
O33	--H33	..O08	[1444.01]	0.89(2)	1.78(2)	2.6713(15)	178(2)
C05	--H05B	..O33	[2666.02]	0.99	2.60	3.3060(18)	128
C10	--H10B	..O24	[1555.02]	0.99	2.44	3.1532(19)	129
C14	--H14A	..O12	[ ]	0.99	2.34	2.7650(19)	105
C14	--H14B	..N35	[1665.03]	0.99	2.55	3.481(2)	156
C23	--H23A	..O08	[ ]	0.99	2.34	2.7619(17)	104
C23	--H23B	..N35	[1565.03]	0.99	2.56	3.535(2)	167
C37	--H37B	..O12	[2666.01]	0.98	2.56	3.494(2)	159

p1932a: co-crystal of PZQ and 4-hydroxybenzoic acid (**7**)

4-Hydroxybenzoic acid (26.6 mg) and PZQ (12.0 mg) were ground separately and combined in approximately 15 mL of diethylether. The solution was slowly evaporated at room temperature, and yielded colorless block-like crystals after approx. five days.

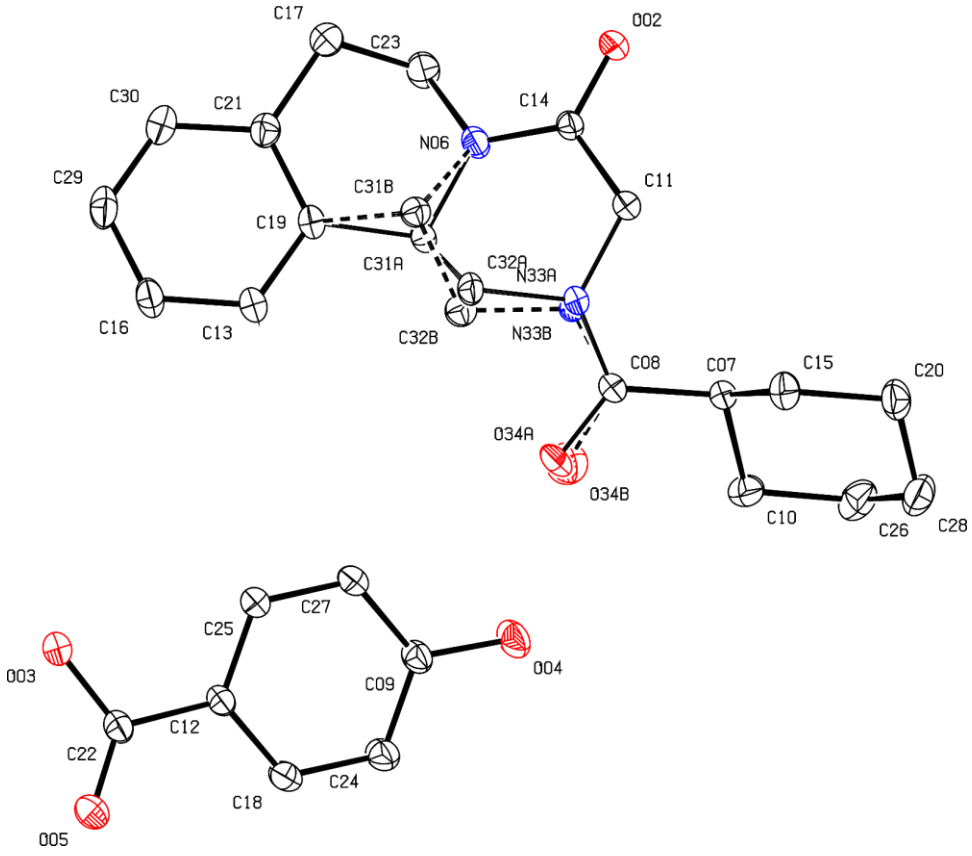


Figure S17: ORTEP plot of the co-crystal containing PZQ and 4-hydroxybenzoic acid (p1932a).

Donor	---	H	....Acceptor	[	ARU	]	D - H	H...A	D...A	D - H...A
O03	--H03		..O02	[	1444.01]		0.881(15)	1.816(16)	2.6798(8)	166.2(16)
O04	--H04		..O34A	[	1555.01]		0.853(18)	1.849(18)	2.6993(12)	174.8(18)
O04	--H04		..O34B	[	1555.01]		0.853(18)	1.68(2)	2.513(17)	165.3(17)
C11	--H11A		..O05	[	1666.02]		0.99	2.24	3.1731(9)	157
C23	--H23B		..O02	[	]		0.99	2.33	2.7625(10)	105
C27	--H27		..O34A	[	1555.01]		0.95	2.53	3.1845(12)	126
C31A	--H31A		..O04	[	2666.02]		1.00	2.55	3.3073(10)	133
C32A	--H32B		..O34A	[	]		0.99	2.33	2.7060(12)	101

p2054a: co-crystal solvate of PZQ, 4-aminosalicylic acid and acetonitrile (**12**)

An equimolar mixture of PZQ (103 mg) and 4-aminosalicylic acid (50 mg) was dissolved in 1.5 mL of hot acetonitrile (approx. 65°C) and divided over two vials with closed lids. The solutions were left to slowly cool down to room temperature, both resulting in colorless needle-shaped crystals.

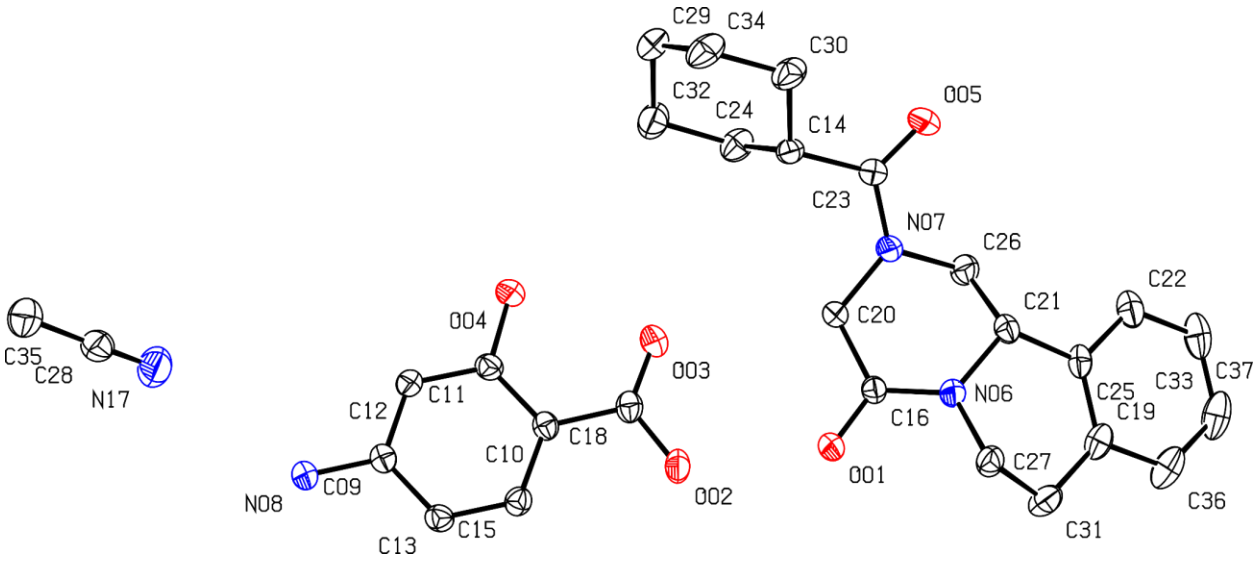


Figure S18: ORTEP plot of the co-crystal solvate containing PZQ, 4-aminosalicylic acid and acetonitrile (p2054a).

Donor	---	H	....Acceptor	[	ARU	]	D - H	H...A	D...A	D - H...A
O02	--H02		..O01	[	1555.01]		0.84	1.82	2.643(2)	164
O04	--H04		..O03	[	]		0.84	1.84	2.584(2)	147
N08	--H08A		..N17	[	1555.03]		0.88	2.33	3.149(3)	155
N08	--H08B		..O05	[	1444.01]		0.88	1.99	2.8567(18)	169
C20	--H20B		..O03	[	1555.02]		0.99	2.46	3.138(2)	125
C26	--H26A		..O05	[	]		0.99	2.28	2.711(2)	105
C27	--H27A		..O01	[	]		0.99	2.32	2.748(2)	105
C35	--H35A		..O01	[	1445.01]		0.98	2.53	3.445(3)	156

p2040a: co-crystal of PZQ and orcinol (**29**)

71 mg of a manually ground, equimolar mixture PZQ and orcinol was partially dissolved in 4 mL of diethylether and heated to approx. 30 °C. The warm solution was filtered and stored in a closed glass vial (plastic lid) at room temperature. After 8 days, the vial was stored at 5 °C, from which a powder precipitated after approx. 14 days. The saturated solution was collected and again stored at 5°C. After 8 days, the vial was opened and briefly blown over with nitrogen, evaporating some of the solvent. Colorless needle-like crystals were obtained after one day.

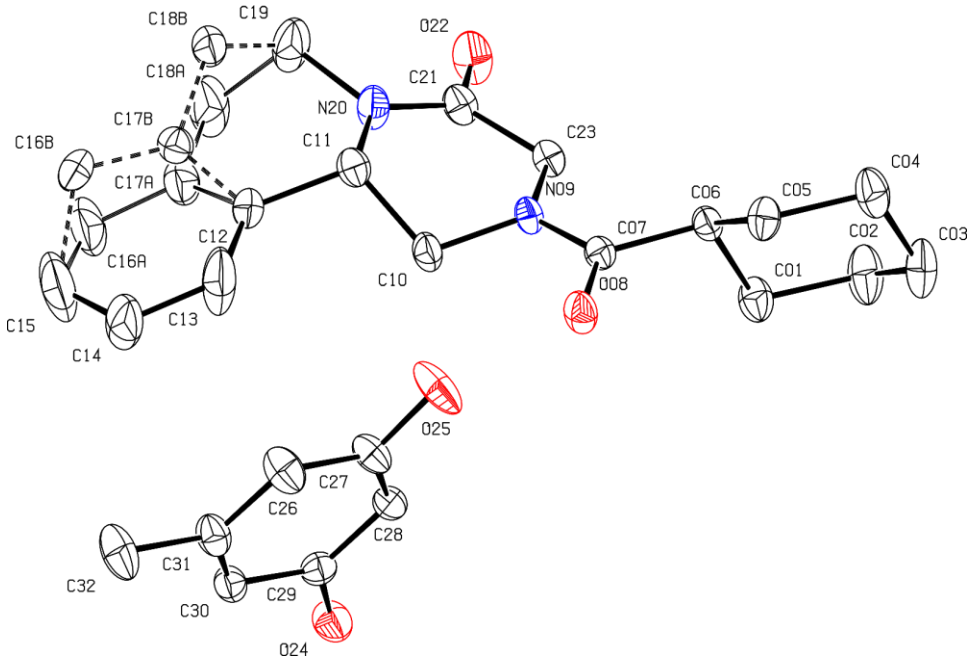


Figure S19: ORTEP plot of the co-crystal containing PZQ and orcinol (p2040a).

Donor	--- H....	Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O24	--H24	..O22	[2555.01]	0.91(2)	1.77(2)	2.6813(17)	175(2)
O25	--H25	..O08	[1555.01]	0.85(3)	1.82(3)	2.658(2)	167(3)
C05	--H05A	..O24	[2645.02]	0.99	2.51	3.292(2)	135
C10	--H10A	..O08	[ ]	0.99	2.32	2.735(2)	104
C10	--H10B	..O25	[1455.02]	0.99	2.42	3.280(3)	144
C11	--H11	..O22	[1655.01]	1.00	2.52	3.450(2)	155
C19	--H19B	..O22	[ ]	0.99	2.30	2.731(3)	105

Discussion of the enantiopure chain co-crystals

The first class of crystal structures are characterized by the formation of enantiopure chains, which are shown for the S-enantiomer of PZQ in Figures 5 and 6. An exact mirror image of the chain, containing the opposite enantiomer, is also present in these structures, as all co-crystals have crystallized in centrosymmetric space groups (crystallographic details in Table S3). The forces responsible for holding chains of opposite chirality together are of a weaker nature then the hydrogen bonding interactions in the chains themselves (*e.g.* additional short contacts between PZQ's chiral hydrogen atoms and the oxygen atoms on 4-hydroxybenzoic acid's hydroxyl group (see Figure S17 and corresponding hydrogen bonding interaction table).

As discussed in the main text, the cocrystal solvates with 2,5-dihydroxybenzoic acid (p1821a, Figure 5b and S16) and 4-aminosalicylic acid (p2054a, Figure 5d and S18) are isostructural. An overlay of their chains (along the [1,1,1] direction, Figure S20) does show that slight orientational differences (shown using distance *d* in Figure 5) prevent the structures from being exact copies, but the resemblance is nonetheless striking.

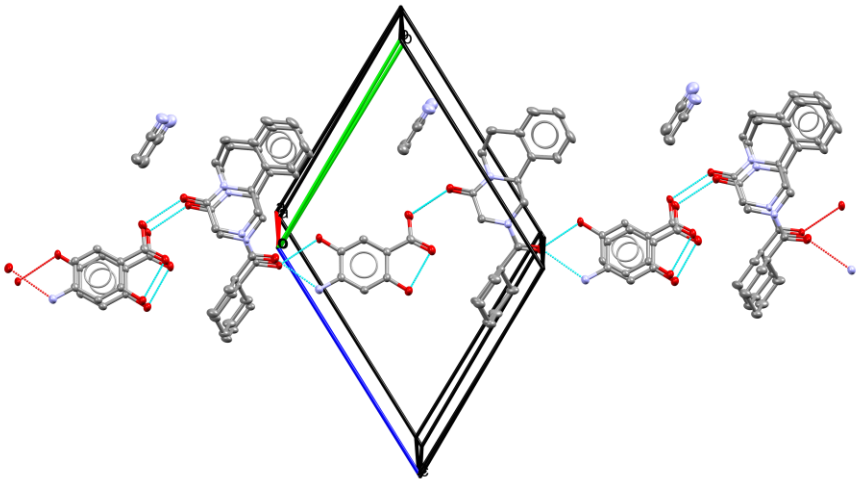


Figure S20: Structural overlay of the cocrystal solvates with 2,5-dihydroxybenzoic acid (p1821a) and 4-aminosalicylic acid (p2054a).

Moreover, although exhibiting a very similar hydrogen bonding pattern and intermolecular spacings, it was not possible to match the atomic position of 2,5-dihydroxybenzoic acid's binary co-crystal chain (p1829a, Figure 5a, along the [1,-1,0] direction) with that of its acetonitrile solvate (p1821a, Figure 5b).

4-Hydroxybenzoic acid (p1932a, Figure 5c), on the other hand, is slightly tilted compared to the other coformers forming enantiopure chains, and although also running along the same [1,1,1] direction, its unit cell parameters differ from the co-crystal solvates (Table S3). Its chain can therefore not be matched with those of the former two.

S3.2 – Racemic chains

Table S4: Crystallographic data of the co-crystal structures characterized by the formation of racemic chains.

	p1931a	**p2044a**	**p2024a**
Crystal data			
Chemical formula	$C_{19}H_{24}N_2O_2 \cdot C_6H_6O_2$	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_4 \cdot C_2H_3N$	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_4$
M_r	422.51	507.57	466.52
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $C2/c$	Monoclinic, $P2_1/n$
Temperature (K)	150	150	150
a, b, c (Å)	12.5288 (5), 18.1766 (7), 9.7350 (4)	27.2832 (7), 8.4014 (2), 26.9948 (6)	20.236 (3), 11.1971 (16), 21.478 (3)
α, β, γ (°)	90, 102.9855 (13), 90	90, 123.5050 (9), 90	90, 105.752 (5), 90
V (Å^3)	2160.27 (15)	5159.5 (2)	4683.9 (11)
Z	4	8	8
Radiation type	Mo Kα	Mo Kα	Mo Kα
μ (mm−1)	0.09	0.09	0.09
Crystal size	0.81 × 0.54 × 0.42	0.39 × 0.31 × 0.13	0.56 × 0.31 × 0.20
Data collection			
Diffractometer	Bruker D8 Quest Apex3		
Absorption correction	Multi-scan SADABS 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10		
T_{min}, T_{max}	0.712, 0.747	0.696, 0.747	0.639, 0.747
No. of measured, independent and observed [I > 2σ(I)] reflections	83150, 8266, 7272	58729, 9795, 8873	201987, 17660, 11582
R_{int}	0.027	0.022	0.070
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.771	0.769	0.767
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.127, 0.98	0.039, 0.114, 1.00	0.073, 0.200, 1.12
No. of reflections	8266	9795	17660
No. of parameters	286	354	631
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.50, −0.35	0.46, −0.22	0.78, −0.41

p1931a: co-crystal of PZQ and hydroquinone (**15**)

57.2 mg of PZQ and 20.8 mg of hydroquinone were combined and dissolved in approx. 15 mL of diethylether. The solution was divided over two glass vials with pierced lid, and left for evaporation at room temperature. After two days, needle-like crystals were obtained (possibly pure hydroquinone), and the saturated solution was isolated and again slowly evaporated. This yielded colorless block-shaped crystals after two days, which were further analyzed with SC-XRD.

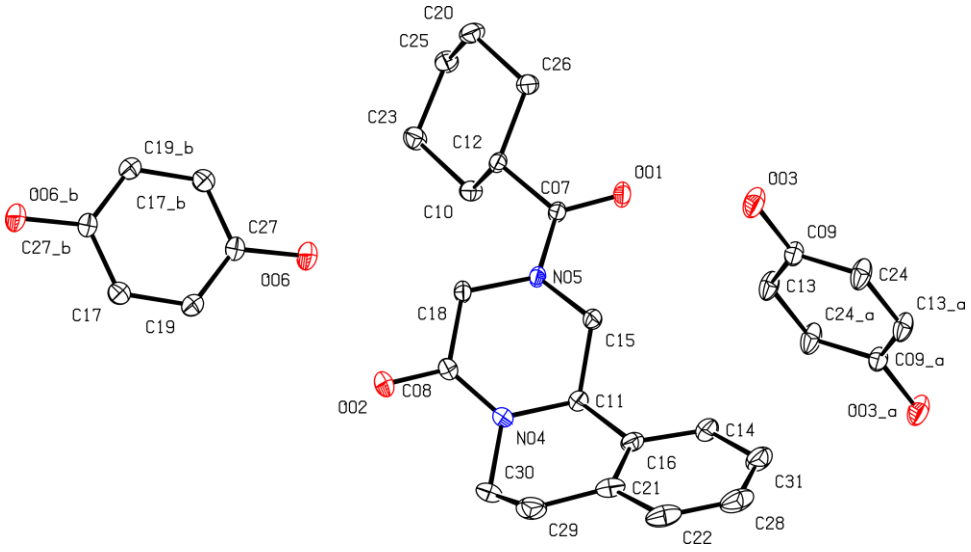


Figure S21: ORTEP plot of the co-crystal containing PZQ and hydroquinone (p1931a).

Donor	--- H	....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O03	--H03	..O01	[1555.01]	0.876(17)	1.808(17)	2.6842(10)	178.9(16)
O06	--H06	..O02	[1555.01]	0.837(19)	1.955(19)	2.7386(11)	155.6(18)
C13	--H13	..O01	[1555.01]	0.95	2.57	3.2495(10)	129
C15	--H15B	..O01	[ ]	0.99	2.33	2.7221(9)	103
C18	--H18B	..O03	[3666.02]	0.99	2.42	3.1820(11)	133
C30	--H30B	..O02	[ ]	0.99	2.34	2.7678(12)	105

p2044a: co-crystal solvate of PZQ, 3,5-dihydroxybenzoic acid and acetonitrile (**24**)

50 mg of an equimolar mixture containing PZQ and 3,5-dihydroxybenzoic acid was dissolved in 1 mL of acetonitrile and filtered using a 0.2µm wwPTFE syringe filter (Pall Corporation). Slow evaporation resulted in colorless block-shaped crystals after approximately five days.

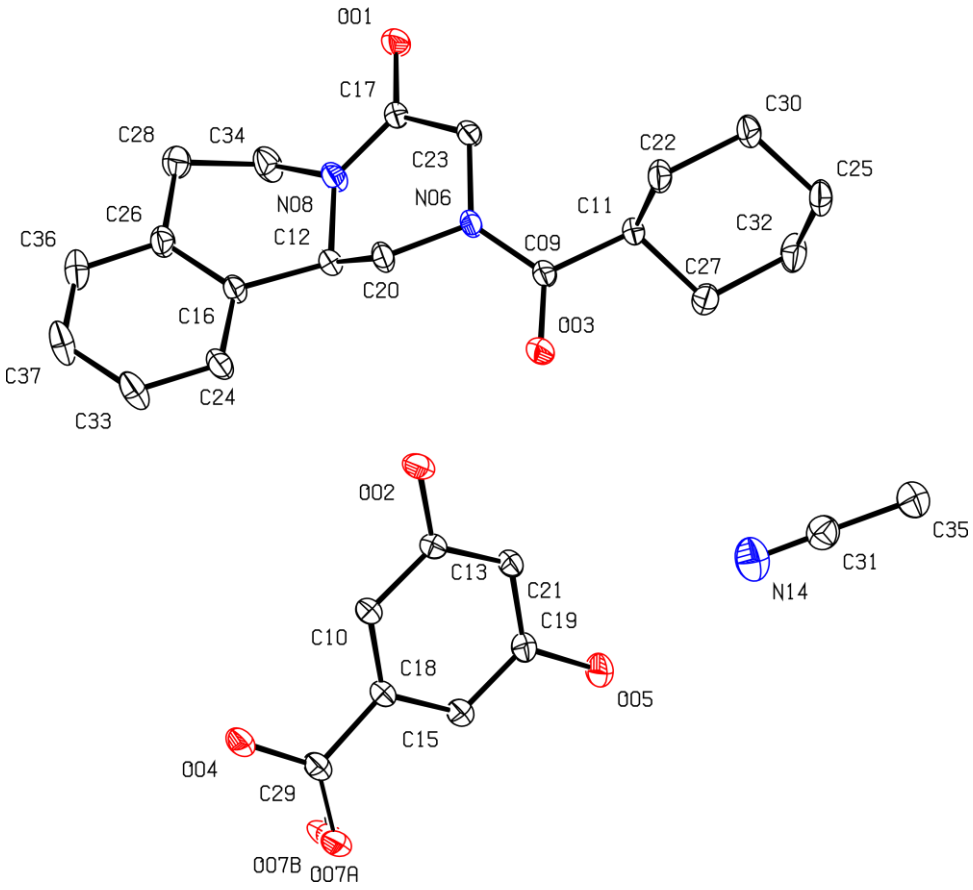


Figure S22: ORTEP plot of the co-crystal solvate containing PZQ, 3,5-dihydroxybenzoic acid and acetonitrile (p2044a).

Donor	---	H	....Acceptor	[	ARU	]	D - H	H...A	D...A	D - H...A
O02	--H02		..O03	[	1555.01]		0.908(18)	1.746(17)	2.6542(10)	177.9(14)
O04	--H04		..O01	[	4564.01]		0.89(2)	1.83(2)	2.7015(10)	166.1(17)
O05	--H05		..N14	[	1555.03]		0.898(17)	2.013(18)	2.8703(15)	159.2(14)
C12	--H12		..O03	[	6646.01]		1.00	2.59	3.5666(9)	165
C20	--H20B		..O02	[	1555.02]		0.99	2.41	3.3802(8)	167
C20	--H20B		..O03	[	]		0.99	2.38	2.7817(10)	104
C23	--H23A		..O07A	[	4565.02]		0.99	2.23	3.064(6)	141
C23	--H23A		..O07B	[	4565.02]		0.99	2.27	3.04(2)	134
C23	--H23B		..O05	[	6656.02]		0.99	2.51	3.4027(10)	150
C28	--H28B		..O05	[	8555.02]		0.99	2.57	3.4300(11)	146
C34	--H34A		..N14	[	6646.03]		0.99	2.63	3.2888(12)	124
C34	--H34B		..O01	[	]		0.99	2.35	2.7685(11)	105
C35	--H35C		..O01	[	8454.01]		0.98	2.59	3.3821(11)	138
C35	--H35E		..O05	[	3666.02]		0.98	2.50	3.3612(12)	146

p2024a: co-crystal of PZQ and 2,4-dihydroxybenzoic acid (**28**)

An equimolar mixture (71 mg) was partially dissolved in 4 mL diethylether at heated to approx. 40 °C. The warm solution was filtered using a 0.2µm wwPTFE syringe filter (Pall Corporation) and stored at room temperature in a glass vial with plastic cap. Within two days, colorless block-shaped crystals were formed.

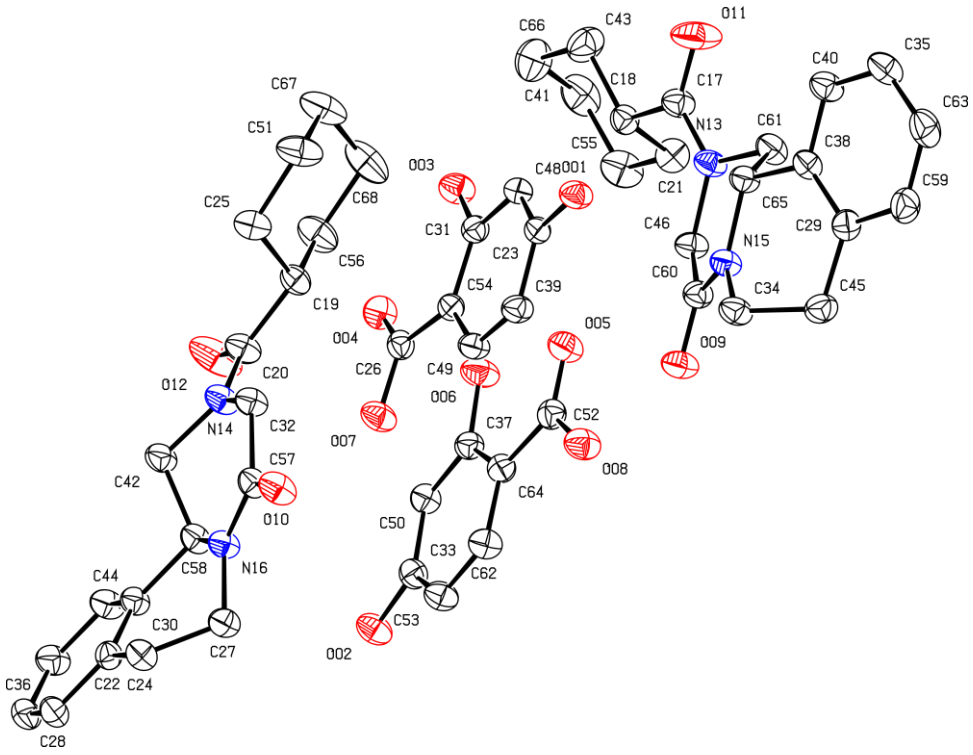


Figure S23: ORTEP plot of the co-crystal containing PZQ and 2,4-dihydroxybenzoic acid (p2024a).

Donor	--- H	Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O01	--H01	..O12	[4565.02]	0.85(2)	1.82(2)	2.660(2)	170(3)
O02	--H02	..O11	[4464.01]	0.86(3)	1.79(3)	2.643(2)	172(3)
O03	--H03	..O04	[ ]	0.89(3)	1.79(3)	2.610(2)	154(2)
O06	--H06	..O05	[ ]	0.86(3)	1.85(3)	2.620(2)	148(3)
O07	--H07	..O10	[1555.02]	0.90(3)	1.74(3)	2.612(2)	163(2)
O08	--H08	..O09	[1555.01]	0.88(3)	1.76(3)	2.612(2)	163(3)
C18	--H18	..O03	[1555.03]	1.00	2.59	3.490(2)	150
C27	--H27A	..O10	[ ]	0.99	2.34	2.765(2)	105
C34	--H34A	..O09	[ ]	0.99	2.34	2.767(2)	105
C42	--H42A	..O12	[ ]	0.99	2.26	2.697(3)	105
C46	--H46A	..O09	[3666.01]	0.99	2.48	3.437(2)	163
C46	--H46B	..O05	[1555.04]	0.99	2.52	3.293(3)	135
C61	--H61A	..O11	[ ]	0.99	2.26	2.695(2)	105

Discussion of the racemic chain co-crystals

The co-crystal solvate containing 3,5-dihydroxybenzoic acid and acetonitrile (p2044a, Figure 7b and S22) exhibits a racemic chain running along the [0,0,1] direction, and strongly resembles the enantiopure chains presented in Figure 5. Here, both *R*- and *S*-enantiomers of PZQ form hydrogen bonds in a similar fashion, and point in the same direction. As slight rotation or tilt of 3,5-dihydroxybenzoic acid can be seen in Figure 7b, depending on the handedness of the enantiomer with which the hydroxyl- and carboxylic acid groups form hydrogen bonds, respectively.

A similar periodic tilt of the coformer is also present in the hydroquinone co-crystal (p1931a, Figure 7a, along the [-1, 0, 2] direction), yet enantiomers of different chirality point in opposite directions.

This also the case for the racemic chain formed with 2,4-dihydroxybenzoic acid (p2024a, Figure 7c), but the coformer also periodically flips along the chain. Given its structural similarity to 4-hydroxybenzoic acid and the emergence of an SE and SAT phase of which we did not succeed to grow a single crystal, it remains unclear whether a co-crystal polymorph with an enantiopure stacking such as in Figure 5 could exist.

S3.3 – Racemic pairs

Table S5: Crystallographic data of the co-crystal structures characterized by the formation of racemic pairs.

	p1822a	**p2026a**	**p2046a**
Crystal data			
Chemical formula	$C_{19}H_{24}N_2O_2 \cdot C_7H_6O_3 \cdot H_2O$	$C_{19}H_{24}N_2O_2 \cdot C_8H_8O_4$	$C_{19}H_{24}N_2O_2 \cdot C_7H_4N_2O_6$
M_r	468.53	480.54	524.52
Crystal system, space group	Triclinic, *P-1*	Monoclinic, $P2_1/n$	Triclinic, *P-1*
Temperature (K)	150	150	150
a, b, c (Å)	6.8292 (6), 13.0390 (12), 14.4336 (13)	17.3526 (5), 6.1401 (2), 22.6698 (7)	6.916 (1), 12.8758 (19), 14.327 (2)
α, β, γ (°)	70.664 (3), 83.297 (3), 75.581 (3)	90, 90.7322 (12), 90	89.538 (6), 82.815 (6), 78.327 (7)
V (Å^3)	1173.73 (18)	2415.20 (13)	1239.4 (3)
Z	2	4	2
Radiation type	Mo Kα	Mo Kα	Mo Kα
μ (mm−1)	0.09	0.09	0.11
Crystal size	0.32 × 0.18 × 0.14	0.40 × 0.32 × 0.08	0.46 × 0.14 × 0.07
Data collection			
Diffractometer	Bruker D8 Quest Apex3		
Absorption correction	Multi-scan SADABS 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10		
T_{min}, T_{max}	0.669, 0.745	0.659, 0.747	0.688, 0.747
No. of measured, independent and observed [I > 2σ(I)] reflections	11371, 4923, 3279	87579, 9225, 7485	35566, 9476, 7586
R_{int}	0.042	0.034	0.026
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.635	0.770	0.770
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.049, 0.154, 0.98	0.046, 0.130, 1.04	0.045, 0.125, 1.03
No. of reflections	4923	9225	9476
No. of parameters	317 (3 restraints)	382 (12 restraints)	343
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.22, −0.34	0.41, −0.27	0.43, −0.36

p1822a: co-crystal hydrate of PZQ, salicylic acid and water (**5**)

An equimolar mixture containing 26 mg of salicylic acid and 74 mg of PZQ was dissolved in a minimal amount of acetone, which was slowly evaporated at room temperature. Colorless plate-like crystals were obtained after several days of evaporation.

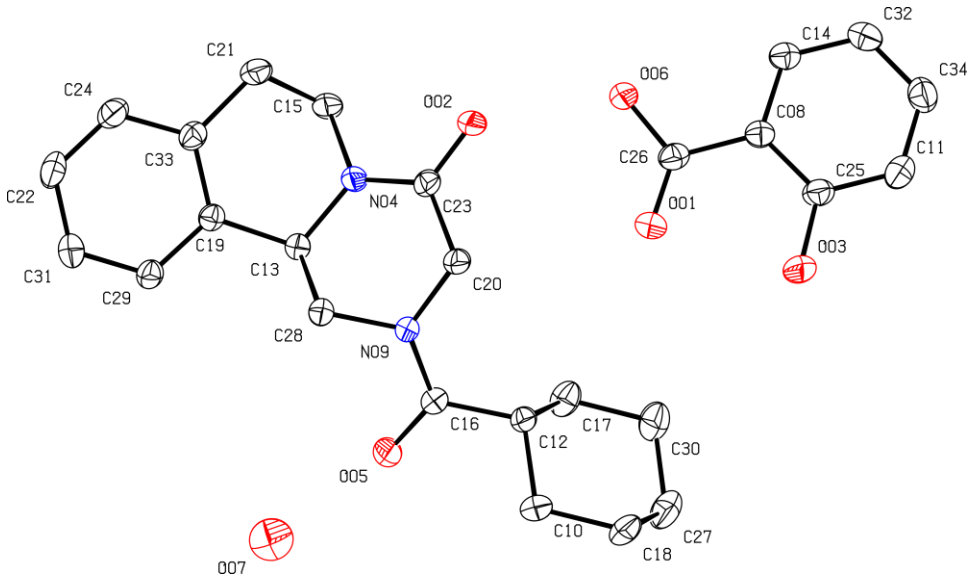


Figure S24: ORTEP plot of the co-crystal hydrate containing PZQ, salicylic acid and water (p1822a).

Donor	--- H	....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O03	--H03	..O01	[ ]	0.84	1.86	2.598(2)	146
O06	--H06	..O02	[1555.01]	0.84	1.74	2.564(2)	166
O07	--H07A	..O05	[1555.01]	0.87(3)	1.97(2)	2.832(3)	169(4)
O07	--H07B	..O05	[2556.01]	0.87(3)	1.98(4)	2.838(3)	172(3)
C15	--H15B	..O02	[ ]	0.99	2.32	2.737(3)	104
C20	--H20A	..O01	[1555.02]	0.99	2.42	3.285(2)	145
C24	--H24	..O03	[1554.02]	0.95	2.56	3.402(2)	148
C28	--H28B	..O05	[ ]	0.99	2.36	2.767(2)	103
C32	--H32	..O02	[2766.01]	0.95	2.59	3.391(3)	142

p2026a: co-crystal of PZQ and vanillic acid (**20**)

A mixture containing 167 mg of PZQ and 93 mg of vanillic acid was manually ground, and 43 mg was dissolved in 1 mL of acetone. Slow evaporation of the solution resulted in colorless block-shape crystals.

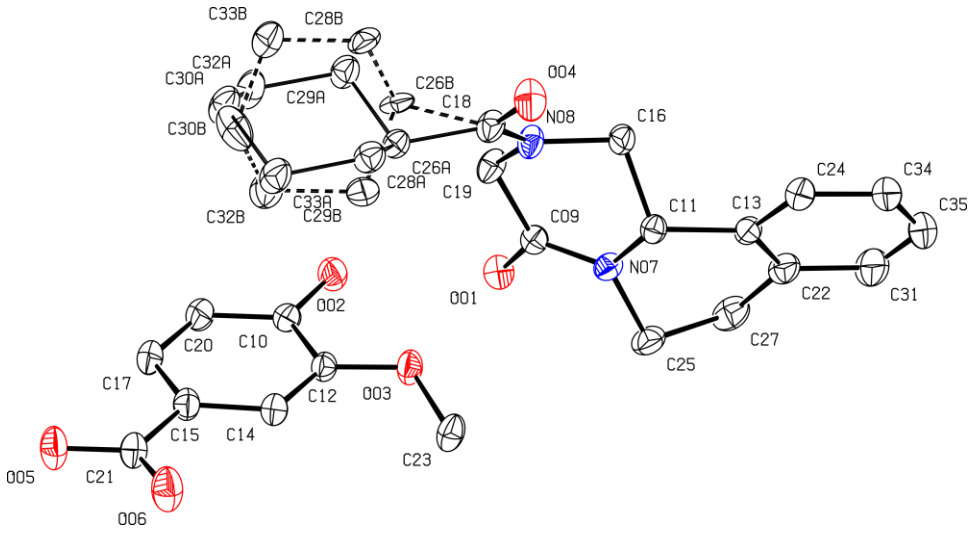


Figure S25: ORTEP plot of the co-crystal containing PZQ and vanillic acid (p2026a).

Donor	---	H	....Acceptor	[	ARU	]	D - H	H...A	D...A	D - H...A
O02	--H02	..O01	[	1555.01]	0.921(17)	1.755(16)	2.6534(10)	164.4(16)		
O02	--H02	..O03	[	]	0.921(17)	2.322(18)	2.7024(11)	104.4(12)		
O05	--H05	..O06	[	3667.02]	0.87(4)	1.74(4)	2.6080(13)	176(3)		
C11	--H11	..O01	[	1565.01]	1.00	2.37	3.3213(11)	158		
C16	--H16A	..O04	[	]	0.99	2.33	2.7508(13)	104		
C23	--H23A	..O02	[	1565.02]	0.98	2.46	3.2986(13)	143		
C25	--H25A	..O01	[	]	0.99	2.32	2.7482(12)	105		

p2046a: co-crystal of PZQ and 3,5-dinitrobenzoic acid (**13**)

163 mg of PZQ and 110 mg of 3,5-dinitrobenzoic acid were first combined and manually ground. 77 mg of the mixture was dissolved in 1.2 mL of ethyl acetate, which was completely evaporated, resulting in small needle-like crystals. The residue was partially re-dissolved in a mixture of 1.5 mL ethyl acetate and 1 mL n-heptane, leaving some crystallites as seeds. Slow evaporation yielded colorless/slightly yellow needles suitable for single-crystal X-ray diffraction.

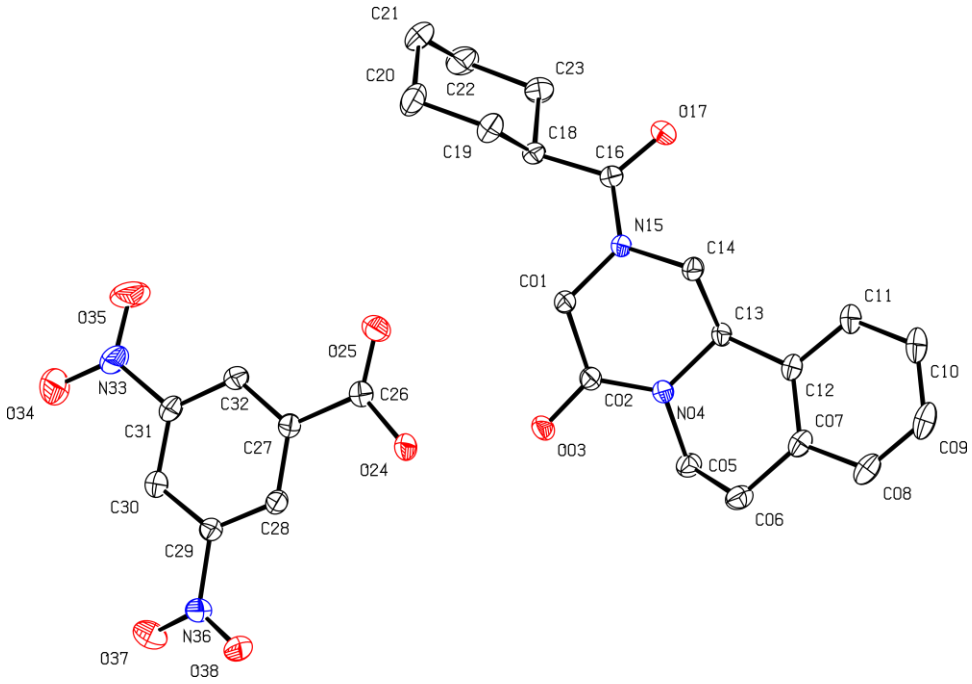


Figure S26: ORTEP plot of the co-crystal containing PZQ and 3,5-dinitrobenzoic acid (p2046a).

Donor	--- H	....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O24	--H24	..O03	[1555.01]	0.84	1.79	2.5665(11)	153
C01	--H01B	..O03	[2766.01]	0.99	2.47	3.1658(13)	127
C05	--H05B	..O03	[ ]	0.99	2.32	2.7438(13)	105
C10	--H10	..O17	[2676.01]	0.95	2.27	3.1433(14)	152
C14	--H14B	..O17	[ ]	0.99	2.32	2.7402(12)	105
C28	--H28	..O38	[2756.02]	0.95	2.54	3.2865(13)	136

Discussion of the racemic pair co-crystals

In contrast to the chain-forming co-crystals presented above, a class of co-crystals forming enantiomer pairs, similar to one of PZQ's racemic compounds TELCEU01, was identified. The *R*- and *S*-enantiomers form intermolecular interactions to each other through the formation hydrogen bonds *via* the carbonyl groups on the piperazinone moieties.

A strong resemblance to TELCEU01's racemic pairs was observed for the co-crystal with vanillic acid (p2026a, Figure S25 and 8c), and only a small difference in intermolecular spacing between enantiomers is present compared to TELCEU01 (*d* in Figure 8a and 8c). From the new co-crystals with coformers containing carboxylic acid groups, the co-crystal with vanillic acid is the only where the formation of carboxylic acid dimers is observed. Similar to the case of 2,4-dihydroxybenzoic acid, we did not succeed to grow a single crystal of the phase obtained after SE with MeCN, and the possibility for vanillic acid to form an enantiopure or racemic chain co-crystal through hydrogen bonds with its carboxylic acid group seems plausible.

For 3,5-dinitrobenzoic acid (p2046a, Figure S26 and 8d), the enantiomers are shifted compared to the racemic compound, resulting in interactions between PZQ's aromatic rings and carbonyl groups. This is illustrated in Figure 8d with d_1, and d_2 highlights the original interacting atoms in TELCEU01.

In the co-crystal hydrate with salicylic acid (p1822a, Figure S24 and 8b), the enantiomers are bridged by hydrogen bonds with two water molecules, and attempts to grow a co-crystal anhydrate (where the enantiomers interact in a similar fashion to TELCEU01) were unsuccessful.

It is also noteworthy to mention that, although forming a racemic chain, hydroquinone (Figure 7a) also appears to fulfill a bridging function similar to the water molecules.

S3.4 – Racemic networks

Table S6: Crystallographic data of the co-crystal structures characterized by the formation of racemic networks.

p2057a	
Crystal data	
Chemical formula	$C_{19}H_{24}N_2O_2 \cdot C_6F_4I_2$
M_r	714.26
Crystal system, space group	Triclinic, *P-1*
Temperature (K)	150
a, *b*, *c* (Å)	5.4090 (5), 13.2117 (11), 17.9727 (18)
α, *β*, *γ* (°)	84.566 (9), 85.373 (8), 83.989 (7)
V (Å^3)	1268.3 (2)
Z	2
Radiation type	Mo Kα
μ (mm−1)	2.53
Crystal size	0.60 × 0.06 × 0.04
Data collection	
Diffractometer	Bruker D8 Quest Apex3
Absorption correction	Multi-scan SADABS 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10
T_{min}, T_{max}	0.474, 0.990
No. of measured, independent and observed [I > 2σ(I)] reflections	42343, 9720, 7754
R_{int}	0.042
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.771
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.036, 0.067, 1.03
No. of reflections	9720
No. of parameters	371 (12 restraints)
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.23, −1.47

p2057a: co-crystal of PZQ and 1,4-diiodotetrafluorobenzene (**6**)

81 mg of 1,4-diiodotetrafluorobenzene and 63 mg of PZQ (1:1 molar ratio) were combined and manually ground for 5 minutes. 25 mg of this mixture was dissolved in 1.4 mL EtOH, which was treated with ultrasound and heated to speed up dissolution. Slow evaporation of the solution resulted in colorless needle-shaped crystals.

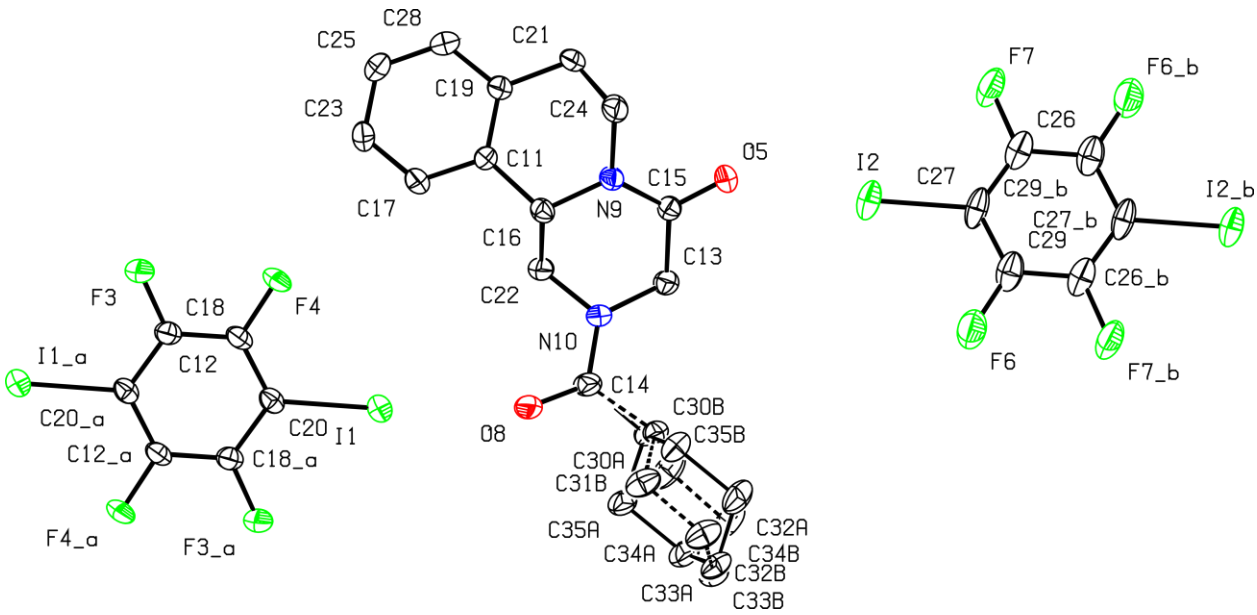


Figure S27: ORTEP plot of the co-crystal containing PZQ and 1,4-diiodotetrafluorobenzene (p2057a).

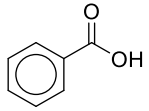
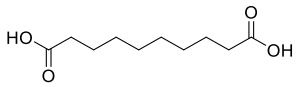
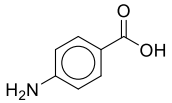
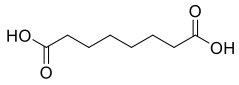
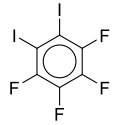
Donor	--- H	....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
C16	--H16	..O5	[1655.01]	1.00	2.37	3.335(3)	162
C22	--H22A	..O8	[ ]	0.99	2.30	2.727(3)	105
C24	--H24A	..O5	[ ]	0.99	2.32	2.739(3)	104
C28	--H28	..F6	[1645.03]	0.95	2.47	3.291(3)	144

Discussion of the racemic network co-crystal

Unlike the other coformer hits, 1,4-diiodotetrafluorobenzene does not contain functional groups suitable for hydrogen bond formation. In this co-crystal (p2057a, Figure S27 and 9), halogen bonds are observed between the coformer's iodone groups and PZQ's carbonyl groups, and C-H…F interactions with the cyclohexyl and aromatic moieties of PZQ. Therefore, a two-dimensional network is formed rather than a zero-dimensional pair or one-dimensional chain. Similar to the racemic chains, a slight tilt of the coformer is observed depending on the handedness of the PZQ molecules on its left and right side.

S4 – Additional predictions for PZQ

Table S7: Fifty additional predictions for PZQ based on the 8 known co-crystals from the CSD combined with the data obtained from this article (including co-crystal solvates).

Rank	**1**	**2**		**4**	**5**
					
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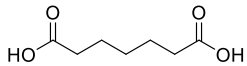
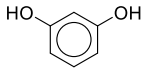
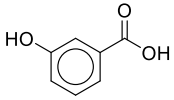
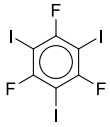
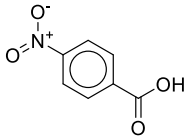
Score	15.8791	13.6777	12.0758	11.3656	11.3421
Precision	0.601	0.568	0.544	0.531	0.531
Rank	**6**	**7**	**8**	**9**	**10**
					
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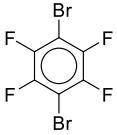
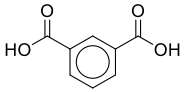
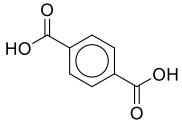
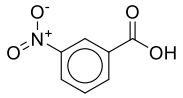
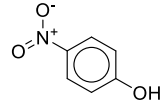
Score	10.5386	9.99093	9.83193	9.49392	8.64079
Precision	0.517	0.507	0.504	0.498	0.481
Rank	**11**	**12**	**13**	**14**	**15**
					
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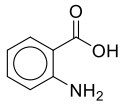
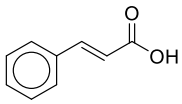
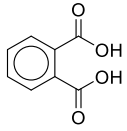
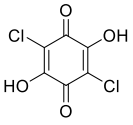
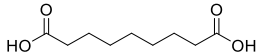
Score	7.83224	7.50875	7.44369	7.29471	6.56224
Precision	0.465	0.458	0.457	0.453	0.429
Rank	**16**	**17**	**18**	**19**	**20**
					
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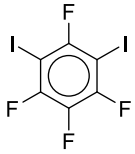
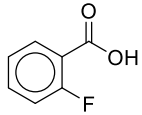
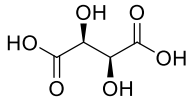
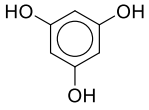
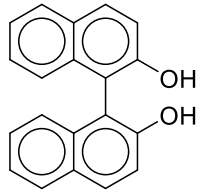
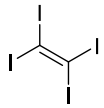
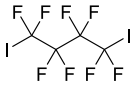
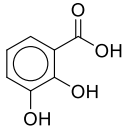
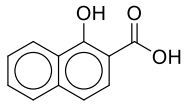
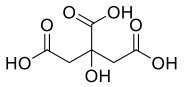
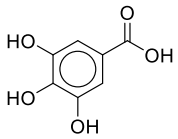
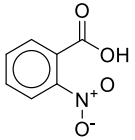
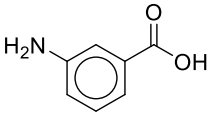
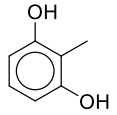
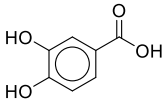
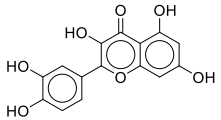
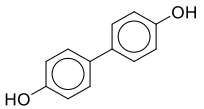
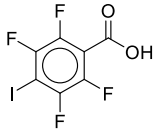
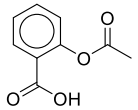
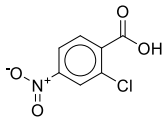
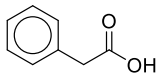
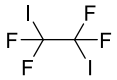
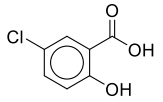
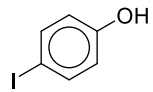
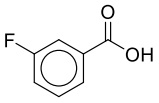
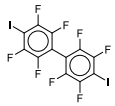
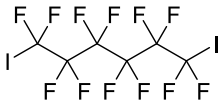
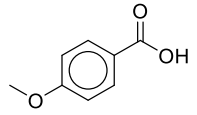
Score	6.48775	6.18309	5.36911	5.29269	5.26422
Precision	0.426	0.415	0.383	0.38	0.378
Rank	**21**	**22**	**23**	**24**	**25**
					
SMILES	Fc1c(F)c(F)c(c(c1I)F)I	OC(=O)c1ccccc1F	O[C@@H]([C@@H](C(=O)O)O)C(=O)O	Oc1cc(O)cc(c1)O	Oc1ccc2c(c1c1c(O)ccc3c1cccc3)cccc2
Score	5.06931	4.77063	4.72269	4.51707	4.48473
Precision	0.37	0.356	0.353	0.343	0.342

Rank	**26**	**27**	**28**	**29**	**30**
					
SMILES	IC(=C(I)I)I	FC(C(C(I)(F)F)(F)F)(C(I)(F)F)F	OC(=O)c1cccc(c1O)O	OC(=O)c1ccc2c(c1O)cccc2	OC(=O)C(CC(=O)O)(CC(=O)O)O
Score	4.0039	4.00281	3.9277	3.91269	3.89201
Precision	0.316	0.316	0.312	0.311	0.31
Rank	**31**	**32**	**33**	**34**	**35**
					
SMILES	OC(=O)c1cc(O)c(c(c1)O)O	O=N(=O)c1ccccc1C(=O)O	II	Nc1cccc(c1)C(=O)O	Oc1cccc(c1C)O
Score	3.80266	3.68767	3.60334	3.55884	3.53423
Precision	0.305	0.298	0.293	0.29	0.289
Rank	**36**	**37**	**38**	**39**	**40**
					
SMILES	OC(=O)c1ccc(c(c1)O)O	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	Oc1ccc(cc1)c1ccc(cc1)O	Fc1c(F)c(C(=O)O)c(c(c1I)F)F	CC(=O)Oc1ccccc1C(=O)O
Score	3.52782	3.36844	3.35739	3.34748	3.30083
Precision	0.288	0.279	0.278	0.277	0.275
Rank	**41**	**42**	**43**	**44**	**45**
					
SMILES	OC(=O)c1ccc(cc1Cl)N(=O)=O	Oc1c(O)cccc1O	OC(=O)Cc1ccccc1	FC(C(I)(F)F)(I)F	Clc1ccc(c(c1)C(=O)O)O
Score	3.29311	3.23944	3.23614	3.21784	3.14741
Precision	0.274	0.271	0.271	0.269	0.265
Rank	**46**	**47**	**48**	**49**	**50**
					
SMILES	Oc1ccc(cc1)I	Fc1cccc(c1)C(=O)O	Fc1c(c2c(F)c(F)c(c(c2F)F)I)c(F)c(c(c1F)I)F	FC(C(C(I)(F)F)(F)F)(C(C(C(I)(F)F)(F)F)(F)F)F	COc1ccc(cc1)C(=O)O
Score	3.10146	3.03964	3.02853	3.01592	2.98191
Precision	0.263	0.259	0.259	0.258	0.256

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[3] Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, C71, 3–8.