Halogen bonding and pharmaceutical cocrystals: The case of a widely used preservative

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SI 1. Cambridge Structure Database Analysis.

All the five halogens can work as XB donor sites. Iodine is usually a better donor than bromine, chlorine, and fluorine as the heavier the halogens the more positive the σ-hole and the more asymmetric the distribution of the electron density. For a given halogen atom, its XB donor ability increases with the electron withdrawing ability of the moiety it is bound to and in organohalogen derivatives this ability increases moving from haloalkanes to haloalkenes to haloalkynes. We thus identified 1-iodoalkyne derivatives as ideal candidates to test the potential of XB in the formation of pharmaceutical cocrystals. A search in the Cambridge Structural Database (CSD) (see below criteria used for the CSD query) for supports our choice.

Most of the structures containing the 1-iodoalkyne group show short contacts with electron donors of pharmaceutical relevance (66 structures of 1-iodoalkenes are reported in the CSD and 56 of them show short contacts with oxygen and nitrogen atoms(neutral electron donor sites) or halogenated anions (charged electron donor sites). The median values of C-I···D (D is an electron donor atom) distances and angles (Figure SI 1.1) are 3.13 Å and 174.2°, respectively. These values are consistent with the presence of a remarkably positive σ-hole on the iodine atom and confirm that 1-iodoalkynes are reliable XB donors. The asymmetric distribution of the electron density around the iodine atom, resulting in a negative belt orthogonal to the C-I bond, is confirmed by the angular distribution of short C-I···H HBs, the median value of the interaction being 88.2°.

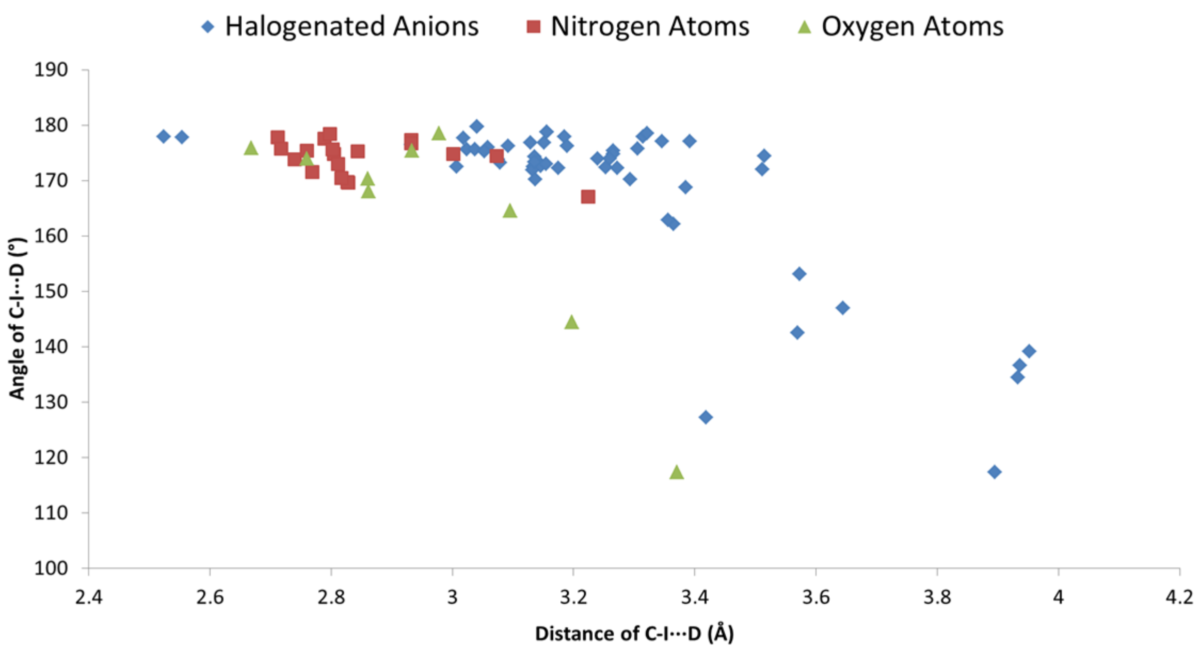


Figure SI 1.1. Scatterplot of short contacts given by 1-iodoalkynes with different electron donor sites. Blue rhombi: halogenated anions; Brown square: nitrogen atoms; Light green triangles : oxygen atoms. Angles are in deg (°). Distances are in Å.

An analysis of structures in CSD has been helpful also in identifying CCFs candidates. Black bars in Figure SI 1.2 represent all the "short intermolecular contacts" (as identified by ConQuest 1.14) between 1-iodoalkynyl moieties and three classes of electron density donors of pharmacological relevance. Gray bars represent those contacts that can be classified as XBs (if a C-I···D angle in between 140° and 180° is chosen as classification criterion). Nitrogen, oxygen atoms and halogenated anions give the smaller reductions in the contact number, if any, when applying the XB classification criterion. They are therefore the first choice when trying to elicit the XB donor potential of an 1-iodoalkynyl moiety. Moreover, an ideal XB acceptor must be: I) sterically accessible, II) not involved in self-aggregation processes and III) free from other competing XB donor or acceptor sites. We thus selected as CCFs two pyridyl derivatives (*i.d.* **BiPyEt** and **BiPy**) and two halide anions (*i.e.* **TBAI** and **$CaCl_2$**). Pyridine nitrogen typically works as monodentate

XB acceptors [1][i] while halide anions work as mono-, bi-, tri-, or tetradentate acceptors as a function of the structure of the XB donor and of the overall crystal packing requirements. [2][ii]

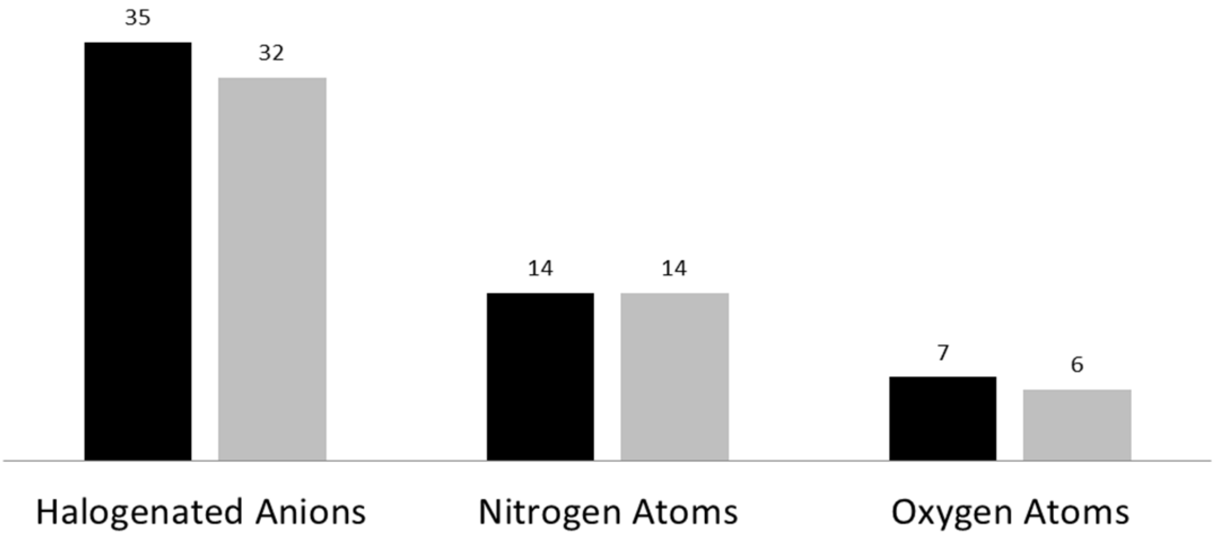


Figure SI 1.2. Total number of short intermolecular contacts (black bars) and XB contacts (gray bars) occurring in CSD between 1-iodoalkynes and selected XB acceptors.

Cambridge Structural Database (Version 5.33, 1 update Nov. 2011). Research performed using ConQuest (Version 1.14). Criteria used for the query: (I) iodine atom is bound to C≡C; (II) iodine atom interacts (via contact keyword) with halogenated anion, nitrogen atom and oxygen atoms; (III) the charge on iodine atom is set equal to zero; (IV) No filters were applied during the search.

Nc is ‘normalized contact’. We define ‘normalized contact’, the ratio Nc = Dij/(rvdWi + rvdWj), whereDij is the distance between the atomsi and j and rvdWi and rvdWj are the van der Waals radii for atomsiand j, respectively. If the electron donor j is an anionic atom, rvdWj is substituted by rPj , the Pauling ionic radius of anion atom j. van der Waals radii and Pauling ionic radii were obtained from web of element (http://www.webelements.com/).

Pauling ionic: F-: 1.36 Å; Cl-: 1.81 Å; Br-: 1.95 Å; I-: 2.16 Å.

Van der Waals radii. I: 1.98 Å; N: 1.55 Å; O: 1.52 Å.

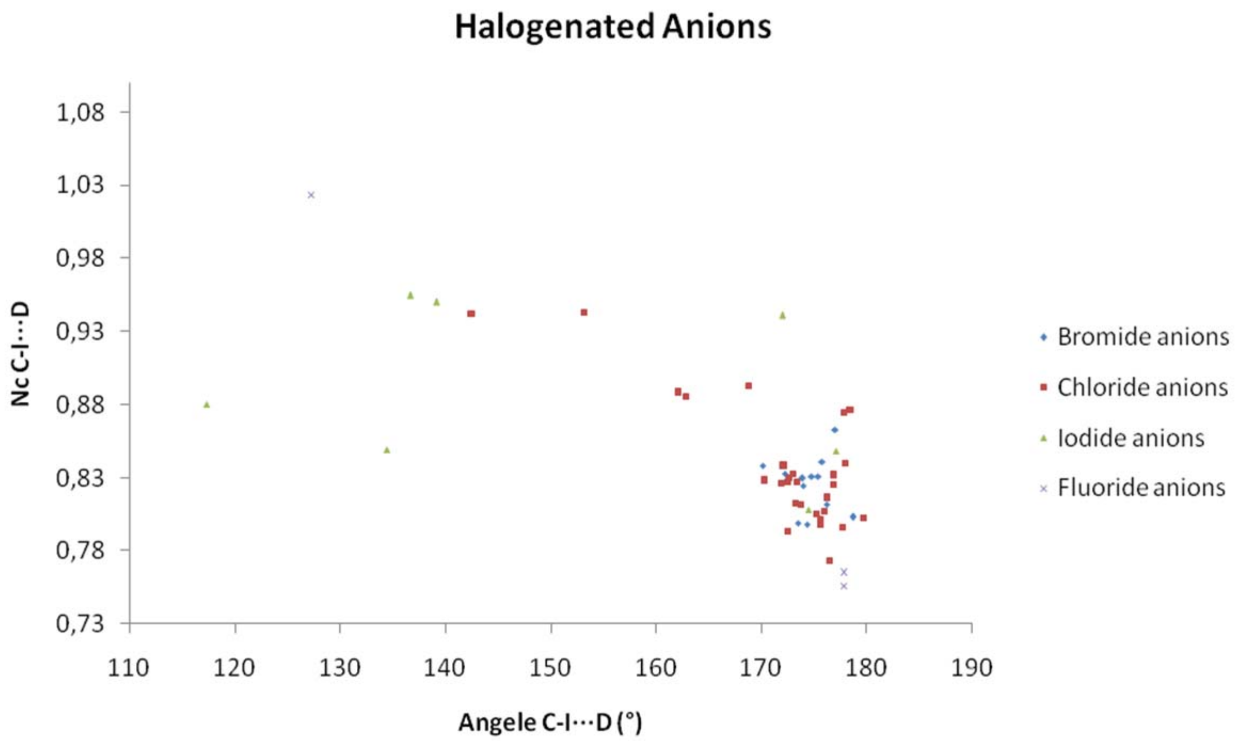


Figure SI 1.3. Scatterplot of short contacts given by 1-iodoalkynes with halogenated anions as electron donor sites (C-I···D). Angles are in deg (°). Normalized contact (Nc).

The median values of C-I···D (D is halogenated anions) distances and angles are 3.18 Å and 174°, respectively. Number of entry for Fluoride anions: 2; Chloride anions: 20; Bromide anions: 10; Iodide anions: 3.

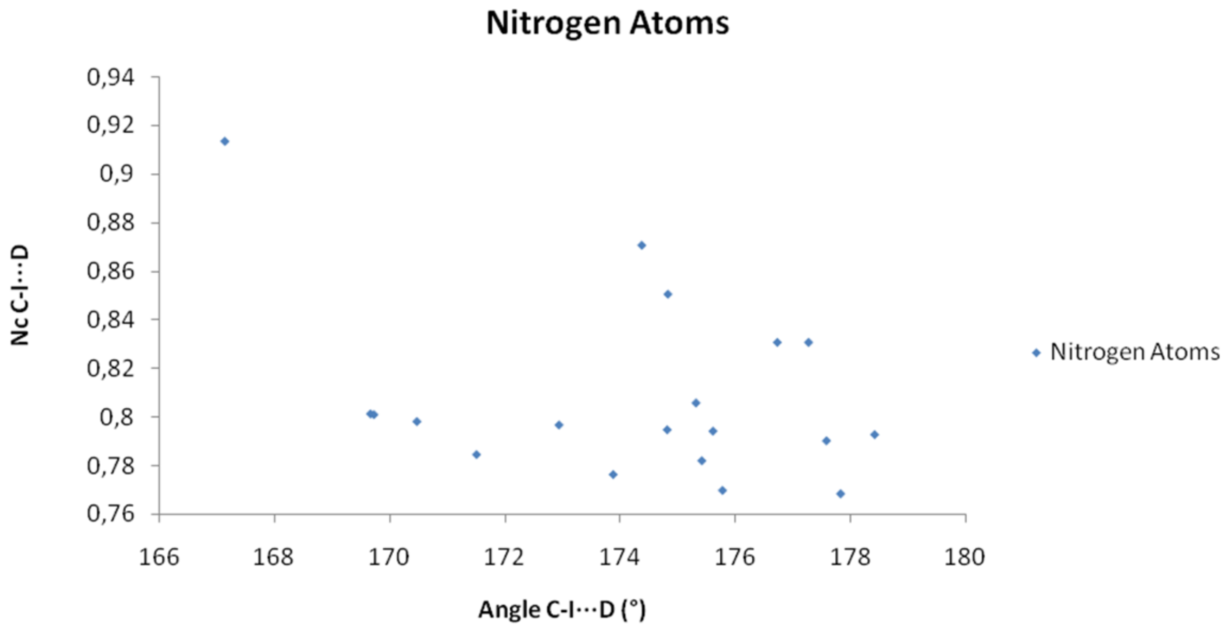


Figure SI 1.4. Scatterplot of short contacts given by 1-iodoalkynes with nitrogen atoms as electron donor sites (C-I···D). Angles are in deg (°). Normalized contact (Nc).

The median values of C-I···D (D is nitrogen atoms) distances and angles are 2.81 Å and 174.8°, respectively.

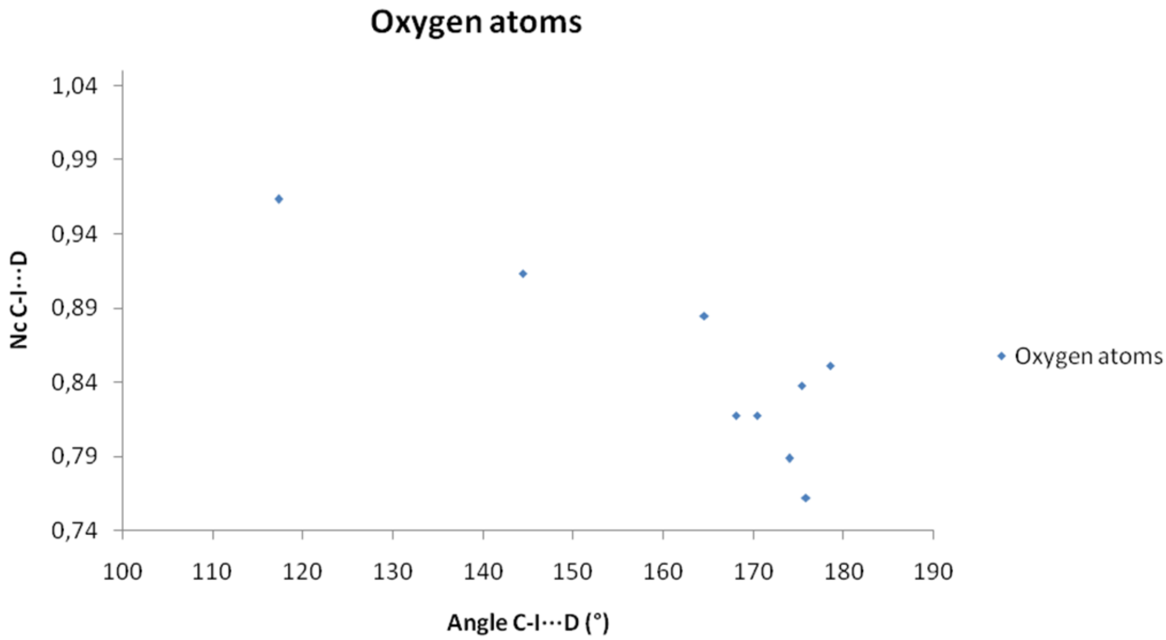


Figure SI 1.5. Scatterplot of short contacts given by 1-iodoalkynes with oxygen atoms as electron donor sites (C-I···D). Angles are in deg (°). Normalized contact (Nc).

The median values of C-I···D (D is oxygen atoms) distances and angles are 2.93 Å and 170.4°, respectively.

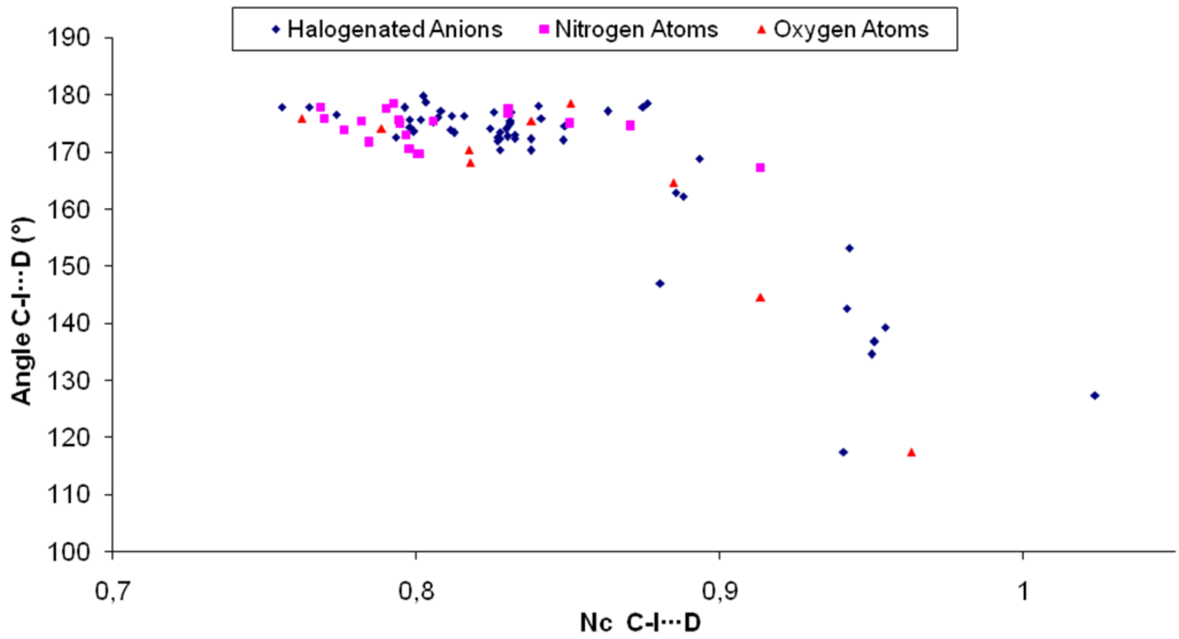


Figure SI 1.6. Scatterplot of short contacts given by 1-iodoalkynes with different electron donor sites. Blue rhombi: halogenated anions; Pink square: nitrogen atoms; Red triangles: oxygen atoms. Angles are in deg (°). Normalized contact (Nc).

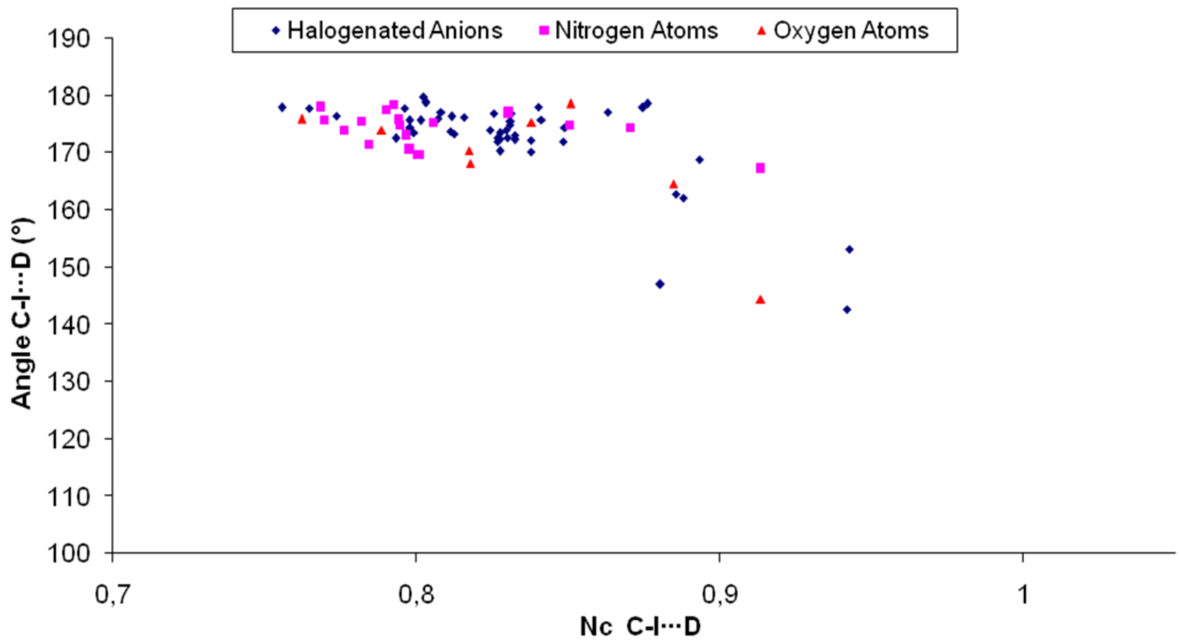


Figure SI 1.7. Scatterplot of short contacts given by 1-iodoalkynes with different electron donor sites when XB classification criterion is applied (C-I···D angle in between 140° and 180°). Blue rhombi: halogenated anions; Pink square: nitrogen atoms; Red triangles: oxygen atoms. Angles are in deg (°). Normalized contact (Nc).

The median values of C-I···D (D is an electron donor atom) distances and angles (using XB classification criterion) are 3.08 Å and 172.7°, respectively.

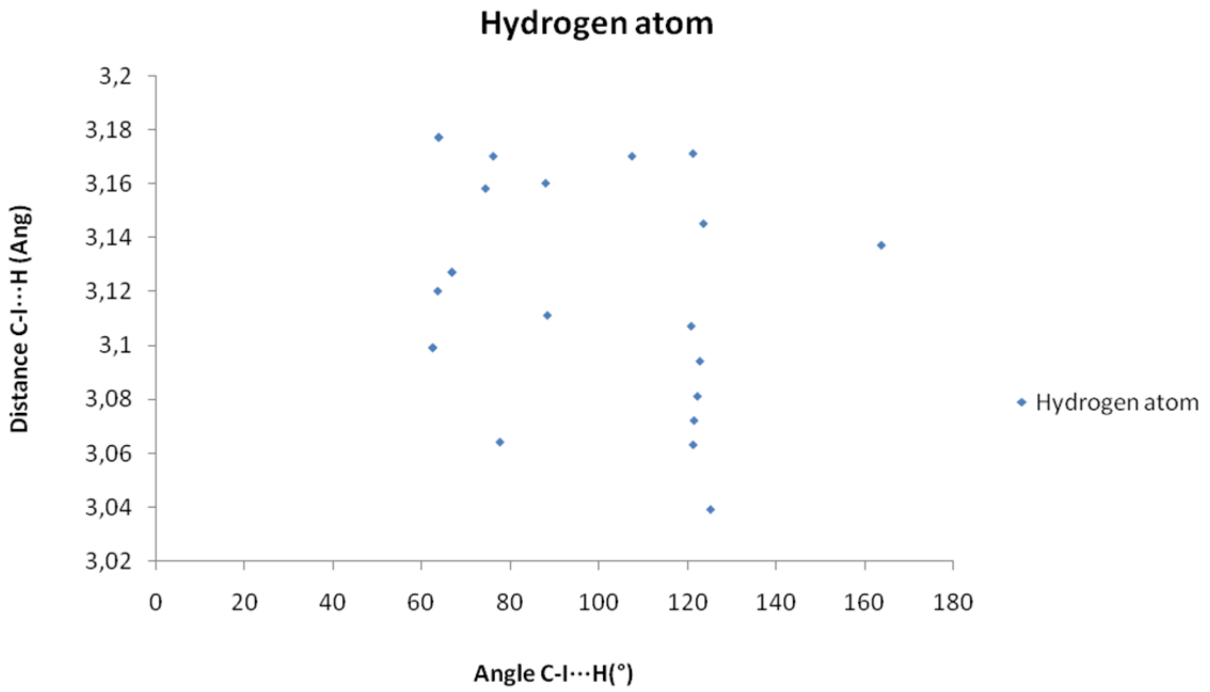


Figure SI 1.8. Scatterplot of short contacts given by 1-iodoalkynes with hydrogen atoms as electron acceptor sites (C-I···H). Angles are in deg (°). Distances I···H are in Å.

The median values of C-I···H distances and angles are 3.12 Å and 88.2°, respectively.

SI 2. Infrared Spectroscopy (FT-IR). The IR characterization of samples was performed on a Nicolet Nexus FTIR spectrometer equipped with Smart Endurance ATR-device. Spectra were measured over the range of 4000-550 cm^{-1} and analyzed using Omnic software v6.2. Peak values are given in wavenumbers and rounded to 1 cm^{-1} upon automatic assignment. The peak intensity is described as: strong (s); medium (m), weak (w) and broad (b).

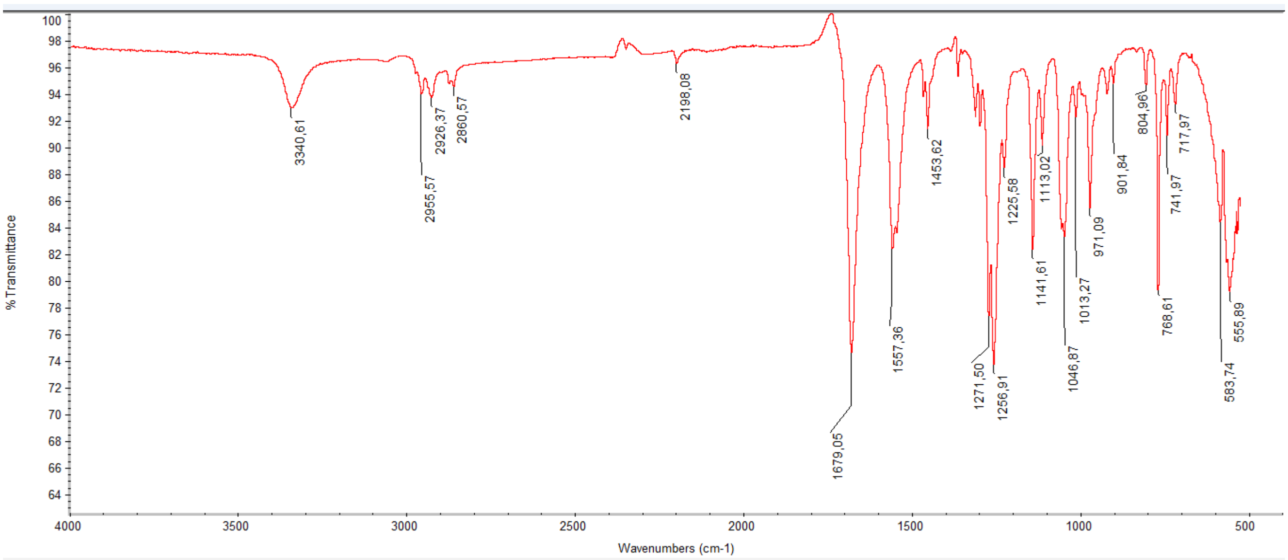


Figure SI 2.1. (ATR)-IR spectrum of crystalline **IPBC**.

(ATR)-FTIR ν: 3314 (w), 2955 (w), 2926 (w), 2860 (w), 2198 (w), 1679 (s), 1557 (m), 1454 (m), 1271 (s), 1257 (s), 1226 (m), 1141 (m), 1113 (w), 1047 (m), 1013 (m), 971 (w), 901 (w), 804 (s), 769 (s), 584 (s) cm^{-1}.

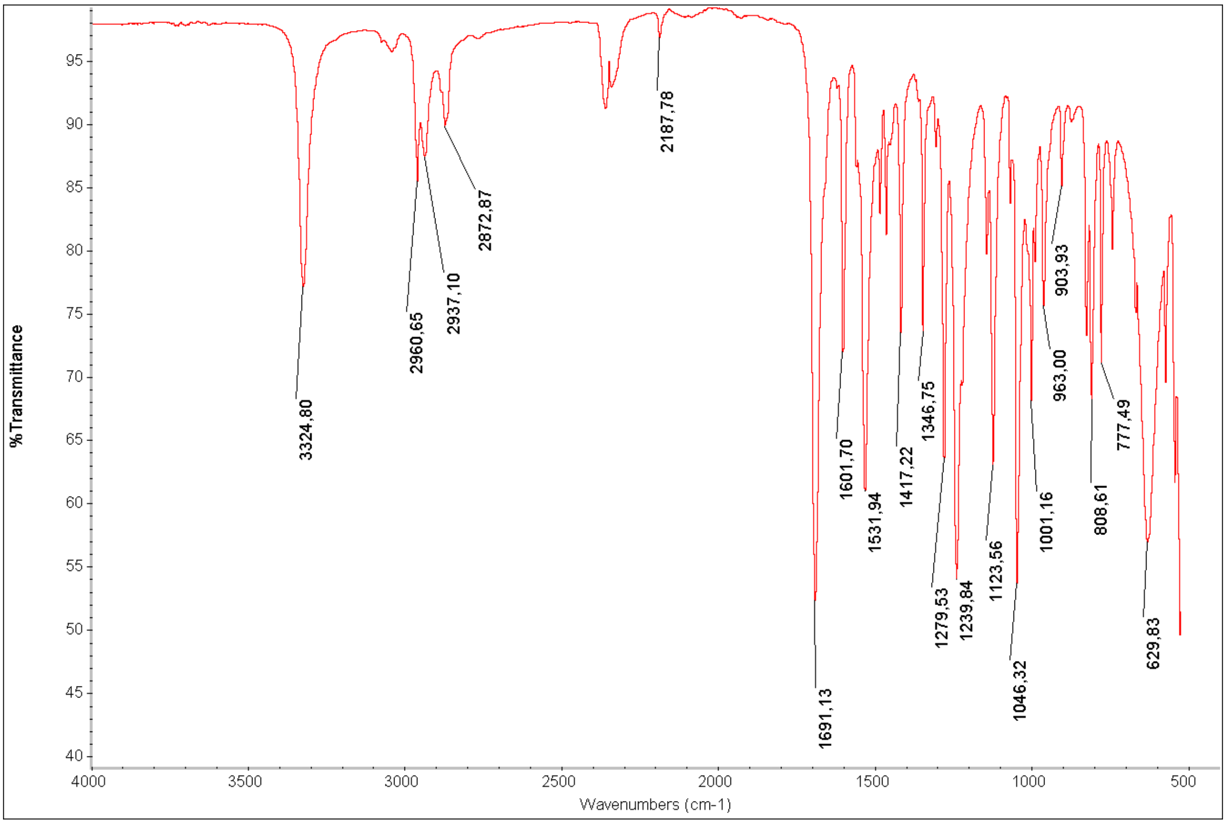


Figure SI 2.2. (ATR)-IR spectrum of cocrystal **1**.

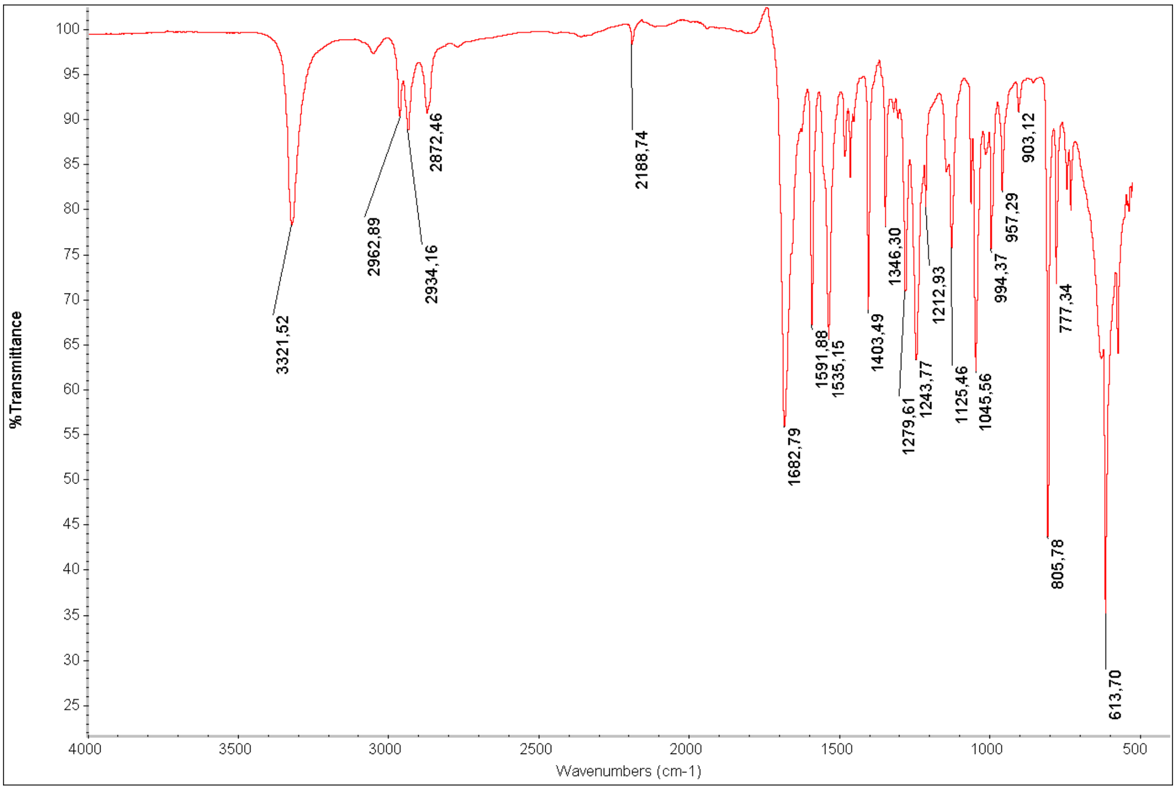


Figure SI 2.3. (ATR)-IR spectrum of cocrystal **2.**

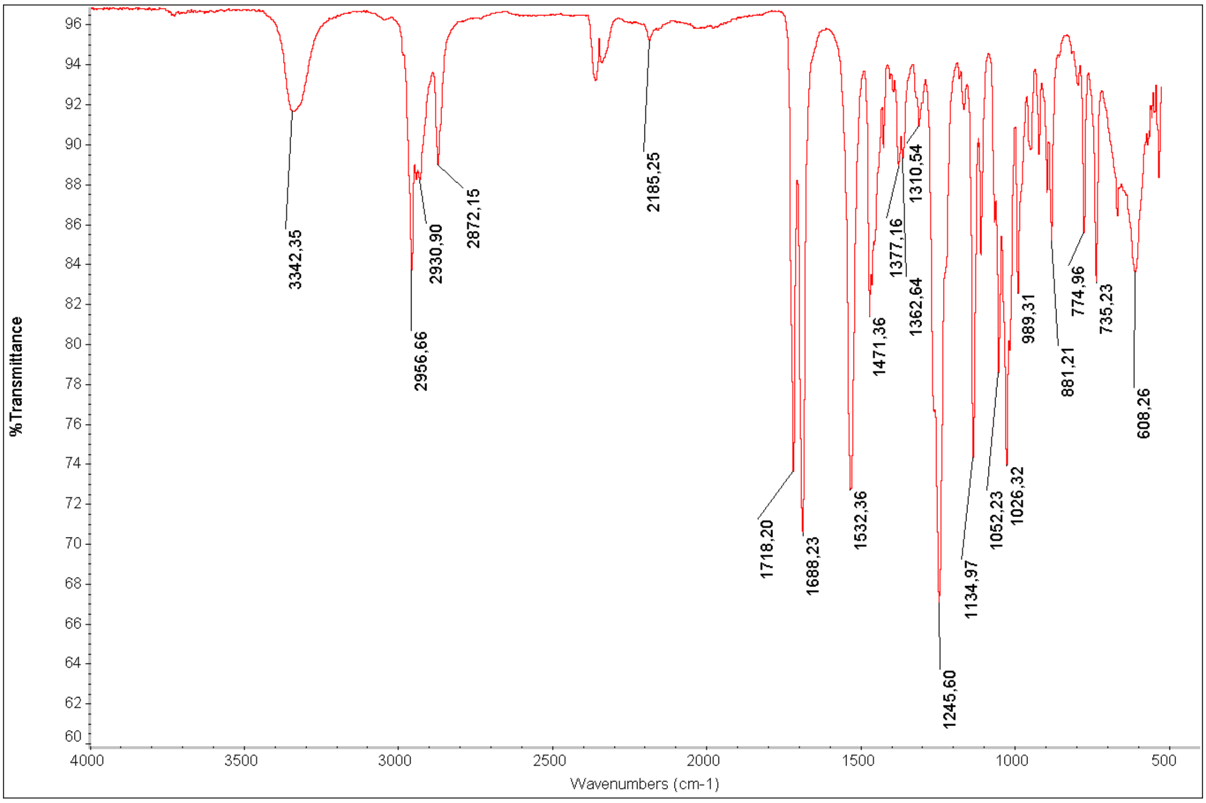


Figure SI 2.4. (ATR)-IR spectrum of cocrystal **3.**

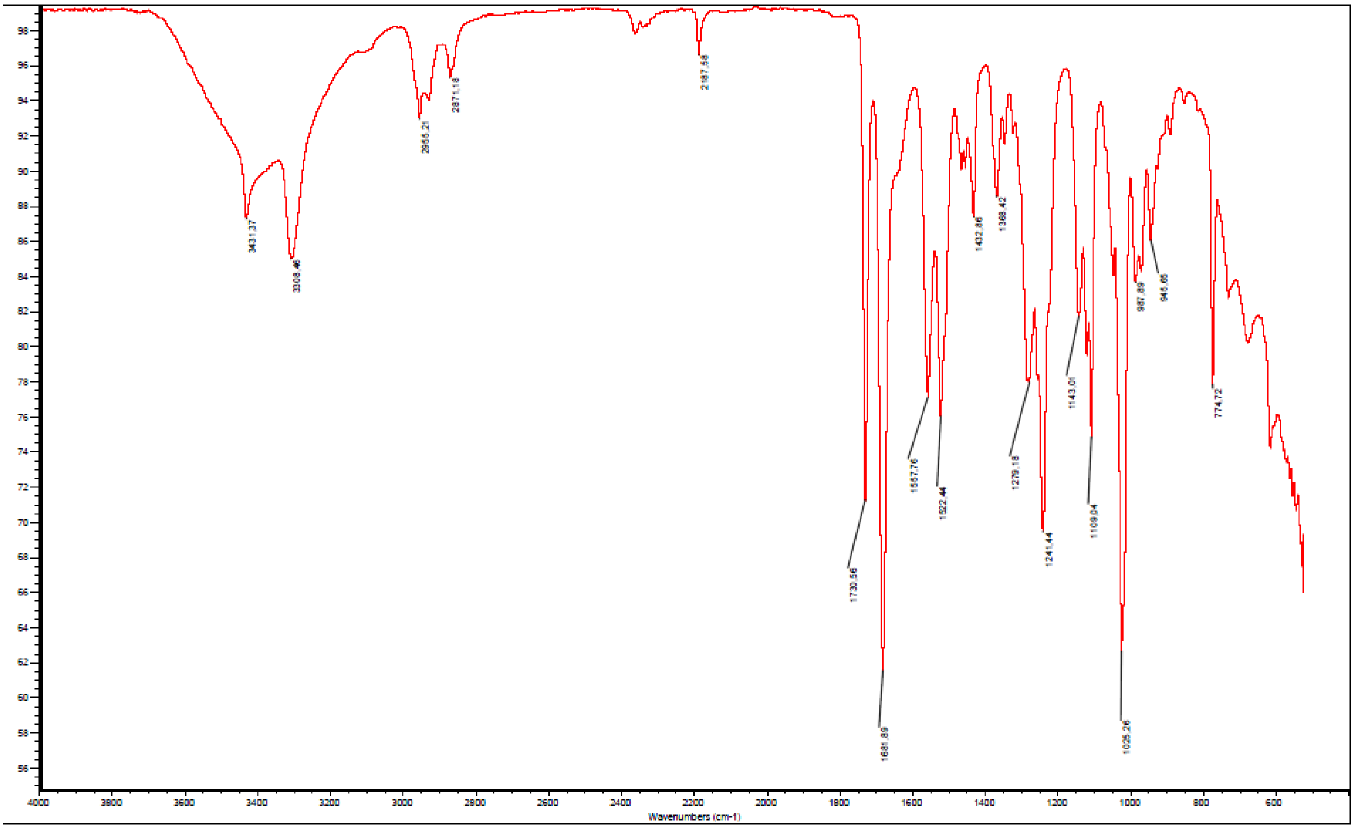


Figure SI 2.5. (ATR)-IR spectrum of cocrystal **4.**

SI 3. Differential Scanning Calorimetry (DSC). Thermal analysis was performed on a Mettler Toledo DSC 823e differential scanning calorimeter. Aluminum pans were used for all samples, and the instrument was calibrated using an indium standard. For reference, an empty pan sealed in the same way as the sample was used. The samples were heated in the DSC cell from 25 °C to the required temperature (melting point of the cocrystal) at a rate of 10 °C/min.

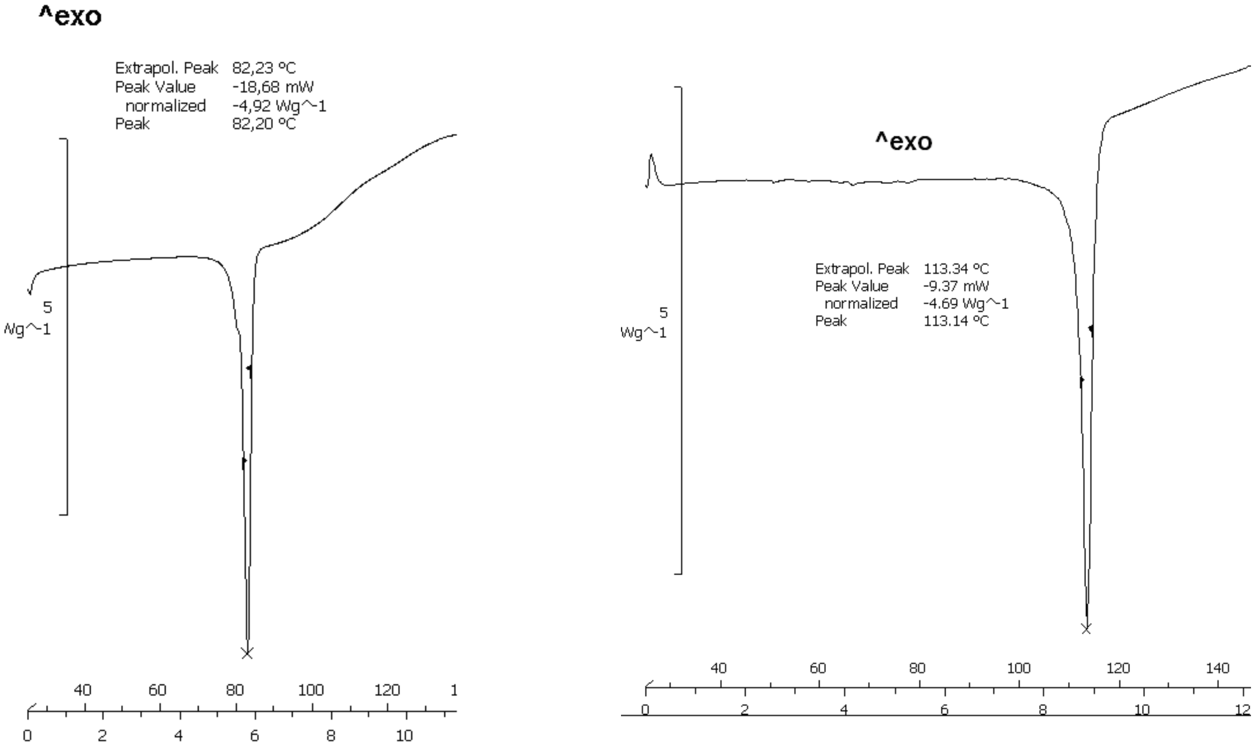


Figure SI 3.1. Left: DSC thermogram of cocrystal **1**. Right: DSC thermogram of cocrystal **2**.

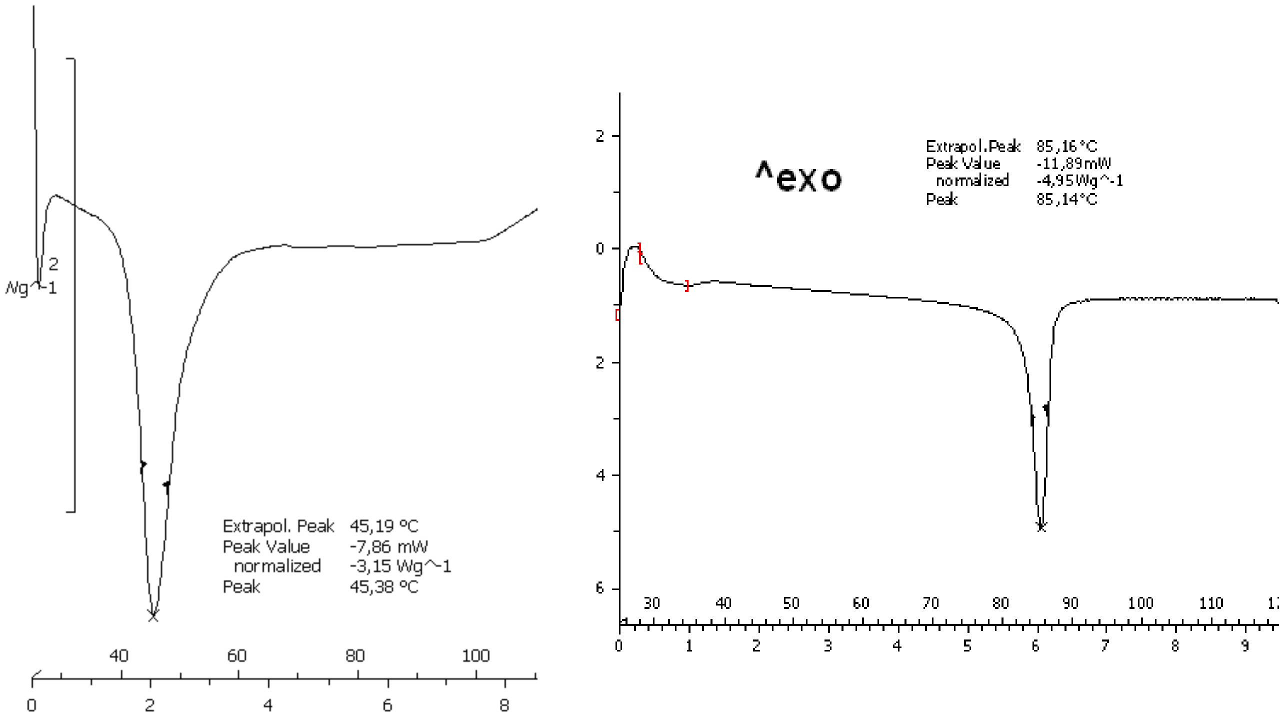


Figure SI 3.2. Left: DSC thermogram of cocrystal **3**. Right: DSC thermogram of cocrystal **4**.

SI 4. Powder X-ray Diffraction (PXRD). A Bruker AXS D8 powder diffractometer was used for all PXRD measurements with experimental parameters as follows: Cu-Kα radiation (λ= 1.54056Å). Scanning interval: 5-40°2θ. Step size 0.016°, exposure time 1.5 s per step. The experimental PXRD patterns and calculated PXRD patterns from single crystal structures were compared to confirm the composition of bulk materials.

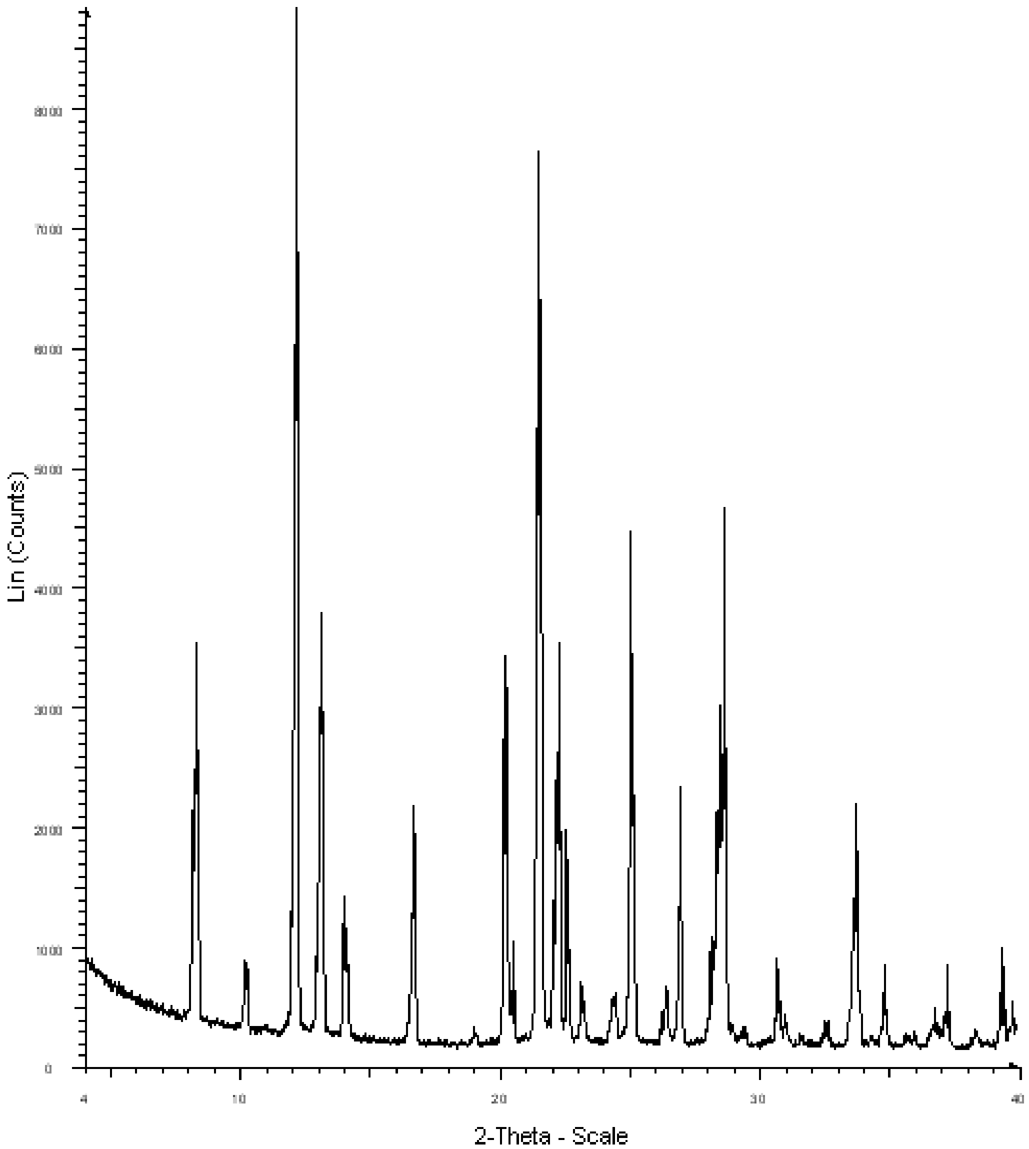


Figure SI 4.1. Experimental PXRD pattern of **IPBC**.

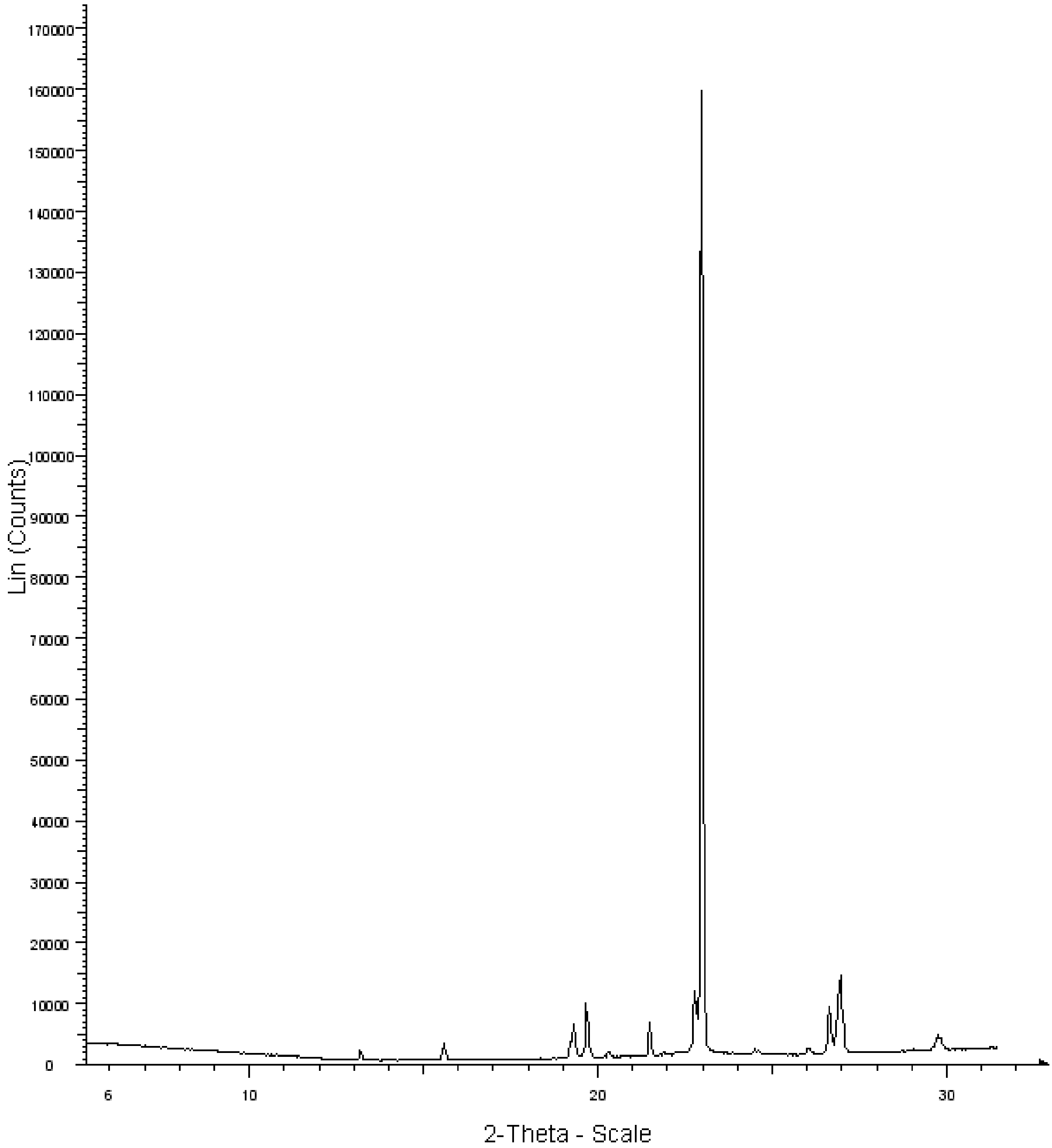


Figure SI 4.2. Experimental PXRD pattern of **BiPyEt**.

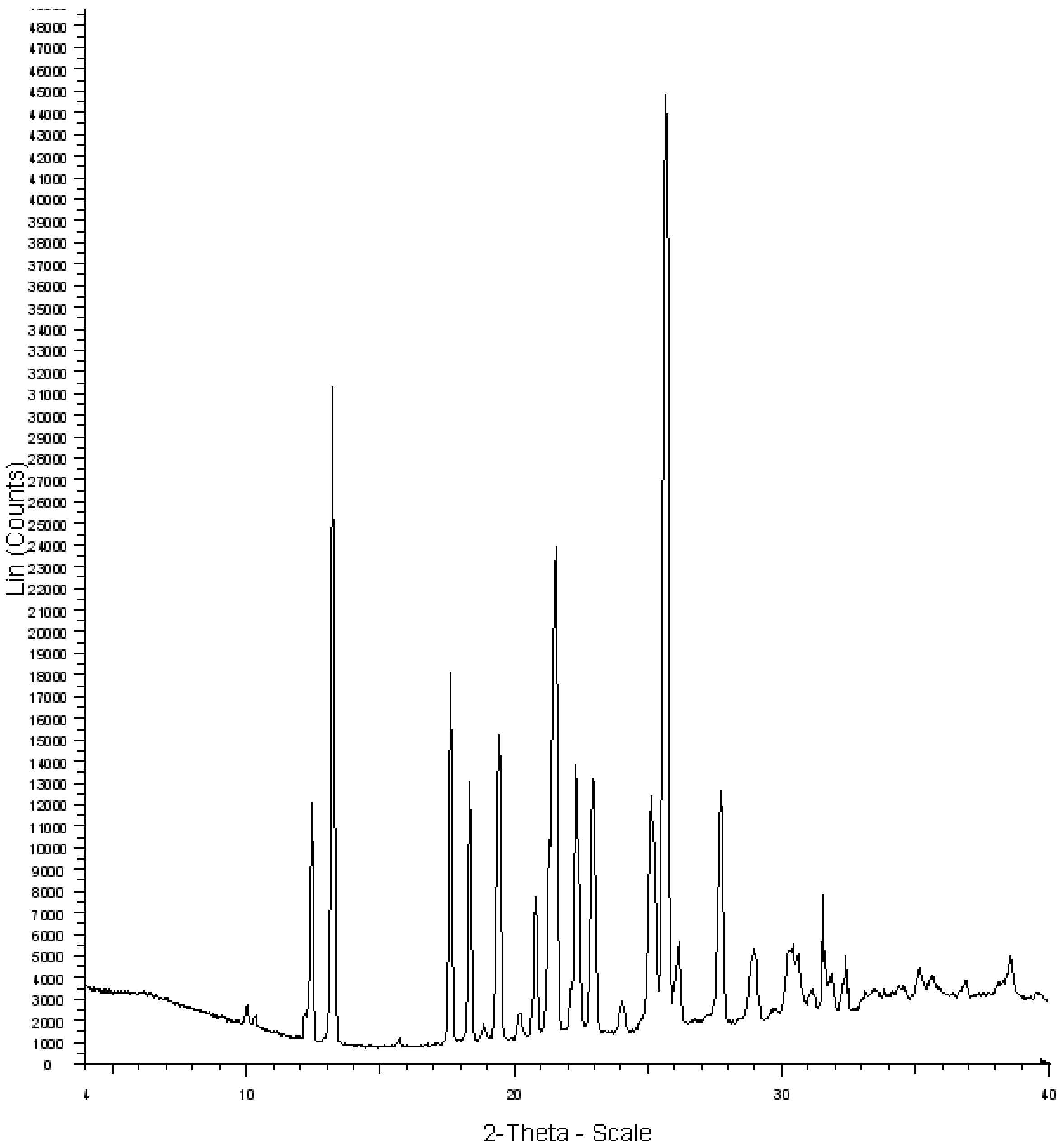


Figure SI 4.3. Experimental PXRD pattern of **BiPy**.

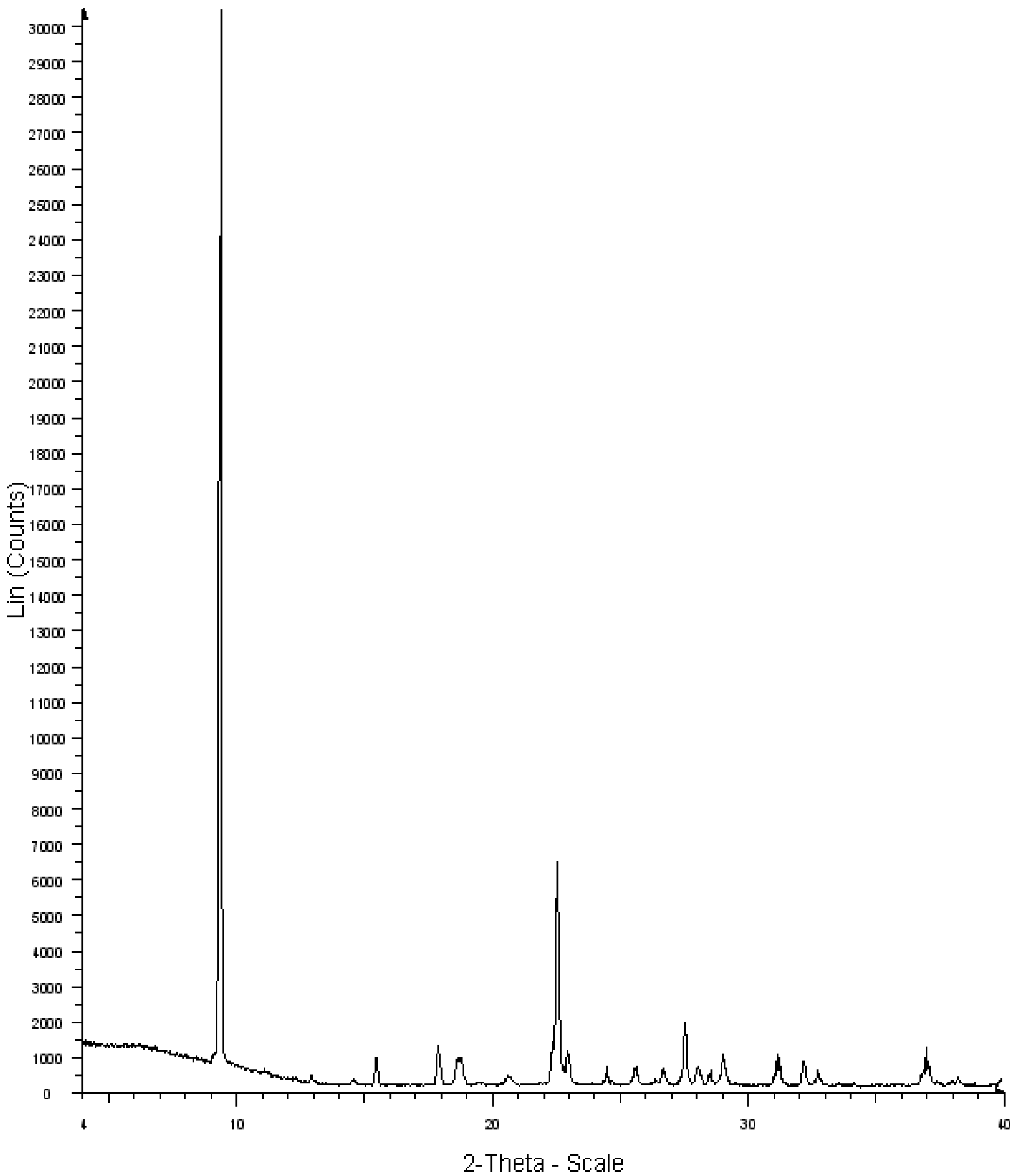


Figure SI 4.4. Experimental PXRD pattern of **TBAI**.

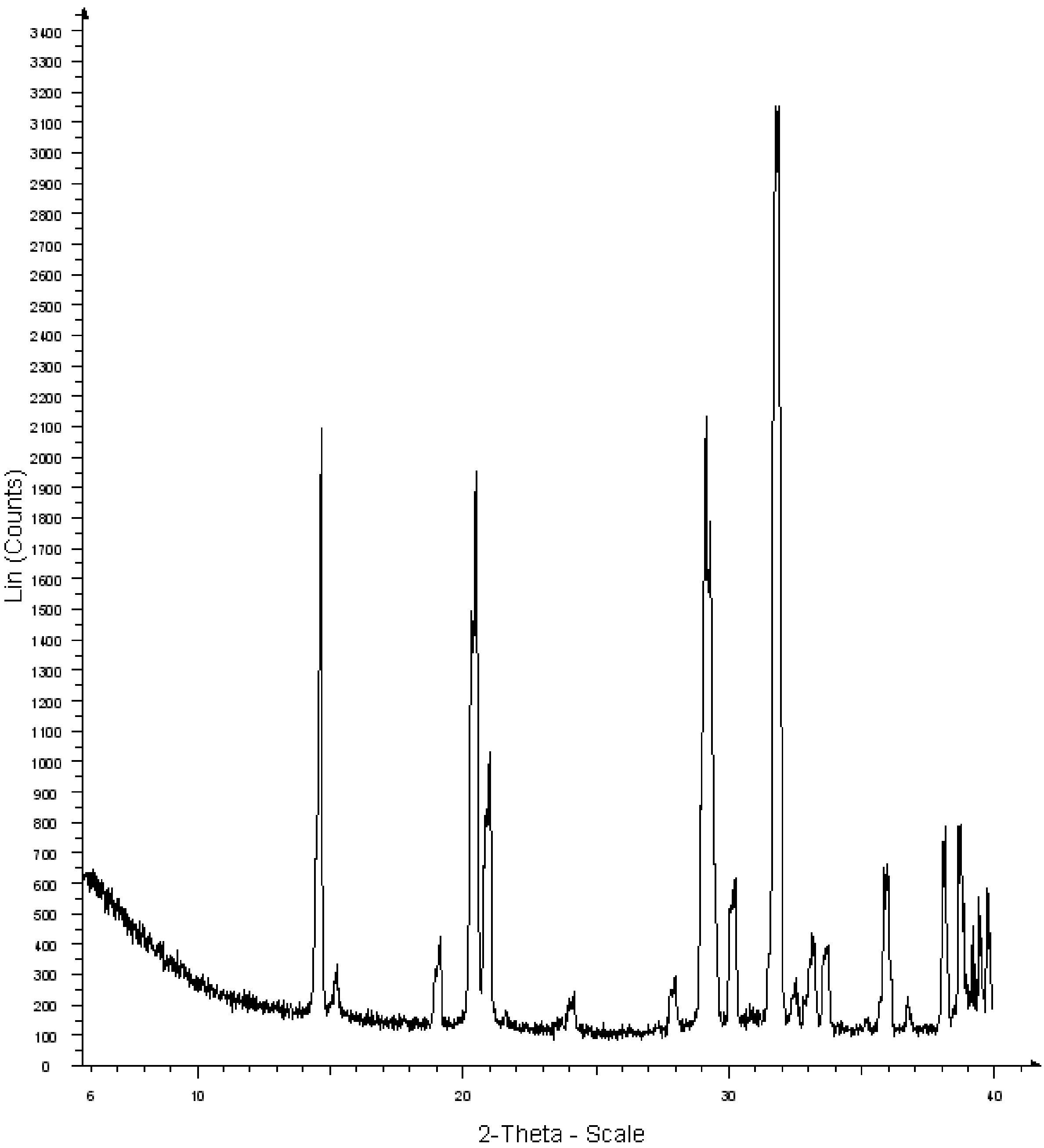


Figure SI 4.5. Experimental PXRD pattern of **$CaCl_2$**.

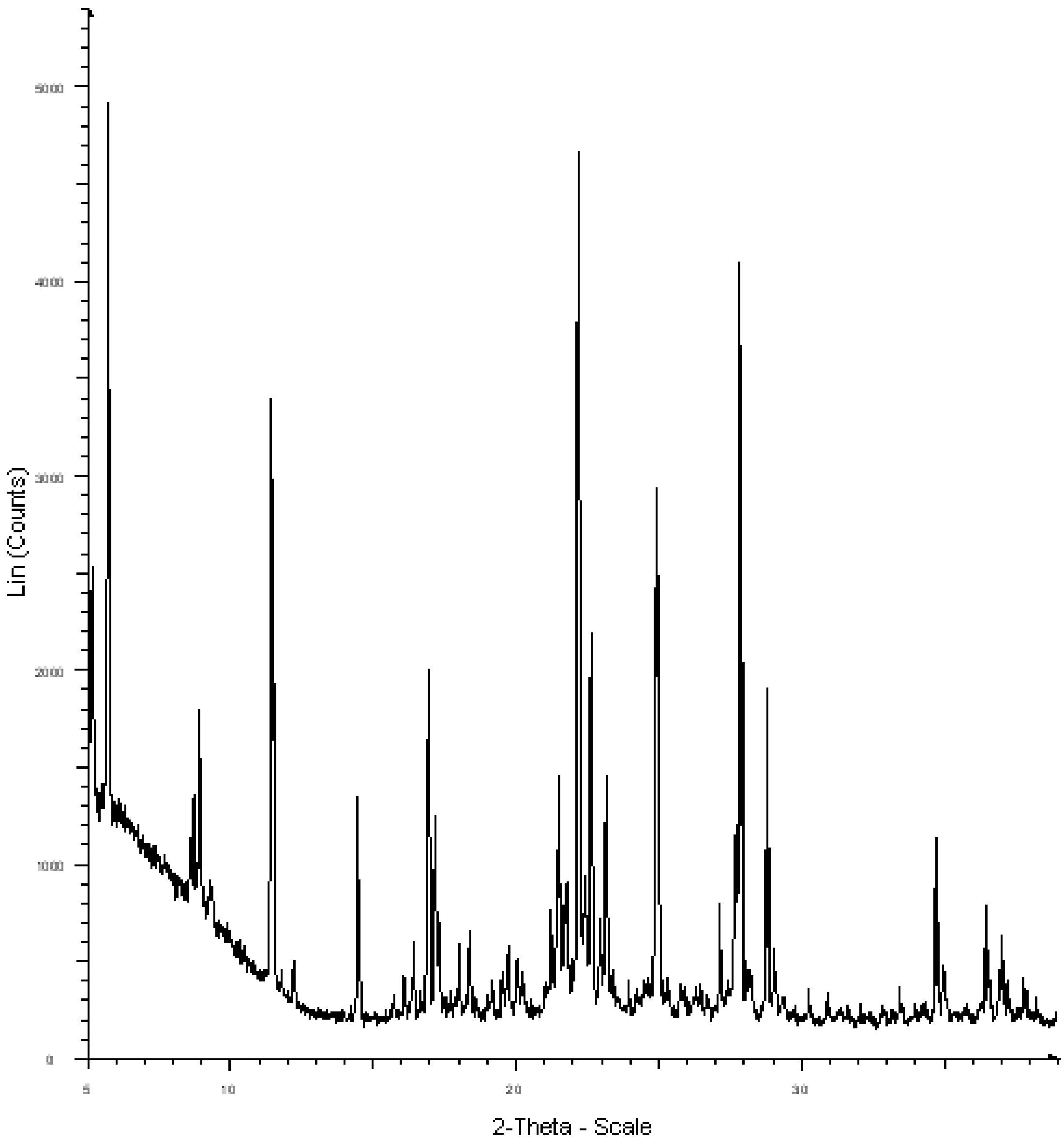


Figure SI 4.6. Experimental PXRD pattern of cocrystal **1**.

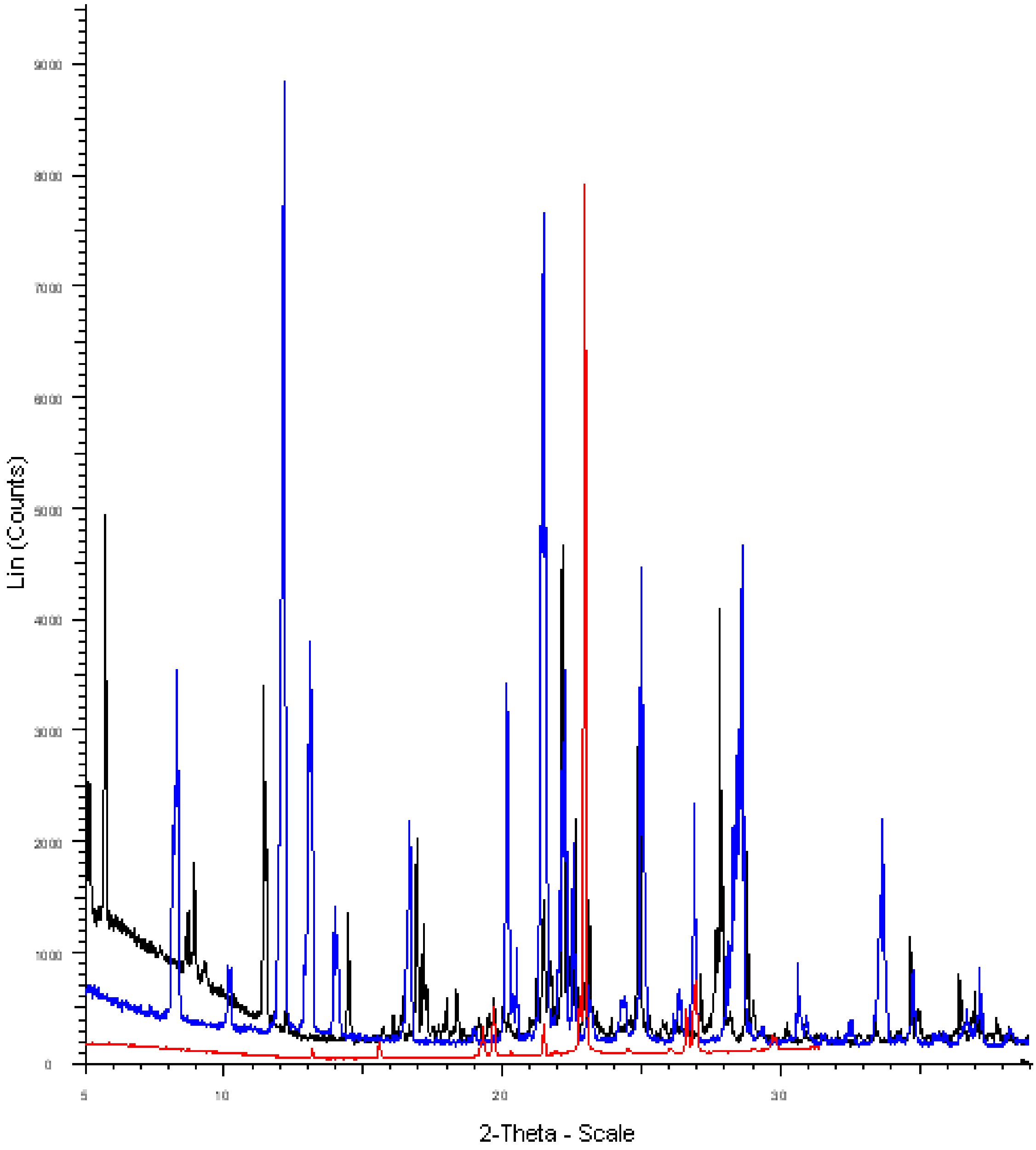


Figure SI 4.7. Experimental PXRD patterns of cocrystal **1** (black line), **BiPyEt** (red line) and **IPBC** (blue line).

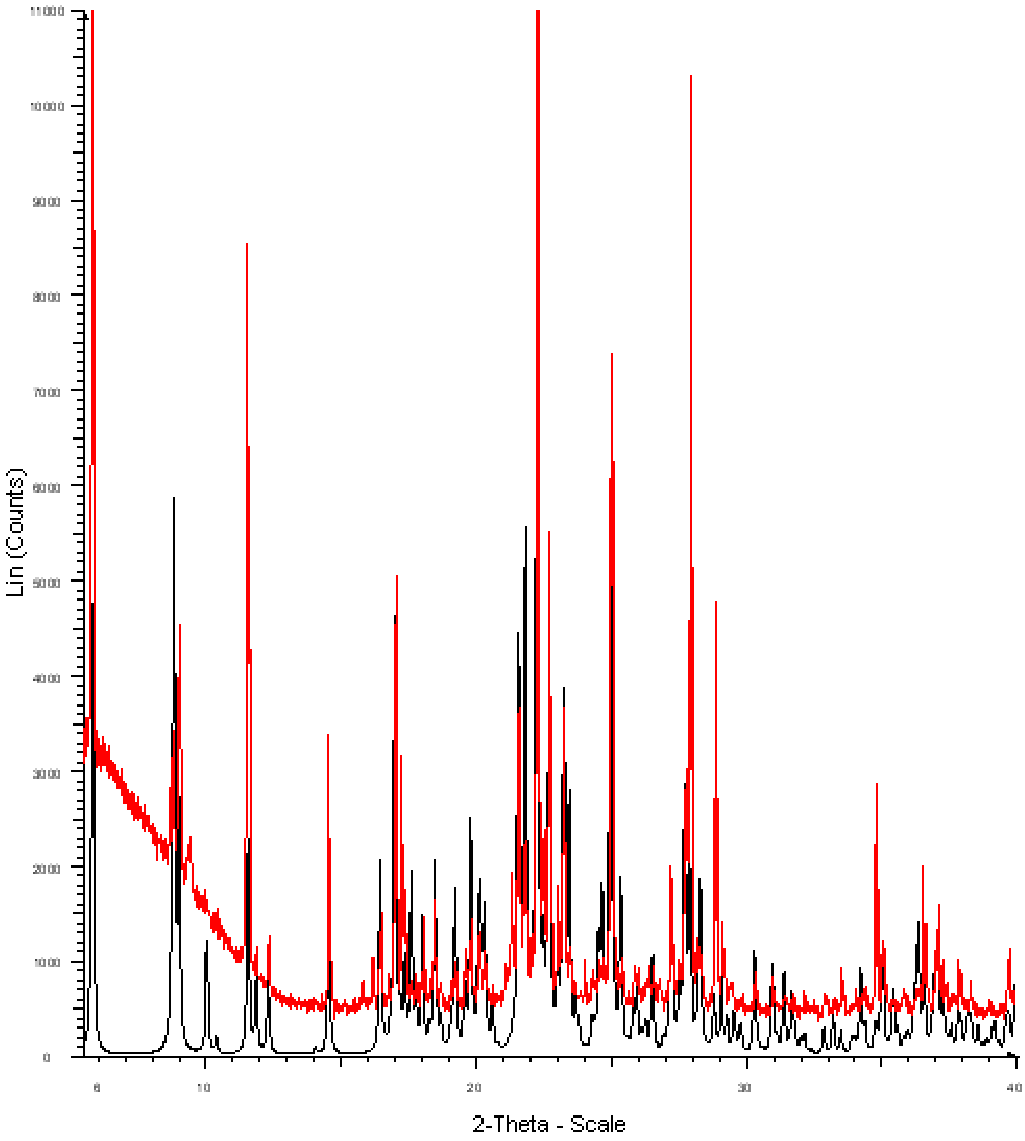


Figure SI 4.8. Superimposed PXRD patterns of cocrystal **1:** Experimental (red line) and simulated from single crystal (black line).

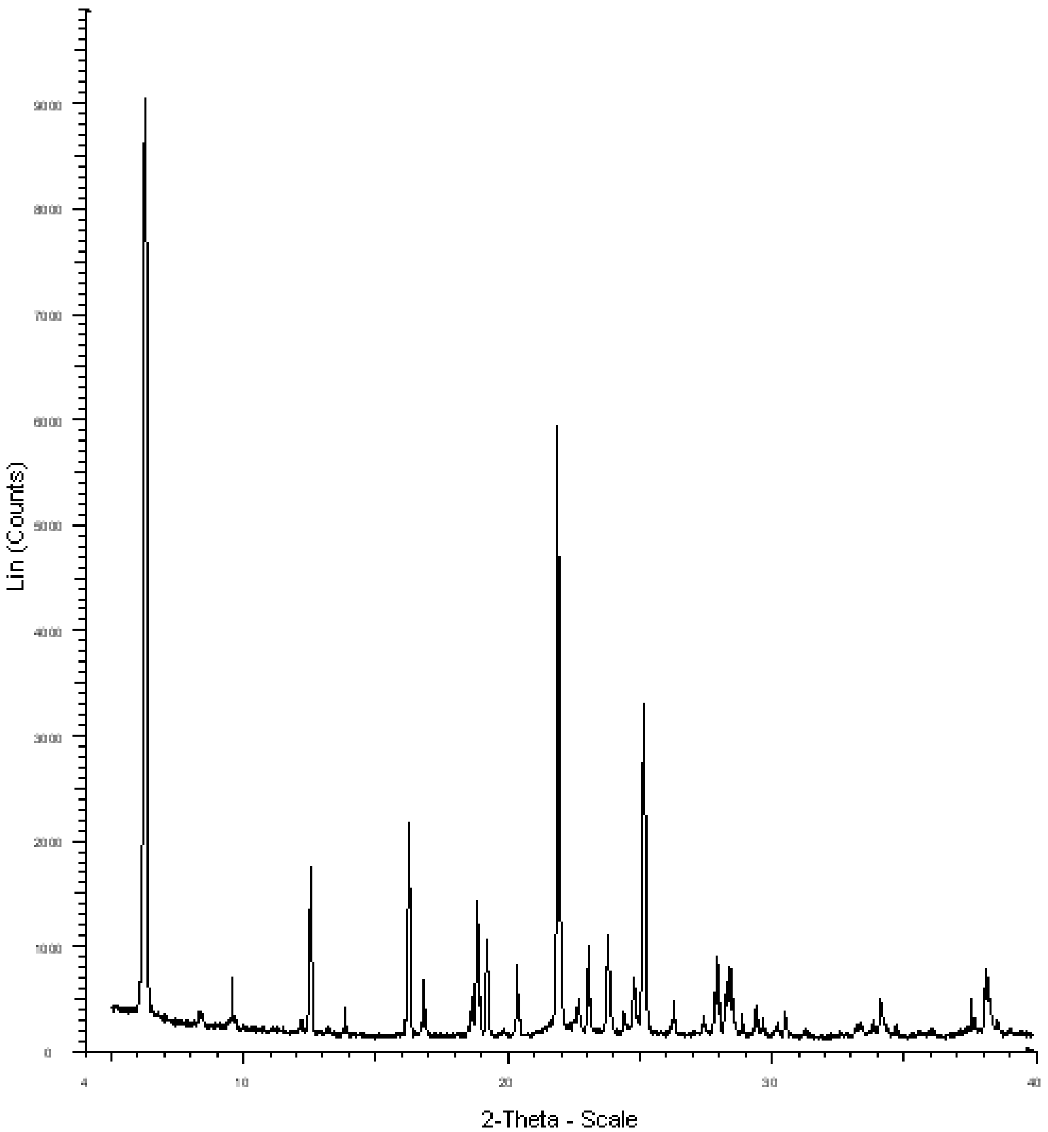


Figure SI 4.9. Experimental PXRD pattern of cocrystal **2**.

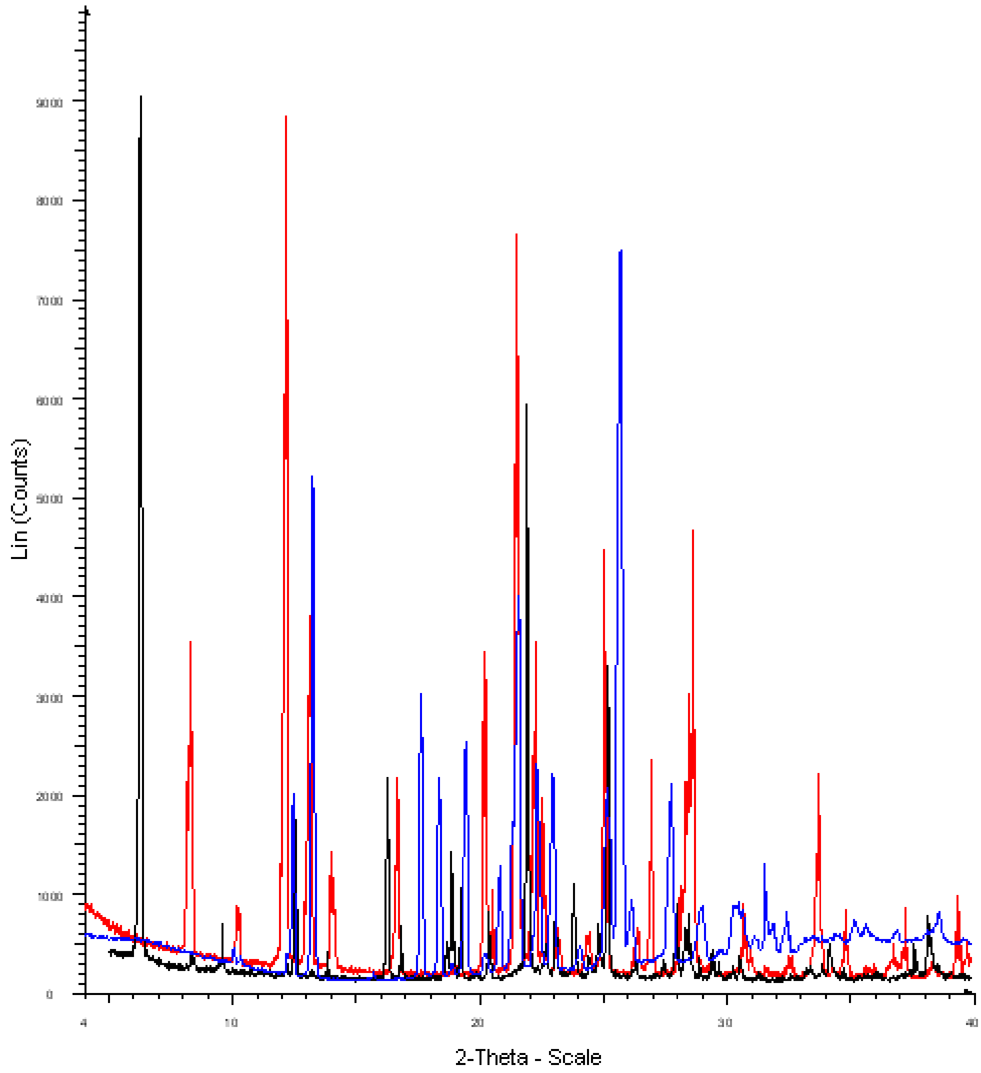


Figure SI 4.10. Experimental PXRD patterns of cocrystal **1** (black line), **DIPY** (blue line) and **IPBC** (red line).

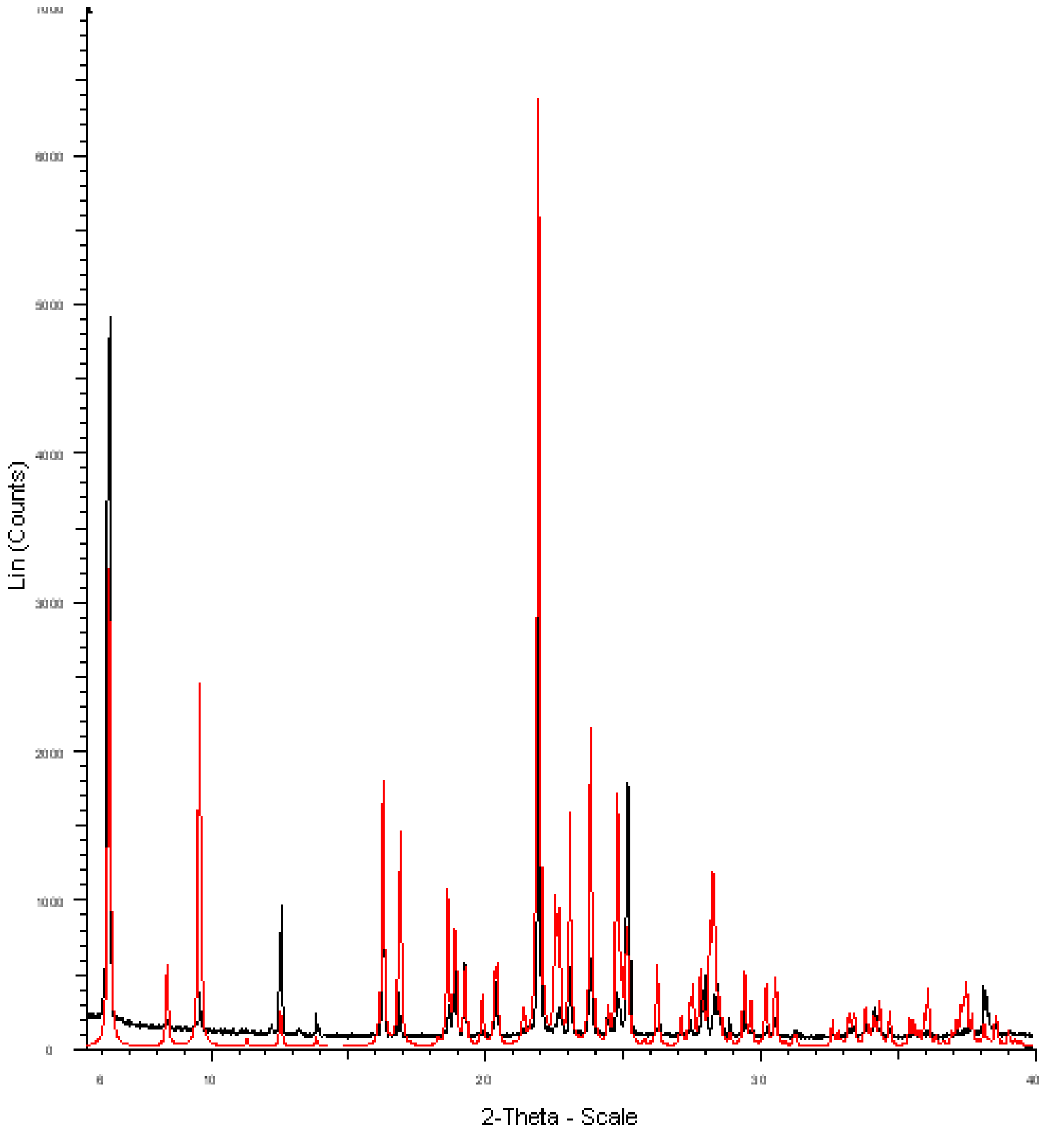


Figure SI 4.11. Superimposed PXRD patterns of cocrystal **2**: Experimental (black line) and simulated from single crystal (red line).

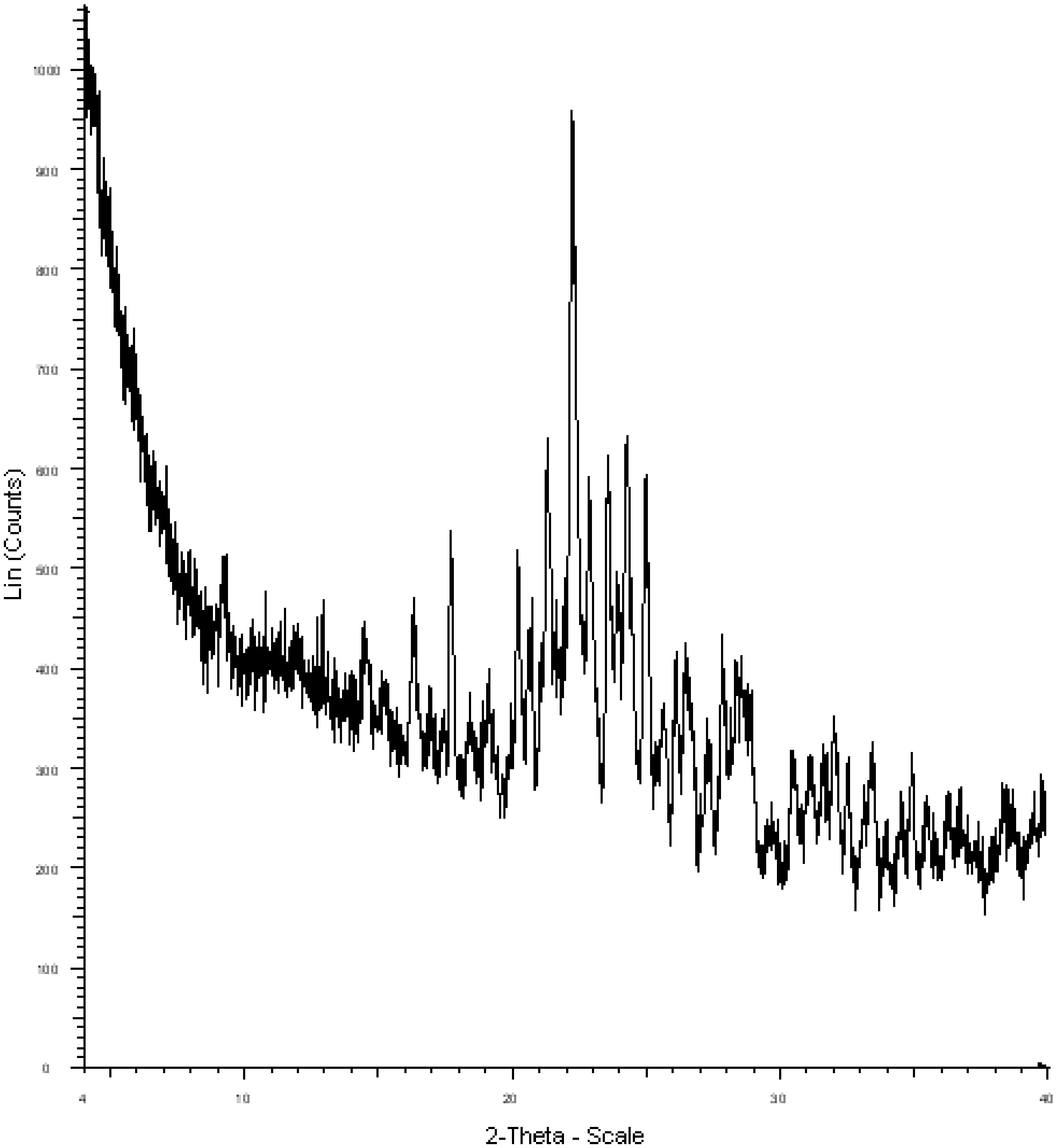


Figure SI 4.12. Experimental PXRD pattern of cocrystal **3**. The cocrystal **3** shows a very poor crystallinity.

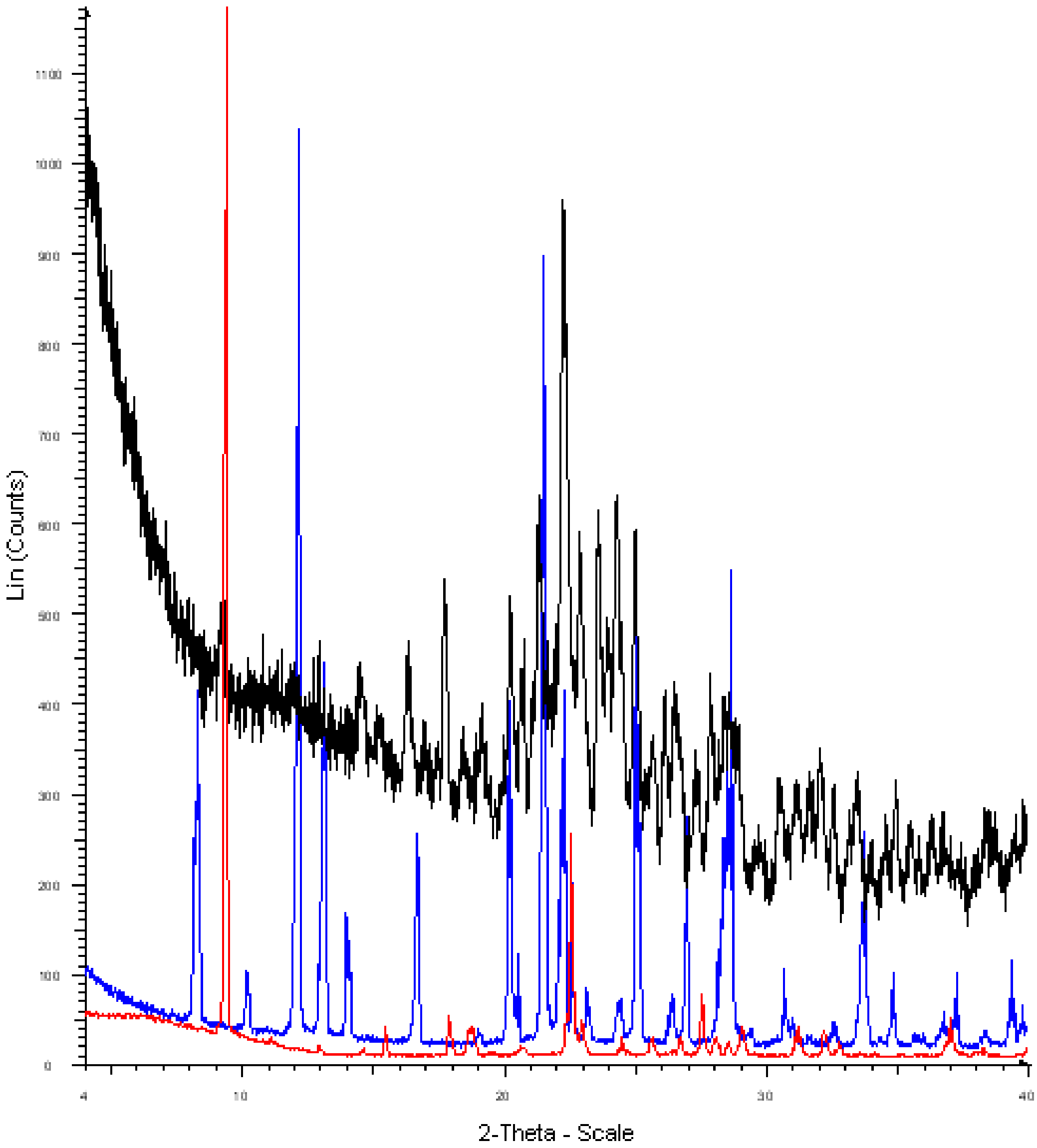


Figure SI 4.13. Experimental PXRD patterns of cocrystal **3** (black line), **TBAI** (red line) and **IPBC** (blue line).

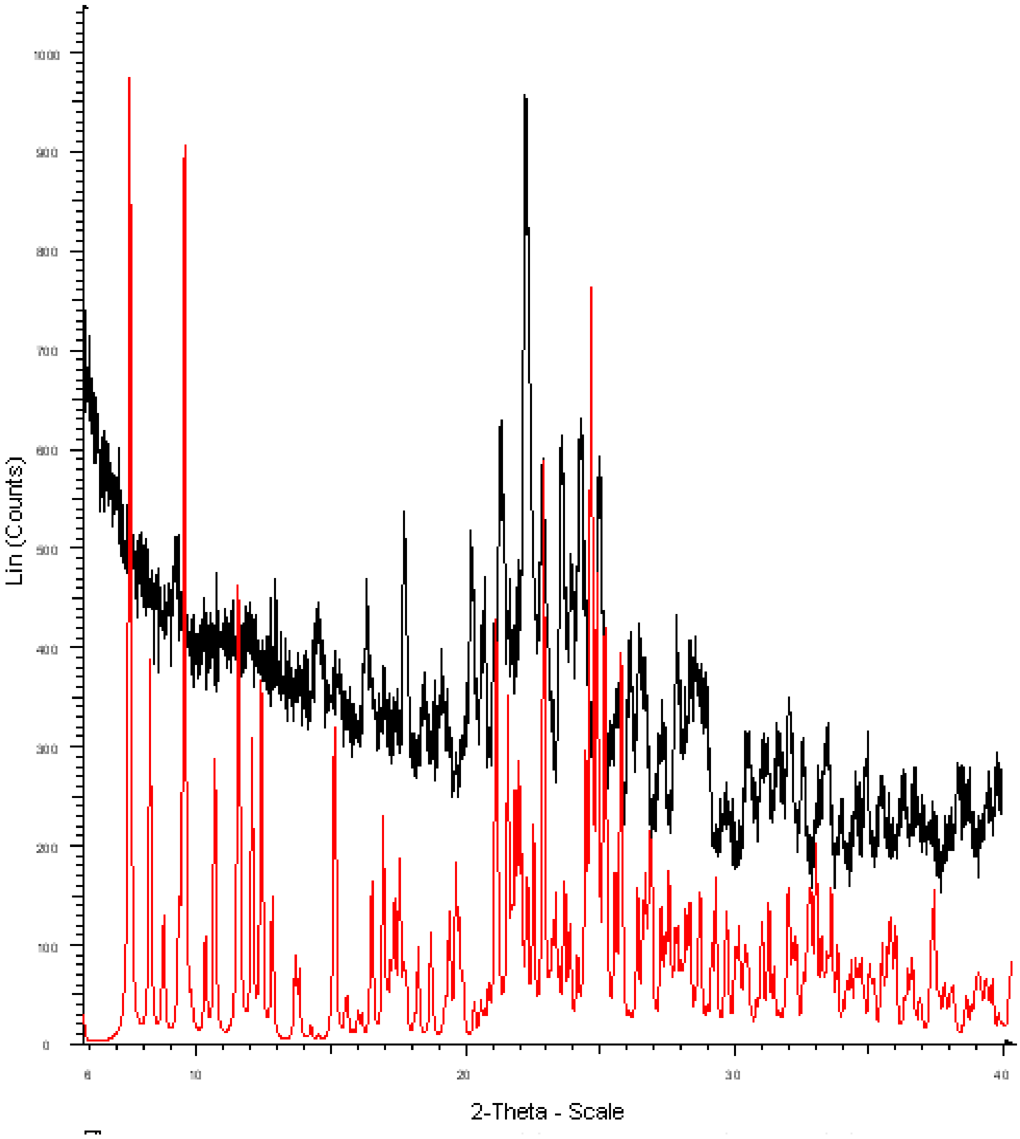


Figure SI 4.14. Superimposed PXRD patterns of cocrystal **3**: Experimental (black line) and simulated from single crystal (red line). Small differences in simulated from single crystal and bulk sample are due to poor crystallinity of cocrystal **3**. The PXRD was collected at room temperature (297 k) while the single crystal data were collected a 103 K.

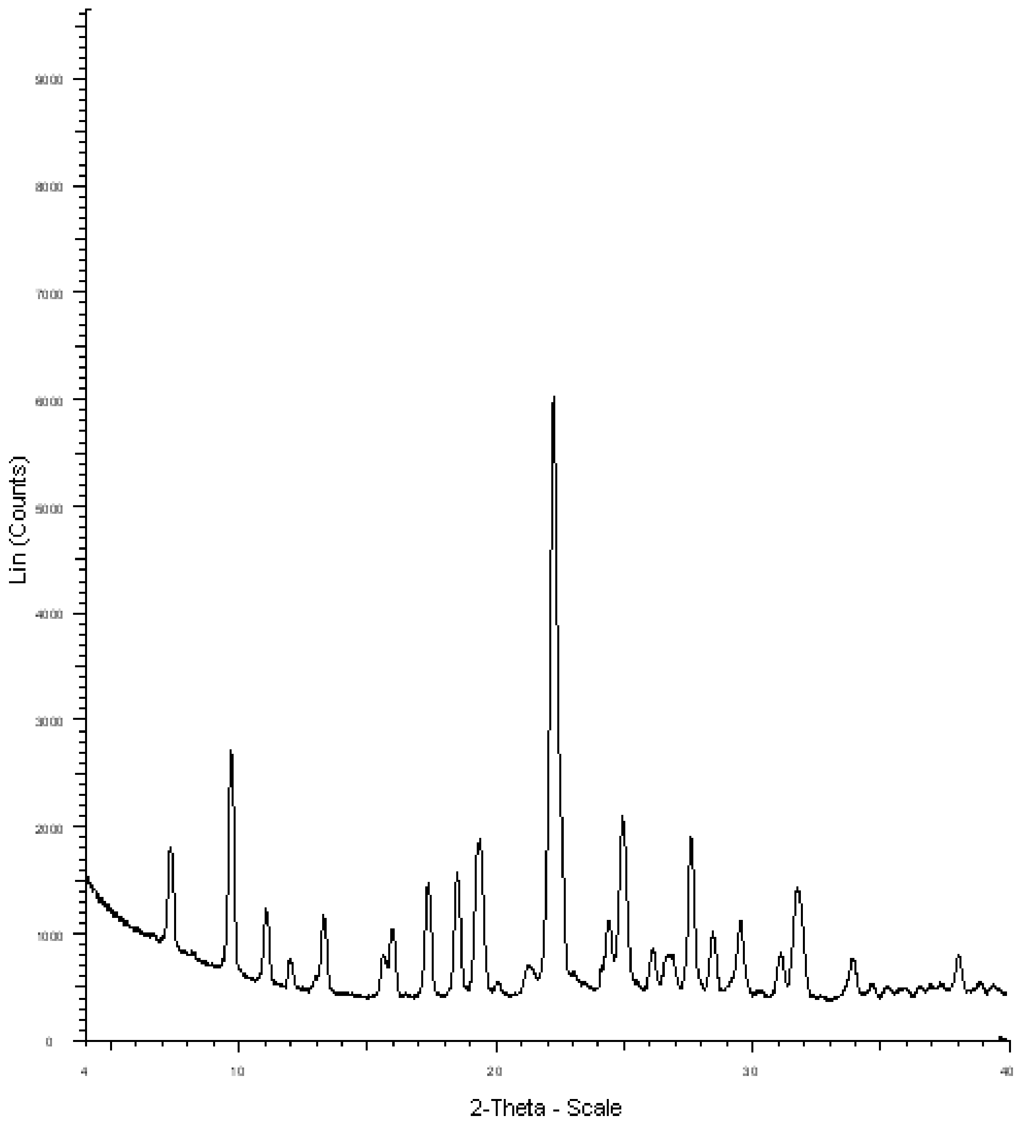


Figure SI 4.15. Experimental PXRD pattern of cocrystal **4**.

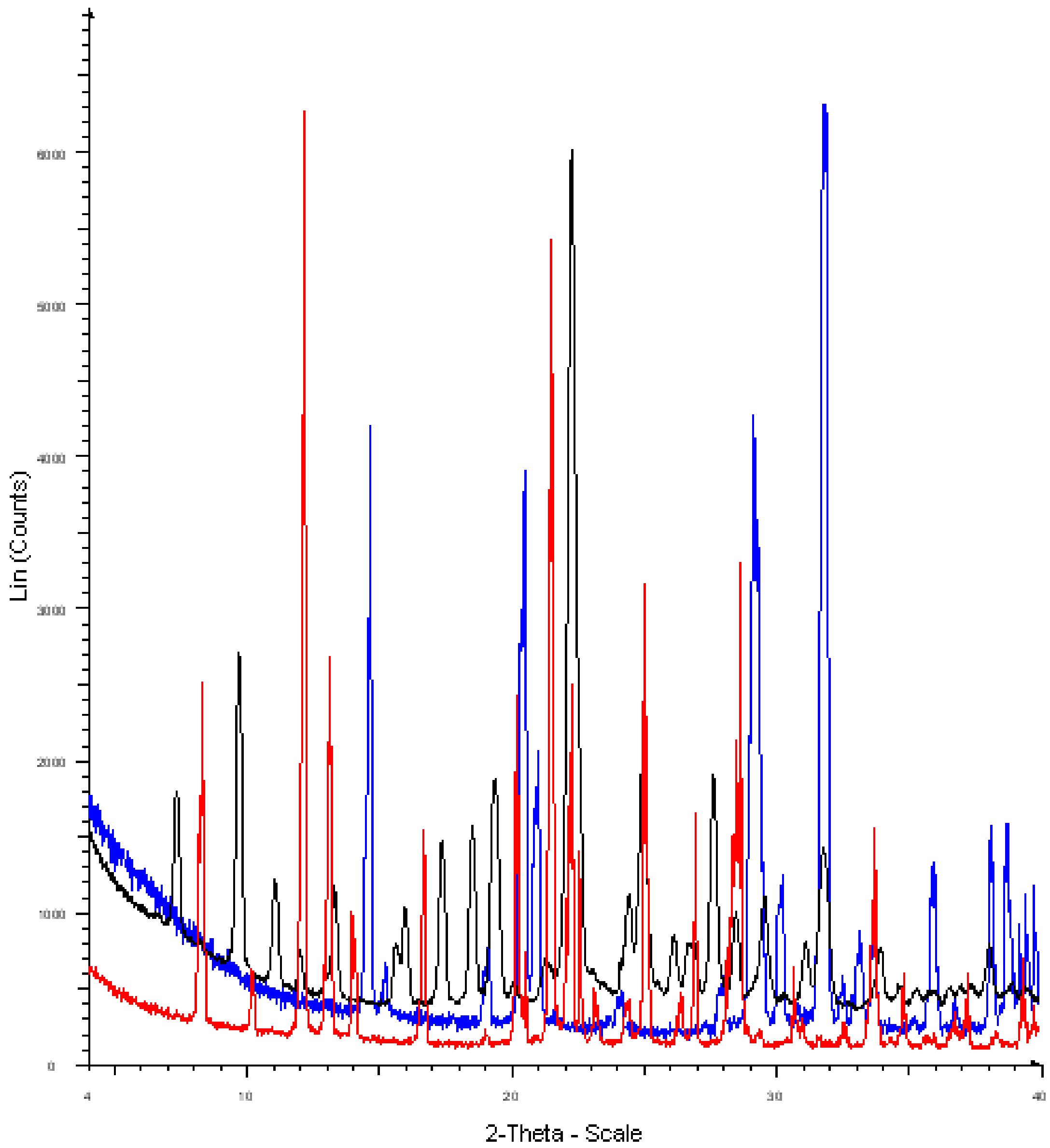
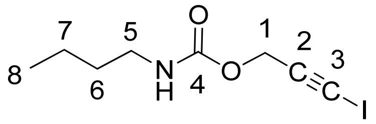


Figure SI 4.16. Experimental PXRD patterns of cocrystal **4** (black line), $\mathbf{CaCl_2}$ (blue line) and **IPBC** (red line).

SI 5. ^{1}H and ^{13}C Nuclear Magnetic Resonance. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker AV400 or 250 MHz spectrometer. The experiments were carried out in different solvents as such $CDCl_3$and methanol-*d*$_4$.



SI Scheme 5.1. Hydrogen and **c**arbon atoms labeling in **IPBC**.

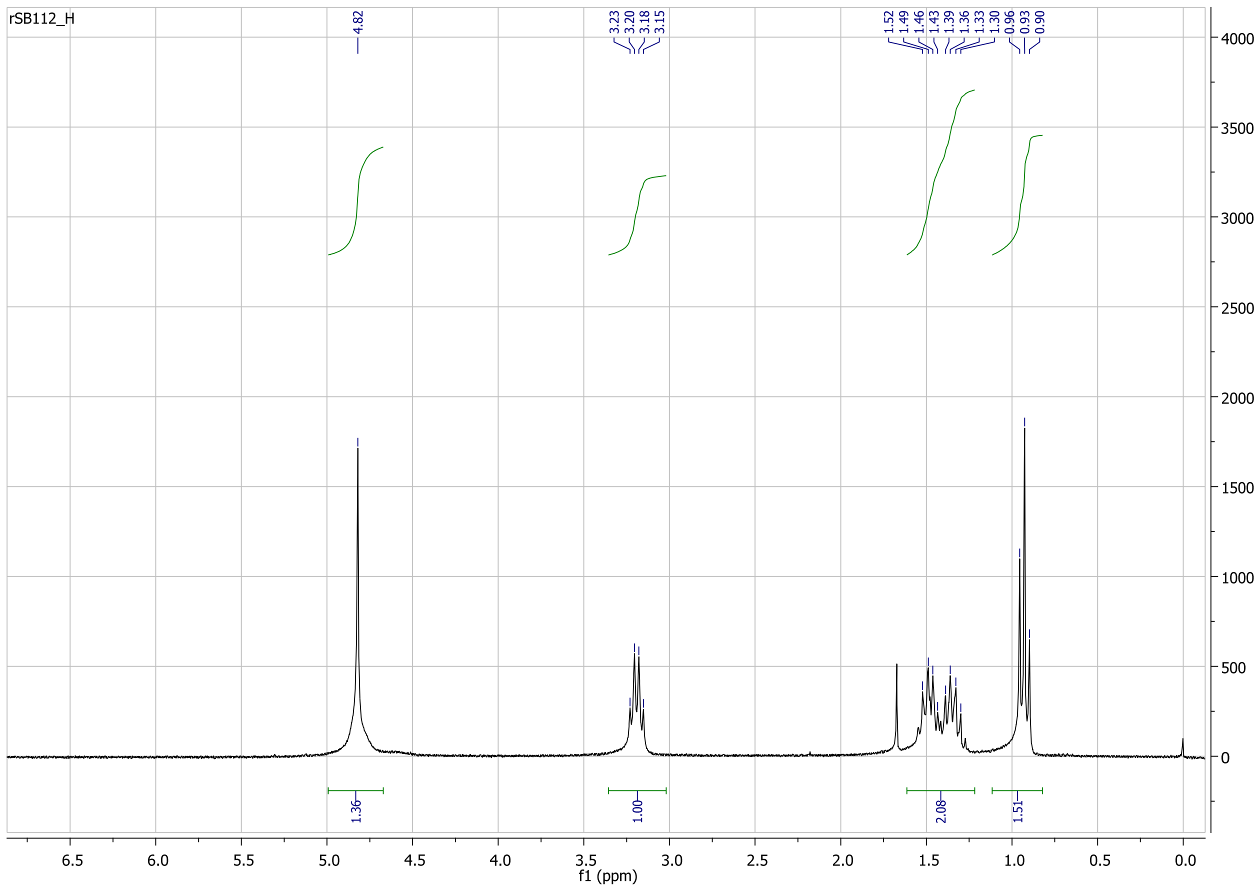


Figure SI 5.1. ^{1}H NMR spectrum in $CDCl_3$ of **IPBC**.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.82 (s, 3H, H1 overlap with NH hydrogen), 3.19 (dd, 2H, *J* = 13.0, 6.7 Hz, H5), 1.52 – 1.30 (m, 4H, H6 and H7), 0.93 (t, 3H, *J* = 7.2 Hz, H8).

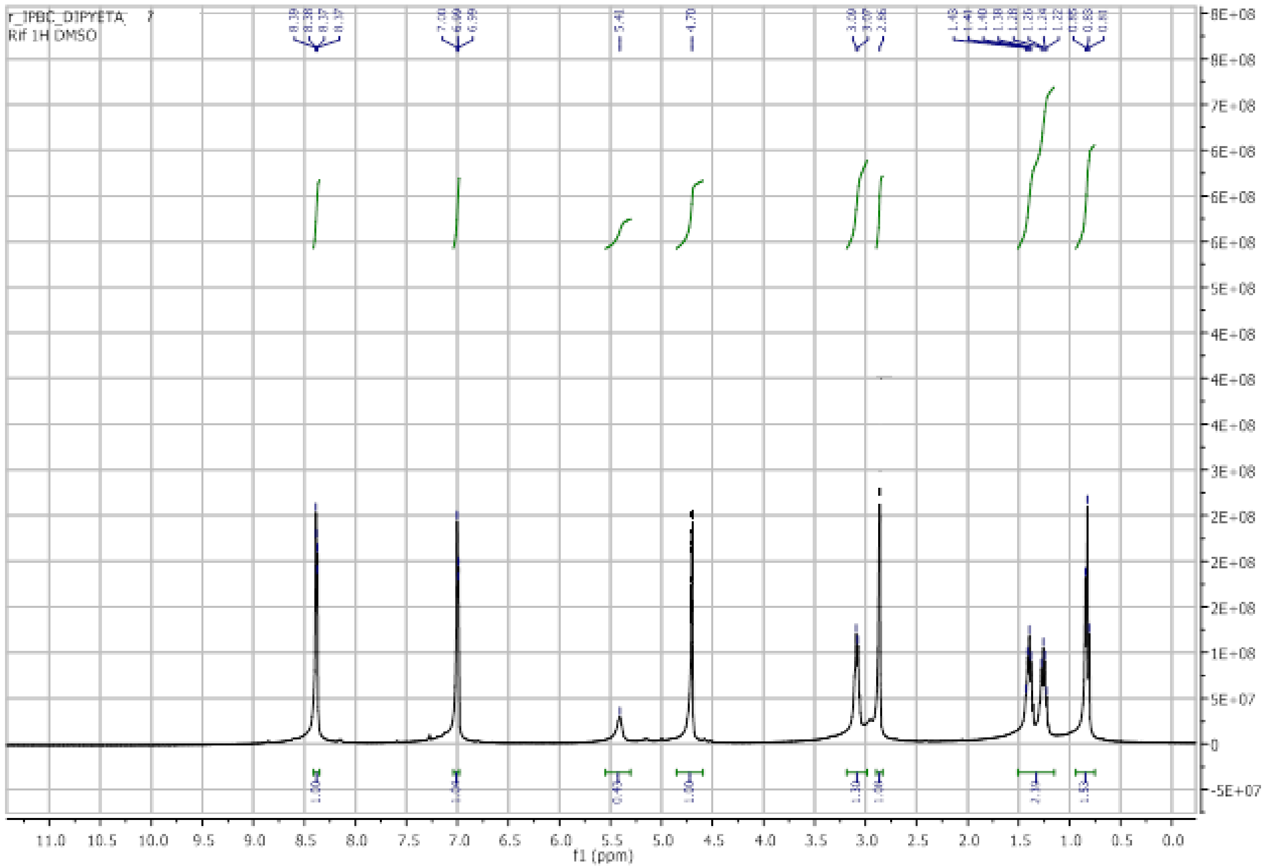


Figure SI 5.2. ^{1}H NMR spectrum in $CDCl_3$ of cocrystal **1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (dd, 4H, *J* = 4.5, 1.4 Hz, H_{py}), 7.04 - 6.98 (m, 4H, H_{py}), 5.41 (bs, 2H, NH), 4.70 (s, 4H, H1), 3.11 - 3.01 (m, 4H, H5), 2.86 (s, 4H, $H_{CH2BiPyEt}$), 1.47 - 1.37 (m, 4H, H6), 1.33 - 1.21 (m, 4H, H7), 0.83 (t, 6H, *J* = 7.3 Hz, H8).

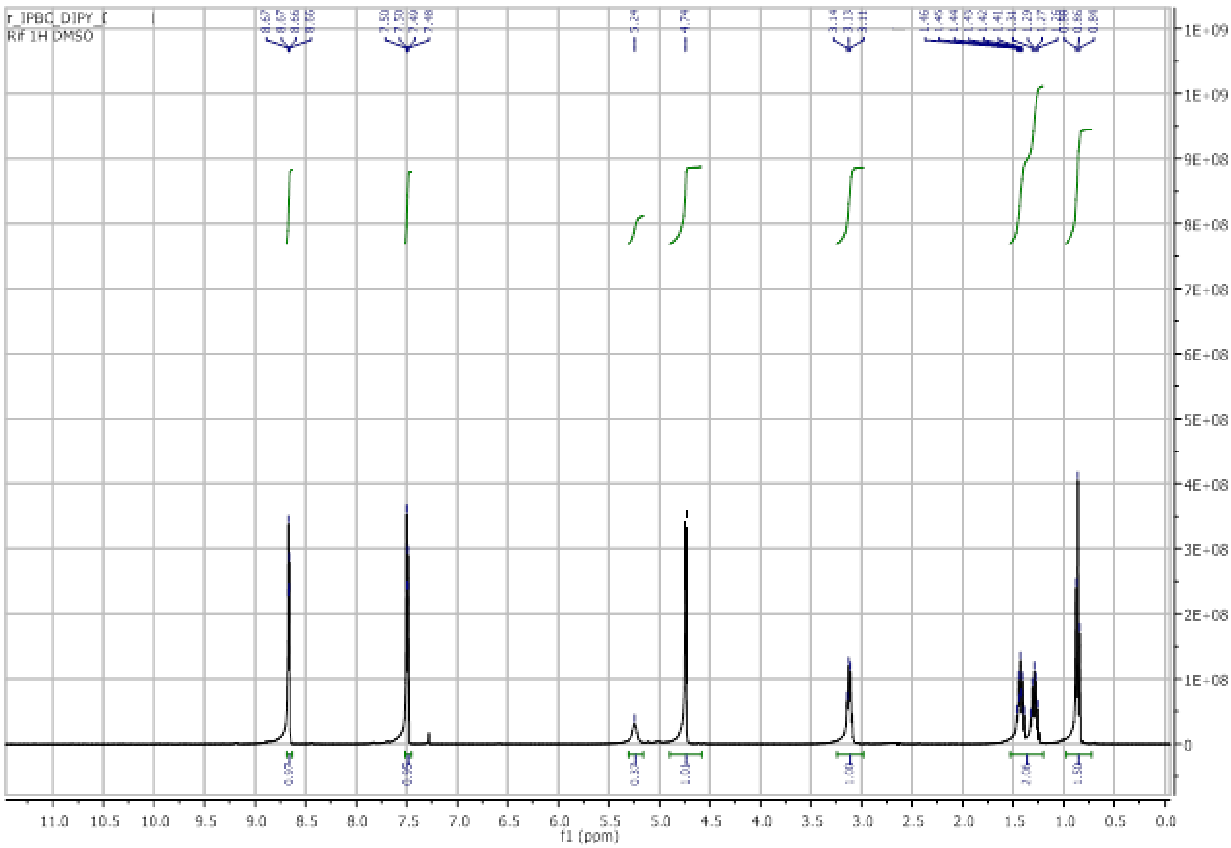


Figure SI 5.3. ^{1}H NMR spectrum in $CDCl_3$ of cocrystal **2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (dd, 4H,J = 4.5, 1.7 Hz,H_{py}), 7.49 (dd, 4H, J = 4.5, 1.7 Hz, H_{py}), 5.24 (bs, 2H, NH), 4.74 (s, 4H, H1), 3.24 – 2.99 (m, 4H, H5), 1.46 - 1.39 (m, 4H, H6), 1.33 - 1.23 (m, 4H, H7), 0.86 (t, 6H, J = 7.3 Hz, H8).

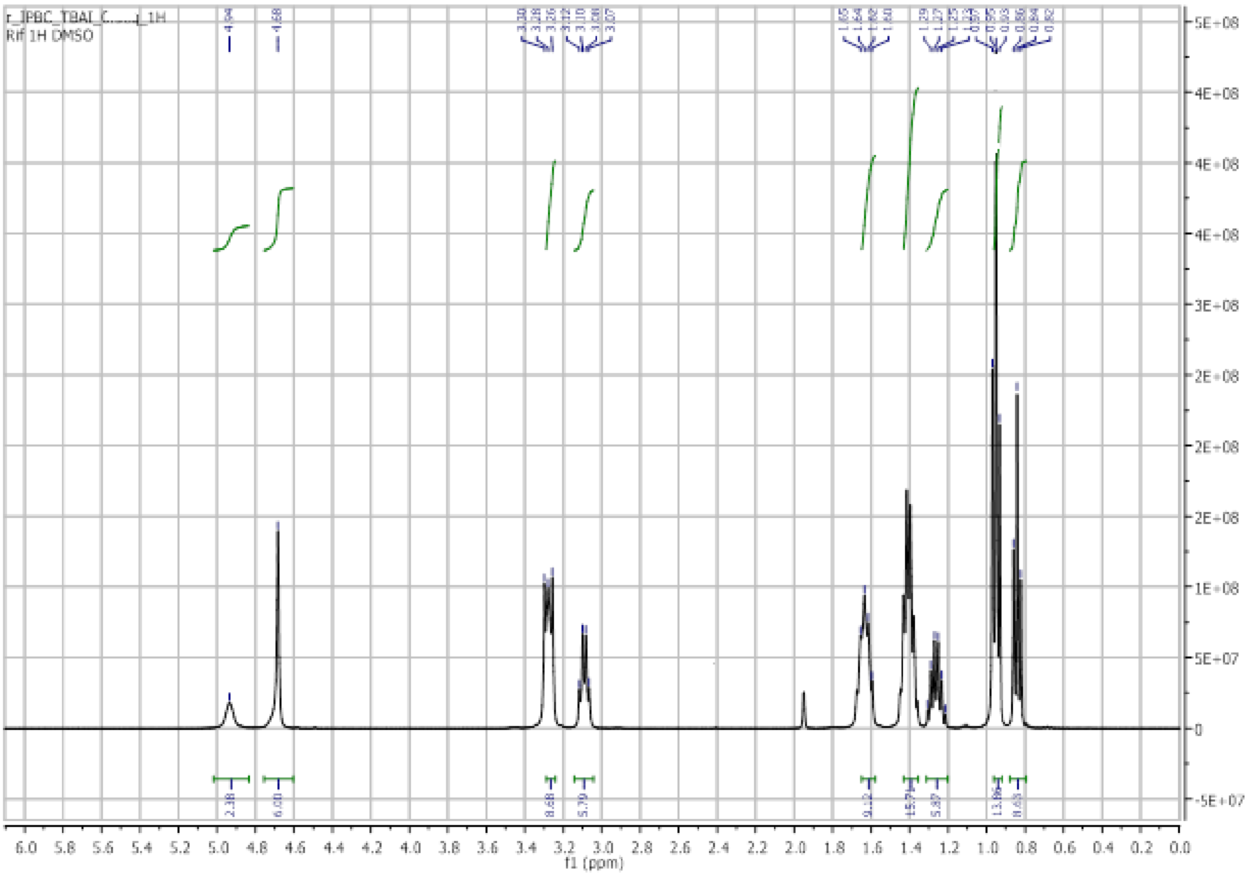


Figure SI 5.4. ^{1}H NMR spectrum in $CDCl_3$ of cocrystal **3**.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.94 (bs, 3H, NH), 4.68 (s, 6H, H1), 3.35 - 3.22 (m, 8H, H_{TBAI}), 3.09 (dd, 6H, *J* = 13.3 and 6.7 Hz, H5), 1.72 - 1.56 (m, 8H, H_{TBAI}), 1.47 -1.34 (m, 14H, H6 and H_{TBAI}), 1.31 - 1.22 (m, 6H, H7), 0.95 (t, 12H, *J* = 7.3 Hz, H_{TBAI}), 0.84 (t, 9H, *J* = 7.3 Hz, H8).

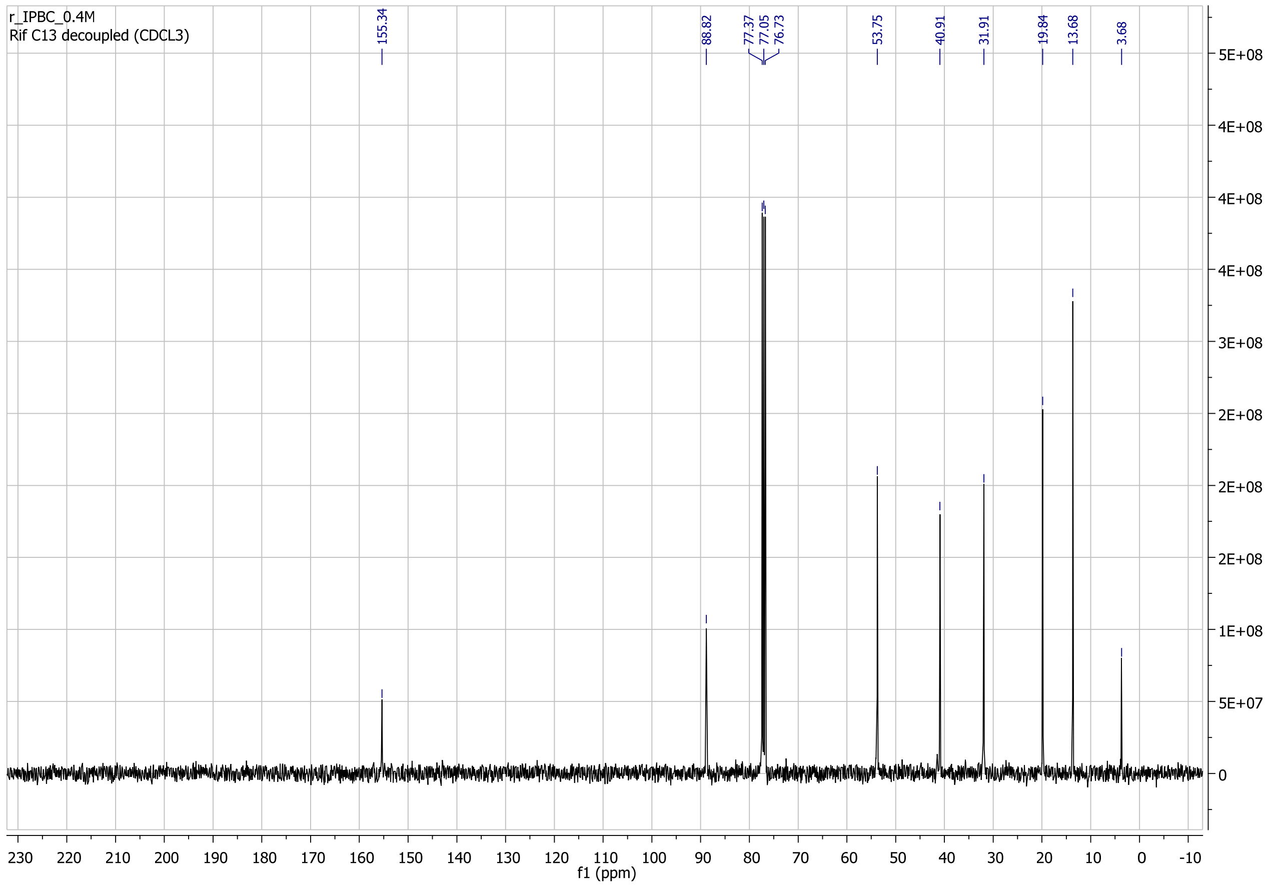


Figure SI 5.5. ^{13}C NMR spectrum in $CDCl_3$ of pure 3-iodo-2-propynyl-*N*-butylcarbamate **(IPBC**, 0.4 M)**:** (101 MHz, $CDCl_3$) δ: 155.34 (C4), 88.82 (C2), 53.75 (C1), 40.91 (C5), 31.91 (C6), 19.84 (C7), 13.68 (C8), 3.68 (C3) ppm.

3-Iodo-2-propynyl-*N*-butylcarbamate (**IPBC**) and adducts **1**, **2** and **3** were dissolved in $CDCl_3$. 0.4 M concentration respects to **IPBC** was used in all the experiments. Incremental amount of XB acceptor has been added in order to evaluate the chemical shift variation of the carbon bound to iodine (Scheme 1)^{13}C NMR spectrum of cocrystal **4** was recorded in methanol-d_4.

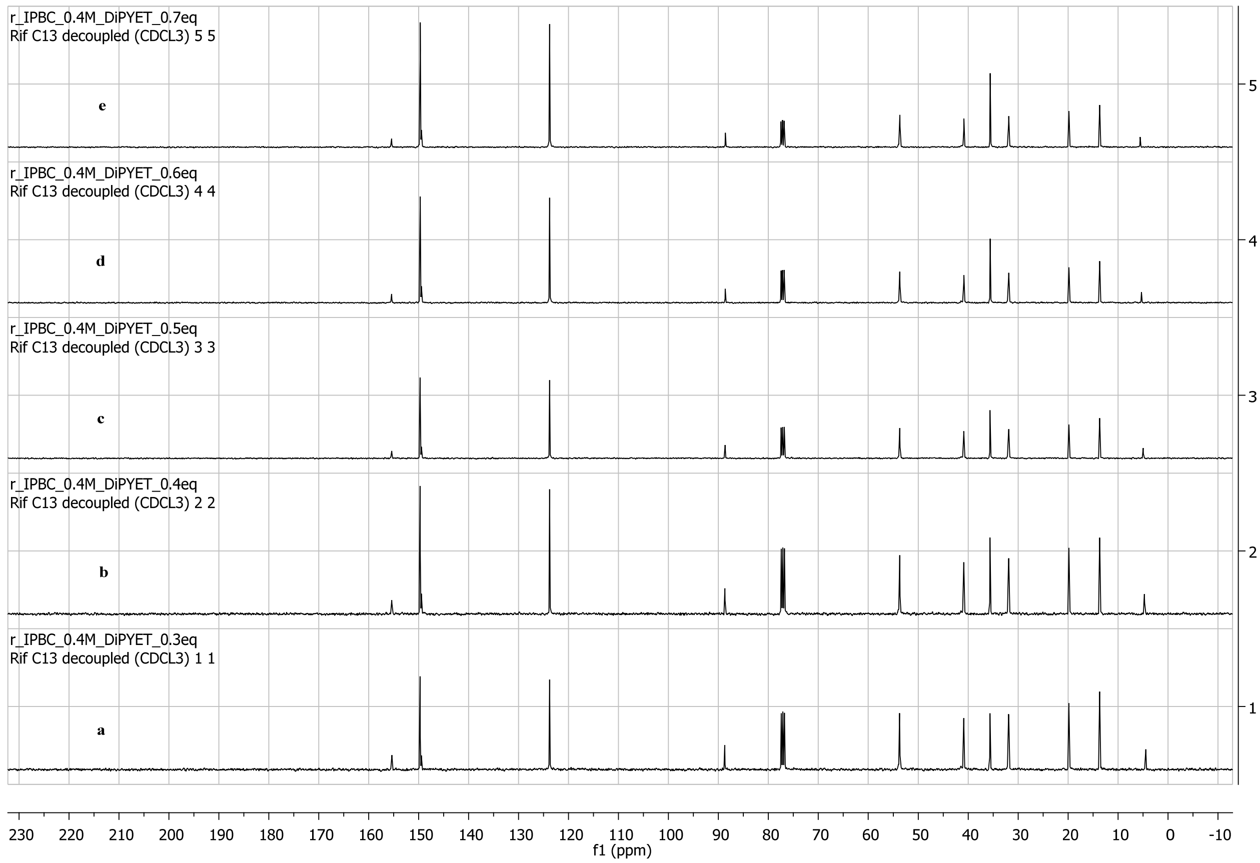


Figure SI 5.6. ^{13}C NMR spectrum in $CDCl_3$ of cocrystal **1** with different **BiPyEt** equivalent (0.3, 0.4, 0.5, 0.6 and 0.7 eq)**.**

(a) ^{13}C NMR (0.3 eq of **BiPyEt**), (101 MHz, $CDCl_3$) δ: 155.38, 149.74, 149.48, 123.80, 119.51, 88.73, 77.41, 77.10, 76.78, 53.72, 40.89, 35.62, 31.90, 19.83, 13.67, 4.45 ppm. **(b)** ^{13}C NMR (0.4 eq of **BiPyEt**), (101 MHz, $CDCl_3$) δ: 155.40, 149.73, 149.48, 123.80, 88.70, 77.43, 77.11, 76.79, 53.71, 40.88, 35.61, 31.89, 19.83, 13.67, 4.71 ppm. **(c)** ^{13}C NMR (0.5 eq of **BiPyEt**), (101 MHz, $CDCl_3$) δ: 155.41, 149.72, 149.48, 123.80, 88.67, 77.44, 77.13, 76.81, 75.31, 53.70, 40.87, 35.61, 31.89, 19.82, 13.67, 4.96 ppm. **(d)** ^{13}C NMR (0.6 eq of **BiPyEt**), (101 MHz, $CDCl_3$) δ: 155.43, 149.71, 149.48, 123.79, 88.62, 77.46, 77.15, 76.83, 53.69, 41.45, 40.86, 35.59, 31.88, 19.82, 13.67, 5.31 ppm. **(e)** ^{13}C NMR (0.7eq of **BiPyEt**), (101 MHz, $CDCl_3$) δ: 155.44, 149.69, 149.48, 123.79, 88.59, 77.48, 77.16, 76.85, 53.68, 40.85, 35.58, 31.87, 19.82, 13.67, 5.56 ppm.

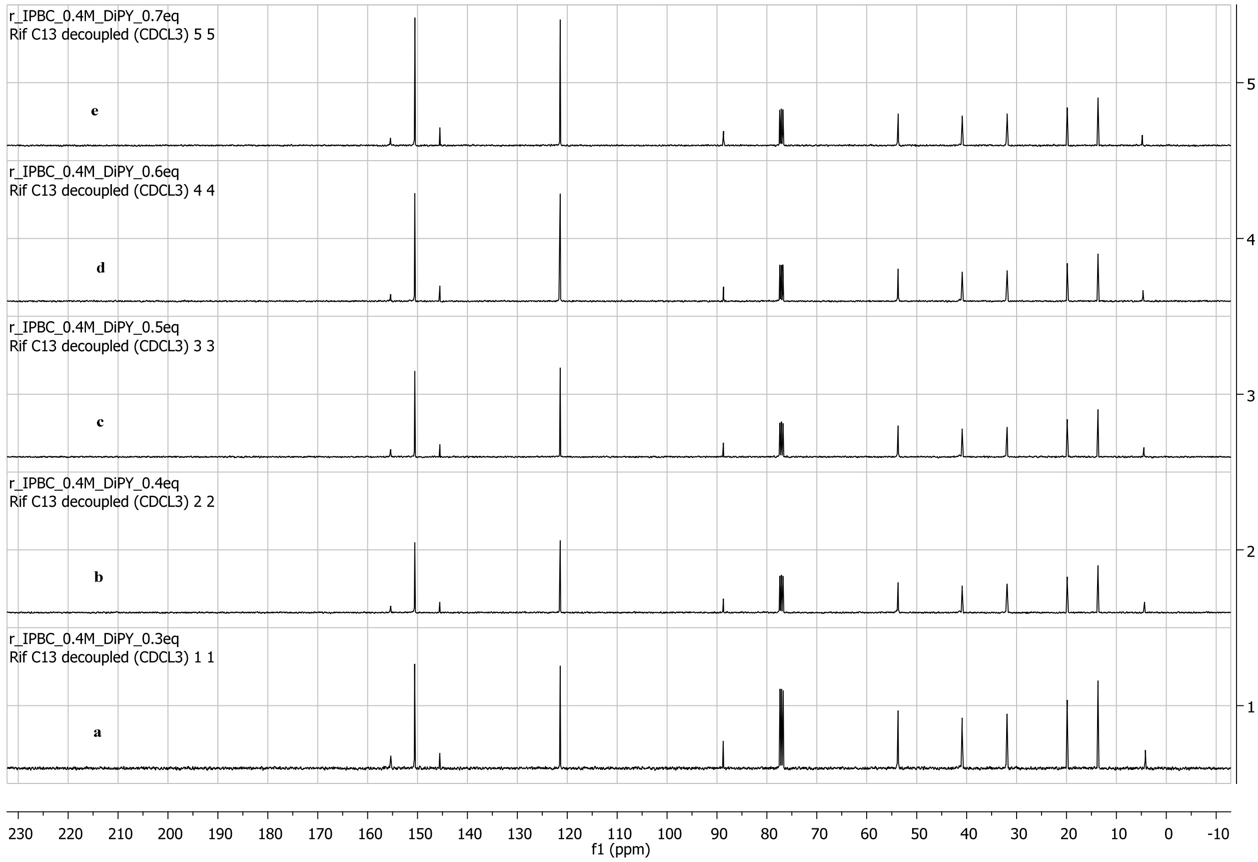


Figure SI 5.7. ^{13}C NMR spectrum in $CDCl_3$ of cocrystal **2** with different **BiPy** equivalent (0.3, 0.4, 0.5, 0.6 and 0.7 eq)**.**

(a) ^{13}C NMR (0.3 eq of **BiPy**), (101 MHz, $CDCl_3$) δ: 155.38, 150.58, 145.55, 121.42, 88.76, 77.40, 77.08, 76.76, 53.73, 40.89, 31.90, 19.83, 13.67, 4.18 ppm. **(b)** ^{13}C NMR (0.4 eq of **BiPy**), (101 MHz, $CDCl_3$) δ: 155.39, 150.57, 145.55, 121.42, 88.74, 77.41, 77.10, 76.78, 53.73, 40.89, 31.89, 19.83, 13.67, 4.35 ppm. **(c)** ^{13}C NMR (0.5 eq of **BiPy**), (101 MHz, $CDCl_3$)δ: 155.40, 150.56, 145.54, 121.42, 88.73, 77.42, 77.11, 76.79, 53.73, 40.88, 31.89, 19.83, 13.67, 4.48 ppm. **(d)** ^{13}C NMR (0.6 eq of **BiPy**), (101 MHz, $CDCl_3$) δ: 155.41, 150.55, 145.54, 121.42, 88.71, 77.43, 77.12, 76.80, 53.72, 40.88, 31.88, 19.83, 13.67, 4.65 ppm. **(e)** ^{13}C NMR (0.7eq of **BiPy**), (101 MHz, $CDCl_3$) δ: 155.42, 150.54, 145.53, 121.42, 88.69, 77.44, 77.13, 76.81, 53.71, 40.87, 31.88, 19.82, 13.67, 4.80 ppm.

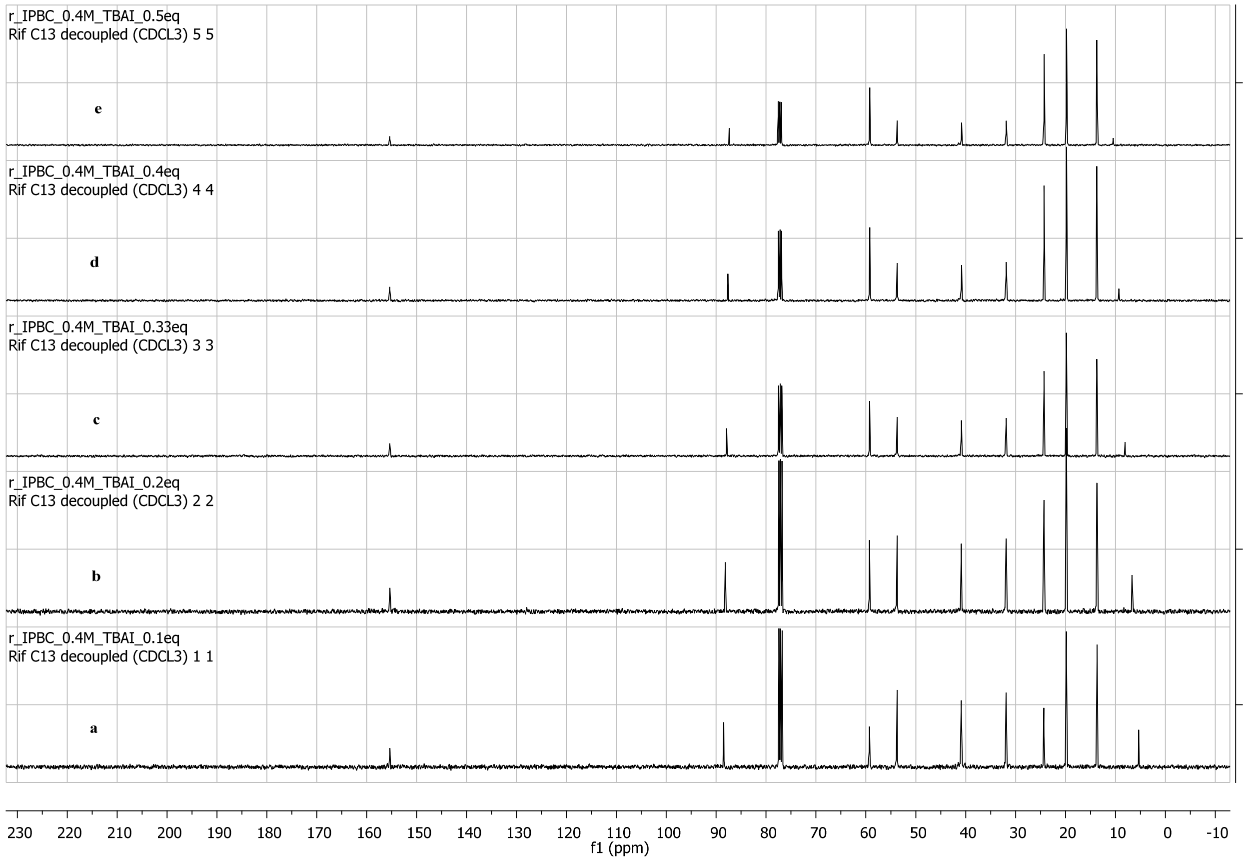


Figure SI 5.8. ^{13}C NMR spectrum in $CDCl_3$ of cocrystal **3** with different **TBAI** equivalent (0.1, 0.2, 0.3, 0.4 and 0.5 eq)**.**

(a) ^{13}C NMR (0.1 eq of **TBAI**), (101 MHz, $CDCl_3$) δ: 155.36, 88.47, 77.40, 77.08, 76.77, 59.29, 53.75, 40.89, 31.90, 24.34, 19.83, 13.75, 13.67, 5.33 ppm. **(b)** ^{13}C NMR (0.2 eq of **TBAI**), (101 MHz, $CDCl_3$) δ: 155.37, 88.19, 77.43, 77.12, 76.80, 59.26, 53.75, 40.87, 31.89, 24.33, 19.83, 13.75, 13.66, 6.69 ppm. **(c)** ^{13}C NMR (0.3 eq of **TBAI**), (101 MHz, $CDCl_3$) δ: 155.39, 87.90, 77.47, 77.15, 76.83, 59.24, 53.74, 40.86, 31.88, 24.31, 19.81, 13.75, 13.65, 8.07 ppm. **(d)** ^{13}C NMR (0.4 eq of **TBAI**), (101 MHz, $CDCl_3$) δ: 155.39, 87.64, 77.50, 77.18, 76.87, 59.22, 53.73, 40.84, 31.87, 24.30, 19.80, 13.73, 13.65, 9.30 ppm. **(e)** ^{13}C NMR (0.5 eq of **TBAI**), (101 MHz, $CDCl_3$) δ: 155.40, 87.40, 77.54, 77.22, 76.90, 59.20, 53.72, 40.82, 31.86, 24.29, 19.78, 13.72, 13.64, 10.42 ppm.

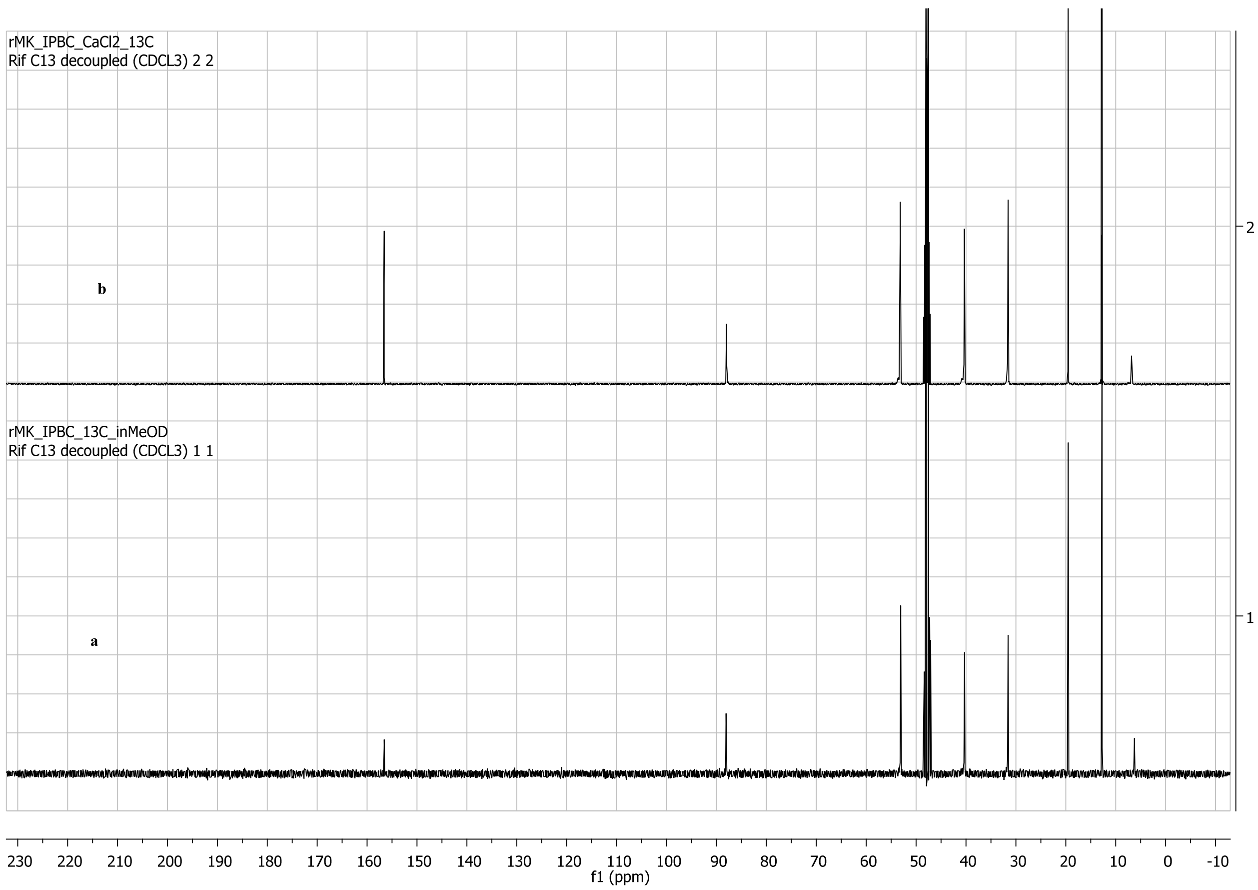


Figure SI 5.9. ^{13}C NMR spectrum in methanol-d_4 of **IPBC** (a) and cocrystal **4** (b).

SI. 6. Solid-state NMR.

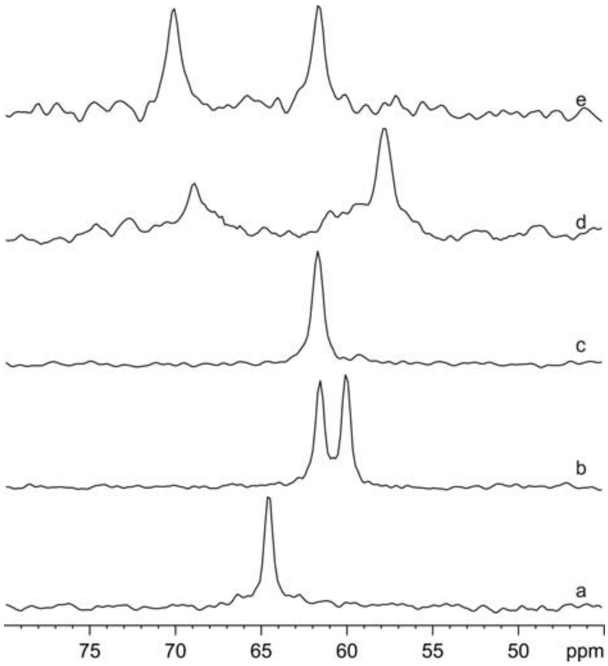


Figure SI 6.1. NH region of the ^{15}N (40 MHz) CPMAS spectra of pure **IPBC** (a), **1** (b), **2**, (c), **3** (d),and **4** (e) recorded at 9 kHz.

SI. 7. Powder flow properties measurement.

Table SI 7.1 Values of angle of repose for cocrystal **4.**

Funnel/flat surface distance: 25 mm

Measurement	L (pixel)	H (pixel)	Angle of repose (°)
01	624	149	25.5
02	779	128	18.2
03	709	113	17.7
04	638	128	21.9
05	553	113	22.2
06	1460	241	18.3
07	1176	225	20.9
08	1233	225	20.1
09	1290	227	19.4
10	1403	241	19.0

Average	**20.3±2.4**

Funnel/flat surface distance: 50 mm

Measurement	L (pixel)	H (pixel)	Angle of repose (°)
11	1105	128	13.0
12	723	113	17.4
13	879	113	14.4
14	1049	92	9.9
15	921	128	15.5
16	1729	176	11.5
17	1772	170	10.9
18	1474	184	14.0

Average	**13.3±2.5**

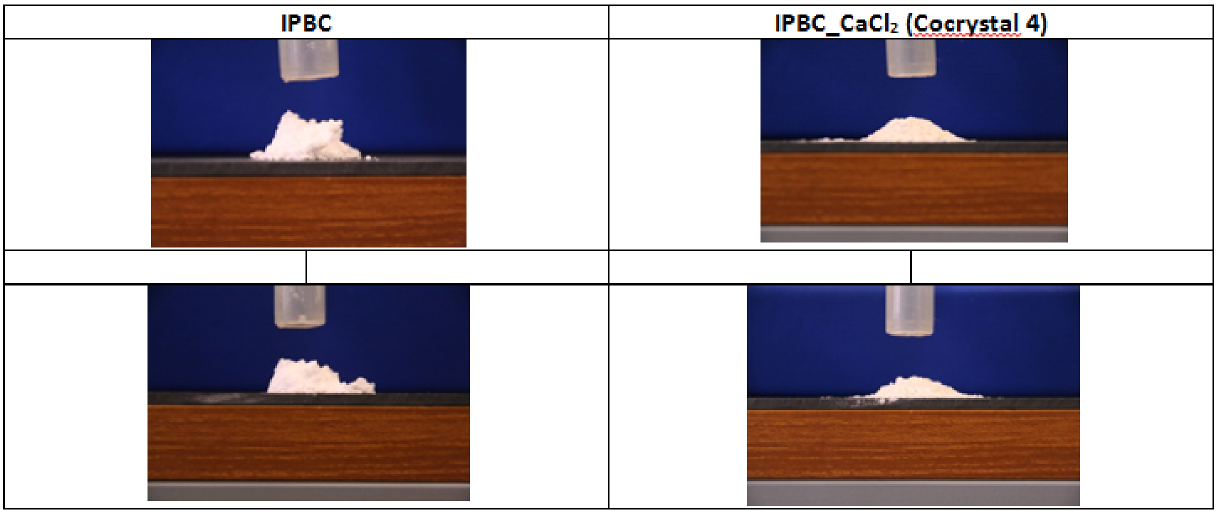


Figure SI 7.1. Pictures of cones of **IPBC** (left) and cocrystal **4** (right) powders, taken after flowing the powders through the funnel from 25 mm height.

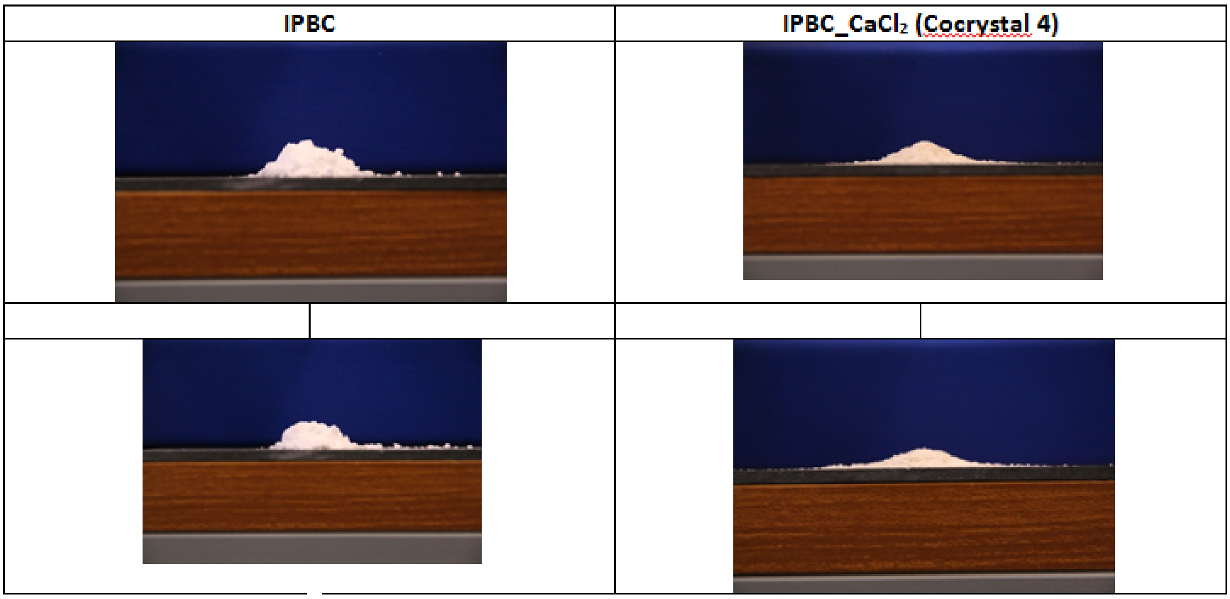


Figure SI 7.2. Pictures of cones of **IPBC** (left) and cocrystal **4** (right) powders, taken after flowing the powders through the funnel from 50 mm height.

SI 8. Crystal structure figures and check cif

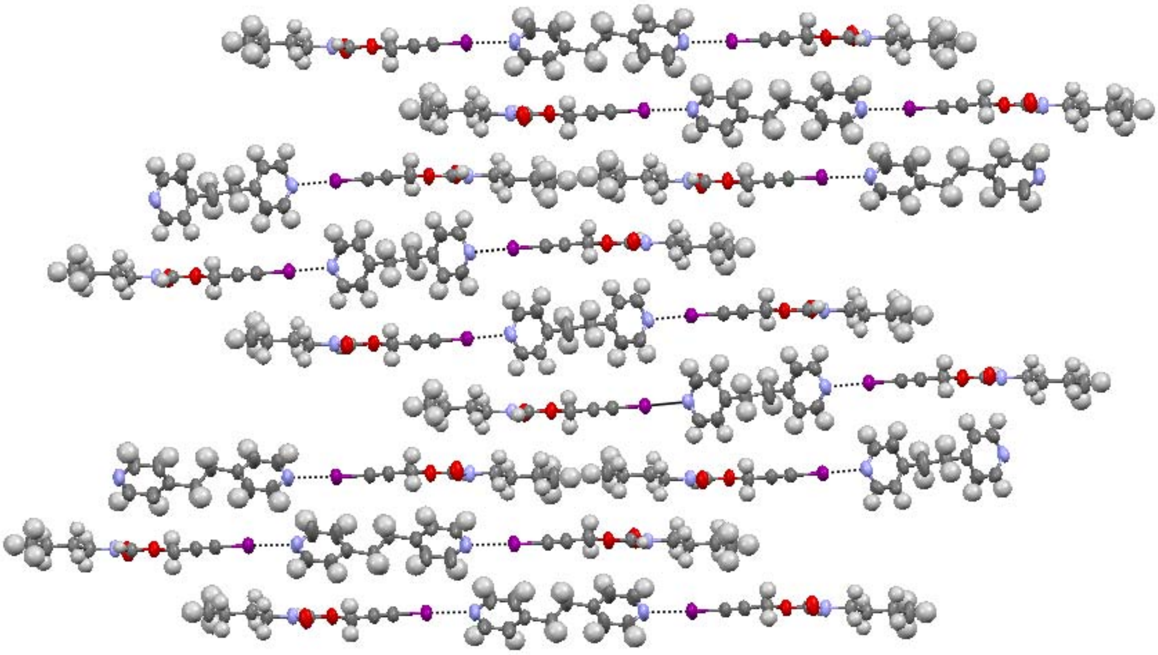


Figure SI 8.1. Halogen bonded trimer present in cocrystal **1.** View alog *b*-axies (+30° in *z*).Colour code: Gray: carbon; red: oxygen; Blue: nitrogen; Purple: iodine; Hydrogen: white. XBs are pictured as black dotted lines.

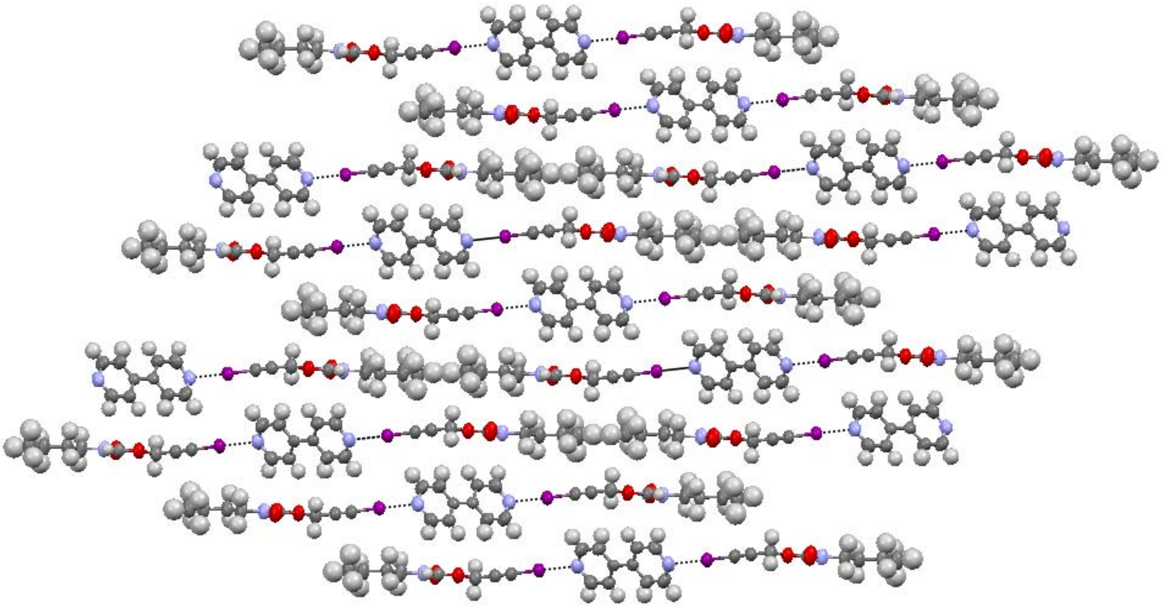


Figure SI 8.2. Halogen bonded trimer present in cocrystal **2.** View alog *b*-axies (-30° in z).Colour code as in Figure SI 7.1. XBs are pictured as black dotted lines.

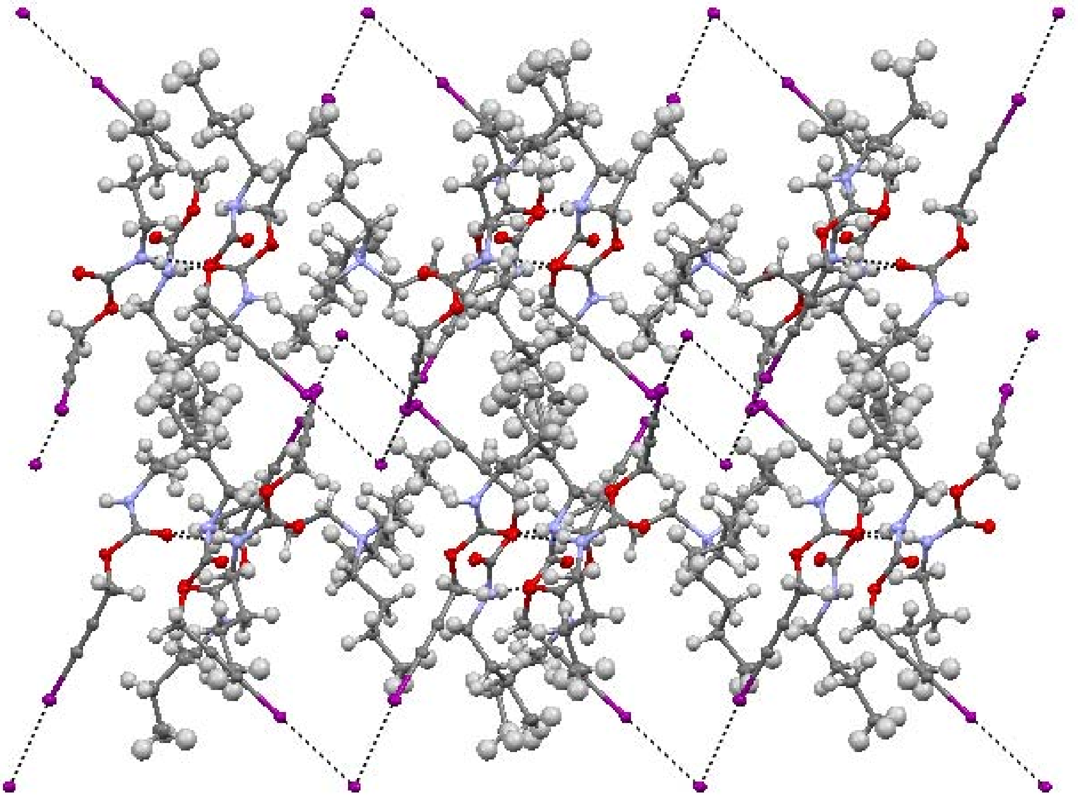


Figure SI 8.3. Crystal packing of cocrystal **3.** View alog *b*-axies.Colour code as in Figure SI 7.1. XBs and HBs are pictured as black dotted lines.

Check cif SI 8.4. Print screen of check cif for cocrystal **1.**

checkCIF/PLATON (standard)

Structure factors have been supplied for datablock(s) sb30

No syntax errors found. CIF dictionary
Please wait while processing .... Interpreting this report
Structure factor report

Datablock: sb30

```
Bond precision:     C-C = 0.0073 A              Wavelength=0.71073

Cell:         a=30.666(3)    b=4.9869(4)    c=21.068(2)

              alpha=90       beta=92.115(6) gamma=90

Temperature: 297 K
```

	Calculated	Reported
Volume	3219.7(5)	3219.7(5)
Space group	P 2/c	P 2/c
Hall group	-P 2yc	-P 2yc
Moiety formula	C12 H12 N2, 2(C8 H12 I N O2)	C12 H12 N2, 2(C8 H12 I N O2)
Sum formula	C28 H36 I2 N4 O4	C28 H36 I2 N4 O4
Mr	746.41	746.41
Dx,g cm-3	1.540	1.540
Z	4	4
Mu (mm-1)	1.989	1.989
F000	1480.0	1480.0
F000'	1476.73	
h,k,lmax	39,6,27	39,6,27
Nref	7427	7414
Tmin,Tmax	0.723,0.905	0.594,0.746
Tmin'	0.545	

```
Correction method= MULTI-SCAN

Data completeness= 0.998       Theta(max)= 27.500

R(reflections)= 0.0383( 4592)      wR2(reflections)= 0.1234( 7414)

S = 1.077            Npar= 353
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT919_ALERT_3_B Reflection # Likely Affected by the Beamstop ...        1
PLAT934_ALERT_3_B Number of (Iobs-Icalc)/SigmaW .gt. 10 Outliers .        2
```

Alert level C

```
PLAT241_ALERT_2_C Check High     Ueq as Compared to Neighbors for       C26
PLAT242_ALERT_2_C Check Low      Ueq as Compared to Neighbors for       C18
PLAT242_ALERT_2_C Check Low      Ueq as Compared to Neighbors for        N4
PLAT242_ALERT_2_C Check Low      Ueq as Compared to Neighbors for       C24
PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor ....       3.5
PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor ....       2.1
PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor ....       2.2
PLAT360_ALERT_2_C Short  C(sp3)-C(sp3) Bond  C17    -   C17_a  ...      1.43 Ang.
PLAT360_ALERT_2_C Short  C(sp3)-C(sp3) Bond  C23    -   C23_b  ...      1.36 Ang.
PLAT911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L=  0.600         5
PLAT912_ALERT_4_C Missing # of FCF Reflections Above STh/L=  0.600         8
PLAT918_ALERT_3_C Reflection(s) # with I(obs) much smaller I(calc)         1
PLAT939_ALERT_3_C Large Value of Not (SHELXL) Weight Optimized S .     48.36
```

Alert level G

```
PLAT005_ALERT_5_G No _iucr_refine_instructions_details in CIF ....          ?
PLAT431_ALERT_2_G Short Inter HL..A  Contact  I1     ..  N3     .      2.81 Ang.
PLAT431_ALERT_2_G Short Inter HL..A  Contact  I2     ..  N4     .      2.84 Ang.
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd.  #         2
            C12 H12 N2
```

0 ALERT level A = Most likely a serious problem - resolve or explain
2 ALERT level B = A potentially serious problem, consider carefully
13 ALERT level C = Check. Ensure it is not caused by an omission or oversight
4 ALERT level G = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
11 ALERT type 2 Indicator that the structure model may be wrong or deficient
5 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Check cif SI 8.5. Print screen of check cif for cocrystal **2.**

checkCIF/PLATON report

No syntax errors found. CIF dictionary
Please wait while processing .... Interpreting this report

Datablock: sb104_n

Bond precision: C-C = 0.0054 A Wavelength=0.71073

Cell: a=28.683(2) b=4.9270(4) c=21.429(2)
alpha=90 beta=99.92(2) gamma=90

Temperature: 296 K

	Calculated	Reported
Volume	2983.1(5)	2983.1(4)
Space group	C 2/c	C 2/c
Hall group	-C 2yc	-C 2yc
Moiety formula	C8 H12 I N O2, 0.5(C10 H8 N2)	C8 H12 I N O2, 0.5(C10 H8 N2)
Sum formula	C13 H16 I N2 O2	C13 H16 I N2 O2
Mr	359.18	359.18
Dx,g cm-3	1.599	1.599
Z	8	8
Mu (mm-1)	2.144	2.144
F000	1416.0	1416.0
F000'	1412.71	
h,k,lmax	38,6,29	38,6,29
Nref	3924	3916
Tmin,Tmax	0.391,0.807	0.444,0.541
Tmin'	0.344	

Correction method= MULTI-SCAN

Data completeness= 0.998 Theta(max)= 28.860

R(reflections)= 0.0302(2785) wR2(reflections)= 0.0859(3916)

S = 1.043 Npar= 227

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level A

PLAT431_ALERT_2_A Short Inter HL..A Contact I1 .. N2 .. 2.82 Ang.

Alert level C

PLAT241_ALERT_2_C Check High Ueq as Compared to Neighbors for C5
PLAT242_ALERT_2_C Check Low Ueq as Compared to Neighbors for C4
PLAT242_ALERT_2_C Check Low Ueq as Compared to Neighbors for C11

Alert level G

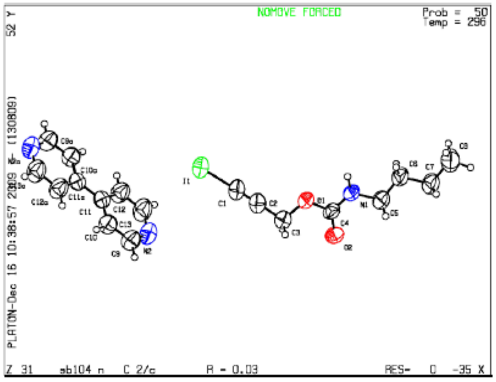
PLAT860_ALERT_3_G Note: Number of Least-Squares Restraints 60
PLAT164_ALERT_4_G Nr. of Refined C-H H-Atoms in Heavy-Atom Struct. 15

1 ALERT level A = In general: serious problem
0 ALERT level B = Potentially serious problem
3 ALERT level C = Check and explain
2 ALERT level G = General alerts; check

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
4 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low
1 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

PLATON version of 13/08/2009; check.def file version of 12/08/2009

Datablock sb104_n - ellipsoid plot



Check cif SI 8.6. Print screen of check cif for cocrystal **3.**

checkCIF/PLATON report

```
No syntax errors found.                              CIF dictionary
Please wait while processing ....                    Interpreting this report
```

Datablock: mk227

```
Bond precision:      C-C = 0.0026 A              Wavelength=0.71073
Cell:         a=10.7688(9)   b=20.204(2)    c=23.735(2)
              alpha=90       beta=94.778(2) gamma=90
Temperature: 103 K
                    Calculated                    Reported
Volume              5146.2(8)                     5146.1(8)
Space group         P 21/c                        P 21/c
Hall group          -P 2ybc                       -P 2ybc
Moiety formula      C16 H36 N, 3(C8 H12 I N O2), I C16 H36 N 1+, 3(C8 H12 N O2
                                                  I), I 1-
Sum formula         C40 H72 I4 N4 O6              C40 H72 I4 N4 O6
Mr                  1212.62                       1212.62
Dx,g cm-3           1.565                         1.565
Z                   4                             4
Mu (mm-1)           2.464                         2.464
F000                2400.0                        2400.0
F000'               2393.24
h,k,lmax            17,32,37                      16,31,37
Nref                21739                         19710
Tmin,Tmax           0.519,0.642                   0.372,0.448
Tmin'               0.509
Correction method= MULTI-SCAN
Data completeness= 0.907        Theta(max)= 34.450
R(reflections)= 0.0228( 16146)    wR2(reflections)= 0.0499( 19710)
S = 1.050              Npar= 703
```

```
The following ALERTS were generated. Each ALERT has the format
       test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.
```

Alert level B

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PLAT230_ALERT_2_B Hirshfeld Test Diff for    I3     --  C25     ..       7.49 su
PLAT431_ALERT_2_B Short Inter HL..A Contact  I1     ..  I4      ..       3.48
Ang.
PLAT431_ALERT_2_B Short Inter HL..A Contact  I1     ..  I3      ..       3.49
Ang.
PLAT431_ALERT_2_B Short Inter HL..A Contact  I1     ..  I2      ..       3.49
Ang.
```

Alert level C

```
PLAT042_ALERT_1_C Calc. and Reported MoietyFormula Strings  Differ        ?
PLAT731_ALERT_1_C Bond    Calc   0.961(16), Rep    0.961(7) ......       2.29
su-Ra
              C3   -H3A     1.555   1.555                 #        12
PLAT731_ALERT_1_C Bond    Calc   0.960(17), Rep    0.959(8) ......       2.13
su-Ra
              C4   -H4A     1.555   1.555                 #        14
PLAT731_ALERT_1_C Bond    Calc   0.961(17), Rep    0.961(8) ......       2.13
su-Ra
              C4   -H4B     1.555   1.555                 #        15
PLAT731_ALERT_1_C Bond    Calc   0.965(15), Rep    0.964(7) ......       2.14
su-Ra
              C6   -H6B     1.555   1.555                 #        22
PLAT731_ALERT_1_C Bond    Calc   0.964(15), Rep    0.965(7) ......       2.14
su-Ra
              C7   -H7A     1.555   1.555                 #        24
PLAT731_ALERT_1_C Bond    Calc   0.963(17), Rep    0.963(7) ......       2.43
su-Ra
              C7   -H7B     1.555   1.555                 #        25
PLAT731_ALERT_1_C Bond    Calc   0.963(15), Rep    0.963(7) ......       2.14
su-Ra
              C13  -H13A    1.555   1.555                 #        42
PLAT731_ALERT_1_C Bond    Calc   0.963(16), Rep    0.964(7) ......       2.29
su-Ra
              C14  -H14B    1.555   1.555                 #        46
PLAT731_ALERT_1_C Bond    Calc   0.960(18), Rep    0.960(8) ......       2.25
su-Ra
              C16  -H16B    1.555   1.555                 #        51
PLAT731_ALERT_1_C Bond    Calc   0.966(17), Rep    0.965(8) ......       2.13
su-Ra
              C24  -H24B    1.555   1.555                 #        74
PLAT731_ALERT_1_C Bond    Calc     0.96(2), Rep    0.962(8) ......       2.50
su-Ra
              C24  -H24C    1.555   1.555                 #        75
PLAT731_ALERT_1_C Bond    Calc   0.963(18), Rep    0.961(8) ......       2.25
su-Ra
              C32  -H32B    1.555   1.555                 #        97
PLAT731_ALERT_1_C Bond    Calc   0.962(19), Rep    0.962(8) ......       2.37
su-Ra
              C32  -H32C    1.555   1.555                 #        98
PLAT731_ALERT_1_C Bond    Calc     0.96(2), Rep    0.960(8) ......       2.50
su-Ra
              C40  -H40B    1.555   1.555                 #       120
```

Alert level G

```
PLAT860_ALERT_3_G Note: Number of Least-Squares Restraints .......        930
PLAT164_ALERT_4_G Nr. of Refined C-H H-Atoms in Heavy-Atom Struct.         69
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         21
             I2  -C17 -C18 -C19   -98.00  6.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         23
             C17 -C18 -C19 -O1    122.00  4.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         31
             I3  -C25 -C26 -C27    93.00 15.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         33
             C25 -C26 -C27 -O3     15.00 15.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         41
             I4  -C33 -C34 -C35   -25.00 11.00   1.555   1.555   1.555   1.555
PLAT710_ALERT_4_G Delete 1-2-3 or 2-3-4 Linear Torsion Angle ... #         43
             C33 -C34 -C35 -O5    -75.00  6.00   1.555   1.555   1.555   1.555
```

```
 0 ALERT level A = In general: serious problem
 4 ALERT level B = Potentially serious problem
15 ALERT level C = Check and explain
 8 ALERT level G = General alerts; check

15 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
 4 ALERT type 2 Indicator that the structure model may be wrong or deficient
 1 ALERT type 3 Indicator that the structure quality may be low
 7 ALERT type 4 Improvement, methodology, query or suggestion
 0 ALERT type 5 Informative message, check
```

SI. 9. References

[i] (a) Bertani, R.; Metrangolo, P.; Moiana, A.; Perez, E.; Pilati, T.; Resnati, G.; Rico-Lattes, I.; Sassi, A. *Adv.Mater.* **2002**, *14*, 1197-1201. (b) Metrangolo, P.; Meyer, F.; Pilati, T.; Proserpio, D.M.; Resnati, G. *Chem.-Eur.J.* **2007**, *13*, 5765-5772. (c) Lucassen, A. C. B.; Zubkov, T.; Shimon, L. J. W.; van der Boom, M. E. *CrystEngComm* **2007**, *9*, 538-540. (d) Cincic, D.; Friščić,T.; Jones, W. *CrystEngComm* **2011**, *13*, 3224-3231.(e) Aakeröy, C.B.; Schultheiss, N.C.; Rajbanshi, A.; Desper, J.; Moore, C. *Cryst.Growth Des* .**2009**, *9*, 432-441. (f) Prasang, C.; Whitwood, A.C.; Bruce, D.W. *Cryst. Growth Des.* **2009**, *9*, 5319-5326. (g) Padgett, C.W.; Walsh, R.D.; Drake, G.W.; Hanks, T. W.; Pennington, W.T. *Cryst.GrowthDes.* **2005**, *5*, 745-753.

[ii] (a) Farina, A.; Meille, S.V.; Messina, M.T.; Metrangolo, P.; Resnati, G.; Vecchio, G. *Angew.Chem.,Int.Ed.* **1999**, *38*, 2433-2436. (b) Fox, D. B.; Liantonio, R.; Metrangolo, P.; Pilati,T.;Resnati, G. *J. Fluorine Chem.* .**2004**, *125*, 271-281.(c) Schoth, R.-M.; Lork, E.; Kolomeitsev, A. A.; Roschenthaler, G.-V. *J. Fluorine Chem.***1997**, *84*, 41-44 (d) Gattuso, G.; Pappalardo, A.; Parisi,M.F.; Pisagatti,I.; Crea, F.; Liantonio, R.; Metrangolo, P.; Navarrini, W.; Resnati, G.; Pilati,T.; Pappalardo, S. *Tetrahedron* **2007**, *63*, 4951-4958. (e) Casnati, A.; Cavallo, G.; Metrangolo, P.; Resnati, G.; Ugozzoli, F.; Ungaro, R. *Chem.-Eur.J* .**2009**, *15*, 7903-7912.