# Electronic supplementary information (ESI)

## Affinity predictions computations and mechanosynthesis of carbamazepine based cocrystals

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**Table S1.** X-ray diffraction data for the CBZ:DL-MA cocrystal and the pure compounds carbamazepine (CBZ) and DL-mandelic acid (DL-MA)

| CBZ | | DL-MA | | CBZ:DL-MA | |
|---|---|---|---|---|---|
| *2θ* / ° | *Intensity* / % | *2θ* / ° | *Intensity* / % | *2θ* / ° | *Intensity* / % |
| 10.11 | 4.9 | 10.89 | 23.9 | 6.45 | 76.3 |
| 12.71 | 11.8 | 13.85 | 22.0 | 8.95 | 6.7 |
| 13.04 | 90.3 | 14.06 | 13.4 | 9.33 | 27.7 |
| 13.60 | 12.6 | 16.80 | 83.1 | 10.10 | 12.6 |
| 14.14 | 27.4 | 17.79 | 13.4 | 10.35 | 34.3 |
| 14.97 | 41.5 | 18.31 | 99.4 | 12.94 | 32.6 |
| 15.27 | 100.0 | 19.13 | 47.5 | 14.22 | 5.4 |
| 15.82 | 61.1 | 20.03 | 100.0 | 15.29 | 3.4 |
| 17.07 | 20.9 | 20.78 | 63.8 | 16.39 | 50.1 |
| 18.66 | 44.3 | 21.13 | 28.0 | 16.67 | 4.9 |
| 19.46 | 45.0 | 21.36 | 2.6 | 17.01 | 22.9 |
| 19.76 | 10.1 | 21.93 | 67.6 | 17.61 | 44.1 |
| 20.36 | 34.4 | 22.87 | 83.0 | 17.95 | 8.7 |
| 20.59 | 21.3 | 23.18 | 4.4 | 18.53 | 51.8 |
| 21.96 | 8.2 | 23.70 | 1.9 | 18.70 | 31.5 |
| 23.37 | 29.1 | 24.70 | 5.3 | 19.32 | 5.6 |
| 23.89 | 45.4 | 25.45 | 26.1 | 19.47 | 7.3 |
| 24.75 | 34.7 | 26.27 | 31.0 | 20.28 | 61.9 |
| 24.92 | 59.0 | 27.96 | 63.3 | 20.57 | 13.3 |
| 26.30 | 5.5 | 28.95 | 7.6 | 20.81 | 7.4 |
| 26.68 | 40.7 | 29.64 | 3.4 | 21.32 | 18.1 |
| 27.16 | 46.3 | 29.89 | 6.8 | 21.77 | 50.5 |
| 27.30 | 45.1 | 30.61 | 15.3 | 22.28 | 5.7 |
| 27.57 | 64.3 | 33.16 | 16.9 | 22.91 | 6.4 |
| 29.01 | 5.7 | 33.57 | 8.7 | 23.92 | 46.7 |
| 29.40 | 9.2 | 35.69 | 7.7 | 24.36 | 7.6 |
| 29.89 | 4.9 | | | 24.90 | 12.3 |
| 30.85 | 6.4 | | | 25.05 | 8.3 |
| 32.04 | 18.4 | | | 25.64 | 100.0 |
| 32.68 | 3.1 | | | 26.63 | 2.8 |
| | | | | 27.28 | 17.5 |
| | | | | 27.59 | 14.9 |
| | | | | 27.87 | 2.7 |

| | | |
|---|---|---|
| | 28.39 | 12.4 |
| | 29.07 | 4.4 |
| | 29.27 | 8.7 |
| | 30.08 | 14.5 |
| | 30.53 | 7.4 |
| | 30.85 | 12.3 |
| | 31.44 | 5.7 |
| | 32.16 | 2.9 |
| | 33.02 | 8.2 |
| | 33.69 | 2.9 |
| | 34.65 | 6.7 |

**Table S2.** X-ray diffraction data for the CBZ:INDO cocrystal and the pure compounds carbamazepine (CBZ) and indomethacin (INDO).

| **CBZ** | | **INDO** | | **CBZ:INDO** | |
|---|---|---|---|---|---|
| ***2θ* / °** | ***Intensity* / %** | ***2θ* / °** | ***Intensity* / %** | ***2θ* / °** | ***Intensity* / %** |
| 10.11 | 4.9 | 10.16 | 30.7 | 5.28 | 15.3 |
| 12.71 | 11.8 | 11.60 | 83.4 | 7.50 | 5.3 |
| 13.04 | 90.3 | 12.73 | 16.8 | 8.40 | 6.8 |
| 13.60 | 12.6 | 15.72 | 2.2 | 10.62 | 33.6 |
| 14.14 | 27.4 | 16.66 | 69.1 | 11.92 | 100.0 |
| 14.97 | 41.5 | 17.01 | 34.1 | 13.56 | 21.9 |
| 15.27 | 100.0 | 17.29 | 40.0 | 15.09 | 7.9 |
| 15.82 | 61.1 | 18.38 | 6.2 | 15.97 | 2.5 |
| 17.07 | 20.9 | 18.57 | 12.6 | 16.88 | 28.1 |
| 18.66 | 44.3 | 19.32 | 26.2 | 17.71 | 28.9 |
| 19.46 | 45.0 | 19.61 | 44.9 | 18.01 | 17.6 |
| 19.76 | 10.1 | 20.36 | 13.1 | 18.89 | 77.3 |
| 20.36 | 34.4 | 20.87 | 4.1 | 19.18 | 85.9 |
| 20.59 | 21.3 | 21.41 | 5.5 | 20.25 | 28.0 |
| 21.96 | 8.2 | 21.81 | 100.0 | 20.44 | 30.6 |
| 23.37 | 29.1 | 22.86 | 17.0 | 20.73 | 44.1 |
| 23.89 | 45.4 | 23.17 | 18.1 | 20.99 | 58.2 |
| 24.75 | 34.7 | 24.02 | 15.4 | 21.92 | 44.0 |
| 24.92 | 59.0 | 25.53 | 11.5 | 23.05 | 49.4 |
| 26.30 | 5.5 | 25.71 | 6.4 | 23.30 | 43.0 |
| 26.68 | 40.7 | 26.22 | 10.3 | 24.00 | 13.7 |
| 27.16 | 46.3 | 26.62 | 63.7 | 25.50 | 50.2 |
| 27.30 | 45.1 | 26.93 | 15.2 | 25.98 | 23.9 |
| 27.57 | 64.3 | 27.50 | 9.3 | 26.51 | 4.3 |
| 29.01 | 5.7 | 28.29 | 10.6 | 26.97 | 31.0 |
| 29.40 | 9.2 | 28.79 | 9.9 | 27.41 | 31.7 |
| 29.89 | 4.9 | 29.36 | 21.2 | 27.83 | 6.9 |
| 30.85 | 6.4 | 30.42 | 12.3 | 28.38 | 2.7 |
| 32.04 | 18.4 | 30.77 | 3.4 | 29.04 | 6.8 |
| 32.68 | 3.1 | 32.68 | 7.3 | 29.67 | 27.7 |

| | | | |
|---|---|---|---|
| 32.99 | 3.8 | 30.19 | 7.9 |
| 33.59 | 4.8 | 30.55 | 2.8 |
| 34.12 | 7.1 | 31.10 | 19.6 |
| 34.92 | 2.6 | 31.86 | 6.1 |
| | | 32.24 | 14.5 |
| | | 32.75 | 4.1 |
| | | 34.04 | 3.0 |
| | | 34.38 | 3.9 |

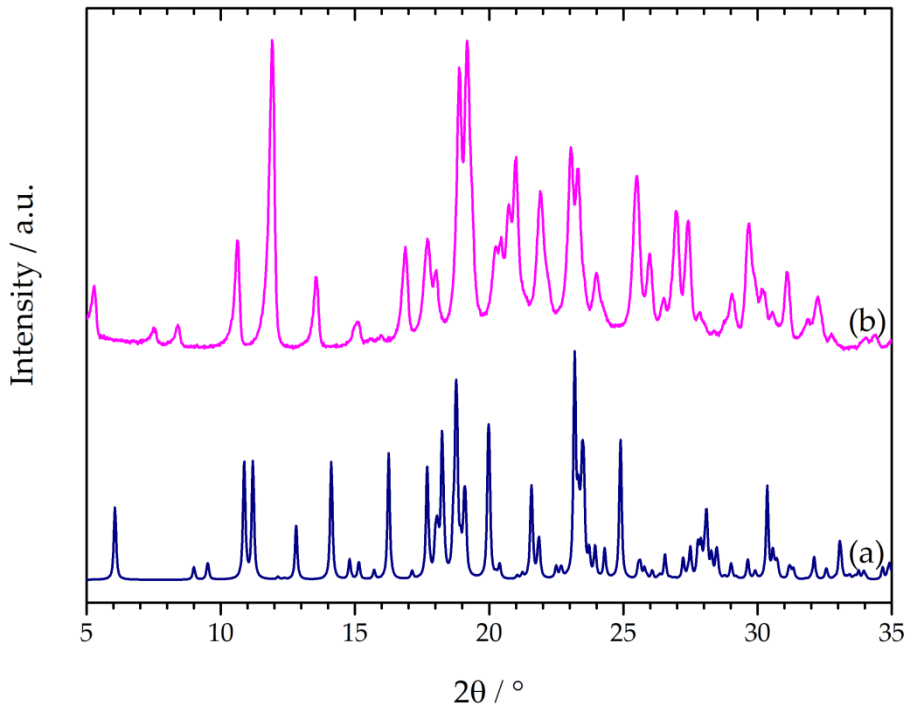


**Figure S1.** PXRD patterns of the (a) CBZ:INDO simulated from the literature vs the (b) CBA-INDO cocrystal obtained by LAG (this work).

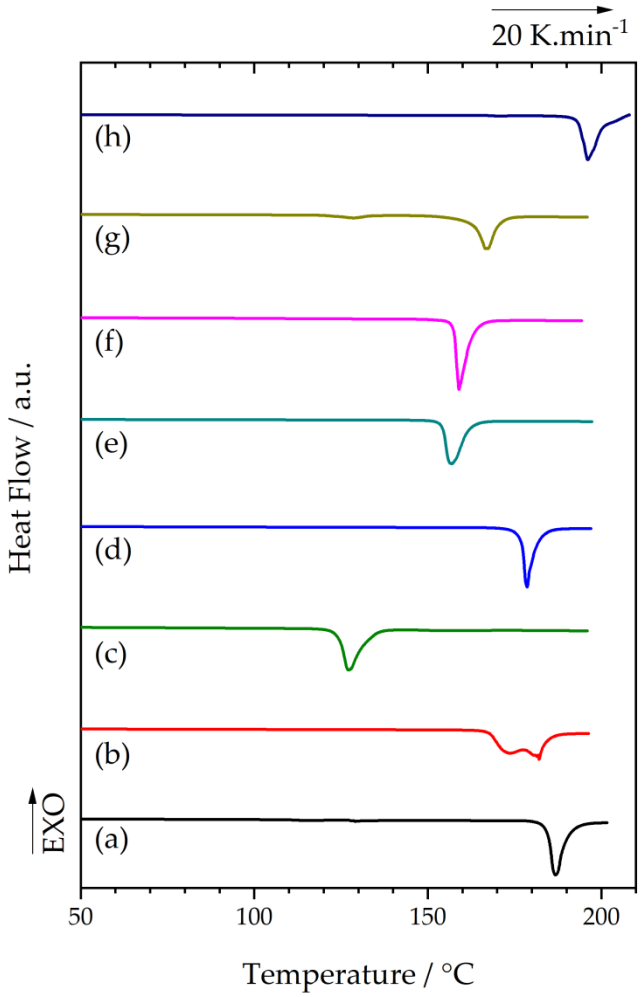


**Figure S2.** DSC thermograms of carbamazepine based cocrystals reported in the literature and obtained by LAG in this study. (a) CBZ-fumaric acid, (b) CBZ-succinic acid, (c) CBZ-adipic acid, (d) CBZ-saccharin, (e) CBZ-isonicotinamide, (f) CBZ-nicotinamide, (g) CBZ-urea and (h) CBZ-thiourea (2:1).

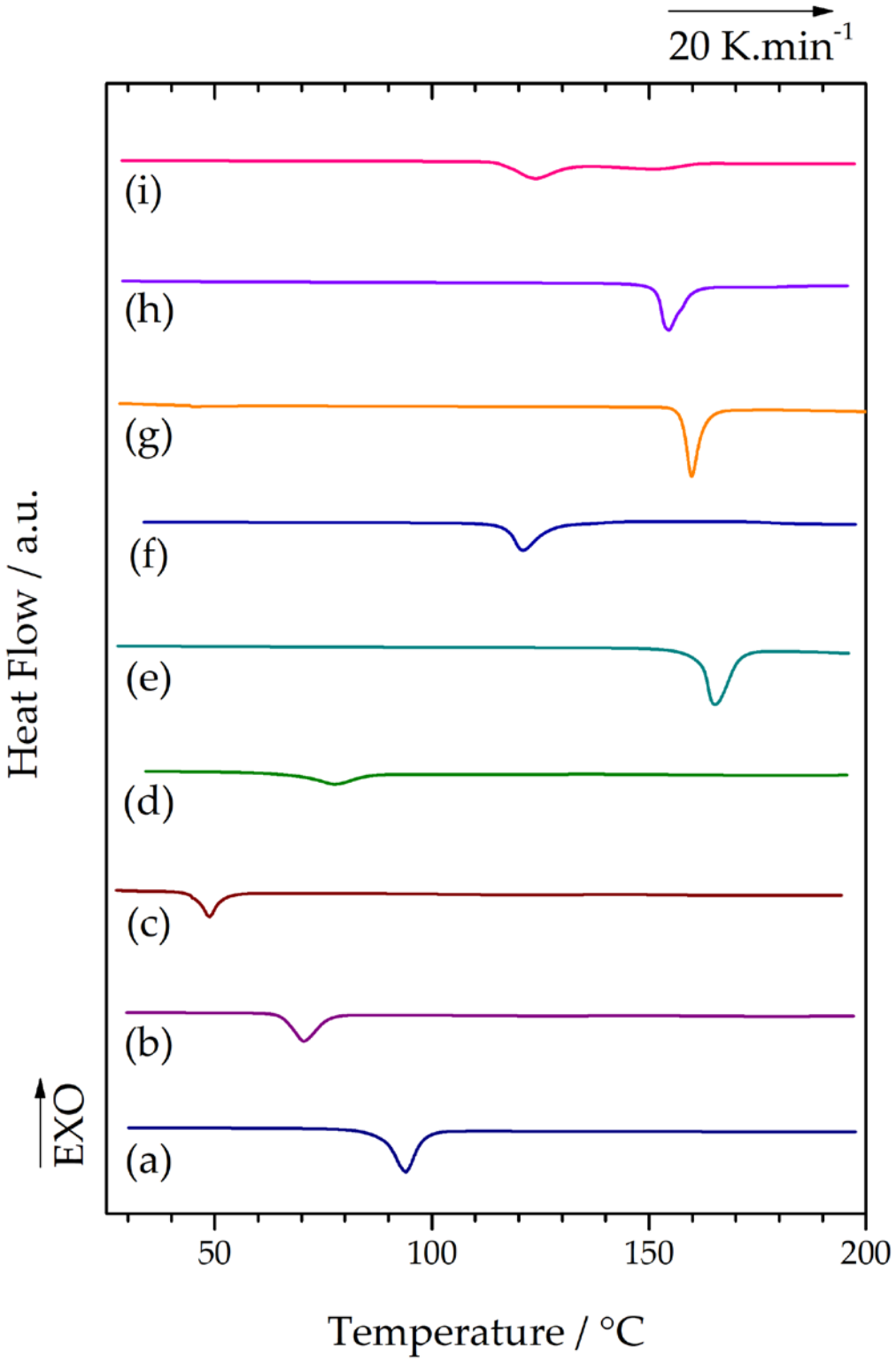


**Figure S3.** DSC thermograms of physical mixtures with carbamazepine after LAG with (a) RS-flurbiprofen, (b) RS-ibuprofen, (c) S-ibuprofen, (d) RS-ketoprofen, (e) lactulose, (f) simvastatin, (g) theophylline, (h) caffeine and (i) paracetamol.

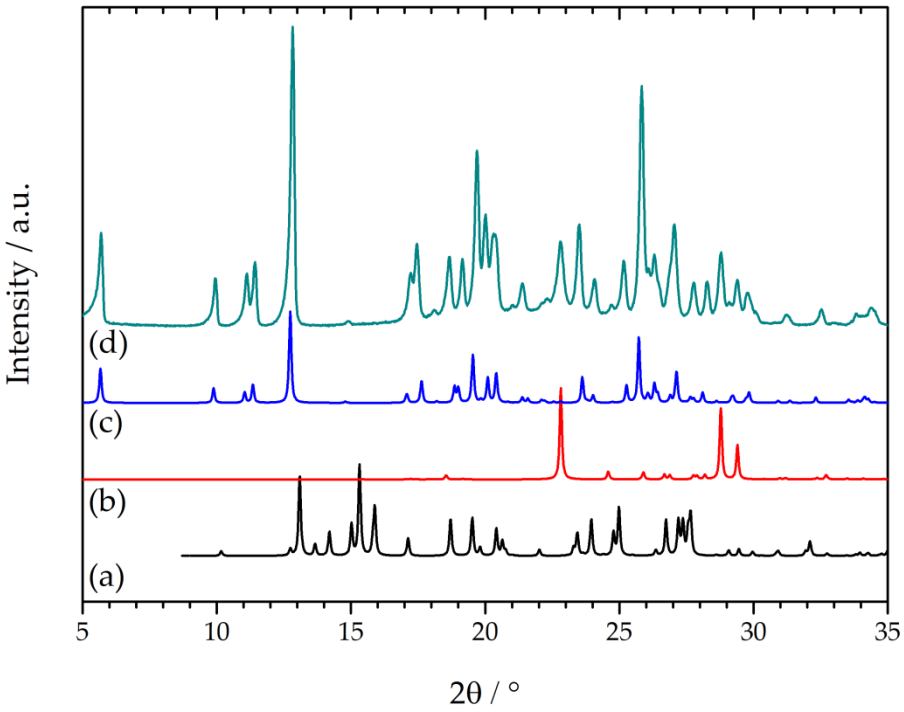


**Figure S4.** PXRD patterns of the carbamazepine-fumaric acid based cocrystal obtained by LAG compared to the pure compounds and the cocrystal in the CSD. (a) Carbamazepine form III (CBZ), (b) fumaric acid, (c) CSD CBZ-fumaric acid cocrystal (Refcod:WEYFEN) , and (d) CBZ:fumaric acid cocrystal. **Quantitative analysis by Rietveld**: 96.5 % of WEYFEN and 3.5 % of fumaric acid (CSD Refcod FUMAAC).

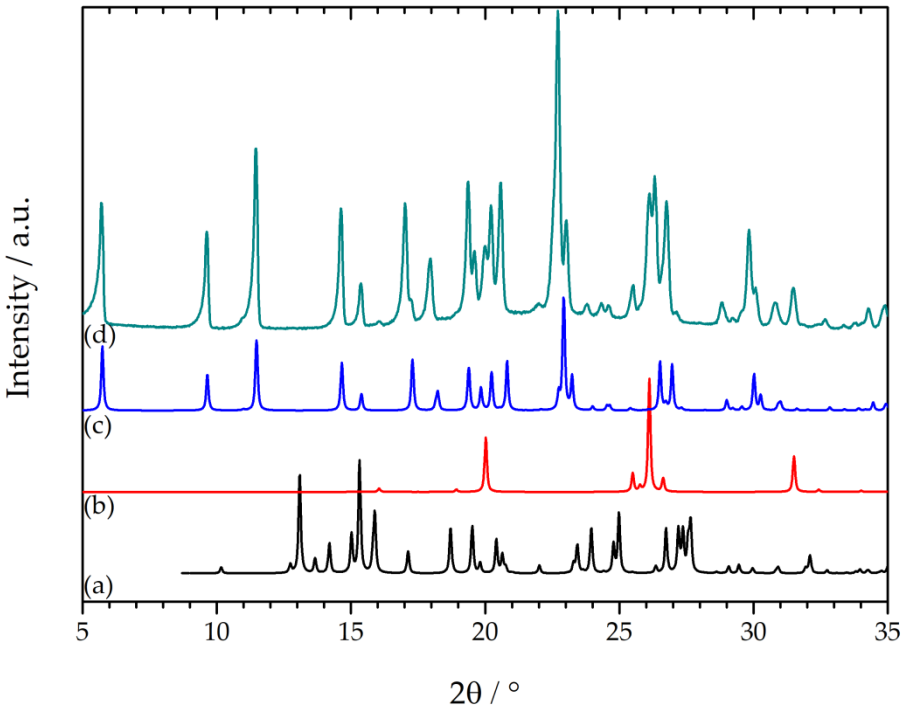


**Figure S5.** PXRD patterns of the carbamazepine-succinic acid based cocrystal obtained by LAG compared to the pure compounds and the cocrystal in the CSD. (a) Carbamazepine form III (CBZ), (b) succinic acid, (c) CSD CBZ-**(hemikis)**succinic acid cocrystal (Refcod: XOBCIB) , and (d) CBZ:succinic acid cocrystal. **Quantitative analysis by Rietveld**: 61.8 % of XOBCIB and 38.2 % of succinic acid (CSD Refcod SUCAB02).

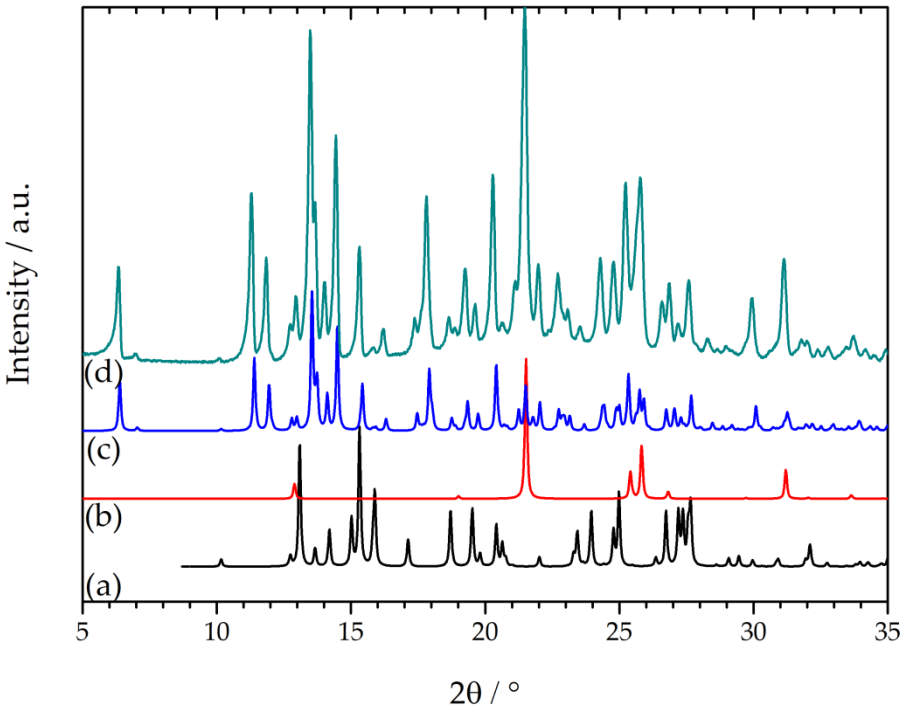


**Figure S6.** PXRD patterns of the carbamazepine-adipic acid based cocrystal obtained by LAG compared to the pure compounds and the cocrystal in the CSD. (a) Carbamazepine form III (CBZ), (b) adipic acid, (c) CSD CBZ-adipic acid cocrystal (Refcod:MOXWEB) , and (d) CBZ:adipic acid cocrystal. **Quantitative analysis by Rietveld**: Not possible as problem with the CIF file.

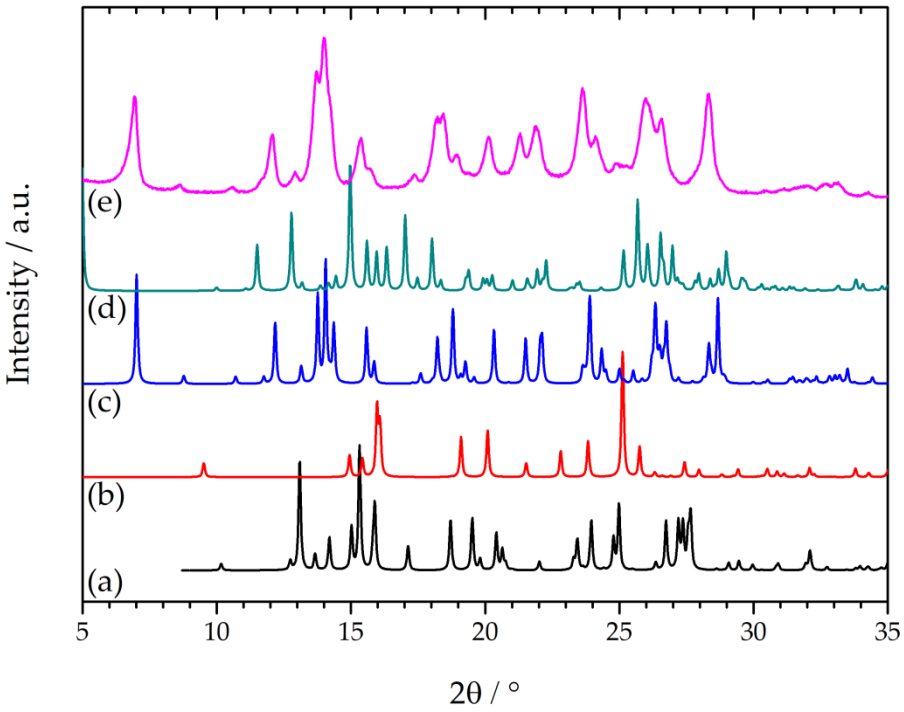


**Figure S7.** PXRD patterns of the carbamazepine- saccharin based cocrystal obtained by LAG compared to the pure compounds and the cocrystals in the CSD. (a) Carbamazepine form III (CBZ), (b) saccharin, (c) CSD CBZ-saccahrin cocrystal form I ( Refcod: UNEZAO) , (d) CSD CBZ-saccharin cocrystal form II (Refcod: UNEZAO01) and (e) CBZ:saccharin cocrystal. This system was grinded for 60 min in total, which would explained the broader Bragg peaks compared to the rest of the systems. **Quantitative analysis by Rietveld**: 100% of UNEZAO.

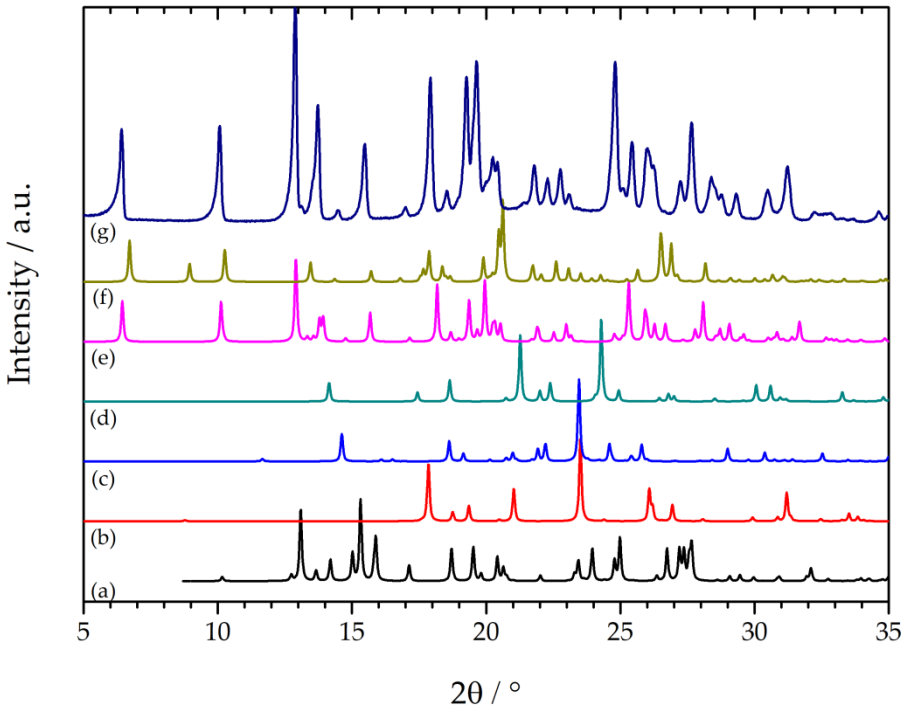


**Figure S8.** PXRD patterns of the carbamazepine- isonicotinamide based cocrystal obtained by LAG compared to the pure compounds and the cocrystals in the CSD. (a) Carbamazepine form III (CBZ), (b) Isonicotinamide form I, (c) Isonicotinamide form II, (d) Isonicotinamide form III, (e) CSD CBZ-isonicotinamide cocrystal form I ( Refcod:LOFKIB) , (f) CSD CBZ-isonicotinamide cocrystal form II (Refcod: LOFKIB01) and (g) CBZ:isonicotinamide cocrystal. **Quantitative analysis by Rietveld**: 98.5 % of LOFKIB and 1.5 % of LOFKIB01.

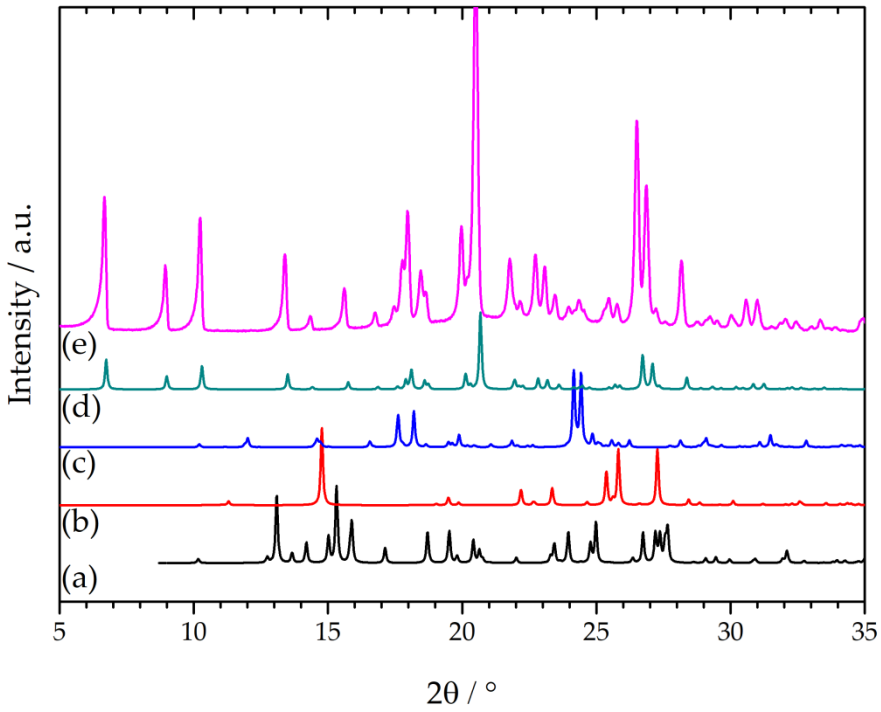


**Figure S9.** PXRD patterns of the carbamazepine-nicotinamide based cocrystal obtained by LAG compared to the pure compounds and the cocrystals in the CSD. (a) carbamazepine form III (CBZ), (b) nicotinamide form I, (c) nicotinamide form II, (d) CSD CBZ-nicotinamide cocrystal (Refcod: UNEZES) and (e) CBZ:nicotinamide cocrystal. **Quantitative analysis by Rietveld**: 100 % of UNEZES.

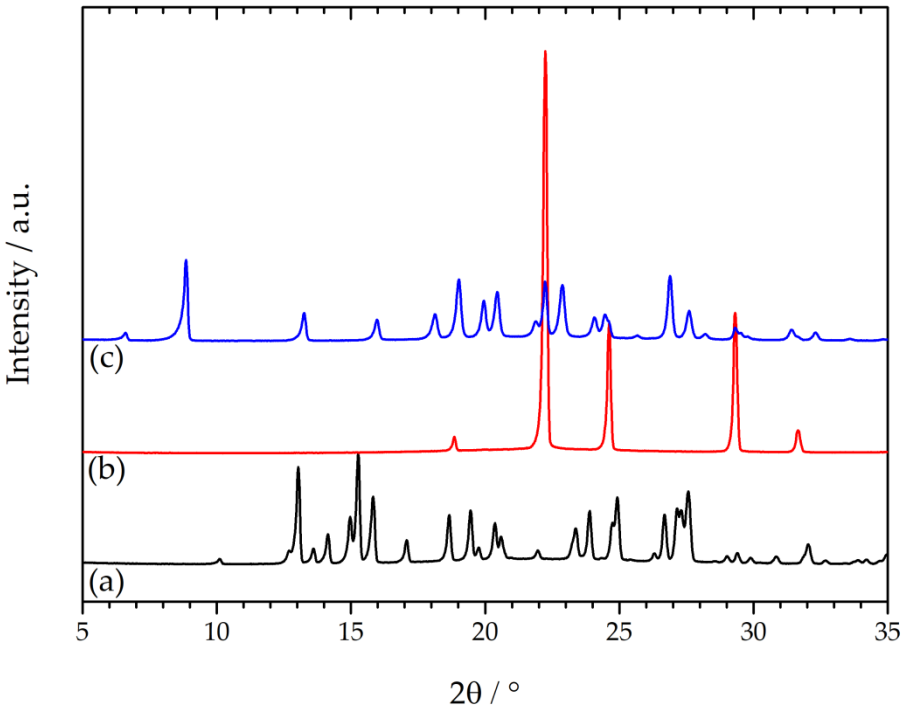


**Figure S10.** PXRD patterns of the carbamazepine-urea based cocrystal obtained by LAG compared to the pure compounds. (a) Carbamazepine form III (CBZ), (b) urea, (c) CBZ-urea cocrystal. No quantitative analysis was possible as the known cocrystal is not in the CSD. Possible rests of urea are observed but not of CBZ.

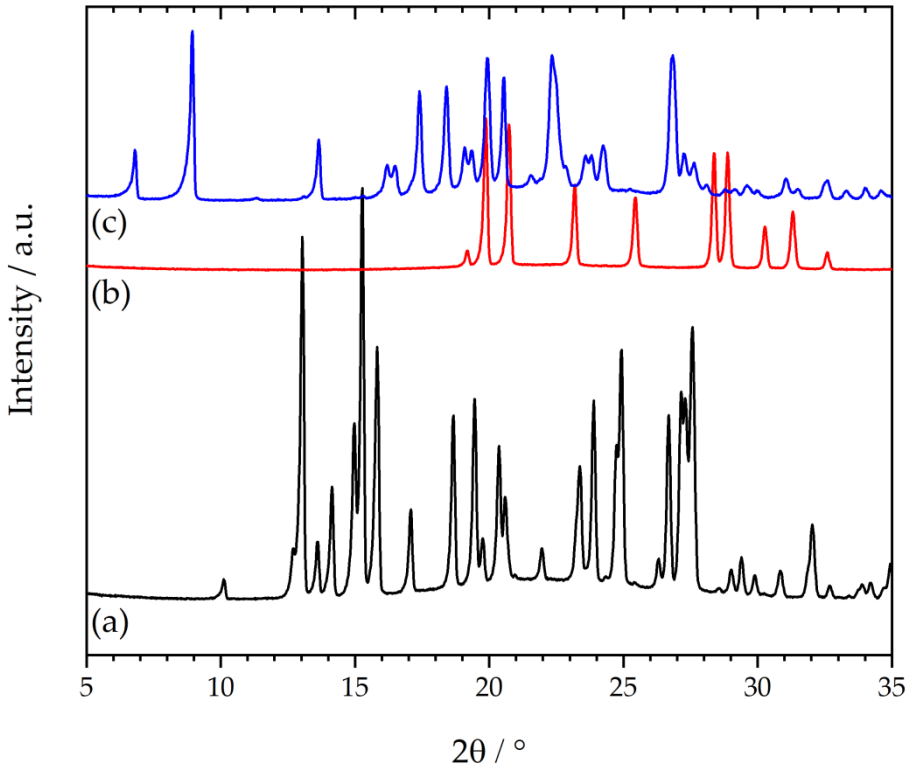


**Figure S11.** PXRD patterns of the carbamazepine-thiourea based cocrystal obtained by LAG compared to the pure compounds. (a) Carbamazepine form III (CBZ), (b) thiourea, (c) CBZ-thiourea (2:1) cocrystal. No quantitative analysis was possible as the known cocrystal is not in the CSD. Not rest of any pure compound are obtained at a molar ratio de (2:1).