Electronic Supplementary Material (ESI) for CrystEngComm.

Electronic Supporting Information (ESI)

Polymorphs and cocrystals of Haloprogin: An antifungal agent

Michele Baldrighi,[a] Davide Bartesaghi,[a] Gabriella Cavallo,[a] Michele R. Chierotti,[b] Roberto Gobetto,[b] Pierangelo Metrangolo,*[a] Tullio Pilati,[a] Giuseppe Resnati,*[a] and Giancarlo Terraneo*[a]

[a] NFMLab-Laboratory of Nanostructured Fluorinated Materials (NFMLab), Department of Chemistry, Materials, and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Via L. Mancinelli 7, 20131 Milan, Italy.

[b] Department of Chemistry, Università di Torino, Via P. Giuria 7, 10125 Torino, Italy.

Index:

Synthesis of (1,2,4-trichloro-5-[(3-iodoprop-2-yn-1-yl)oxy]benzene, 1)

1.1. Synthesis of 1,2,4-trichloro-5-(prop-2-yn-1-yloxy)benzene (A): in a round bottom flask equipped with a magnetic stirrer were mixed 1.0 g of 2,4,5-trichlorophenol (5.06 mmol), 662.6 mg of 3-bromo-1-propyne (5.57 mmol) and 768.6 mg (5.57 mmol) of potassium carbonate dissolved in 8 mL of acetone. The reaction was stirred under reflux for 5 hours, and allowed to cool down, then the solids were filtered and the solution was evaporated under vacuum, giving 1.165 g (98%) of pure product. M.p. 63-64 °C; FTIR (selected bands):3092, 2984, 2122, 1476, 1457, 1235, 1080, 1024, 870, 672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47 (s, 1H), 7.18 (s, 1H), 4.76 (d, *J* = 2.4 Hz, 2H), 2.59 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 152.32, 131.31, 131.28, 125.55, 122.83, 116.23, 77.24, 77.12, 57.52.

1.2. Synthesis of 1,2,4-trichloro-5-((3-iodoprop-2-yn-1-yl)oxy)benzene (Haloprogin, 1): a round bottom flask equipped with a magnetic stirrer was charged with 200 mg of **A** (0.85 mmol) dissolved in 15 mL of methanol. A solution of iodine (284 mg, 1.12 mmol) in methanol and a 10% water solution of sodium hydroxide (77.5 mg, 1.94 mmol) were dropped simultaneously over 20 minutes. The reaction was stirred overnight, then 20 mL of water were added, causing the formation of a white precipitate. The mixture was stirred for 30 min, then the solid material was recovered by filtration, washed two times with cold water and dried over a nitrogen flux, affording 221 mg of the pure product (72% yield). M.p.: 111-112 °C; FTIR (selected bands): 2187, 1581, 1472, 1453, 1232, 1077, 1028, 866, 724, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (s, 1H), 7.15 (s, 1H), 4.89 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.20 (C4), 131.22(C8), 131.13(C6), 125.51(C7), 122.73 (C5), 116.16 (C9), 87.64 (C2), 58.91 (C3), 6.97 (C1). ^{13}C NMR (101 MHz, C_5D_5N) δ (ppm) 152.65 (C4), 131.14 (C8), 131.10 (C6), 124.62 (C7), 122.40(C5), 116.14 (C9), 86.78(C2), 59.06 (C3), 18.58 (C1).

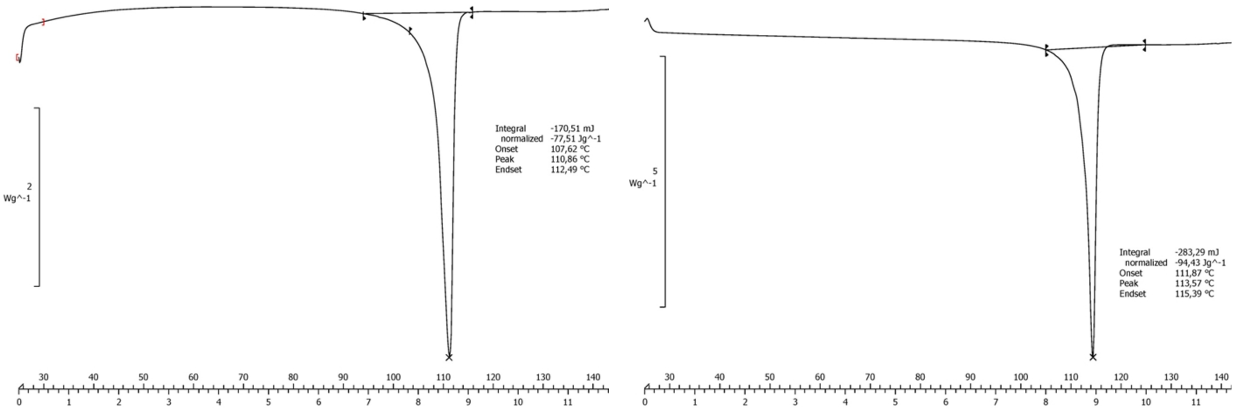
1.3. Crystallization experiments.

General crystallization procedure: in a 2.5 mL glass vial 10 mg of **1** (0.027 mmol) were dissolved in 1.5 mL of the selected organic solvent or solvent mixture (see below). The vial was left open under a hood at room temperature in order to allow the evaporation of the solvent. The identification of the obtained form was performed by checking the unit cell parameters of selected crystals.

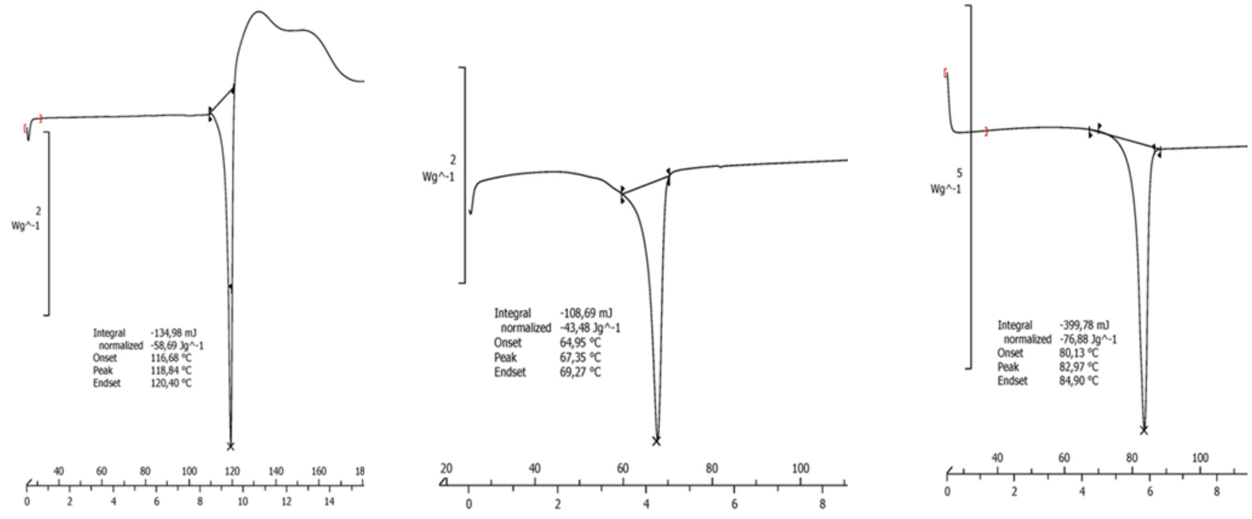
Crystallization solvent	Obtained form
$CHCl_3$	**1a**
MeOH	**1a**
CH_2Cl_2	**1a**
CH_3CN	**1a**
DMSO	**1a**
$CHCl_3$/MeOH 9:1; 1:1; 1:9	**1a**
$CHCl_3$/MeOH/CH_3CO_2Na	**1b and 1c**

1. Thermal analysis (DSC plots)

2.1. DSC of polymorph 1a (left) and 1b (right).

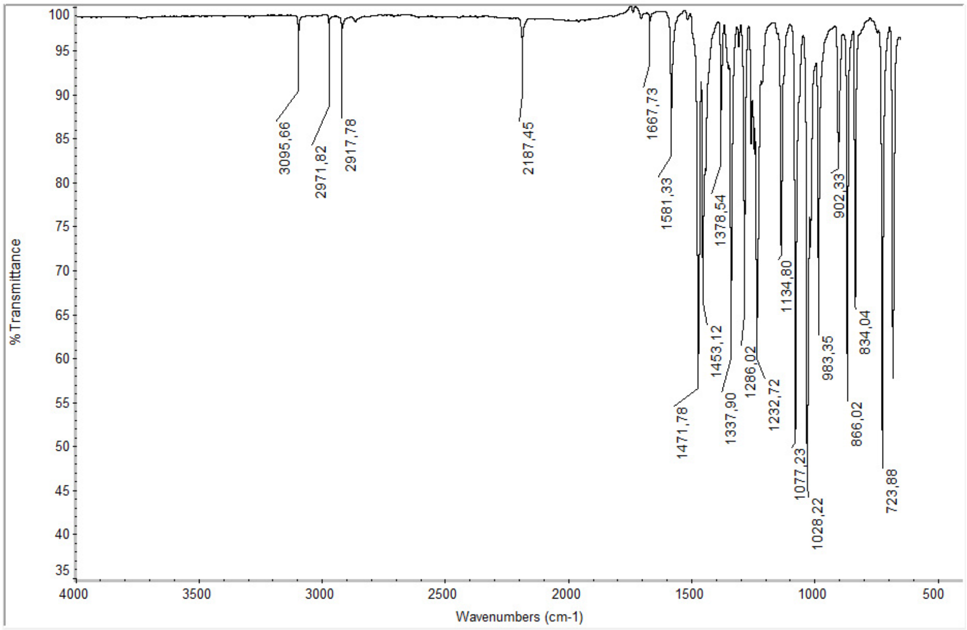


2.2. DSC of 4 (left), 5a (mid), and 5b (right).

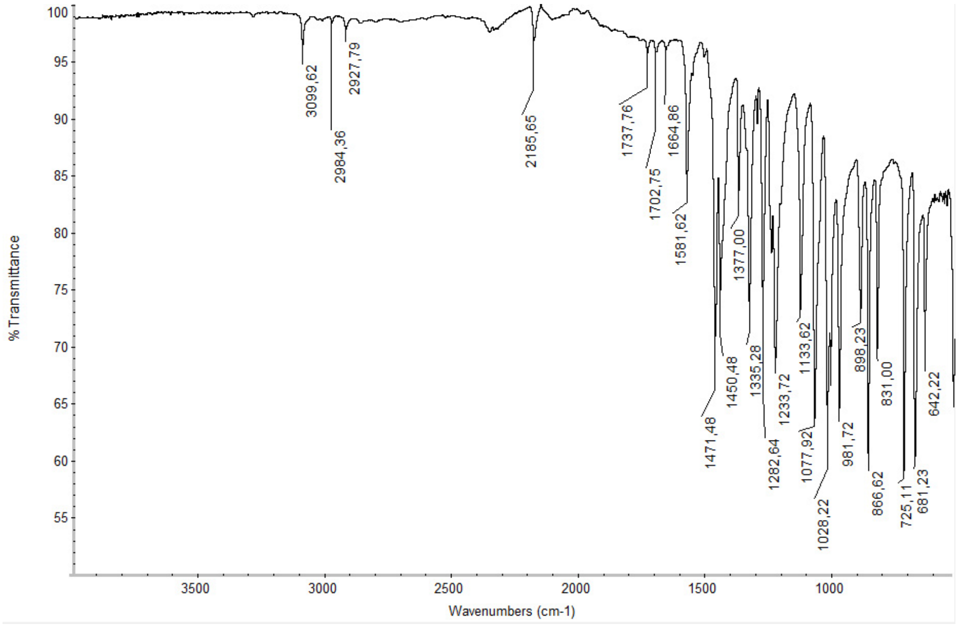


3. Vibration spectra (FTIR)

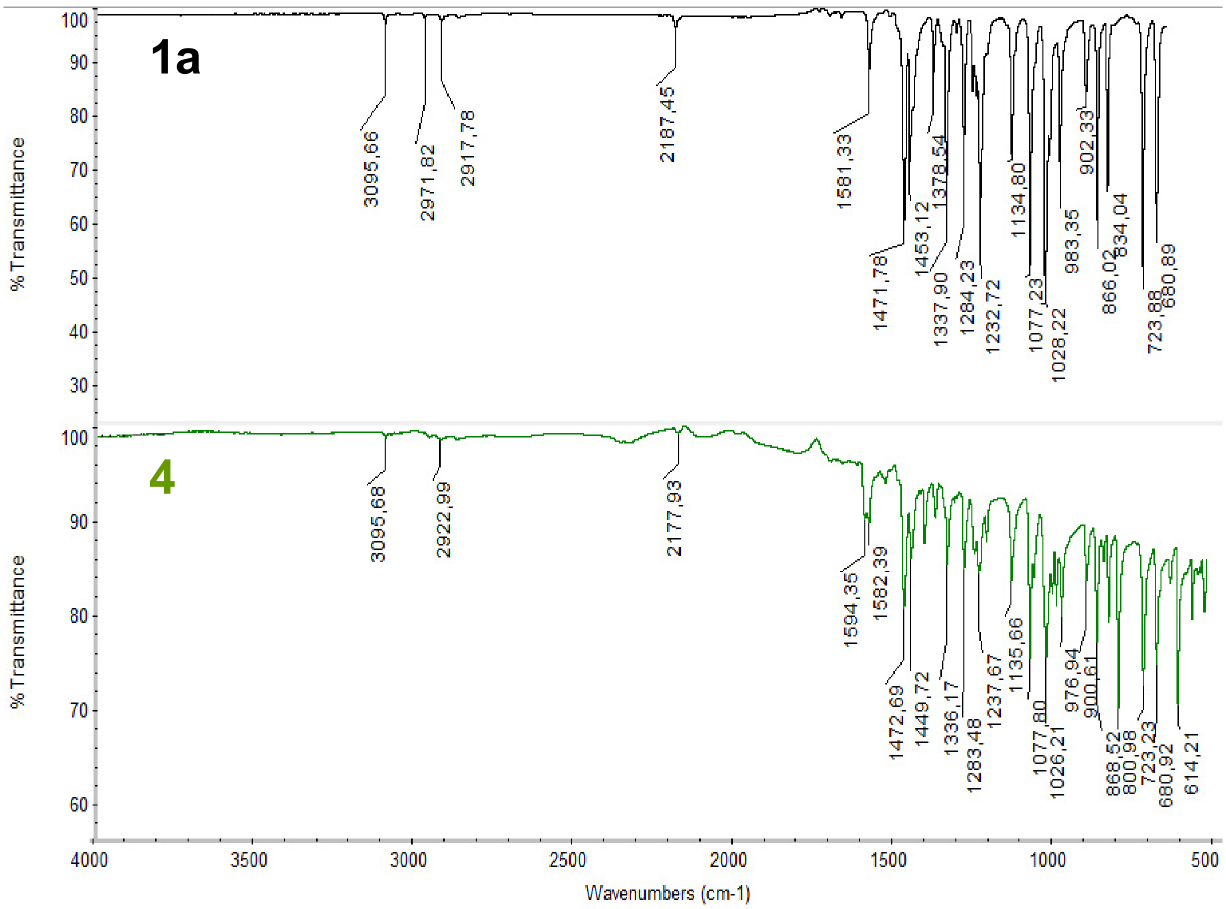
3.1. FTIR spectrum of 1a.



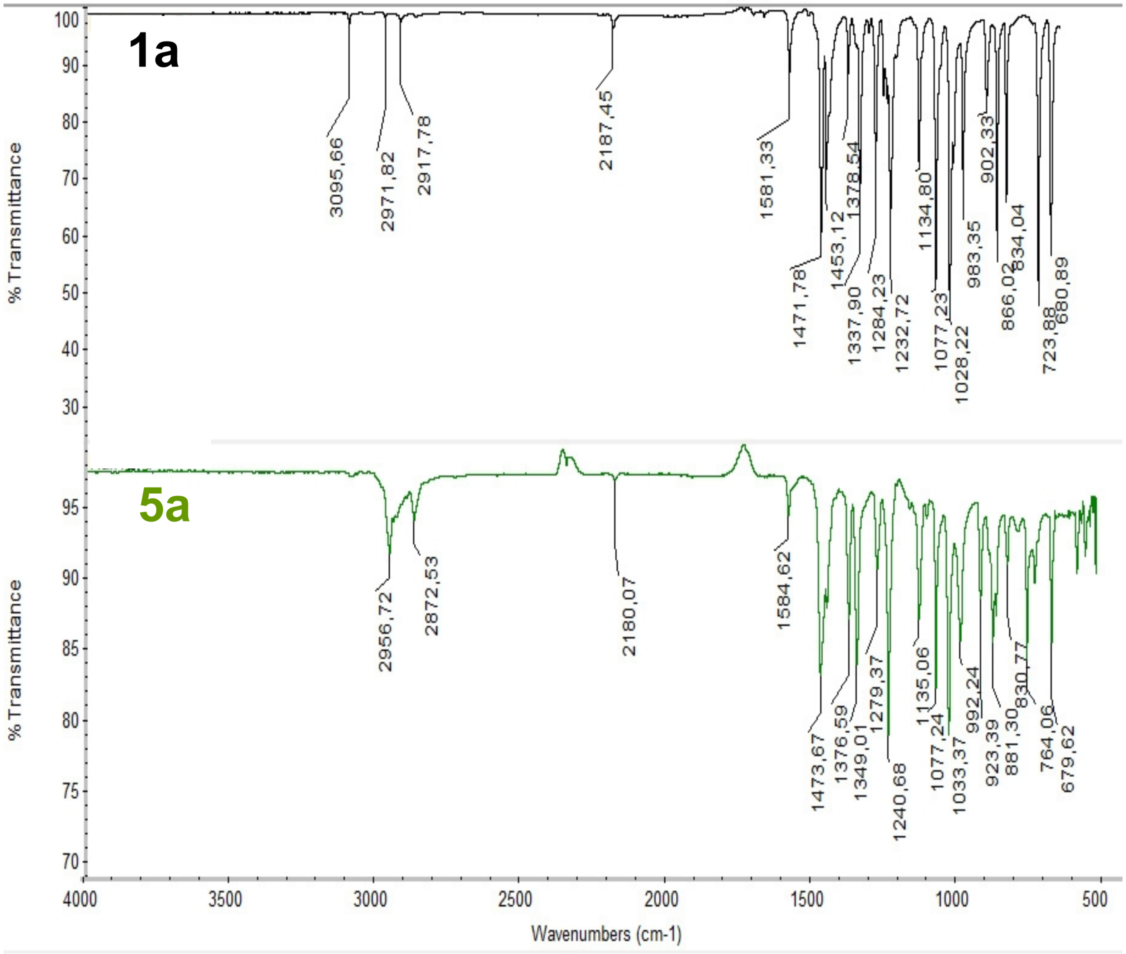
3.2. FTIR spectrum of 1b.



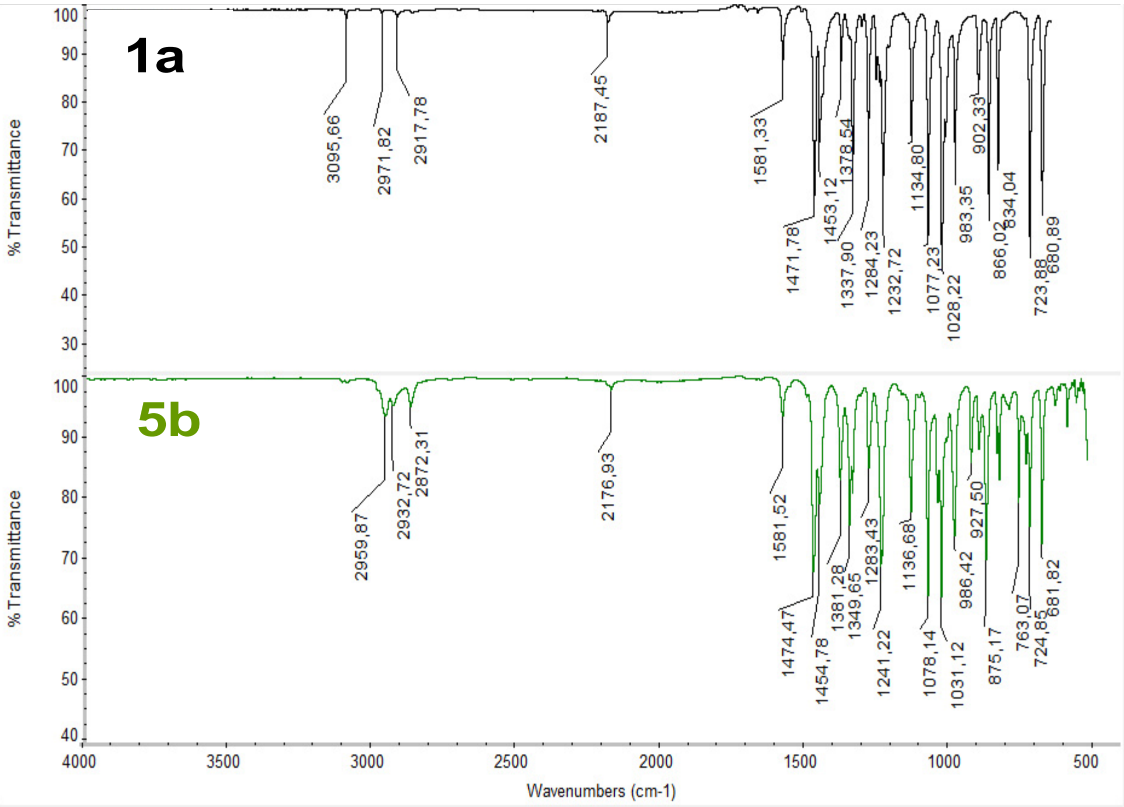
3.3. FTIR spectrum of 4.



3.4. FTIR spectrum of 5a.

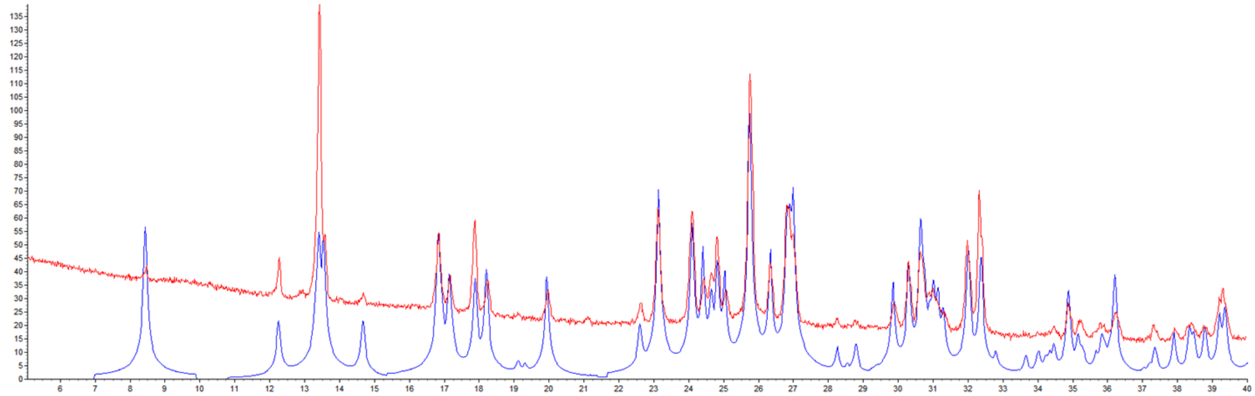


3.4. FTIR spectrum of 5b.



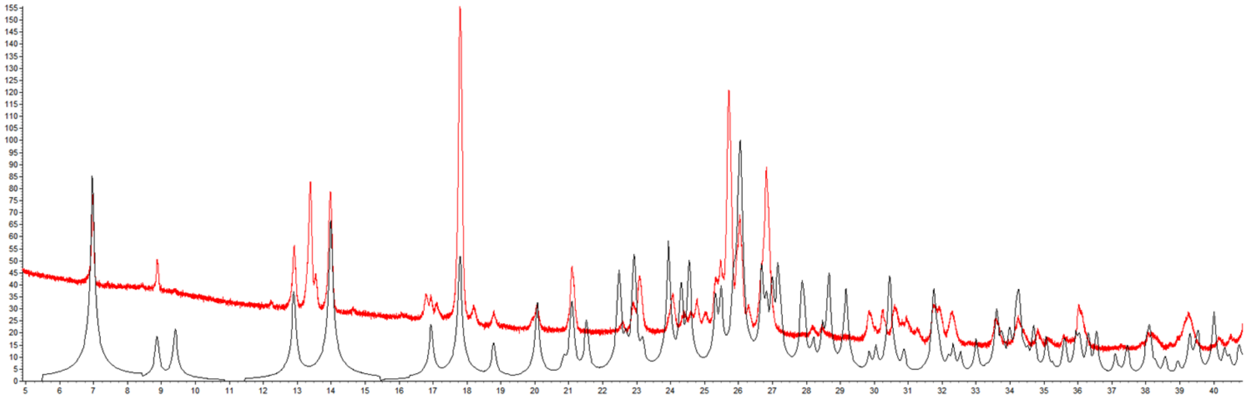
4. Powder XRD

4.1. PXRD pattern of polymorph 1a.

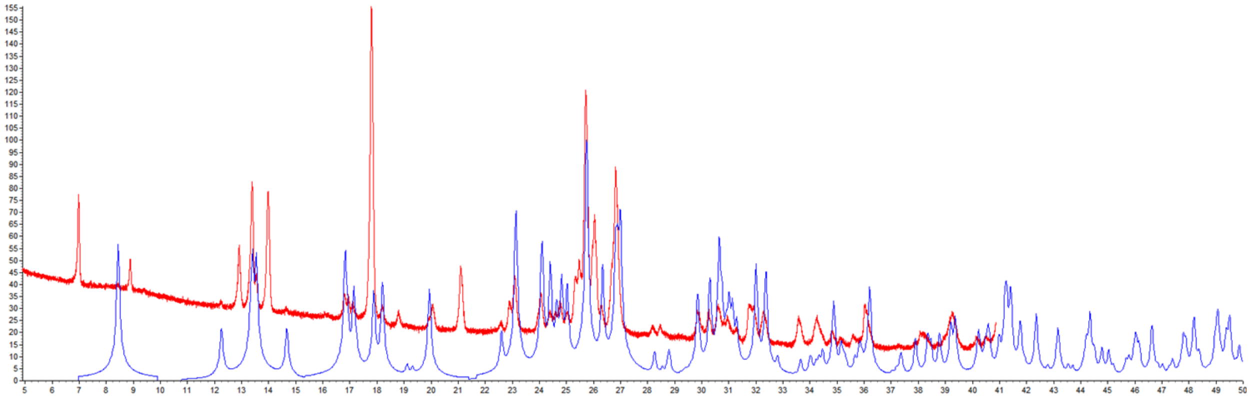


Red line: experimental powder pattern of **1a**. Blue line: simulated from single crystal of **1a**.

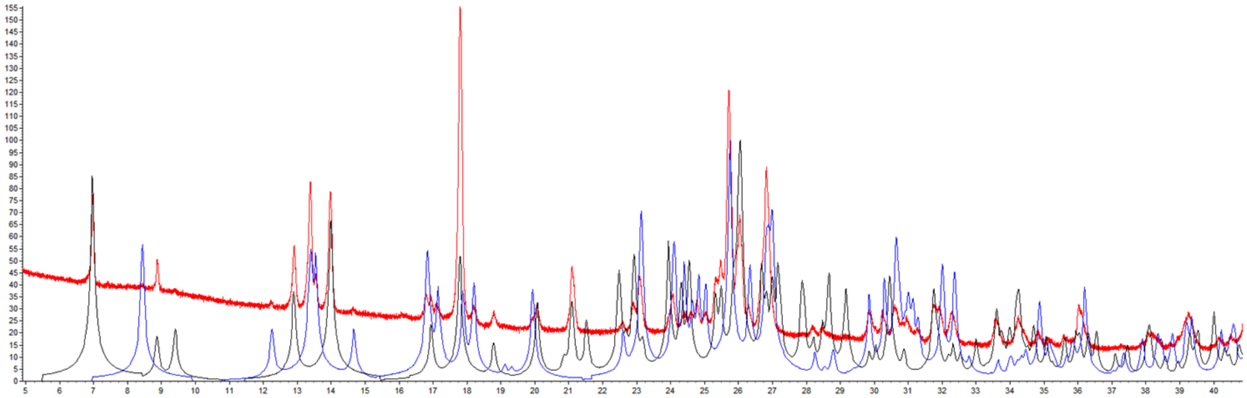
4.2. PXRD pattern of mixture of polymorphs 1a and 1b.



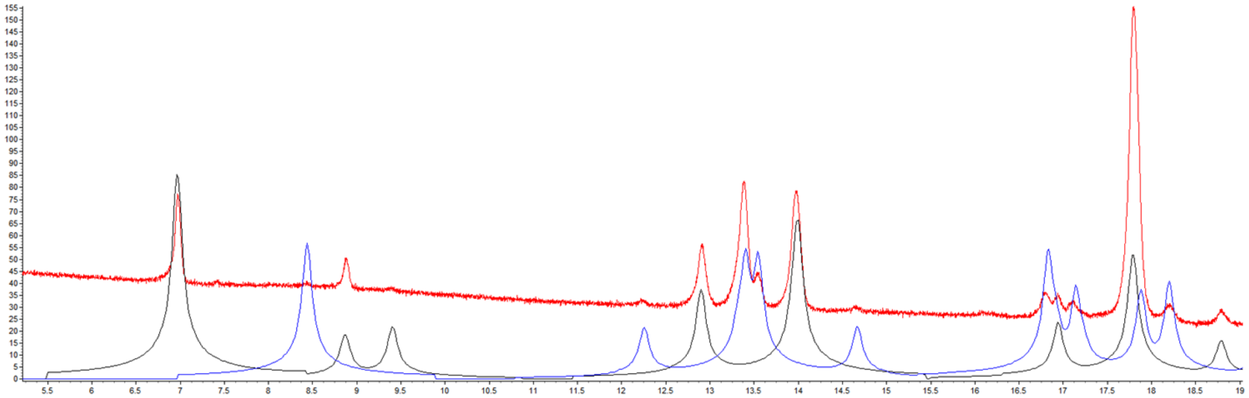
Red line: experimental powder pattern of **1b** and **1a** mixture. Black line: simulated from single crystal of **1b**.



Red line: experimental powder pattern of **1b** and **1a** mixture. Blue line: simulated from single crystal of **1a**.



Red line: experimental powder pattern of **1b** and **1a** mixture. Blue line: simulated from single crystal of **1a**. Black line: simulated from single crystal of **1b**.

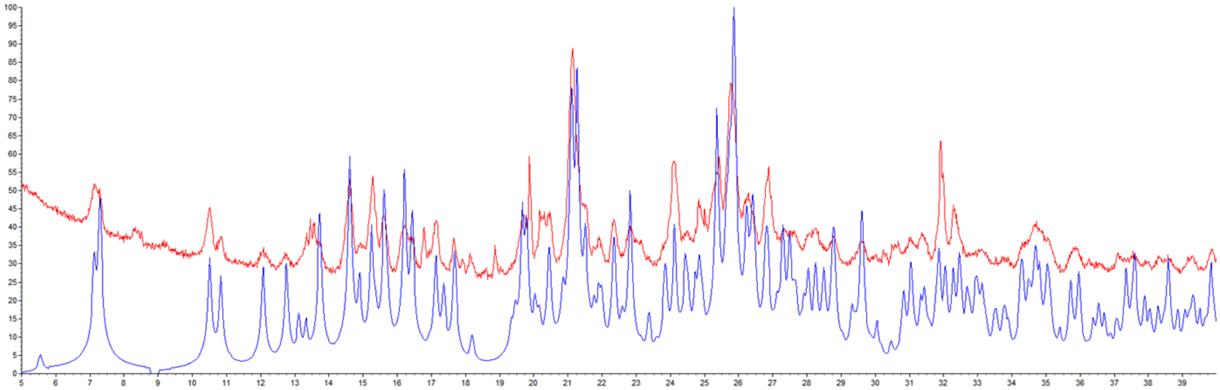


Region between 5.5° and 19° (2 theta). Red line: experimental powder pattern of **1b** and **1a** mixture. Blue line: simulated from single crystal of **1a**. Black line: simulated from single crystal of **1b**.

The polymorph **1b** was obtained when a chloroform solution of haloprogin was allowed to slowly diffuse into a saturated methanol solution of sodium acetate and the resulting solvents mixture was slowly evaporated at room temperature. Few crystals of **1b** were obtained along with massive quantities of **1a**. The samples used in PXRD experiment were obtained by selecting the **1b** crystals over **1a**. Therefore since **1b** crystals were always obtained along with large quantities of **1a** the reported powder patterns show a mixture of **1b** and **1a**.

The number of crystals for the polymorph **1c** were very few (much lower than **1b**) and extremely unstable. The low stability and the insufficient amount of this sample did not allow for the obtainment of PXRD data.

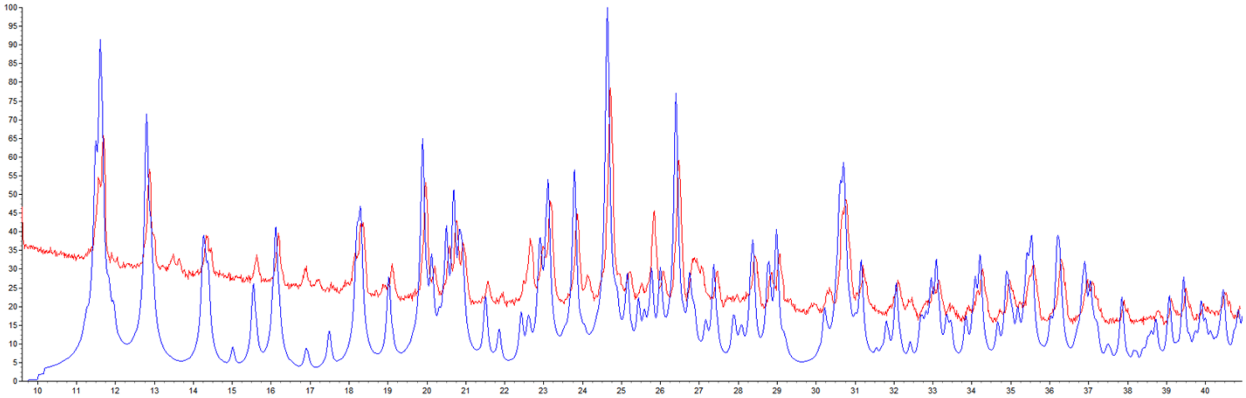
4.2. PXRD pattern of co-crystal 4.



Red line: experimental powder pattern of **4**. Blue line: simulated from single crystal of **4**.

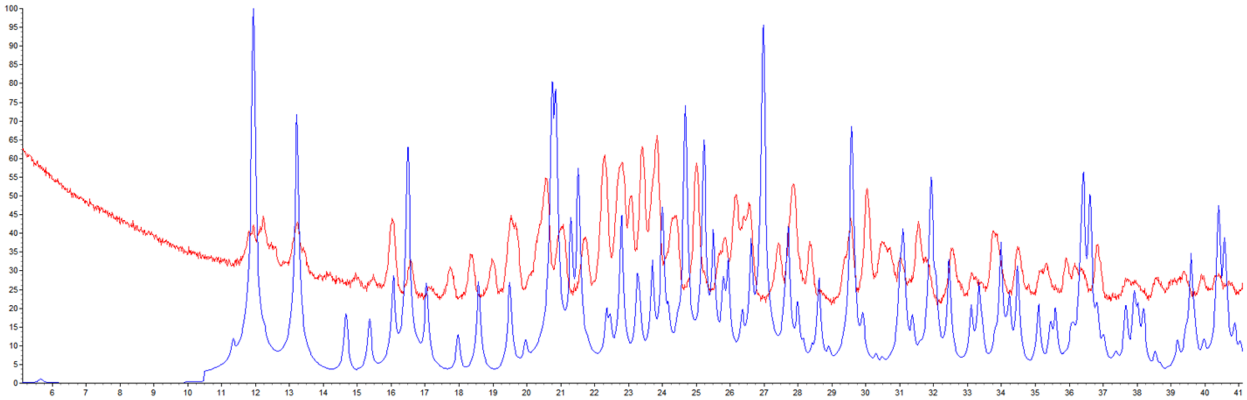
The sample of **4** was prepared by slow evaporation and then was finely ground.

4.3. PXRD pattern of co-crystal 5a.



Red line: experimental powder pattern of **5a**. Blue line: simulated from single crystal of **5a**.

4.4. PXRD pattern of co-crystal **5b**.



Red line: experimental powder pattern of **5b**. Blue line: simulated from single crystal of **5b**.

5 SSNMR

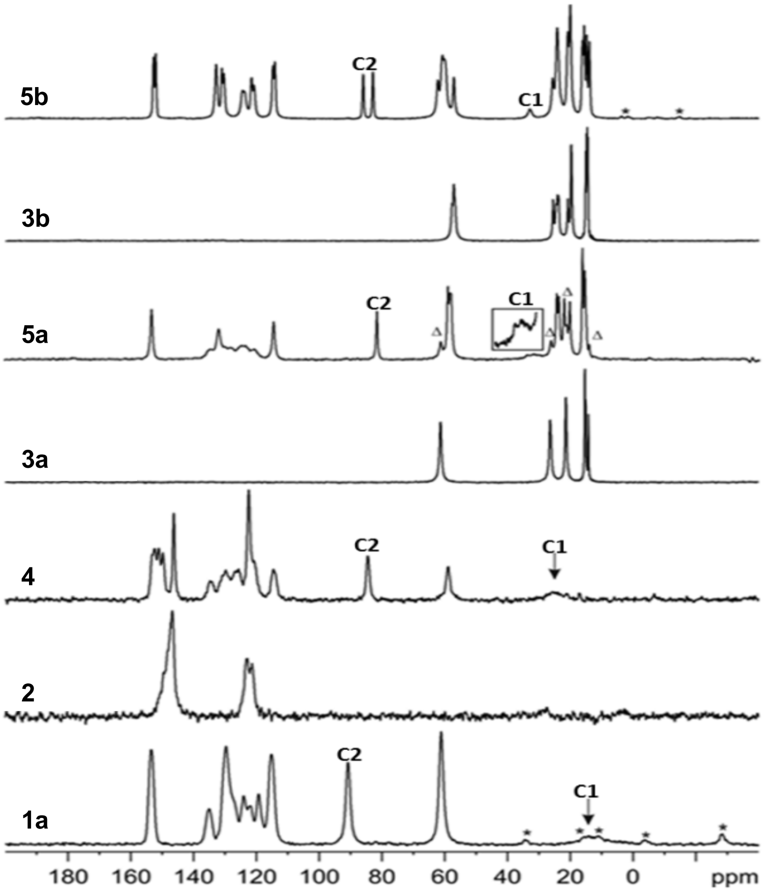
5.1. Chemical shift assignments

Table S1. ^{13}C and ^{15}N chemical shift assignments for pure reagents (**1a**, **2**, **3a**, and **3b**), and for the **4**, **5a**, and **5b** co-crystals.

Atom	note	**2**	**3**	**3B**	**1A**	**4**	**5A**	**5B**
$C1^A$	CH[a]/CH_2[b]	149.6/148.2/146.9	61.3	56.9/57.3/57.9		151.2/149.8	58.0/58.3	57.3/62.4
$C2^A$	CH[a]/CH_2[b]	123.1/121.5	26.3	23.9/24.3/24.7/25.7		122.4	23.7/24.5	24.4/25.7
$C3^A$	C_q[a]/CH_2[b]	146.9	21.3	19.9/21.0		146.4	20.3/22.0	20.2/21.0
$C4^A$	CH_3	-	14.1/15.0/15.2	14.5/14.8/15.0/15.3			15.5/16.2	14.1/14.9/15.8/16.3
C1	C_q				14.4	25.1	31.6	33.0
C2	C_q				91.1	84.6	81.5	83.1/86.2
C3	CH_2				61.3	58.9	59.0	60.3/60.9
C4	C_q				153.7	152.5	153.1	152.2/152.9
C5	C_q				119.5[c]/122.3[c]	120.8	120.5[c]/123.3[c]	121.0[c]/121.7[c]
C6	CH				129.9	129.8	131.9	130.5/131.2
C7	C_q				124.3/127.6[c]/sh	126.5	123.7[c]/128.1[c]	124.0/124.6
C8	C_q				135.4	134.8	134.3	133.0
C9	CH				115.5	114.6	114.4	114.3/115.0
N	N_t	289.0	-	-	-	273.7	-	-

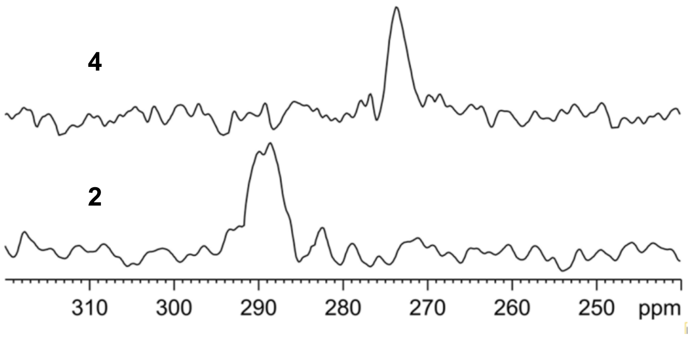
[a] Bipyridine. [b] Tetra *n*-butylammonium iodide or chloride. [c] Two values observed due to a second-order effect of dipolar coupling to the quadrupolar chlorine-35/37 (both spin 3/2) or iodine-127 (spin 5/2) nuclei which splits or broadens the signals.

5.2. Full ^{13}C CPMAS spectra of 5b, 3b, 5a, 3a, 4, 2, and 1a from top to bottom, respectively.



^{13}C (100.65 MHz) CPMAS spectra of all reagents and co-crystals were recorded at the spinning of 12/13 kHz. Asterisks and triangles mark spinning sidebands and unreacted **3a**, respectively. Assignments of relevant peaks are also reported.

5.3. ^{15}N CPMAS spectra.



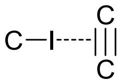
^{15}N (40.55 MHz) CPMAS spectra of pure **2** (bottom) and of **4** (top) recorded at the spinning of 9 kHz.

6 Cambridge Structural Database (CSD) Search, version 5.34, update 1 (Nov. 2012)

6.1. XB contacts involving the iodoethynyl moiety and π-electrons on triple bond.

The CSD search has been performed on the fragment reported below. Restrictions: 3D coordinates, no disordered structure, no errors, no polymeric structure. Angle between C-I···centroid of triple bond (C*) between 140° and 180°, distance between I and centroid of triple bond between 2 Å and 3.8 Å.

Fragment used in the CSD search.



N° of hits: 13

Distance I···C* median value: 3.466 Å.

Angle C-I···C* median value: 165.6°

CSD Refcode
AVIYEK
BAMPIQ
BOBGUV
DIACET
ELIMES
QAQTOS
RAXKOR
RETRIR
SIVYEC
TOJBUQ
XASWOD
XUNRII
YAPCUP