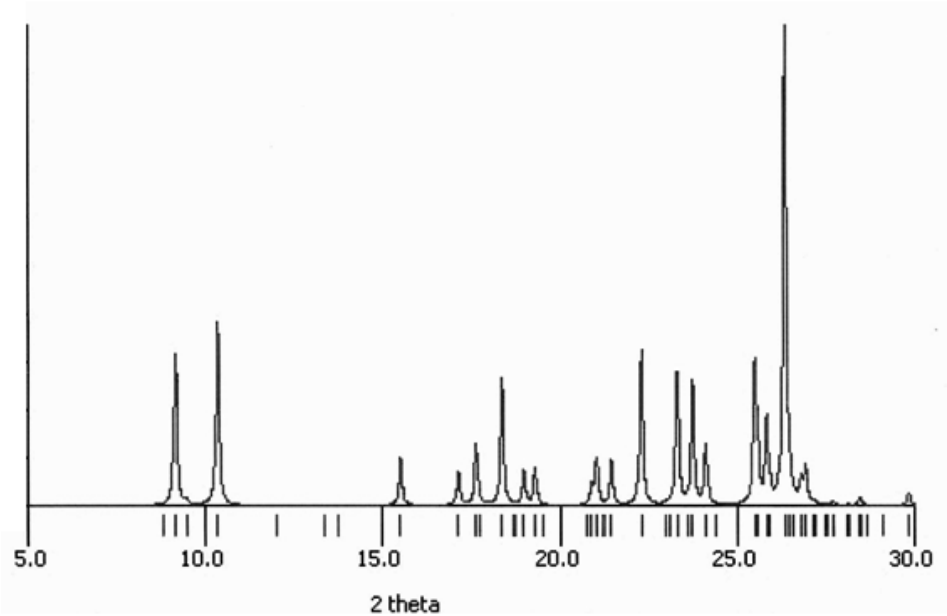
Powder X-Ray Diffraction (PXRD)

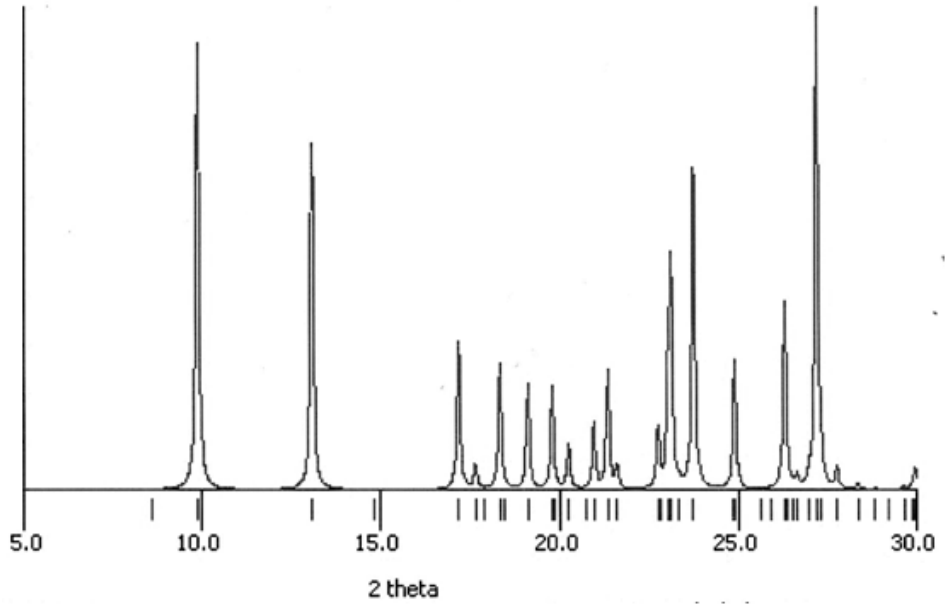
Powder X-ray diffraction data were collected at 298 K on a Siemens D5000 instrument using monochromated CuKα_1 radiation (λ = 1.5406 Å).

For the slurry experiments, the relatively high backgrounds are due to small sample sizes removed during the slurrying.

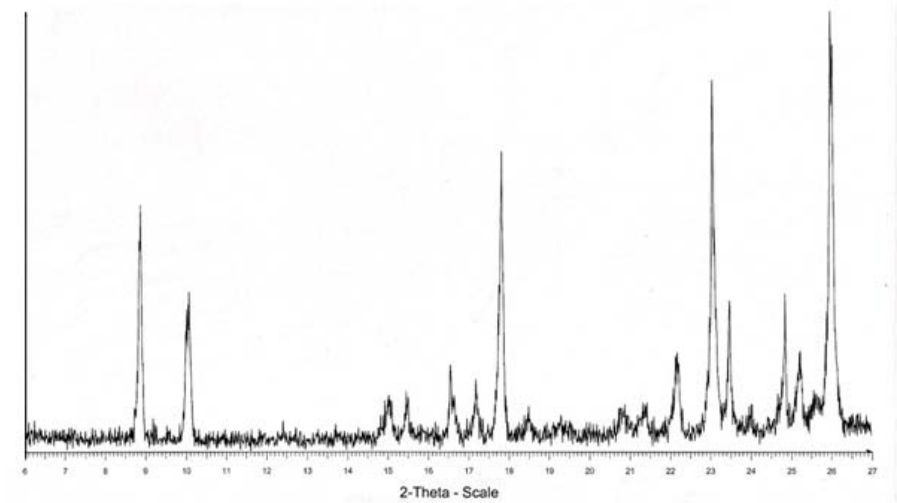
5-Cl-Aspirin



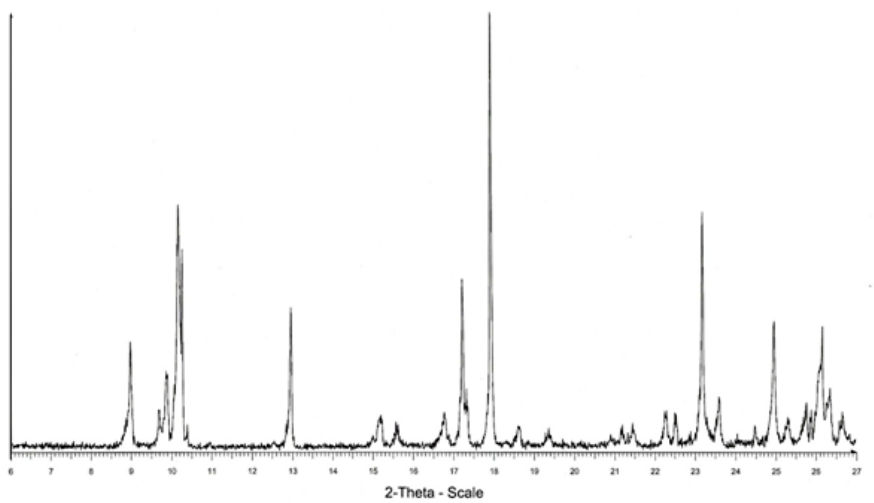
Simulated pattern for **5-Cl-A** form I
(120 K; Hursthouse *et al.*, 2010)



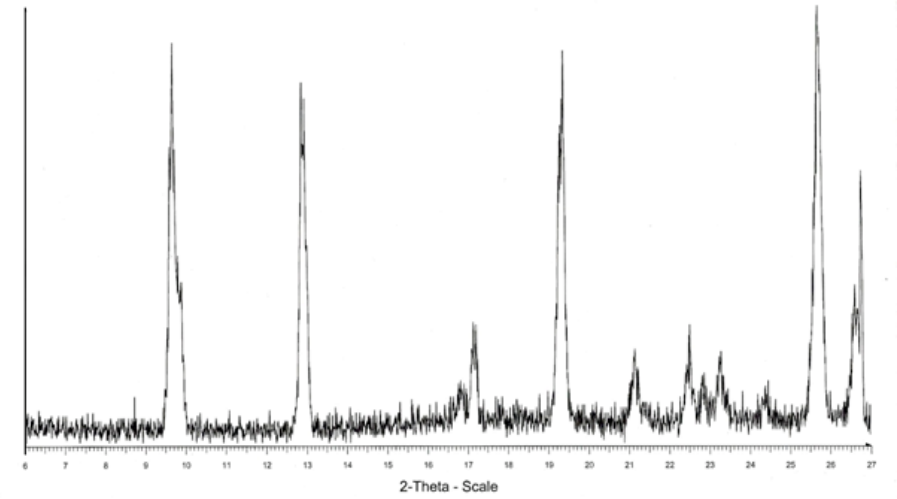
Simulated pattern: **5-Cl-A** form II (150 K)



Synthesis of 5-Cl-A with heating at 60°C for 10 mins: initial solid product – only form I



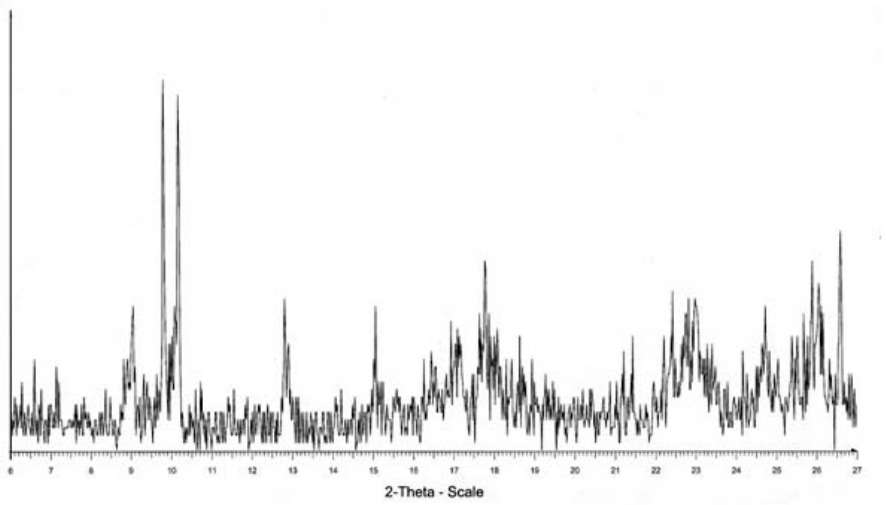
Synthesis of 5-Cl-A with heating at 60°C for 20 mins: initial solid product – mixture of forms I and II



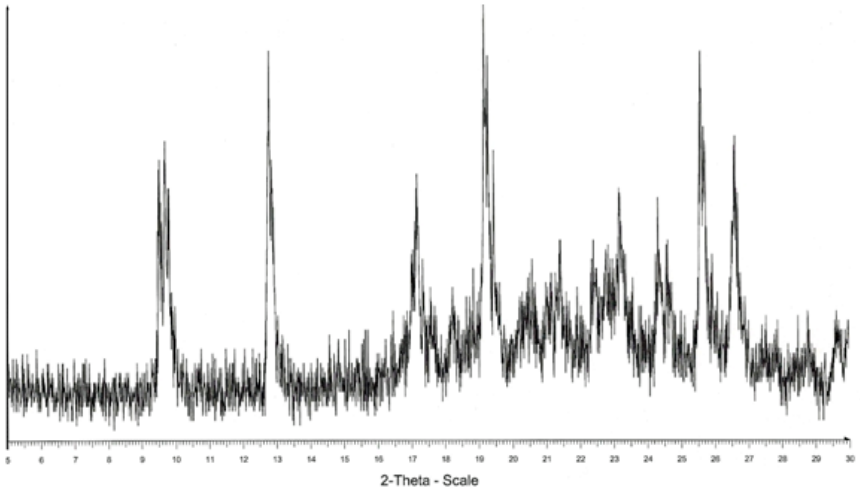
Synthesis of 5-Cl-A with heating at 60°C for 2 hrs: initial solid product – only form II

Summary for 5-Cl-A synthesis:

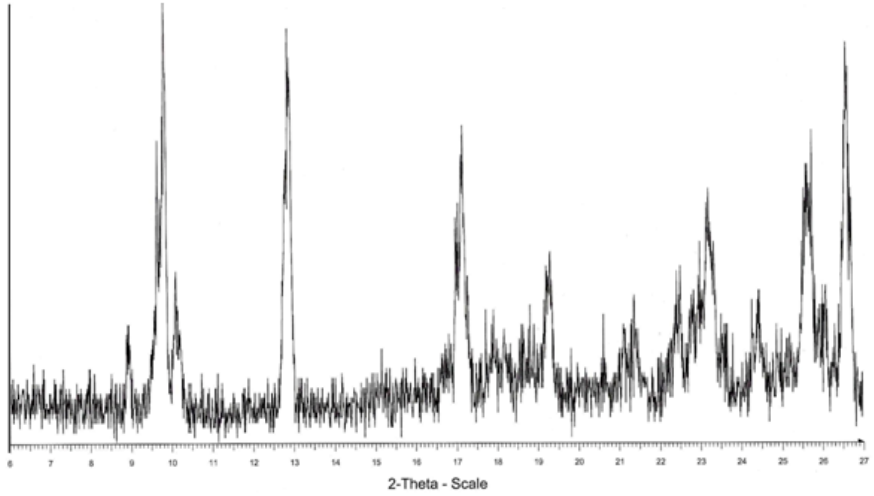
- During reaction step (5-Cl-salicylic acid in acetic anhydride with H_2SO_4(aq) at 60°C), the duration of heating determines the polymorph produced as the initial solid product.
- **5-Cl-AA** is not visible in any of the product PXRD patterns, but shown to be present by ^{13}C NMR (see section S5).



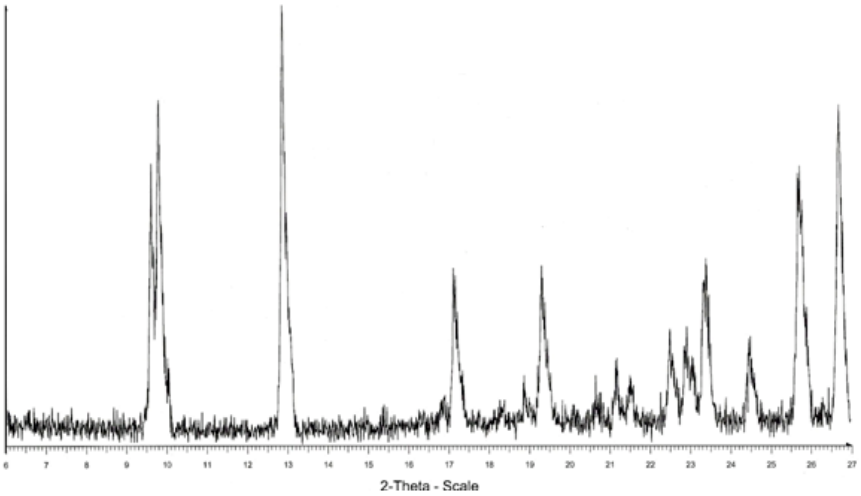
5-Cl-A form I slurry in acetonitrile (1 day):
mixture of forms I and II



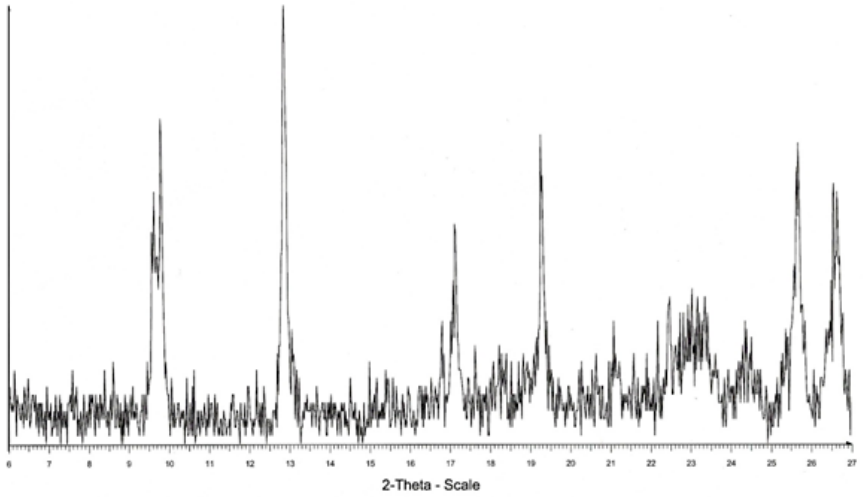
5-Cl-A form I slurry in acetonitrile (7 days):
only form II



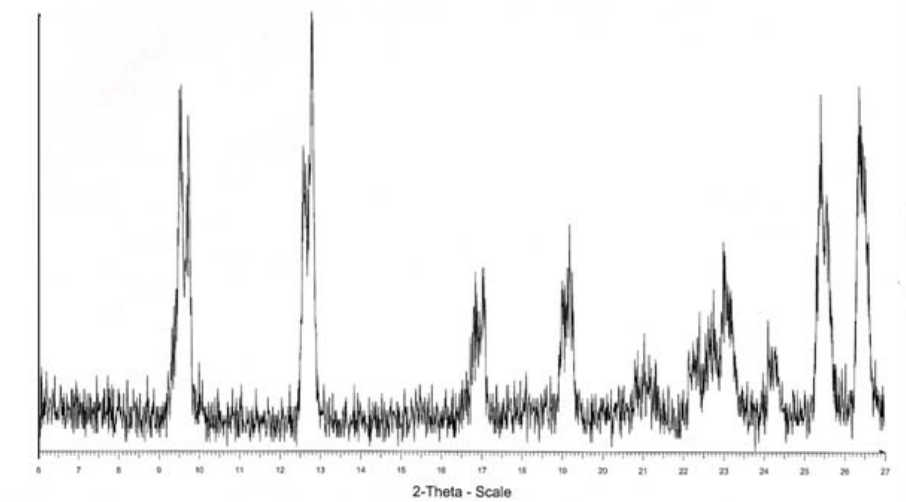
5-Cl-A form I slurry in acetone (1 day):
mixture of forms I and II



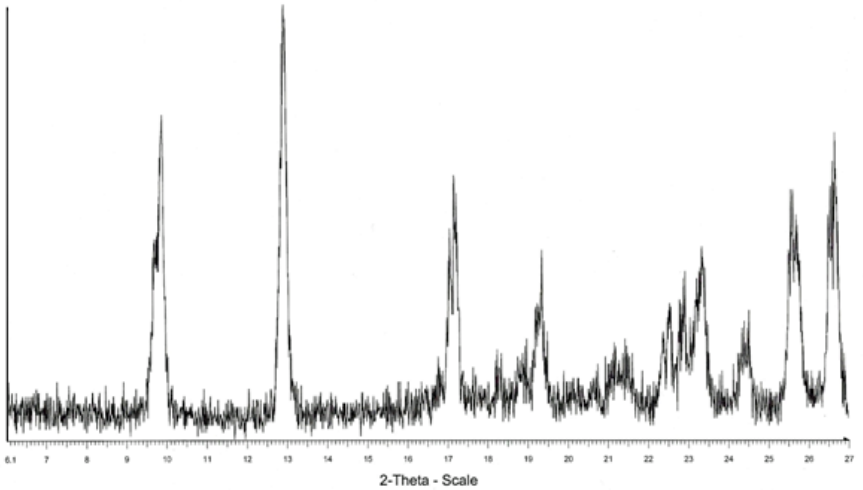
5-Cl-A form I slurry in acetone (7 days):
only form II



5-Cl-A form I slurry in ethanol (7 days):
only form II



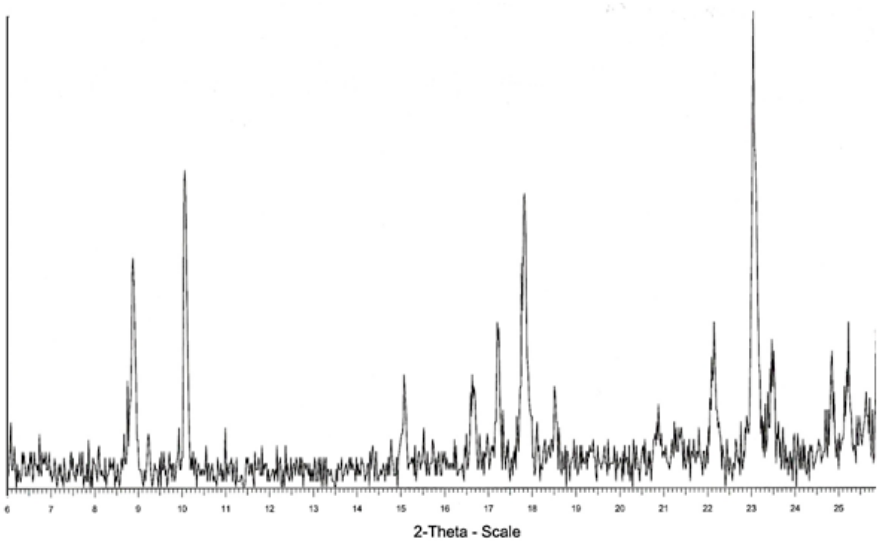
5-Cl-A form I slurry in 2-propanol (7 days):
only form II



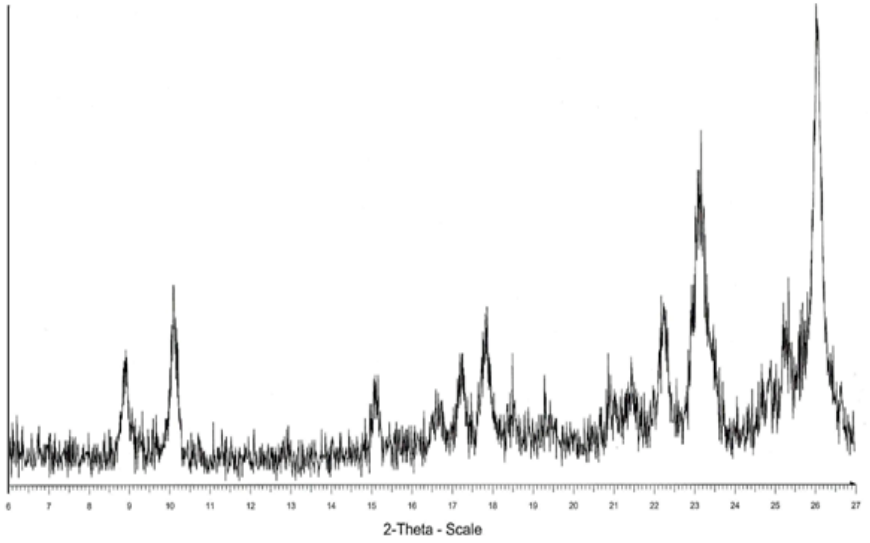
5-Cl-A form II slurry in acetonitrile (7 days):
only form II

Summary for 5-Cl-A slurrying experiments:

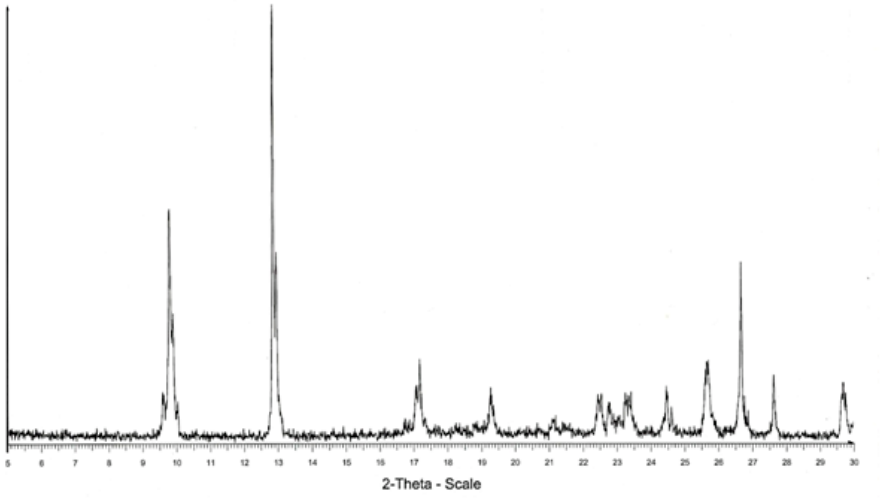
- Form I transforms to form II over a period of days in the following examined solvents: acetonitrile, acetone, ethanol, 2-propanol
- Control tests starting with form II show identical behaviour (only acetonitrile shown)



5-Cl-A freeze drying (from solution in acetone): only form I



5-Cl-A solid-state grinding (Retsch MM400 ball mill, 25 ml vessel, one steel ball Ø10 mm, 30 mins, 17.5 Hz): only form I

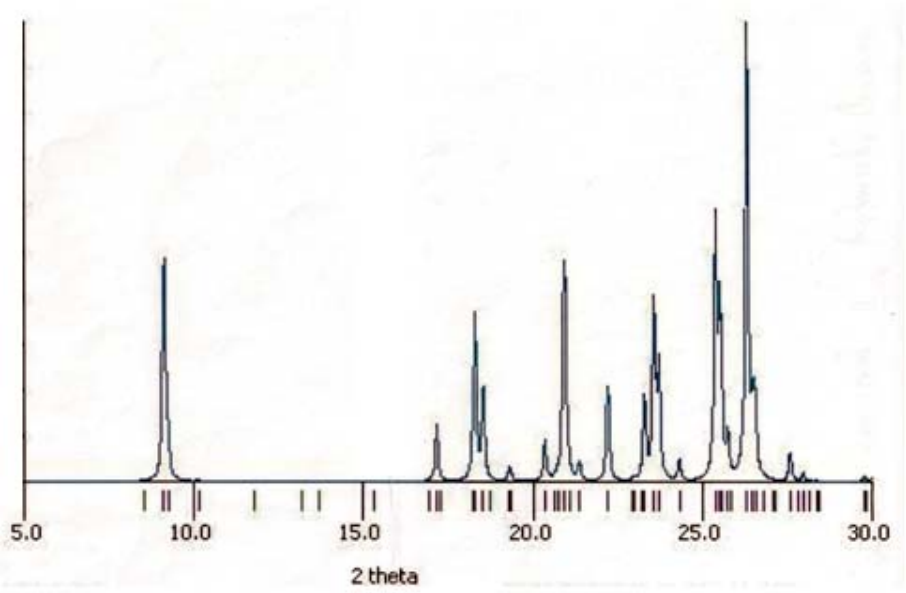


Recrystallisation of 5-Cl-A from EtOH/acetone in the presence of 10 mol % 5-Cl-AA (slow evaporation, *ca* 3 days) – only form II

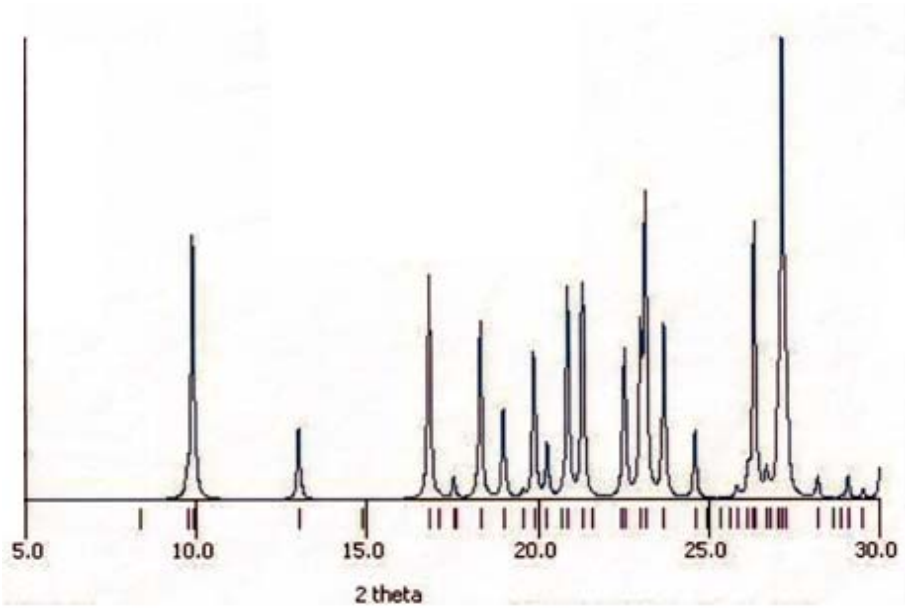
5-Cl-A:

- Freeze drying produces only form I
- Solid-state grinding converts form II→form I
- In all solvents used, slow recrystallisation usually provides mixtures of forms I and II. However, slow recrystallisation with addition of **5-Cl-AA** (5–20 mol %) produces only form II

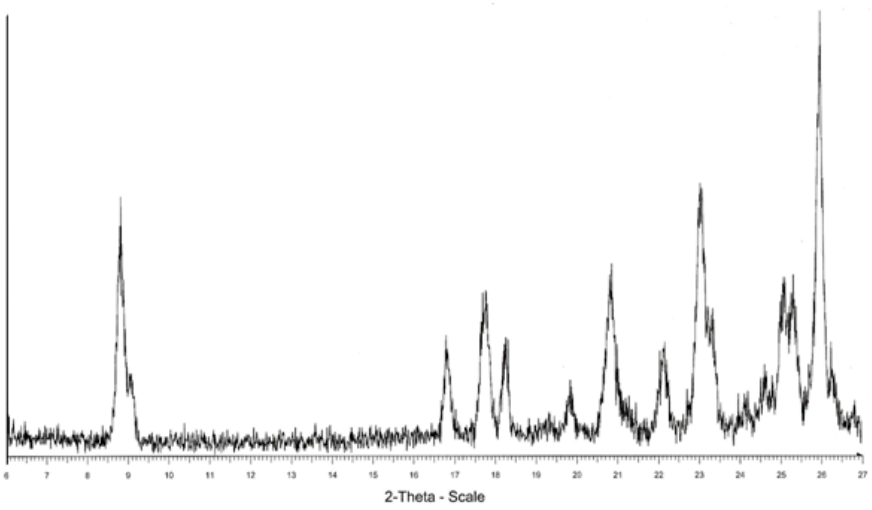
5-Br-Aspirin



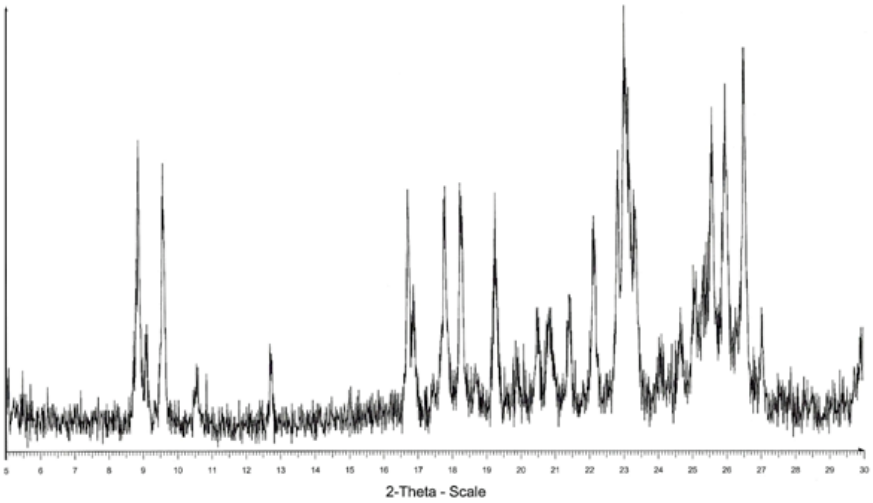
Simulated pattern for **5-Br-A** form I
(120 K; Hursthouse *et al*., **2010**)



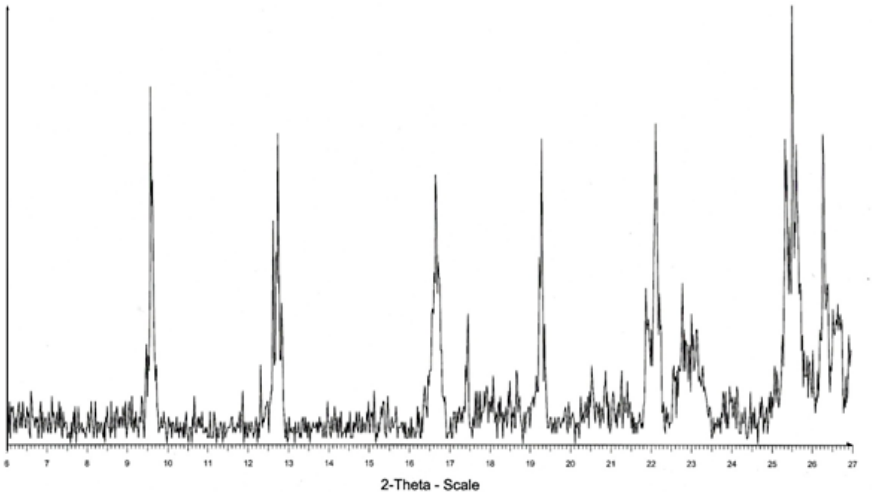
Simulated pattern: **5-Br-A** form II (150 K)



Synthesis of 5-Br-A with heating at 60°C for 20 mins: initial synthesis product – only form I



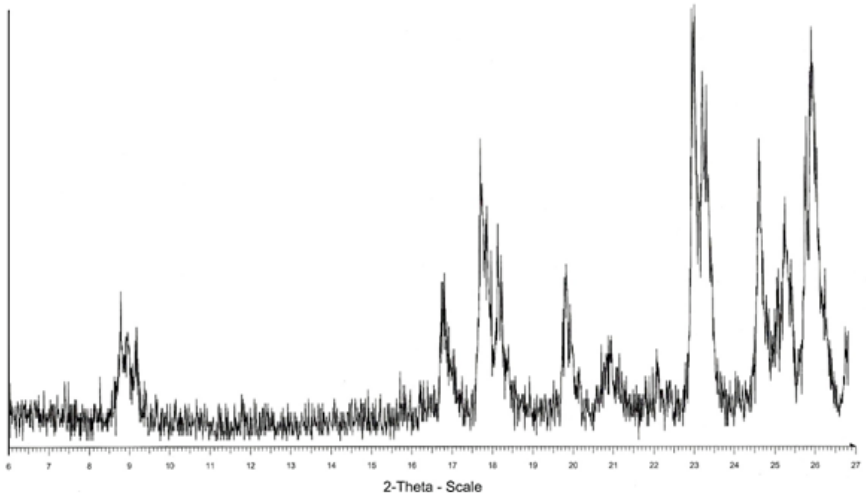
Heating of 5-Br-A form I in acetic anhydride at 90°C for 2 hrs – mixture of forms I and II (crystalline **5-Br-AA** also visible $2\theta \approx 10.6°$)



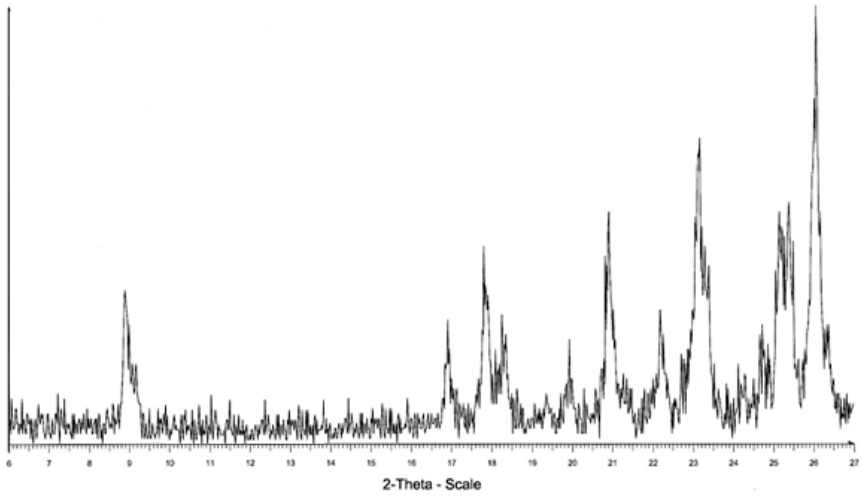
Heating of 5-Br-A form I in acetic anhydride at 90°C for 5 hrs – only form II

Summary for 5-Br-A synthesis:

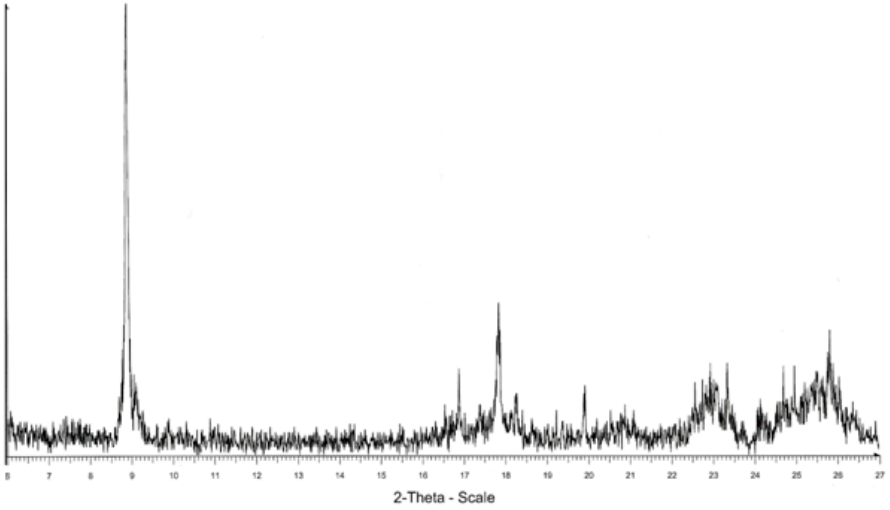
- During reaction step (5-Br-salicylic acid in acetic anhydride with H_2SO_4(aq) at 60°C for 20 mins), only form I is produced
- Heating in acetic anhydride at 90°C yields a mixture of form I and form II after 2 hours
- Heating in acetic anhydride at 90°C for 5 hours produces only form II



5-Br-A form II slurry in acetone (7 days):
only form I



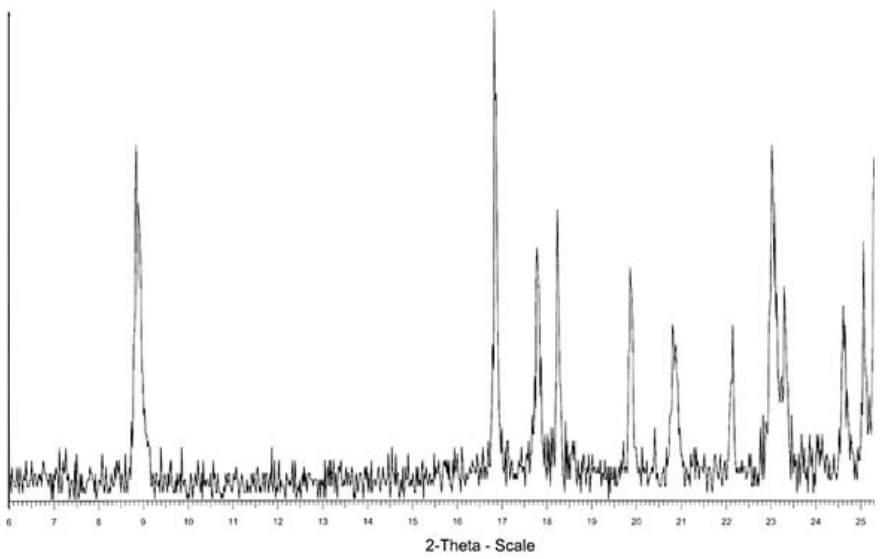
5-Br-A form II slurry in 2-propanol (7 days):
only form I



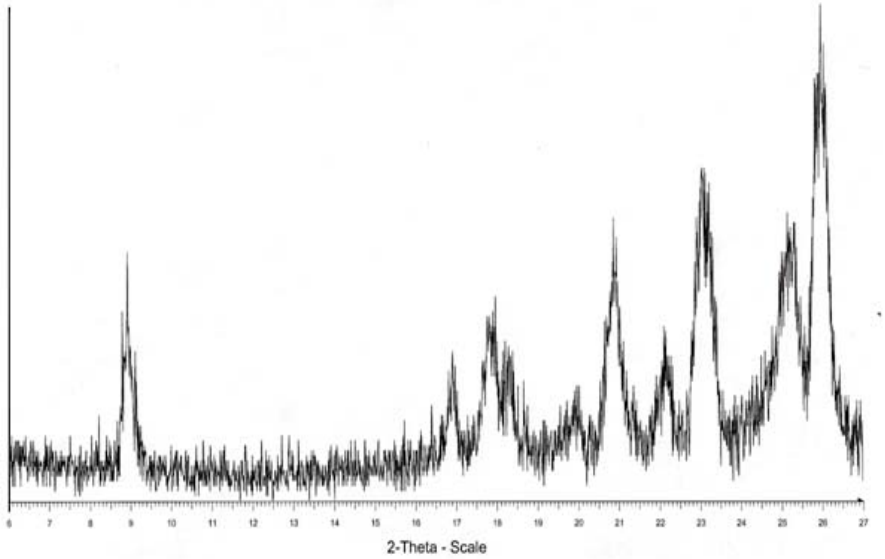
5-Br-A form II slurry in acetonitrile (7 days):
only form I

Summary for 5-Br-A slurrying experiments:

Form II transforms to form I over a period of days in the following examined solvents: acetonitrile, acetone, 2-propanol. Comparative experiments for **5-Cl-A** and **5-Br-A** show that **5-Br-A** transforms at a more rapid rate



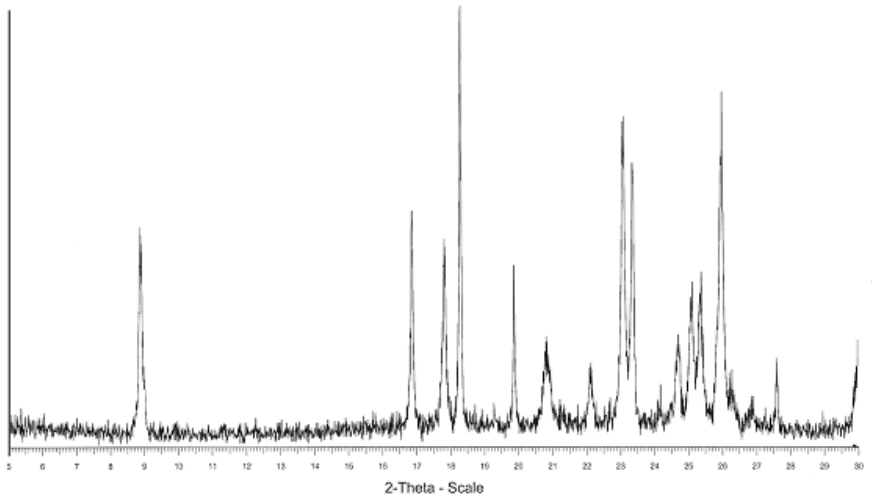
5-Br-A freeze drying (from solution in acetone): only form I



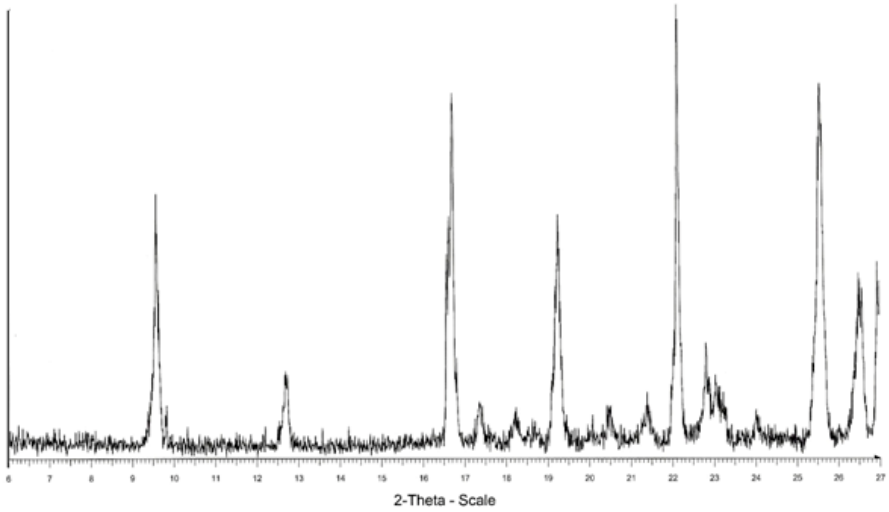
5-Br-A solid-state grinding (Retsch MM400 ball mill, 25 ml vessel, one steel ball Ø10 mm, 30 mins, 17.5 Hz): only form I

5-Br-A:

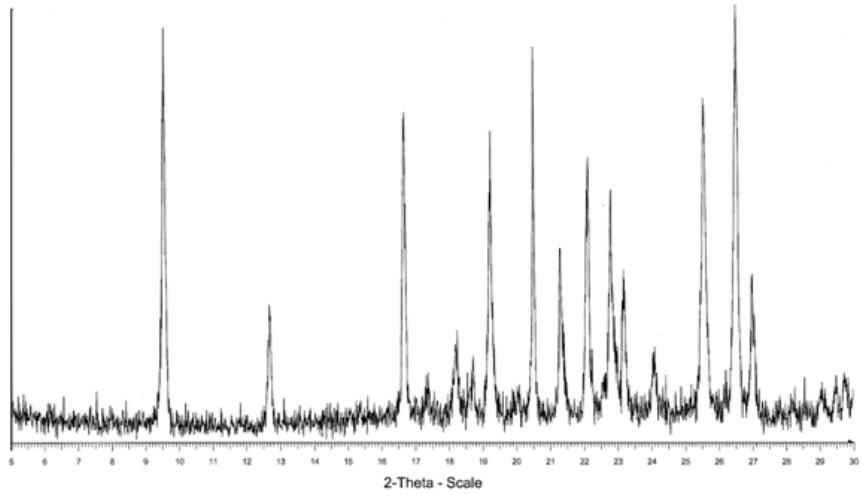
- Freeze drying produces only form I
- Solid-state grinding converts form II→form I



Recrystallisation of 5-Br-A from EtOH/acetone (slow evaporation, *ca* 3 days) – only form I



Recrystallisation of 5-Br-A from EtOH/acetone with 10 mol % 5-Br-AA (refrigerator, slow evaporation, *ca* 5 days) – only form II

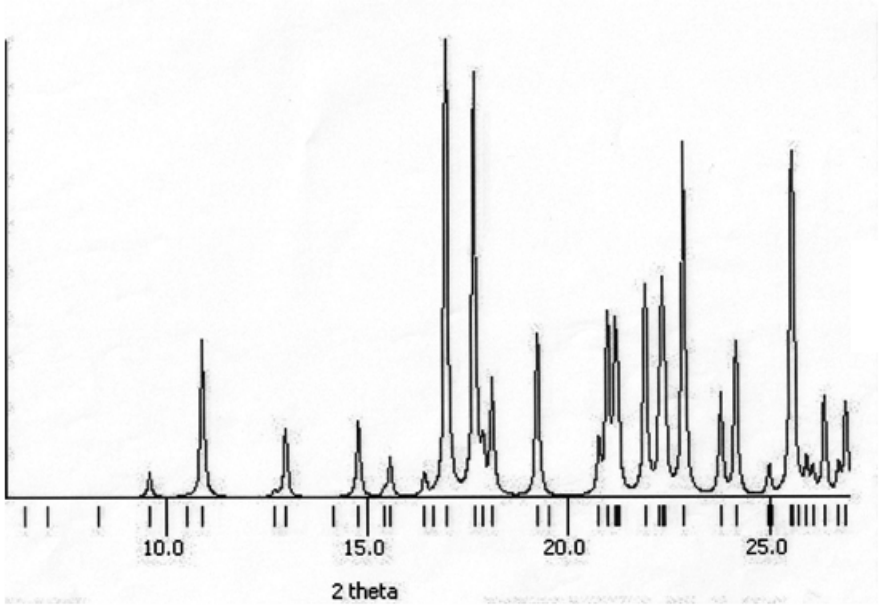


Recrystallisation of 5-Br-A from EtOH/acetone with 10 mol % 5-Br-AA (ambient, slow evaporation, *ca* 3 days) – only form II

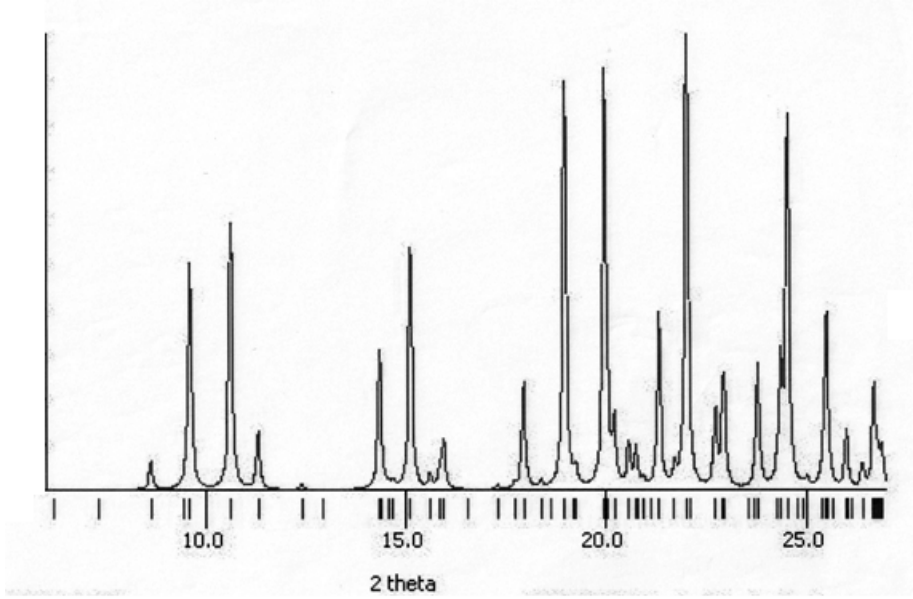
Recrystallisation of 5-Br-A:

- Recrystallisation of the pure compound from acetone/EtOH produces only form I
- Recrystallisation from acetone/EtOH in the presence of **5-Br-AA** (5–20 mol %) produces only form II

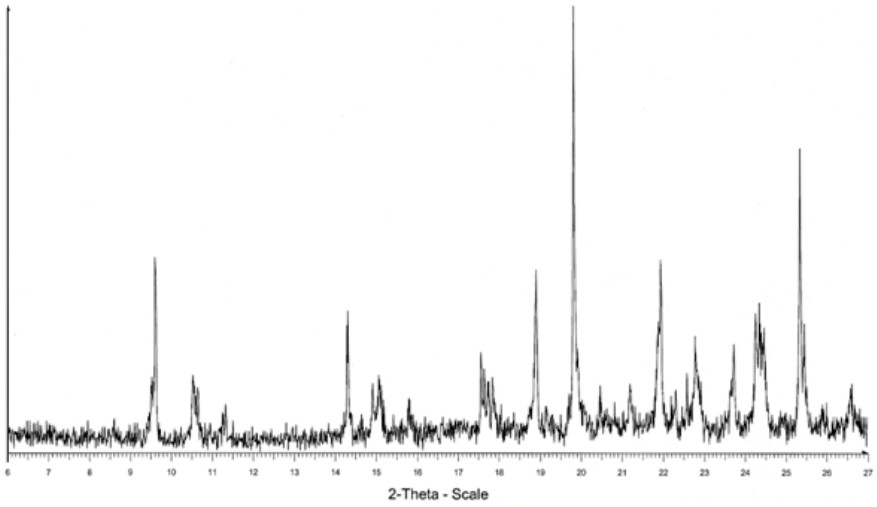
5-Cl-Aspirin Anhydride



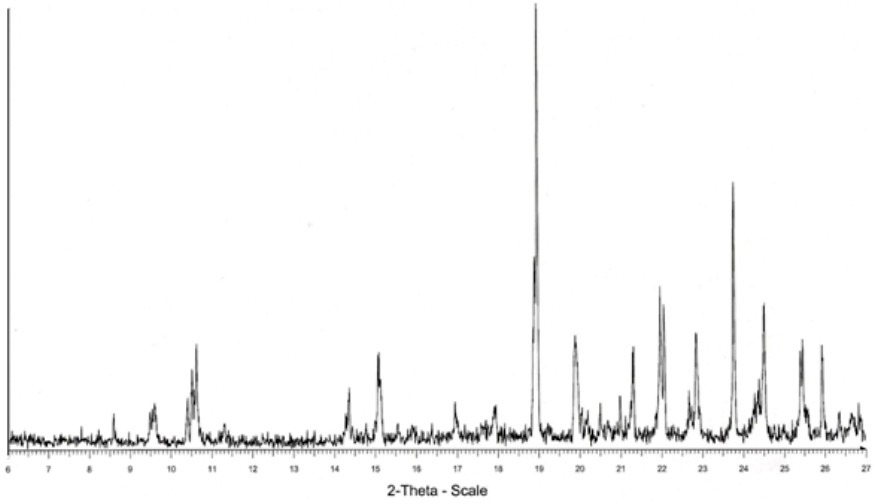
Simulated pattern for **5-Cl-AA** form I (orthorhombic, 150 K)



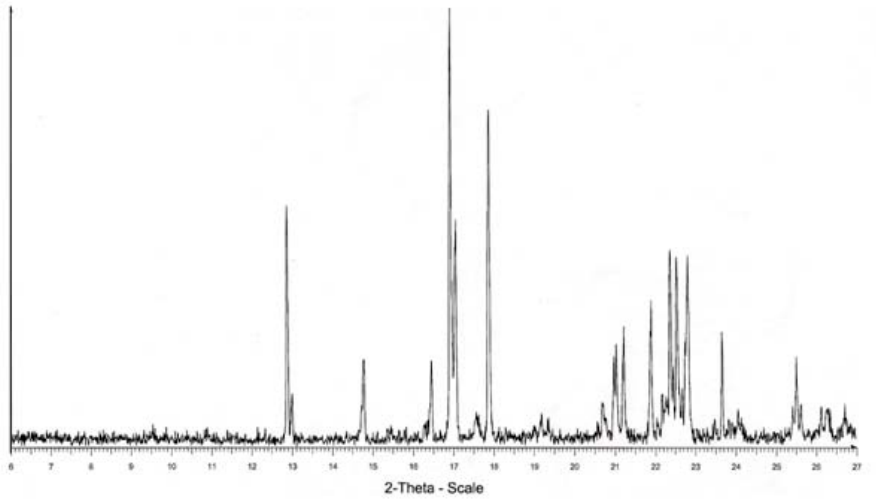
Simulated pattern for **5-Cl-AA** form II (monoclinic, 150 K)



5-Cl–AA synthesis product (oil, according to procedure in S1) recrystallised from hot EtOH (78°C, 10 mins) –monoclinic form



Heating 5-Cl–AA in EtOH (78°C, 2 hrs) – monoclinic form



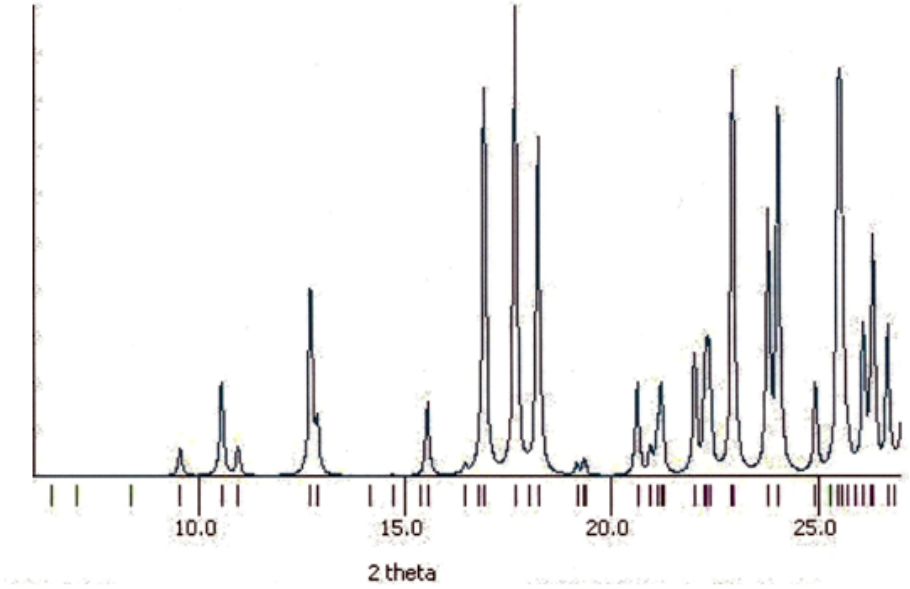
Recrystallisation of monoclinic form of 5-Cl-AA from EtOH/acetone mixture (ambient, slow evaporation, *ca* 3 days) – orthorhombic form*

Recrystallisation of 5-Cl-AA:

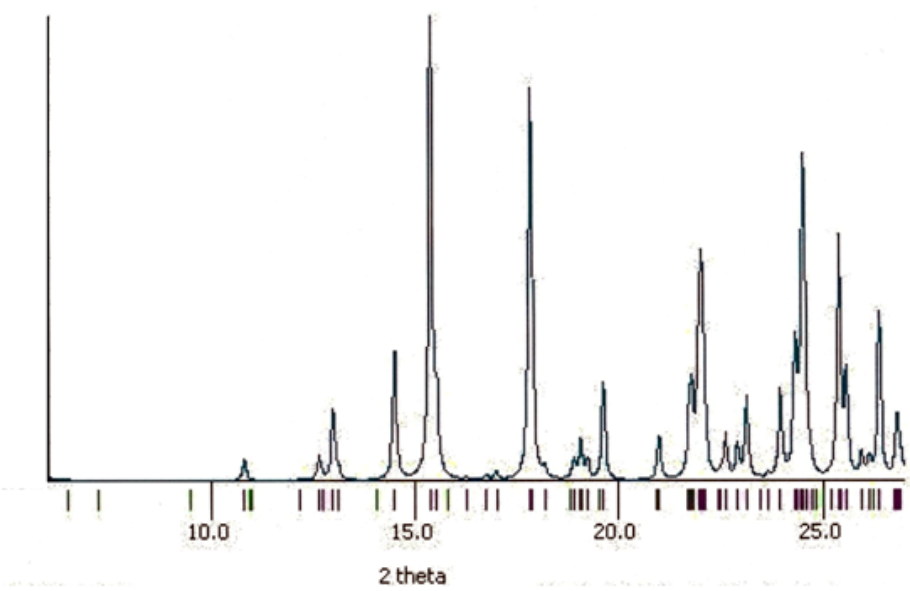
- Recrystallisation of the pure compound from hot EtOH produces monoclinic form
- Ambient recrystallisation from organic solvents (except MeCN) produces orthorhombic form

* **Note:** this pattern was measured from hand-selected single crystals, and is clearly subject to preferred orientation (for example, the peak expected at ca 11° 2-theta has very low intensity). Nonetheless, the match to the orthorhombic form (page 11) is clear.

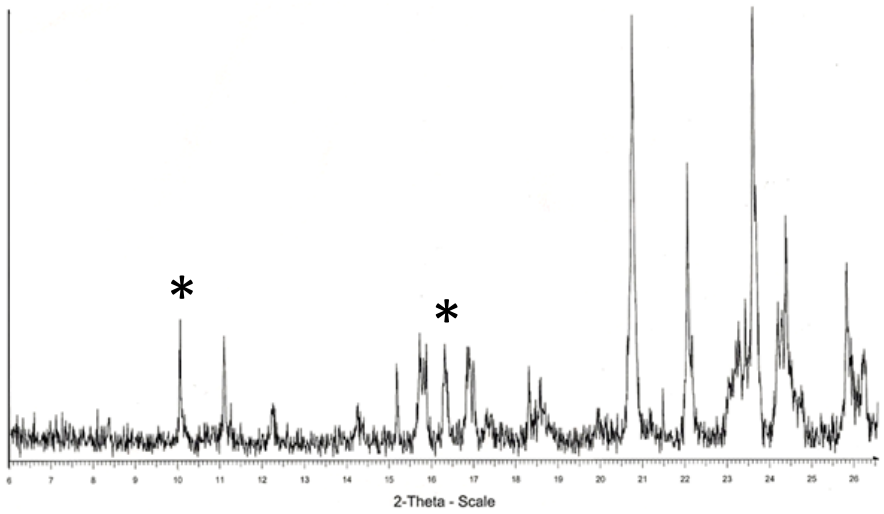
5-Br-Aspirin Anhydride



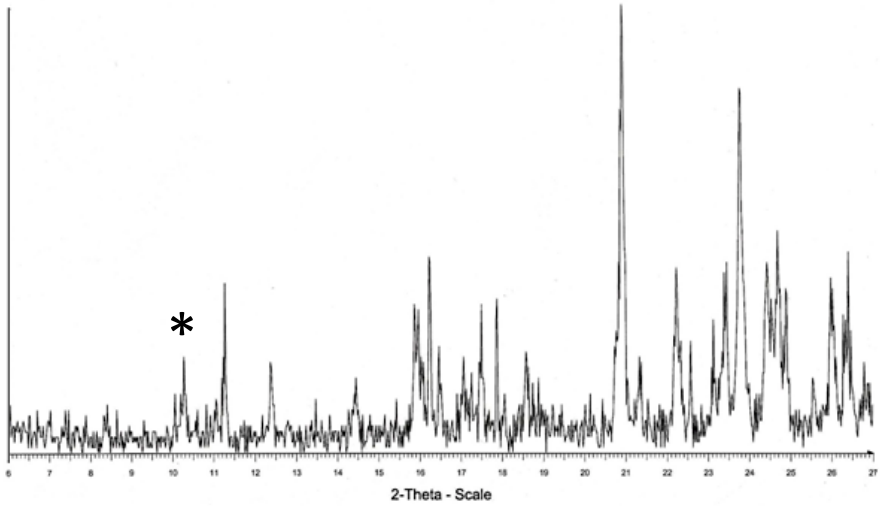
Simulated pattern for **5-Br-AA** form I (orthorhombic, 150 K)



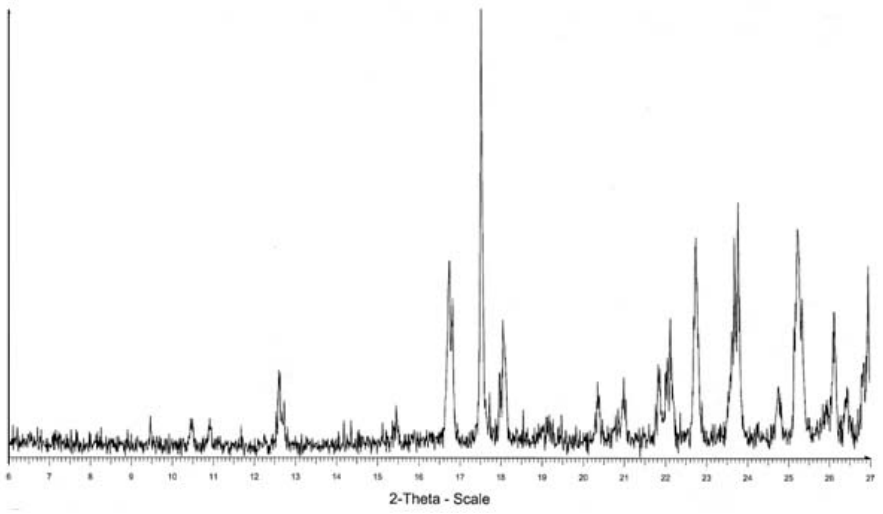
Simulated pattern for **5-Br-AA** form II (monoclinic, 150 K)



5-Br–AA synthesis product (oil, according to procedure in S1) recrystallised from hot EtOH (78°C, 10 mins) – monoclinic form.
Peaks marked * correspond clearly to 5-Br-A form II.



Heating 5-Br–AA in EtOH (78°C, 2 hrs) – monoclinic form

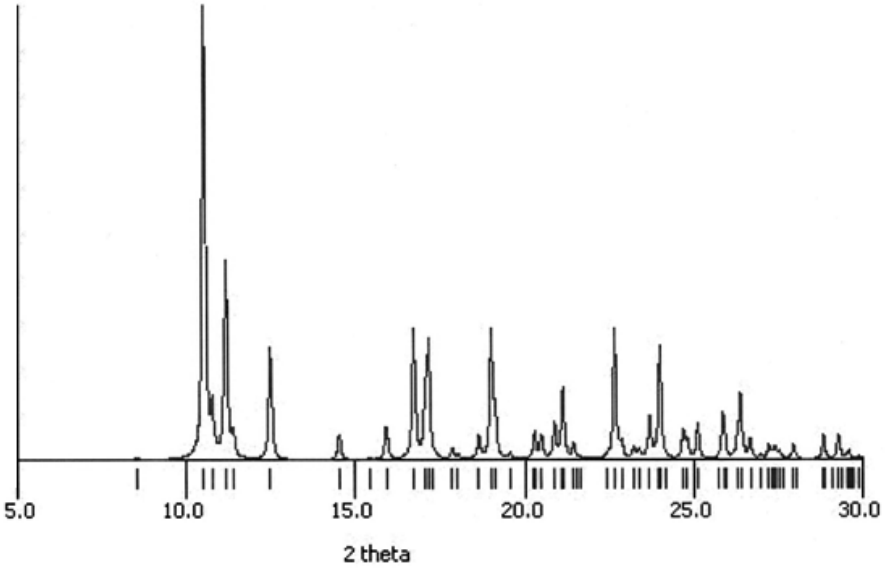


Recrystallisation of monoclinic form of 5-Br-AA from EtOH/acetone mixture (ambient, slow evaporation, *ca* 3 days) – orthorhombic form

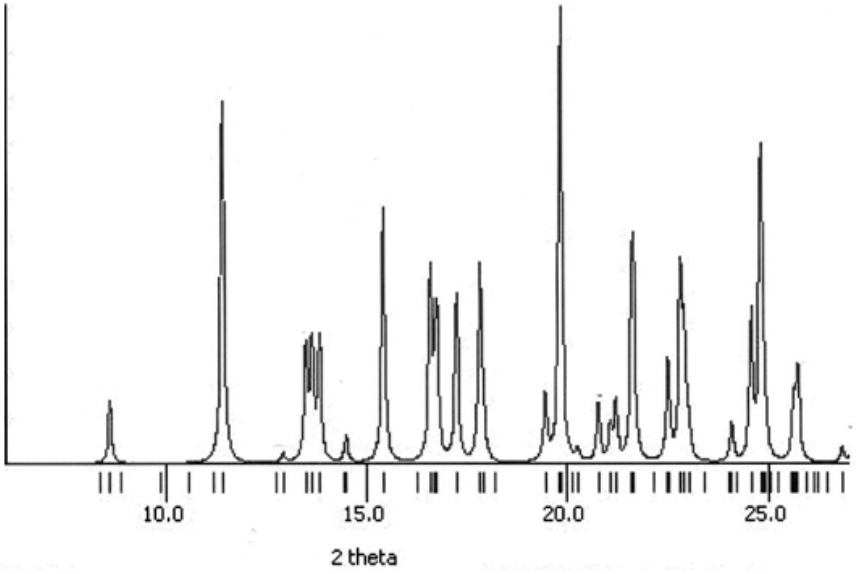
Recrystallisation of 5-Br-AA:

- Recrystallisation of the pure compound from hot EtOH produces monoclinic form
- Ambient recrystallisation from organic solvents (except MeCN) produces orthorhombic form

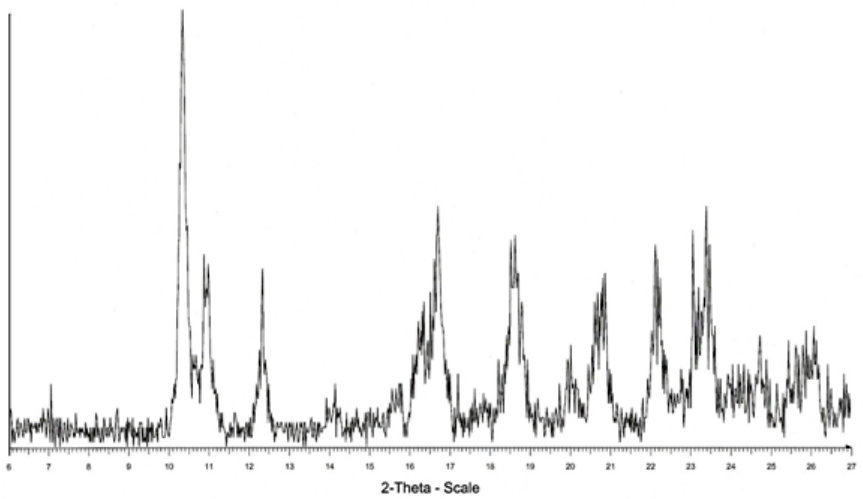
5-Me-Aspirin Anhydride



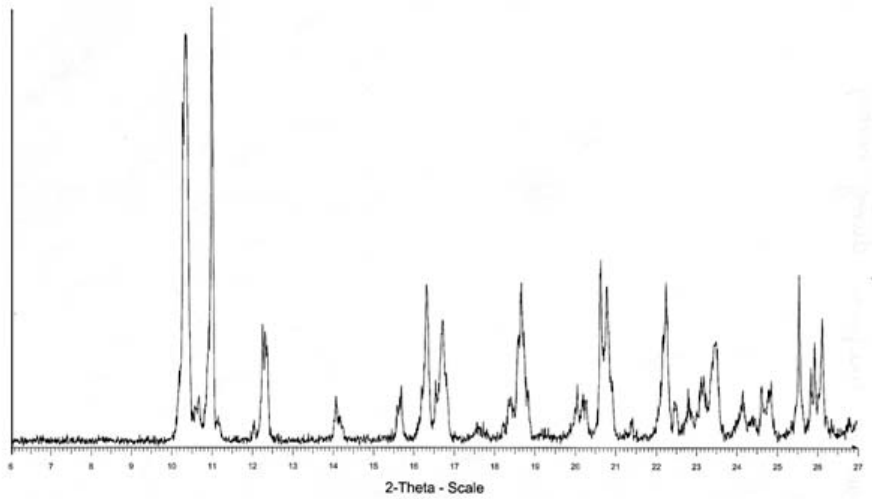
Simulated pattern for **5-Me-AA** form I (triclinic, 150 K)



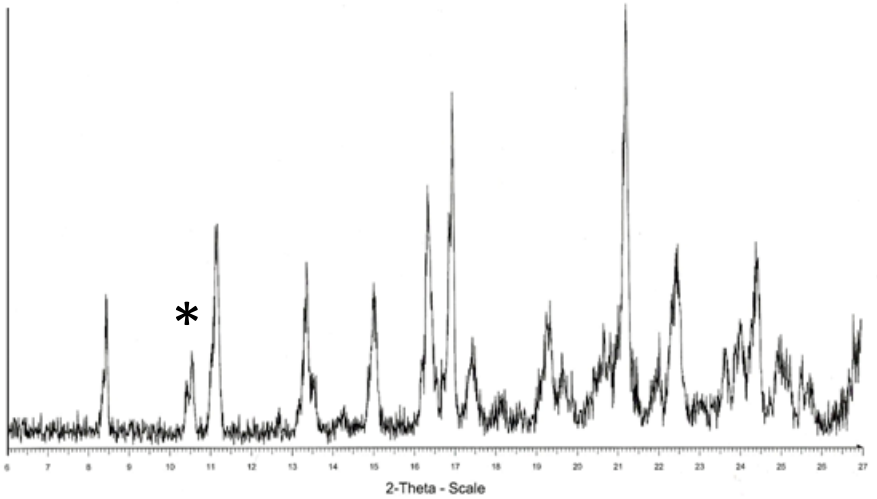
Simulated pattern for **5-Me-AA** form II (monoclinic, 150 K)



5-Me-AA synthesis product (oil, according to procedure in S1) recrystallised from acetone (freezer, –10 °C, 1 day) – triclinic form



Heating 5-Me-AA in acetone (56°C, 1 hr) – triclinic form

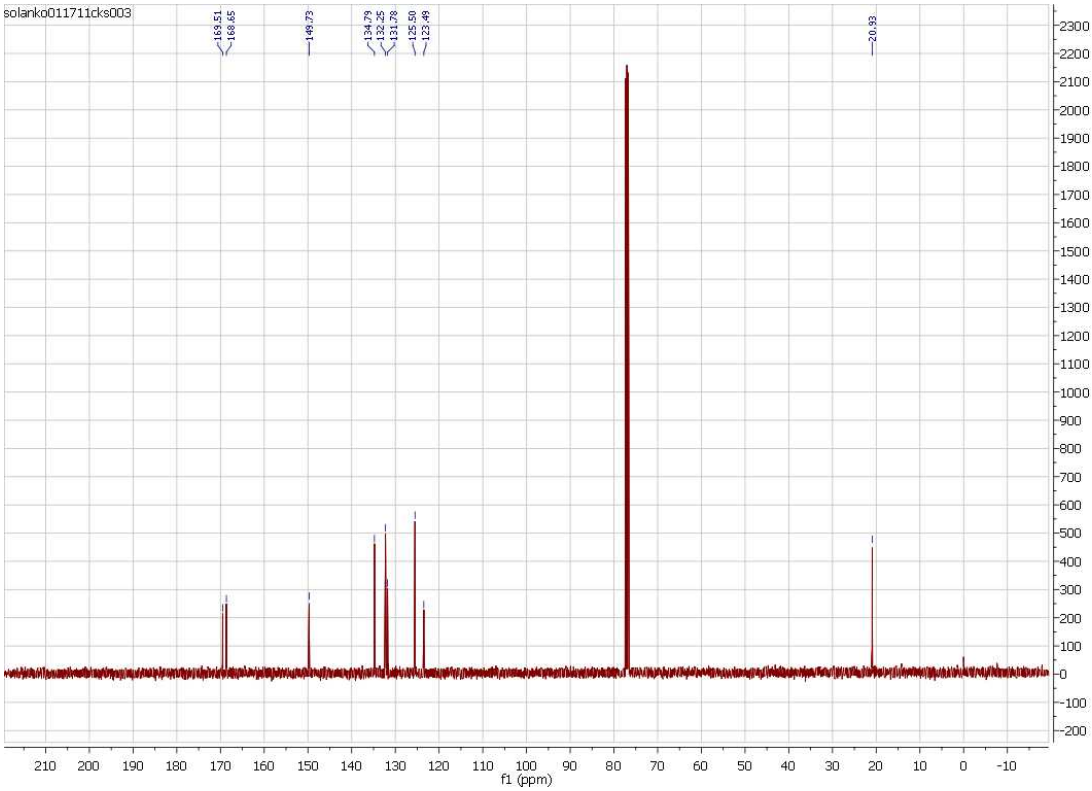


Heating 5-Me-AA in acetone (56°C, 1 hr) with 15 mol % 5-Me-AA – monoclinic form. The marked peak corresponds to the largest diffraction peak in **5-Me-A**.

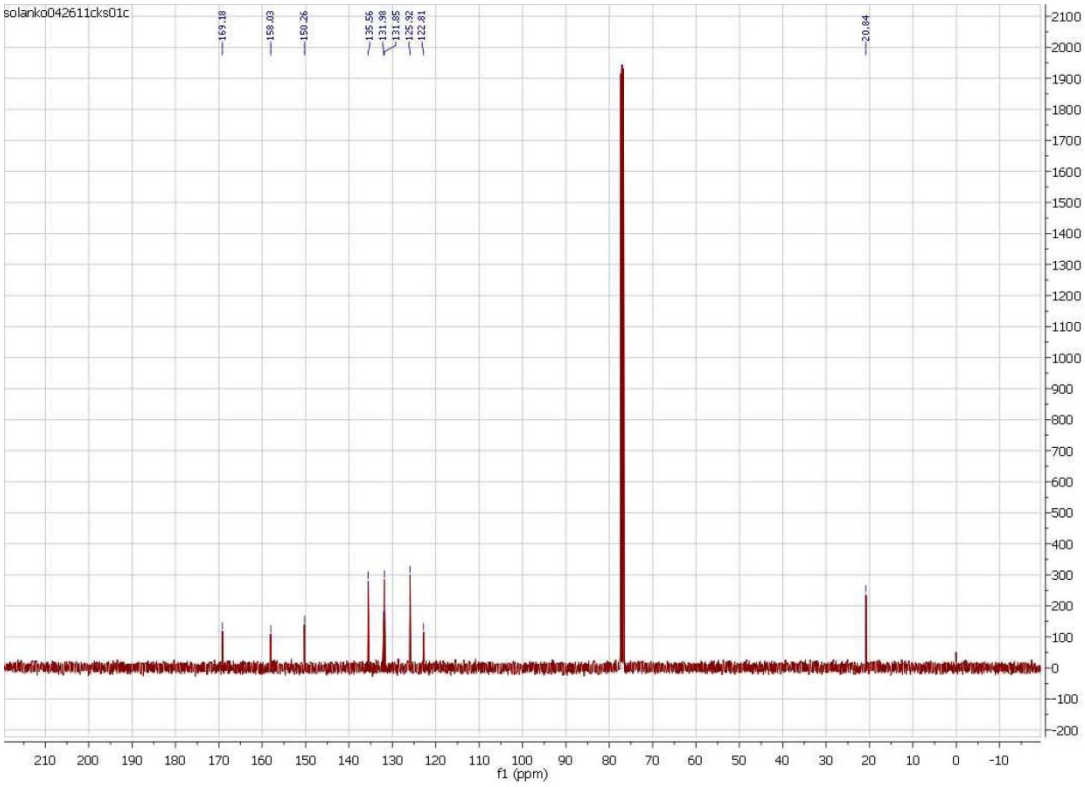
Recrystallisation of 5-Me-AA:

- Recrystallisation of the pure compound from acetone or EtOH, with or without heating, produces triclinic form
- Recrystallisation from acetone or EtOH, with heating and addition of 10-15 mol % **5-Me-A** produces monoclinic form

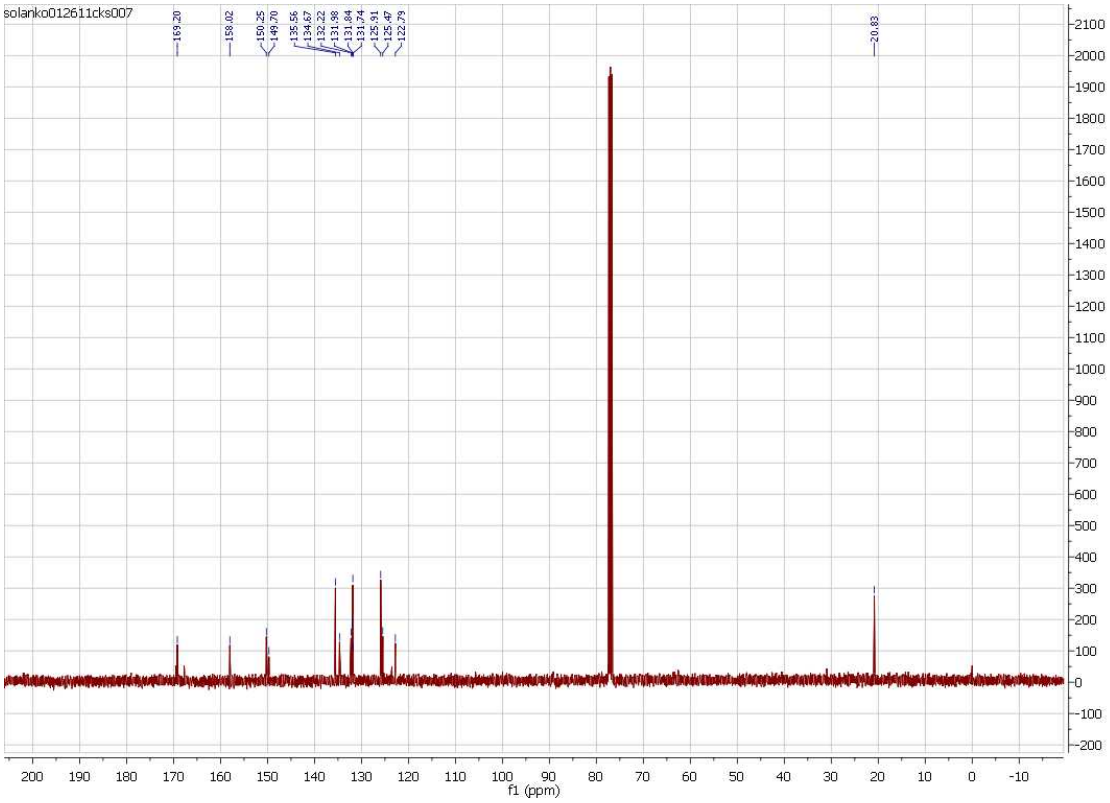
Solution ^{13}C NMR ($CDCl_3$)



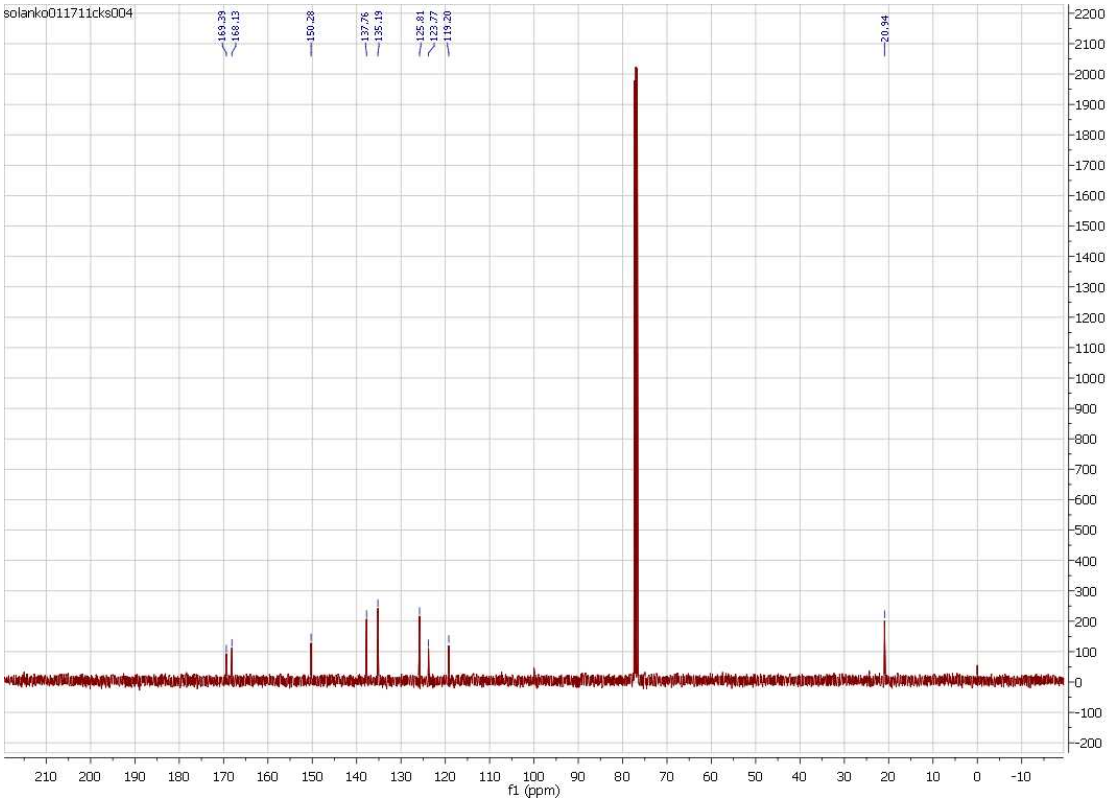
5-Cl-A



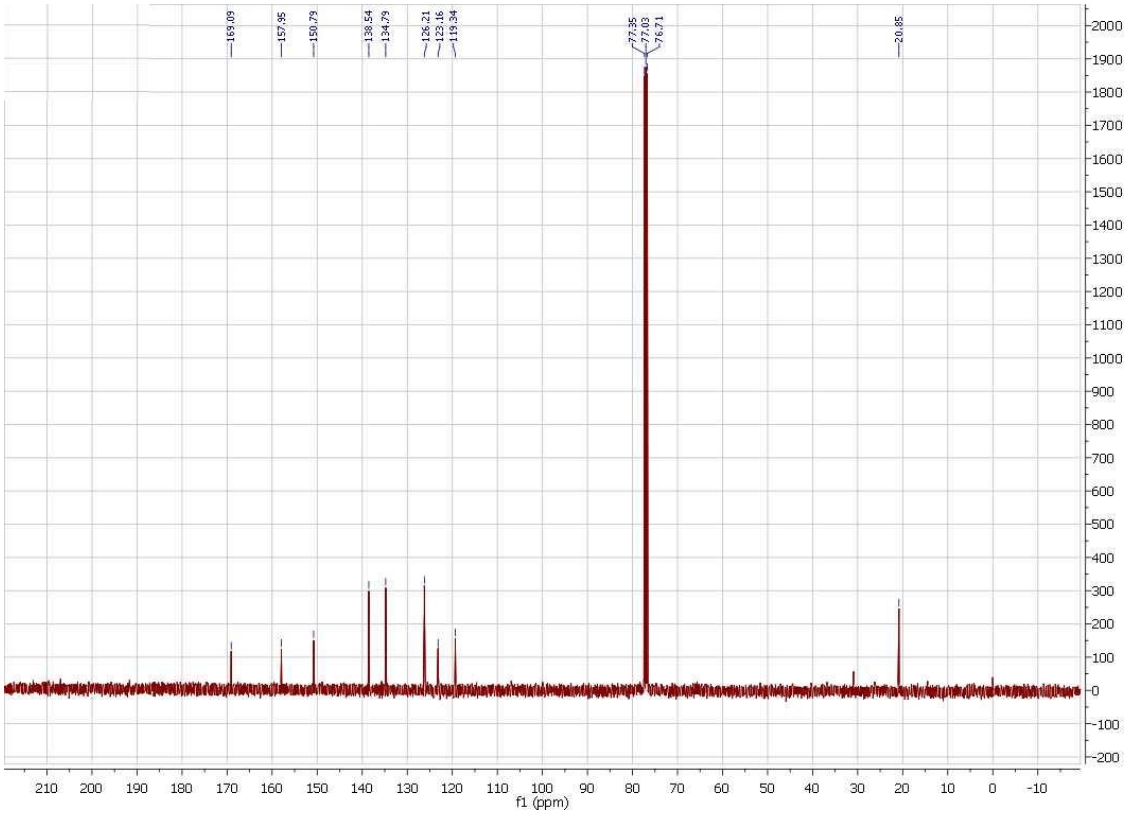
5-Cl-AA (prepared by method in main manuscript, principal diagnostic peak 158.0 ppm)



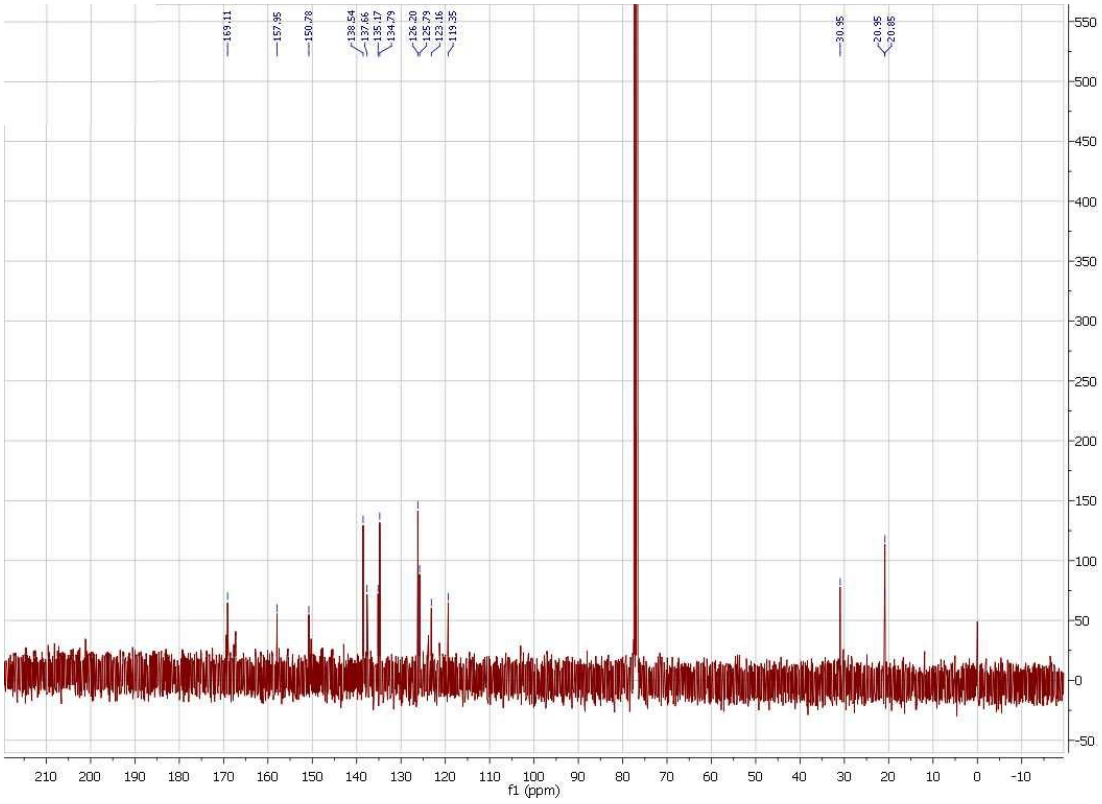
5-Cl-A after 4 h heating in acetic anhydride



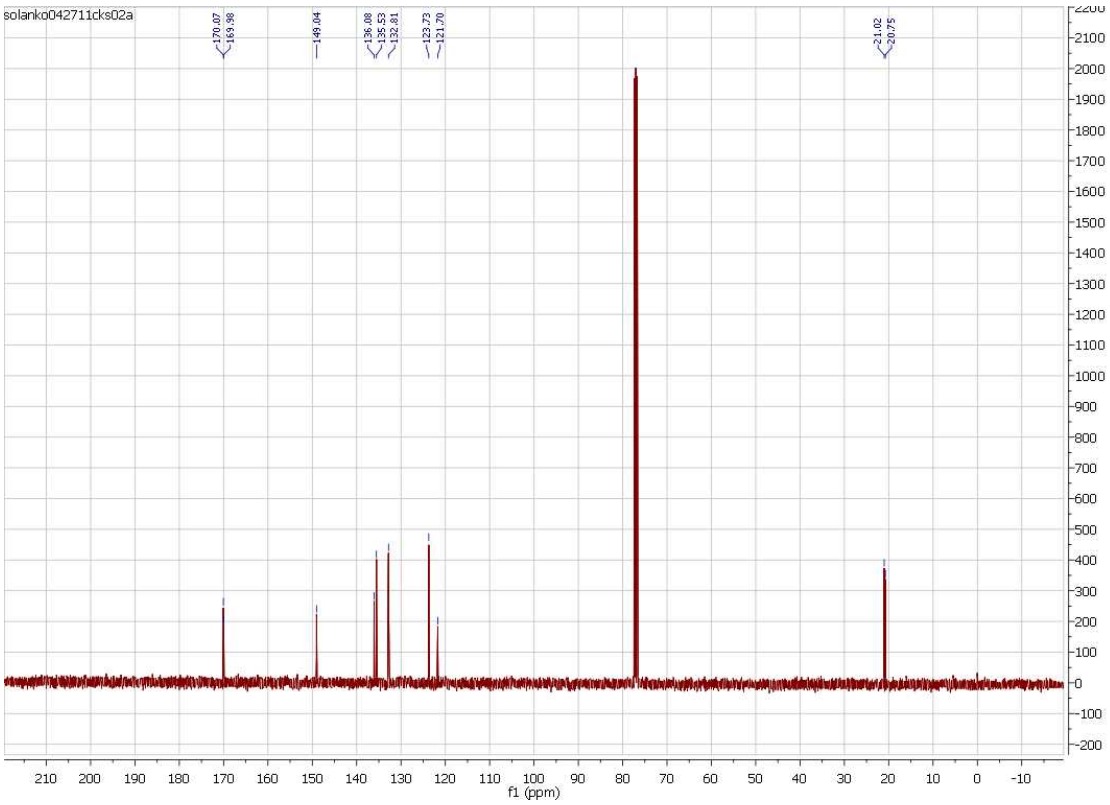
5-Br-A



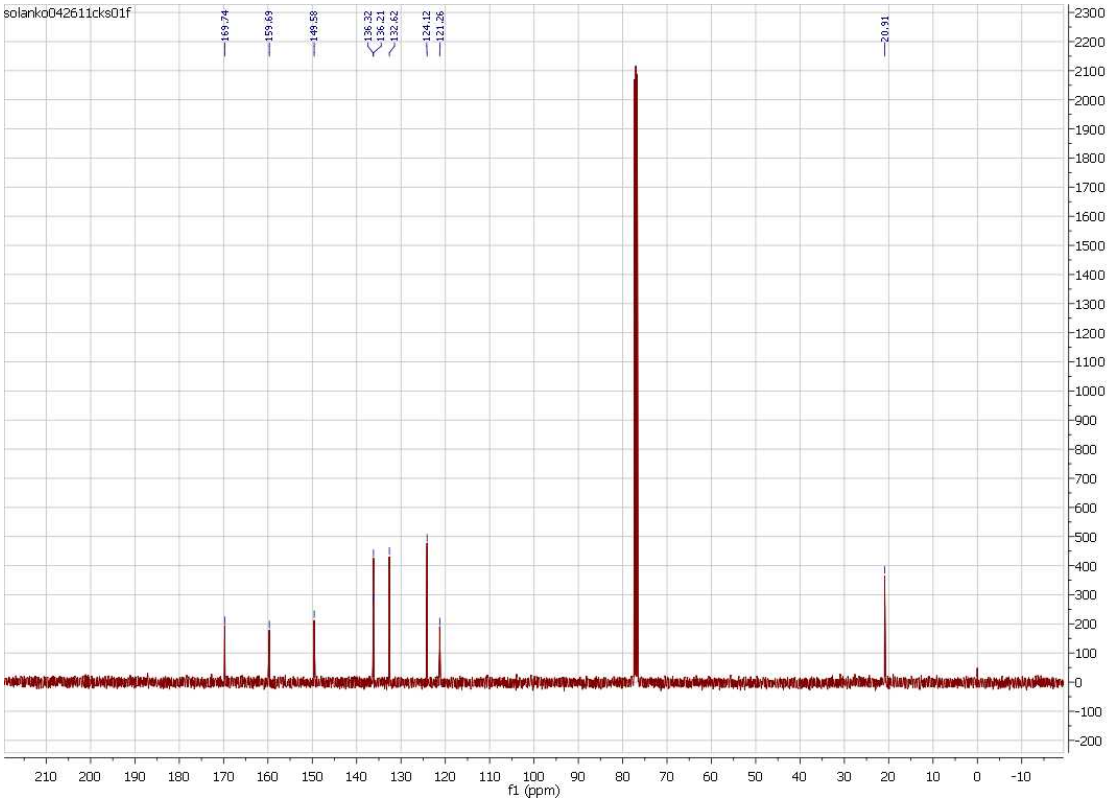
5-Br-AA (prepared by method in main manuscript)



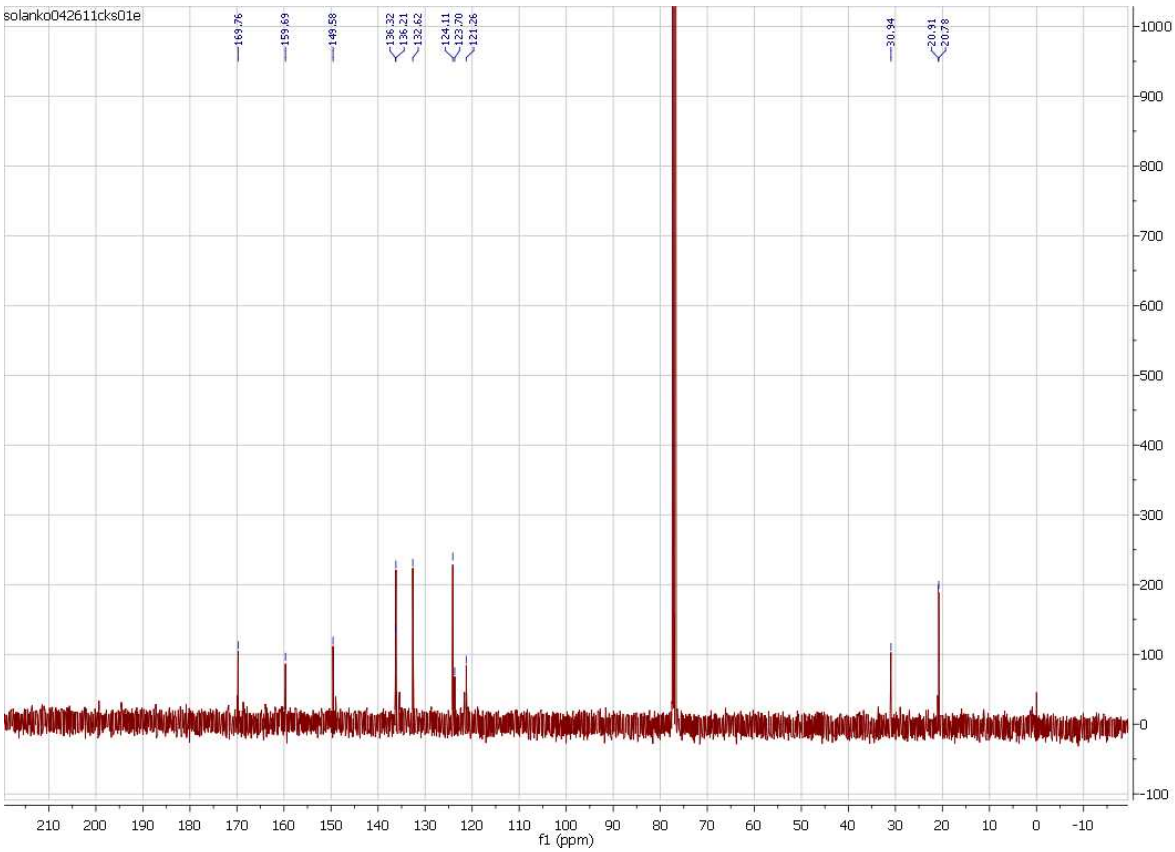
5-Br-A after 4 h heating in acetic anhydride (zoom)



5-Me-A



5-Me-AA (prepared by method in main manuscript)



5-Me-A after 4 h heating in acetic anhydride (zoom)

The solutions of **5-X-A** after heating in acetic anhydride clearly contain **5-X-A** and **5-X-AA** (principal diagnostic peak 158–160 ppm). Several of the spectra also contain an additional peak at 30.9 ppm that is not attributable to either **5-X-A** or **5-X-AA**. The peak position is appropriate for CH_3 in acetone. It does not correspond to any other expected impurity in this system (for example, salicylic acid, acetic anhydride, acetic acid, *etc*.)