In this study, co-crystals for Praziquantel (PZQ), an anthelmintic drug used to treat schistosomiasis, are predicted with network-based link prediction. Single crystals of twelve co-crystal indications were grown and subjected to a structural analysis with single-crystal X-ray diffraction.
Supporting Information:
"Co-crystals of Praziquantel: Discovery by Link Prediction"

Jan-Joris Devogelaer,† Maxime D. Charpentier,‡ Arnoud Tijink,† Valérie Dupray,¶ Gérard Coquerel,§ Karen Johnston,┴ Hugo Meekes,† Paul Tinnemans,† Elias Vlieg,† Joop H. ter Horst,‡ and René de Gelder*,†

† Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6525AJ Nijmegen, The Netherlands
‡ EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization (CMAC), Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), Technology and Innovation Centre, University of Strathclyde, 99 George Street, Glasgow G1 1RD, United Kingdom
¶ Normandie Univ, UNIROUEN, SMS, 76000 Rouen, France
┴ University of Strathclyde, Department of Chemical and Process Engineering, 75 Montrose Street, Glasgow G1 1XJ, United Kingdom

E-mail: r.degelder@science.ru.nl

Table of contents

S1 – Materials 2
S2 – Experimental techniques, conditions and powder diffraction results 3
S3 – Crystallographic data and analysis of the discovered co-crystal structures 10
S4 – Additional predictions for PZQ 30
## 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-Diodotetrafluorobenzene     | 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       | 90-10-5   | Fluorochem recryst. from MeCN | 99% |
| 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° < 2θ < 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 |Fh|| 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           | EtOH (1.42) & AcOEt (2.36)                             | S1         |
| 5    | Salicylic acid                  | EtOH            | EtOH           | EtOH (10.59), MeCN (2.17) & AcOEt (9.24)               | S2         |
| 6    | 1,4-Diodotetrafluorobenzene    | MeCN            | MeCN           | EtOH (5.03)                                             | S3         |
| 7    | 4-Hydroxybenzoic acid           | MeCN            | MeCN           | EtOH (8.26) & MeCN (0.93)                              | S4         |
| 8    | Terephthalic acid               | MeCN            | MeCN           | EtOH (3.35), MeCN (1.45) & AcOEt (3.38)               |            |
| 9    | 4-Aminobenzoic acid             | MeCN            | MeCN           | EtOH (4.10) & AcOEt (0.75)                              |            |
| 10   | Isophthalic acid                | MeCN            | MeCN           | EtOH (3.35), MeCN (1.45) & AcOEt (3.38)               |            |
| 11   | Azelaic acid                    | EtOH            | EtOH           | EtOH (10.59), MeCN (2.17) & AcOEt (9.24)               |            |
| 12   | 4-Aminosalicylic acid           | MeCN            | MeCN           | EtOH (8.26) & MeCN (0.93)                              |            |
| 13   | 3,5-Dinitrobenzoic acid         | MeCN            | MeCN           | MeCN (0.89)                                             | S6         |
| 14   | trans-Cinnamic acid             | MeCN            | MeCN           | MeCN (0.89)                                             |            |
| 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 (-0) | MeCN, MeOH  | EtOH (6.25), MeCN (2.99) & AcOEt (8.74)               |            |
| 18   | Phthalic acid                   | MeCN            | MeCN           | EtOH (3.65)                                             |            |
| 19   | D(-)-Tartaric acid              | MeCN            | MeCN           | EtOH (3.65)                                             |            |
| 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 mixture of the coformer 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-diodotetrafluorobenzene 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-diodotetrafluorobenzene
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.

| Crystal data | p1829a | p1821a | p1932a | p2054a | p2040a |
|--------------|--------|--------|--------|--------|--------|
| Chemical formula | C₁₉H₂₃N₂O₅·C₇H₆O₄ | C₁₉H₂₃N₂O₂·C₇H₆O₄·C₂H₃ | C₁₉H₂₃N₂O₂·C₇H₆O₃ | C₁₉H₂₃N₂O₂·C₇H₇NO₃·C₂ | C₁₉H₂₃N₂O₂·C₇H₆O₂ |
| Mᵣ | 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, P2₁/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 (Å³) | 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 | | | | | |
| Absorption correction | | | | | |
| SADABS 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M., & Stalke D., J. Appl. Cryst. 48 (2015) 3-10 | | | | | |
| Tmin, Tmax | 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, R̃ | 0.044 | 0.034 | 0.023 | 0.030 | 0.044 |
| (sin θ/λ)max (Å⁻¹) | 0.772 | 0.668 | 0.770 | 0.668 | 0.668 |
| Refinement | | | | | |
| R[F² > 2σ(F²)], wR(F²), 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 |
| Δρmax, Δρmin (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.

![ORTEP plot of the co-crystal containing PZQ and 2,5-dihydroxybenzoic acid (p1829a).](image)

| Donor | --- | H...Acceptor | ARU  | D - H | H...A | D...A | D - H...A |
|-------|-----|---------------|------|-------|-------|-------|----------|
| O01   | --H01 | .023          | 1555.01 | 0.89(2) | 1.74(2) | 2.6146(15) | 167.5(19) |
| O03   | --H03 | .019          | 5545.01 | 0.91(3) | 1.71(3) | 2.621(3)  | 174(2)    |
| O03   | --H03 | .035          | 5545.01 | 0.91(3) | 1.84(4) | 2.74(2)   | 174(2)    |
| O04   | --H04 | .002          |        | 0.92(3) | 1.76(3) | 2.5881(16) | 149(2)    |
| C21   | --H21B | .002         | 1555.02 | 0.99   | 2.29   | 3.0852(19) | 137       |
| C26   | --H26A | .019         |        | 0.99   | 2.32   | 2.743(3)  | 104       |
| C26   | --H26A | .035         |        | 0.99   | 2.45   | 2.86(2)   | 105       |
| C26   | --H26A | .003         | 5455.02 | 0.99   | 2.53   | 3.4090(18) | 148       |
| C27   | --H27A | .023         |        | 0.99   | 2.31   | 2.744(2)  | 105       |
| C28   | --H28A | .004         | 4565.02 | 0.99   | 2.47   | 3.4123(18) | 159       |
| C31   | --H31 | .003          | 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  | acceptor | ARU  | D - H | H...A   | D...A   | D - H...A |
|--------|----------|------|-------|---------|---------|-----------|
| O25    | --H25    | .012 | 1555.01 | 0.91(2) | 1.74(2) | 2.6311(15) | 166.3(17)  |
| O29    | --H29    | .024 | [      ] | 0.89(2) | 1.78(2) | 2.5991(17) | 152.7(17)  |
| O33    | --H33    | .008 | 1444.01 | 0.89(2) | 1.78(2) | 2.6713(15) | 178(2)     |
| C05    | --H05B   | .033 | 2666.02 | 0.99    | 2.60   | 3.3060(18) | 128        |
| C10    | --H10B   | .024 | 1555.02 | 0.99    | 2.44   | 3.1532(19) | 129        |
| C14    | --H14A   | .012 | [      ] | 0.99    | 2.34   | 2.7650(19) | 105        |
| C14    | --H14B   | .N35 | 1665.03 | 0.99    | 2.55   | 3.481(2)  | 156        |
| C23    | --H23A   | .008 | [      ] | 0.99    | 2.34   | 2.7619(17) | 104        |
| C23    | --H23B   | .N35 | 1565.03 | 0.99    | 2.56   | 3.535(2)  | 167        |
| C37    | --H37B   | .012 | 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.

![ORTEP plot of the co-crystal containing PZQ and 4-hydroxybenzoic acid (p1932a).](image)

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

| 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     |
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.

Donor --- H....Acceptor [   ARU    ]      D - H      H...A      D...A      D - H...A
O24 --H24   .022  [ 2555.01]     0.91(2)     1.77(2)    2.6813(17)   175(2)
O25 --H25   .008  [ 1555.01]     0.85(3)     1.82(3)    2.658(2)     167(3)
C05 --H05A  .024  [ 2645.02]     0.99       2.51       3.292(2)   135
C10 --H10A  .008  [       ]     0.99       2.32       2.735(2)   104
C10 --H10B  .025  [ 1455.02]     0.99       2.42       3.280(3)   144
C11 --H11   .022  [ 1655.01]     1.00       2.52       3.450(2)   155
C19 --H19B  .022  [       ]     0.99       2.30       2.731(3)   105

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

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.

| Crystal data | p1931a | p2044a | p2024a |
|--------------|--------|--------|--------|
| **Chemical formula** | C_{19}H_{34}N_{2}·C_{6}H_{6}O_{2} | C_{19}H_{34}N_{2}·C_{6}H_{6}O_{2}·C_{2}H_{7}N | C_{19}H_{34}N_{2}·C_{7}H_{6}O_{4}·C_{2}H_{3}N |
| **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 (Å³)** | 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 θ/λ)_{max} (Å⁻¹)** | 0.771 | 0.769 | 0.767 |

#### Refinement

| \( R (I^2 > 2σ(I^2)), wR(F^2), S \) | 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 |
| **Δρ_{max}, Δρ_{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 .001      | 1555.01 | 0.876(17) | 1.808(17) | 2.684(10) | 178.9(16) |
| O06   | ---H06 .002      | 1555.01 | 0.837(19) | 1.955(19) | 2.738(11) | 155.6(18) |
| C13   | ---H13 .001      | 1555.01 | 0.95 | 2.57 | 3.249(5) | 129 |
| C15   | ---H15B .001     |       | 0.99 | 2.33 | 2.722(9) | 103 |
| C18   | ---H18B .003     | 3666.02 | 0.99 | 2.42 | 3.182(11) | 133 |
| C30   | ---H30B .002     |       | 0.99 | 2.34 | 2.767(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).
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.

![ORTEP plot of the co-crystal containing PZQ and 2,4-dihydroxybenzoic acid (p2024a).](image)

| Donor  | --- | Acceptor | ARU    | D - H  | H...A  | D...A  | D - H...A |
|--------|-----|-----------|--------|--------|--------|--------|-----------|
| O01    | --H01 | .012 | [ 4565.02] | 0.85(2) | 1.82(2) | 2.660(2) | 170(3)    |
| O02    | --H02 | .011 | [ 4464.01] | 0.86(3) | 1.79(3) | 2.643(2) | 172(3)    |
| O03    | --H03 | .004 | []       | 0.89(3) | 1.79(3) | 2.610(2) | 154(2)    |
| O06    | --H06 | .005 | []       | 0.86(3) | 1.85(3) | 2.620(2) | 148(3)    |
| O07    | --H07 | .010 | [ 1555.02] | 0.90(3) | 1.74(3) | 2.612(2) | 163(2)    |
| O08    | --H08 | .009 | [ 1555.01] | 0.88(3) | 1.76(3) | 2.612(2) | 163(3)    |
| C18    | --H18 | .003 | [ 1555.03] | 1.00    | 2.59    | 3.490(2) | 150       |
| C27    | --H27A | .010 | [ ]       | 0.99    | 2.34    | 2.765(2) | 105       |
| C34    | --H34A | .009 | [ ]       | 0.99    | 2.34    | 2.767(2) | 105       |
| C42    | --H42A | .012 | [ ]       | 0.99    | 2.26    | 2.697(3) | 105       |
| C46    | --H46A | .009 | [ 3666.01] | 0.99    | 2.48    | 3.437(2) | 163       |
| C46    | --H46B | .005 | [ 1555.04] | 0.99    | 2.52    | 3.293(3) | 135       |
| C61    | --H61A | .011 | [ ]       | 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.

| Crystal data | p1822a | p2026a | p2046a |
|--------------|--------|--------|--------|
| Chemical formula | C_{19}H_{24}N_{2}O_{2}·C_{7}H_{6}O_{3}·H_{2}O | C_{19}H_{24}N_{2}O_{2}·C_{8}H_{8}O_{4} | C_{19}H_{24}N_{2}O_{2}·C_{7}H_{4}N_{2}O_{6} |
| M_r          | 468.53 | 480.54 | 524.52 |
| Crystal system, space group | Triclinic, P-1 | Monoclinic, P21/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 (Å³) | 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 |
| Tmin, Tmax | 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 |
| Rint | 0.042 |
| 0.034 |
| 0.026 |
| (sin θ/λ)max (Å⁻¹) | 0.635 |
| 0.770 |
| 0.770 |

Refinement

| R[F² > 2σ(F²)], wR(F²), 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 |
| Δρmax, Δρmin (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.

![ORTEP plot of the co-crystal hydrate containing PZQ, salicylic acid and water (p1822a).](image)

| Donor | H...Acceptor | ARU | D - H | H...A | D...A | D - H...A |
|-------|--------------|-----|-------|-------|-------|-----------|
| O03   | --H03        | .001 |       | 0.84  | 1.86  | 2.598(2)  | 146     |
| O06   | --H06        | .002 | [1555.01] | 0.84  | 1.74  | 2.564(2)  | 166     |
| O07   | --H07A       | .005 | [1555.01] | 0.87(3) | 1.97(2) | 2.832(3)  | 169(4)  |
| O07   | --H07B       | .005 | [2556.01] | 0.87(3) | 1.98(4) | 2.838(3)  | 172(3)  |
| C15   | --H15B       | .002 | [2556.01] | 0.99   | 2.32   | 2.737(3)  | 104     |
| C20   | --H20A       | .001 | [1555.02] | 0.99   | 2.42   | 3.285(2)  | 145     |
| C24   | --H24        | .003 | [1554.02] | 0.95   | 2.56   | 3.402(2)  | 148     |
| C28   | --H28B       | .005 | [2766.01] | 0.99   | 2.36   | 2.767(2)  | 103     |
| C32   | --H32        | .002 | [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).](image)

| Donor   | H...Acceptor | [ ARU ] | D - H  | H...A   | D...A  | D - H...A |
|---------|--------------|---------|--------|---------|--------|-----------|
| O02     | --H02        | .001    | [1555.01] | 0.921(17) | 1.755(16) | 2.6534(10) | 164.4(16) |
| O02     | --H02        | .003    | [    ]  | 0.921(17) | 2.322(18) | 2.7024(11) | 104.4(12) |
| O05     | --H05        | .006    | [3667.02] | 0.87(4)   | 1.74(4)   | 2.6080(13) | 176(3)    |
| C11     | --H11        | .001    | [1565.01] | 1.00     | 2.37    | 3.3213(11) | 158       |
| C16     | --H16A       | .004    | [    ]  | 0.99     | 2.33    | 2.7508(13) | 104       |
| C23     | --H23A       | .002    | [1565.02] | 0.98     | 2.46    | 3.2986(13) | 143       |
| C25     | --H25A       | .001    | [    ]  | 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        | .003  | 1.555.01 | 0.84 | 1.79 | 2.5665(11) | 153       |
| C01    | --H01B       | .003  | 2.766.01 | 0.99 | 2.47 | 3.1658(13) | 127       |
| C05    | --H05B       | .003  | [ ]    | 0.99 | 2.32 | 2.7438(13) | 105       |
| C10    | --H10        | .017  | 2.676.01 | 0.95 | 2.27 | 3.1433(14) | 152       |
| C14    | --H14B       | .017  | [ ]    | 0.99 | 2.32 | 2.7402(12) | 105       |
| C28    | --H28        | .038  | 2.756.02 | 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 d1, and d2 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.

| Crystal data          | p2057a          |
|-----------------------|-----------------|
| Chemical formula      | C₁₉H₂₄N₂O₂·C₆F₄I₂ |
| \(M_r\)               | 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) |
| \(V\) (Å³)            | 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                 |
| \((\sin \theta/λ)_{max}\) (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 |
| \(\Delta ρ_{max}, \Delta ρ_{min}\) (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.

![ORTEP plot of the co-crystal containing PZQ and 1,4-diiodotetrafluorobenzene (p2057a).]

**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 iodine 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**
| Rank | 1  | 2  | 4  | 5  |
|------|----|----|----|----|
| SMILES | OC(=O)c1cccc1 | OC(=O)CCCCCCCCCC(=O)O | OC(=O)c1cccc1N | OC(=O)CCCCCCCC(=O)O | Fc1e(F)e(F)c(c1F)I |
| 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 |
|------|----|----|----|----|----|
| SMILES | OC(=O)CCCCCCCC(=O)O | Oc1cccc1c1O | Oc1cccc1c1C(=O)O | Fc1e(F)c(F)c(c1D)I | OC(=O)c1cccc1c1N(=O)=O |
| 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 |
|------|----|----|----|----|----|
| SMILES | Fc1e(Br)c(F)c(c1F)Br | OC(=O)c1cccc1c1C(=O)O | OC(=O)c1cccc1c1C(=O)O | OC(=O)c1cccc1c1N(=O)=O | OC(=O)c1cccc1c1N(=O)=O |
| 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 |
|------|----|----|----|----|----|
| SMILES | OC(=O)c1cccc1N | OC(=O)C=C/c1cccc1 | OC(=O)c1cccc1c1c(=O)O | OC(=C)(=O)c1cccc1c1c(=O)O | OC(=O)CCCCCCCC(=O)O |
| 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 | Fc1e(F)c(F)c(c1F)I | OC(=O)c1cccc1F | Oc1cccc1c1c(=O)O | Oc1cccc1c1c(=O)O | Oc1cccc1c1c(=O)O |
| Score | 5.06931 | 4.77063 | 4.72269 | 4.51707 | 4.48473 |
| Precision | 0.37 | 0.356 | 0.353 | 0.343 | 0.342 |

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 | 26 | 27 | 28 | 29 | 30 |
|------|----|----|----|----|----|
| SMILES | IC(=C(I)I)I | FC(C(C(I)(F)F)(F)c1ccc(c1)O)F | OC(=O)c1ccccc(c1)O | OC(=O)c1ccccc(c1)O | OC(=O)c1ccccc(c1)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)c1ccccc(c1)O | O=N(=O)c1ccccc1C(=O)O | OC(=O)c1ccccc(c1)O | Ne1ccc(c1)C(=O)O | Oc1ccc(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)c1ccccc(c1)O | Oe1cc(O)c2e(c2e=O)c1ccccc(c1)O | Oe1ccccc(c1)O | Fe1e(F)e(C(=O)O)e(c(c1)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)c1ccccc(c1Cl)N(=O)=O | Oc1c(O)c1ccccc1O | OC(=O)Cc1ccccc1 | FC(C(I)(F)F)(I)F | Clc1ccc(c1C(=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 | Oc1cc(c1)I | Fe1ccc(c1)C(=O)O | Fe1e(c2e(F)e(F)c(c2F)F)Ie(F)e(c(c1)F)F | FC(C(C(I)(F)F)(F)F)(C(C(C(I)(F)F)(F)F)(F)F)F | OC(=O)c1ccccc(c1)O |
| Score | 3.10146 | 3.03964 | 3.02853 | 3.01592 | 2.98191 |
| Precision | 0.263 | 0.259 | 0.259 | 0.258 | 0.256 |
References

[1] ter Horst, J; Deij, M. A.; Cains, P. W. Discovering New Co-Crystals. *Crystal Growth & Design* **2009**, *9*, 1531–1537.

[2] Krause, L; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *Journal of Applied Crystallography* **2015**, *48*, 3–10.

[3] Sheldrick, G. M. Crystal structure refinement with SHELX. *Acta Crystallographica Section C: Structural Chemistry* **2015**, *71*, 3–8.
